



Management

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THE BASICS OF PAIN

The following account contains material quoted directly from the publications by the Australian and New Zealand College of Anaesthetists titled “Acute Pain Management: Scientific Evidence” 2nd edition 2005 and Massachusetts’s Handbook of Anesthesia’s chapter titled “Pain”.

Introduction

The International Association for Study of Pain (IASP) defines pain as “an unpleasant sensory **and emotional** experience associated with actual or potential tissue damage or described in terms of such damage (1).

It is important to emphasize that pain is not just a physical sensation, but also an **emotional experience**. There is usually an emotional component contributing to the pain experience. A simple definition of pain - “*Pain is what the patient says, hurts (2)*” The emphasis is on *the patient’s* experience. The patient must be believed about the pain.

The emotional component is variable from person to person and in the same person from time to time. Pain is an individual, multi-factorial experience influenced by culture, previous pain events, beliefs, mood and ability to cope. Management of pain has to take these facts into consideration.

The untreated or the under-treated pain condition can cause physical damage and also worsen the pain experience by muscle spasm, peripheral and central sensitization and recruitment and by muscle spasm. Unrelieved acute pain can cause chronic pain, and long standing pain can cause anatomical changes in the nervous system.

Pain can be classified in several ways, but the most relevant, in terms of therapeutic options, is the classification of pain into **nociceptive** (somatic and visceral) and **neuropathic** pain (3). A detailed account of the classification of pain is given later.

Apart from the identification of the type of pain, it is also necessary to quantitate pain. Several scoring systems are available such as the numerical scale. It needs to be remembered that the patient is the only person who can quantitate his/her pain. Evaluation of pain will be covered in another lecture.

Acute pain is defined as “pain of recent onset and probable limited duration. It usually has an identifiable temporal and casual relationship to injury or disease” (4). Chronic pain is defined as “pain which persists beyond the time of healing of an injury and often there may not be any clearly identifiable cause” (4).

Mechanism of pain sensation

The anatomy and physiology of pain are very complex. It is easy to understand, if the anatomy of the system is studied in terms of the four major physiologic processes that are involved: transduction (nociceptors), transmission (primary afferent fibres, dorsal horn, ascending tracts), interpretation (cortical and limbic processing) and modulation (descending control and neuro-humoral mediators).

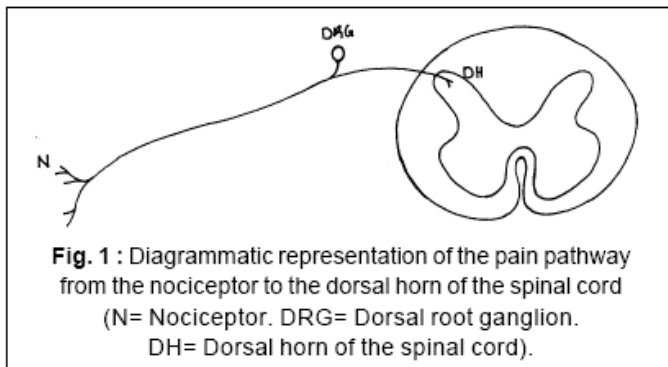


Fig. 1: Diagrammatic representation of the pain pathway from the nociceptor to the dorsal horn of the spinal cord

Nociceptors

Potentially tissue damaging sensory information is conveyed to the CNS by way of free nerve endings located within the cutaneous and non-cutaneous tissue (viscera and somatic tissue). These free nerve endings are called nociceptors. The nociceptors relay the sensory information to the dorsal horn of the spinal cord via slow conducting, small diameter, unmyelinated C-fibres and by fast conducting, thinly myelinated A - delta fibres.

C – fibres

These fibres exhibit polymodal responses that allow the individual to discriminate between mechanical, thermal and chemical injury. When injury occurs, a variety of chemical mediators are released in the injured area producing the features of inflammation. Some of these mediators (substance P and calcitonin gene-related peptide [CGRP]) play a role in producing nociceptor hypersensitivity or primary hyperalgesia in the injured area and also secondary hyperalgesia in the surrounding tissues.

Primary afferent fibres

These consist of the unmyelinated C fibres and the myelinated A delta fibres, which are activated by the nociceptors. The majority of the input to the CNS is through the C fibres. These afferents have their cell bodies located within the dorsal root ganglion (DRG). The difference in conduction speed between the 2 types of fibres is the basis for 'first' and 'second' pain (or fast and slow pain).

Neurotransmitters

There are numerous types of neurotransmitters involved in the pain pathways. They are usually divided into fast acting excitatory (aspartate, kainate) or inhibitory (gamma-amino butyric acid [GABA], glycine) amines or more slowly acting excitatory (substance P) or inhibitory (encephalin, galanin) modulators.

Numerous receptor types are also present in these pathways, including opioid and N-methyl-D-Aspartate [NMDA] receptors.

Dorsal horn

The next step in pain transmission occurs at the synapse between the primary afferents and neurons found within the dorsal horn. Cutaneous sensory fibres travel in the sensory nerves, whilst visceral afferent pain fibres travel in the parasympathetic and sympathetic systems. The afferents enter the spinal cord by way of the DRG to terminate on neurons within the dorsal horn. The dorsal horn is arranged in 10 layers or laminae (Rexed's laminae) and the C fibres and A – delta fibres terminate within different lamina. The neurons within the different laminae then synapse on to second order neurons, which form the ascending tracts.

The second order neurons are further subdivided based on their responses to pain. For example, wide-dynamic range neurons respond to mechanical and noxious stimuli. Nociceptive-specific neurons are activated only by painful stimuli.

Ascending tracts

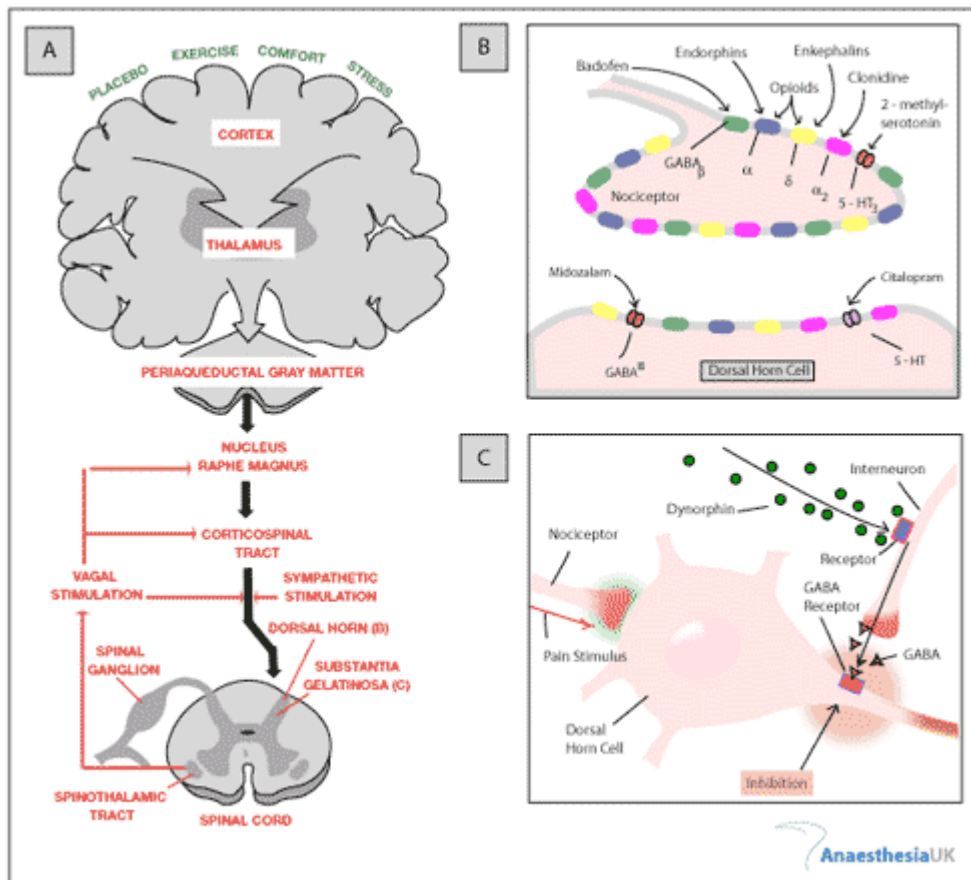
The axons from the second order neurons ascend to higher brain structures. There are a number of ascending tracts including the spinothalamic tract (STT), spinoreticular, spinothalamic and spinoamygdala tracts, of which the STT in the ventrolateral aspect of the spinal cord is the most important.

The first cortical synapse is within the thalamus; from here 3rd order neurons send axons to the somatosensory cortex and to regions of the brain involved in affective responses to pain. In this way the CNS is 'wired' to allow for a sensory and emotional response to an acutely painful stimulus.

Pain modulation and descending tracts

Modulation of the pain experience occurs at a number of central sites. The periaqueductal gray area in the midbrain and the raphe magnus area in the medulla are the key centres, but other nuclei located in the thalamus and hypothalamus also play their part. The receptor systems involved in these pain-modulation centres include opioid, noradrenergic and serotonergic types.

Descending tracts occupy the dorsolateral aspect of the spinal cord to terminate in the dorsal horn, where they directly (onto STT neurons) or indirectly (via interneurons) modulate afferent input from the periphery. (Figure 2 Physiology of Pain, courtesy of Anaesthesia UK)



A:
Antinociceptive pathways are activated when pain signals in the spinothalamic tract reach the brain stem and thalamus. The periaqueductal gray matter and nucleus raphe magnus release endorphins and enkephalins. A series of physio-chemical changes then produce inhibition of pain transmission in the spinal cord.

B:
70% of endorphin and enkephalin receptors are in the presynaptic membrane of nociceptors. Thus, most of the pain signal is stopped before it reaches the dorsal horn. The signal is then further weakened by dynorphin activity in the spinal cord. The site of action of various analgesics is shown.

C:
Dynorphin activation of alpha-receptors on inhibitory interneurons causes the release of GABA. This causes hyperpolarization of dorsal horn cells and inhibits further transmission of the pain signal.

For a more detailed description of the applied physiology of pain, please refer to Chapter 1 of Acute Pain Management Scientific Evidence (2nd edition) 2005. ANZCA and Faculty of Pain Medicine (5).

Classification of Pain

The peripheral nerve ending (nociceptor) transmits the pain impulse to the dorsal horn of the spinal cord, where it gets modified before onward transmission to the brain. Any pain caused primarily by stimulation of the nociceptor can be said to be **nociceptive** pain. If pain is caused by impulse generation within the pathway proximal to the nociceptor (this could be in the nerve, the spinal cord or the brain and in other words the peripheral or the central nervous system that is responsible for the transmission of acute pain), it is called **neuropathic** pain (fig 3).

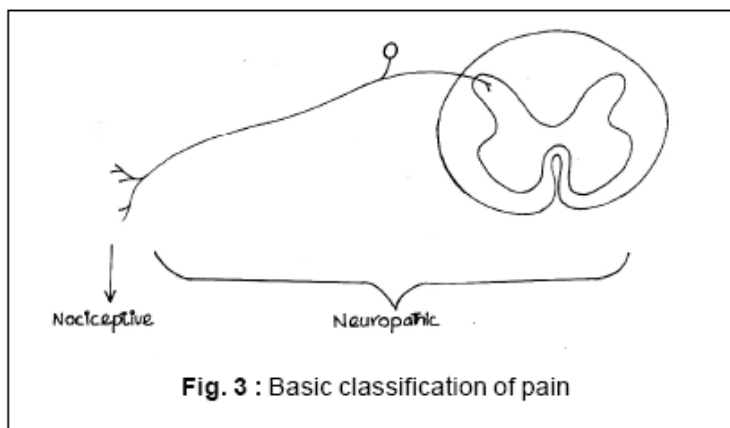


Fig. 3: Basic classification of pain

Nociceptive pain can be subdivided to somatic and visceral pain, depending on the site of origin. Somatic pain may be described as sharp, hot or stinging, it is generally well localized and is associated with local and surrounding tenderness. By contrast, visceral pain may be described as dull, cramping or colicky. It is often poorly

localized and may be associated with tenderness locally or in the area of referred pain, or with symptoms such as sweating and cardiovascular changes (3).

Neuropathic pain can be sub-classified into peripheral and central, depending on the site of origin of the abnormal impulse. The relevance is that central neuropathic pain often behaves differently from peripheral neuropathic pain, particularly in its response to drugs. Central neuropathic pain is the commonest in injury to the central nervous system – eg. Spinal cord injuries, stroke etc (12).

It must be remembered that pain originally of peripheral nerve origin, can become centrally established – by somehow altering the CNS. Once this has happened, a peripheral nerve block or neurolysis may not successfully remove the pain.

Features of the pain that may suggest a diagnosis of neuropathic pain include descriptions such as burning/shooting/stabbing; the paroxysmal or spontaneous nature of pain with no obvious precipitating factors; if it has a neural or dermatomal distribution; the presence of dysaesthesias (spontaneous or evoked unpleasant abnormal sensations), hyperalgesia (increased response to a normally painful stimulus), allodynia (pain due to a stimulus that does not normally evoke pain

such as light touch) or areas of hypoaesthesia; and regional autonomic features (changes in colour, temperature and sweating) and phantom phenomena (4).

Why treat Pain?

1. **Relieving suffering:** The highest attainable standard of health is enshrined in the 1948 Universal Declaration of Human Rights as a fundamental right of every human being. Relief from pain is part of that basic human right to health (5.1)
2. **Avoiding Respiratory, Cardiovascular and Gastro-Intestinal complications:** Pain causes reflex muscle spasm. This has two negative implications: Poor peri-operative analgesia leads to immobility and prolonged recovery and may lead to or exacerbate other co-morbidities (5.2)
3. **Untreated pain will keep getting worse (6).** This is true for surgical trauma too. Unrelieved acute pain may lead to chronic pain conditions. Risk factors that predispose to the development of long-term post surgical pain include the severity of pre and post-operative pain, intra-operative nerve injury, and psychological vulnerability. There are several neurophysiological reasons for this:
 - a). **Recruitment of nociceptors:** Silent' or 'sleepy' nociceptors are those that do not respond to noxious stimuli normally; but are activated in the inflamed tissues. Once they are recruited, the same degree of peripheral stimulus generates a greater number of electrical impulses, thereby resulting in worsening of pain.
 - b). **Central recruitment:** With persisting pain, adjacent spinal segments (or adjacent supraspinal areas) get recruited, so that pain gradually spreads to larger areas (7).
 - c). **Sensitisation of nociceptors:** The nociceptors get sensitized with time so that the response threshold is lowered. Chemicals involved in the inflammatory process mediate this peripheral sensitization. Other agents also implicated are purines, cytokines, leukotrienes, nerve growth factor and various neuro-peptides. Prostaglandins are believed to have a major role in this process of sensitization and this accounts for the reduction in pain obtained with the use of non-steroidal anti-inflammatory drugs (NSAIDs) (8).
 - d). **Central sensitization ("wind-up" phenomenon):**
The dorsal horn cells get sensitized. This is compared to a wound-up spring, hence the common term, "wind-up" phenomenon (9). When the painful stimulus persists, the same peripheral input produces a progressively increasing electrical response from the dorsal horn cell. It manifests as:
 - An increase in the receptive field for sensitised dorsal horn neurons
 - An increase in the duration of response and
 - A reduction in the response threshold.

N-Methyl D Aspartate (NMDA) is believed to be the most important neurotransmitter involved in the “wind-up” phenomenon (10).

e). **Neuroanatomical re-organisation:** This often seems to accompany central sensitization. In the face of continued barrage of pain impulses, the integrity of the dorsal horn of the spinal cord gets disturbed so that neurons sub serving input from A-beta fibres form functional connections with neurons in lamina-2 sub serving input from A-delta and C fibres. Thus, stimulation of A-beta fibres, which normally causes sensations only of touch and pressure, in this case causes pain (8). This is called **allodynia** (such abnormal sensations can also occur in peripheral nerve lesions).

Summary

It is now well accepted that unrelieved post-operative pain has a detrimental impact on short-term recovery and may contribute to peri-operative morbidity and mortality. This recognition has inspired many institutions in the developed world to set up Acute Pain Services (APS) in an attempt to provide effective post-operative pain relief. The advent of the APS has led to the successful and safe implementation of multimodal pain management techniques and specialized pain relief methods, such as Patient Controlled Analgesia (PCA) and epidural infusions, in surgical wards (13). Implementation of these methods may represent real advances in both improving patient well-being and in reducing post-operative morbidity (14).

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THE EVALUATION OF PAIN

The following is a review of the chapter on assessment of pain in “Acute Pain Management: Scientific Evidence” 2nd Edition 2005, published by the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine.

Assessment

A proper assessment and measurement of pain is essential for diagnosis of the cause of pain, selecting the appropriate analgesic regime and for evaluation/modification of the therapy according to patient’s response. Methods of assessment must take into account the physiological, psychological and environmental factors that influence the pain experience.

The assessment of pain must include a general medical history and physical examination, a specific “pain history” and an evaluation of associated disability. A complete pain history provides diagnostic clues that may distinguish different underlying pain states such as nociceptive or neuropathic pain (1).

Fundamentals of a pain history

1. **Site of pain**
 - a. primary location: description and or body map diagram
 - b. radiation
2. **Circumstances associated with pain onset**
3. **Character of pain**
 - a. sensory descriptors e.g. sharp, throbbing, aching
 - b. McGill Pain Questionnaire: includes sensory and affective descriptors (Malacca 1987)
4. **Intensity of pain**
 - a. at rest
 - b. on movement
 - c. temporal factors
 - i. duration
 - ii. current pain; during last week; highest level
 - iii. continuous or intermittent
 - d. aggravating or relieving factors
5. **Associated symptoms (e.g. nausea)**
6. **Effect of pain on activities and sleep**
7. **Treatment**
 - a. current and previous medications – dose, frequency of use, efficacy, side effects
 - b. other treatment e.g. transcutaneous electrical nerve stimulation
 - c. health professionals consulted
8. **Relevant medical history**

- a. prior or coexisting pain conditions and treatment outcomes
 - b. prior or coexisting medical conditions
- 9. Factors influencing the patient's symptomatic treatment**
- a. belief concerning the causes of pain
 - b. knowledge, expectations and preferences for pain management
 - c. expectations of outcome of pain treatment
 - d. reduction in pain required for patient satisfaction or to resume 'reasonable activities'
 - e. typical coping response for stress or pain, including the presence of anxiety or psychiatric disorders (e.g. depression or psychosis)
 - f. family expectations and beliefs about pain, stress and postoperative course.

(From Acute Pain Management: Scientific Evidence)

Measurement

Pain is an individual, multi-factorial experience influenced by culture, previous pain events, mood, fear, anxiety, prognosis and the ability to cope. Hence, most measures of pain in clinical use are based on self-report. These measures have been shown to produce sensitive and consistent results if done properly (2).

In certain situations self-reporting measures may not be suitable (e.g. patients with cognitive impairment, reduced conscious states, children, language differences, unco-operativity or severe anxiety) and other measures of pain assessment will be needed.

Recording of pain as the "fifth vital sign" aims to increase awareness and utilization of pain assessment (3). Regular and repeated measurements of pain as determined by duration and severity of pain, patient needs, type of intervention(s) and response to that intervention(s) may lead to improved pain management (3, 4). Such measures should ideally include assessments of static (rest) and dynamic (on sitting, coughing or moving the affected part) pain. Whereas static measures may relate to the ability to sleep, dynamic measures can provide a simple test of mechanical hyperalgesia and determine whether analgesia is adequate for recovery of function (1, 5).

In an ideal world, assessment of pain should become as basic as measuring pulse and blood pressure and the pain measurement recorded as the fifth vital sign. There are assessment tools available that are simple to use and understand. These methods are even useful and adaptable to understaffed wards or in the developing world (6, 7).

One-dimensional measures of pain

A number of pain scales are available that measure either pain intensity or the degree of pain relief following an intervention. See Template 2.

- a) **Categorical:** These scales use words to describe the magnitude of pain or the degree of pain relief (2). The verbal descriptor scale (VDS) is the most commonly used and it involves a four or five point scale grading the pain as none, mild, moderate, severe and excruciating etc. This scale lacks sensitivity, but it has the advantage of simplicity.
- b) **Numerical scale:** These can have both written or verbal forms, and is an eleven point scale where '0' means 'no pain' and '10' is the 'worst imaginable pain', or their degree of pain relief from '0' representing 'no relief' to '10' representing 'complete relief'.

Visual Analogue Scale (VAS). A 100 mm horizontal line scale with verbal anchors at both ends (no pain/no pain relief at one end and worst imaginable pain/complete pain relief at the other), is in common use for rating pain intensity or pain relief. The patient is asked to mark the line and the 'score' is the distance in millimeters from the left side of the scale to the mark.

VAS ratings greater than 70 mm are indicative of 'severe pain' and 0-5 mm 'no pain', 6-44 mm 'mild pain' and 45-69 mm 'moderate pain' (8, 9). The VAS has been shown to be a linear scale for patients with acute postoperative pain; therefore results are equally distributed across the scale, such that the difference in pain between each successive increment is equal (10).

Verbal Numerical Rating Scale (VNRS). Similar to the VAS, except the patient is asked to imagine that '0' represents 'no pain' and '10' represents the 'worst imaginable pain'. These are simple to administer and give consistent results and correlate well with the VAS (11).

Multidimensional measures of pain

Rather than assessing only pain intensity, multidimensional tools provide further information about the nature of the pain and its impact on the individual.

Specific scales have been developed that identify (and/or quantify) descriptive factors specific for neuropathic pain and which may include bedside sensory examination and allow evaluation of response to treatment (12).

- a) **McGill Pain Questionnaire (MPQ):** MPQ measures the sensory, affective and evaluative aspects of pain, thus measuring pain multi-dimensionally. The questionnaire contains about 20 aspects. Questions 1 to 10 represent sensory aspects of pain, 11 to 15 represent affective aspect of pain, and question 16 represents the evaluative aspect of pain. Questions 17 to 20 represent other miscellaneous aspects of pain. Each subunit has 2 to 5 words under them, representing increasing degree of pain and a numerical value. The sum of all points gives a rank value, which is termed the Pain Rating Index (13). The MPQ can be used in children over 12 years of age.
- b) **Brief pain Inventory.** Assesses pain intensity and associated disability.

Patients with special needs

Validated tools are available for neonates, infants and children, but must be both age and developmentally appropriate.

Faces Pain Scale (or ***Happy-Sad Face Scale***). A child or an illiterate person could use a set of faces to indicate the severity of his pain. This scale, portraying a child's face in different moods (smiling to crying with distress) is shown to the child and the child is asked to select the facial expression that best suites the pain expression. This assesses the affective and fear component of pain.

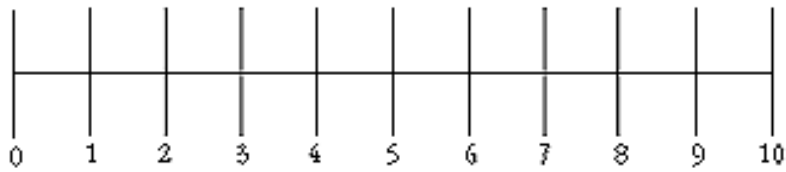
Summary

A thorough and regular assessment of pain is important because it leads to improved acute pain management. Self-reporting of pain should be used whenever appropriate as pain is by definition a subjective experience. The pain measurement tool chosen should be appropriate to the individual patient. Developmental, cognitive, emotional, language and cultural factors should be considered. Scoring should incorporate different components of pain, including scores of static and dynamic pain in the postoperative period.

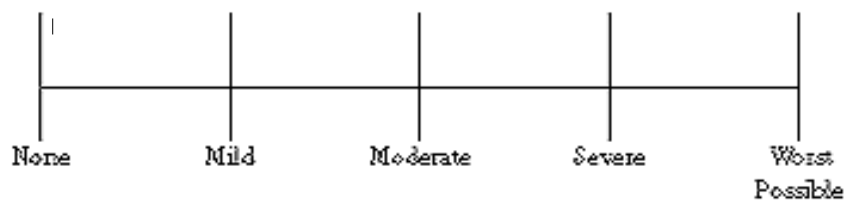
Uncontrolled or unexpected pain requires a reassessment of the diagnosis and consideration of alternative causes of pain.

Template 2. Pain Intensity scales

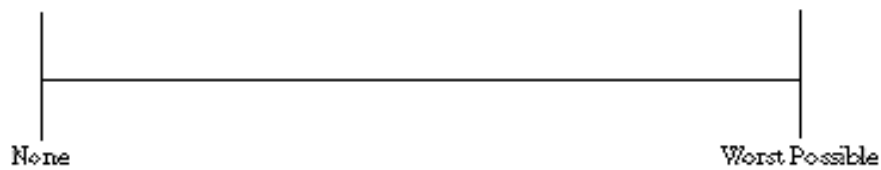
Numeric



Categorical



Visual Analogue Scale



Pain Relief Scale



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SYSTEMICALLY ADMINISTERED ANALGESIC DRUGS

Postoperative pain

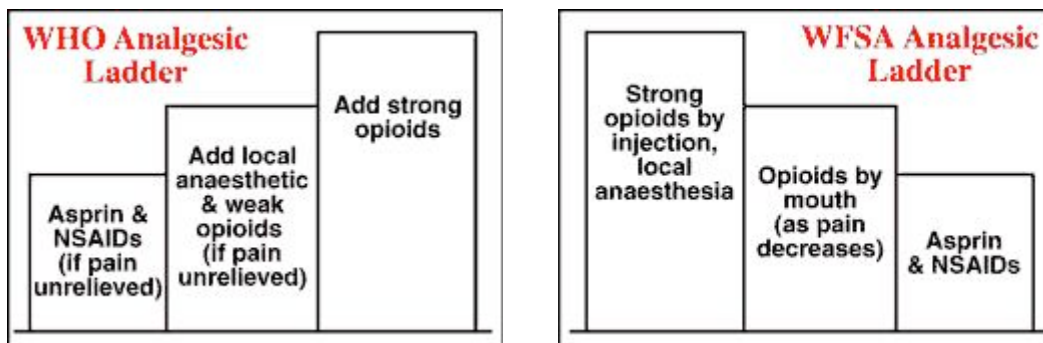
Patients undergoing surgery report that their greatest concern is postoperative pain. A survey published by Apfelbaum *et al* in 2003, found that 31% of patients suffered from severe or extreme pain and a further 47% suffered moderate pain after surgery. (4) Pain is now considered the ‘fifth vital sign’ and its control has now been recognized as an important element of the patient’s recovery after surgery. There are moves afoot to include it on standard observation charts along with blood pressure, heart rate, temperature and respiration.

In an effort to improve postoperative analgesia, anaesthetists have recognized that it is not enough to focus on just one modality or drug receptor type to treat pain. The concept of multi-modal analgesia has evolved in an effort to improve pain control and limit the incidence of side effects from individual agents (particularly the opioids).

WHO analgesic ladder

The World Health Organisation has recommended an “analgesic ladder” for the relief of cancer pain. It starts with simple analgesics such as aspirin and paracetamol for mild pain, mild opioids for moderate pain (such as codeine and tramadol) and strong opioids (such as morphine) for severe pain. In many situations, the use of adjuvants can improve the overall treatment of a painful condition. Some adjuvants are used to control anxiety and fear. It is recommended that drugs be given regularly rather than on demand.

All drugs have side effects and it may be necessary to administer agents to reduce or alleviate the side effects of analgesic medication. For example, opioids can produce nausea and constipation, which may require pharmacological management.



Simple analgesics

Paracetamol:

Paracetamol is an analgesic and antipyretic agent. The mechanism of action is not clear but it seems to have a central effect, probably by inhibition of COX-3 to inhibit prostaglandin synthesis in the hypothalamus. It also inhibits prostaglandin production independent of cyclooxygenase. (1) It is only a weak inhibitor of peripheral prostaglandin synthesis and has little anti-inflammatory action.

Paracetamol undergoes glucuronidation and sulphate conjugation in the liver and is then excreted by the kidneys. A small proportion of paracetamol is metabolised by the cytochrome P450 system to form a potentially hepatotoxic metabolite. This metabolite N-acetyl-*p*-benzoquinoneimine (NAPQI) is normally conjugated by glutathione to a non-toxic metabolite that is then excreted in the urine. Hepatic glutathione may be depleted if large amounts of NAPQI are produced after a large dose of paracetamol. Hepatic necrosis may result. Paracetamol should be used with caution in those with active liver disease; ethanol related liver disease and glucose-6-phosphate-dehydrogenase deficiency.

Paracetamol produces few side effects. It may be administered via the oral, rectal or intravenous route. It is rapidly and reliably absorbed from the small bowel and the oral route of administration is preferred as absorption from the rectum is slow and incomplete, except in neonates (7). The time to peak analgesic effect is between one and two hours.

Paracetamol is a weak analgesic with a dose-related effect. There is a ceiling effect. That is, once a maximum dose is achieved, further analgesia is not possible even with a higher dose. It is used on its own to treat mild to moderate pain. It can be used with either non-steroidal anti-inflammatory agents or weak opioids to treat moderate pain.

Single doses of paracetamol are effective in the treatment of postoperative pain. The number needed to treat (NNT) for at least 50% pain relief over 4-6 hours is 3.8 with 1g or 3.5 with 500 mg. It is effective when used as an adjuvant to opioid analgesia and is able to reduce the dose requirements for opioids by 20-30% when it is given regularly. A reduction in opioid consumption will not necessarily reduce the frequency or severity of opioid related side effects. (2) The use of a non-steroidal inflammatory agent will improve the efficacy of paracetamol.

Paracetamol is administered regularly as a part of a multimodal analgesic regimen. One gram every four to 6 hours orally is used. It is recommended that the maximum duration of regular therapy be limited to 72 hours to avoid toxicity. The maximum daily dose in an adult is restricted to one gram. In infants between 0 to 3 months, the maximum daily dose is 60 mg/kg/day and in older children, 90 mg/kg/day. (7)

Dosing Guidelines in Children: (7)

Age	Oral initial dose (mg/kg)	Rectal initial dose (mg/kg)	Maintenance oral or rectal (mg/kg)	Interval (h)	Duration at maximal dose (h)	Maximum daily dose (mg/kg)
Preterm 28-32 weeks	20	20	15	12	48	35
Preterm 32-36 weeks	20	30	20	8	48	60
0-3 months	20	30	20	8	48	60
>3 months	20	40	20	6	48	90 then 60 after 48 h
Adult	20	40	15 (30 PR)	4 (6 PR)	72	4g/day (5 PR)

Toxicity related to paracetamol overdose can cause liver failure. Hepatotoxicity has not been described in children with doses of less than 150 mg/kg per 24 hours, and death has not been reported from doses less than 300 mg/kg/day in previously well children. Care should be exercised if there is chronic illness or malnutrition as glutathione stores may be depleted. If overdose occurs, treatment with methionine or N-acetylcysteine may be lifesaving and prevent liver damage. (6)

Non-steroidal analgesics (NSAIDs):

Non-steroidal agents have their primary role in relief of nociceptive pain associated with tissue damage or inflammation. Their main effect is achieved via the inhibition of COX, which in turn reduces the production of prostaglandins from arachidonic acid. There is both peripheral and central inhibition of COX. (3)

Prostaglandins lower the threshold of excitability of nociceptors to inflammatory mediators and cyclooxygenase is crucial for the conversion of arachidonic acid to prostaglandins. (5)

Prostaglandins reduce the pain threshold at the site of injury (primary hyperalgesia), which results in central sensitisation and a reduction in the pain threshold in the tissue surrounding the injury (secondary hyperalgesia). (3)

There appear to be two forms of input from peripheral inflamed tissue to the central nervous system. The first is mediated by electrical activity in sensitised nerve fibres, which are sensitive to peripherally active COX-2 inhibitors and neural blockade; and the second is a humoral signal that originates from the inflamed tissue which produces a widespread induction of COX-2 in the central nervous system, which is sensitive to centrally acting COX-2 inhibitors. The implication is that patients who receive spinal or epidural anaesthesia might also need a centrally acting COX-2 inhibitor to reduce postoperative pain. (3)

There are two iso-enzymes of cyclooxygenase, COX-1 and COX-2. COX-1 is the constitutive enzyme. It is important for the formation of thromboxane and prostaglandins. Inhibition of this enzyme is responsible for the side effects seen with the use of most of the non-specific non-steroidal anti-inflammatory drugs (NSAIDs), including gastric ulcers and platelet inhibition. COX-2 selective inhibitors were developed in order to reduce these complications of NSAIDs.

Non-steroidal agents have a ceiling effect for analgesia and are therefore not sufficient to produce effective pain relief after major surgery. They are very useful for the management of mild to moderate postoperative pain, and should be considered the drugs of choice in these situations. There is a significant opioid sparing effect with the concomitant use of NSAIDs with opioids for major surgery. Postoperative analgesic requirements can be reduced by 30-50% if NSAIDs are used.

There is no sedation or respiratory depression associated with the use of NSAIDs and they are very useful for pain at rest and with movement. The number needed to treat for NSAIDs varies from 1.6 for ibuprofen 800mg to 3.4 for intramuscular ketorolac. (3)

The Oxford League Table of Analgesics was constructed so as to compare analgesic efficacy of different agents. The information is from systematic reviews of randomised, double blinded single dose studies in patients with moderate to severe pain. The outcome measure is at least 50% pain relief over 4-6 hours. From this the number of patients needed to treat is calculated.

Analgesic	Dose (mg, oral)	NNT
Ibuprofen	400	2.5
Ibuprofen	200	2.7
Aspirin	1200	2.4
Aspirin	600	4.4
Diclofenac	100	1.8
Diclofenac	50	2.7
Morphine	10 (IM)	2.9
Paracetamol	1000	3.8
Paracetamol	500	3.5

Non steroidal agents are capable of reducing sensitisation that arises from noxious inputs throughout the entire perioperative period and therefore, NSAIDs should be used throughout the entire perioperative period until the surgical wound is healed.

The use of perioperative non-steroidal medications reduces analgesic requirements, and should reduce opioid related side effects. The use of NSAIDs with intravenous patient-controlled morphine can reduce the risk of postoperative nausea and vomiting and sedation by 30 and 29%

respectively. (5) However, there is no reduction in itch, urinary retention or respiratory depression.

Adverse effects from NSAIDs are mostly due to the inhibition of COX-1. The most common are gastrointestinal upset (peptic ulceration), decreased platelet aggregation causing an increased bleeding time and changes in renal blood flow leading to a fall in glomerular filtration. Other side effects include, a rise in blood pressure, fluid retention (with the risk of precipitation of heart failure), headaches, confusion, bone marrow suppression, anaemia, hepatotoxicity, glomerulopathy and interstitial nephritis and precipitation of asthma in patients with nasal polyps. (5) A history of aspirin-exacerbated respiratory disease is a contraindication to the use of NSAID use, but there is no contraindication to its use in other people with asthma. Coxibs do not seem to cause the same problem as aspirin or other NSAIDs. (1) The use of aspirin is not recommended for children because of its association with Reye's syndrome, which is a serious disorder of hepatic and cerebral function.

Prostaglandins have important effects on bone metabolism. They have osteoblastic and osteoclastic activity, and are essential in bone repair. There has been some concern about the use of peri operative NSAIDs, particularly in spinal fusion. The inhibition of COX-2 over prolonged periods in large doses in animals will delay or inhibit bone healing. The use of NSAIDs is not contraindicated for the management of fracture-associated pain as long as the duration of treatment is used in the lowest effective dose and over short periods of time (not weeks or months). (7, 1)

	Time to peak (hours)	Elimination half-life (hours)	Dose range (mg)	Dosing interval (hours)
<i>Salicylates</i>				
Aspirin	1-2	0.25	300-600	4
Diflusal	2-4	8-12	250-500	12
<i>Acetic acids</i>				
Indomethacin	1-2	6	50-100	6-12
Diclofenac	2	1	25-50	8-12
Sulindac	2-4	7	100-200	12
Ketorolac	1	4-6	10	4-6
Ketorolac IM	1	4-6	10-30	4-6
Ketorolac (over 65 years)	1	7	10 oral or 10-15 IM	6-8 oral or 4-6 IM
<i>Propionic acids</i>				
Ibuprofen	0.5-1.5	2-2.5	200-400	6-8
Ketoprofen	0.5-2	1.5	100	12-24
Naproxen	1-2	15	250-500	12
Tiaprofenic acid	1.5	3	200-300	8-12
<i>Oxicams</i>				
Piroxicam	2-4	53	10-20	24
Tenoxicam	1-2.6	72	10-20	24
<i>Anthranilic acids</i>				
Mefenamic acid	2-4	3-4	500	8

NSAIDs should be avoided in infants less than 6 months of age, and in children with an allergy to the NSAID. Other contraindications are dehydration, hypovolaemia, renal or hepatic failure, coagulation disorders, peptic ulcer disease and in the presence of a significant risk of haemorrhage. (7)

COX-2 Selective inhibitors:

The coxibs are selective inhibitors of cyclooxygenase-2. They were developed because it was hoped that there would be a reduction in side effects related to inhibition of COX-1 by non-selective non-steroidal anti-inflammatory agents, particularly platelet dysfunction, renal toxicity

and gastrointestinal toxicity. They have a similar analgesic efficacy for the management of postoperative pain. The NNT for a 50% reduction in pain for the COX-2 inhibitors are 1.6, 1.9 and 2.2 for valdecoxib 40 mg, rofecoxib 50 mg and parecoxib 40 mg respectively.

