10. Locally and regionally administered analgesic drugs

10.1 Drugs used for local and regional analgesia

10.1.1 Local anaesthetics

LAs exert analgesic effects by blocking sodium channels, impeding neuronal excitation and conducting impulses. LA consist of a hydrophilic amine and a lipophilic aromatic ring connected by an intermediate chain, which can have either an ester or amide linkage. Commonly used amide agents available in South Africa are lignocaine (injectable and topical), bupivacaine, levobupivacaine and ropivacaine, with articaine and mepivacaine available in cartridge form (mainly for dental use). Prilocaine is available in a topical formulation as part of EMLA. Ester LA available are cocaine, amethocaine (tetracaine) and benzocaine, all for topical application.

Short-duration LAs

- Lignocaine is the most widely used short-duration LA in acute pain management.
- Although the plasma half-life of lignocaine is approximately 90 minutes, the duration of the LA effect is also determined by the site of administration, the dose and the presence or absence of vasoconstrictors.
- The hydrophilic nature of lignocaine is overcome by delivering the drug in high concentrations. This results in good diffusion into nerve bundles with little separation of sensory and motor blocking actions.

Long-duration LAs

- The three commonly used long-duration LA agents are bupivacaine, levobupivacaine and ropivacaine.
- These drugs are structurally related. Bupivacaine is a racemic mixture of the S- and R-enantiomers, while both levobupivacaine and ropivacaine are solely S-(levo)-enantiomers.
- Duration of action is 2–9 hours and is influenced by site of administration and dose, but is minimally influenced by the addition of vasoconstrictors.

Summary of evidence-based efficacy and safety features of LA agents

- A continuous perineural infusion of lignocaine provides less effective analgesia and results in denser motor block than ropivacaine, levobupivacaine or bupivacaine.
- There are no differences in terms of the quality of analgesia or motor blockade between ropivacaine, levobupivacaine and bupivacaine when given in low doses for regional analgesia.
- Ropivacaine and levobupivacaine cause less severe CV and CNS toxic effects than racemic bupivacaine.

- A lipid emulsion (20% intralipid) is effective in the resuscitation of circulatory collapse due to local anaesthetic toxicity (LAST) and must be used in conjunction with advanced cardiac life support.
- Resuscitation following accidental overdose with ropivacaine is more likely to be successful than resuscitation after a bupivacaine overdose.

10.1.2 Opioids

- Although peripheral opioid receptors have been identified, there is currently little clinical evidence to support the use of opioids for possible peripheral or local effects.
- When compared to placebo, intra-articular morphine following knee arthroscopy does not improve analgesia.
- There is currently no conclusive evidence that opioids have a peripheral effect at perineural level.
- Evidence for clinically-relevant peripheral opioid effect after topical administration is also inconclusive.

10.1.3 Adjuvant drugs

Alpha-2 agonists

- Clonidine prolongs the duration of analgesia and anaesthesia when added to LAs for plexus blocks, peribulbar blocks and peripheral nerve blocks, but is associated with increased hypotension and bradycardia.
- Adding clonidine to lignocaine IV regional anaesthesia delays tourniquet pain.

Magnesium

- Magnesium sulphate improves intra- and postoperative analgesia and tourniquet tolerance when added to lignocaine IV regional analgesia.
- The long-term effects of perineural magnesium are unknown and adding magnesium to LA when performing nerve blocks is not advised.

Ketamine

- Ketamine has been shown to have peripheral analgesic qualities as it reduces pain when applied topically in oral mucositis.

10.1.4 Anti-inflammatory drugs

Corticosteroids

There is evidence to support the use of corticosteroids for their peripheral analgesic action in various clinical settings.

- Subacromial injections of corticosteroids are more effective than oral NSAIDs when treating rotator cuff tendonitis.
- Intra-articular steroids, in combination with an LA, reduce pain, analgesic consumption and the duration of immobilisation after knee arthroscopy. There is, however, an increased risk of septic arthritis following intra-articular corticosteroids.
- Combining dexamethasone with lignocaine for IV regional anaesthesia improves analgesia for up to 24 hours.
- Adding dexamethasone (perineural or IV) to LA increases duration of peripheral nerve blocks significantly compared to LA only. Perineural dexamethasone prolongs the LA nerve block by about three hours compared to IV dexamethasone.

