

5. REGIONALLY AND LOCALLY ADMINISTERED ANALGESIC DRUGS

5.1 LOCAL ANAESTHETICS

Local anaesthetics exert their effect as analgesics by the blockade of sodium channels and hence impeding neuronal excitation and/or conduction.

5.1.1 Short-duration local anaesthetics

Lignocaine (lidocaine) is the most widely used short-duration local anaesthetic in acute pain management. Although the plasma half-life is approximately 90 minutes, the duration of local anaesthetic effect depends very much on the site of administration, dose administered and the presence or absence of vasoconstrictors. Although lignocaine is hydrophilic, it is delivered in high concentrations and therefore usually diffuses well into nerve bundles, resulting in little separation of sensory and motor blocking actions (Covino & Wildsmith, 1998).

The use of lignocaine in ongoing acute pain management is usually restricted to the short-term re-establishment of a local anaesthetic infusion block; it is unsuited to long-term (ie days) use because of the development of tachyphylaxis or acute tolerance (Mogensen, 1995). For example, 24-hour continuous perineural infusions of lignocaine resulted in less effective analgesia and more motor block than infusions of the long-acting local anaesthetic agent ropivacaine (Casati, Vinciguerra et al, 2003 **Level II**).

5.1.2 Long-duration local anaesthetics

The three commonly used long-duration local anaesthetic agents, bupivacaine, levobupivacaine and ropivacaine, are structurally related (Markham & Faulds, 1996; McLeod & Burke, 2001; Casati & Putzu, 2005). Whereas bupivacaine is a racemic mixture of S- and R-enantiomers, levobupivacaine is the S- (or levo) enantiomer of bupivacaine; ropivacaine is likewise an S-enantiomer.

The issue with relative potency emerges with lower doses and concentrations of local anaesthetics. When doses are carefully titrated, a minimum local anaesthetic concentration (MLAC) can be found at which 50% of patients will achieve a satisfactory analgesic block. In obstetric epidural analgesia, two separate studies found the MLAC of bupivacaine was 0.6 times that of ropivacaine (Capogna et al, 1999 **Level II**; Polley et al, 1999 **Level II**). The motor-blocking potency showed a similar ratio of 0.66 (Lacassie et al, 2002 **Level II**).

When comparing bupivacaine with levobupivacaine, the 'percentage' bupivacaine solution is by weight of bupivacaine hydrochloride, whereas % levobupivacaine solution is for the active molecule alone (even though presented as the hydrochloride). This means that the molar dose of equal 'percentage concentration' is 13% higher for levobupivacaine (Schug, 2001). The sensory MLAC potency ratio of levobupivacaine to bupivacaine is 0.98, although if correction is made for molar concentrations this falls to 0.87 (neither value being different from unity) (Lyons et al, 1998 **Level II**). Levobupivacaine has been shown to have slightly less motor-blocking capacity than bupivacaine with a levobupivacaine/ bupivacaine potency ratio for epidural motor blockade of 0.87 (95% CI, 0.77-0.98) (Lacassie & Columb, 2003 **Level II**). Another labour epidural analgesia study has found no difference in MLAC between levobupivacaine and

ropivacaine with a ropivacaine/ levobupivacaine potency ratio of 0.98 (95% CI 0.80 to 1.20) (Polley et al, 2003 **Level II**).

Epidural local anaesthetics

For *postoperative* epidural infusions, dose-ranging studies established that 0.2% ropivacaine was a suitable concentration (Scott et al, 1995 **Level II**; Schug et al, 1996 **Level II**). Therefore, most investigators compare infusions of bupivacaine or levobupivacaine at 0.1% or 0.125% with ropivacaine 0.2%, which removes any imbalance in comparative potency.

The majority of studies find similar analgesic outcomes with postoperative epidural infusions based on these strengths (Jorgensen et al, 2000 **Level II**; Macias et al, 2002 **Level II**; Casati, Santorsola et al, 2003 **Level II**). Motor block is of clinical relevance in low thoracic or lumbar epidural infusions and has been reported to be less intense with epidural ropivacaine than with bupivacaine (Zaric et al, 1996 **Level II**; Muldoon et al, 1998 **Level II**; Merson, 2001 **Level II**). However, this finding has not been supported by other authors.

Ropivacaine 0.2% and levobupivacaine 0.125% provided similar analgesia with similar adverse effects and no motor block when infused via thoracic epidural catheters for lung surgery (De Cosmo et al, 2008 **Level II**). Patient-controlled lumbar epidural analgesia for prostatectomy using ropivacaine 0.2% or levobupivacaine 0.125% resulted in similar pain relief, adverse effects and incidence of motor block (Heid et al, 2007 **Level II**). These two local anaesthetics in these concentrations were also equivalent to 0.125% bupivacaine after hip surgery (Koch et al, 2008 **Level II**). However, epidural ropivacaine 0.165% was inferior to levobupivacaine 0.125% after orthopaedic surgery (Smet et al, 2008 **Level II**). In a comparison between ropivacaine 0.2%, bupivacaine 0.125% and lignocaine 0.5%, the regression of sensory blockade under continuous infusion was least with ropivacaine (Kanai et al, 2007 **Level II**).

The relevance of dose, not concentration or volume of local anaesthetic infused, was confirmed in two trials. The same dose of a mixture of levobupivacaine in three different concentrations (0.5%, 0.25%, and 0.15%) and sufentanil administered during continuous thoracic epidural infusion for thoracotomy resulted in similar efficacy and adverse effects (Mendola et al, 2009 **Level II**) as did two concentrations (0.15% and 0.5%) of levobupivacaine in another trial (Dernedde et al, 2008 **Level II**).

Neither infusions of bupivacaine 0.125% nor ropivacaine 0.2% interfered with neurophysiological assessments after scoliosis surgery (Pham Dang et al, 2008 **Level II**).