COX-2 is expressed in the kidney and is regulated in response to alterations in intravascular volume. It has been implicated in the maintenance of renal blood flow, mediation of renin release and regulation of sodium excretion. COX-2 inhibitors have similar effects as the NSAIDs on renal function.

COX-2 inhibitors produce less clinically significant peptic ulceration than the NSAIDs. (1)

The use of conventional NSAIDs before total joint arthroplasty has been associated with a two-fold increase in the incidence of perioperative bleeding. However, discontinuing NSAIDs before joint surgery results in an arthritic flare, leading to increased preoperative pain, which is the leading cause for increased postoperative pain. Coxibs administered perioperatively for total joint arthroplasty have been shown to reduce perioperative pain without increased bleeding. (3)

With the introduction and high rates of usage of the coxibs, there have been concerns about the observed higher incidence in stroke and cardiovascular events. This phenomenon may not be specific to COX-2 inhibitors and may be related to all NSAIDs. It is recommended that all NSAIDs and coxibs be given in the lowest effective dose for the shortest duration for the treatment of pain.

Opioid analgesics

Opioids are the mainstay of systemic analgesia for moderate to severe acute pain. They also have a place in the management of chronic pain, particularly cancer related pain. Opioids act on endogenous opioid receptors located in the spinal cord, brain and the periphery. There are three important receptor types, mu, delta and kappa receptors. These receptors respond to endogenous opioid peptides, the enkephalins, beta-endorphin and dynorphins, as well as to exogenous opioids. Potent opioid analgesics are mu-1 agonists, and specific delta and kappa agonists may also produce analgesia.

The naturally occurring opioids are morphine, papaverine, codeine and thebaine. They are found in the juice of the poppy *Papaver somniferum*. The semi-synthetic drugs resemble morphine but do not occur in nature. They include diamorphine (heroin), hydromorphone, hydrocodone, buprenorphine and oxycodone. The synthetic opioids include levophanol, buprophanol, methadone, pentazocine, pethidine (meperidine), fentanyl, sufentanil and alfentanil. (8)

Mu receptors are the primary receptors in analgesia. They are located in the periaqueductal grey matter in the brain and in the substantia gelatinosa in the spinal cord. Activation of the mu receptors causes analgesia, euphoria, respiratory depression, nausea and vomiting, bradycardia, miosis, decreased gastrointestinal motility and dependence.

Kappa receptors mediate analgesia, less respiratory depression, dysphoria and hallucinations. Delta receptors are located in the spinal cord and supraspinally. They mediate analgesia. (8)

Opioid analgesics may act as pure agonists of specific receptors, mixed agonist-antagonist drugs with opposing effects at distinct receptor subtypes or partial mu agonists. There is a ceiling effect to analgesia found with the partial agonists and mixed agonist-antagonist drugs. (8) Antagonists are drugs that bind to receptors but do not stimulate them. They may reverse the effect of opioid agonists. (9)

Effects of Opioids:

Analgesia

Analgesia is mediated via the mu receptor with some contribution from effects of the delta receptor. All full mu receptor agonists can theoretically produce the same degree of analgesia, and it is possible to make comparisons between them and calculate equi-analgesic doses. One must be careful when doing this, as there is a large interindividual variability in absorption, metabolism and sometime efficacy of different drugs. It is suggested that if change is to be made from one opioid to another, that the alternative opioid be started at a lower than equi-analgesic dose in the first instance. (9) There is also a large interindividual variability in susceptibility to the adverse effects of different opioids, so if a side effect is particularly troublesome, it may be of use to change over to another opioid. (9)

Opioid	IV/IM (mg)	Oral (mg)	Half-life (hours)
Morphine	10	30	2-3
Fentanyl	0.15-0.2		3-5
Tramadol	100	100	5-7
Oxycodone	10	20	2-3
Pethidine	100	400	3-4

Respiratory depression

Opioids produce dose-dependent respiratory depression. There may a decrease in respiratory rate and or tidal volume, intermittent airway obstruction when the patient is asleep (obstructive apnoea), or irregular respiratory rhythm with central apnoea, especially when the patient is asleep. Respiratory depression is worse in the elderly or in neonates. Tolerance to respiratory depression occurs with ongoing opioid use. Respiratory depression is closely linked to sedation and monitoring of respiratory rate is a poor marker of true respiratory depression, as desaturation can occur even in those patients with a normal respiratory rate. It is recommended that sedation level be monitored instead. (1)

Opioids also inhibit the cough reflex, and histamine mediated bronchospasm may occur.

Nausea and vomiting

Nausea and vomiting is mediated via stimulation of the chemoreceptor trigger zone and the upper gastrointestinal tract. There is also an increase in vestibular sensitivity, so nausea tends to occur with movement. (8) Nausea and vomiting should be treated with antiemetic agents. Some patients may benefit from change over to a different opioid. Pain itself may cause nausea and vomiting, so adequate pain relief needs to be established.

Other central nervous system effects

Sedation occurs with increasing doses of opioids and precedes respiratory depression. Mild sedation and cognitive impairment are common side effects of opioid use. Tolerance to both develops quickly.

Miosis or pupillary constriction occurs with opioid use and is not necessarily an indication of excessive dose. (9)

Rapid intravenous administration of large doses of opioids or chronic oral therapy has been associated with myoclonus and muscle rigidity.

Cardiovascular effects

Opioids can cause hypotension via various mechanisms. Vascular sympathetic tone is reduced, arterial and venous vasodilatation can occur as a direct effect on smooth muscle tone or histamine release. Baroreceptor inhibition and peripheral vasodilation causes postural hypotension. Vagally mediated bradycardia occurs with large doses of intravenous opioids.

Pruritus

Histamine release causes cutaneous vasodilatation and may also cause local urticaria resulting in itch. Pruritus may be centrally mediated, but the mechanism is not clear. Itch is common after neuraxial administration of opioids, and is partially reversed with the administration of naloxone, an opioid antagonist.

Gastrointestinal and Genitourinary effects

Opioids reduce gastric emptying; increase bowel transit time and cause constipation. Urinary retention occurs due to inhibition of the micturition reflex. It is particularly troublesome after intrathecal opioid administration.

Fentanyl:

Fentanyl is a synthetic opioid. It is a phenylpiperidine and is 50-80 times as potent as morphine. It is very lipid soluble and does not cause histamine release. It can be used in doses of 2-10mcg per kg as an analgesic or in larger doses for anaesthesia (20-100mck/kg). The time to onset is rapid and peak effect is achieved in five minutes after intravenous administration. Its duration of action is short (30-60 minutes) after a single intravenous injection due to rapid tissue uptake. The time to peak effect is 30 minutes and duration of action is one to two hours after intramuscular injection.

Fentanyl is metabolised to inactive metabolites by the liver, so it is safe to use in those with renal failure. (9) For acute pain, it is given intravenously, epidurally or intrathecally. It can also be administered via the mucous membranes or the skin for the management of breakthrough and chronic pain. It has a high first pass effect, so it is not really active orally. It comes as fentanyl citrate for injection 50 mcg per ml or as a patch for use in chronic pain (25, 50, 75 and 100 mcg per hour). (8)

Morphine:

Morphine is an agonist at all opioid receptor subtypes. It is effective when given via the oral route but its oral bioavailability is 30% due to a significant first pass effect. As a result, higher concentrations of its metabolites are produced with oral as opposed to parenteral administration. The metabolites are morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) and are excreted by the kidneys, so they accumulate in renal impairment. M6G is an analgesic but M3G is not and may be a cause of myoclonus, seizures, hyperalgesia and allodynia with long-term use. Patients with liver failure are able to tolerate morphine because glucuronidation is rarely impaired.

Morphine may be administered via many routes including the intravenous, intramuscular, subcutaneous, oral, transmucosal, rectal, epidural and intrathecal routes. The dose ranges for each route of administration are different. Slow release preparations are available for oral administration for the treatment of chronic pain.

The elimination half-life of morphine is 2-3 hours and the duration of analgesia is 3-6 hours. It is the least lipid soluble of the opioids and distributed widely throughout the body but is not able to penetrate tissues easily. Because it is so water soluble, it is able to spread rostrally (cranially) when given via the epidural and intrathecal routes and cause delayed respiratory depression.

Intrathecal doses of preservative free morphine of 100 to 400 mcg are able to produce analgesia for up to 24 hours. Patients given these doses are less likely to develop respiratory depression than those given larger doses. The equivalent dose for epidural analgesia is 1-4 mg. If higher doses are used, the patients need to be monitored for delayed respiratory depression in a high dependency area. (8)

The dose requirements for morphine vary greatly between patients, but correlate most closely to the age rather than the weight of the patient (for adults). There may be a ten-fold variability in dose-requirements for each age group. In adult patients over 20 years of age undergoing major surgery, opioid requirements for the first 24 hours can be estimated with the following formula:

Average requirements for 1st 24 hours = 100-age (in years)

It is thought that the decline in opioid requirements with age is due to a reduction in the perception of pain and pharmacokinetic factors. (9)

Due to the variability in dose requirements, patient response should be monitored frequently. Tolerance to morphine can develop rapidly, particularly in those who do not have pain.

It may take up to 15 minutes or more following an intravenous injection to see the maximum effect of morphine, due to its poor lipid solubility. The aim of pain treatment is to achieve analgesia without excessive sedation. It is recommended that initial doses of morphine (and indeed fentanyl) be titrated to effect. An initial dose is given based on the appropriate age-related dose range and a dose interval is chosen dependent on the route of administration (shorter with intravenous, longer with subcutaneous). The pain level and sedation levels are assessed regularly and there is monitoring for the presence of other side effects after which there is an alteration in subsequent doses according to patient response. The aim is to achieve patient comfort (not necessarily pain free), with a low sedation score and adequate respiratory rate (above 8 breaths per minute in most cases). (9)

Histamine release occurs commonly with the administration of intravenous morphine. It does not necessarily mean that there is an allergy present. The most common adverse effects are nausea, vomiting and constipation. Opioid naïve patients are more likely to develop respiratory depression.

Meperidine (Pethidine)

Pethidine has analgesic actions at the mu opioid receptors as well as some local anaesthetic activity and atropine like actions. Intrathecal pethidine can be used as the sole agent for anaesthesia. The atropine like activity may lead to a dry mouth and mild tachycardia.

Pethidine can be administered as an intravenous or intramuscular injection or by the oral or neuraxial routes. The dose and the duration of action vary depending on the route of administration. Parenteral and oral doses are similar. The time of onset is approximately 10 minutes and peak effect is one hour when given by injection. The duration of analgesia varies between 2 to 4 hours. The usual dose is 50-100 mg (or 1 mg per kg of body weight) intramuscular injection. It can be given intravenously, when it is titrated in increments of 10-40 mg boluses every 5 minutes or so.

Pethidine and morphine produce the same side effects when given in equipotent doses. Some patients who have more nausea with one opioid may tolerate a different opioid better.

Pethidine is metabolised in the liver and the metabolites are excreted via the kidneys. One of its main metabolites, norpethidine, has mu receptor activity and has a long half-life (15-20 hours). High levels of norpethidine can lead to excitation of the central nervous system. Patients receiving large doses of pethidine or those with impaired renal function will accumulate norpethidine and may show signs of toxicity. The treatment of toxicity is conservative and no naloxone should be administered, as it will worsen the condition of the patient by reversing the sedation. (9) The upper dose of pethidine is limited to 1000 mg in the first 24 hours and 600-700 mg per day thereafter to avoid the accumulation of its metabolite norpethidine, which causes seizures.

Pethidine has some important interactions with other medications including tramadol (where it can increase the risk of serotonin syndrome) and monoamine oxidase (MAO) inhibitors. The interaction with MAO inhibitors can manifest as excessive respiratory depression, delirium, hyperpyrexia and convulsions. It should be avoided if the patient is on these medications.

Tramadol:

Tramadol acts centrally as an analgesic agent. It has some mu-receptor activity via its metabolite O-desmethyl-tramadol (M1) and it inhibits the reuptake of noradrenaline and serotonin at nerve terminals. (9) Its action on mu-receptors accounts for 40% of its analgesic activity. The ability to inhibit noradrenaline and serotonin reuptake is responsible for its efficacy in neuropathic pain.

Tramadol causes less sedation, respiratory depression and constipation than other opioids, but nausea and vomiting may still be troublesome.

The risk of serotonin syndrome is increased when it is used in combination with selective serotonin reuptake inhibitors or tricyclic antidepressants, but is rare with the doses used clinically for analgesia. Its use is contraindicated with monoamine oxidase inhibitors (used for depression).

Tramadol can be given as a tablet or injection and oral bioavailability is high, so doses are similar for both routes. Its main use is for the treatment of mild to moderate pain on its own, or it may be part of a multi-modal regimen for the treatment of severe pain. The doses are 2-3 mg per kilogram (typically 50-100 mg for adults) as a loading dose, followed by 1-2 mg per kg (50-100 mg for an adult) 4-6 hourly (up to 600 mg/day). The main metabolite may accumulate in renal failure and may cause respiratory depression.

Naloxone:

Naloxone is an opioid antagonist at all receptor sites. It is the most commonly used antagonist to treat opioid overdose. It has a short half-life of 60 minutes compared to the half-life of the opioids, so repeated doses or an infusion of naloxone may be required to treat opioid overdose. It is possible to give small doses to reverse some of the effects of opioids without reversing all of their analgesic effects.

The dose of naloxone for the treatment of respiratory depression and excessive sedation is 40-100 mcg intravenously and can be repeated as required. It is possible to administer naloxone intramuscularly in larger doses (400 mcg). It is not absorbed well via the gastrointestinal tract.

Hypertension, tachycardia, nausea and vomiting may be seen after naloxone administration for the reversal of opioids. It is thought that these effects are caused by a sudden surge in sympathetic activity. Rarely, rapid reversal of opioid effects may cause acute withdrawal syndrome, arrhythmias and acute pulmonary oedema.

Adjuvant medications

Adjuvant analgesics are drugs that were originally used for another purpose other than analgesia, but ones that may relieve pain in certain situations. They are usually used with other analgesics or non-drug pain treatments, and they characteristically take several days to have an effect.

N-Methyl-D-aspartate (NMDA) receptor antagonists:

Persistent pain may activate NMDA receptors in the spinal dorsal horn, producing central sensitisation (spinal cord neuron hyperexcitability, which leads to hyperalgesia and allodynia) and inadequate response to opioids. NMDA receptor antagonists may attenuate central sensitisation.

Because there is evidence for NMDA receptor involvement in many types of pain, including inflammatory, postoperative, neuropathic and ischaemic pain, NMDA receptor antagonists are useful in patients with these conditions.

NMDA receptor antagonists are able to prevent the development of wind up and central sensitisation and may down regulate hyperexcitability after sensitisation occurs. They are better described as anti-allodynic, anti-hyperalgesic and tolerance protective rather than analgesic. (9)

Ketamine is the only NMDA receptor antagonist in common use. (5) It is used in sub-anaesthetic doses via the intravenous or intramuscular routes to help control acute and chronic pain. It can be used in large doses to treat acute pain, particularly in the out of hospital emergency setting, where it is useful to maintain sympathetic nervous system outflow to maintain blood pressure and cardiac output.

Antidepressant drugs:

Antidepressant drugs such as the tricyclic antidepressants (amitriptyline, nortriptyline, desipramine) and the selective serotonin reuptake inhibitors (fluoxetine and venlafaxine) can relieve pain in people who do not have depression.

Tricyclics are more effective than the other antidepressants and are usually started at a low dose at nighttime. The starting dose for amitriptyline is 5-10 mg at night for those patients over 60 years of age, or 10-25mg in those under 60, with a dose increase of 10 or 25mg every 3-5 days. A satisfactory response occurs at levels between 25 and 100 mg per day. (9) The side effects include sedation, postural hypotension and dry mouth (secondary to anticholinergic activity). Tricyclics act by inhibiting serotonin and noradrenaline reuptake in the central nervous system; they also block sodium channels and alpha-2 adrenergic receptors and have NMDA receptor antagonist activity, which may contribute to their analgesic effects.

Tricyclic antidepressants are used in the management of chronic neuropathic pain (diabetic neuropathy, postherpetic neuralgia), chronic headache and back pain. They have been used to treat acute neuropathic pain, but there is little evidence for their effectiveness in acute nociceptive pain. (1)

Anticonvulsant drugs:

Anticonvulsants are used in the treatment of chronic neuropathic pain such as diabetic neuropathy and postherpetic neuralgia, as well as trigeminal neuralgia. They may have some application for acute neuropathic pain states, but there is limited data available. Gabapentin and pregabalin have been studied for use in acute nociceptive pain after surgery and have been found to reduce postoperative analgesic requirements. (1)

Anticonvulsants are thought to work by several mechanisms including the blockade of voltage-gated sodium channels (carbamazepine and lamotrigine) or calcium channels (carbamazepine, valproate, lamotrigine, gabapentin and pregabalin) and enhancement of inhibitory GABAergic neurotransmission (clonazepam) or inhibition of glutamate release (carbamazepine, valproate, lamotrigine, gabapentin and pregabalin). (9)

Carbamazepine

Carbamazepine is used primarily for trigeminal neuralgia. It has an initial half-life of 24-60 hours but this falls to 12 or 20 hours after two to four weeks, due to induction of its own metabolism. This may require a dose increase. There is no direct correlation between plasma levels and its analgesic efficacy. The dose is titrated against the clinical response and adverse effects. (5)

The adverse effects of carbamazepine include central nervous system toxicity such as sedation, nausea, diplopia and vertigo, rash, bone marrow toxicity, hyponatremia, and hepatic toxicity. It is recommended that haematological, renal, electrolyte and hepatic functions be assessed before introduction of carbamazepine and at least every three to six months after treatment has been commenced.

The starting dose of carbamazepine is low at 50 to 100 mg every 12 hours, and is increased every one to three days to a maximum of 1,500 mg per day. Therapeutic doses are usually about 800 to 1,200 mg per day but the range of doses needed to treat neuropathic pain is not known precisely and is often less than the dose required for the treatment of epilepsy. If there are side effects during the initiation of therapy, the dose is reduced to the previous level for a few days before attempting to increase it again.

Sodium valproate

Sodium valproate acts by inhibiting excess firing of neurons by pre and post-synaptic action involving GABA. It may be useful in the treatment of neuropathic pain. It has very good oral bioavailability and the peak concentration occurs at one to two hours after a dose with a plasma half-life of 7 to 17 hours. It is extensively metabolised. Adverse effects are less common than with carbamazepine but include rashes, nausea, ataxia, hepatic dysfunction and thrombocytopenia.

Gabapentin

Gabapentin and pregabalin have become first line treatment for neuropathic pain in many centres because of their better side effect profile compared to the other anti-epileptic medications. Their uses extend to spinal cord injury and post-amputation pain. They have been shown to reduce opioid consumption when used as a component of multi-modal postoperative analgesia and they can prevent some chronic post surgical pain conditions. (9)

Although gabapentin is an analogue of gamma-amino butyric acid (GABA), it is not an agonist at GABA receptors. Its effect is based on binding to neuronal calcium channels.

Gabapentin uptake relies on an active transport mechanism and has an unreliable dose-response relationship, so a large range of doses may be required (300-3600 mg daily). It requires 8 hourly dosing to be effective. It is excreted unchanged in the urine and the dose must be reduced in renal impairment. Pregabalin has a linear dose-response relationship and is taken twice daily in doses of 75-300 mg for neuropathic pain. (9)

The most common adverse effects are dizziness, drowsiness, ataxia and peripheral oedema.

Alpha-2 Antagonists:

There are alpha-2 adrenoreceptors on peripheral sensory nerves, in the spinal cord and in the brain stem. They inhibit pain transmission. This accounts for the analgesic effect of the noradrenaline reuptake inhibitors such as tramadol and tricyclic antidepressants. The alpha-2 receptors in the spinal cord are the site of action of alpha-2 adrenergic agonist drugs such as clonidine.

Clonidine can be used for acute pain in combination with opioids, in conjunction with local anaesthetics in nerve blocks or for epidurals and for the treatment of neuropathic pain or other chronic pain. It was originally used as a central antihypertensive, but has also been used for sedation, in the management of opioid withdrawal syndrome and alcohol withdrawal. If it is used for a prolonged period of time, it may itself induce a withdrawal syndrome if it is ceased abruptly. This is characterized by restlessness, headache, nausea, insomnia, rebound hypertension and arrhythmias.

The most common side effects of clonidine are sedation and hypotension, but other effects include bradycardia, dizziness, dry mouth, decreased bowel motility and diuresis. (9)

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LOCAL ANAESTHETICS

Introduction

Local anaesthetics are agents that reversibly block conduction of impulses in nerves by blocking sodium channels. With progressive increases in the concentration of local anaesthetic around nerves, autonomic, sensory and somatic motor impulses are blocked. Removal of local anaesthetic is followed by spontaneous return of conduction with no residual or structural damage to the nerves. Clinically, local anaesthetics are used to block transmission of action potentials along pain fibres to different parts of the body.

The first local anaesthetic introduced into clinical practice was cocaine. Structurally, it is an ester of benzoic acid and methyl ecgonine. It is an alkaloid derived from the coca tree, which is found in Peru and Bolivia and has been in use for 5 000 years. The Incas in Peru utilized the local anaesthetic properties of coca and attempted to perform surgery, including amputations, excisions, bone transplants and cauterisations. Cocaine was isolated from the coca leaf and described by Albert Niemann in 1860. In 1884, Carl Köhler introduced cocaine as a topical anaesthetic for eye surgery. Its chemical structure was determined in 1895, when it was established that the local anaesthetic properties were due to esterification of a basic alcohol with benzoic acid.

Cocaine was the main local anaesthetic agent available until 1904, when Alfred Einhorn synthesized procaine, another ester. Newer local anaesthetics were introduced in the search for less toxic agents with a faster onset and longer duration of action and by 1943, Nils Löfgren and Bengt Lundquist had developed lidocaine. After its introduction into clinical practice in 1948, many local anaesthetic techniques were reintroduced, and by 1950, Hansen from Baltimore had reported its use for spinals, epidurals, local infiltration, saddle blocks and intravenous anaesthesia.

In the search for longer acting and more potent agents, mepivacaine and bupivacaine were developed. Bupivacaine was introduced in 1963. Its greatest advantage was its longer duration of action and potency. It produced a more selective sensory block than lidocaine and became the drug of choice for obstetric anaesthesia. It soon became apparent however, that bupivacaine's greatest disadvantage was its toxicity. It is more cardiotoxic than lidocaine, and the ventricular arrhythmias that it produces are resistant to treatment. More recently, ropivacaine and levobupivacaine have been introduced in their levo-enantiomeric forms as less cardio toxic agents than bupivacaine.

Pharmacokinetics and pharmacodynamics

Local anaesthetics consist of a lipophilic portion (commonly an aromatic ring) and a hydrophilic chain (such as a tertiary amine) joined by either an ester (-CO-) or an amide (-NHC-) bond. The agents are grouped into either esters or amides according to the intermediate bond. The esters in

common use include cocaine, procaine, chlorprocaine, benzocaine and tetracaine (amethocaine). The amides in common clinical use include lidocaine, prilocaine, mepivacaine, bupivacaine, levobupivacaine and ropivacaine.

Lengthening the connecting hydrocarbon chain or increasing the number of carbon atoms on the tertiary amine or aromatic ring changes the drug's lipid solubility. The more lipid soluble drugs have a higher potency, longer duration of action and increased toxicity. Increased lipid solubility enhances the partitioning of the drug to the site of action and reduces the rate of metabolism. The receptor site on the sodium channels is hydrophobic.

Increasing the molecular size of local anaesthetics influences the rate of dissociation from the receptor sites. The smaller molecules dissociate more rapidly and have a shorter duration of action.

The amide local anaesthetics bind extensively to alpha-1 acid glycoprotein. Those agents with greater protein binding have a longer duration of action and tend to be more potent, but also have a slower onset of action. In the case of chiral molecules such as bupivacaine and ropivacaine, the R (+) isomer is moderately more potent than the S (-) isomer.

The relative potencies of the local anaesthetic agents are, in increasing magnitude: procaine 1, cocaine 2, prilocaine 3, lignocaine and mepivacaine 4, bupivacaine and ropivacaine 16, and tetracaine 64. Procaine is short acting, whilst cocaine, lidocaine, prilocaine and mepivacaine have an intermediate duration of action and bupivacaine, ropivacaine and tetracaine have the longest duration of action.

The rate of onset of anaesthesia depends on the rate of diffusion of local anaesthetic across nerve membranes. This is determined by the concentration of the drug, degree of ionisation, lipid solubility and physical characteristics of the surrounding tissues. Local anaesthetics are weak bases and poorly soluble in water in their pure form. They are synthesized as their water-soluble hydrochloride salts with a pH of 6 to increase their solubility and stability. The pKa (pH at which 50% of the drug is in its ionised state, and 50% is un-ionised) of most local anaesthetics is between 7.5 and 9. Therefore, at the physiologic pH of 7.4, less than 50% of the drug is non-ionised (lipid soluble). The ionised (cationic) form of the drug is the active form at the sodium channel receptor, but is less able to cross cell membranes to reach the site of action on the inner surface of the cell membrane. The agents with a pKa closest to 7.4 have the most rapid onset of action because the un-ionised form can rapidly cross the cell membrane. Where there is tissue acidosis, even less of the local anaesthetic is un-ionised and able to cross the cell membrane, which accounts for the observation that local anaesthetics are less effective when injected into infected tissues.

The duration of action of a local anaesthetic is proportional to the length of time that it is in contact with the nerve. Therefore, removal of the local anaesthetics from the site of action will determine the duration of action of the drug. More lipid soluble and protein bound drugs have a longer duration of action.

The route of administration, site of injection, the total dose given, protein binding, lipid solubility and local tissue blood flow influence systemic absorption of local anaesthetics. Injection of a drug into highly vascular tissue results in more rapid absorption and higher blood levels.

Lidocaine has intrinsic vasodilator properties. The addition of a vasoconstrictor such as epinephrine will reduce plasma uptake, increasing the duration of action and reduce peak plasma concentrations. The addition of epinephrine will lower blood levels by up to 30%. The addition of epinephrine will not be as effective in prolonging the duration of action of the more potent, lipid soluble drugs such as bupivacaine and ropivacaine.

The distribution of ester local anaesthetics has not been studied due to their rapid metabolism. The amides are widely distributed after intravenous injection in a biphasic fashion. They are distributed to the vessel rich group of tissues first (brain, liver, kidney and heart) and then to moderately perfused tissues such as muscle and the gastrointestinal tract. There is some sequestration in fat.

With the exception of cocaine, the esters undergo rapid hydrolysis by plasma cholinesterase, so tend to have a shorter duration of action. The liver is also able to hydrolyse esters. One of the breakdown products is para-amino benzoic acid, which has been associated with allergic reactions.

The clearance of amide local anaesthetics is dependent predominantly on liver metabolism. Renal excretion of the unchanged drug is minimal. The amides are metabolised by liver microsomes. The initial step is the conversion of the amide base to amino carboxylic acid and a cyclic aniline derivative. Further metabolism involves the hydroxylation of the aniline and N-dealkylation of the amino carboxylic acid.

Prilocaine is metabolised the most rapidly, followed by lidocaine, mepivacaine, ropivacaine, bupivacaine and levobupivacaine. Drugs that are bound strongly to plasma proteins such as bupivacaine and ropivacaine have little free drug that can be cleared by the liver, so tend to have a lower clearance.

Placental transfer occurs by passive diffusion. The uterine vein to maternal vein or arterial levels are expressed as a ratio (UV/M) to enable comparison between local anaesthetic agents. The values for each agent are: lidocaine 0.52, bupivacaine 0.31-0.44, prilocaine 1-1.18 and mepivacaine 0.7. An inverse correlation occurs between the ability to cross the placenta and degree of protein binding of the agents. Thus, bupivacaine is the drug of choice in obstetric anaesthesia compared to prilocaine.

Local anaesthetic agents block the propagation of action potentials in nerve axons via the inhibition of passage of sodium through voltage-gated sodium channels in the neural membrane. These voltage-gated channels also exist in cardiac muscle and neuronal cell bodies.

The intracellular environment has a low sodium and high potassium relative to the intercellular space. The axonal membrane maintains a transmembrane potential of -60 to -90 mV. This is due to the presence of impermeable anions within the cell and the active transport of sodium out of and potassium into the cell. When the nerve is stimulated, the firing level or threshold potential is reached (typically 15 mV above the resting membrane potential). At the threshold potential, the sodium channels open and the rapid influx of sodium depolarises the membrane to $+40$ mV. The sodium channels then close (inactivate) and the voltage-gated potassium channels open to re-polarize the cell membrane. Re-polarization returns the sodium channels to the resting state.

Local anaesthetics prevent the large transient rise in permeability of the membrane to sodium that normally occurs during an action potential. The rate of depolarisation is decreased so that the threshold for firing is not achieved. There is no effect on the resting membrane potential.

The sodium channels exist in three states during various phases of the action potential: the activated-open, inactivated-closed and resting-closed states. Local anaesthetics cross the cell membrane in their unionised state and become ionised inside the cell. This ionised form then binds to the receptor on the intracellular surface of the sodium channel in its inactivated-closed state to make it impermeable to sodium.

Local anaesthetic agents will also block potassium and calcium channels, but the concentration of local anaesthetic required is much higher than that needed for nerve conduction blockade.

There is frequency and voltage dependence of local anaesthetic action. This means that the degree of block achieved by the local anaesthetic depends on how the nerve has been stimulated and on the resting membrane potential. The resting nerve is less sensitive to local anaesthetic agents. A higher frequency of stimulation and a more positive membrane potential cause a greater degree of block by the local anaesthetic. The activated and inactivated states of the sodium channels predominate at more positive membrane potentials and the resting state predominates at the more negative resting membrane potential. The local anaesthetic can access the binding site within the pore of the sodium channel only when the channel is open. Once it binds to the receptor, the local anaesthetic stabilizes the channel in its inactivated state making it impermeable to sodium.

The smaller local anaesthetics dissociate more rapidly from the binding site. A higher frequency of stimulation is thus required to allow these drugs to bind to the receptor during the action potential.

Nerve impulses can skip up to three blocked nodes of Ranvier. Each nerve has a critical blocking length that is proportional to its diameter. Therefore, local anaesthetic must block a longer length of a thicker axon in order to block three nodes, compared to a smaller nerve fibre.

Smaller nerve fibres are more sensitive to local anaesthetics. They generate longer action potentials at high frequencies. Relatively speaking, at the same diameter, myelinated fibres are more readily blocked than non-myelinated fibres. The sensitivity of fibres to local anaesthetics is

thus (most to least sensitive), myelinated B fibres, small unmyelinated C fibres, small myelinated A-delta fibres, A-gamma fibres, A-beta fibres and A-alpha fibres. Therefore, pain, temperature, touch, deep pressure and motor function are predominantly blocked in that order. In mixed nerves, the motor fibres are located on the outer layer, so paradoxically; they may be blocked before the sensory and pain fibres.

Local anaesthetics are administered in order to block pain neurotransmission. This can be done by topical application to mucous membranes; infiltration of sensory nerve endings (eg in skin) or by placement of local anaesthetic near nerves, nerve roots or the spinal cord.

The most useful and effective local anaesthetics for topical anaesthesia are cocaine, amethocaine, lidocaine and prilocaine. They have a relatively rapid onset of action (within ten minutes) and their duration of action is in the order of 30-60 minutes. Absorption of local anaesthetics through skin is slow and less reliable, but is possible with the use of higher concentrations of local anaesthetic. Amethocaine gel and eutectic mixture of local anaesthetics (EMLA) are useful for surface anaesthesia of the skin.

The amide local anaesthetics with an intermediate duration of action such as lidocaine, prilocaine and mepivacaine are commonly used to provide infiltration anaesthesia for minor procedures. They act at unmyelinated nerve endings where the onset of anaesthesia is rapid. The duration of anaesthesia varies dependent on the local anaesthetic used. Lidocaine, mepivacaine and prilocaine have an intermediate duration of action (1-2 hours) and bupivacaine will produce anaesthesia for just over three hours. Nerve and plexus blocks are commonly performed using amide local anaesthetics.

It is possible to provide anaesthesia for the lower half of the body using epidural and spinal anaesthesia. Epidural injection of local anaesthetics is an effective technique for the relief of labour pain. The doses of local anaesthetics required for spinal anaesthesia are approximately ten times lower than those used for epidural anaesthesia, because the local anaesthetic is being deposited directly into the cerebrospinal fluid that bathes the spinal cord and around the nerve roots in the epidural space.

August Bier first described intravenous regional anaesthesia in 1908. It is useful for short procedures on a limb. A tourniquet is applied to the arm or leg, the limb is exsanguinated and the tourniquet is inflated before the intravenous administration of local anaesthetic. The anaesthetic agents used for intravenous regional anaesthesia need to possess low toxicity, as the total dose may be high. Prilocaine and lidocaine are the agents most commonly used.

Toxicity

Local anaesthetics act on all excitable tissue to affect sodium, potassium and to a lesser extent, calcium channels. Toxicity to local anaesthetics predominantly manifests as central nervous system and cardiac toxicity. All local anaesthetics are potentially neurotoxic if applied directly to neural tissue in large concentrations, and some produce allergic reactions.

Systemic toxicity occurs due to high plasma concentrations of local anaesthetic. This occurs due to direct intravenous injection or absorption of local anaesthetic from the site of administration. The total dose injected, vascularity of the injection site, the physicochemical properties of the drug and the presence of epinephrine in the local anaesthetic mixture will influence the ultimate plasma concentration.

Local anaesthetics vary in their ability to cause systemic toxicity. The safest local anaesthetics are the esters chloroprocaine and procaine. Local anaesthetics may be ranked from least to most toxic: chloroprocaine, procaine, prilocaine, lidocaine, mepivacaine, ropivacaine, levo-bupivacaine, bupivacaine, tetracaine (amethocaine), dibucaine (cinchocaine) and cocaine. The more potent local anaesthetics tend to be more toxic to the central nervous system and cardiovascular system.

The route of administration and site of injection influence ultimate plasma concentration levels. Absorption from mucous membranes is rapid so the maximum dose administered should be reduced accordingly. A higher blood level will be produced from intercostal nerve blockade than from subcutaneous infiltration. Plexus blocks are associated with the slowest rates of absorption. The addition of epinephrine to the solution of local anaesthetic will slow its rate of absorption and reduce the maximum blood concentration by 30-50%, particularly for those drugs with intrinsic dilator properties.

The prevention of local anaesthetic toxicity is based around the avoidance of accidental intravascular injection, the limitation of the total dose given for anaesthesia, the addition of epinephrine to the solution, the use of less toxic agents and the division of doses into aliquots of 5 millilitres, 15 seconds apart. The division of the dose reduces the peak blood level (and therefore potential toxicity), and allows the anaesthetist to identify the onset of symptoms before injecting the entire dose. When using mixtures of local anaesthetics, it must be borne in mind that the toxic effects of anaesthetic agents are additive.

The safe maximum doses for infiltration are 4 mg/kg of plain lidocaine (7 mg/kg with epinephrine), 2 mg/kg of plain bupivacaine, 6 mg/kg of prilocaine, 3.5 mg/kg of ropivacaine, and 12 mg/kg of procaine. The safe doses for the performance of intercostal nerve blocks are 25% lower. The safe maximum doses for plexus blockade are 5 mg/kg of plain lidocaine (7 mg/kg with epinephrine), 2 mg/kg of bupivacaine and 7 mg/kg of prilocaine.

Local anaesthetics produce minimal effects on the central nervous system in non-toxic doses. At toxic levels, the initial change seen is excitability, which is probably due to depression of inhibitory neurons. This is observed as CNS irritability and convulsions. At higher plasma concentrations, CNS depression occurs which leads to respiratory arrest. CNS toxicity is exacerbated by hypercarbia and acidosis. The patient may report tongue numbness and circumoral tingling initially, followed by restlessness, vertigo, tinnitus, difficulty focusing, slurred speech and muscle twitching. Muscle twitching, drowsiness, seizures and apnoea occur with higher plasma concentrations.

Lignocaine, procaine and prilocaine cause central nervous system toxicity when plasma concentrations reach about 5 to 10 micrograms per millilitre. Bupivacaine and etidocaine cause central nervous system toxicity at about 1.5 micrograms per millilitre. The severity of signs increases with increasing plasma concentrations.

In the heart, toxic blood levels of local anaesthetics depress cardiac conduction and excitability, which may lead to atrio-ventricular block, QRS widening and cardiac arrest. Myocardial contractility is depressed, which reduces cardiac output and blood pressure.

The effect on blood pressure is biphasic. At lower concentrations, vasoconstriction occurs, and at high concentrations, there is vasodilatation. Cocaine is the exception in that it produces vasoconstriction at all concentrations. Cardiovascular toxicity usually occurs at higher doses and plasma concentrations of local anaesthetics than those required to produce central nervous system toxicity.

Bupivacaine is unique in that cardiac toxicity occurs very rapidly. Inadvertent intravenous injection of bupivacaine will produce severe hypotension, cardiac arrhythmias and atrio-ventricular block. Its dissociation from cardiac sodium channels is slow and resuscitation is difficult and prolonged.

The recommended treatment for cardiac toxicity is supportive. That is, the treatment of hypoxia, hypercarbia and metabolic acidosis, the control of seizures with benzodiazepines, thiopental or propofol and cardiopulmonary resuscitation. Vasopressin is useful to support the circulation, as norepinephrine and epinephrine may induce ventricular arrhythmias. Cardioversion and amiodarone is the treatment of choice for ventricular arrhythmias. Cardiopulmonary bypass may be required. There have been reports of the successful use of intralipid to treat toxicity related to bupivacaine (as well as ropivacaine).