Nonsteroidal anti-inflammatory drugs

Administering NSAIDs at the site of pain is an attractive alternative to oral or parenteral routes, potentially minimising systemic side effects of the drug.

- Topical NSAIDs (possibly excluding indomethacin) are effective in treating acute strains and sprains, providing short-term functional improvement with side effects comparable to placebo. Gel formulations of diclofenac, ibuprofen and ketoprofen, as well as diclofenac patches, work best.
- Topical NSAIDs also provide effective analgesia for traumatic corneal abrasions and are effective for short-term relief of sore throat following tracheal intubation (benzydamine, e.g. Andolex® and flurbiprofen, e.g. Strepsils intensive®).
- Adding a non-selective NSAID to an LA solution for IV regional anaesthesia improves postoperative analgesia.

10.2 Regional and local analgesic techniques

10.2.1 Peripheral nerve blocks and the infusion of local anaesthetics

- Peripheral nerve blocks may be performed either as a single-shot or via an indwelling perineural catheter.
- Evidence of efficacy of peripheral nerve blocks has been confirmed in various clinical settings:
  - Continuous peripheral nerve blocks, regardless of catheter location, provides better postoperative analgesia than systemic opioids, and leads to a reduction in opioid use and side effects (i.e. nausea, vomiting, pruritus and sedation).
  - Continuous peripheral nerve blocks have been shown to be safe when used at home provided that there are adequate resources and patient education is provided.
  - Single-shot infraclavicular blocks provide effective analgesia and less nausea following hand and wrist surgery, and earlier ambulation and hospital discharge compared to GA.

- Following open shoulder surgery, single-shot or continuous interscalene analgesia provides better analgesia and improved patient satisfaction, with reduced opioid-related side effects compared to opioid-based IV PCA.
- A femoral nerve block provides better analgesia than parenteral opioid-based techniques after total knee arthroplasty.
- An adductor canal femoral nerve block, with quadriceps muscle function sparing, may facilitate earlier mobilisation after total knee arthroplasty.
- A continuous femoral nerve block is equianalgesic to epidural analgesia, but with fewer side effects following total knee arthroplasty.
- Continuous posterior lumbar plexus analgesia and continuous femoral analgesia are equally effective following total knee arthroplasty.
- When compared to nerve localisation using a peripheral nerve stimulator, ultrasound-guided blocks are faster to perform, have a more rapid onset and longer duration of action, and are more often successful.

The advantages and disadvantages of peripheral nerve blocks are outlined in Table I.

Table I: Advantages and disadvantages of peripheral nerve blocks

Advantages	Disadvantages
Excellent analgesia	Small risk of bleeding with anticoagulation
Avoids the complications of systemic analgesics	Continual monitoring of analgesia, together with an adjustment of the dose or infusion rate, is mandatory
Promotes early mobilisation and physiotherapy	Potential local anaesthetic toxicity with prolonged infusion (a rare complication)
	Catheter migration with resulting ineffective analgesia
	Infection risk with indwelling catheter
	Possible nerve damage

10.2.2 Interfascial plane blocks

- Interfascial plane blocks, in which LA are introduced into fascial planes where sensory nerves usually course, have been widely applied over the last 10 years.
  - Transversus abdominus plane (TAP) blocks and rectus sheath blocks have emerged as effective treatment modalities for postoperative pain following abdominal and hernia surgery, providing excellent analgesia and decreasing opioid requirements. Breathing and coughing is more comfortable, and early mobilisation and discharge are facilitated. A reduction in persistent postoperative pain with TAP blocks after CS is reported.
  - Paravertebral blocks have been shown to be effective after breast surgery as well as thoracotomy.