At concentrations of 0.5% or greater, there were no significant differences in onset time and intensity or duration of sensory blockade between bupivacaine, levobupivacaine or ropivacaine used for epidural analgesia (Cheng et al, 2002 **Level II**; Casati, Santorsola et al, 2003 **Level II**).

Local anaesthetic/opioid combinations

The quality of pain relief from low-dose epidural infusions of plain local anaesthetic consistently benefits from the addition of adjuvants such as opioids (Crews et al, 1999 **Level II**; Scott et al, 1999 **Level II**; Hubler et al, 2001 **Level II**; Senard et al, 2002 **Level II**) or alpha-2 adrenoceptor agonists (Milligan et al, 2000 **Level II**; Niemi & Breivik, 2002 **Level II**) (see Section 5.3). Potential dose-sparing benefits are more obvious for local anaesthetic side effects (hypotension and motor block) than for opioid-related side effects (Walker et al, 2002 **Level I**).

Comparisons of patient-controlled epidural analgesia (PCEA) using ropivacaine 0.2%, ropivacaine 0.125% and levobupivacaine 0.125%, all with sufentanil 1 mcg/mL (6 ml background plus 2 ml bolus), showed no differences in pain relief or motor block; patients given 0.2% ropivacaine used similar volumes, thus receiving more total dose of local anaesthetic and the same amount of sufentanil (Sitsen et al, 2007 **Level II**). Similarly, there

was no difference in analgesia and no motor blockade reported in a PCEA comparison of ropivacaine 0.05%, 0.075% and 0.1%, with fentanyl 4 mcg/mL and droperidol 25 mcg/mL added to all solutions (Iijima et al, 2007 **Level II**). In another comparison of PCEA 0.625% bupivacaine with fentanyl 3 mcg/mL and 0.15% ropivacaine alone, there was no difference in pain relief; patient satisfaction was lower with PCEA ropivacaine even though it led to fewer opioid-related effects (Pitimana-aree et al, 2005 **Level II**).

No studies directly compare fentanyl to morphine when added to local anaesthetic epidural infusions, although a retrospective audit of the use of high thoracic epidural following cardiac surgery suggested improved pain control and lowered infusion rate using ropivacaine 0.2% with morphine 20 mcg/ml compared with fentanyl 2 mcg/ml (Royse et al, 2005 **Level III-3**).

For information relating to the use of epidural local anaesthetics or opioid/local anaesthetic combinations for *labour* pain see Section 11.1.2.

Peripheral local anaesthetics

A number of studies have compared different local anaesthetics or doses of local anaesthetics used for continuous peripheral nerve blockade (CPNB).

At concentrations of 0.5% or greater, there were no significant differences in onset time and intensity or duration of sensory blockade between bupivacaine, levobupivacaine or ropivacaine in sciatic (Casati et al, 2002 **Level II**), interscalene (Casati, Borghi et al, 2003 **Level II**) or axillary brachial plexus blocks (McGlade et al, 1998 **Level II**). The intensity and duration of motor block is frequently less with ropivacaine compared with bupivacaine or levobupivacaine, but this has little effect on the quality of block for surgery (McGlade et al, 1998 **Level II**; Casati, Borghi et al, 2003 **Level II**).

A comparison of three concentrations (0.1%, 0.2%, 0.3%) of ropivacaine for continuous femoral nerve blockade following total knee arthroplasty found that infusions of 0.2% and 0.3% ropivacaine had equivalent quality of postoperative analgesia (Brodner et al, 2007 **Level II**). After similar surgery, there was no difference in pain relief or motor block between patient-controlled femoral nerve blockade with 0.125% levobupivacaine and 0.2% ropivacaine (Heid et al, 2008 **Level II**).

Comparisons of two different patient-controlled CPNB regimens found different results depending on the location of the block; the regimens were ropivacaine at 4 mL/hr 0.4% (bolus 2 mL) or 8 mL/hr 0.2% (bolus 4 mL). For continuous popliteal nerve blockade, the larger volumes of the dilute local anaesthetic were more likely to cause an insensate limb (Ilfeld et al, 2008 **Level II**); for continuous interscalene nerve block there was no difference between the two solutions (Le et al, 2008 **Level II**), and for continuous infraclavicular nerve block the smaller volumes of the more concentrated local anaesthetic were more likely to cause an insensate limb (Ilfeld et al, 2009 **Level II**).

Another comparison of patient-controlled continuous interscalene blockade using 0.25% levobupivacaine, 0.25% ropivacaine and 0.4% ropivacaine reported less effective pain relief with the lower concentration of ropivacaine (Borghi et al, 2006 **Level II**).

Continuous popliteal sciatic nerve blockade using 0.2% ropivacaine, 0.2% levobupivacaine and 0.125% levobupivacaine resulted in similar pain relief after foot surgery, but fewer patients had complete recovery of motor function at 24 and 48 hours with 0.2% levobupivacaine (Casati et al, 2004 **Level II**).

5.1.3 Local anaesthetic toxicity

Direct toxicity

Lignocaine (5%) infused via lumbar subarachnoid microcatheters has been associated with case reports of cauda equina syndrome (Rigler et al, 1991 **Level IV**; Schell et al, 1991 **Level IV**). This suggested that high local concentrations of lignocaine were potentially neurotoxic and led to the technique falling into disfavour.