The levo-enantiomers, levobupivacaine and ropivacaine, were developed in the anticipation that cardiac toxicity could be reduced. Like bupivacaine, they are capable of producing cardiac toxicity at high enough doses and if the dose is injected intravascularly. Fortunately, it appears that the cardio toxicity produced by ropivacaine is more amenable to standard treatment than bupivacaine.

Cocaine produces sympathetic nervous system stimulation by blockade of neuronal norepinephrine and dopamine uptake. Coronary vasoconstriction with cocaine may lead to cardiac ischemia.

Methemoglobinemia occurs with large doses of prilocaine due to the production of ortho-toluidine during its metabolism. The o-toluidine oxidizes haemoglobin to methemoglobin. In adults, this is rarely of any clinical significance and resolves spontaneously. It may be treated with the administration of methylene blue (1 mg/kg).

True allergy to local anaesthetics is rare, but it is more likely for esters than amides due to the production of para-amino benzoic acid during metabolism. Some preservatives such as methylparaben are capable of producing allergic reactions.

The application of high concentrations of local anaesthetic to neural tissue can produce direct toxicity. Chloroprocaine and lidocaine appear to be more neurotoxic than the other local anaesthetics used for spinal anaesthesia. The mechanism of the neurotoxicity is unclear. It is postulated that interference with neuronal transport or calcium homeostasis may be the cause. In crayfish nerve, lidocaine has been reported to induce irreversible loss of membrane potential, implying that disruption of the membrane is the mechanism for direct neurotoxicity. The same has been found for rat sciatic nerve.

All local anaesthetic agents result in reversible myonecrosis if injected into muscle. Procaine is the least toxic and bupivacaine has the greatest myotoxicity. Increased intracellular calcium levels have been implicated as the cause of myotoxicity.

Specific agents

Cocaine:

Cocaine is still a clinically useful local anaesthetic agent. It is commonly used to provide topical anaesthesia of the airway and in ear, nose and throat procedures. It is available in one, four and ten percent solutions. Its vasoconstrictor properties are useful for reducing bleeding.

Cocaine's main limitations are its toxicity, addictive properties and short duration of action. It stimulates the central nervous system and produces euphoria with excitement and restlessness at lower doses, but convulsions, coma and medullary depression in high doses. It blocks catecholamine uptake in the central, peripheral and sympathetic nervous system. It will also sensitise the myocardium to endogenous and exogenous catecholamines. In the cardiovascular system, it causes vasoconstriction, tachycardia and hypertension. At high doses, it can cause direct myocardial depression, ventricular fibrillation and myocardial infarction due to its ability to constrict the coronary vessels.

Cocaine is extensively metabolised in the liver where it undergoes hydrolysis. It is also metabolised by plasma esterases. Its metabolites, benzoylecgonine, ecgonine methyl ester and ecgonine, are then excreted via the kidneys.

Procaine:

Procaine is an amino ester with low potency, slow onset and short duration of action. It has a pKa of 8.9 and is highly ionised in the plasma, which makes it very water-soluble. It is hydrolysed in vivo to para-aminobenzoic acid, which is then excreted by the kidneys. It is commonly used to reduce the pain of intramuscular injection of penicillin and in dentistry.

Chloroprocaine:

Chloroprocaine is an ester local anaesthetic, which was introduced in 1952. It is a chlorinated derivative of procaine with a rapid onset and short duration of action. It has low toxicity due to its rapid metabolism. The plasma half-life is 25 seconds. It is preserved in calcium EDTA, which has the potential to bind calcium in muscles and produce tetany.

Tetracaine (Amethocaine):

Tetracaine is a potent, long-acting ester, which is hydrolysed by plasma pseudocholinesterase to produce para-aminobenzoic acid. It is also very toxic. The suggested maximum therapeutic dose is one to 1.5 mg per kilogram of body weight. It is used as a topical agent for ophthalmic surgery and can be used alone or with lidocaine to provide topical anaesthesia of the skin for venous cannulation. Its potency is sixteen times that of lidocaine.

Lignocaine:

Lignocaine is an aminoethylamide local anaesthetic that was introduced into clinical practice in 1948. It remains a very versatile local anaesthetic in that it can be given via many routes, and comes in multiple formulations. It has an intermediate duration of action, a relatively rapid onset, is not irritating to tissues and is water-soluble. It also has antiarrhythmic properties (Class Ib arrhythmic) and because of its low toxicity, it has been used to treat ventricular arrhythmias via intravenous infusion.

Lidocaine is absorbed rapidly but this can be delayed with the addition of epinephrine, which will prolong its duration of action and reduce toxicity, allowing for a larger dose to be administered. In the presence of epinephrine, more molecules of the drug are present with less dilution by tissue fluid and the local anaesthetic block is more intense.

Lidocaine undergoes N-dealkylation in the liver by mixed function oxidases to monoethylglycine xylidide and glycine xylidide, which both have some local anaesthetic properties and are capable of producing toxicity. Further metabolism produces monoethylglycine and xylidide, which are excreted by the kidneys.

Prilocaine:

Prilocaine is an intermediate acting amino amide with similar pharmacology to lidocaine. It has very little intrinsic dilator properties and is not normally used with adrenaline. It is commonly used for intravenous regional anaesthesia because of its low toxicity.

Prilocaine was developed when lidocaine was about to come off patent in the search for a drug with fewer side effects. Indeed, it is less toxic than lidocaine, but its main metabolite, o-toluidine can cause methemoglobinemia, which is a significant problem in small children. The upper limit of safe dosage is 8 mg/kg.

Mepivacaine:

Mepivacaine was introduced in 1957. It is an intermediate acting amino amide local anaesthetic with an onset time similar to that of lidocaine and a 20% longer duration of action. It is used for

infiltration, nerve and epidural block but is not effective topically. The safe upper limit for dosage is 7 mg/kg.

Mepivacaine is not suitable for obstetric use because it crosses the placenta where the foetal pH is lower, so it exists in its ionised form and is “trapped” there (UV/M ratio of 0.7) and the foetus is unable to metabolise it.

Bupivacaine:

Bupivacaine was developed one year after mepivacaine and was able to produce a more selective sensory block and less motor block than lidocaine. Structurally, it is closely related to mepivacaine and ropivacaine. It is four times as potent as lidocaine with a longer duration of action but slower onset. It is more lipid soluble and is more protein bound than lidocaine. The duration of action of a nerve block is approximately four to six hours and onset time for plexus anaesthesia is typically ten to twenty minutes. The addition of epinephrine to bupivacaine has not been shown to significantly reduce plasma levels of bupivacaine, nor extend its duration of action. Bupivacaine is very suitable for obstetric anaesthesia due to its favourable foetal to maternal ratio (UV/M ratio of 0.31-0.44).

Higher potency is related to toxicity and bupivacaine has been shown to be very toxic, particularly to the myocardium. Bupivacaine is more cardiotoxic than lidocaine because it is able to block cardiac sodium channels and dissociates more slowly from them during diastole. The block becomes cumulative and the resulting arrhythmia is very difficult to treat.

The liver metabolises bupivacaine. It undergoes dealkylation of the piperidine nitrogen to form desmethyl mepivacaine (pipecolyl xylidide), which is also the metabolite produced from mepivacaine and ropivacaine metabolism.

Bupivacaine is a chiral atom and demonstrates stereo-selectivity. The R (+) enantiomer is more potent but also more cardio-toxic as it binds more avidly to cardiac sodium channels. It was for this reason that the S (-) isomer, levobupivacaine, was made available. It has been shown to be less cardio-toxic than the racemic mixture but also about 13% less potent.

Ropivacaine:

Ropivacaine is a pipecolyl xylidide amino amide local anaesthetic whose pharmacology is similar to that of bupivacaine in that it is highly protein bound, very lipid soluble has a long duration of action and is more potent than lidocaine. It is less potent than bupivacaine (about 30 %). Ropivacaine is also a chiral atom like bupivacaine and is marketed as its S (-) enantiomer, which is less toxic than its R (+) isomer. Ropivacaine has intrinsic vasoconstrictor properties and the addition of epinephrine is not necessary as it has minimal effect on the duration of action and plasma uptake of ropivacaine.

Although ropivacaine was developed as a less cardiotoxic agent than bupivacaine, it also has the potential to produce cardiac toxicity. The reports of cardiac toxicity reactions with ropivacaine show that the toxicity is more amenable to treatment than with bupivacaine.

Eutectic Mixture of Local Anaesthetics (EMLA):

In the 1970s, chemists at Astra discovered that a mixture of lidocaine and prilocaine produced a highly concentrated liquid that could be used in emulsions. EMLA is a mixture of 2.5% lidocaine and 2.5% prilocaine with a melting point of 16 degrees Celsius that is lower than either compound alone. It exists as oil at room temperature and can penetrate intact skin to produce anaesthesia to a maximum depth of 5 mm when left on the skin under an occlusive dressing for at least one hour. The duration of anaesthesia is approximately two hours.

Amethocaine gel 4% (see 3.4.4 above) can be used instead of EMLA to provide topical anaesthesia of the skin. It is applied to the area and covered by an occlusive dressing for several minutes. It has the advantage of a more rapid onset, longer duration and greater potency than EMLA.

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THE MANAGEMENT OF POSTOPERATIVE PAIN

The following account contains material quoted directly from the publication by the Australian and New Zealand College of Anaesthetists titled "Acute Pain Management: Scientific Evidence" 2nd edition 2005.

Introduction

Pain is a common presenting feature of many disease processes, it is usually associated with actual or impending tissue damage. Acute pain in the peri-operative setting is defined as pain that is present in a surgical patient because of pre-existing disease, a surgical procedure or a combination of these. It is an unpleasant and inevitable component of the post surgical experience. Any individual, who undergoes surgery, has the right to expect and obtain adequate relief of postoperative pain. Patients, however, continue to silently suffer postoperative pain because of lack of a concerted effort on the part of the anaesthetic and surgical team to relieve this pain. If one considers adequate pain relief to be a basic human right of the patient, failure to relieve pain is tantamount to a moral and ethical lapse on the part of the doctor.

The modern anaesthetist is a peri-operative physician and takes on the responsibility of ensuring patient comfort throughout the pre-operative, intra-operative and postoperative periods. Though most of us administer generous doses of potent analgesics to patients during surgery with the objective of providing good intra-operative analgesia, the same quality of care often does not extend into the postoperative period. The end result is a dissatisfied, miserable and anxious patient. Besides the distress caused by pain, patients are often unable to breathe adequately, cough effectively, move enough to tend to their own daily needs or participate in their own rehabilitation. This often results in feelings of helplessness, fear, anxiety and depression. Thus, there is a definite need for doctors involved in the postoperative care of a patient to not only understand the adverse effects of pain, but also to provide a comprehensive and effective pain management plan for their post surgical patients.

Adverse effects of peri-operative pain (1, 2, 3)

Pain results in physiological and psychological responses in the patient, the majority of which are detrimental to postoperative outcome. It therefore stands to reason that adequate relief of pain might translate to better postoperative outcome.

Physiologic responses

Severe acute pain produces an increase in sympathetic tone that manifests as an increase in heart rate, blood pressure, cardiac output, and systemic and coronary vascular resistances. These adverse cardiovascular effects can be minimised by epidural anaesthesia that is high enough to block the cardiac sympathetic fibres (T1 to T5). Effective peri-operative analgesia by other means also affords cardiovascular protection. Pain associated with thoracic and upper abdominal surgery can cause significant postoperative respiratory dysfunction. Pain causes an increase in

muscle tone around the site of injury. This “muscle splinting”, coupled with voluntary reductions in respiratory muscle excursions, causes reduction in lung volumes (tidal volume, vital capacity and functional residual capacity), regional lung collapse (atelectasis) and reduced alveolar ventilation, all of which ultimately result in hypoxemia and hypercapnia. These respiratory changes also result in a reduced ability to cough, retention of secretions and an increased risk of chest infections. Adequate peri operative pain relief, coupled with breathing exercises, can reverse these adverse respiratory effects.

Increased sympathetic activity associated with pain also results in decreased gastrointestinal motility (gastric stasis and paralytic ileus), increased intestinal secretions and increased smooth muscle sphincter tone. Continuation of epidural anaesthesia with local anaesthetics for several days into the postoperative period helps not only to improve gastrointestinal motility through direct effect of the epidural blockade, but also minimises the need for opioids (and its associated adverse effects on gastrointestinal motility).

The neuroendocrine and metabolic changes that constitute the stress response to surgery result in an aggravated catabolic state that results in weight loss and negative nitrogen balance. Maintenance of epidural anaesthesia with local anaesthetics for 48 to 72 hours into the postoperative period has a salutary effect on these adverse metabolic effects.

Psychological responses

Acute postoperative pain causes fear and anxiety in hospitalised patients. If left unattended, it can progress to anger, resentment and animosity towards medical personnel who may be perceived as withholding pain relief. Sleep deprivation may aggravate these feelings. Adequate attention to pain relief can help in promoting a feeling of well being which has a positive influence on postoperative outcome.

Clinical assessment of acute pain

Pain can be evaluated by various scoring systems. Irrespective of the scoring system used, one must record postoperative pain both at rest and during specifically directed movement (chest physiotherapy for thoracotomies, passive knee movements following knee surgery, etc). It should be recorded as frequently as once in 5 minutes during the initial phase when bolus injections of intravenous opioids or epidural opioids / local anaesthetics are being given in an incremental manner. Once adequate basal analgesia has been established, the frequency of assessment can be reduced to once every 2 hours during the first 24 to 48 hours, and once every 4 hours thereafter. In addition, pain scores should be considered along with sedation scores and the traditional ward recordings of temperature, pulse rate, blood pressure and respiratory rate. These six observations constitute the minimum set of data to be recorded in the postoperative chart (with pain score and sedation score being given the status of the 5th and 6th vital signs). Recording postoperative pain is one way of focusing the attention of all caregivers on the presence of acute postoperative pain, and the need for its management.

Management of acute postoperative pain

Management strategies for postoperative pain are aimed at reducing a patient's pain to a tolerable level. Complete abolition of pain should not be the objective and is certainly not desirable, as pain serves a protective function. Although the traditional approach has been to begin pain therapy when surgery is complete, the concept of "pre-emptive analgesia" has become increasingly popular wherein antinociceptive treatment is started before the onset of pain. Such treatment prevents the establishment of altered central processing that normally amplifies postoperative pain by sensitising the central nervous system to sensory input. Just as "balanced anaesthetic techniques" are used to meet the intraoperative anaesthetic needs of patients by making use of several agents, "balanced analgesia" uses several modalities of pain management to provide a pain- and stress-free state, thereby promoting good postoperative outcome. The multimodal technique of pain management involves administration of two or more drugs that act by different mechanisms via a single route (eg. epidural opioids + local anaesthetics +/- clonidine) for providing superior analgesic efficacy with equivalent or reduced adverse effects. As recommended by the American Society of Anesthesiologists (ASA), whenever possible, anaesthetists should employ multimodal pain management therapy.

Systemic opioids (4).

Systemic opioids have been the mainstay of management of moderate to severe pain in the past and still continue to be a popular choice around which other strategies are built. All opioids given in equi analgesic doses produce the same analgesic effect. Opioids are usually administered via the oral, rectal, intramuscular (IM), intravenous (IV), subcutaneous (SC) or transdermal routes.

Ideally, opioid administration should begin with an individualised prescription tailored to the needs of the patient. The prescription should indicate the agent, dose, frequency and route of administration. Age rather than weight is a better predictor of opioid requirement in the first 24 hours after surgery. The average 24-hour morphine requirements (in mg) using the patient controlled analgesia technique following major surgery in patients aged between 20 and 70 years is given by the formula $100 - \text{age in years}$. Thus, a 40-year old will need 60 mg of morphine in 24 hours. This simple formula can be used to initiate systemic opioid therapy in the immediate postoperative period.

Specific opioids.

Codeine is classified as a weak opioid, but the molecule itself is devoid of any analgesic activity. Codeine-6-glucuronide is the principle metabolite, but it is also of similar potency to the parent drug. A minor pathway metabolises codeine to morphine (2-10% of the dose given) and this accounts for most of the analgesic activity. The enzyme responsible for this minor pathway is cytochrome isoenzyme P450 (CYP) 2D6, which is lacking in 9% of Caucasians. Codeine is usually combined with paracetamol, which helps in providing additional pain relief.

Dextropropoxyphene is also a weak opioid that is often combined with paracetamol for pain relief. However the incidence of dizziness is very high. Nordextropropoxyphene, the major metabolite is excreted via the kidneys and its accumulation can result in central nervous system (CNS), respiratory or cardiovascular depression.

Diamorphine (also called diacetylmorphine or heroin) is rapidly hydrolysed to monoacetylmorphine (MAM) and morphine. Diamorphine and MAM are far more lipid soluble than morphine and can penetrate the CNS more rapidly. MAM and morphine that are thought to be responsible for the analgesic effects of diamorphine. There is no difference between parenteral diamorphine and morphine in terms of analgesic activity and side effects.

Methadone is commonly used for maintenance therapy in patients who are opioid addicts because of good oral bioavailability (60-95%), high potency and a long duration of action. In addition, its lack of active metabolites, low cost. Its NMDA antagonistic activity and serotonin reuptake inhibitor activity is useful in treating chronic pain. Its use in treating acute pain is limited by its long and unpredictable duration of action and risk of accumulation of metabolites.

Morphine is the opioid most widely used in the management of acute pain. It is metabolised into morphine-6-glucuronide and morphine-3-glucuronide in the liver. Morphine-6-glucuronide is a μ -opioid receptor agonist and is more potent than morphine while morphine-3-glucuronide has low affinity for opioid receptors and has no analgesic activity. It is sometimes associated with neurotoxic side effects such as allodynia, hyperalgesia and myoclonus. Both the metabolites accumulate in presence of renal dysfunction, at higher doses, in the older age group and with oral administration.

Oxycodone is a potent oral opioid agent, used in acute pain management for patients able to tolerate oral intake. It is metabolised to noroxycodone and oxymorphone, both of which are weakly active and only contribute minimally to any clinical effect. It is available in immediate-release and controlled-release formulations and can also be used as “step-down” analgesia following parenteral opioid regimes.

Pethidine is a synthetic opioid still widely used despite its multiple disadvantages. Studies have found that it is no better than morphine in the treatment of renal and biliary colic, including its effects on the sphincter of Oddi. Pethidine induces more nausea and vomiting than morphine when used parenterally. Accumulation of its active metabolite, norpethidine, is associated with neuro-excitatory side effects (tremors, twitches, multifocal myoclonus and seizures). As impaired renal function increases the half-life of norpethidine, patients in renal failure are at increased risk of norpethidine toxicity.

In view of these facts, the use of pethidine should be discouraged in favour of other opioids.

Fentanyl is increasingly used in the treatment of acute pain because of its lack of active metabolites and fast onset of action. Its limitation is its short half-life.

Tramadol is an atypical centrally acting analgesic. It has effects as an opioid agonist (mainly its metabolite, O-desmethyl-tramadol at the μ -opioid receptor) and a serotonin and noradrenaline reuptake inhibitor. The World Health Organisation lists it as a weak opioid. The risk of respiratory depression is significantly lower at equianalgesic doses compared to other opioids and it does not depress the hypoxic ventilatory response. It has limited effects on gastrointestinal motor function compared to morphine - causing less constipation and lesser effects on gastric emptying/post operative bowel recovery. Nausea and vomiting are the most common side effects and tramadol does not increase seizure incidence when compared to other analgesic agents.

Routes of systemic opioid administration (4).

Oral Route.

Oral administration is simple, non-invasive, has good efficacy in most settings and has high patient acceptability. Apart from the severe acute pain situation it is the route of choice providing there are no contraindications to its use.

Limitations include nausea/vomiting or delayed gastric emptying, when absorption is likely to be impaired. Rates of absorption will vary according to the formulation of the drugs. Bioavailability will also vary between drugs. Titration of pain relief with oral analgesic drugs is slower compared to other routes.

Rectal Route.

Is useful when other routes are unavailable. It results in uptake into the sub mucosal venous plexus of the rectum that drains into the inferior, middle and superior rectal veins. Drug absorbed from the lower half of the rectum through the inferior and middle rectal veins will pass into the inferior vena cava, bypassing the portal system. Any absorption into the superior rectal vein enters the portal system, subjecting it to hepatic first-pass metabolism.

Limitations to this route include variability of absorption, possible rectal irritation, cultural factors and contraindications such as rectal lesions, recent colorectal surgery and immune suppression.

Intramuscular(IM) and Subcutaneous Routes.

IM and subcutaneous (SC) injections of analgesic agents are still commonly employed for the treatment of moderate or severe pain. The quality of pain relief is less with IM or SC regimens than IV dosing. Absorption may be impaired in conditions of poor perfusion (eg. hypovolemia, shock, hypothermia or immobility) leading to inadequate early analgesia and late absorption of the drug depot when perfusion is restored.

The placement of SC plastic cannulae allow the use of intermittent SC injections without repeated skin punctures and also enables the provision of continuous SC infusions, which are as effective as continuous IV infusions.

Intravenous Route.

The intravenous route has the advantage of producing prompt and predictable blood levels. This route allows precise titration of analgesic requirements to the needs of the patient. Once adequate analgesia has been obtained with IV boluses, maintenance can be achieved by IV or SC infusions.

The intravenous route is used in postoperative intensive care units or high dependency units to obtain rapid control of pain. It is also the preferred route in patients who are hypotensive or hypovolemic as it produces instantaneous and predictable therapeutic blood levels. While continuous infusions provide a steady blood level, it must be remembered that it may take up to 5 half lives of a drug (20 hours in the case of morphine) to achieve 95% of the final steady state concentration. Thus, inadequate analgesia in a patient receiving an IV infusion is best dealt with by IV boluses rather than by increasing the infusion rate of the drug.

Table - 1: Intravenous dosage of commonly used opioids

<i>Drug Dosage</i> <i>Intravenous bolus</i>	<i>Intravenous infusion</i>
Morphine 0.01-0.2 mg/kg	0.01-0.02 mg/kg/h
Pethidine 0.1-1.0 mg/kg	0.1-0.2 mg/kg/h
Fentanyl 1-5 mcg/kg	0.5-2.0 mcg/kg/h
Tramadol 0.5-1.0 mg/kg	0.1-0.2 mg/kg/h

Transdermal Route.

Transdermal drug delivery allows continuous parenteral administration of drug without the need for needles or infusion devices. Lipid-soluble drugs such as fentanyl are suitable. Transdermal fentanyl patches are available with different delivery rates ranging from 25 to 100 micrograms/hour. Currently available patches have a slow onset and offset of action and absorption continues for up to 72 hours while the patch is in place.

Limitations include the slow onset and offset times due to the formation of a significant transdermal 'reservoir', which makes short-term titration impossible. These factors make transdermal fentanyl patches unsuitable for acute pain management and are currently restricted to chronic and cancer pain treatments.

Adverse effects of opioids (4).

Common adverse effects of opioids are sedation, pruritus, nausea, vomiting, slowing of gastrointestinal function and urinary retention. Clinically meaningful adverse effects are dose-related. Once a threshold dose is reached, every 3-4 mg increase of morphine-equivalent dose per day is associated with one additional adverse event per patient day.

Respiratory depression is the most feared side effect that can usually be avoided by careful titration of the dose against effect. The majority of studies investigating opioid related hypoxia in the postoperative period have found that measurement of respiratory rate as an indicator of respiratory depression is of little value as hypoxemic episodes often occur in the absence of a low respiratory rate. As respiratory depression is almost always preceded by sedation, the best early clinical indicator of drug accumulation/respiratory depression is increasing sedation.

Supplemental oxygen for 48 hours following major surgery is beneficial, particularly in elderly and high risk patients, because of the link between postoperative hypoxemia, tachycardia and myocardial ischaemia.

Postoperative nausea and vomiting (PONV) are very common adverse effects of opioids. The risk is significantly reduced by the use of droperidol, dexamethasone and ondansetron, all of which are equally effective. Omission of nitrous oxide and the use of total intravenous anaesthesia using propofol are as effective in decreasing the incidence of PONV.

Opioid induced pruritus is usually treated with naloxone, naltrexone and droperidol. Minimum effective doses of these drugs are not yet known.

Patient Controlled Analgesia (4, 5).

Patient controlled analgesia (PCA) is a technique wherein patients self-administer small doses of an analgesic agent (usually by the IV or SC route) when they experience pain. This technique not only gives patients control over their pain, but also overcomes some of the problems associated with pharmacodynamic and pharmacokinetic variability among individual patients.

Most intravenous-PCA (IV-PCA) devices consist of a microprocessor-controlled pump that is triggered by pressing a button. When triggered, a preset amount (incremental dose) of drug is delivered intravenously. A timer in the pump prevents administration of an additional bolus until a specified period (lockout interval) has elapsed. Thus, individual patients can titrate opioids to their own needs within the boundaries of safety drawn by the anaesthetist. The incremental doses and lockout periods for some of the commonly used opioids for patient controlled analgesia are given in table 2.

Table - 2: Guidelines for patient controlled intravenous opioid administration

Drug Demand (Concentration) dose	Lockout interval (minutes)	Continuous basal infusion
Morphine (1 mg/ml) 1–2 mg	5–10	0 – 2 mg/h
Pethidine (10 mg/ml)* 10–20 mg	5–10	0 – 20 mg/h
Fentanyl (10 mcg/ml) 20- 50 mcg	5–10	0 – 60 mcg/h
Sufentanil 4–6 mcg	5–10	0 – 8 mcg/h
Tramadol 10–20 mg	5–10	0 – 20 mg/h

*Only if patient is intolerant to all other opioids.

Adequate analgesia can be established by titrating intravenous loading doses prior to starting patient controlled opioid administration. Elderly or compromised patients may need smaller doses of opioid.

Most PCA pumps provide the option of adding a continuous background infusion to the basic patient controlled mode. This technique has the advantage of providing more controlled blood levels and improved analgesia (especially during sleep) with fine-tuning of opioid requirements being done by the patient. The disadvantages include difficulty in predicting optimal background infusion rate (resulting in a possible overdose in some individuals) and loss of one of the safety features of the PCA technique because sleeping patients can continue to receive medications irrespective of their needs. Background infusion is now not recommended in adults for routine use; however, it may be useful in opioid-tolerant patients.

When IV access is difficult to obtain, PCA can be administered through the SC route. A standard PCA pump attached to an administration set can be used to deliver the drug into the SC plane through a cannula or a butterfly needle. The drug concentration is usually increased 5-fold to avoid administration of large volumes of fluid into the subcutaneous plane.

Patient controlled epidural analgesia (PCEA) is the second most commonly used route of PCA delivery for acute pain management. The advantages include superior analgesia, increased patient satisfaction and decreased side effects. Optimal PCEA variables have not been clearly determined. For postoperative analgesia, 2 to 4 ml of 0.0625% to 0.25% bupivacaine with a lockout interval of 10 to 20 minutes and a continuous infusion of 3 to 10 ml/hr is commonly

used. Continuous infusion has been recommended with PCEA to optimise the potential physiological benefits of epidural analgesia and maintain continuous neural blockade. Adding a lipid soluble opioid to the local anaesthetic solution provides superior analgesia.

Other routes of PCA delivery include oral PCA, intranasal PCA (PCINA), transdermal PCA and regional PCA (PCRA).

Neuraxial analgesia

Intrathecal opioids (6).

Intrathecal opioids are now widely used alone or as useful adjuncts in the treatment of acute pain. They bind to specific receptors in the dorsal horn in the spinal cord. Combining low doses of opioids with local anaesthetic agents for intrathecal administration has been shown to increase the speed of onset, density of block and the duration of analgesia.

Highly lipid soluble opioids such as fentanyl and sufentanil produce minimal rostral spread, a relatively small dermatomal band of analgesia and limited duration of action unlike hydrophilic opioids such as morphine which have a greater degree of rostral spread, delayed respiratory depression and extensive dermatomal analgesia. Recent studies have shown that intrathecal administration of lipophilic opioids can also result in respiratory depression that occurs in the first 20-30 minutes after injection. This is due to the rapid distribution of the drug in the cerebrospinal fluid. However this effect lasts only for a few minutes unlike morphine, which peaks by approximately 6 hours and persists for about 18-24 hours.

Internationally, opioids and adjunct analgesics are supplied as preparations that include preservatives. Benzyl alcohol and the parabens have been implicated as a cause of neurotoxicity after intrathecal administration and hence are to be avoided. The pharmacological properties of commonly used intrathecal opioids is summarised in table 3.

Table - 3: Pharmacologic properties of common opioids used for intrathecal analgesia

Opioid	Usual dose range (mcg)	Onset (min)	Duration (h)
Morphine	100 - 500	45 - 75	18 – 24
Fentanyl	5 – 25	5 – 10	1 – 4
Sufentanil	2.5 – 10	5 – 10	2 – 6

Side effects of intrathecal opioids include pruritus, nausea and vomiting, urinary retention and respiratory depression.

Epidural analgesia (7).

The epidural route is more popular for postoperative pain management as the technique can be used alone or in combination with general anaesthesia. The epidural technique has been found to provide better pain relief than systemic opioids and also decrease the incidence of postoperative complications. Lumbar epidural catheters can be kept in place for prolonged periods. An epidural catheter placed in a location congruent to the incision dermatome has been shown to provide superior analgesia. Segmental analgesia for upper abdominal surgery can be obtained by placing the catheter at T8 to T10 levels.

Morphine administered in the lumbar region can provide good postoperative analgesia for upper abdominal and thoracic surgeries as well. The hydrophilic nature of morphine results in its rostral spread, making it possible to obtain good pain relief for upper abdominal and thoracic procedures following administration through a catheter placed in the lumbar region.

Fentanyl, on the other hand, is lipophilic and hence needs to be administered close to the segmental level where analgesia is required. Morphine has a slower onset of action as compared to fentanyl. In addition, fentanyl tends to produce a more definable segmental block as compared to morphine. The initial bolus dose of morphine is in the range of 1 to 6 mg, followed by an infusion at a rate of 0.1 to 1.0 mg/hr. The bolus dose produces analgesia within 30 minutes and the effect lasts for 6 to 24 hours.

Fentanyl in a bolus of 25 to 100 micrograms produces analgesia in 5 minutes, the effect lasting for up to 1.5 to 3 hours. The rate of infusion of fentanyl is 25 to 100 micrograms/hour. Elderly patients need much lower doses of drugs to produce effective analgesia. The effective total dose of epidural morphine needed in 24-hours can be predicted by the formula:

Effective 24-hour epidural morphine dose (mg) = $18 - (\text{age} \times 0.15)$.

Opioids can either be administered alone or in combination with 0.0625-0.125% bupivacaine. When opioids are being administered by the epidural or subarachnoid route, concurrent systemic use of other opioids or sedatives must be avoided. Patients should be closely monitored for systemic effects of opioids such as decreased respiratory rate or excessive sedation. When combined with local anaesthetics, one should also monitor haemodynamics and motor blockade.

DepoDur™ is a novel analgesic formulation of morphine for postoperative pain management intended for epidural administration. It consists of morphine encapsulated within liposomes to provide extended release of the drug. DepoDur™ given as a single epidural injection before surgery has been shown to produce pain relief for up to 48 hours.

Nonopioid analgesic techniques (8).

An increasing number of complex surgeries are performed on an outpatient basis for which the use of IV-PCA, spinal or epidural analgesia are not practical for pain management. Extensive use of peri operative opioids is associated with side effects such as PONV, pruritus, urinary retention and paralytic ileus. Non-opioid analgesic techniques have thus emerged as adjuncts for peri operative pain management. These techniques are incorporated as a part of multimodal or balanced analgesia techniques.

Local anaesthetic techniques.

Local infiltration of incisions with long acting local anaesthetics, peripheral nerve/plexus blocks, and continuous neuraxial blocks can provide effective and safe analgesia into the postoperative period. In addition, use of these can decrease the incidence of PONV. Infiltration of 0.25% bupivacaine along surgical incisions provides effective analgesia for several hours. In a similar manner, regional techniques that can be recommended include interscalene block for shoulder surgery, sciatic and femoral nerve block for surgery on the lower limb, intercostal block for thoracic and upper abdominal procedures, and interpleural analgesia for surgery on the gall bladder and kidney (unilateral). The disadvantage of local anaesthetic techniques is that they are effective only for 6-8 hours. Pain control can be improved by the use of continuous techniques for local anaesthetic (LA) infusion. Long acting LA suspensions and delayed release formulations containing liposomes / polymer micro-spheres may minimise the need for continuous catheter delivery systems in the future.

Nonopioid analgesics.

Though opioids by several routes have been the mainstay of pain management techniques, they do not provide the complete solution in patients experiencing severe postoperative pain. Addition of a non-sedating, non-opioid analgesic to an opioid is now a popular multimodal form of therapy that provides superior analgesia to either drug alone. Non-opioid analgesics serve as good therapeutic adjuncts to opioids in the first 24 to 48 hours, and they can be used as sole analgesics beyond 48 hours.

Nonsteroidal anti-inflammatory drugs (NSAIDs) such as acetaminophen, ibuprofen, ketorolac, diclofenac and COX-2 inhibitors are popular drugs used for this purpose. These drugs are administered by the oral, rectal or intramuscular routes to supplement opioid-based analgesia. They are often administered along with premedication in the technique termed “preemptive analgesia”. While traditional NSAIDs such as acetaminophen, ibuprofen, ketorolac and diclofenac inhibit both COX-1 and COX-2 forms of the cyclo-oxygenase enzyme, newer NSAIDs inhibit the inducible form of the enzyme (COX-2), which is released following surgical trauma, sepsis and hypoxia.

Paracetamol is used in clinical practice as an effective analgesic and antipyretic. It acts by inhibiting central cyclo-oxygenase-2 (COX-2) in the central nervous system. It also inhibits the putative central ‘COX-3’ that is selectively susceptible to paracetamol. It modulates the inhibitory descending serotonergic pathways and prevents prostaglandin production at cellular

transcription level. Paracetamol given alone is effective for mild to moderate pain. It is a useful adjunct to opioids in more severe pain. It is used orally in doses of 10-15 mg/kg every 4 to 6 hours with a maximum dose not exceeding 90 mg/kg/day. Single oral doses in excess of 90 mg/kg can result in severe liver damage and acute tubular necrosis. The drug can also be given rectally in an initial dose of 35-40 mg/kg, followed by 20 mg/kg every 6 hours. Intravenous paracetamol preparations are as effective as ketorolac and are equivalent to morphine after surgery.

Oral ibuprofen in a dose of 6-10 mg/kg every 6th hours is known to produce a 30% reduction in opioid requirements.

Intramuscular ketorolac (10 and 30 mg doses) has been found to be as effective as IM morphine (12 mg) for relieving pain on the 1st and 2nd postoperative days following major surgery. A study on patients undergoing cholecystectomy revealed that morphine (10 mg IM) provided superior analgesia when compared to Ketorolac (30 mg IM). The usual dosing regimen for ketorolac is 30 mg IM initially, followed by 10 mg IM 6 hourly, for a maximum of 3 days. Care is to be taken when dosing the elderly and those with renal impairment.

Diclofenac can be given by rectal or IM routes as adjuncts to opioid medications in the management of postoperative pain. While rectal suppositories are available in strengths of 12.5, 25, 50 and 100 mg, the intramuscular preparation is available as 75 mg/3 ml ampoule.

COX-2 inhibitors such as rofecoxib and valdecoxib are available for oral administration. These drugs are administered orally as preemptive analgesics along with premedication. Parecoxib, a prodrug of valdecoxib, is the only injectable COX-2 inhibitor available. It is administered as a one-off perioperative dose.

On the basis of current evidence, NSAIDs are not sufficiently effective as sole agents for providing pain relief following major surgery though they may be effective following minor or moderate surgery. When combined with opioids, they decrease opioid requirements and also minimize opioid-related adverse effects. They occasionally increase bleeding time and can result in increased blood loss. But a recent systematic review of the literature suggested that evidence supporting bleeding tendency was equivocal at best. COX-2 inhibitors have been found to have a negative influence on bone growth. Hence, COX-2 inhibitors are not to be used for more than 3 to 5 days following surgery.

Analgesic adjuncts (9).

NMDA antagonists: Ketamine, dextromethorphan, magnesium and adenosine have been tried as analgesic adjuncts for postoperative pain management. These have been shown to inhibit the receptor-gated calcium currents that amplify neuronal firing. Ketamine has been shown to be a useful adjunct when given as an IV bolus, continuous IV infusion (0.5 mg/kg/hr to 20 mg/hr) or epidural infusion (0.25 mg/kg/hr) without any increase of adverse CNS effects.

a2 agonists: Low dose clonidine has proved to be a useful adjunct analgesic when given neuraxially (150 mcg intrathecally or 2-3 mcg/kg epidurally), and in combination with peripheral nerve blocks (0.5 mcg/kg). Higher doses are associated with adverse effects such as sedation, bradycardia and hypotension and should be avoided.

Neostigmine: Intrathecal administration of 25-100 mg neostigmine has been associated with high incidence of nausea and vomiting, bradycardia, hypotension, sweating, agitation and distress. Hence, it is not recommended for intrathecal use. Neostigmine is being investigated as an analgesic adjunct for intra-articular and epidural use.

Pain management in special groups

Pain management in children (10).