- Randomised controlled data is currently lacking regarding newer plane blocks, but indications may be summarised as follows:
  - Breast surgery: pectoralis II, erector spinae plane block or serratus plane block
  - Mini thoracotomy: pec II plus erector spinae block
  - Thoracotomy: serratus plane or erector spinae plane
  - Midline abdominal surgery, including abdominal hernia repair: four-quadrant TAP or erector spinae or quadratus lumborum plane block
  - Lumbar spine surgery: erector spinae plane blocks

10.2.3 Surgical site administration of analgesics

Analgesia administered into or surrounding a surgical wound is an attractive and safe method of blocking noxious stimuli resulting from a surgical insult. This method can take the form of intracavity analgesia (intraperitoneal and intra-articular), musculofascial and subdermal infiltration.

- Peri-articular surgical wound infiltration
  - In hip and knee surgery, single-dose, large-volume, low-concentration LA infiltration of capsule, ligaments and other soft tissue is effective in reducing short-term pain and hospital stay.
  - This technique has been proven beneficial in patients undergoing total knee replacement, with less conclusive data in hip replacement.
  - Periarticular catheter techniques are not recommended due to concerns of catheter-related sepsis.
  - Periarticular techniques for shoulder surgery have not been studied adequately enough to make recommendations.
- Intra-articular techniques
  - When compared with placebo, intra-articular morphine alone following knee arthroscopy does not improve analgesia.
  - Postoperative pain is reduced to a limited degree by single-shot intra-articular LA. Intra-articular bupivacaine infusions have been associated with chondrolysis and are not recommended.
  - Intra-articular NSAIDs, such as ketorolac, result in improved pain relief after surgery. However, long-term follow-up has not been undertaken and the effect on bone healing is unknown.
  - Following knee joint arthroscopy, intra-articular steroids, in combination with either an LA or opioid, reduce pain, analgesic consumption and the duration of immobilisation.

- Local infiltration and continuous wound infusions for abdominal surgery
  - In order for analgesia to be effective, infiltration of peritoneal, musculofascial and subdermal planes are required.
  - Continuous LA wound infusions after laparotomy lead to a reduction in pain at rest and during movement, most notably during first 24 hours postoperatively. Decreased opioid consumption, postoperative nausea and vomiting, and length of hospital stay are reported, while there is no difference in the incidence of wound infections.
  - The infiltration of the wound with LA agents provides good and long-lasting analgesia after inguinal hernia repair, abdominal hysterectomy and ventral hernia repair, but is of limited value in laparoscopic cholecystectomy. With ventral hernia repair, additional infiltration of LA around the perimeter of the mesh creates a field block which covers the fascia closure as well as the mesh fixation sites. Preperitoneal or subfascial catheters allow for continuous LA infusion and prolonged analgesia.
  - There are no studies that compare surgical site infiltration with interfascial plane blocks. Current evidence suggests that a TAP block offers comparable degrees of analgesia to surgical site infiltration with significantly longer duration of action.
- Intraperitoneal LA
  - May reduce early postoperative pain scores following laparoscopic cholecystectomy, but the generalised use of intraperitoneal LA in laparoscopic surgery is of unproven benefit.
  - The benefits of adding adjuncts like magnesium and dexmedetomidine to the mixture remain unproven.

LA doses and infusion rates for peripheral nerve blocks, interfascial plane blocks and surgical site infiltration in adults are covered in Table II.

Table II: Local anaesthetic doses and infusion rates for peripheral nerve blocks in adults

Technique	Drugs	Adult dose	Considerations
Plexus block	Bupivacaine	LD: 0.25–0.50%, 20–40 ml CI: 0.12–0.25%, 5–10 ml/hour	Maximum 2 mg/kg or 6 mg/kg/24 hours Maximum 150 mg or 1 ml/kg bolus
	Levobupivacaine	As for bupivacaine	As for bupivacaine
	Ropivacaine	LD: 0.50–0.75%, 10–40 ml CI: 0.20%, 0.10 ml/kg/hour	Maximum 800 mg/24 hours or 28 mg/hour dose/kg? Maximum 1 ml/kg bolus
Minor nerve blocks, surgical site infiltration and interfascial plane blocks	Bupivacaine	0.25–0.50%, 1–60 ml	Maximum 2.5 mg/kg or 150 mg
	Levobupivacaine	0.25–0.50%, 1–60 ml	Maximum 2.5 mg/kg or 150 mg

LD – loading dose, CI – continuous infusion

10.2.4 Intravenous regional analgesia

IV regional analgesia is a less commonly used technique of administering peripherally-acting analgesics. IV regional analgesia doses are outlined in Table III.