Transient Neurological Symptoms (TNS) is a clinical syndrome associated with spinal anaesthesia. Patients experience pain or muscle spasms in the buttocks or lower limbs following initial recovery from the spinal anaesthetic. The onset of symptoms is usually within 24 hours of the procedure and it fully resolves spontaneously within a few days. A meta-analysis was performed of all randomised and pseudo-randomised (Level II and Level III-1) studies comparing the frequency of TNS and neurological complications after spinal anaesthesia with lignocaine to other local anaesthetics; the overall incidence was 14.2% following lignocaine and the relative risk (RR) for developing TNS after spinal anaesthesia with lignocaine compared with other local anaesthetics (bupivacaine, prilocaine, procaine, levobupivacaine, ropivacaine and 2-chloroprocaine) was 7.31 (95% CI 4.16 to 12.86); there was no association with baricity or lignocaine concentration in the individual studies that compared these factors (Zaric et al, 2009 **Level I**).

Systemic toxicity

There are consistent laboratory data showing that the S-enantiomers of the long-acting amide local anaesthetics exhibit less central nervous system (CNS) or cardiac toxicity than the R-enantiomers or the racemic mixtures for doses resulting in equivalent sensory nerve conduction block. It is difficult to define relative toxicities for these agents because it depends on the parameters measured.

There is a lack of scientific data available to determine the safe dose of local anaesthetic. However the upper limit of a safe dose should take into account patient weight, age and comorbidities. There is a pharmacokinetic rationale to support fractional dosing by incremental injection of local anaesthetic. There are case reports of systemic local anaesthetic toxicity occurring using ultrasound guidance, although a meta-analysis found a significantly decreased risk of vascular puncture using ultrasound (RR 0.16; 95% CI 0.05 to 0.47) (Abrahams et al, 2008 **Level I**).

In blinded human volunteer studies, CNS symptoms were detected at IV doses and plasma levels that were 25% higher for ropivacaine compared with bupivacaine (Scott et al, 1989 **Level II**) and 16% higher for levobupivacaine than bupivacaine (Bardsley et al, 1998 **Level II**). Although these data show that CNS toxicity might occur less frequently or be less severe with the S-enantiomers, all local anaesthetics are toxic. A rapid IV bolus of any of these agents may overwhelm any of the more subtle differences found at lower plasma concentrations.

Severe myocardial depression and refractory ventricular fibrillation have been described as the hallmark of accidental IV administration of moderately large doses of bupivacaine. This has been attributed to the slow dissociation of bupivacaine from the myocardial sodium channel, which is less marked with levobupivacaine and ropivacaine (Mather & Chang, 2001; Mather et al, 2005). Animal studies confirm that higher systemic doses of ropivacaine and levobupivacaine are required to induce ventricular arrhythmias, circulatory collapse or asystole (Ohmura et al, 2001), with the ranking of toxicity risk being bupivacaine > levobupivacaine > ropivacaine (Grobán & Dolinski, 2001).

Controlled human studies are only possible when looking at surrogate endpoints such as ECG changes or myocardial depression and suggest a similar ranking of effect (Scott et al, 1989 **Level II**; Knudsen et al, 1997 **Level II**; Bardsley et al, 1998 **Level II**; Mather & Chang, 2001 **Level II**), with bupivacaine being the most toxic and levobupivacaine being less toxic and similar to ropivacaine (Stewart et al, 2003 **Level II**).

Successful resuscitation from a massive overdose is of greater relevance in clinical practice. A canine study investigating resuscitation and survival following local anaesthetic-induced circulatory collapse showed survival rates of 50%, 70% and 90% with bupivacaine, levobupivacaine and ropivacaine respectively (Groban & Dolinski, 2001).

Case reports of accidental toxic overdose with ropivacaine and bupivacaine suggest that outcomes are more favourable and resuscitation more straightforward (in particular requiring less cardiovascular [CV] support) with ropivacaine (Pham-Dang et al, 2000; Chazalon et al, 2003; Huet et al, 2003; Klein et al, 2003; Soltesz et al, 2003; Khoo & Corbett, 2006; Kimura et al, 2007).

Total plasma levels of local anaesthetic tend to rise during the first 48 hours of postoperative infusion, although free levels remain relatively low (Emanuelsson et al, 1995; Scott et al, 1997). Thus, in published studies, toxicity due to systemic absorption from epidural or perineural infusions has not been a problem. However, the risk of accidental absolute overdose with postoperative infusions suggests that the less toxic agents should be used in preference and that the doses administered should be the minimum needed for efficacy.

There is basic scientific evidence and several case reports to support the use of IV lipid emulsion therapy for systemic local anaesthetic toxicity resulting in CV collapse (Felice & Schumann, 2008 **Level IV**). Animal experimental data (Weinberg et al, 2003; Weinberg et al, 1998) have been supported by a few case reports of successful resuscitation following bupivacaine (Rosenblatt et al, 2006), ropivacaine (Litz et al, 2006), levobupivacaine (Foxall et al, 2007), mepivacaine/prilocaine (Litz et al, 2008) and mepivacaine/bupivacaine (Warren et al, 2008) toxicity. The mechanism of action of the lipid emulsion may be due to partitioning of local anaesthetic within the emulsion itself (Weinberg, 2006) or mitochondrial substrate enhancement in the myocardium (Weinberg et al, 2000). Uncertainties relating to dosage, efficacy and side effects still remain and therefore it is recommended that lipid emulsion only be administered after advanced cardiac life support has commenced, including adrenaline administration, and convulsions controlled (Corman & Skledar, 2007 **Level IV**). Guidelines have been established to facilitate management of local anaesthetic toxicity, which now include reference to lipid emulsion therapy (AAGBI, 2007). It should be noted that local anaesthetic toxicity might recur following successful initial resuscitation, suggesting a need for continued intensive observation if a large dose of local anaesthetic has been administered (Marwick et al, 2009).