Children constitute a special category of patients needing specific considerations for postoperative pain management. Children feel pain and remember pain, just like adults. Pain in children produces similar deleterious physiological and psychological effects. This is true for neonates and preterm infants as well.

Assessment and treatment of pain presents problems in the paediatric age group because of developmental, cognitive and emotional differences. Alternate routes of drug administration such as the sublingual, rectal and transdermal routes are more popular.

Opioid clearance is prolonged in the neonate and the older infants. This makes the paediatric population more prone to the respiratory depressant effects of opioids.

Caudal epidural is a popular route for providing pain relief for lower abdominal, lower limb and perineal procedures. The Armitage formula (table 4) may be employed to calculate the dose of drug for caudal analgesia. (11)

Table - 4: Dose requirements for caudal analgesia in children (from Armitage 1)

Site of surgery	Dose of drug * (0.25% bupivacaine)
Lower limb/perineal (below T12)	0.5 ml/kg
Lower abdominal (between T10-T12)	1.0 ml/kg
Upper abdominal/thoracic (above T10)	1.25 ml/kg

* If the total predicted volume of 0.25% bupivacaine exceeds 20 ml, the concentration of bupivacaine is reduced to 0.1875%

Other regional techniques can also be used for providing excellent pain relief in children.

- Block of the dorsal nerve of penis or application of lignocaine jelly can provide postoperative analgesia following circumcision.
- Block of the iliohypogastric and ilioinguinal nerves provides excellent pain relief following herniotomy and orchidopexy.
- Infraorbital nerve block provides exemplary pain relief following cleft lip surgery.

NSAIDs by oral, rectal or parenteral routes are useful in providing pre-emptive analgesia in children. However, like in adults, these are best considered as adjuncts rather than primary agents for pain management. NSAIDs have similar adverse effect profiles in children as in adults.

Oral paracetamol is used in a dose of 15 mg/kg every 6 hours with the maximum daily dose not to exceed 90 mg/kg in otherwise normal children. The maximum daily oral dose of paracetamol should not exceed 75 mg/kg in term neonates or 40 mg/kg in premature less than 32 weeks. Rectal paracetamol is used in an initial dose of 30 mg/kg followed by 20 mg/kg every 6 hours.

Oral ibuprofen is used in a dose of 10 mg/kg every 6 to 8 hours. Oral diclofenac is used in a dose of 0.5-1.0 mg/kg every 8 hours. Rectal suppositories of diclofenac are also available.

Intramuscular ketorolac is administered in a dose of 0.25-0.5 mg/kg every 6 hours.

Pain management in the elderly

Advances in anaesthetic and surgical techniques means that increasingly elderly patients are undergoing more major surgeries. Factors that can combine to make effective control of acute pain in the elderly more difficult include a higher incidence of co-existing diseases and concurrent medications (which increases the risk of drug-drug and disease-drug interactions); age-related changes in physiology, pharmacodynamics and pharmacokinetics; alteration of responses to pain; and difficulties with assessment of pain, including problems related to cognitive impairment.

Alteration in pharmacokinetics and pharmacodynamics of drugs mandate the decrease in bolus and infusion doses of opioids; and the need to titrate and continuously monitor the patient for overdose.

Due to sensory neuronal degeneration and neurochemical changes associated with aging, elderly patients have a higher pain threshold. But, their ability to tolerate severe pain is limited and physiological changes such as hypertension and tachycardia can be detrimental. Delirium is a common form of cognitive impairment in the elderly in the postoperative period. They may need more time to understand and respond to questions regarding pain. Verbal descriptive scale (VDS) has shown to be a more reliable measure of pain than the VAS or NRS (numerical rating scale) in the elderly.

It is safer to employ a combination of pharmacological and non-pharmacological techniques of pain relief in the elderly.

NSAIDs and Paracetamol: Elderly patients are more likely to suffer adverse gastric and renal side effects following administration of NSAIDs. Renal failure is of particular concern as they are more likely to have pre-existing renal impairment. Selective COX-2 inhibitors have a significantly lower incidence of gastrointestinal complications and have no antiplatelet effects. However, the incidence of renal side effects is similar to nonselective NSAIDs. Paracetamol has proved to be safe and there is no need of dose reduction in the elderly.

Opioids: Elderly patients require less opioid than younger patients. However, a large inter-patient variability still exists and doses must be titrated to effect in all patients. Morphine and fentanyl requirements are decreased two- to four-fold. Elimination half-lives of opioids are prolonged and rapid accumulation of metabolites such as morphine-6-glucuronide or norpethidine can occur because of reduced renal function. Sedation occurs earlier than respiratory depression. Hence, the doses must be titrated under close monitoring.

The incidence of pruritus, nausea and vomiting is less in the elderly. PCA is an effective method of postoperative analgesia with better patient tolerance, decreased confusion and decreased incidence of pulmonary complications.

Local anaesthetics: Elderly patients are more sensitive to the action of local anaesthetic agents because of a slowing of conduction velocity of neurons and a decrease in the number of neurons. The duration of epidural and subarachnoid block is prolonged. When local anaesthetics and opioids are used in combination for continuous epidural techniques for postoperative pain relief, age-based doses or infusion rates are recommended. The elderly individual is susceptible to hypotension during neuraxial analgesia.

Pain management in special areas

Opioid analgesics continue to be the gold standard for treating moderate to severe pain, drugs such as morphine being low cost and highly effective. However, the availability and use of opioids is not uniform across the globe. It is thought that 87% of the world's morphine is used by 10 major industrial countries and only the remaining 13% by 85% of the global population (12).

There are many barriers to opioid use in developing countries, including concerns at the government level over risks of addiction and abuse leading to stringent import laws and limitations on prescription.

Due to the diversity of situations and problems facing the developing countries, the provision of anaesthesia and analgesia is seen as a low priority in comparison with the treatment of other major conditions like malaria, HIV/AIDS and tuberculosis. Despite the challenges facing the

developing countries, there are basic interventions that are effective – training of medical and nursing staff in pain management, use of multimodal analgesic and access to reliable drug supplies. Opioid use should be encouraged where possible, along with the introduction of effective systems for opioid administration – reliable supply, safe storage, recording of use and education regarding effects and side-effects. There are several countries where this system has been implemented successfully and pain management has improved significantly (13).

There can be no single set of solutions that can be applied globally. The administration of effective analgesia does not depend on sophisticated technology (13). The WHO analgesic ladder outlines simple methods using minimal resources to treat cancer pain and the World Federation of Societies of Anaesthesiologists (WFSA) has further modified this model to treat acute pain (14). It commences therapy with strong parenteral opioids, ketamine and/or local anaesthetic. There is then a step down to oral opioids and finally to paracetamol and NSAIDs. These models are easy to use, and understand and are very cost effective.

Summary

Pain relief after surgical procedures continues to be a major medical challenge. The introduction of the Acute Pain Services in many countries has led to a successful and safe implementation of multi-modal pain management strategies and an increase in the use of specialized pain relief methods.

The key points in improving postoperative pain management are education of staff on pain management, the regular assessment and documentation of pain as the fifth vital sign and the use of multi-modal pain management strategies.

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KETAMINE

Ketamine is a phencyclidine derivative, released for clinical use in the 1970s. Its receptor binding is not completely known however ketamine's principal site of action is probably as an antagonist at the N-methyl-D-aspartate (NMDA) receptors. Ketamine also has effects at many other neurochemical systems including the opioid, dopamine and serotonin receptors.

Ketamine is a unique drug. It will provide intense analgesia and anaesthesia (induction and/or maintenance) with cardiovascular stability and some preservation of airway reflexes. Ketamine may be used as the sole anaesthetic agent or in combination with other drugs.

Being water and lipid soluble allows ketamine to be administered by several routes including oral, rectal, subcutaneous, intramuscular, intravenous, epidural and trans-nasal routes. The high lipid solubility is reflected by ketamine's large volume of distribution of 1 – 3 L/kg. The usual routes of administration are intravenous or intramuscular. (Ketamine used within the epidural space must be preservative free).

Intravenous ketamine preparation can be taken orally but has a very bitter taste. An oral preparation is available. After oral administration, there is incomplete gastro-intestinal absorption and first pass hepatic metabolism. Oral or rectal bioavailability is only 16%; therefore oral doses need to be approximately six times greater than intravenous doses. Intramuscular bioavailability is up to 93%.

Plasma half-life, clearance and volume of distribution relative to body weight are not significantly different between adults and children, although absorption following intramuscular injection is more rapid in children.

The usual preparation of ketamine is a racemic mixture of two stereoisomers: S (+) and R (-). Both the S and R isomers have the same side effects but the S isomer has 4 times greater affinity for the NMDA receptor and also binds to mu and kappa opioid receptors. A pure S isomer preparation is available in some countries.

The racemic mixture is prepared in a slightly acidic solution, available as 10 mg/ml, 50 mg/ml and 100 mg/ml concentrations containing the preservative benzethonium chloride. The pure S formulation is available in 5 mg/ml and 25 mg/ml concentrations.

After intravenous administration, ketamine is rapidly distributed into highly perfused tissues, such as the brain, heart and lungs, achieving levels 4 to 5 times higher than corresponding plasma concentrations with a α half life of 11 to 16 minutes. Ketamine is then redistributed to muscle and peripheral tissues, and eventually fatty tissue. Termination of the anaesthetic effect may be caused by redistribution from brain to other tissues.

Ketamine undergoes hepatic metabolism. The primary metabolic pathway involves N-demethylation via the cytochrome P450 system to norketamine, which is then hydroxylated to hydroxynorketamine. Norketamine has one-third the potency of ketamine. This metabolite is subsequently hydroxylated and conjugated to water-soluble compounds for renal excretion. Ketamine's clearance is 19 ml/kg/min, which accounts for its short elimination half-life of 2 to 3 hours. Dose reductions should be considered in patients with cirrhosis or other types of liver disease.

Clinical

A patient receiving ketamine will usually maintain airway patency with some preservation of pharyngeal and laryngeal reflexes. However it does not guarantee the prevention of aspiration.

Ketamine has minimal effect on the central respiratory drive as reflected by an unaltered response to carbon dioxide. Transient apnoea is more likely to occur with rapid intravenous administration. Intravenous Ketamine should be administered over at least 60 seconds. Neonates and young infants may be at more risk of respiratory complications. Supplemental oxygen administration will reduce episodes of mild hypoxia and all patients must be observed at all times during ketamine anaesthesia. Apnoea, laryngospasm and other forms of respiratory obstruction have occurred.

Ketamine relaxes bronchial smooth muscle. Ketamine is equally as effective as halothane in preventing experimentally induced bronchospasm.

There is a wide variation in individual cardiovascular response to ketamine. Blood pressure increases (25%) and as does stroke volume (20%) and heart rate (20%) whilst systemic vascular resistance is unaltered. The blood pressure usually increases rapidly over 3 to 5 minutes, returning to baseline levels in 20 minutes. Interestingly the cardiovascular changes are independent of the ketamine dose (0.5 mg/kg causing the same changes as 1.5 mg/kg) and subsequent doses cause less cardiovascular effects. Ketamine is ideal for shocked patients but must be used with care in extreme cases where the patient's catecholamine stores are depleted as it may then cause hypotension.

Low dose ketamine produces analgesia with higher doses causing "dissociative anaesthesia" (a cataleptic state that resembles normal sleep) in that it appears to selectively interrupt association pathways of the brain. Ketamine anaesthetised patients have profound analgesia but keep their eyes open and maintain many reflexes. Pupils dilate moderately and nystagmus occurs. A small increase in intra-ocular pressure is sustained for 15 minutes (increased tone of extra ocular muscles plus increased blood flow).

Lacrimation and salivation is common, as is an increase in skeletal muscle tone. Patients may have seemingly purposeful movement of arms, legs, trunk and the head. Ketamine increases cerebral metabolism, cerebral blood flow and intracranial pressure.

Ketamine, like other phencyclidines, produces undesirable psychological reactions during awakening. Common reactions include vivid dreaming, nightmares and hallucinations often associated with excitement, confusion, euphoria and fear. These reactions vary in severity and incidence. They usually occur within the first hour of emergence and resolve within several hours. Factors that affect the incidence include adult age, higher doses and rapid administration, male gender and concurrent drugs.

Emergence hallucinations occur in 5- 30% of patients after ketamine anaesthesia, with a lower incidence in females and children. The incidence may be reduced by premedication with benzodiazepines (0.15 mg/kg oral 1 hour pre-operatively or 0.1 mg/kg intravenously on induction) or oral promethazine pre-operatively. Small doses of thiopentone or propofol have been reported to successfully reduce emergence hallucinations however their use increases the risk of intra-operative respiratory depression. Benzodiazepines or promethazine may be used for rescue treatment of hallucinations post-operatively but increase the risk of respiratory complications. Promethazine is also an effective anti-emetic. Hallucinations are not a problem with the lower doses of ketamine used for analgesia.

Animal studies of incomplete cerebral ischaemia and reperfusion suggest that ketamine may be neuro-protective, reducing necrosis and improving neurological outcome. Epidural ketamine (preservative free) prolongs the duration of a single shot epidural by binding to NMDA receptors on the dorsal horn.

Ketamine is a potent analgesic. The plasma level at which pain thresholds are elevated is 0.1 µg/ml or higher, therefore analgesia last several hours after ketamine anaesthesia, which requires higher blood levels.

Analgesic doses of ketamine have a postoperative opioid-sparing effect; used with patient controlled analgesia morphine, the incidence of postoperative nausea and vomiting is reduced. Ketamine may reduce opioid requirements in opioid-tolerant patients and may be a useful adjunct in conditions of allodynia and hyperalgesia. In the management of acute pain in specific clinical situations, both lignocaine and ketamine reduce acute post-amputation stump pain. Perioperative ketamine may prevent severe phantom limb pain.

Ketamine is likely to be excreted in breast milk and can cross the placenta but in amounts that are unlikely to be of clinical relevance. It is indicated for use in caesarean sections and does not seem to have any effects on the neonate. Limited studies in animals have not shown that ketamine causes birth defects; however it crosses the placenta.

Relative contraindications to ketamine relate to specific pharmacological actions and patient diseases. Because ketamine will raise intracranial pressure (ICP) and intra-ocular (IOP) pressure it may not be suitable for patients with raised ICP, raised IOP or open eye injuries. Ketamine must be used with care in coronary artery disease given that it causes a rise in blood pressure and tachycardia with associated increase in myocardial oxygen demand. Psychiatric disease such as schizophrenia or a history of adverse reactions to ketamine also constitutes a relative

contraindication. Ketamine may not be suitable for patients with airway instability or tracheal pathology, a high predisposition to laryngospasm and patients who are not adequately fasted.

There have been reports of supraventricular tachycardia (SVT) and hypertension in patients who are hyperthyroid or taking thyroxine.

Ketamine and barbiturates, being chemically incompatible because of precipitate formation, should not be injected from the same syringe.

Administration

Anaesthesia.

The dosage of most anaesthetic drugs need to be reduced in the elderly, and though evidence is lacking the advice is probably prudent.

The reported anaesthetic dose range is between 1 – 4.5 mg/kg intravenously and 6.5 – 13 mg/kg intramuscularly. Intravenous (i.v) anaesthesia may usually be achieved with 1 – 3 mg/kg by slow i.v injection. Usually in combination with oral premedication with atropine and diazepam or iv induction doses of atropine 10-20 µg/kg and diazepam 0.1 mg/kg.

IV administration has a peak effect within 1 – 5 minutes. Surgery can usually commence after 2 minutes and surgical anaesthesia last 10 – 15 minutes. IV maintenance can be achieved by boluses of 0.5 mg/kg or an infusion of 1 – 4 mg/min in the average adult. The infusion rate needs to be titrated against clinical observation. The higher rates may be required in spontaneously breathing patients. [Add 500 mg of ketamine to a 500 ml bag and run at 1 – 4 ml/min or 0.25 – 1 drop/kg/min. A normal adult intravenous giving set has 15 drops/ml. Stop the infusion 10 -15 minutes prior to the completion of surgery].

Intramuscular ketamine anaesthesia may be achieved with ketamine 5 – 10 mg/kg (atropine 20 µg/kg). Surgery may commence in 5 minutes and anaesthesia lasts approximately 20 minutes. Surgical anaesthesia may be extended by boluses of 3 – 5 mg/kg.

Oral ketamine (500 mg in an adult, 15 mg/kg in paediatrics) has a peak effect after 15 – 30 minutes.

Analgesia.

Severe postoperative pain in an adult may be reliably treated with a loading dose of 0.5 – 1 mg/kg intramuscularly or 0.1 – 0.2 mg/kg i.v plus an infusion at 0.1- 0.2 mg/kg/hr.

The addition of (preservative free) ketamine 0.5 mg/kg to caudal 0.5-ml/kg bupivacaine 0.25% provides significantly longer duration of analgesia without an increase in adverse reactions.

Sedation.

2 -6 mg/kg oral ketamine will produce sedation

EPIDURAL ANAESTHESIA AND ANALGESIA

Epidural anaesthesia is a commonly used regional technique for both surgery and postoperative analgesia. It has some important distinctions from spinal anaesthesia. The site of insertion, site of deposition of local anaesthesia, method of insertion and equipment required is different from spinal anaesthesia, as is the quality of the block and time to onset. If a catheter technique is used, it is very convenient to extend the duration of the block to provide postoperative analgesia.

Both epidural and spinal anaesthesia produce what is known as a neuraxial block. This means that the spinal cord and spinal nerves are anaesthetised. Deposition of local anaesthetic into the spinal space produces blockade of conduction much more rapidly, as the meninges do not need to be traversed in order to reach the site of action. A smaller dose of local anaesthetic is required as it rapidly diffuses through the cerebrospinal fluid to produce sensory and motor blockade.

Epidural anaesthesia was first described in the early part of the twentieth century, but was made much more practical with the introduction of the Tuohy needle and catheter in 1945. There was little interest in the technique of epidural anaesthesia for general surgery until the 1970s and 1980s when continuous epidural blocks were popularised for labour analgesia. It became clear that epidural anaesthesia offered advantages over general anaesthesia with respect to attenuation of the stress response to surgery, decreasing the amount of blood loss, increased patency of vascular grafts and improvements in postoperative pain therapy. (1)

Indications for epidural insertion

The primary indications for epidural insertion are to provide surgical anaesthesia, labour analgesia and postoperative analgesia. Epidural anaesthesia can be used as the sole anaesthetic for procedures on the lower limbs including joint surgery and vascular reconstruction, pelvic and lower abdominal procedures. The advantages over spinal anaesthesia include the ability to extend the duration of the block via introduction of local anaesthetic through the catheter if the procedure is prolonged and the ability to provide postoperative analgesia with dilute concentrations of local anaesthetic and opioids.

Epidural anaesthesia is regularly used in conjunction with general anaesthesia for thoracic and abdominal procedures to provide intra and postoperative analgesia.

Epidural analgesia is indicated for the pain of labour and for operative delivery in obstetrics. It is particularly useful for the patient with a high-risk pregnancy such as twins, breech, pre-eclampsia and some types of cardiac disease. A functioning labour epidural can be extended to provide surgical anaesthesia for caesarean section.

Analgesia for thoracic trauma, particularly rib fractures, can be provided by the use of epidural analgesic infusions. This is advantageous, as it allows the patient to deep breathe and cough with minimal pain, thereby avoiding respiratory complications. (3)

Contraindications to epidural insertion

Epidural anaesthesia is not without side effects and risk. The most feared complications are those that cause permanent neurologic injury or death. There are relatively few contraindications to epidural insertion. Some are absolute and others are relative contraindications. In the patient with relative contraindications, the risk of insertion needs to be carefully weighed against the benefits of epidural anaesthesia.

The absolute contraindications to insertion are patient refusal, the presence of a coagulopathy or full anticoagulation, skin infection at the site of insertion, raised intracranial pressure (accidental dural puncture in these patients may lead to brainstem herniation) and uncorrected hypovolemia, as might occur in massive haemorrhage.

The relative contraindications to epidural insertion are pre-existing neurologic disorders, fixed cardiac output states such as with stenotic valvular lesions and abnormalities of the vertebral column which make insertion difficult.

Technique

It is recommended that an epidural be placed in the middle of the dermatomal segments to be covered for postoperative pain relief.

The technique of identifying the epidural space most commonly involves a loss of resistance to fluid or hanging drop technique. The hanging drop technique is less commonly used and relies on the presence of a negative pressure in the epidural space, which is believed to result from the negative pleural pressure in the thoracic region. This is not as reliable for the insertion of a lumbar epidural.

The loss of resistance technique is performed with either saline or air in a syringe that has low resistance. There are advantages in using saline over air, including a lower risk of dural puncture or missed segments. There is also the potential problem of an air bubble that can expand with the use of nitrous oxide, which can then cause compression of a nerve root. A false loss of resistance can be encountered, particularly if the needle deviates from the midline, when the needle tip can enter the paravertebral or prevertebral space. The distance from the skin to the epidural space is usually 4-6 cm, but this will increase in the obese patient.

Epidural anaesthesia can be performed either as a single injection technique or as a continuous catheter technique. It is more common to use a continuous technique. The most common needle design is the Tuohy needle, which has a directional tip. It comes in different sizes ranging from

20 gauge to 16 gauge through which a soft-tipped, multi-orifice catheter can be passed into the epidural space.

The most common problems encountered in locating the epidural space occur due to failure to identify and stay in the midline or due to bony abnormality. Patient positioning is important, because the epidural space is difficult to enter if there is inadequate flexion of the spine. Flexion allows for the exposure of the ligamentum flavum. Sometimes a paramedian approach is required, particularly in the thoracic region.

Other problems that can occur during insertion include unintentional dural puncture, entry into an epidural vein with either the needle or catheter and paraesthesia. If paraesthesia occurs, the catheter or needle should be repositioned. Dural puncture should be apparent by the free flow of cerebrospinal fluid through the needle or catheter, as should intravascular insertion by the aspiration of blood. A test dose is recommended however, as not all cases of dural puncture or intravascular cannulation will be obvious. In a recent review of test doses for intravascular placement, Leslie and Bell (2) noted that up to 10% of catheters will enter a vessel, most of which will be recognised, but 1% may not be recognised or may migrate into a vessel subsequently.

The most common predisposing factor for epidural vessel cannulation is distension of the epidural veins secondary to an intraabdominal mass. Several methods have been described to detect intravascular placement of an epidural catheter all of which have a substantial false negative rate. Aspiration of the catheter is more successful with the use of multi-orifice catheters, as the lumen of a single hole catheter is easily blocked. It is best performed immediately after insertion, as the eyes of the catheter are likely to block after a period of time in situ. If the epidural catheter is correctly located, a fluid meniscus in the catheter should fall when the end of the catheter is raised to a height of 30cm above the insertion point and clear fluid should be seen when the distal end is lowered by 30cm. This is a useful test, but may not be reliable in the pregnant patient who is in labour.

The epidural test dose containing adrenaline is the best-known pharmacological method for detecting intravascular placement. A positive response to adrenaline is considered to be an increase in heart rate of 20 beats per minute or an increase in systolic blood pressure of 15mmHg within 2 minutes of the test dose. This is not as reliable in pregnancy or labour or patients on beta-blockers. The optimal dose of adrenaline is 15 micrograms.

In the pregnant patient, it has been recommended that epidural fentanyl in a dose of 100 micrograms be used. A potential problem is respiratory depression, which has been reported with the use of epidural fentanyl. If fentanyl is used as the test dose, it should be preceded by a dose of local anaesthetic test dose to exclude intrathecal placement. (2)

Physiologic effects of epidural blockade

The physiologic effects of epidural blockade are similar to those of spinal anaesthesia. Because neuraxial administration of local anaesthetics blocks nerve conduction in spinal segments and nerves, one can expect all modalities of nerve function to be affected. Sympathetic blockade is relatively easy to achieve because the nerve fibres are small. Pain, temperature, sensory and motor fibres will also be blocked. The motor fibres are the largest myelinated fibres and are most resistant to blockade.

Sympathetic blockade causes a loss of vascular tone and vasodilatation in the blocked segments. This will reduce venous return and therefore cardiac output and blood pressure. Typically, sympathetic blockade extends to two segments above the sensory block level. If the cardiac sympathetic fibres are also blocked, then there will be unopposed vagal input to the heart, which will result in bradycardia. Sympathetic nerve supply to the adrenal glands prevents the release of catecholamines, which will exacerbate hypotension. Sympathetic outflow extends from the first thoracic to the second lumbar segments and blockade of this outflow can potentially block the neurohumoral stress response to surgery.

A blockade of sympathetic outflow from the fifth thoracic to the first lumbar segments, which supplies the gastrointestinal tract leads to predominance of the parasympathetic outflow. The result is increased peristalsis and relaxation of the sphincters, which is thought to be the mechanism of earlier return of postoperative gastrointestinal function.

A high thoracic block will affect the nerve supply to the intercostal muscles, which leads to a reliance on diaphragmatic breathing. The ability to cough effectively can be impaired, and the patient may complain of difficulty breathing. If the block is too high and extends to the cervical segments (C4), diaphragmatic function is lost and the patient's ventilation will need to be supported.

Urinary retention is a common problem with epidural anaesthesia. It can be exacerbated by hypotension, which causes a reduction in glomerular filtration rate.

Epidural analgesia and peri operative outcome

Epidural analgesia has been shown to provide superior analgesia when compared with parenteral opioids. A reduction of the peri operative stress response and respiratory complications has also been demonstrated. There is still some controversy over whether epidural analgesia offers a reduction in postoperative morbidity and mortality. In previous meta-analyses of trials, epidural analgesia has been shown to reduce pulmonary complications, improve bowel recovery and reduce the incidence of myocardial infarction. (4)

In aortic surgery, a large randomised trial showed that mortality and major complications were significantly reduced. (5) A recent meta-analysis showed that patients undergoing abdominal aortic surgery who received thoracic epidural analgesia had a shorter duration of tracheal

intubation, reduction in cardiovascular complications, myocardial infarction, acute respiratory failure, gastrointestinal complications and renal insufficiency. (10) When epidurals are used for lower limb vascular surgery, the rate of graft occlusion is reduced. (12)

The MASTER trial included 888 high risk patients who were undergoing major abdominal surgery, showed that the quality of analgesia was better with epidurals and that there was a reduction in respiratory failure but failed to show a significant difference in mortality at 30 days or in overall morbidity. (6)

The studies of outcome after epidural analgesia have been criticized because they have been underpowered (that is, the numbers of patients were too small) to detect a difference in the incidence of rare events such as mortality and serious complications.

Two recent meta-analyses reaffirm the superior analgesic efficacy of epidural anaesthesia and analgesia over patient controlled opioid analgesia at all time periods measured in the first 72 hours postoperatively regardless of epidural agent or type of surgery. (8) One meta-analysis of trials up to June 2003 showed that there is a reduction in 30-day mortality by 21% in those receiving neuraxial blockade. Lower morbidity was also found, including a lower incidence of deep vein thrombosis, pulmonary embolism, peri operative blood loss, postoperative transfusion, pneumonia, respiratory depression and renal failure. (9)

Epidurals attenuate the neurohumoral stress response to surgery and this is thought to be the mechanism for an improvement in outcome. To achieve an effective ablation of the stress response, the epidural block needs to be established with local anaesthetic prior to surgery and extend from the fourth thoracic to the sacral segments. The attenuation of the stress response remains undisputed in the literature.

There is sufficient evidence to show that the recovery of bowel function is faster in those receiving epidural analgesia compared with opioids. It is postulated that an improvement in outcome could be shown if the patients receiving epidural analgesia were mobilized, given early nutrition and early rehabilitation. (4)

Thoracotomy pain is universally regarded as severe and can lead to adverse outcomes such as atelectasis, pneumonia and respiratory failure. Effective analgesia can allow for deep breathing, coughing and chest physiotherapy to help ameliorate these adverse outcomes. Epidural analgesia is efficacious in these situations, but paravertebral block can produce comparable analgesia and improvements in pulmonary function, with potentially fewer complications.

When thoracic epidurals are used to treat the pain of multiple rib fractures, the incidence of pneumonia and need for ventilation is reduced. (12)

There is evidence to support the use of regional anaesthesia over general anaesthesia in managing elderly patients with hip fractures. The benefits include less postoperative delirium,

less deep vein thrombosis, pulmonary embolism and pneumonia. (8) In elective hip and knee surgery, epidurals offer better analgesia and reduced operative blood loss.

In the obstetric patient, epidurals provide superior pain relief. The risk of caesarean section is not increased with the use of epidurals, but second stage of labour may be prolonged and there is an association with a higher instrumental delivery rate. (8)

Epidural management

Epidurals have a wide range of applications. It is most common to insert a catheter through the epidural needle once the epidural space has been identified. Indeed, there is little use for single shot epidural techniques, as this only increases the risk of intravascular or intrathecal injection which can have catastrophic consequences.

Surgical anaesthesia requires a dense sensory block and moderate to dense motor block. A concentrated preparation of local anaesthetic is used. The options include 2% lignocaine 10-20ml with or without adrenaline 1:200,000 or bupivacaine 0.5% which has a slower onset time but longer duration of action.

For labour analgesia, 0.125% to 0.25% bupivacaine can be used to establish a block to T10 (which is required for first stage pain). Typically 5-10ml is required of the 0.25% solution, and more for the dilute solution. A weak concentration of local anaesthetic with or without a lipid soluble opioid such as fentanyl 2 microgram per millilitre is then used to maintain analgesia via an infusion. Alternatively intermittent boluses of local anaesthetic can be used during labour.

In the postoperative patients, it is advantageous to add an opioid (fentanyl 2-4 micrograms per ml) to a mixture of dilute local anaesthetic (bupivacaine 0.125% or 0.0625%) in order to minimize motor blockade but still allow for good analgesia via the action of the opioids on the dorsal horn in the spinal cord. Several studies have shown that the addition of an opioid to the local anaesthetic solution provides superior analgesia and reduces the incidence of side effects.

Opioids alone via the epidural route are of limited benefit and the combination of low concentrations of local anaesthetics and opioids provides better analgesia than either component alone. (12)

Postoperative epidural analgesia requires ongoing management by the anaesthetist from the time of insertion until a few days after removal of the epidural catheter. (7) An acute pain service is ideal. This will consist of a nurse and an anaesthetist, who will visit the patient every twelve hours postoperatively to ensure that the patient is receiving adequate analgesia and that there are no complications developing. The postoperative care of epidural infusions and catheters requires trained nurses that are able to recognize and manage potential problems. They should be in communication with the acute pain service and surgical team.

Monitoring

Patients with an epidural need frequent monitoring. Standard monitoring should include 5 minutely observations for 20 minutes after a bolus or initiation of an epidural infusion. The blood pressure, pulse and respiration are monitored. After 20 minutes has passed, the same observations are recorded every 10 minutes for 40 minutes.

Upon initiation of analgesia, observations are recorded ½ hourly for 2 hours and then hourly for 2 hours.

The respiratory rate, sedation score and pain score are measured hourly until 12 hours and 2 hourly thereafter. Blood pressure, heart rate and temperature are monitored every 4 hours. The level of sensory block and degree of motor block is checked hourly until a level of block is established and once a shift (every 8 hours) if there has been no change in the infusion or further bolus dosing.

The insertion site is inspected once every nursing shift for inflammation and catheter migration.

Nursing staff are given instructions to report to the pain management team. Reportable observations include: persistent severe pain, severe limitation of function, moderate sedation (the patient is unable to remain awake), pruritus that requires treatment, nausea and vomiting that does not respond to prescribed treatment and urinary retention, motor block, high block above the fourth thoracic dermatome, hypotension and bradycardia.

Back pain is considered a medical emergency. Unexpected or new back pain, pain, inflammation or swelling at the insertion site of the epidural, a temperature of over 38.5 degrees Celsius, increase in motor or sensory block and new urinary or faecal incontinence are indicators of spinal cord compression and must be addressed immediately.

Complications of epidural anaesthesia

Complications of epidural anaesthesia are rare but have the potential to cause serious morbidity and mortality.

Local anaesthetic toxicity is a potentially devastating complication if a large bolus of bupivacaine (or ropivacaine) is injected into a blood vessel. It has the potential to cause ventricular arrhythmias that are very difficult to treat. Indeed, one of the reasons 0.75% bupivacaine was taken off the US market was due to cardiac arrests caused by bupivacaine toxicity in obstetric patients.

Epidural catheters should be tested for intravascular placement as outlined previously, and all doses should be fractionated with careful monitoring of the patient between doses. Early symptoms of local anaesthetic toxicity are light-headedness, tinnitus, tingling around the mouth, a metallic taste and a feeling of impending doom. This is followed by confusion, tremor, convulsions, coma and cardiorespiratory arrest. Treatment should be supportive, with

benzodiazepines or other anticonvulsants (thiopentone) and cardiopulmonary resuscitation. If bupivacaine (levo-bupivacaine or ropivacaine) toxicity occurs, it is now recommended that a dose of 20% intralipid be administered (1ml/kg) in addition to other resuscitative measures.

Total spinal anaesthesia is a potential complication of epidural anaesthesia. It occurs when an epidural dose of local anaesthetic (typically 10-20ml) is administered into the intrathecal space. The result is profound hypotension, unconsciousness, dilated pupils and brainstem anaesthesia. Management involves, securing the airway, ventilating the patient and administering fluids and vasopressors.

It is recommended that a test dose of local anaesthetic be administered before the administration of the full dose of epidural local anaesthetic. Three millilitres of 2% lignocaine is recommended as the test dose and at 6 minutes, the anaesthetist tests for a spinal block (S1 block). It should be borne in mind that a full spinal block can take up to 20 minutes to evolve and all subsequent doses of local anaesthetic should be given in increments 3-5 minutes apart.

Respiratory depression is reported to occur at a rate of 1.1 to 15.1%. (12) It can occur due to systemic absorption of opioid from the epidural space, cranial spread of opioid (especially with the hydrophilic opioids such as morphine) or due to a high block or total spinal anaesthesia. The rate of postoperative respiratory depression when an epidural is used for analgesia is similar to the rate caused by systemic opioid administration via patient controlled analgesic systems. All patients should be appropriately monitored and clinicians need to be wary of the administration of systemic opioids or sedatives during epidural opioid administration.

Hypotension occurs due to sympathetic blockade and is worse with higher concentrations of local anaesthetics and with increasing block height. Hypovolemia is often responsible for hypotension with postoperative epidural infusions.

Permanent nerve injury is the most feared complication of epidural anaesthesia. The reported incidences in large case series are in the range of 0.005 to 0.05%. The risk of a severe neurological complication after obstetric epidural analgesia has been recently quoted at 1:25,000. (12)

Direct trauma to the spinal cord is possible if the epidural is inserted above the termination of the spinal cord (typically at the lower border of the first lumbar vertebra in an adult, but potentially down to the third lumbar vertebra) and through the dura and meninges. There have been cases of intrinsic spinal cord lesions possibly caused by direct trauma from the needle or injection of fluid into the spinal cord. The anaesthetist should be proficient in the insertion of lumbar epidural anaesthesia prior to learning thoracic epidural anaesthesia. A careful and controlled technique is required to avoid spinal cord trauma.

Inadvertent epidural injections of solutions and medications intended for intravenous use have occurred with disastrous consequences. The management of epidural infusions requires trained

staff, and the used of specific epidural connectors on giving sets with no injection ports so that it is impossible to cross connect them with intravenous lines. (4)

The risk of epidural abscess or haematoma is rare with estimates varying from 1:1700 to 1:200,000. In a review of 8,210 epidurals inserted for postoperative analgesia over 16 years, Cameron et al (11) found two spinal haematomas and six epidural abscesses, giving a rate of 1:4105 for spinal haematoma and 1:1368 for epidural abscess. One patient required surgical decompression and the others were treated conservatively. There were no long-term neurologic sequelae. The overall incidence of major neuraxial events related to epidural catheter use for postoperative analgesia was about 1:1000.

Early diagnosis was a key factor in allowing for conservative management, particularly of those with epidural abscess, before neurologic signs were apparent. The investigation of choice is magnetic resonance imaging (MRI) in those suspected of having an epidural abscess or haematoma, but computerized tomography with myelography has been used when MRI is not available.

In the patients with abscesses, the indications for scanning were evidence of local infection and fever, back pain and neurologic signs. There was a significant association between duration of catheterisation and infection. For each postoperative day the epidural remained in situ, the risk of site infection increased by 40% per day. The patient who required surgical decompression in this series had an initial MRI on the basis of fever, insertion site infection and back pain which was reported to be normal. This patient then developed neurologic signs two days later that prompted a repeat scan, which showed an abscess from T1-T9, which was surgically decompressed. This case highlights the importance of continued follow up.

Because epidural insertion site infection is a factor in the formation of epidural abscess, a strict aseptic technique should be used during insertion of an epidural catheter, including sterile hand scrub, sterile gown, gloves and mask with skin preparation with an alcohol-based solution (such as chlorhexidine) and draping.

The clinical indications for imaging on suspicion of spinal haematoma in this series were prolonged leg weakness, back pain, leg pain and catheter displacement during full anticoagulation. The introduction of low-molecular-weight heparin (LMWH) for deep venous thrombosis prophylaxis has been identified as a factor in the rise in postoperative epidural haematoma, particularly in elderly females. It is imperative that the insertion and removal of epidural catheters occurs during periods of normal coagulation, and that if a catheter is dislodged during the peak activity of the LMWH, the patient is closely monitored for signs of a haematoma.