Table III: Intravenous regional analgesia doses

Drug	Dose	Comments
Lignocaine	Maximum dose of 200 mg or 2 mg/kg	Dilute to 40 ml total volume Adding dexamethasone or ketorolac may prolong analgesia Adding clonidine and magnesium delay tourniquet pain

10.2.5 Topical analgesia

Topical application of locally-acting analgesics is potentially associated with a favourable drug side effect profile. The evidence-based topical use of several drugs is summarised in Table IV.

Table IV: Clinical use of topically applied analgesic agents

Drug	Application	Comments
EMLA	Venous ulcer debridement	
Amethocaine	IV cannulation in children	Superior to EMLA
Local anaesthetic on swab	Direct application to tonsil bed with tonsillectomy	Similar analgesia to local anaesthetic infiltration
Ketamine	Mouthwash	Reduced pain from oral mucositis
NSAID Mucosal	Eyedrops	Traumatic corneal abrasions
	Lozenges/oral sprays (benzydamine, flurbiprofen)	Postanaesthesia sore throat following intubation
Transdermal	Gel formulations of diclofenac, ibuprofen and ketoprofen, and diclofenac patches	Acute soft tissue strains and sprains

EMLA – eutectic mixture of local anaesthetics (lignocaine and prilocaine), IV – intravenous, NSAID – nonsteroidal anti-inflammatory drug

10.3 Safety considerations for regional and local analgesic techniques

10.3.1 Anticoagulation

Caution is advised when performing blocks in patients with impaired coagulation where direct pressure in the event of a traumatised blood vessel is not possible (e.g. during a lumbar plexus block, psoas compartment block or infraclavicular brachial plexus block), as a plexopathy may follow haematoma-induced pressure. Guidelines for the removal of peripheral catheters from noncompressible sites are the same as those for the removal of epidural catheters.

10.3.2 Nerve injury

- Most nerve injuries following nerve blocks present as a transient neuropathy with paraesthesia and resolve within 3–6 months.
- The incidence of late neurological injury persisting for more than 6–12 months is approximately 0.04%. (4 per 10 000).
- Permanent neurological injury has been reported following the injection of a LA directly into the cervical spinal cord while an interscalene block was performed GA.
- While ultrasound guidance has been shown to reduce the incidence of intravascular injection, the effect on neurological injury has not been elucidated.

10.3.3 Toxicity

Accidental IV injection or the rapid absorption of a LA in vascular-rich areas can lead to LAST.

- The highest incidence is seen with paravertebral blocks, followed by upper and lower extremity peripheral nerve blocks.
- Risk factors for LAST include small muscle mass, extremes of age and pre-existing heart disease or carnitine deficiency.
- Half the cases of LAST have a delayed onset (> 1 hour) or atypical presentation, with no seizures and only CV toxicity.
- Minimising LAST-related morbidity requires correct patient selection, block choice, drug and dose, complete monitoring and use of ultrasound-guided regional anaesthesia when possible.

10.3.4 Infection

Although the bacterial colonisation of indwelling continuous peripheral nerve catheters is high (16–57%), serious infections and abscess formation are rare. Groin and axilla catheters, catheter placement ≥ 48 hours, and repeated dressing changes are risk factors for colonisation. Catheter tunnelling significantly reduces bacterial colonisation to 6%.

The strongest recommendations for preventing infections are hand hygiene and effective skin preparation, preferably with an alcohol-based chlorhexidine solution. If continuous catheters are used, the full surgical aseptic technique (cap, mask, sterile gown and gloves, and large drapes) is recommended.

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