Key messages

1. Lignocaine is more likely to cause transient neurologic symptoms than bupivacaine, prilocaine and procaine (**N**) (**Level I** [Cochrane Review]).
2. The quality of epidural analgesia with local anaesthetics is improved with the addition of opioids (**U**) (**Level 1**).
3. Ultrasound guidance reduces the risk of vascular puncture during the performance of regional blockade (**N**) (**Level I**).
4. Continuous perineural infusions of lignocaine (lidocaine) result in less effective analgesia and more motor block than long-acting local anaesthetic agents (**U**) (**Level II**).

5. There are no consistent differences between ropivacaine, levobupivacaine and bupivacaine when given in low doses for regional analgesia (epidural and peripheral nerve blockade) in terms of quality of analgesia or motor blockade (**U**) (**Level II**).
6. Cardiovascular and central nervous system toxicity of the stereospecific isomers ropivacaine and levobupivacaine is less severe than with racemic bupivacaine (**U**) (**Level II**).
7. Lipid emulsion is effective in resuscitation of circulatory collapse due to local anaesthetic toxicity, however uncertainties relating to dosage, efficacy and side effects still remain and therefore it is appropriate to administer lipid emulsion once advanced cardiac life support has begun and convulsions are controlled (**N**) (**Level IV**).

The following tick box represents conclusions based on clinical experience and expert opinion.

- Case reports following accidental overdose with ropivacaine and bupivacaine suggest that resuscitation is likely to be more successful with ropivacaine (**U**).

5.2 OPIOIDS

5.2.1 Neuraxial opioids

Opioid receptors were described in the spinal cord of the rat in 1976 (Pert et al, 1976) and the same year a potent analgesic effect of directly applied intrathecal morphine was reported in these animals (Yaksh & Rudy, 1976). Opioid analgesia is spinally mediated via presynaptic and postsynaptic receptors in the substantia gelatinosa in the dorsal horn (Yaksh, 1981). Spinal opioid receptors are 70% mu, 24% delta and 6% kappa (Treman & Bonica, 2001), with 70% of all mu and delta receptors being presynaptic (predominantly small primary afferents) and commonly co-located, and kappa receptors being more commonly postsynaptic. Antinociception may be further augmented by descending inhibition from mu-opioid receptor activation in the periaqueductal area of the brain, which may be potentiated by neuraxial opioids. In addition to this, a local anaesthetic action has been described for pethidine (meperidine), which may contribute to the clinical effect when administered intrathecally (Jaffe & Rowe, 1996). The first clinical use of intrathecal morphine was for analgesia in cancer patients (Wang et al, 1979).

Neuraxial opioids may cause respiratory depression, sedation, nausea, vomiting, pruritus, urinary retention and decreased gastrointestinal motility. Depending on type and dose of the opioid, a combination of spinal and systemic mechanisms may be responsible for these adverse effects. Many of these effects are more frequent with morphine and are to some extent dose related (Dahl et al, 1999 **Level I**; Cole et al, 2000 **Level I**). Late onset respiratory depression, which is believed to be a result of the cephalad spread of opioids within the cerebrospinal fluid, is also seen more commonly with hydrophilic opioids such as morphine (Cousins & Mather, 1984).

Intrathecal opioids

The lipid solubility of opioids largely determines the speed of onset and duration of intrathecal analgesia; hydrophilic drugs (eg morphine) have a slower onset of action and longer half-lives in cerebrospinal fluid with greater dorsal horn bioavailability and greater cephalad migration compared with lipophilic opioids (eg fentanyl) (Bernards et al, 2003).

Safety studies and widespread clinical experience with morphine, fentanyl and sufentanil have shown no neurotoxicity or behavioural changes at normal clinical intrathecal doses (Hodgson et al, 1999 **Level IV**). Other opioid agonists or partial agonists do not have animal or human safety data.

Early clinical studies used very high intrathecal morphine doses (ie 500 mcg or more), however adequate postoperative analgesia with fewer adverse effects may be obtained with significantly less morphine — although at lower doses there is not a clear dose-response relationship for some side effects or pain relief (Meylan et al, 2009 **Level I**). A meta-analysis comparing intrathecal morphine doses of less than 300 mcg, equal to or greater than 300 mcg, and placebo reported a greater risk of respiratory depression and of nausea and vomiting with the higher, but not lower, doses of morphine, while the incidence of pruritus was increased for all doses (Gehling & Tryba, 2009 **Level I**).

Following hip and knee arthroplasty, intrathecal morphine (100 to 300 mcg) provided excellent analgesia for 24 hours after surgery with no difference in side effects; after hip arthroplasty only there was a significant reduction in postoperative patient-controlled (PCA) morphine requirements (Rathmell et al, 2003 **Level II**). Following knee arthroplasty, intrathecal morphine 500 mcg compared with 200 mcg reduced supplemental rescue analgesia (tramadol) over 24 hours with no difference in adverse event rates (Bowrey et al, 2005 **Level II**), and 200 mcg was as effective as 300 mcg with no difference in side effects; both were superior to 100 mcg (Hassett et al, 2008 **Level II**). After hip arthroplasty, 100 mcg and 200 mcg doses of intrathecal morphine produced good and comparable pain relief and reductions in postoperative morphine requirements; 50 mcg was ineffective (Murphy et al, 2003 **Level II**).

When combined with low-dose bupivacaine for Caesarean section, 100 mcg intrathecal morphine produced analgesia comparable with doses as high as 400 mcg, with significantly less pruritus (Girgin et al, 2008 **Level II**). A single dose of morphine (100 mcg) added to a spinal anaesthetic for Caesarean section prolonged the time to first postoperative analgesic administration resulting in at least 11 hours of effective analgesia. Adverse effects included pruritus (43%), nausea (10%) and vomiting (12%). The rate of respiratory depression was low (see below). In these patients, sufentanil and fentanyl showed no analgesic benefits (Dahl et al, 1999 **Level I**).