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ACUTE PAIN SERVICE

Acute pain management remains suboptimal. One of the reasons is the inappropriate use of analgesic medications. Many drugs will provide analgesia when used in the correct way or in combination with other medications as part of an overall “acute pain regimen”.

Staff who prescribe and deliver analgesia need to be educated in the safe use of medications; and patients need to be educated about analgesia. Many staff and patients fear that the patient will become addicted to opioids if it is used for postoperative analgesia. This is not true and analgesia should not be withheld from a patient in pain.

The provision of safe guidelines for the use of medications as well as frequent assessment of the patient is the cornerstone of acute pain management. Hospital based protocols for the ward management of patients in pain will improve safety and efficacy of analgesia. (2)

In an ideal world, each hospital would have an acute pain management team, which is lead by a physician (the anaesthetist) and is staffed by doctors, nurses and paramedical staff. There would be two pain rounds per day (morning and afternoon), with a once weekly (or more frequent) teaching round for the students and junior staff. In reality, this is not always practical and it is possible to safely administer pain relief with some basic education of ward and medical staff.

More sophisticated methods of pain relief such as epidural and intravenous patient controlled analgesia systems require at least a basic pain management service, with regular review of these patients by the pain specialist (anaesthetist).

History and development of acute pain management services (APS)

Acute pain services were introduced as an attempt to improve postoperative pain management and to improve patient safety. The first services were introduced in 1985. In 1988, Ready introduced the first APs in the United States.

There has been strong support for the concept of acute pain management services. 30-70% of North American and European hospitals have an acute pain service. Hospitals with a strong teaching commitment and university affiliation are more likely to have an APS.

The implementation of APS has been associated with an improvement in patient satisfaction and a reduction of pain scores. There is no data to show a reduction in side effects and morbidity. Disappointingly, nearly one third of patients experience moderate to severe pain in the postoperative pain setting. It is estimated that persistent post-surgical pain will occur in 10-40% of patients. (1)

In the United Kingdom, only 2.5% of teaching hospitals had an acute pain service in 1990, by the end of 1994, 42.7% had one and by 2000, this number had more than doubled to 89.4%. 73% of US hospitals and 77% of New Zealand teaching hospitals have an acute pain service. (3)

Structure of the acute pain service

The original recommendations were that the APS be an anaesthesia-based multidisciplinary team with medical, nursing, pharmacy and physiotherapy personnel. Some services employ a psychologist and have a surgeon as part of the team. In the UK in 2000, pharmacists and physiotherapists were part of the team in 50% and 12 % of services respectively, but nurses and anaesthetists were members of the acute pain team in 91% and 99% of hospitals surveyed. Out of hours epidural services were covered by anaesthetists in 94% of hospitals, nurses in 29% and other medical staff in 1.3%. (3)

A 24-hour multidisciplinary service is the ideal, but was found not to be viable in many European hospitals, where the model is different. There is a specialist nurse and anaesthetist for acute pain in most European hospitals, but some only employ an anaesthetist (or an anaesthetic trainee supervised by a consultant anaesthetist) and others use the anaesthetist on call for acute pain management.

A nurse based physician supervised model has been recommended as a cost effective alternative to the multidisciplinary team when funds are limited. (1)

Physiotherapists can be valuable members of the team. Physiotherapy is useful to help patients deep breathe and cough as well as to provide passive exercise. The physiotherapist looking after the patient needs to be aware of the risks of postural hypotension, motor block and sedation in patients receiving advanced pain management techniques such as patient controlled intravenous opioid analgesia or epidural analgesia.

The surgical team looking after the patient needs to be aware of the method of postoperative pain management. There needs to be close collaboration with surgical and other specialties involved in the patient's care. (5)

Running the service

Patients are visited daily by the whole team on a ward round. The ward nurses looking after the patient will report any problems with management during the round as well as in between rounds. There needs to be one team member available on call to manage acute problems.

The patient's charts are reviewed with particular attention to adequacy of analgesia, incidence of side effects and difficulty with postoperative mobilization or rehabilitation.

The team may suggest changes to medication regimens such as adding a non-steroidal anti-inflammatory drug and regular doses of paracetamol. The appropriateness or otherwise of medications are reviewed, particularly where there is the potential for drug interactions or side effects.

After hours, a member of the APS, usually an anaesthetist or trainee is available for review of the patients as required.

The functions of the acute pain service are primarily to ensure safe and adequate analgesia for the patients in acute pain (mostly post surgical, but some medical and trauma patients). The other important functions of the APS are to educate and train other staff and develop specific policies, protocols and guidelines for treatment and monitoring. In many units, there will be at least one session dedicated to teaching. Often this is provided in the wards in an ad hoc fashion. In Australia, only 40.5% of the acute pain teams were able to run dedicated medical staff sessions one to five times per week. (3)

Teaching by the APS team is one of its essential duties. Anaesthetists, registrars, ward and recovery nurses, residents, surgical registrars and consultants are among those who can receive valuable training from the APS.

Anaesthetic training would ideally include acute pain management at an early stage, as the trainee is often approached to manage patients in acute pain. The nursing staff on the wards needs to be taught to monitor the patients and manage pain. The use of well-designed protocols, patient information sheets and information packages for the nursing and junior medical staff can facilitate good acute pain management.

Monitoring of the patients

There are a number of potential side effects from the use of drugs and techniques to relieve pain including mild and more serious ones. Pruritus and mild sedation are common but not life-threatening whereas nausea, vomiting and lower limb motor blockade may delay recovery and the rare side effects of epidural haematoma, and opioid induced respiratory arrest can be life threatening. (6)

The ward staff records vital signs, sedation scores and pain scores. Where the patient is receiving an opioid infusion or patient controlled intravenous analgesia (PCIA or PCA), the doses of opioid administered are recorded, and any unsuccessful demands on the PCA are noted. The patients with epidural analgesia have motor block and sensory levels recorded.

Pain is now considered to be the “fifth vital sign” after pulse, temperature, respiration and blood pressure. Control of pain is an essential part of patient care. Even the patient who is not receiving advanced techniques of pain management, will benefit from adequate monitoring of his pain.

Aside from the five vital signs, patients with PCA opioids or an epidural will require monitoring of sedation using sedation scoring, which will reflect the level of respiratory depression, motor and sensory block (for epidurals with local anaesthetic), and urine output. Saturation monitoring is desirable if it is available.

Sedation score	
0	No sedation
1	Mild sedation, occasionally drowsy, easy to rouse
1S	Asleep, easy to rouse
2	Moderate sedation, unable to remain awake
3	Difficult to rouse

The aim is for a sedation score of 0 or 1. A sedation score of 2 indicates that sedation is increasing and that it may worsen. Frequent observation will be required and there may need to be a reduction in opioid doses or an increase in interval between doses. A sedation score of 3 indicates that a patient has received too much opioid and that the infusion should be ceased and naloxone administered. The nurses should seek immediate medical attention. (6)

Pain scores are recorded in several ways as previously described. The most useful are the verbal rating scales and visual analogue scales.

When a patient is receiving epidural analgesia, motor blockade should be assessed with the aim of reducing lower limb weakness, identifying inadvertent intrathecal migration of an epidural catheter, detecting spinal cord compression, epidural haematoma and abscess. (6)

The Bromage scale is used:

Bromage Score	Motor Block
0	None, full flexion of hip and knee
1	Partial, just able to move knees and feet
2	Only able to move feet
3	Complete, unable to move feet or knees.

The aim of postoperative analgesia is a Bromage score of 0 to 1. A patient with a motor deficit must not ambulate unaided. A prolonged motor block must be reported to the anaesthetist as it may signify spinal cord compression and will require immediate attention. The infusion of local anaesthetic will need to be stopped to ensure that the motor block recedes. A new dense motor block that develops rapidly may indicate that the epidural catheter has migrated intrathecally or that there is spinal cord compression.

Sensory level is recorded for patients with epidural anaesthesia. The frequency of assessment will vary depending on the unit protocol but is generally once every 2-4 hours if there has been no change to an infusion or more frequently after a bolus or if the patient reports pain or motor block. It is desirable for the block height to be lower than the fourth thoracic dermatome (or nipple level) to avoid a high block. (6)

The patient should be instructed to report back pain and the APS will inquire about back pain and inspect the epidural insertion site once daily. The cause of back pain can be direct nerve damage, epidural abscess or haematoma. Mild back pain may occur due to positioning or an underlying condition. Severe back pain is a medical emergency, particularly if it is accompanied by urinary or faecal incontinence, fever, increase in sensory or motor block or local inflammation or swelling. (6)

Where to look after patients

Patients who are managed with epidurals for postoperative analgesia have most often had complex and major surgery. There may be a medical or surgical indication to look after these patients in a high dependency setting.

It is generally agreed that patients who have had spinal opioids be carefully observed because of the risk of respiratory depression. This needs to be in a high level area such as recovery (or the Post Anaesthesia Care Unit) or a high dependency unit and the duration of observation should be for 12-24 hours. Many hospitals in Europe (60%) nurse these patients on the general surgical wards with frequent observation. (3)

Patients who are receiving intravenous opioids (via infusion or PCA) and those with epidurals may be looked after on the wards provided there is frequent observation for vital signs and sedation. The nursing staff and medical staff need to be trained to look after such patients. If there is no acute pain service or trained staff on the wards, it is safer to look after such patients in a high dependency area or intensive care.

Does an APS improve patient outcome?

The introduction of APS has led to increased use of specialized pain methods and the use of these methods may represent an improvement of patient comfort. Available data indicates that

the implementation of APS is associated with a significant reduction in patients' postoperative pain rating. (1)

It is difficult to come up with a meaningful analysis of the benefits of an acute pain service as the structure of services varies between hospitals and patient groups vary with respect to co-morbidities. Some have reported that the presence of an APS reduces pain scores in patients and side effects of different analgesic techniques. (4)

Staff education and the use of clear local guidelines improve pain assessment, pain relief and prescribing practices, and the presence of an acute pain service will facilitate this.

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LABOUR ANALGESIA

Labour pain is frequently described as the most severe pain that a woman will experience during her lifetime. The pain of first stage of labour is due to cervical dilatation and effacement and uterine contraction. It is visceral pain, which means it is poorly localised and is mediated by the spinal segments from the tenth thoracic to the first lumbar segment. It is referred to the lower abdomen, lower back and anterior part of the thighs. The second stage of labour is somatic, which means that it is better localised. The pain is due to the stretching of the perineum and is mediated by the sacral segments two, three and four.

Pain in labour induces a stress response in the mother as well as significant respiratory and cardiovascular changes. When she is in labour, painful contractions increase minute ventilation by as much as 300%, which leads to hypocarbia and alkalemia. In between contractions, the patient may hypo ventilate, which can result in maternal and foetal hypoxia. Cardiac output is increased by 40% at term due to increased stroke volume and heart rate. Contractions in labour will further increase the cardiac output and there is a peak increase in cardiac output in the immediate post partum period.

Non-pharmacological methods of pain relief require patient preparation and antenatal education. Almost all non-pharmacological methods can facilitate more successful coping with labour pain, which increases emotional satisfaction and enhances the feeling of autonomy. Strategies to try include, remaining upright and mobile in early labour, bathing, breathing techniques and the presence of a support person in labour.

Pharmacologic methods of pain relief include the use of nitrous oxide, parenteral opioids and regional anaesthesia.

Nitrous oxide can be effective for 50% of women in labour. For maximal results, breathing of nitrous oxide (mixed with oxygen) should start 45 seconds before the contraction. This is difficult to time effectively. The low blood-gas solubility of nitrous oxide allows for a rapid onset and offset of action. It is important that the woman self-administers the gas to maintain safety. The side effects include dizziness, excessive sedation and loss of awareness if there is prolonged self-administration. The most frequently used dose of nitrous oxide is 50% with a range of 0 to 70% for labour.

Pethidine (Meperidine) is the most frequently use parenteral opioid in labour in Australia. The dose is one to 1.5 mg/kg every four hours. The dose should be timed so that ideally, there is greater than four hours between the dose and delivery of the baby so as to avoid neonatal respiratory depression. If neonatal depression occurs, naloxone 0.1mg/kg should be administered. Pethidine is effective in approximately 30 to 50% of women in labour. Another 30% of women will find the same dose ineffective. A dose of pethidine will take 30-45 minutes to have an effect. The common maternal side effects include, drowsiness, dizziness, disorientation and nausea. In a double blinded randomised, placebo controlled trial of

intramuscular pethidine for first stage of labour pain in 50 women, Tsu et al showed a greater reduction of the VAS pain score in the pethidine group (-17mm) than in the intramuscular saline group at 30 minutes ($p=0.009$). The time to first request for subsequent analgesia was also greater in the pethidine group (232 minutes compared to 75 minutes). The authors concluded that systemic pethidine was more effective at relieving labour pain than placebo but that its analgesic effect was modest.

Regional analgesia for labour encompasses pudendal nerve block, para-cervical block, spinal, and epidural and combined spinal and epidural block. Regional anaesthesia is the most effective form of analgesia for labour.

Epidural analgesia

Epidurals are the most effective and consistently reliable way of relieving childbirth pain. An epidural will provide conduction anaesthesia of the spinal nerves and the spinal cord. (Neuraxial block) The aim is to provide analgesia by blocking the A-delta and C fibres of the spinal segments involved in the transmission of labour pain. However, because spinal nerves transmit motor, autonomic and other sensory impulses, they will be blocked too if a large enough dose of local anaesthetic is applied to them.

The conduct of epidural analgesia for labour requires the operator to explain the procedure and gain consent for the procedure. A skilled assistant should be in attendance during the insertion and after the block has been established. The assistant should help to position the patient and perform 5 minutely observations of maternal blood pressure and heart rate, height of the block and foetal heart rate for 20 minutes after a top up or the establishment of the epidural block. Where an epidural infusion is in use in labour and the block is stable, observations can be performed 1/2 hourly with continuous cardiography monitoring.

Intravenous access is established before the conduct of the epidural. A fluid bolus of at least 500ml of balanced salt solution is given. Resuscitation drugs and equipment should be immediately available and checked.

Drugs used in the epidural space:

The aim is to provide analgesia with little motor blockade. Pain free mobility requires the blockade of C and A-delta fibres whilst preserving A-alpha fibres. This is best achieved by using low concentrations of local anaesthetic agents and opioids. Modern epidurals will consist of high-volume low-concentration doses of anaesthetic. Apart from the differential blockade, this will also reduce the incidence of hypotension.

Traditionally bupivacaine was the local anaesthetic of choice for epidural analgesia. Its advantages are its long duration of action and potency. The disadvantages of bupivacaine are its relatively slow onset and its cardiac toxicity with inadvertent intravenous injection due to its rapid binding to and slow dissociation from cardiac sodium channels.

Newer single enantiomer drugs have been developed with the promise of lower cardiac toxicity. They are ropivacaine and levo-bupivacaine. Ropivacaine has been shown to be less potent and its therapeutic index, which is the margin between its effective dose and toxic dose, is smaller than for bupivacaine, so its safety advantage may not be as great as originally thought.

Centrally administered opioids act on the opioid receptors in the substantia gelatinosa of the dorsal horn of the spinal cord. They are more effective at C-fibre blockade than A-delta fibre blockade and are more effective for first stage pain relief than for delivery. They will not cause motor block or numbness or hypotension. The agents most commonly used are fentanyl or sufentanil, because they are very lipid soluble and penetrate the dura. This allows for a more rapid onset and shorter duration of action than morphine, which may take two hours to cross the dura and when given intrathecally, its effects may last 24 hours. The most common side effects of centrally administered opioids are pruritus, nausea and vomiting, urinary retention and respiratory depression. When given intrathecally, opioids may cause uterine hyperactivity and a self-limiting foetal bradycardia. This is thought to be due to a decrease in maternal catecholamines. (3)

Techniques:

After positioning the patient in the lateral or sitting position, the skin is prepared with antiseptic solution. The correct spinal level for epidural insertion is identified (usually L3-4 or L4-5) and local anaesthetic is infiltrated into the skin and subcutaneous tissues. An 18 or 16G Tuohy needle is inserted with the bevel directed cephalad. A loss of resistance technique is used to identify the epidural space and a 20g catheter is fed so that 3-4cm remains in the epidural space. The catheter can then be tested with a 3ml dose of local anaesthetic (generally 2% lignocaine) to ensure that it is correctly positioned. The total dose of local anaesthetic is then inserted in increments until the correct block height is attained. (T10 upper level for 1st stage of labour) This may take up to 20 minutes with longer-acting local anaesthetics such as bupivacaine or ropivacaine. An infusion of weak local anaesthetic with opioid is commenced to provide ongoing analgesia during the labour. Further top ups via the catheter may be given for breakthrough pain.

Loss of resistance to saline or air

The epidural space is best located in the lumbar area with a loss of resistance to fluid technique. Air has been used for many years but may present some problems. There is the potential for a large amount of air to be introduced into either the epidural or subarachnoid space, or indeed into an epidural blood vessel. As a result, the patient may end up with a patchy block, headache or neck pain, pneumocephalus or an air embolus. There is a smaller chance of dural puncture if saline rather than air is used for loss of resistance.

How far to thread the catheter

Most modern catheters are multi-orifice catheters and should be threaded into the epidural space far enough so that the catheter will not get dislodged during labour, yet not so far that it emerges from an intervertebral foramen, which may cause a unilateral block. The optimal depth is 4 cm.

Test dosing

The catheter should be tested to ensure that it is not in the intrathecal space or intravascular. The recommended test dose is lignocaine 45mg, which will produce a spinal block if the catheter is intrathecal. It is important to allow enough time for the dose to be effective. Immediate testing (within one minute) will not produce a motor block. A 45mg dose of intrathecal lignocaine will produce a motor block at S1 after 6 minutes. To test for intravenous placement in labour, the options include the use of epinephrine or fentanyl. The heart rate response in labour is unpredictable so fentanyl is preferred. An intravenous bolus will produce sedation within 5 minutes.

Options for the maintenance of the block:

Epidural bolus administration

All epidural regimens commence with a bolus dose to achieve analgesia. Ongoing analgesia can be managed with intermittent boluses by the anaesthetist or midwife; typically 0.5% or 0.25% bupivacaine is used. The problems associated with boluses include pain in between boluses, moderate to severe motor block and hypotension after bolus dosing.

Epidural infusions

It has become routine to use continuous infusions of dilute local anaesthetic plus lipid soluble opioids. The use of infusions (over intermittent boluses) has the advantage of better pain relief with less motor block. Common infusion solutions are: bupivacaine 0.125% with fentanyl 2mcg/ml, ropivacaine 0.2% with fentanyl 2mcg/ml or more recently, bupivacaine 0.0625% with fentanyl 2 mcg/ml at a rate of 10-12ml/hr.

Patient Controlled Epidural Analgesia

PCEA may offer the advantages of greater patient autonomy and satisfaction, lower overall doses of local anaesthetic and reduced need for physician or midwife epidural top ups. Dilute solutions of bupivacaine (0.1%) or ropivacaine (0.1% to 0.2%) or levobupivacaine (0.1%) are used with or without opioid. The usual dose is 3-5 ml with a lockout of 10-20 minutes. A background infusion may be beneficial when labour is induced, as it is more likely to be a prolonged and more painful labour.

Side effects:

The side effects of the epidural depend largely on the dose of local anaesthetic used. Any neuraxial block will block nerve conduction in motor, sensory and sympathetic fibres to some extent.

A loss of sensation is inevitable and some degree of motor block can be expected. This generally means the patient cannot ambulate, will require a urinary catheter and may require a lift-out forceps delivery.

The autonomic blockade will produce vasodilatation and may create hypotension. If the block extends to the T1-4 fibres, then bradycardia may also occur.

Shivering is very common. The cause is not clear, but there may be a degree of heat loss (although the women often do not complain of feeling cold) and it is more common with larger doses of local anaesthetic.

Side effects will also occur due to drug administration. For example, pruritus, nausea, urinary retention and respiratory depression may occur with the administration of epidural opioids.

Complications:

The complications of epidural analgesia range from the more common but mild to the rare and catastrophic.

Incomplete epidural block

The incidence of an incomplete block is about 10%, and of failed block is 1%. In the presence of a unilateral block, it may be helpful to partially withdraw the catheter and give a top up with the patient positioned with the painful side lowermost. If there is sacral pain, missed segments or back pain, fentanyl 50 to 100mcg via the catheter may be tried.

Total spinal anaesthesia 1:10,000

If a large dose of local anaesthetic has been administered into the subarachnoid space, then this will cause a high spinal block and will lead to refractory hypotension and a loss of consciousness requiring intubation and ventilation until the block wears off. Total spinal anaesthesia may be heralded by sudden hypotension, rapid profound analgesia and motor block and nasal stuffiness. The patient may develop apnoea, unconsciousness and dilated pupils. Management will include ensuring oxygenation and protecting the airway with a cuffed endotracheal tube if the patient loses consciousness, treatment of hypotension and bradycardia, monitoring of the foetus that may require urgent delivery.

Bloody tap

The incidence of blood in the needle is 0.3-1.7% and 3-9% in the catheter. The incidence of intravascular injection is 1:10,000. If a bloody tap occurs, the needle or catheter should be removed and the epidural inserted one intervertebral space more cephalad. Further doses should be given by the anaesthetist in increments of no greater than 3mls of 0.25% bupivacaine to avoid intravascular injection.

Local anaesthetic toxicity is another potentially severe complication. If injected intravenously, the large dose used to establish an epidural block may cause fitting and loss of consciousness. If a large dose of bupivacaine is injected intravenously into an epidural vein, cardiac toxicity will occur.

Dural tap

Accidental dural puncture is usually recognized when it occurs by the free flow of CSF through the needle or catheter. The incidence is roughly 1 in 300 epidural insertions. When it is recognized, there are usually no serious complications. However, about 60% of the women will develop a post dural puncture headache, some of which will require an epidural blood patch. If an intrathecal catheter is inserted and recognized as such, the anaesthetist may consider using sub-arachnoid analgesia. If this decision is made, all top ups should be given by the anaesthetist

and the catheter removed after delivery. The patient should be allowed to mobilize and followed up for three days for the development of a post dural puncture headache. Simple analgesia should be given for a headache and an epidural blood patch may be offered if the headache is severe or does not resolve.

Convulsions

Convulsions may be related to local anaesthetic toxicity, pregnancy related (eclampsia) or be due to co-existing disease (such as epilepsy, hypoglycaemia or cerebral pathology). The main threat to mother and baby is from hypoxia. The airway should be protected and the fit terminated with an appropriate anticonvulsant dependant on the cause.

Severe hypotension 1:1000

Occurs due to the combination of autonomic blockade with subsequent vasodilatation with or without bradycardia if thoracic segments are blocked and hypovolaemia and aortocaval compression.

Neural injury Epidural infection leading to abscess or epidural haematomata will cause compression of the spinal cord leading to paraplegia if the mass is not compressed within 6 hours. This is rare.

The incidence of permanent paralysis is rare and is of the order of 1: 80,000.

Neural injury due to parturition (obstetric palsy - often a foot drop or obturator nerve palsy from a difficult forceps delivery) occurs in one in 3000 deliveries. These are temporary and resolve within 6 weeks. Similarly, nerve root injury from needling of the epidural space may occur and are mostly temporary.

Back pain

Backache occurs in up to 50% of women who have had a baby regardless of whether or not they have received an epidural. Most of this is related to changes in posture, relaxation of the pelvic joints and childbirth itself. Bruising and tenderness over the epidural needle insertion site is common. This is generally not a problem.

Does epidural analgesia slow the progress of labour?

Epidural analgesia in labour has been blamed for slow progress in labour and the increase in likelihood of caesarean section. It has been suggested that motor block in second stage increases the need for instrumental delivery. The problem is that women with abnormal presentations and long labours experience greater pain and become fatigued, necessitating regional analgesia so there is an association with instrumental delivery, but this does not necessarily imply causation. In a Swedish study, which looked at that country's medical birth register during a two-year period, it was found that there was no clear association between epidural use and caesarean section or instrumental delivery. Therefore, there is no indication that the use of epidurals should be restricted in order to improve instrumental delivery rates.

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CHRONIC PAIN PHARMACOLOGY

Chronic non-cancer pain disorders are a broad group with complex and poorly understood aetiologies. This diverse group of disorders should require a diverse range of medications. There is, however, only a limited range of medications available.

Recognition of chronic non-cancer pain as a health issue is a recent phenomenon. Research and development of medications specifically targeted at these disorders is still in its early stages. Medications currently used were designed either for acute pain or for completely different disorders and serendipitously discovered to help pain.

There are two main categories of medications used for chronic non-cancer pain – analgesic agents and antineuropathic agents. Table 1 gives a comprehensive list of medications for chronic non-cancer pain. Many of these drugs have low effectiveness or limitations to their use. Opioids, gabapentin and tricyclic antidepressants are the most frequently used.

Opioids

The use of opioids for chronic non-cancer pain has been controversial in the past. Their effectiveness is now well established for nociceptive and neuropathic pain conditions. The pharmacology of these drugs will be discussed in another lecture.

The number needed to treat (NNT) for opioids in chronic non-cancer pain is 2.2. This includes neuropathic and nociceptive pain conditions. The number needed to harm (NNH) is 8.4.

There is no evidence that one opioid is better than another for treating chronic pain. The most commonly used agents are morphine and oxycodone. Methadone has nonopioid effects including NMDA antagonism. These effects may give it an additional analgesic effect over other opioids.

The dose of opioids used should start low and be titrated to effect. Patients should be maintained on the lowest effective dose to minimise side effects. Slow release oral or transdermal preparations are the most appropriate. The use of rapid release preparations should be minimised and the parenteral route is inappropriate for long-term therapy. There is no theoretical ceiling dose at which opioids become ineffective. However, care should be taken to ensure that opioids are effective in an individual patient before prescribing large doses.

Most side effects of acute opioid use are only a problem when initially starting opioids or changing the dose. The concerns of long-term opioid use include addiction, constipation, mental clouding, tolerance, opioid hyperalgesia and neuroendocrine effects. Opioid addiction is much more rare than previously thought when opioids are used for analgesia. The incidence is only between 0.05 -0.5% and fear of causing addiction is not a justified reason for withholding these drugs from the general population.

Analgesic	Dose	NNT	NNH	Comment
Paracetamol	4g/day	4-16		Suitable for chronic nociceptive pain eg osteoarthritis, very limited role in other pain conditions
NSAIDS				
Tramadol	200 - 400mg/day	3.4 3.8	8.3	Effective in nociceptive and neuropathic pain, generally used second line after opioids
Opioids	Theoretically no upper dose limit	2.2	8.4	Effective in chronic nociceptive and neuropathic pain, but less effective than in acute and cancer pain
Morphine				
Oxycodone				
Methadone				
Ketamine				Effective in nociceptive and neuropathic pain, limited to systemic administration
Antineuropathics				
Antidepressants				
Tricyclics	10-50mg/day	2.2	2.8	First line for neuropathic pain, also useful in other chronic pain conditions
Amitriptyline				
Nortriptyline				
Desipramine				
SNRIs				Less side effects than TCA's and used in antidepressant dose but much more expensive
Duloxetine				
Antiepileptics	300-3200mg/day	3.5	2.6	First line treatment for neuropathic pain, possible synergistic effect with TCA's. Less side effects than older antiepileptics
Gabapentin				
Pregabalin	75-600mg/day			
Carbamazepine	200-1200mg/day	3	3.4	Effective but less well tolerated
Phenytoin	300-600mg/day	2.1	3.2	
Valproate				Limited evidence of effectiveness
Lamotrigine				Ineffective
Antiarrhythmics	150-600mg/day			Limited evidence of effectiveness
Mexilitine				
Lignocaine	0.1-1.5 mg/kg/h			Effective in neuropathic pain, limited to systemic administration

Table 1: Chronic non-cancer pain medications

Patients do not become tolerant to the constipating effects of opioids and vigilance combined with prophylactic treatment is required. Mental clouding and drowsiness vary considerably between patients, as some will tolerate very high doses and others will not.

Tolerance develops to all opioids, however, it is not a continuous process as previously thought. Patients will continue to become more tolerant for several weeks after starting treatment and then reach a stable level allowing long term dose stability.

Opioids have only recently been accepted as appropriate treatment for chronic non-cancer pain and new problems associated with long-term use are still being discovered. Opioid induced hyperalgesia and neuroendocrine changes are among them. Opioid induced hyperalgesia is where high dose morphine therapy for two to three years may produce a state of increased pain, which become worse with increasing doses of morphine. It is likely that this also occurs with other opioids. The doses and duration of opioid therapy required and how to predict who will be affected is not known. Analgesia can be re-established by rotating treatment to another opioid.

Opioids cause panhypopituitarism, mainly affecting testosterone. This causes loss of libido in men and women in the short term. It is not yet known if this leads to long-term problems.

Tramadol

Tramadol is a unique analgesic drug for moderate pain. The pharmacology and its use in acute pain is discussed elsewhere.

It has a NNT of 3.4 for all types of pain and an NNT of 3.8 for neuropathic pain. The unique actions of tramadol make it useful for pain resistant to other treatments. However, it is poorly tolerated with a NNH for withdrawal from trials of 8.3.

The doses used for chronic pain is 200 – 400mg/day.

Tricyclic Antidepressants (TCA)

Tricyclic antidepressants are a large group of chemically similar drugs. They have complex CNS actions. Serotonin and noradrenaline reuptake inhibition accounts for most of their antidepressant effect. This is also the likely mechanism of analgesic action and increased level of noradrenaline in the spinal cord is the key effect. They also have other actions and many of their adverse effects are due to anticholinergic actions. In addition to their direct analgesic effect, they may help in chronic pain by improving sleep, decreasing opioid tolerance and enhancing mood. Amitriptyline has the greatest evidence of analgesic effectiveness. However, nortriptyline and desipramine have less anticholinergic side effects and have a similar effectiveness in pain management.

The antidepressant dose of amitriptyline and nortriptyline is 75 – 150mg. They are beneficial in pain disorders at much lower doses; in the range of 10-50mg. Therefore, these drugs are generally better tolerated when used for pain than in depression, though concurrent depression is common with chronic pain and often requires a second, better-tolerated agent.

TCA's are the first line agents for treatment of neuropathic pain conditions such as diabetic peripheral neuropathy (DPN) or post herpetic neuralgia (PHN). They have the smallest NNT of any antineuropathic agent. The NNT is 2.4 for DPN and 2.8 for PHN. The overall NNT for neuropathic pain is 3.6.

They have also been shown to be beneficial in other chronic pain disorders including fibromyalgia, headache and back pain. The NNT for these conditions is between three and five. They have not been shown to be beneficial in acute pain, but are useful for selected patients, particularly those with an acute neuropathy.

Minor side effects are common with tricyclic antidepressants. They have a number needed to harm (NNH) for minor side effects of 6.0. However, the NNH of severe side effects requiring patients to withdraw from drug trials is 28. The common side effects include blurred vision, postural hypotension, urinary retention, dry mouth and drowsiness. Due to the anticholinergic effects, these drugs should be used with caution in patients with a history of cardiac arrhythmias, unstable cardiac disease, seizures and glaucoma. There is also the potential for a serotonin syndrome to develop when TCA's are taken with other serotonin reuptake inhibitors eg other antidepressants and tramadol.

Serotonin and Noradrenaline Reuptake Inhibitor (SNRI)

The new SNRI duloxetine is as effective as TCA's in the treatment of diabetic peripheral neuropathy and fibromyalgia. However, this agent is not widely available yet.

Venlafaxine does not seem to be as effective as duloxetine for pain probably due to a lesser effect on noradrenaline reuptake. It is still a useful second line agent with a NNT of 3.1 for neuropathic pain.

The mechanism of action is similar to TCA's and therefore unlikely to be beneficial in combination with these agents.

The dosage of these drugs for pain is the same as the antidepressant dose; venlafaxine is 37-150 mg/day and duloxetine is 40-60 mg/day.

The NNH for venlafaxine is 9.6 for minor adverse effects, but a significant NNH of 16 for severe side effects requiring patients to withdraw from drug trials. Common side effects are nausea, headache, dry mouth and dizziness.

Antiepileptics

Gabapentin:

Gabapentin is an antiepileptic designed as an agonist at gamma amino butyric acid (GABA) receptors. It actually has no effect at these receptors and the mechanism of action is still not completely understood. The mechanism of analgesic action is modulation of presynaptic N-type

voltage gated calcium channels in the spinal cord. This leads to decreased release of excitatory neurotransmitters.

Gabapentin has a NNT of 3.2 for post herpetic neuralgia and 3.8 for DPN. This is similar to the figures quoted for other antiepileptic agents. However, there is high quality evidence for the effectiveness of gabapentin compared with the evidence for other antiepileptics which is based largely on smaller, poorly designed trials. Therefore, gabapentin is considered by many to be the first line antiepileptic for neuropathic pain.

Gabapentin or the similar drug pregabalin, have been used in several other pain conditions including myofascial pain, fibromyalgia and chronic headache and show promising results. They are used clinically as second line agents in these conditions pending further research.

Gabapentin has also been shown to have an opioid sparing effect in postoperative pain in several trials. These trials used high doses of gabapentin and had significant rates of sedation. The clinical relevance and practical use of gabapentin in this setting has not yet been established.

The gabapentin dose is 300 – 3200 mg/day and the pregabalin dose is 150 – 600 mg/day.

The NNH for minor side effects is 3.7 and there is no difference between drug and placebo in NNH causing major harm. Common side effects are fatigue, somnolence, dizziness, weight gain and ataxia.

Pregabalin has the same mechanism of action as gabapentin and it seems to have a similar effect profile. Pregabalin has some pharmacokinetic advantages including consistent bioavailability and quicker onset. However, it is currently the more expensive of the two.

Carbamazepine:

The mechanisms of action of carbamazepine are complex and only partially known. It is effective as an antiepileptic, a mood stabiliser in mania and as an analgesic for neuropathic pain. Important actions in pain management are probably voltage gated sodium channel blockade and inhibition of glutamate release from excitatory neurons. Inhibition of sodium channels stabilises hyperexcitable membranes thereby reducing spontaneous and repetitive firing. Other actions may include decreased breakdown of catecholamines, anticholinergic effects and antidiuretic activity.

Carbamazepine is an effective treatment for neuropathic pain based on the limited data available. It has a NNT of 1.8 for trigeminal neuralgia and 3.3 for DPN. There is no evidence of benefit in acute and non-neuropathic pain states.

The carbamazepine dose is 200 – 1200 mg/day.

It has a NNH of 3.7 for minor side effects and the NNH for major harm is not significantly different from placebo. However, these figures are based on limited data and, anecdotally, carbamazepine appears to be less well tolerated and more dangerous than gabapentin. Typical

side effects include dizziness, ataxia, fatigue, headache, diplopia, nausea and vomiting, allergic dermatitis, leucopenia, thrombocytopenia and anti-diuretic hormone effects including oedema and hyponatraemia. Rare but severe side effects include aplastic anaemia, cardiac arrhythmias and a delayed multiorgan hypersensitivity disorder.

Carbamazepine is metabolised in the liver by the cytochrome P450 3A4 system. It is also a potent inducer of this and other liver enzyme systems. This leads to interactions with a wide range of drugs metabolised by these systems including methadone, paracetamol, tramadol, NSAIDs, TCAs, hormonal contraceptives and warfarin.

Phenytoin:

Phenytoin is a membrane stabiliser acting by blockade of voltage gated sodium channels. It has antiepileptic and antiarrhythmic actions.

It has a NNT 2.1 for diabetic peripheral neuropathy based on a single randomised control trial and weak evidence of benefit in other neuropathic pain conditions.

The dose of phenytoin is 300-600 mg/day.

It has a NNH of 3.2 for minor side effects and the NNH for major harm is not significantly different from placebo. Common side effects include nystagmus, fatigue and ataxia.

Others:

Sodium valproate and lamotrigine have been used for neuropathic pain. A recent review concluded that lamotrigine is unlikely to be beneficial in pain management. There is only weak evidence that valproate is effective in neuropathic pain.

Class 1B Antiarrhythmics

Antiarrhythmics from Vaughan Williams class 1B are membrane stabilisers of both cardiac and neuronal cells. Medications from this class used for pain include phenytoin, mexilitine and lignocaine.

Mexilitine is a sodium channel blocker with some evidence of effectiveness in neuropathic pain. The dose is 150-600 mg/day. Gastrointestinal side effects especially dyspepsia, are very common and it is often poorly tolerated.

Felodipine, a class 1C sodium channel blocker, has also been used for neuropathic pain but the evidence of effect is only anecdotal.

Parenteral Medications

Lignocaine:

Lignocaine is a local anaesthetic and a class 1B antiarrhythmic. The mechanism of action when used systemically for pain is complex.

Systemic lignocaine has been used for decades in the treatment of pain. It has been shown to be an effective analgesic for neuropathic pain. The use of lignocaine is limited by the need for parenteral administration. It is used for acute neuropathies such as from trauma or Guillian Barre syndrome and to provide temporary analgesia while altering a patient's oral regimen in chronic neuralgias.

Lignocaine is also given as a short infusion or bolus to provide prolonged relief to patients with chronic neuropathic pain for several weeks. However, there is little evidence of benefit from this widely used technique.

The lignocaine dosage is 0.1 – 1.5 mg/kg/hr for acute pain or a large bolus may be given over 2-3 hours for chronic pain.

Ketamine:

Ketamine is a NMDA receptor antagonist. It is used as an anaesthetic and analgesic agent. It is effective in both nociceptive and neuropathic pain.

Ketamine is used in acute pain to reduce opioid use and improve pain relief in patients with severe pain that is unrelieved by morphine.

The requirement for the parenteral route of administration limits ketamine's use for chronic pain. There is evidence that a five-day ketamine infusion can improve pain control for a period of many weeks in cancer pain that is poorly controlled with high dose opioids. The proposed mechanisms are a decrease in opioid tolerance leading to a better response to concurrent opioids or reversal of central sensitisation.

Ketamine can also be used to provide temporary analgesia while improving a patient's oral regimen, especially during opioid rotation.

The ketamine dose is 0.05 – 0.25 mg/kg/hr as a continuous infusion.

Summary

Complex biological and psychosocial influences contribute to chronic non-cancer pain. Medications are therefore often of only limited benefit. Broad management strategies that combine medication with physical and psychological rehabilitation provide more favourable outcomes.

Somatic pain conditions can usually be treated by following the WHO analgesic ladder. However, analgesics are often ineffective and the use of adjuncts to target central sensitisation can be helpful.

Neuropathic pain classically does not respond to simple analgesics. A better stepwise approach would be to start with a TCA, followed by an anti-epileptic and then an opioid.

With all pharmacotherapy for chronic pain it is important to balance the potential risks of long term therapy with its benefits, and to stop medications that prove ineffective. It is essential to include a thorough biopsychosocial assessment and address the patient's physical and psychological well being as part of the management plan.

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CHRONIC PAIN PHYSIOLOGY

Chronic pain is defined as pain that has persisted beyond normal tissue healing time (IASP). This definition does not specify the duration but it is frequently stated as three or six months. Chronic pain disorders are caused by a combination of pathophysiological changes, and behavioural and psychosocial factors. Pathophysiological changes producing pain without ongoing tissue damage include peripheral nerve injury, and changes to spinal cord and brain function that maintain and amplify pain. Psychosocial changes are complex but share common themes, which are a belief that pain is harmful or potentially severely disabling; fear-avoidance behaviour (avoiding a movement or activity due to misplaced anticipation of pain) and reduced activity levels; tendency to low mood and withdrawal from social interaction; and an expectation that passive treatments, rather than active participation, will help.

Nociceptive pain and peripheral sensitization produce persistent pain and are caused by conditions with ongoing tissue damage and inflammation, such as malignancy and rheumatological conditions. These mechanisms are covered in another lecture.

Other mechanisms of chronic pain include peripheral neuropathic pain, central neuropathic pain, and central sensitization. Tissue damage involves some damage to peripheral nerves and central sensitization occurs to an extent with all injuries. The current opinion is that peripheral neuropathic pain and central sensitization are involved in most chronic pain states to varying degrees. These processes will normally resolve as an injury heals and the reasons they persist in some people in the absence of ongoing tissue damage is a topic of speculation.

Peripheral Neuropathic Pain

Damage to peripheral nerve fibres results from trauma, infection, toxins or metabolic injury. This can lead to pain through dysfunction of damaged C and A δ fibres and altered function of intact sensory fibres.

Injured neurons become hyperexcitable and this state is characterized by increased spontaneous electrical activity and decreased action potential

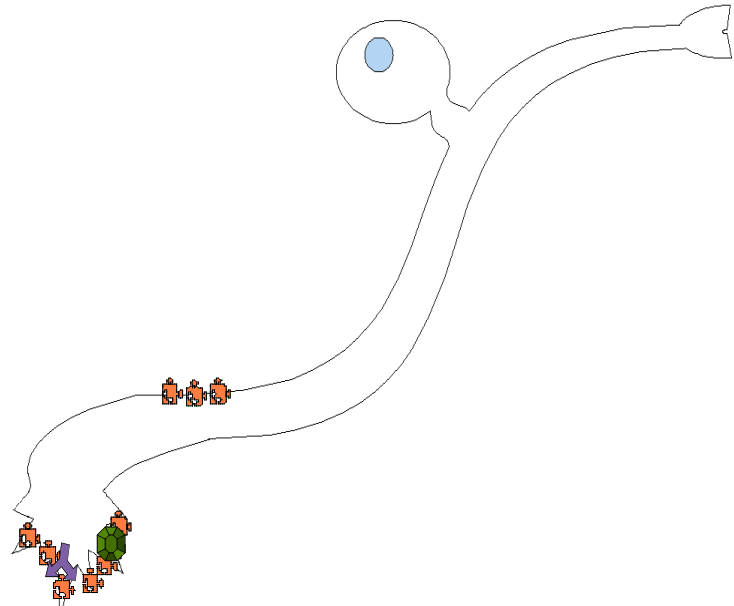




Fig 1: **Damaged peripheral C fibre**

 Na⁺ channels cluster at the site of damage and at other points along the axon

 Other membrane receptors and channels also become crowded

(AP) thresholds. This occurs at the injured terminal and at previously inactive sites along the axon. As part of the regeneration process, the injured nerve sprouts multiple new terminals, which form hyperexcitable neuromas. Neuromas have up to 50% more sodium channels than normal terminals. Sodium channels are also found clustered along injured nerve axons, particularly at sites of demyelination (fig 1). The increased number of sodium channels produces greater spontaneous activity. Sodium channels and other cell proteins are produced in the cell body, which is located in the dorsal root ganglion (DRG), and then transported along the axon to their destination. Production of these proteins continues despite injury to the nerve, leading to accumulation at the site of injury. It is likely that other transmembrane channels and receptors also accumulate. This leads to increased ectopic electrical activity and decreased thresholds to mechanical, thermal and chemical irritants.

Nerve injury leads to demyelination and disruption of Schwann cells. Subsequent close membrane apposition and mediator release from damaged cells allows interaction between neurons. This process enables impulses from one fibre to generate impulses in neighbouring fibres (fig 2). This is known as cross-talk or ephaptic transmission. Cross-talk can occur between sensory fibres of the same or different modalities. Impulses from intact sensory neurons can produce action potentials in injured pain neurons.

Inflammatory mediators, released by glial cells and other immune cells within the nerve, may also alter transmission in neurons.

In summary, the symptoms of peripheral neuropathic pain are produced by a combination of hyperexcitability, ectopic activity and ephaptic transmission in injured nerves. These symptoms include spontaneous paroxysmal pain, hyperalgesia (increased pain from painful stimulus), dysaesthesia (unpleasant, non painful sensations) and allodynia (pain from non painful stimulus).

Central Sensitization

Central sensitization consists of an amplification of pain signals during transmission and processing in the central nervous system. It results in primary and secondary hyperalgesia and allodynia. Primary hyperalgesia is hyperalgesia in the area of tissue damage. Secondary hyperalgesia is hyperalgesia in a region outside the area of tissue damage. Clinically, people will experience severe pain from a relatively small persistent nociceptive input.

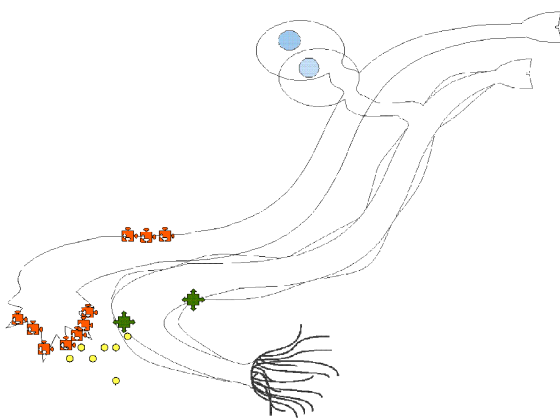


Fig 2: **Neuronal Ephaptic Cross-talk**
Functional interactions develop between neighbouring axons

Primary hyperalgesia is hyperalgesia in the area of tissue damage. Secondary hyperalgesia is hyperalgesia in a region outside the area of tissue damage. Clinically, people will experience severe pain from a relatively small persistent nociceptive input.

Central sensitization is due to neuronal plasticity; the ability of neurons to modify their function by synapsing with different cells, altering the strength of current synapses and altering their response to inputs. These changes occur in the DRG, dorsal horn and supraspinal structures, in response to

repetitive firing in pain fibres and the release of inflammatory mediators.

DRG

The DRG contains the cell bodies of peripheral sensory neurons. Peripheral nerve function is affected by alterations in the DRG. These include phenotypic switching, ephaptic transmission and variation in neurotransmitters release.

Phenotypic switching is a shift in the genetic expression within neurons, which causes functional changes. A β fibres can begin functioning as pain neurons resulting in hyperalgesia and allodynia.

Ephaptic transmission consists of impulses in one neuron generating impulses in a neighbouring neuron. The neuronal anatomical arrangement in the DRG is different to that in the peripheral nerve. This allows ephaptic transmission between neurons supplying areas remote to each other, producing in a wider area of referred pain.

Peripheral neuronal neurotransmitters are produced in the cell bodies of the DRG. An increase in the production of excitatory neurotransmitters and a decrease in the production of inhibitory neurotransmitters produces corresponding changes in their release in the dorsal horn.

Alterations in the DRG are probably due to a combination of peripheral inflammatory mediators; inflammatory mediators released in the DRG by glial cells; and increased pain fibre activity.

Dorsal Horn

Pain signals undergo modulation in the dorsal horn before cerebral transmission. Central sensitization involves a change in the modulation of pain signals causing amplification of pain. The change is due to complex changes in the functioning and interactions between dorsal horn neurons.

Pain C fibres terminate at first order pain neurons in lamina 1 and 2 (fig 3). The axons of first order neurons then ascend in the contralateral spinothalamic tracts to the brain. The axons also interact with other neurons within the spinal cord. First order neurons become hyperexcitable and increase their receptive field. Their receptive field widens as neurons send out projections to other peripheral C fibres. One consequence is that the summation of the impulses from multiple C fibres increases the likelihood of generating action potentials in the dorsal horn

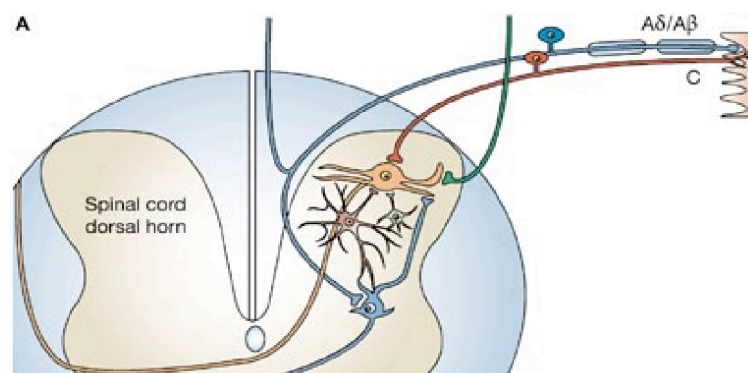


Fig 3 **Pain transmission in the dorsal horn**

neurons. The other consequence is greater crossover of receptive fields and a subsequent increase in the number of first order neurons that will respond to a given input.

Interneurons in the dorsal horn synapse with numerous neurons on different levels and in different lamina. These interneurons modulate the function of first order pain neurons in response to input from multiple sources. Most of these interneurons are inhibitory, providing tonic pain signal inhibition and increased inhibition in response to large C fibre input. They also increase inhibition in response to input from other sensory modalities and are used as an explanation for Wall and Melzack's gate control theory of pain. In central sensitization these interneurons decrease their inhibition and undergo apoptosis. This leads to greater transmission of pain inputs via first order neurons.

Wide dynamic range (WDR) neurons are able to transmit pain and other sensory information. They have synapses with both A β fibres and dorsal horn pain neurons. Multiple impulses from pain neurons recruit these cells to transmit pain. This is a possible cause of allodynia.

In chronic pain states, A β sensory neurons terminating in the dorsal horn can sprout axon extensions that extend into the pain processing areas of the dorsal horn. These extensions can then modulate pain transmission and it is likely that impulses in these sensory neurons cause impulses in pain neurons and produce allodynia.

The cause of all these changes is the subject of much active research; the prospect of drugs targeted at the reversal of these changes provides the economic drive. The two most popular theories involve glutamate receptors and glial cells.

Glutamate is the most common excitatory neurotransmitter in pain pathways and indeed the entire CNS. Glutamate has many significant receptors; the NMDA receptor is the most important in pain. This receptor is normally blocked by a magnesium ion and is only activated in response to repetitive C fibre firing. Activation of the NMDA receptor leads to increased calcium in first order neurons and subsequent hyperexcitability. More importantly, activation also triggers gene transcription, which can result in permanent changes to cell function. A particularly significant gene is the c-fos gene. C-fos is a proto-oncogene whose product, Fos, is a transcription factor. In dorsal horn neurons it increases the expression of opioid peptides resulting in an increase in dynorphin levels. Dynorphin inhibits the analgesic effect of morphine and produces hyperalgesia.

Glial cells provide support and protection for neurons. They outnumber neurons by approximately ten to one. A recent concept is that glial cells also have a role in information processing in the brain. Glial cells have synaptic connections with other glial cells and with neurons. Production and transmission of action potentials occurs slowly in glial cells, however, they form a large and active network. Glial cells also release multiple chemicals that act as autocooids. These autocooids influence the function of local neurons and glial cells. Glial cells respond to peripheral inflammation and nerve injury by releasing proinflammatory cytokines.

Cytokine release leads to hyper-excitability in surrounding neurons and it is also postulated that this release may lead to other cellular changes.

Supraspinal

Changes in the brain are much more difficult to study than spinal cord changes due to the complexity of the brain. It is likely that alterations in brain function in response to pain are more complex and important than the changes that have been discovered in the spinal cord. Recognised supraspinal changes include cortical reorganisation, and alterations in activity of descending tracts.

Cortical reorganisation refers to changes in the representation of body parts in the thalamus and cortex. After amputation or denervation of a somatic region, the representation of that region shrinks and is replaced by larger representations of areas adjacent to that region. The magnitude of these shifts can be greater than 30 mm for cortical representations. Cortical reorganisation causes amputees to localise painful stimuli from other parts of the body to the phantom limb.

Descending tracts from the brain into the dorsal horn modulate processing in the dorsal horn. Both inhibitory and facilitatory tracts modulate pain signalling. In chronic pain states, there is decreased tonic firing in the descending inhibitory tracts resulting in an increased transmission of pain sensations.

Central sensitization is an intricate process that is not fully understood. This sensitization can produce a dramatic increase in pain sensation and is presumed to be a common element in many chronic pain disorders.

It is likely that central sensitization is a normal response to injury as is peripheral inflammation and sensitization. Central sensitization would normally resolve as the injury heals. It is not known why central sensitization persists in some people, but it may be related to the nature of injury and predisposing psychological and physiological factors.

Summary

Chronic pain disorders are due to complex pathophysiological changes. Chronic pain involves a combination of nociceptive pain, neuropathic pain and central sensitization. Our understanding of these mechanisms is rudimentary and effective treatments directed at these processes are yet to be created. Currently available medical science offers a very limited range of treatments, which are often ineffective. Treatment limitations have led to the development of multidisciplinary therapies aimed at improving function and quality of life despite the persistence of pain.

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CANCER PAIN: ASSESSMENT AND MANAGEMENT

In 1986 the World Health Organisation (WHO) promoted education and opioid availability in an attempt to improve pain management for people with cancer. Twenty years later cancer pain is still under-treated. Two thirds of cancer patients suffer severe pain. More than 85% of these sufferers can and should have their pain controlled by basic principles.

Assessment

Assessment of the patient with cancer pain involves diagnosing the nature, cause and psychosocial impact of pain. Psychosocial factors can be as important in the aetiology and impact of the pain as biological factors. Therefore, the assessment should evaluate for anxiety, depression and the patients beliefs about pain. These issues must be identified and addressed as part of a comprehensive management plan.

Cancer pain is somatic, visceral, neuropathic or mixed in nature. It can be caused by the direct effects of the tumour or metastasis; Para neoplastic syndromes; treatments and investigations; and incidental non-cancer disorders. Table 1 lists common pain syndromes associated with cancer.

An assessment of cancer pain should diagnose the cause of pain; assess the severity of pain and the impact on the patient. The patient should be the prime assessor of their pain and sudden severe pain should be recognised as a medical emergency.

Table 1
Pain syndromes in patients with cancer

<i>Caused by cancer</i>	<i>Caused by anticancer treatment</i>
Tumour involvement of bone:	Post-surgery:
metastases to the cranial vault and base of skull	acute postoperative pain
metastases to vertebral body	post-thoracotomy syndrome
fracture of the odontoid process	post-mastectomy syndrome
C7-T1 metastases	post-neck-dissection syndrome
L1 metastases	phantom limb syndrome
sacral syndrome	Post-chemotherapy
Tumour involvement of viscera	oral mucositis
Tumour involvement of nervous system:	bladder spasms
cranial neuralgia	aseptic necrosis of the femoral head
- trigeminal	steroid pseudorheumatism
- glossopharyngeal	post-herpetic neuralgia
peripheral nerves	peripheral neuropathy
intercostal neuropathy	Post-radiotherapy:
brachial plexopathy	oral mucositis
lumbosacral plexopathy	oesophagitis
radiculopathy	skin burns
leptomeningeal metastases	radiation fibrosis of brachial and lumbar plexus
spinal cord compression	radiation myelopathy
intracranial metastases	radiation-induced second primary tumour

Adapted from reference 1

Management

Principles (adapted from 2)

- Patients should be educated about pain and take an active role in its management
- Treatment should be based on the principles outlined by the WHO Cancer Pain Relief program
- All patients with moderate to severe pain should have a trial of opioid analgesia
- Analgesia for continuous pain should be given on a regular basis

Treatment Options

Table 2 outlines possible therapeutic approaches to cancer pain. The approaches can be divided into disease modifying therapies and symptom control therapies. Disease modifying therapies

can remove, shrink or reduce the growth of tumours. They may have a curative or a palliative goal and include surgery, radiotherapy and chemotherapy. The role of these therapies in the treatment of cancer pain requires assessment by specialists in each of these fields.

Table 2
Approaches to pain management in cancer patients

Psychological approaches:
understanding
companionship
cognitive behavioural therapies

Modification of pathological process:
radiotherapy
hormone therapy
chemotherapy
surgery

Drugs:
analgesics
antidepressants
anticonvulsants
anxiolytics
neuroleptics

Interruption of pain pathways:
local anaesthetics (lidocaine, bupivacaine)
neurolytic agents (alcohol, phenol, chlorocresol, cold, heat)
neurosurgery (e.g. cordotomy)

Modification of daily activities

Immobilization:
rest
cervical collar or corset
plastic splints or slings
orthopaedic surgery

Adapted from reference 1

Symptom control therapies aim to control pain or other symptoms in order to improve the patients quality of life without altering the disease outcome. They include analgesic medications, adjunct medications and pain relieving interventions.

Analgesics

These medications are cheap and effective in 70 - 90% of patients. Therefore, they are the backbone of effective treatment. There are five guiding principles:

- By mouth
- By the clock
- By the ladder
- For the individual
- Attention to detail

By mouth:

The oral route is the simplest, cheapest and most reliable route of administration. Slow release preparations allow even, constant pain control. The oral route also allows the patient to have considerable control over their treatment. This should always be used if available.

By the clock:

The medications should be given at regular times throughout the day. Each dose should be given before the previous dose has worn off and before pain develops. This provides continuous analgesia. Allowance needs to be made for breakthrough pain on top of this regular analgesic regimen.

By the ladder:

The WHO analgesic ladder (Fig 1) is a three-step approach based on the severity of pain and the response to initial analgesia. This approach was developed in 1986 and despite advances in pain management; it is still a useful tool.

The first step is a non-opioid. If this fails to control the pain a 'weak' opioid is added. If this combination fails to control the pain a strong opioid is substituted for the 'weak' opioid. Only one medication from each step should be used at a time and adjuvant drugs can be added at any step for specific indications.

For the individual:

Drug doses must be titrated to an individual's pain and balanced against the side effects. Drugs for mild to moderate pain are limited in the dose by toxicity, eg. paracetamol and tramadol. Opioids have a large individual response variation and no theoretical upper dose limit. Therefore, the dose must be individualised.

Attention to detail:

The patient must be educated about the need for regular dosing and possible side effects. A detailed written schedule should be provided with the drugs, dose, number of times per day and the reason for use.

Choice of Analgesics

The choice of analgesics is based on the analgesic ladder. Detailed information about these medications can be found elsewhere.

Step one for mild pain involves paracetamol and NSAIDs. Paracetamol is effective and very well tolerated. It is limited by a low maximum dose due to potential liver toxicity at higher doses. NSAIDs have a higher maximum effect but are poorly tolerated by many patients, particularly those with asthma, renal dysfunction, dyspepsia or upper GI ulcers. Both of these medications reduce the dose of opioid required when used in combination with these drugs.

Step two is the so-called 'weak' opioids. The original table had codeine on this step. Since 1986 evidence has shown that codeine has little benefit and causes more side effects than a small dose of morphine. Tramadol has become popular since the original ladder was published. It is suitable for moderate pain and fits on the middle step. Tramadol is not purely a weak opioid. Noradrenaline and serotonin reuptake inhibition accounts for up to 70% of the analgesic action. Due to this, it may have some benefit in combination with strong opioids however this is controversial.

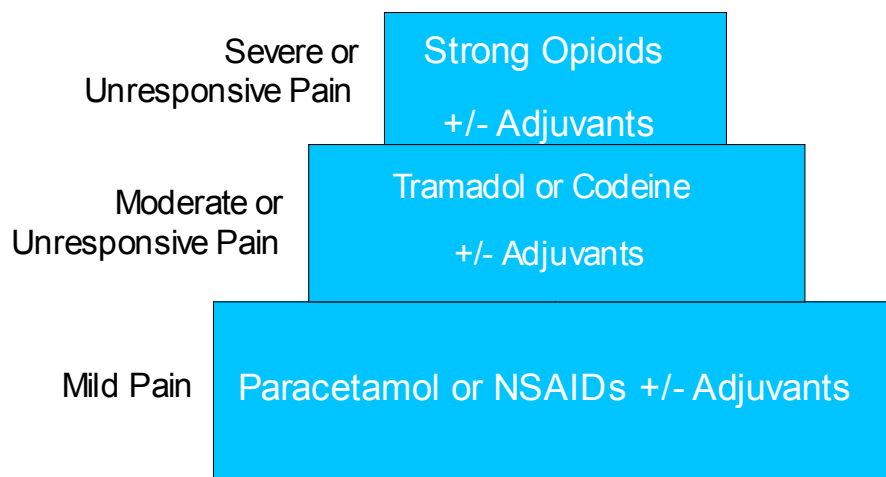


Figure 1 – Three step ladder adapted from the WHO analgesic ladder

Step three involves strong opioids for severe pain or pain not controlled by the first two steps. Morphine is the archetypal strong opioid and it is still the mainstay of analgesic treatment. There seems to be little difference in efficacy and toxicity between different opioid medications. The dose of opioid is titrated against the patient's pain by giving doses every one to two hours until the pain is controlled. The total daily dose is then divided into regular intervals according to the pharmacokinetics of the drug. For normal release oral morphine preparations this would be four hourly. Slow release oral preparations give more stable plasma concentrations. This gives the maximum pain relief with minimum side effects and allows a simple twice daily dosing. For patients who are unable to take oral medications, regular rectal administration or continuous subcutaneous administration via a continuous pump device will still attain consistent pain relief.

Breakthrough pain

Breakthrough pain is transitory moderate or severe pain occurring on a background of adequate pain control. It can occur spontaneously or be caused by activity. Rescue analgesia for these episodes is usually 1/6 of the regular daily opioid dose taken on top of the regular analgesia. A second dose can be taken 30 minutes later if needed. An individualised plan for treating these episodes is needed if the breakthrough pain occurs often or is severe.

Antiemetics

Nausea, related to opioid use or to the tumour, is treated in much the same way as postoperative nausea and vomiting. A dopamine antagonist such as haloperidol 1-2mg/day is often first line and then antiemetics from different classes can be added if required.

Laxatives

Constipation can cause great discomfort in cancer patients and often needs to be treated aggressively. It is beneficial to start a laxative prophylactically when starting opioids. Two senna tablets twice a day is a good initial dose. This can be titrated up or down and stool softeners added to suit the patient. If this is inadequate a laxative enema will be necessary.

Adjuvants

Adjuvant medications can be added to the analgesic ladder at any stage. These consist of analgesic medications and others directed at that pathophysiological processes causing the pain, eg. bisphosphonates, anticholinergics and corticosteroids.

Analgesic Adjuvants

The analgesic medications used as adjuvants include antineuropathic agents and ketamine. These medications are discussed in detail in another lecture. Para-neoplastic syndromes, chemotherapy, surgery and tumour infiltration or compression of peripheral nerves, the spinal cord or cerebral

structures can cause neuropathic pain. The treatment approach is similar to other neuropathic pain states, which commences with a tricyclic antidepressant, adding an antiepileptic and then an opioid.

A ketamine infusion is used as a rescue for acute pain or severe breakthrough pain uncontrolled by opioids. It may also provide pain relief for several weeks when given as an infusion for five days for breakthrough pain.

Corticosteroids

Corticosteroids have many uses in advanced cancer. Table 3 gives a comprehensive list. When corticosteroids are used in the treatment of pain, they are mainly used for pain caused by nerve or spinal cord compression, obstruction of hollow viscus or headache due to raised intracranial pressure. The aim is to shrink the inflammatory penumbra surrounding the lesion to reduce the mass effect.

The dose used for nerve compression is prednisolone 20-40mg/day or dexamethasone 4-6mg/day; for raised intracranial pressure, prednisolone 50-100mg/day or dexamethasone 8-16mg/day. These doses are generally maintained for a week and then slowly reduced till the lowest maintenance dose is found to minimise long-term side effects.

Table 3
Possible indications for corticosteroids in advanced cancer

<i>General uses</i>	<i>Specific indications for use</i>
To improve appetite	Spinal cord compression
To enhance sense of well-being	Nerve compression
To improve strength	Dyspnoea:
Hormone therapy	- pneumonitis (after radiotherapy)
- replacement	- carcinomatous lymphangitis
- anticancer	- tracheal compression/stridor
To relieve pain caused by:	Superior vena caval obstruction
- raised intracranial pressure	Pericardial effusion
- nerve compression	Haemoptysis
- spinal cord compression	Obstruction of hollow viscus:
- metastatic arthralgia	- bronchus
- bone metastasis	- ureter
	- intestine
	Hypercalcaemia (in lymphoma, myeloma)
	Radiation-induced inflammation
	Leukoerythroblastic anaemia
	Rectal discharge (give per rectum)
	Sweating

Adapted from reference 1

Bisphosphonates

Bisphosphonates inhibit osteoclastic bone resorption leading to increased bone mineralisation. They are used in cancer to treat tumour-induced hypercalcaemia and to decrease skeletal events in advanced cancer. These events include pathological fractures and painful bone metastases requiring radiotherapy. Bisphosphonates reduce the rate of growth of bone metastases and it is also likely they prolong the life expectancy in patients with breast or prostatic bony metastases.

Pamidronate and zoledronic acid are the bisphosphonates used in cancer treatment. The doses are pamidronate 30-90 mg intravenously every 3-4 weeks; zoledronic acid 4 mg intravenously every 3-4 weeks.

Anticholinergics

Malignant bowel obstruction can be very painful and distressing. Antimuscarinic drugs, such as hyoscine, can be used to reduce gut secretion and motility.

Benzodiazepines

These drugs are not analgesic in themselves, but may be useful for reducing anxiety and distress associated with pain, especially in the terminal phases of cancer.

Interventions

Coeliac Plexus Block

The coeliac plexus block is used for cancer pain originating from the upper abdominal organs. This is most commonly due to cancer of the head of pancreas.

The coeliac plexus contains the autonomic nerves from the upper abdominal organs including liver, gallbladder, spleen, stomach, kidneys, small bowel and 2/3 of the large bowel. Pain sensation from these organs travels with autonomic nerves and therefore blockade or neurolysis of the plexus will provide analgesia. A block is usually first performed with local anaesthetic to confirm effectiveness and then repeated with phenol or alcohol. These neurolytic techniques will provide 6-12 months pain relief.

For details about this block refer to Anaesthesia UK at

<http://www.anaesthesiauk.com/article.aspx?articleid=100539>

Peripheral Nerve Blocks

Local anaesthetic blocks of peripheral nerves including brachial, femoral and sciatic nerves, provide analgesia for limb pain. Their use is limited by the short duration of action and by the limb function loss. Neurolysis of these nerves can cause deafferentation pain which may be more difficult to treat than the original complaint. However, indwelling catheters by these nerves can be used to deliver continuous infusions or repeated boluses of local anaesthetic agents. This can provide relief for up to a few weeks and can be considered in the terminal stages of cancer.

Neuraxial Infusions

Epidural or intrathecal infusions of local anaesthetics or opioids can provide powerful analgesia while minimising systemic side effects. Catheters can be placed into these spaces using a Seldinger technique. The catheter can then be tunneled subcutaneously so that it exits the skin some distance from the insertion site. A port at the end of the catheter can then be used to infuse medication as boluses or continuously from an external pump. Tunnelling the catheter reduces the risk of dislodging the catheter or infection spreading into the epidural or intrathecal space. A catheter that is tunneled around to the patient's side can be used for many months.

Morphine is 10 times as potent when used epidurally compared to intravenously and 100 times as potent given intrathecally. This means a dose of 1 mg/day given intrathecally is equal to 100 mg given intravenously or 300 mg given orally. Giving morphine by this route allows massive doses to be given with relatively few systemic side effects. It is useful for patients with advanced cancer who have pain that is relieved by high dose morphine but are suffering unmanageable systemic side effects. It is usually given by continuous infusion, but intrathecal morphine has a

very long duration of effect, lasting 24-36 hours, and is suitable for daily bolus dosing. The dose used is usually 1-5 mg/day although much higher doses are sometimes needed.

For pain that is poorly responsive to opioids, local anaesthetics can be given neuraxially. The sensory and motor effects limit the use of these drugs. Infusions of very low concentration local anaesthetics that are carefully titrated can be useful although opioids are generally better tolerated.

Conclusion

Despite 20 years of work by the WHO cancer pain is still under treated internationally. The vast majority of patients can be effectively treated with a few basic principles. The WHO analgesic ladder and the use of strong opioids for moderate to severe pain can make a significant difference to these peoples' lives. The 1996 WHO guideline on cancer pain relief provides a more detailed guide. A Mongolian translation can be ordered from http://whocancerpain.wisc.edu/old_site/eng/publishers/mongolian.html or an English version can be downloaded from <http://whqlibdoc.who.int/publications/9241544821.pdf>

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PAIN MANAGEMENT IN RECOVERY

The effective management of pain in recovery will allow for good pain management on the general ward following surgery. Early management requires repeated bolus administration of analgesics (usually opioids) as well as the use of multimodal analgesia to effectively achieve pain control. It is not acceptable that a patient be returned to the ward in severe pain.

All opioids are able to produce the same degree of analgesia in equivalent doses. The dose administered needs to be individualised, as opioid requirements will vary greatly.

The recovery room is an ideal location for the administration of small intravenous boluses of opioid to achieve early control of pain. It is an area where the patient can be closely monitored for side effects.

In adults, the patient age rather than weight has been shown to be a better predictor of opioid requirement. In the opioid naïve patients between the ages of 20 and 70 years, the first 24 hour morphine requirement can be estimated using the following formula: 100 mg minus the age in years. In children, weight is used to determine the dose of opioid.

Smaller doses will be required if intermittent intravenous boluses of opioid are used. In the patients with renal or hepatic insufficiency, drug metabolism and pharmacokinetics will be altered.

Intravenous intermittent dosing

Intermittent intravenous boluses of opioid can be used to achieve rapid pain relief in the recovery room or following acute trauma. Patients with hypovolemia or hypotension can be treated with intravenous doses. This is preferable to intramuscular or subcutaneous injection in the patient with poor peripheral uptake of drugs.

Small doses of an opioid such as morphine 0.5 to 4 mg every 3 to 5 minutes are given until pain relief is achieved. The patients over 70 years of age are given smaller doses. The patient is continuously monitored for sedation.

Suggested starting doses for intramuscular or subcutaneous morphine and intramuscular pethidine in adults:

Doses will vary according to the age of the patient years					
	20-39	10-59	60-69	70-85	>85
Morphine (subcutaneous every 2 hours)	7.5-12.5 mg	5-10 mg	2.5-7.5 mg	2.5-5 mg	2-3 mg
Pethidine (Intramuscular)	75-125 mg	50-100 mg	25-75 mg	25-50 mg	20-30 mg

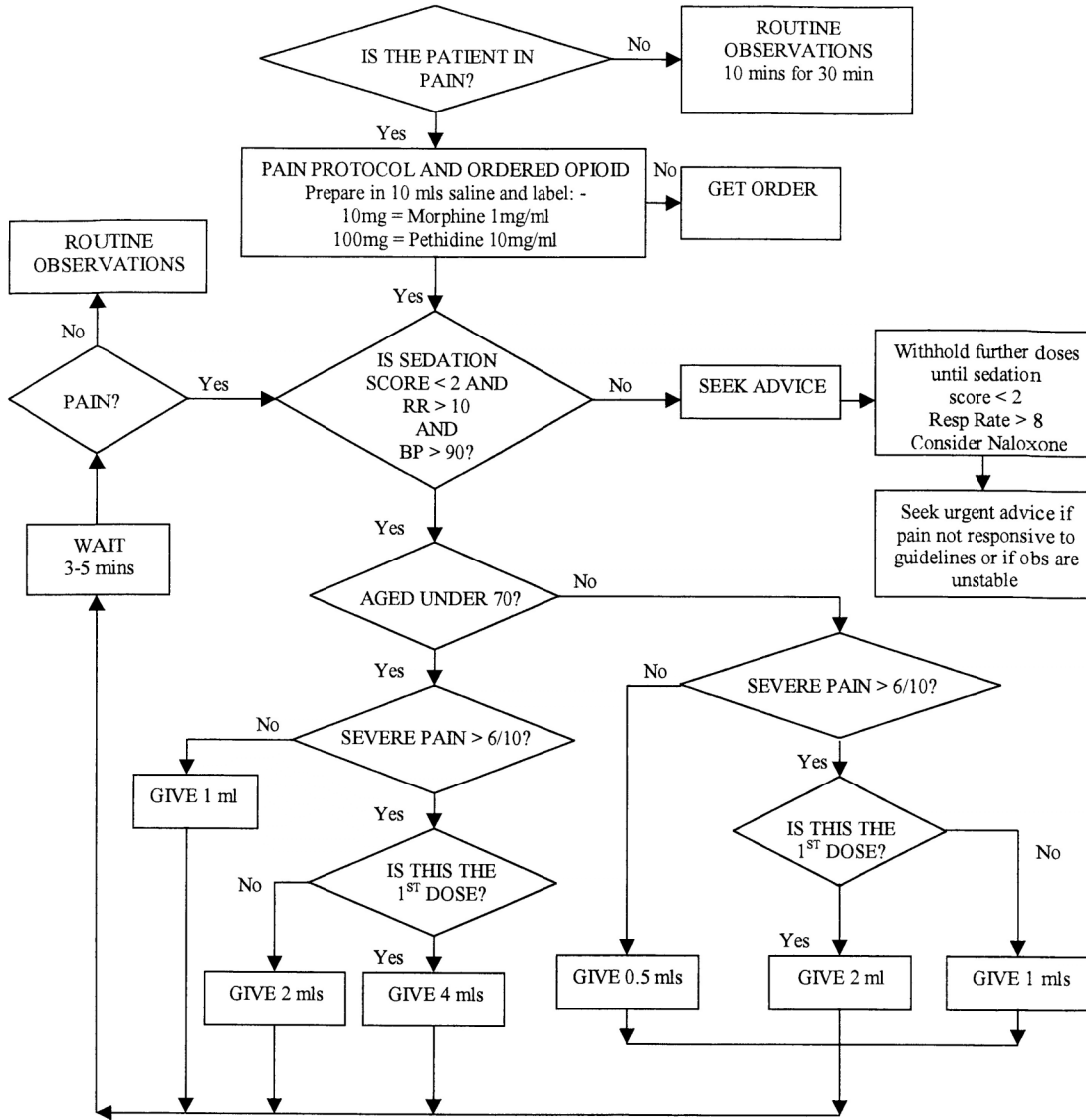
Opioids will lead to respiratory depression when given in large doses. Respiratory depression can be avoided by careful titration of opioid and can be detected with monitoring for sedation. When patients are receiving larger doses by infusion or other respiratory depressant medications are used concurrently, respiratory depression is more likely to occur.

Respiratory rate is an unreliable and late indicator of respiratory depression. Sedation is a better indicator and should be used to monitor patients receiving opioids.

Sedation should be monitored and the patient with severe sedation needs to be treated with small doses of opioid antagonists such as naloxone 0.1 mg intravenously.

Some patients will suffer hypoxemic episodes in spite of high pain scores. Supplemental oxygen is recommended for a number of days postoperatively following major surgery and in the elderly to treat these episodes.

PAIN MANAGEMENT PROTOCOL FOR ADULT PATIENTS IN RECOVERY



SEDATION SCORE	
Observe	Score
Asleep, stirs to touch	S
Alert	0
Sometimes drowsy, easily roused	1
Often drowsy, easily roused	2
Often drowsy, difficult to rouse	3

OBJECTIVES
Pain score: ≤ 4/10 or acceptable to patient
Respiratory rate: ≥ 10
Sedation score: S,0,1
BP: >90 mmHg or adequate for patient
Nausea: nil or controlled with antiemetic

PATIENTS WHO ARE OPIOID DEPENDENT OR TOLERANT
May report persistent high pain scores
May need higher doses
May be more difficult to assess if analgesia is improving.
Seek advice from medical officer at any time

***** IF > 20mls GIVEN IN < 70yr OLD OR >10mls GIVEN IN >70yr OLD SEEK MEDICAL ADVICE *****

HEADACHE

Headache is an extremely common complaint. 85% of people have experienced a headache in the last year and 38% of adults have had a headache in the last week. The causes of headache are numerous and diverse. The International Headache Society (IHS) classifies headaches into 14 groups with over 200 individual types of headache. This diversity makes assessment and diagnosis challenging.