The addition of 10 mcg sufentanil to 0.4 mg intrathecal morphine did not potentiate postoperative analgesia or reduce intraoperative opioid requirements in patients undergoing major colorectal surgery (Culebras et al, 2007 **Level II**). The addition of intrathecal fentanyl to low-dose spinal bupivacaine for anorectal surgery resulted in more pruritus but lower mean recovery and discharge times, with fewer analgesic requests in the fentanyl group (Gurbet et al, 2008 **Level II**).

In a more recent study, intrathecal sufentanil provided shorter postoperative analgesia (mean 6.3 hours) than intrathecal morphine (mean 19.5 hours) with no difference in side effects (Karaman et al, 2006 **Level II**). In another comparison of intrathecal morphine (100 mcg) and intrathecal pethidine (10 mg) for analgesia following Caesarean section in a non-blinded study, patients receiving morphine had longer analgesia and fewer intraoperative side effects than the pethidine group, but experienced more pruritus (Kumar et al, 2007 **Level II**).

For more information on effectiveness and side effects related to the use of intrathecal opioids see Section 7.3.

Epidural opioids

The behaviour of epidural opioids is also governed largely by their lipid solubility. The greater sequestration of lipid soluble opioids into epidural fat and slow re-release back into the epidural space means that elimination from the epidural space is prolonged, resulting in relatively smaller fractions of drug reaching the cerebrospinal fluid (Bernards et al, 2003). Lipophilic opioids (eg fentanyl) have a faster onset but shorter duration of action compared with hydrophilic drugs (eg morphine) (de Leon-Casasola & Lema, 1996; Bernards, 2004).

Morphine is the least lipid soluble of the opioids administered epidurally; it has the slowest onset and offset of action (Cousins & Mather, 1984) and the highest bioavailability in the spinal cord after epidural administration (Bernards, 2004). As it has a prolonged analgesic effect it can be given by intermittent bolus dose or infusion; the risk of respiratory depression may be higher and analgesia less effective with bolus dose regimens (de Leon-Casasola & Lema, 1996).

The evidence that epidural fentanyl acts via a spinal rather than systemic effect is conflicting and it has been suggested that any benefit when comparing epidural with systemic fentanyl alone is marginal (Wheatley et al, 2001; Bernards, 2004). However, the conflicting results may be due to differing modes of administration. An infusion of epidural fentanyl appears to produce analgesia by uptake into the systemic circulation, whereas a bolus dose of fentanyl produces analgesia by a selective spinal mechanism (Ginosar et al, 2003 **Level IV**). There is no evidence of benefit of epidural versus systemic administration of alfentanil or sufentanil (Bernards, 2004)

Pethidine is effective when administered epidurally by bolus dose, continuous infusion and by PCEA. It is more lipid soluble than morphine (but less than fentanyl and its analogues), thus its onset and offset of epidural analgesic action is more rapid than morphine (Ngan Kee, 1998 **Level IV**). The analgesic effect of smaller doses appears to be spinally mediated but systemic effects are likely after larger doses; in the smaller doses it is not known whether the local anaesthetic properties of pethidine contribute significantly to pain relief (Ngan Kee, 1998 **Level IV**). Epidural pethidine has been used predominantly in the obstetric setting. After Caesarean section epidural pethidine resulted in better pain relief and less sedation than IV pethidine (Paech et al, 1994 **Level II**) but inferior analgesia compared with intrathecal morphine, albeit with less pruritus, nausea and drowsiness (Paech et al, 2000 **Level II**).

Diamorphine (diacetylmorphine, heroin) is rapidly hydrolysed to (monoacetylmorphine) MAM and morphine. Diamorphine and MAM are more lipid soluble than morphine and penetrate the CNS more rapidly, although it is MAM and morphine that are thought to be responsible for the analgesic effects of diamorphine (Miyoshi & Lackband, 2001). Epidural administration of diamorphine is common in the United Kingdom and is effective whether administered by intermittent bolus dose or infusion (McLeod et al, 2005).

The quality of epidural analgesia with hydromorphone is similar to morphine (Chaplan et al, 1992 **Level II**). In a comparison of epidural and IV hydromorphone, patients required twice as much IV hydromorphone to obtain the same degree of analgesia (Liu et al, 1995 **Level II**).

The addition of butorphanol to epidural bupivacaine resulted in more rapid and prolonged pain relief compared with butorphanol alone (Bharti & Chari, 2009 **Level II**).

An extended-release suspension of morphine has been developed for epidural use (Depodur™) consisting of morphine molecules suspended in liposome complexes (lipifoam). Extended-release epidural morphine (EREM) has been shown to be effective compared with placebo after hip arthroplasty (Viscusi et al, 2005 **Level II**; Martin et al, 2006 **Level II**) and, using doses of 10 mg or more, to lead to better pain relief compared with standard epidural morphine (4 or 5 mg) and a reduction in the need for supplemental analgesics up to 48 hours after hip arthroplasty (Viscusi et al, 2006 **Level III-1**), lower abdominal surgery (Gambling et al, 2005

Level II) and Caesarean section (Carvalho et al, 2005 **Level II**; Carvalho et al, 2007 **Level II**). Respiratory depression has been reported to occur in up to 5.4% of patients depending on the definition used (Carvalho et al, 2005 **Level II**; Gambling et al, 2005 **Level II**; Viscusi et al, 2005 **Level II**; Martin et al, 2006 **Level II**) and it may require prolonged treatment; in one patient naloxone was required for 62 hours (Martin et al, 2006 **Level II**).

It has been recommended that the liposome preparation of Depodur® not be administered while local anaesthetics are present in the epidural space as this may cause early release of the morphine (Viscusi et al, 2009 **Level II**). When Depodur® was administered within 3 to 15 minutes of a 3 mL test dose of 1.5% lignocaine with adrenaline, higher C_{max} values for morphine were indeed reported compared with C_{max} values when no lignocaine was administered; there was no difference in morphine C_{max} if the interval was greater than 30 minutes (Viscusi et al, 2009 **Level II**). The C_{max} of morphine was unchanged when Depodur® doses were given 15, 30 and 60 minutes after an anaesthetic dose of epidural bupivacaine – 20 ml of 0.25% (Gambling et al, 2009 **Level II**).

5.2.2 Peripheral opioids

Opioid receptors on sensory unmyelinated C nerve fibres mediate peripheral antinociceptive effects in animal studies (Stein et al, 1990). In the presence of inflammation, opioid receptors are transported to the periphery and increased amounts of endogenous opioid peptides are present in infiltrating immune cells (Schafer, 1999; Smith, 2008; Stein, 1995). An experimental model of inflammatory hyperalgesia caused by ultraviolet light showed that analgesia mediated via peripheral opioid mechanisms could also occur in humans (Koppert et al, 1999 **Level II**). In joint studies, the increase in opioid receptors and their endogenous peptides correlated with the degree of inflammation, being more abundant in rheumatoid arthritis than in osteoarthritis and joint trauma (Mousa et al, 2007), consistent with the clinical observation that peripheral opioids are more effective in the presence of inflammation. Intra-articular bupivacaine was less effective than morphine in providing analgesia in patients having ‘high inflammatory arthroscopic knee surgery’, whereas bupivacaine was more effective than morphine in those having ‘low inflammatory surgery’ (Marchal et al, 2003 **Level II**) (see also Section 7.5).

In clinical practice, morphine injected as a single dose into the knee intra-articular space produced analgesia that lasted up to 24 hours, but evidence for a peripheral rather than a systemic effect was not conclusive (Gupta et al, 2001 **Level I**; Kalso et al, 2002 **Level I**).

Confounding variables that hinder analysis included the pre-existing degree of inflammation, type of surgery, the baseline pain severity and the overall relatively weak clinical effect (Gupta et al, 2001 **Level I**). When published trials were analysed taking these confounding factors into consideration, including the intensity of early postoperative pain, the data did not support an analgesic effect for intra-articular morphine following arthroscopy compared with placebo (Rosseland, 2005 **Level I**).

Note: reversal of conclusions

This reverses the Level 1 conclusion in the previous edition of this document; the earlier meta-analyses performed without taking confounding factors into consideration had reported improved pain relief with intra-articular morphine.

The addition of intra-articular sufentanil to a mixture of ropivacaine and clonidine following anterior cruciate ligament repair provided no additional analgesic benefits (Armellin et al, 2008 **Level II**). A mixture of intra-articular bupivacaine and 100 mg tramadol resulted in better pain relief and lower rescue analgesic requirements than use of either drug alone (Zeidan et al, 2008 **Level II**).

There is no evidence for analgesic efficacy of peripheral opioids at non-intra-articular sites, including use with perineural blockade (Picard et al, 1997 **Level I**). While opioid receptors have been identified in the cornea and skin, topically applied opioids have not consistently demonstrated efficacy in pain states such as corneal ulceration (fentanyl) (Zollner et al, 2008 **Level II**), partial thickness burns (morphine) (Welling, 2007 **Level II**), or chronic skin ulceration (morphine) (Vernassiere et al, 2005 **Level II**).

Although commonly used, oral morphine mouthwash in chemotherapy-induced mucositis pain has only limited supporting evidence; a dose-response (beneficial) effect was seen in a small pilot study using 1 mg/mL and 2 mg/mL morphine mouthwash (Cerchietti et al, 2003 **Level II**). Benefit was also evident in a small comparison of morphine mouthwash 30 mg 3-hourly, with a local anaesthetic-based solution, in mucositis associated with chemoradiotherapy in head and neck cancer patients (Cerchietti et al, 2002 **Level II**).

Key messages

1. Intrathecal morphine produces better postoperative analgesia than intrathecal fentanyl after Caesarean section (**U**) (**Level I**).
2. Intrathecal morphine doses of 300 mcg or more increase the risk of respiratory depression (**N**) (**Level I**).
3. Morphine injected into the intra-articular space following knee arthroscopy does not improve analgesia compared with placebo when administered after surgery (**R**) (**Level I**).
4. Evidence for a clinically relevant peripheral opioid effect at non-articular sites, including perineural, is inconclusive (**U**) (**Level I**).
5. Epidural pethidine produces better pain relief and less sedation than IV pethidine after Caesarean section (**U**) (**Level II**).
6. Extended release epidural morphine provides analgesia for up to 48 hours, however central depressant effects, including respiratory depression, may also be increased and prolonged (**N**) (**Level II**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

- No neurotoxicity has been shown at normal clinical intrathecal doses of morphine, fentanyl and sufentanil (**U**).
- Neuraxial administration of bolus doses of hydrophilic opioids carries an increased risk of delayed sedation and respiratory depression compared with lipophilic opioids (**U**).

5.3 ADJUVANT DRUGS

5.3.1 Alpha-2 agonists

Neuraxial

Clonidine is an alpha-2 adrenoceptor agonist that acts as an analgesic at the level of the spinal cord. There is no human or animal evidence of neurotoxicity when preservative-free clonidine is administered intrathecally (Hodgson et al, 1999). Epidural clonidine is approved by the United States Food and Drug Administration (FDA) for relief of chronic cancer pain.

Intrathecal clonidine given in doses from 15 to 150 mcg combined with intrathecal local anaesthetic, significantly prolonged the time to two segment block regression but did not affect the rate of onset of a complete block (Elia et al, 2008 **Level I**). Intrathecal clonidine also prolonged the time to first analgesic request (median 101 min, range 35 to 310 min) and duration of motor block but in a non-dose-dependent manner; intraoperative pain was reduced but hypotension was more frequent (RR 1.8; 95% CI 1.4 to 2.3) (Elia et al, 2008 **Level I**). Others have reported that the addition of either clonidine or dexmedetomidine to intrathecal bupivacaine increased the speed of onset and duration of motor and sensory block without additional side effects (Kanazi et al, 2006 **Level II**).