Table 1 lists a diagnostic approach based on common causes and serious causes that should not be missed. A thorough history and examination is required to differentiate between the wide variety of primary and secondary causes of headache. A biopsychosocial assessment is important for patients with chronic headache of any cause.

The diagnosis of serious causes of headache should be suspected if the patients presents with the red flags listed in table 2. Any new or unaccustomed headache, especially in the middle aged or elderly patient, should be treated with respect and investigated as appropriate.

Common Chronic Headaches

Tension-type headache

This is the most common type of headache with a lifetime prevalence is 79%. The term ‘tension-type’ is used rather than ‘tension’ because of these headaches is more complex than previously thought. The pathophysiology probably involves an interaction of muscular, neuronal and psychological factors.

IHS diagnostic criteria:

- The patient should have had at least 10 of these headaches
- The headaches last 30 minutes to 7 days
- At least 2 of the following 4:
 - Non-pulsatile
 - Mild or moderate intensity
 - Bilateral
 - No aggravation with routine physical activity
- Both of the following:
 - No nausea or vomiting
 - Photophobia or phonophobia are absent or only one present
- Less than 15 headaches per month
- Secondary causes are excluded

Diagnostic Approach to Headache

Probable diagnosis

- Acute
 - Respiratory infection
- Chronic
 - Tension-type headache
 - Combination headache
 - Migraine
 - Analgesic abuse headache

Serious disorders not to be missed

- Cardiovascular
 - Subarachnoid haemorrhage
 - Intracranial haemorrhage
 - Carotid or vertebral artery dissection
 - Temporal arteritis
 - Cerebral venous thrombosis
- Cancer
 - Cerebral tumour
 - Pituitary tumour
- Severe infection
 - Meningitis
 - Encephalitis
 - Intracranial abscess
- Haematoma
 - Subdural/extradural
- Glaucoma
- Benign intracranial hypertension

Pitfalls (often missed)

- Cervical spine disease
- Dental disorders
- Eye disorders
- Sinusitis
- Facial shingles
- Exertional headache
- Hypoglycaemia
- Post-traumatic headache
- Dural puncture headache
- Sleep apnoea
- Rarities
 - Paget's disease
 - Post-sexual intercourse
 - Cushing's syndrome
 - Conn's syndrome
 - Addison's syndrome
 - Dysautonomic cephalgia

Seven Masquerades

- Depression
- Diabetes
- Drugs
- Anaemia
- Thyroid disorder
- Spinal dysfunction
- UTI

Is the patient trying to tell me something?

- There may be an underlying psychogenic disorder

Table 1 (adapted from 1)

Red Flags

History

- Sudden onset
- Severe and debilitating pain
- Fever
- Vomiting
- Altered consciousness
- Worse with bending or coughing
- Worse in the morning
- Neurological abnormalities
- Young obese female
- New headache in elderly
- Trauma
- Tender, poorly pulsatile cranial arteries

Examination

- Altered consciousness
- Meningism
- Abnormal vital signs: BP, temp, respiration
- Focal neurological signs

Table 2 (adapted from 1)

Management:

- Screening for underlying depression or anxiety disorder
- Patient education, reassurance and advice – the aim is to direct patients to modify their lifestyle and avoid tranquillisers and strong analgesics.

Migraine

Migraines affect at least 15% of people. There are a wide range of subtypes with common migraine (migraine without aura) and classical migraine (migraine with aura) being the most common. The median rate of migraine attacks, amongst migraine sufferers, is 1.5 per month. 1% have at least one migraine per week.

IHS diagnostic criteria for common migraine:

- The patient should have had at least 5 of these headaches
- The headaches last 4-72 hours
- At least 2 of the following:
 - Unilateral
 - Pulsing
 - Moderate or severe intensity; inhibiting daily activities
- Both of the following
 - Nausea and/or vomiting
 - Photophobia and phonophobia
- Secondary causes are excluded

IHS criteria for classic migraine

- The patient should have had at least 2 of these headaches
- At least 3 of the following:
 - Fully reversible aura symptoms indicating focal cortical or brainstem functions
 - Aura onset over 4 minutes
 - Aura duration less than 60 min
 - Headache follows aura in less than 60 minutes
- Secondary causes are excluded

Management

- Treatment of acute attack

Migraine Triggers

Exogenous

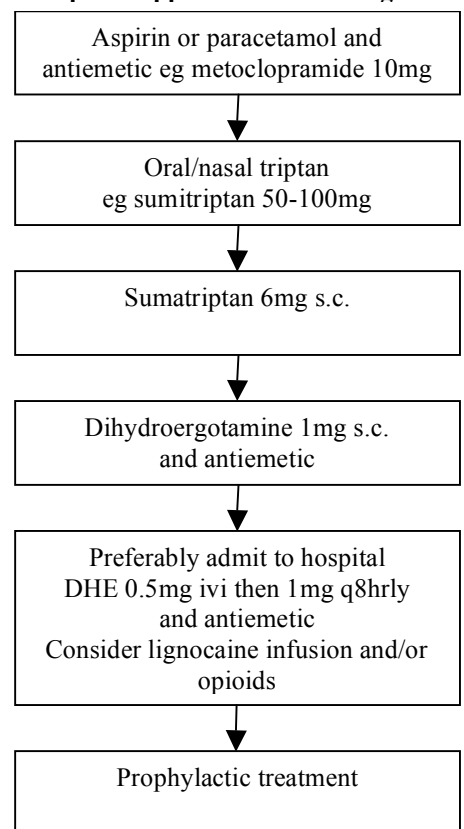
- Foods – chocolate, oranges, tomatoes, cheese
- Alcohol
- Drugs
- Glare or bright light
- Minor head trauma
- Allergen
- Climate change
- Loud noise
- Perfume

Endogenous

- Tiredness
- Stress
- Relaxation after stress
- Exercise
- Hormonal changes
- Hunger

Figure 1

Stepwise approach to acute migraine



- Commence treatment at earliest impending sign
- Rest in quiet, darkened, cool room
- Medication
 - Figure 1 outlines a stepwise approach to medication for acute migraine
- Long term treatment of migraine
 - Patient education, reassurance and advice
 - Avoidance of triggers
 - Consider prophylactic medication for frequent (>2/month) or refractory attacks.
 - Beta blockers – eg propranolol 40mg bd
 - Pizotifen 0.5-2.0mg
 - Tricyclic antidepressants – eg amitriptyline 25-75mg
 - Calcium channel blockers – eg verapamil
 - Lisinopril 10mg BD
 - Sodium valproate
 - Pregabalin
 - Behavioural therapies such as relaxation or biofeedback may also help

Cervicogenic Headache

Headache from neck disorders is more common than realised and can often be successfully treated if recognised. Headache can be caused by any structure innervated by the C2 and C3 nerve roots. The most common cause is the C1/2 and C2/3 facet joints. The diagnostic criteria for cervicogenic headache are controversial.

Typical features of cervicogenic headache

- Occipital and neck region
- Unilateral or bilateral
- Mild to moderate intensity
- Usually occurs daily, lasting 1-6 hours
- Aggravated by neck movements or activity
- Tender to palpation over upper cervical muscles or facet joints

Management

- Physiotherapy – stretching and strengthening exercises
- Medial branch nerve blocks for facet joint pain
- Analgesic medication

Medication Overuse Headache

Medication overuse headache is the most common cause of migraine-like headache occurring on more than 15 days per month. It typically occurs in migraine sufferers who develop a cycle of recurrent headache, for which they take medication and this medication generates further headaches. Medication overuse headaches can be caused by analgesics, including NSAIDs and

opioids; and medications for acute migraine, including ergotamine and triptans. The mechanisms of medication overuse headache are poorly understood.

IHS diagnostic criteria

- Headache present >15 days per month
- Medication taken on >10 days per month for 3 months (15 days per month for simple analgesics)
- Headache has developed or worsened during medication overuse
- Headache resolves within 2 months of ceasing medication
- Ergotamine, simple analgesic, or combination medication overuse headache must have one of the following:
 - Bilateral
 - Pressing/tightening (non-pulsating) quality
 - Mild or moderate intensity
- Triptan overuse headache must have one of the following:
 - Predominantly unilateral
 - Pulsating quality
 - Moderate or severe intensity
 - Aggravated by routine physical activity
 - Associated with one of the following
 - Nausea and/or vomiting
 - Photophobia and phonophobia

Management

- Withdrawal of the medication involved
- The medication may be substituted with another medication for acute headache provided it is not taken more than twice a week
- Migraine prophylaxis may help withdrawal and decrease the risk of recurrence
- Patient education and psychological support is important for successful withdrawal and prevention of recurrence

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BACK PAIN – ACUTE AND CHRONIC

ACUTE LOW BACK PAIN

Acute low back pain (LBP) is defined as pain between the posterior 12th rib and the inferior gluteal folds, with or without referred leg pain, which has been present for less than three months. LBP accounts for at least 5% of all presenting complaints in Australian general practice and 70% of the world's population will have at least one episode. The median time to recovery is seven weeks, however, 30% of patients still have pain at three months and 10-20% will at one year. The relapse rate is has been reported as up to 76% in the 12 months following an episode of acute LBP.

Assessment

The majority of acute LBP will resolve over several weeks with conservative management, therefore, a precise diagnosis is not usually necessary. The major aim of assessment is to identify potentially serious conditions. These conditions are neurological disorders, particularly cauda equina syndrome; infection; cancer; and fractures. Symptoms and signs of these conditions are known as red flags. Table 1 lists red flags.

There are a myriad of psychosocial factors that increase the risk of progression to chronic back pain. These factors are known as yellow flags and are listed in table 2. Screening for yellow flags may be useful if there is little improvement.

Investigations for acute LBP are of no clinical utility unless red flags are present. Blood testing for inflammatory markers, eg white blood cell count and c-reactive protein, is useful if infection is suspected; plain x-rays are indicated for assessment of trauma; MRI is the gold standard for general screening of red flags, including cancer, infection, trauma and cauda equina syndrome.

Management

Many interventions have been used for acute LBP, however, the only treatments that are of proven benefit are supportive treatments to relieve pain and advice to stay active. The evidence is summarised in table 3.

Explanation and reassurance is an important component and aims to increase activity and decrease anxiety. The New Zealand Acute Low Back Pain Guide suggests some useful phrases “The pain will settle - most people make an excellent recovery”; “There is no sign of anything serious and an x-ray is not needed”; “Movement and activity will not cause harm - it is important to stay active”.

Staying active is a key component to recovery. Rest is harmful, but specific exercises are not beneficial. The best approach is to continue their usual activities including work.

Pain relief can be provided by simple analgesia based on the WHO analgesic ladder and by manipulation in the first four weeks. Analgesia and manipulation do not improve recovery. They are used for symptom control and must be combined with activity.

Patients should be reassessed at four to six weeks. If they are improving they should be encouraged to continue activity. If they are not improving they should be reassessed for red and yellow flags and referred for specialist treatment.

Relapse rates are very high for acute LBP and yellow flags should continually be addressed after successful treatment to reduce the risk of relapse.

Red Flags	
<p>General risk factors</p> <ul style="list-style-type: none"> • Age >50 or <20 • Failure to respond to treatment • Unexplained weight loss • Prolonged illness <p>Fractures</p> <ul style="list-style-type: none"> • Major trauma • Minor trauma with: <ul style="list-style-type: none"> ○ Osteoporosis ○ Elderly ○ Steroid use <p>Cauda Equina</p> <ul style="list-style-type: none"> • Neurological deficits • Loss of bladder or bowel control 	<p>Infection</p> <ul style="list-style-type: none"> • Fever • History of body penetration eg surgery or venipuncture • ESR >50 mm/hr • Unexplained neurological deficit <p>Cancer</p> <ul style="list-style-type: none"> • History of cancer • Weight loss • Not relieved by bed rest

Table 1

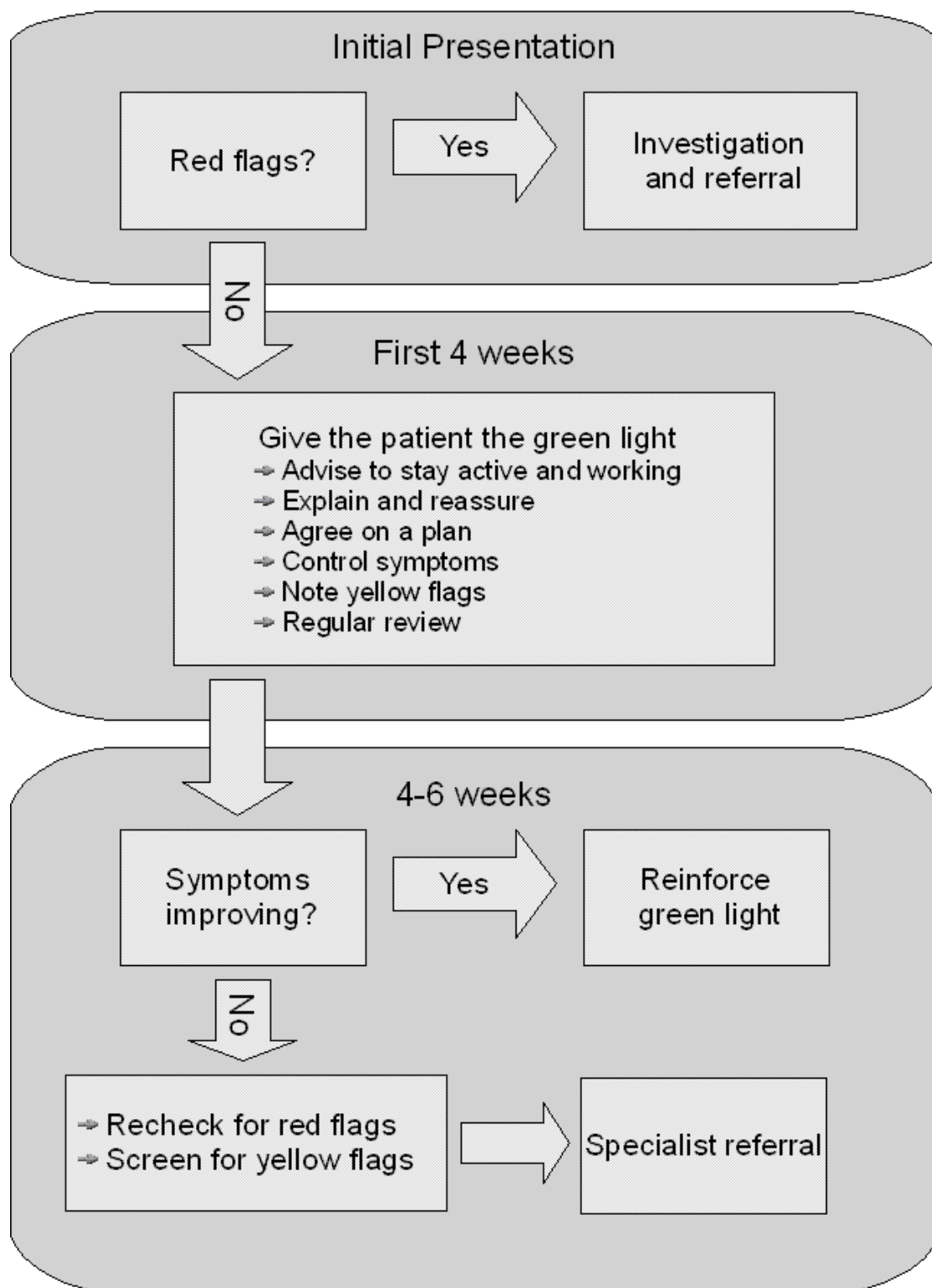
<u>Yellow Flags</u>
<ul style="list-style-type: none"> • Belief that pain and activity are harmful • Sickness behaviours, especially fear avoidance behaviours • Low mood and social withdrawal • Treatment that does not fit best practice • Belief in passive treatments • Problems with compensation claims • Previous back pain requiring time off work • Poor job satisfaction • Heavy work • Overprotective family or lack of support

Table 2 – adapted from 2

Evidence for LBP management options

Evidence of improved clinical outcomes	<ul style="list-style-type: none">• Advise to stay active• Analgesia with paracetamol and NSAIDS• Manipulation in the first 2 weeks• A multidisciplinary approach to management
Evidence of no improved clinical outcomes	<ul style="list-style-type: none">• TENS• Traction• Specific back exercises• Education pamphlets about low back symptoms• Massage• Accupuncture• Surgery (unless disc decompression is indicated)• Epidural steroid injection (unless radiculopathy)
Evidence of harm	<ul style="list-style-type: none">• Use of narcotics or diazepam• Bed rest for more than 2 days• Manipulation under general anaesthetic• Plaster jacket
Insufficient evidence	<ul style="list-style-type: none">• Trunk conditioning exercises• Aerobic conditioning• Shoe lifts or corsets• Biofeedback• Physical agents and passive modalities including ice, heat, short wave diathermy and ultrasound

Management of acute low back pain



Adapted from reference 2

CHRONIC BACK PAIN

Chronic back pain is defined as back pain lasting longer than three months. The prevalence of chronic back pain is around 6%. The common anatomical causes of chronic back pain include facet joint pain (15%), sacroiliac joint pain (15%) and intervertebral disc disruption (40%). Psychosocial yellow flags are also important in the aetiology of chronic pain. An epidemiological study of acute back pain found a yellow flag questionnaire to be better at predicting which patients developed chronic pain than the suspected pathology or the general practitioners clinical assessment.

Assessment

There are no specific characteristics of chronic back pain that enable an examiner to form a reliable anatomical diagnosis. Therefore, the history and examination focuses on screening for red flags and evaluating bio-psycho-social factors. The incidence of red flag conditions in chronic back pain is 1.5 - 3%. Red flag conditions are more frequent among chronic back pain sufferers than those with acute back pain but are still rare.

Bio-psycho-social factors, such as depression, anxiety, social problems and maladaptive pain behaviours, are common among people with chronic back pain. These problems usually require independent treatment and are associated with greater disability and distress than pain itself. Addressing bio-psycho-social factors can dramatically improve a patient's quality of life regardless of pain treatment outcome.

The acknowledgement of the importance of bio-psycho-social factors in chronic back pain patients has led to the development of a multidisciplinary approach towards their management. This is whereby doctors, physiotherapists and psychologists work together to formulate an individualised treatment strategy for each patient. The approach also involves specialist input from anaesthetists, rehabilitation physicians and psychiatrists.

Magnetic Resonance Imaging (MRI) is the most specific and sensitive test for red flags in back pain, however results should be interpreted with caution. Radiological abnormalities prevail in the general population and do not necessarily cause pain. For example, a MRI study of the lumbo-sacral spine in asymptomatic individuals over the age of 60 found nucleus pulposus herniation, disc bulge and spinal stenosis in 40%, 80% and 21% of individuals respectively. Another MRI study revealed disc abnormalities in over half of asymptomatic individuals aged 20 - 39. These findings reiterate the need to correlate radiological abnormalities with history and examination findings.

Management

The WHO analgesic ladder can be applied to chronic back pain, however analgesics will be of little or no benefit in many patients. It is important to stop medications that are not beneficial and cause adverse effects. The use of opioids for back pain is controversial. Opioids provide significant relief for some patients, but can be unhelpful and harmful to others. To determine which patients will benefit, opioids can be prescribed on a trial basis. The opioid trial should have defined goals of pain reduction and function improvement. The goals should be meaningful to the individual patient. If these goals are not met the opioid can be stopped.

Anti-neuropathic agents, such as antidepressants, also have a role in treating chronic back pain, especially when central sensitisation or neuropathic pain are prominent features. These medications, like analgesics, should be started on a trial basis and stopped if ineffective or poorly tolerated.

In clinical trials of chronic back pain, analgesics and anti-neuropathic medications do decrease pain but do not significantly improve activity levels or functional ability. Medications provide only limited benefit to many individuals with chronic back pain and alternative treatment approaches are needed.

Procedural Approach

Many procedures have been used to treat back pain and few have proved successful. Current procedural techniques are comprised of precision diagnosis and treatment of specific causes of back pain. Precision diagnosis applies certain diagnostic procedures to establish the cause of the back pain. As previously mentioned, the common causes of chronic back pain are facet joint pain, sacroiliac joint pain and discogenic pain. The diagnostic procedure for each of these causes is medial branch blocks for facet joints; local anaesthetic joint injection for sacroiliac joints; and provocative discography for intervertebral discs.

Medial branch neurolysis is a specific treatment for facet joint pain with proven benefit. Repeated sacroiliac joint injection with local anaesthetic and/or steroids is commonly used to treat sacroiliac joint pain, however there is a lack of evidence to support this technique. There is currently no effective treatment for discogenic pain. A procedural approach is effective in only 15-30% of chronic back pain patients. The benefit is minimal unless underlying psychological and behavioural problems are also addressed.

Multidisciplinary

Current medical therapies are often of limited benefit to people with disabling chronic back pain. Multidisciplinary programmes aimed at functional reactivation are usually seen as a last resort for chronic back pain sufferers; however, there is greater success with this approach compared with other popular therapies. An intensive, three week full-time, multidisciplinary group

programme has the most supporting evidence. It uses a combination of education, functional reactivation via pacing strategies, and cognitive behavioural therapy. The group programme provides a modest improvement in pain but provides significant improvements in physical function, mood and global quality of life.

Summary

Chronic back pain is a common and debilitating condition. Patient assessment focuses on excluding red flags and identifying bio-psycho-social yellow flags. Current effective treatments encompass a multi-disciplinary approach directed at modifying these yellow flag thoughts, beliefs and behaviours.

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SHORT-BEVEL NEEDLE INGUINAL INFILTRATION BLOCK

This block is described for adults for inguinal hernia repair. Lignocaine 50 ml (1% with 1:200,000 adrenaline) is used as the local anaesthetic agent for fast onset of action however for long acting analgesia, a long acting local anaesthetic such a ropivacaine or bupivacaine is preferable.

The key method of this blockade is using a short bevel needle so that the tissue planes can easily be identified with the appropriate nerves to be blocked lying within these planes.

Patient positioning

The patient lies supine and the surgeon marks the surgical incision line prior to block insertion

Anatomy

To successfully provide anaesthesia for an inguinal herniorrhaphy 3 nerves are to be blocked. These are ilioinguinal (T12 L1), iliohypogastric (T12, L1), and genitofemoral nerves (L1, L2). See Figure 1

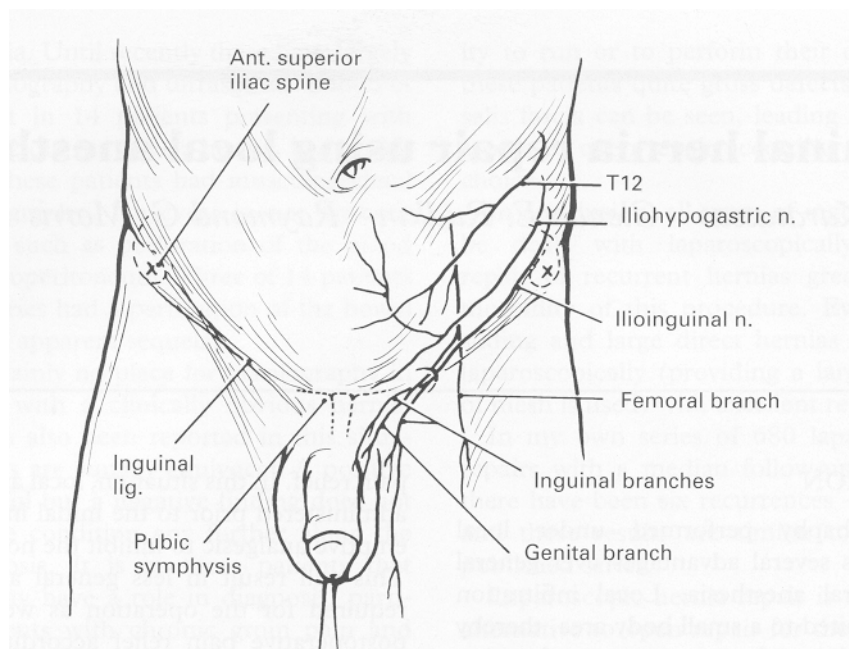


Figure 1.

Description ¹

A mark is made at a point 2cm along a line from the anterior superior iliac spine to the umbilicus with a skin wheal of lignocaine raised; see Figure 2, point A. A hole is made in the skin with a 19 gauge sharp needle. The 22 gauge short-bevel needle is inserted through the skin at an angle of 90 degrees. Care is taken to ensure that there is no resistance from the skin, which could impair recognition of tissue planes. The needle is advanced slowly and after approximately 1cm, a distinct pop is felt. This is the point of penetration of the external oblique aponeurosis. After negative aspiration, 7ml of local anaesthetic are injected. The needle is advanced with pressure on the syringe. At this point the needle is located within the internal oblique muscle where there is difficulty injecting solution through a short-bevel needle into muscle. The needle is further advanced 0.5 cm when a less distinct pop is felt with a loss of resistance to injection. A further 8 ml of local anaesthetic solution is injected after negative aspiration. No attempt is made to fan the needle.

The internal inguinal ring is located 1 cm superior to the mid-inguinal point. At this point the external iliac artery can be palpated. The genitofemoral nerve and the indirect hernia sac lie deep to the internal oblique muscle at this point. The second injection site is a point over the internal inguinal ring, see Figure 2, point B. At this point, a skin wheal is raised with local anaesthetic and a hole is made with a 19 gauge sharp needle. The short-bevel needle is advanced until a very distinct pop is felt as the needle passes through the external oblique aponeurosis. No injection is made at this point in the tissue plane but further pressure applied to the syringe. The needle is advanced until a second less distinct pop of the internal oblique muscle is felt and a loss of resistance to injection detected. This is approximately 4 cm from the skin or more in the obese patient. Any pulsation of the needle means it is in close proximity to the artery. Twenty-five ml of local anaesthetic solution is injected slowly, aspirating at 5 ml intervals. This injection bathes the genitofemoral nerve, and the peritoneal sac in local anaesthetic. No attempt is made to fan the needle.

Finally, the skin is infiltrated along the marked incision line, with the remaining 10 ml of lignocaine or lignocaine diluted to 0.5% solution with normal saline to make a 20 ml volume, see Figure 2, Line C-D. The full length of the marked incision line is infiltrated with a 9 cm 22 gauge spinal needle with the bevel facing down. At the lateral end of the incision 3 ml of local anaesthetic is injected subcutaneously in the direction of the umbilicus.

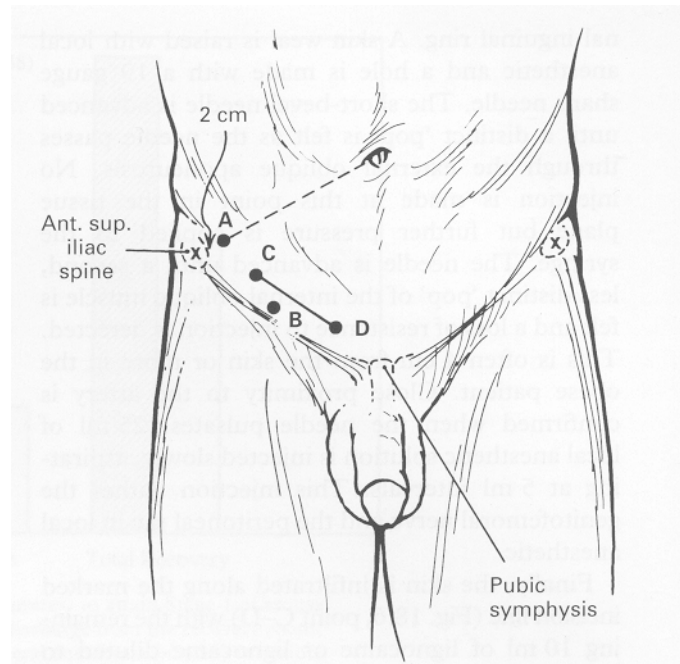


Figure 2

Complications and Side Effects

You can inject into a blood vessel resulting in local anaesthetic toxicity or haematoma. With the large volume of local anaesthetic used, surgical dissection may be difficult. The femoral nerve is often blocked resulting in leg weakness, as the patient is unable to extend the knee. Additional sedation may be required when surgical dissection is made around the spermatic cord.

It must be recognised that achieving good pain control is important for inguinal hernia repair as this group of patients experiences a high incidence of postoperative pain. Sleep disturbance is also common with 30 % of patients waking up with pain.²

References:

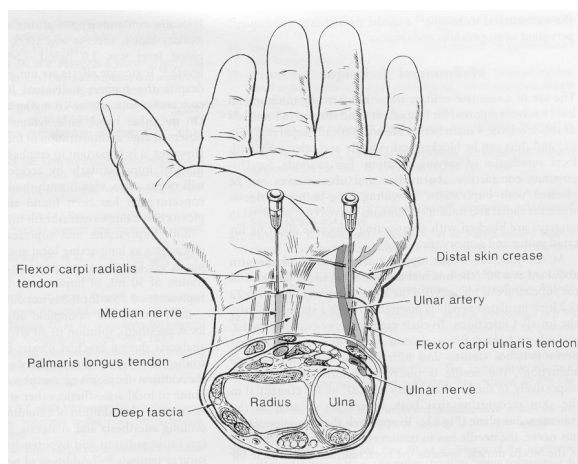
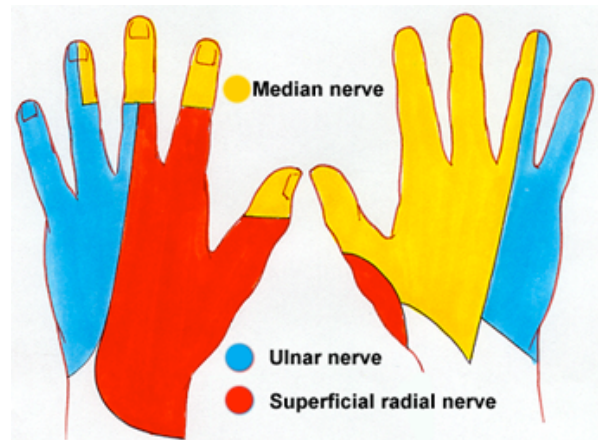
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WRIST BLOCK

This can be easily performed in an awake patient. Don't use adrenaline with the local anaesthetic. Stop injecting if there is resistance to injection or paraesthesia particularly with median nerve injection at the wrist.

Anatomy

Three nerves supply sensation to the hand. These nerves may be conveniently blocked at the wrist. The ulnar nerve runs down in the flexor compartment of the forearm, first covered by the flexor carpi ulnaris (FCU) then passing radial to this muscle. The ulnar artery accompanies the nerve radially. The nerve divides 5 cm from the wrist into a dorsal and a palmar branch, both of which run next to or deep to the FCU tendon. The median nerve runs between the deep and superficial flexor tendons. At the proximal crease it lies between the palmaris longus and the flexor carpi radialis, deep to the flexor retinaculum. If the Palmaris Longus is absent the nerve runs between the flexor tendons and Flexor carpi radialis. The radial nerve lies on the radial side of the forearm at first accompanying the radial artery but then branching about 7 cm above the wrist so at the wrist it has divided into several branches.



Ulnar Nerve Block

Palpate the Flexor Carpi Ulnaris tendon and insert a 27 gauge needle posterolaterally in a horizontal approach and place 5 ml LA into the space.



Median Nerve Block



Identify Palmaris Longus and Flexor Carpi Radialis by flexing the wrist. Inject 5 ml LA beneath the deep fascia. Piercing the deep fascia can result in a 'click', however it is more reliable to insert the needle until it contacts bone. The needle is then withdrawn 2-3 mm and the LA injected. Direct injection into the nerve is strictly avoided.

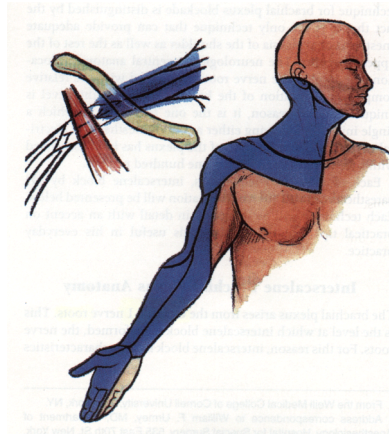
Radial Nerve Block

Place 10 ml LA in a subcutaneous plane from Flexor Carpi Radialis to mid dorsum of the wrist.



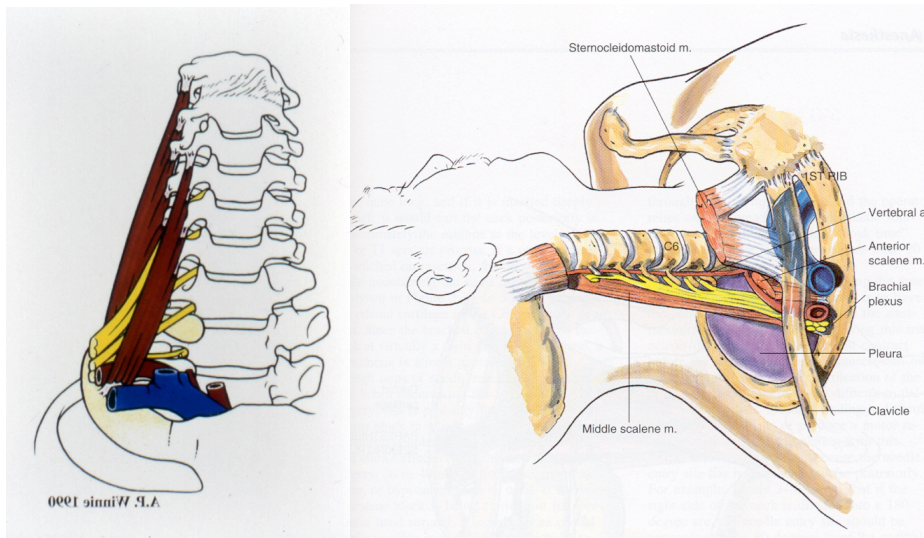
INTERSCALENE BRACHIAL PLEXUS BLOCK

The interscalene approach is recommended for shoulder, upper arm and elbow surgery.



Anatomy

This approach focuses on the ventral roots (C4-T1) as they pass through the scalenus groove. A fascial sheath surrounds the nerves and there are no vessels within the sheath.



Patient Positioning

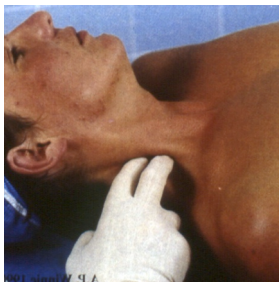
The patient should lie supine, with the head turned away from the side to be blocked, without a pillow.

Landmarks

C6 vertebra, which is found by extending a line laterally from the cricoid cartilage. The external jugular vein crosses the interscalene groove at the level of C6 virtually all the time.

Technique – Winnie’s approach

Ask the patient to lift his head to identify the clavicular head of sternocleidomastoid muscle. Place your index and middle fingers behind the lateral edge of sternocleidomastoid and ask the patient to relax, then your fingers will be lying on the belly of anterior scalene muscle. Roll your fingers laterally across the belly of this muscle until the interscalene groove is palpated.



With both index and middle fingers in the interscalene groove, a 22 gauge needle with extension tubing and syringe attached, is inserted at the level of C6. The direction of the needle should be 45° at all angles, down (caudad), back (posterior) and in (medial). The needle is advanced slowly until a paraesthesia is elicited. Only a paraesthesia below the level of the shoulder is acceptable, since a paraesthesia to the shoulder could result from stimulation of the suprascapular nerve. The needle should never be advanced beyond 2.5 cm to avoid the risk of complications. The needle is aspirated and a few ml of local anaesthetic (LA) is injected. Aspirate every 5 ml. Never inject when resistance (high pressure) to injection of LA is encountered.

Local Anaesthetic

2% lignocaine can be used, with an onset time of 10-20 minutes and duration of analgesia 2-5 hours. Alternatively, 0.5% bupivacaine will have an onset of 20-30 minutes and duration of analgesia 16-18 hours. Volumes such as 15-20 ml can be used successfully for analgesia

Side effects and Complications

Side effects such as Horner’s, hoarseness, cough, and phrenic nerve paresis are common. Block failure can occur and more serious complications such as haematoma, pneumothorax, and neuropathy can occur.