Intrathecal clonidine 100 mcg added to 500 mcg intrathecal morphine resulted in better pain relief and faster time to extubation after cardiac surgery compared with intrathecal morphine alone (Nader et al, 2009 **Level II**). In patients undergoing radical prostatectomy, the addition of clonidine to intrathecal morphine prolonged analgesia compared with intrathecal morphine alone and PCA morphine; intrathecal morphine alone was better than PCA (Andrieu et al, 2009 **Level II**).

A review by Roelants of multiple randomised controlled trials (RCTs) concluded that small doses of intrathecal clonidine (30 mcg) combined with local anaesthetics and opioids prolonged labour analgesia; hypotension may occur and was more common with higher doses of clonidine (Roelants, 2006 **Level II**). Intrathecal clonidine combined with bupivacaine had a postoperative antihyperalgesic effect at 48 hours after elective Caesarean delivery compared with intrathecal bupivacaine-sufentanil and intrathecal clonidine 75 mcg-bupivacaine-sufentanil, however no reduction in pain scores or opioid requirements was observed (Lavand'homme et al, 2008 **Level II**). In another study, the combination of subarachnoid bupivacaine, fentanyl, morphine and clonidine significantly prolonged pain relief following Caesarean section, but with increased sedation (Paech et al, 2004 **Level II**).

The addition of clonidine to PCEA with ropivacaine and morphine after total knee arthroplasty decreased opioid requirements and improved analgesia without increasing side effects (Huang et al, 2007 **Level II**). The addition of clonidine to epidural levobupivacaine, also after hip arthroplasty, significantly reduced postoperative morphine requirements compared with either drug alone (Milligan et al, 2000 **Level II**). Low-dose infusion of clonidine alone via thoracic epidural catheters after spinal surgery reduced systemic opioid requirements and nausea without causing significant sedation or hypotension (Farmery & Wilson-MacDonald, 2009 **Level II**).

In children, addition of clonidine to bupivacaine caudal injection increased the duration (Ansermino et al, 2003 **Level I**) and quality of analgesia without an increase in side effects (Yildiz et al, 2006 **Level II**) (see also Section 10.7.2).

Plexus block

There is evidence of analgesic benefit with the addition of clonidine to local anaesthetics for brachial plexus blocks (Murphy et al, 2000 **Level I**) but many of the studies have methodological limitations.

Clonidine improved duration of analgesia and anaesthesia when used as an adjunct to local anaesthetics for axillary and peribulbar blocks; side effects appeared to be limited at doses up to 150 mcg (McCartney et al, 2007 **Level I**⁹). The addition of clonidine to local anaesthetic solutions used for single-shot peripheral nerve or plexus blocks also prolonged duration of analgesia and motor block (Popping et al, 2009 **Level I**). The effects of the addition of clonidine to lignocaine were similar to those of adding adrenaline in cervical plexus blockade in terms of block onset and duration, although lignocaine absorption was faster when clonidine was used (Molnar et al, 1997 **Level II**). Addition of clonidine to a popliteal fossa nerve block with bupivacaine did not result in any difference in pain relief but did prolong the analgesic effects (YaDeau et al, 2008 **Level II**). There was no difference in pain relief when clonidine was added to a continuous femoral nerve infusion with ropivacaine (Casati et al, 2005 **Level II**).

The use of clonidine with local anaesthetic or opioid also extended analgesia with thoracic paravertebral blocks (Bhatnagar et al, 2006 **Level II**; Burlacu et al, 2006 **Level II**).

Evidence is lacking for the use of clonidine as an adjunct to local anaesthetics for continuous catheter techniques (McCartney et al, 2007 **Level I**⁹).

Intravenous regional anaesthesia

Addition of dexmedetomidine to lignocaine IV regional anaesthesia (IVRA) increased duration and quality of analgesia (Memis et al, 2004 **Level II**). Clonidine was effective in delaying tourniquet pain with IVRA in volunteers (Lurie et al, 2000 **Level III-2**).

Intra-articular

The use of intra-articular clonidine on its own or in addition to local anaesthetic agents improved analgesia after knee joint arthroscopy and decreased opioid consumption (Brill & Plaza, 2004 **Level II**; Alagol et al, 2005 **Level II**).

Intra-articular dexmedetomidine resulted in a longer duration of pain relief compared with IV dexmedetomidine (Al-Metwalli et al, 2008 **Level II**).

5.3.2 Adrenaline

Neuraxial

In postoperative thoracic epidural infusions, the addition of adrenaline (epinephrine) to fentanyl and ropivacaine or bupivacaine improved analgesia (Sakaguchi et al, 2000 **Level II**; Niemi & Breivik, 2002 **Level II**; Niemi & Breivik, 2003 **Level II**). This was not demonstrated with lumbar epidural infusions (Forster et al, 2003 **Level II**). The efficacy of thoracic epidural pethidine infusions after thoracotomy was not improved by addition of adrenaline (Bryson et al, 2007 **Level II**).

The addition of adrenaline (0.2 mg) to intrathecal bupivacaine prolonged motor block and some sensory block modalities (Moore JM et al, 1998 **Level II**).

9 This systematic review includes a study or studies that have since been withdrawn from publication. Please refer to the *Introduction* at the beginning of this document for comments regarding the management of retracted articles. Marret et al (Marret et al, *Anesthesiology* 2009; 111:1279–89) re-examined the data included in this review and concluded that exclusion of data obtained from the retracted publications did not significantly alter the results.