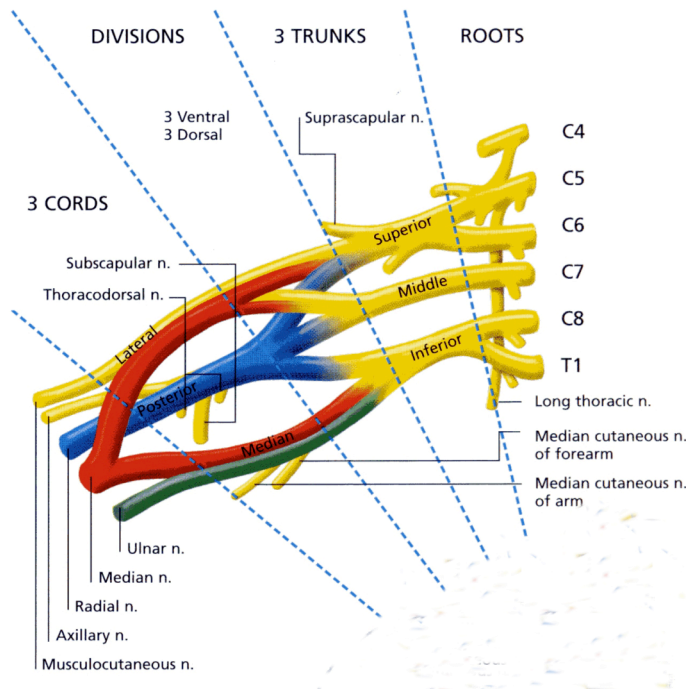
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Plexus Anesthesia. Volume 1. Perivascular techniques of Brachial Plexus Block. Alon P Winnie

AXILLARY BRACHIAL PLEXUS BLOCK (TRANSARTERIAL)

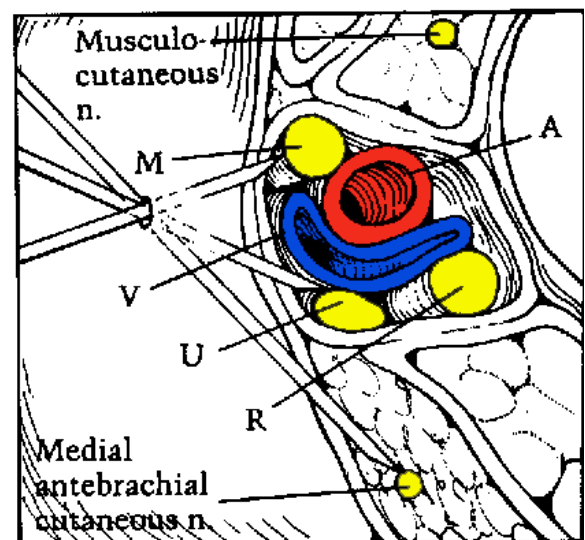
This block is useful for forearm and hand surgery

Anatomy



After passing from the neck between the clavicle and first rib, the brachial plexus enters the upper limb via the axilla. At this point the trunks of the plexus have each divided into an anterior and posterior division, which combine to form 3 cords: lateral, medial and posterior.

All the nerves are in close relationship to the artery and lie within the perivascular sheath. In the lower axilla the trunks divide into the 4 main terminal branches: the median, radial, ulnar and musculocutaneous nerves. The musculocutaneous nerve quickly leaves the perivascular sheath through the coracobrachialis muscle.



Patient Position

The patient lies supine and the upper limb on the side to be injected should be abducted at the shoulder and flexed at right angles at the elbow so that the wrist is at the same level as the patient's head. This is like a "stop sign".



Needle insertion



A 23-gauge needle attached to a plastic extension tube is used with a syringe on the end for aspiration. The axillary artery is palpated and the needle inserted directly over the artery at right angles to it. When arterial blood is seen, the needle is advanced further so as to exit the artery opposite its entry point and where it will be within the perivascular sheath. Using an assistant to aspirate for blood when aspiration is negative 10 ml local anaesthetic injected. This will effectively block the radial nerve. Withdraw the needle almost to skin and angle the needle slightly cephalad, a paraesthesia may be

felt and 5-7 ml of local anaesthetic is injected after negative aspiration to blood. This will block the median nerve. The needle is then angled caudad, aspiration check and another 5-7 ml injected. This will block the ulnar nerve.

Drugs and dose

30-40 ml 1.5% lignocaine or 0.375% bupivacaine with adrenaline 1:200,000

Complications

Acute generalised toxicity. Inadvertent intravenous injection is unlikely if frequent aspirations are made. If it does occur, toxicity will be seen within a few minutes. Neuropathy can also occur.

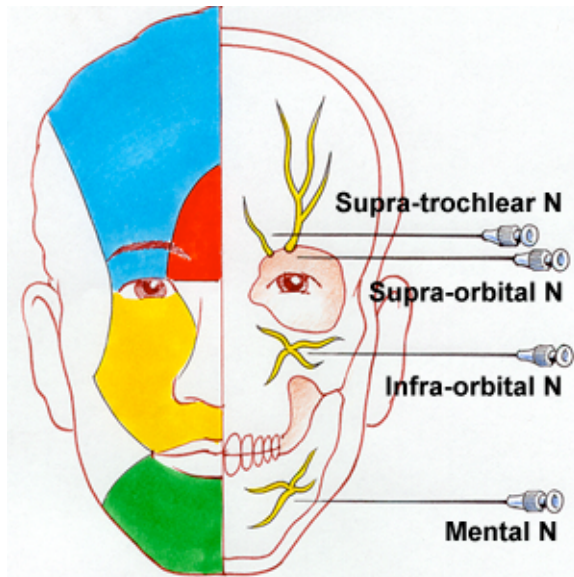
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SOME USEFUL FACIAL NERVE BLOCKS (TRIGEMINAL)

Anatomy

Knowledge of the distribution of the nerves and the sensory dermatomes is the key to success. The bony landmarks of the skull and the foramina are guides.



Division one –Ophthalmic nerve

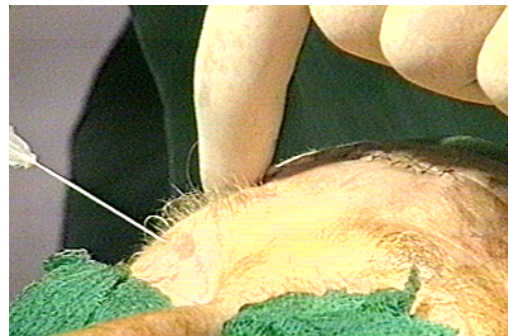
This is sensory to the upper eyelid, forehead, scalp, skin, septum and lateral nasal wall via the following branches: -

Supraorbital/Supratrochlear

The supraorbital nerve ascends through a notch/foramen on the supraorbital rim 2 cm from the midline and supplies the forehead and scalp to the vertex. The supratrochlear is always blocked with it and supplies the skin over the medial part of the forehead, above the nose.

Technique

Raise a central bleb of local anaesthetic (LA) just above the root of the nose and advance it laterally depositing about 5 ml of LA across each supraorbital rim. This can be done unilaterally however there is quite a bit of “crossover”. Ensure that the needle



travels in a horizontal plane and does not deviate inferiorly towards the globe.

Anterior ethmoidal

This is a terminal branch of the nasociliary nerve and it passes through the anterior ethmoidal foramen on the medial wall of the orbit into the anterior cranial fossa, along the cribriform plate and into the nasal cavity. Here it divides into a septal branch, (supplying the nasal septum) and a lateral branch, (supplying the wall of the nose inside and outside), via the external nasal nerve.

Technique

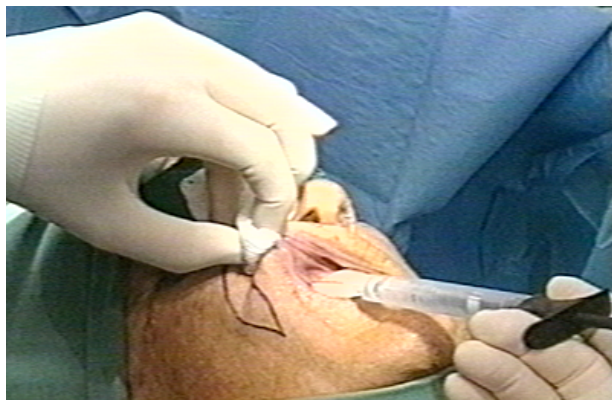
This nerve is blocked as it enters the ethmoidal foramen. A 25 Gauge needle is passed vertically backwards about 1cm above the inner canthus and to a depth of 2cm, depositing about 2mls at 2cm and 1ml on withdrawal. If you're using this block for nasal lesions you practically always need to block the infraorbital nerve as well.

Division two –Maxillary Nerve

The Maxillary nerve exits the skull via the foramen rotundum and gives off branches as it crosses the pterygo-palatine fossa and the floor of the orbit. It emerges through the infraorbital groove as the infraorbital nerve, which supplies the skin of the cheek and some of the side of the nose.

Technique

The trunk of the Maxillary nerve can be anaesthetised by a number of methods as it crosses the pterygo-palatine fossa. The one I use is the antero-lateral approach. Draw a vertical line from the lateral orbital margin to intersect with a horizontal line through the upper lip- this is the point of injection. Pass a needle at 30 degrees to the horizontal on a path directed towards the pupil and to a depth of 4-5 cm, this will get the tip of your needle into the pterygo-maxillary fissure. Always aspirate and then inject 5mls at 5cm and another 5mls after withdrawing the needle about 1cm. I often use a 25 gauge spinal needle and mark it at 5cm.



The infraorbital nerve can be blocked by an intra or extra oral approach. I think the intra oral is easiest and least painful for the patient. Elevate the upper lip and rub a small amount of LA gel over the gum above the incisor. The needle is inserted into the mucous membrane at its reflection from the gum and directed until it is about 1cm from the midpoint of the orbital rim where 2mls of LA are slowly injected.

Division Three – Mandibular nerve.

The mandibular nerve emerges from the skull through the foramen ovale and divides into branches supplying the ear, temporal region, mandible, lower lip, chin and floor of the mouth. The mandibular nerve can be blocked through the mandibular notch but much easier is the mental nerve, which is a terminal branch and supplies the lower lip and the chin.

Technique

As with the infraorbital nerve it can be blocked intra or extra orally. Use topical Lignocaine on the gum and then pass a 25g needle between the apices of the 1st and 2nd premolars: inject 5ml. If the patient is edentulous this is about in line with the angle of the mouth and in line with the supra and infra orbital foramina. The needle is inserted at the junction of the gingiva and labial mucosa. Quite extensive surgery can be performed with this block, including vermilionectomy.



ANKLE BLOCK

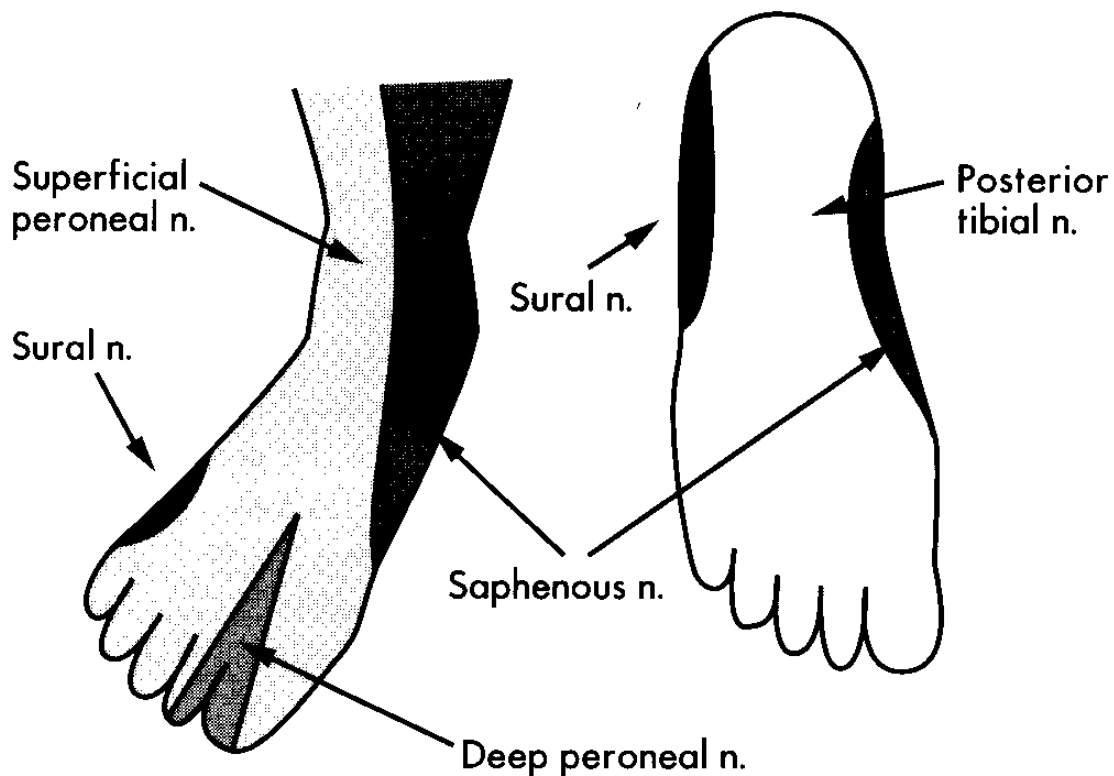
Introduction

Ankle block is a simple, safe, reliable technique with high patient satisfaction, providing excellent anaesthesia for bony or soft tissue surgery of the foot. It is usually used for mid-foot or forefoot surgery. Using long acting local anaesthetic (LA) agents, prolonged postoperative analgesia without motor block can be achieved allowing early ambulation.

Anatomy

Five nerves supply the foot: 4 are branches of the sciatic (tibial, superior and deep peroneal, sural) the fifth (saphenous) is a terminal branch of the femoral nerve. Innervation to the foot is highly variable; therefore, aim to block all 5 nerves, except for great toe surgery where a sural nerve block can be excluded. The tibial and deep peroneal nerves, which are blocked beneath the deep fascia supply bones, joints and muscles of the foot. The sensory distribution of the 5 nerves is shown in Figure 1.

Figure 1



Block the tibial nerve first as it takes longest to take full effect. Allow at least 30 minutes for block onset when using long acting LA agents. To assist patient comfort during insertion of the block, titrate a sedative agent such as intravenous midazolam. Use a technique such that after the initial LA infiltration, further LA is injected through previously anaesthetised areas.

Choice of Local Anaesthetic.

Onset and duration of the ankle block depends mainly on the choice and concentration of LA. There is little advantage in adding adrenaline to the LA and best avoided in patients with peripheral vascular disease or compromised circulation. Short acting local anaesthetics such as lignocaine can be used for surgery however for bony surgery a long acting local anaesthetic is the preferred choice which will provide long acting pain relief. Ropivacaine is a most suitable agent for ankle block with its significant advantages in reduced cardiovascular toxicity and long duration of action, similar to bupivacaine. Using ropivacaine, onset time for ankle block is between 15 to 25 minutes with a mean duration of 9 hours.¹ Bilateral blocks can be performed taking care not to exceed the maximum recommended dose of 200 mg ropivacaine.² More recently, a number of studies have demonstrated prolonged postoperative analgesia with the addition of clonidine (1 mcg/kg) to LA solutions.³

Equipment and patient positioning

Place the patient in the supine position. Use a 35 mm 25 gauge needle to minimize the number of injection sites. It is not necessary to use a nerve stimulator or paraesthesia technique. When a tourniquet is required, use a conical low pressure ankle cuff, placed immediately above the malleoli. This will be tolerated comfortably by the patient for up to 90 minutes. Patients 70 years of age or older are at greater risk of experiencing tourniquet pain.⁴ Set the pressure between 200-250 mmHg or 100 mmHg above systolic blood pressure.

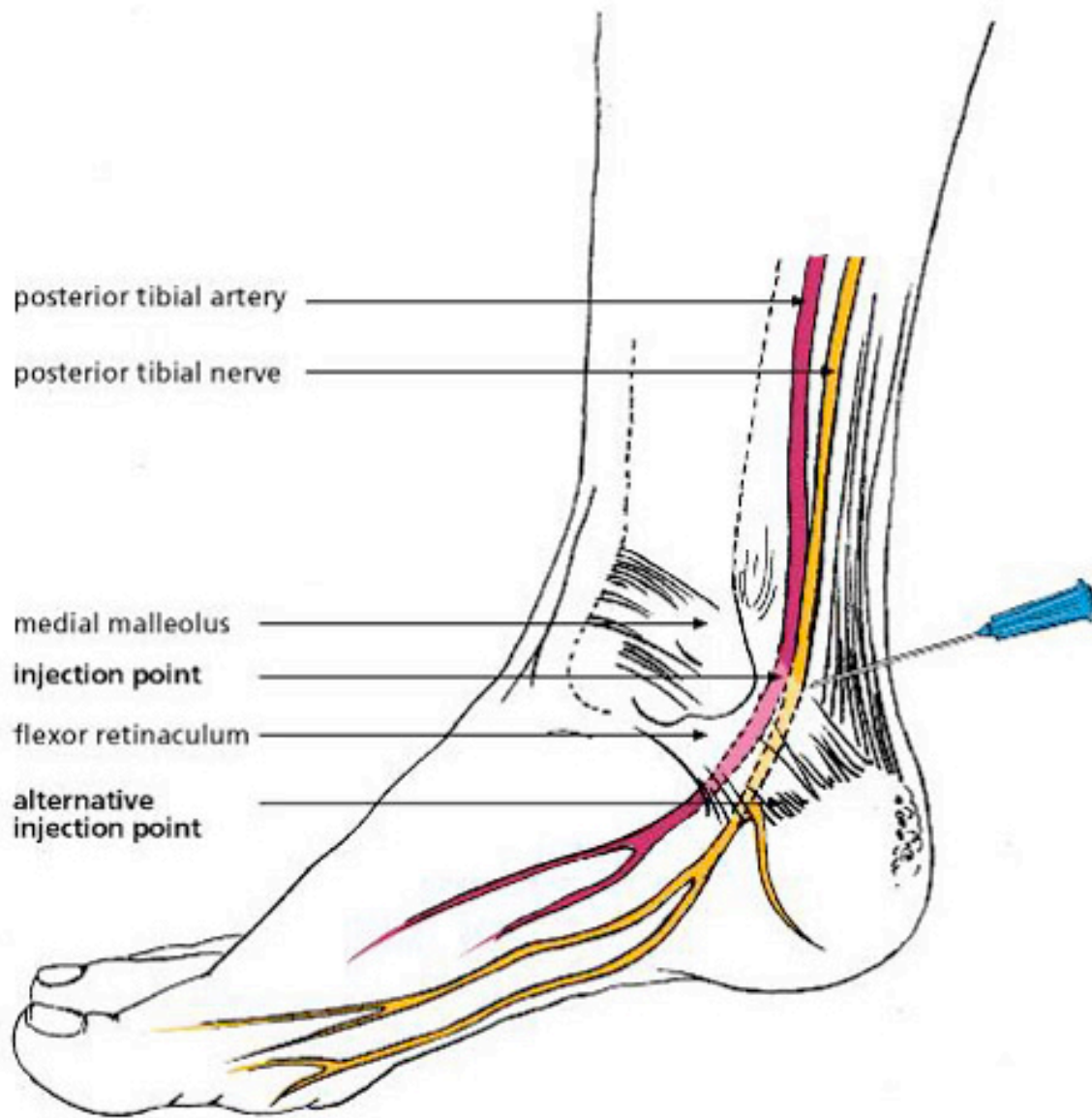
Complications

Ankle block has a low complication rate. Temporary paraesthesia can occur, usually resolving within a few weeks⁵. Systemic toxicity is rare (reported incidence <0.1%)⁶, if it occurs it is usually after intravascular injection. Published work suggests a block failure rate between 0.1 and 3 %⁶. The main causes of block failure are lack of anatomical knowledge, inadequate time for block onset or failure to block a nerve required for the procedure.

Step by step infiltration technique

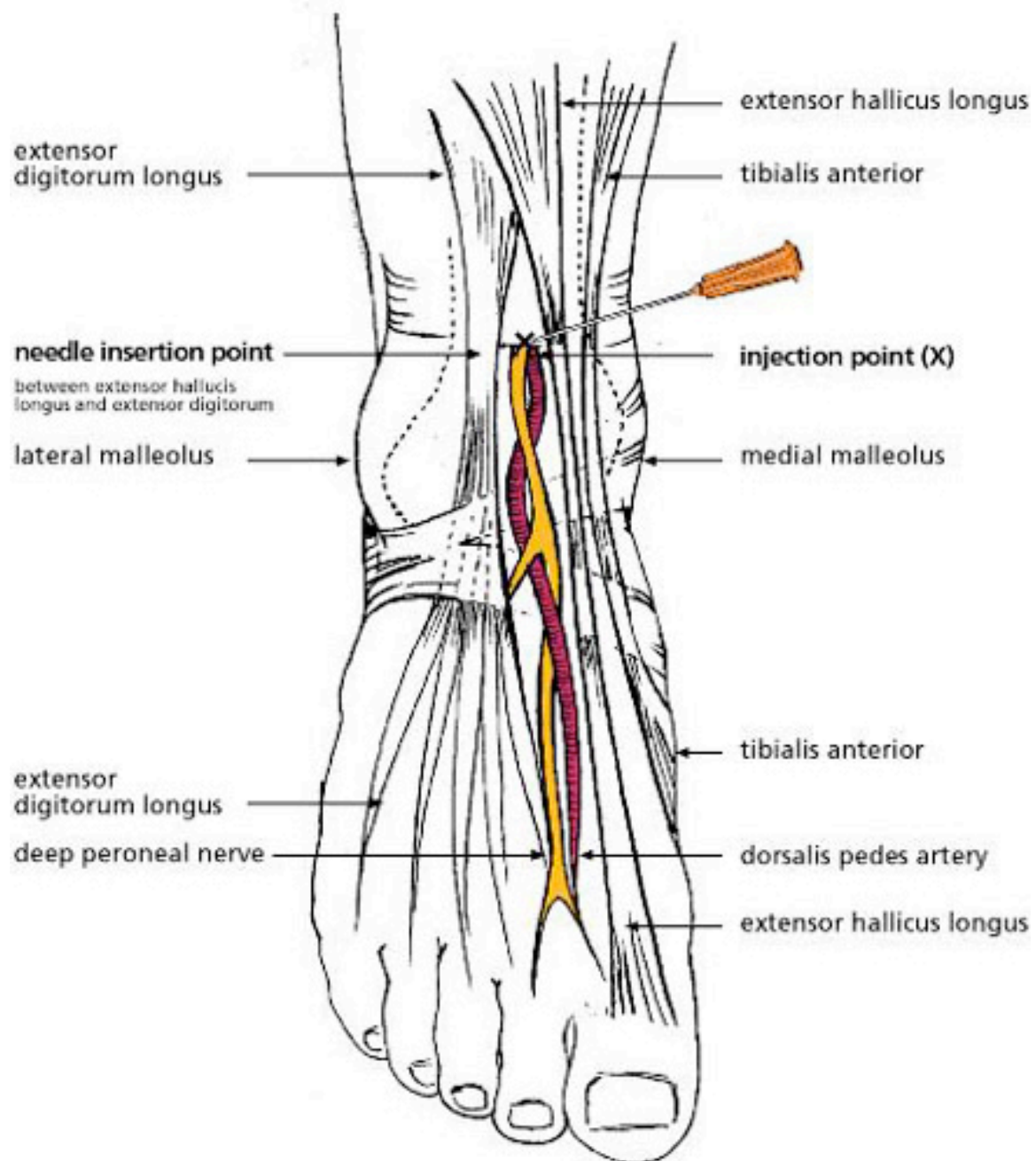
Tibial nerve (8 ml)

Palpate the posterior tibial artery and immediately behind the medial malleolus insert the needle perpendicular to skin and direct it dorsal to the artery, until bone is contacted, withdraw slightly and inject. Alternatively, if arterial pulsation is difficult, insert the needle at a point one-third of the way from the medial malleolus to the posterior apex of the heel.⁷



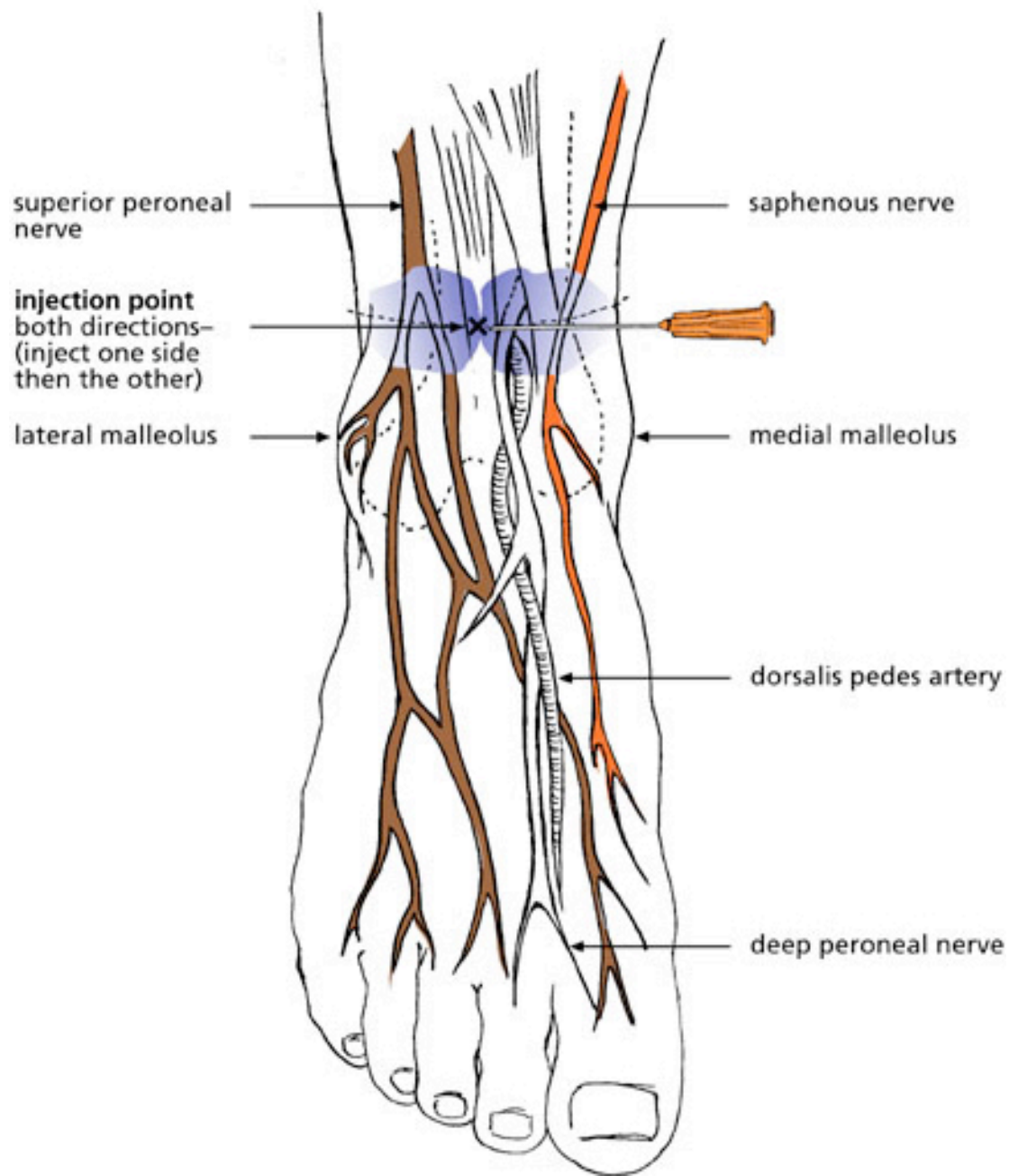
Deep peroneal nerve (5 ml)

Inject LA either side of the dorsalis pedis artery at the level of the malleoli between bone and skin. Alternatively, you may choose to block this nerve at the midtarsal level directly lateral to the extensor hallucis longus tendon and usually medial to the dorsalis pedis artery.

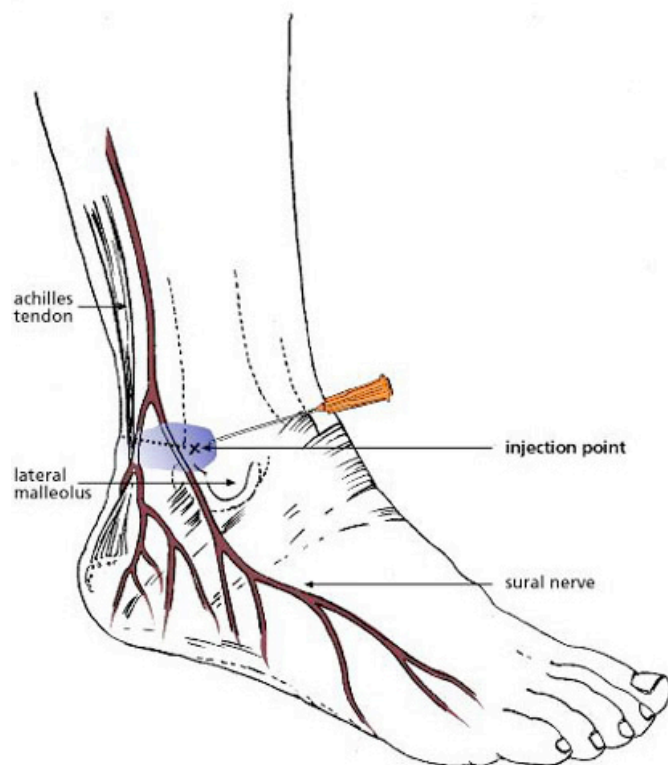


Superficial peroneal nerve (10 ml)
 Inject subcutaneous LA along a line joining the malleoli.

Saphenous nerve (5 ml)
 Block with a perivenous infiltrate of LA 1-2 cm above the medial malleolus (the saphenous nerve runs very close to the saphenous vein) Alternatively, incorporate this block into the superficial peroneal nerve block, by continuing to inject anterior to the medial malleolus.



Sural nerve (5 ml)
Infiltrate LA subcutaneously between the lateral malleolus and the achilles tendon.



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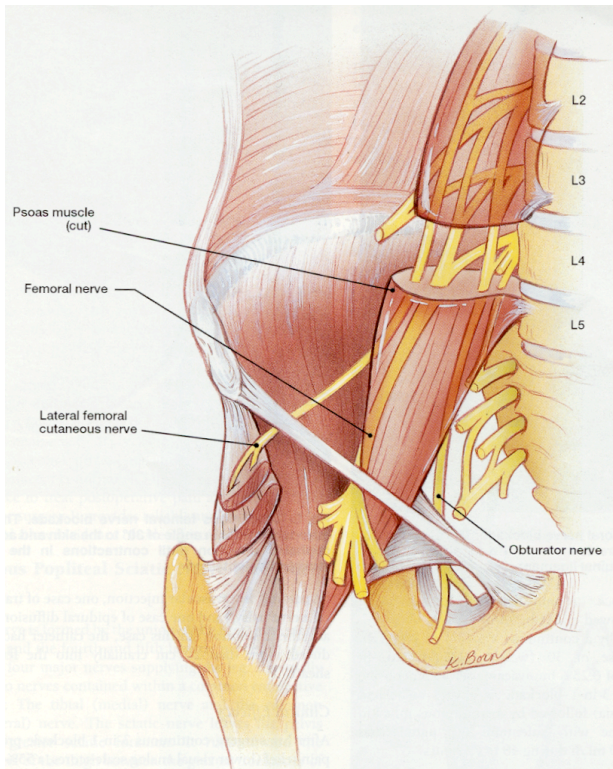
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FEMORAL NERVE BLOCK (FASCIA ILIACA COMPARTMENT BLOCK FICB)

Introduction

First described by Dalens in 1989. FICB is fast to perform and does not require any special equipment other than a short bevel needle. It can be used a “single shot” or as a catheter technique. This block is most useful for analgesia for fractured shaft and neck of femur, anterior cruciate ligament repairs. It can be used for hip surgery; however supplemental analgesia will be necessary.

Anatomy

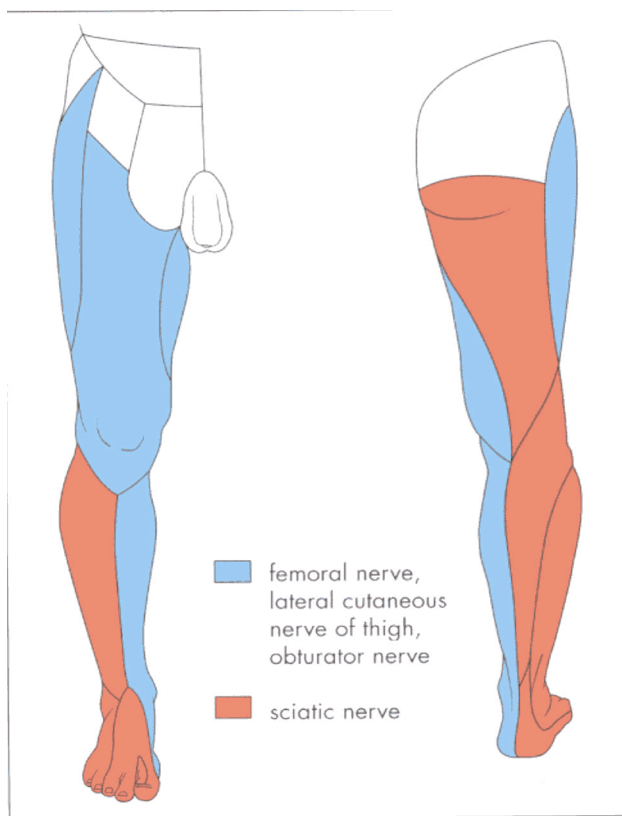


The lumbar plexus is formed from the anterior rami of L1-3 with part of L4.

Dalen’s technique consists of depositing a volume of local anaesthetic immediately posterior to the fascia iliaca at a point 0.5 cm inferior to the junction of the midpoint of the lateral and middle thirds of the inguinal ligament. The ‘Fascia Iliaca Compartment’ represents a potential space defined anteriorly by the fascia iliaca, and posteriorly by the iliacus muscle. The femoral, lateral femoral cutaneous, obturator, and genitofemoral nerves all run a considerable part of their course close to the posterior aspect of the fascia iliaca. Both the obturator and genitofemoral nerves emerge at the medial border of the psoas muscle and require larger volumes of local anaesthetic to block, compared to the femoral and lateral femoral cutaneous nerves. Therefore the rate of successful block of the obturator and genitofemoral nerves is less.

Distribution of Anaesthesia

The femoral and lateral femoral cutaneous nerves are sensory to skin overlying the anterior and lateral aspects of the thigh respectively. The femoral nerve also supplies the hip and knee joints. In the case of the knee joint, the additional innervation from obturator and sciatic nerves is minor. With the hip these are more significant. The shaft of the femur is predominantly supplied from the femoral nerve.



Technique

Place the patient supine, secure IV access, and you can lightly sedate the patient. Mark the inguinal ligament and the femoral artery. In an adult the injection point is 3-4 cm lateral to the femoral artery and 1 cm inferior to the inguinal ligament or 1 cm below the junction of the middle and lateral thirds of the inguinal ligament (child). Using a short bevel needle, approach the skin at an angle of 45° (bevel up). Two ‘pops’ are felt, the first as the fascia lata is penetrated which is quite a definite pop. The second pop (which is felt as the fascia iliaca is penetrated) is less distinct and is often felt as a series of 2-3 pops. The depth of the needle tip at this stage is usually 4 cm in the adult but may be 5 cm in larger individuals.

Local Anaesthetic Drugs

I inject 2 mg/kg of bupivacaine 0.25% (plain) after aspiration in doses of 5-7 ml. The total dose is given over 1-2 minutes or 30-40 ml lignocaine 1% in divided doses.

Complications and Side effects

The main complication is the block not working adequately (10% chance) however this risk is lowered with experience. Femoral nerve neuropathy may occur. This usually resolves over weeks, but beware, the neuropathy may be due to the surgery itself. There is a low risk of infection at the injection site if aseptic techniques are applied. There are no reports of local anaesthetic toxicity however potentially it could occur. Motor blockade of the quadriceps occur and the knee extensor can be blocked which can be a problem for ambulation when the block is working.

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www.developinganaesthesia.org

Welcome to www.developinganaesthesia.org. This web site has been created to promote the advancement of anaesthetic practice and to empower anaesthetists in countries with limited resources. The site also hopes to foster the growth of an online community of anaesthetists throughout the world.

A web-based resource has significant advantages. The information provided can remain current and be tailored to the requirements of the community. Hard copy texts may be expensive, difficult to access and inappropriate to the delivering of anaesthesia outside of tertiary institutions. The majority of journals have similar limitations.

DevelopingAnaesthesia.org is a free, up to date resource, specifically designed to address these problems.

The authors envisage the web site will have five principle functions, though the dynamic nature of web publishing will allow the evolution of the site as directed by the anaesthesia community.

- **1. Continuing education**
DevelopingAnaesthesia.org will provide an anaesthetic educational resource for anaesthetists. The site contains a textbook, articles, case studies and links. with time the site will contain power point and video presentations.
- **2. Anaesthetic training**
DevelopingAnaesthesia.org will provide an anaesthetic educational resource for anaesthetic trainees. The site will contain lecture notes for physiology, pharmacology, equipment, monitoring and statistics.
- **3. Teach the teacher**
DevelopingAnaesthesia.org will provide a resource to aid anaesthetists in educational methods.
- **4. Peer-reviewed publication**
DevelopingAnaesthesia.org will provide a venue for peer-reviewed publication online at no cost to authors or readers. All submitted material (case studies, articles, audits etc) is welcomed and encouraged.
- **5. Discussion forums**
DevelopingAnaesthesia.org has an open forum for discussion, exchange of ideas/experience and seeking advice. A panel of anaesthetists with experience in delivering anaesthesia and teaching in developing countries will moderate the forum but colleges in similar countries may provide the most relevant advice.

Success and the growth of www.developinganaesthesia.org will depend on feedback from the anaesthetic community it serves. Please have a look at the site and register as a user, there is no cost. Registration allows you to participate in forum discussions, submit your own articles and comments and in doing so help foster community growth.

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