5.3.3 Ketamine

Neuraxial

Some commercially available preparations of ketamine contain an untested preservative (benzethonium chloride) and a low pH (pH 3.5 to 5.5) and so cannot be recommended for intrathecal use in humans (Hodgson et al, 1999).

The addition of intrathecal ketamine to bupivacaine did not prolong postoperative analgesia or reduce analgesic requirements, but did lead to significantly more nausea and vomiting, sedation, dizziness, nystagmus and 'strange feelings' (Kathirvel et al, 2000 **Level II**).

Early postoperative analgesia was improved by the use of epidural racemic ketamine with bupivacaine for lower limb amputations, although pain at 1 year was not different; perioperative opioids were not used (Wilson et al, 2008 **Level II**). The combination of ketamine with opioid-based (+/- local anaesthetic) solutions for epidural analgesia improved pain relief (Subramaniam et al, 2004 **Level I**) and may reduce overall opioid requirements (Walker et al, 2002 **Level I**) without increasing the incidence of adverse effects (Walker et al, 2002 **Level I**; Subramaniam et al, 2004 **Level I**).

A combination of bupivacaine, ketamine and midazolam administered intrathecally prolonged the analgesic time following lower limb surgery compared with bupivacaine alone or bupivacaine with ketamine; however the authors cautioned that the safety of such combinations has not yet been established (Murali Krishna et al, 2008 **Level II**).

Use of intrathecal S(+) ketamine with bupivacaine for Caesarean section decreased time to onset and increased spread of the block, but did not prolong the duration compared with fentanyl (Unlugenc et al, 2006 **Level II**).

Caudal epidural ketamine 0.25 to 0.5 mg/kg in children, in combination with local anaesthetic prolonged analgesia with few side effects (Ansermino et al, 2003 **Level I**; Tsui & Berde, 2005) (see also Section 10.7.2).

Peripheral sites

Most studies on the use of ketamine alone or with local anaesthesia, show no analgesic benefit for peripheral neural blockade, such as brachial plexus block for arm surgery, (Lee et al, 2002 **Level II**), intra-articular injection (Rosseland et al, 2003 **Level II**) or wound infiltration such as following Caesarean section (Zohar et al, 2002 **Level II**) or inguinal hernia repair (Clerc et al, 2005 **Level II**), although pain scores were lower with preincisional ketamine versus saline in circumcision (Tan et al, 2007 **Level II**). Adding ketamine to lignocaine IVRA did not result in better pain relief compared with ketamine given intravenously (Viscomi et al, 2009 **Level II**).

Topical

Topical administration of ketamine might result in effective systemic plasma concentrations making it difficult to interpret any local effects (Poyhia & Vainio, 2006). A transdermal ketamine patch (delivering 25 mg over 24 hours) reduced analgesic consumption after gynaecological surgery (Azevedo et al, 2000 **Level II**) but analgesic effects from topical ketamine (3 mL 0.3%) applied to the tonsillar fossa after tonsillectomy, although superior to placebo, added no benefit to topical morphine (Canbay et al, 2008 **Level II**).

Topical ketamine as a mouthwash has been reported to be effective in reducing pain and opioid consumption from oral mucositis at rest and with eating (Slatkin & Rhiner, 2003).

5.3.4 Midazolam

Midazolam, the preservative-free preparation, has been proposed as a potential spinal analgesic due to its action on GABA_A receptors. It is not approved for this indication and efficacy and safety issues remain unclear.

Reports of intrathecal midazolam administration have appeared in the literature for many years, despite concerns regarding potential neurotoxicity (Yaksh & Allen, 2004). Early clinical series (Tucker, Lai et al, 2004 **Level III-2**; Tucker, Mezzatesta et al, 2004 **Level III-2**) and laboratory investigations (Johansen et al, 2004) suggested a low risk of toxicity — neurotoxic damage was not seen in sheep and pigs given continuous intrathecal midazolam (Johansen et al, 2004) and a 1-month questionnaire follow-up of patients who had received intrathecal midazolam failed to show any evidence of neurological or urological complications (Tucker, Lai et al, 2004 **Level III-2**).

A meta-analysis of intrathecal midazolam in perioperative and peripartum patients showed the addition of intrathecal midazolam (typically 2 mg or more) to other spinal medications reduced the incidence of nausea and vomiting and delayed the time to request for rescue analgesia, but had little effect beyond 12 hours (Ho & Ismail, 2008 **Level I**). The incidence of neurological symptoms after intrathecal midazolam was uncommon (1.8%) and did not differ from placebo (Ho & Ismail, 2008 **Level I**). There are insufficient data to exclude the possibility of long-term neurological complications from intrathecal midazolam, although none have yet been reported.

Another study reported that the addition of subarachnoid midazolam for labour pain produced no effect on its own, but potentiated the analgesic effect of intrathecal fentanyl (Tucker, Mezzatesta et al, 2004 **Level II**). Combining intrathecal midazolam (2 mg) with bupivacaine for Caesarean section significantly prolonged the block and reduced nausea without CV or neurological side effects (Prakash et al, 2006 **Level II**).

Midazolam added to bupivacaine for epidural infusion improved analgesia but increased sedation (Nishiyama et al, 2002 **Level II**). In patients having a gastrectomy, single dose preoperative epidural midazolam combined with ketamine improved analgesia and prolonged the time to rescue analgesia compared with epidural ketamine or placebo, with no significant adverse effects (Wang et al, 2006 **Level II**).

Midazolam has been added to caudal epidural analgesia in paediatric surgery; age-related toxicity issues have not been addressed. In combination with bupivacaine it prolonged postoperative analgesia (Kumar et al, 2005 **Level II**; Ansermino et al, 2003 **Level I**).

5.3.5 Neostigmine

Neostigmine acts as a spinal analgesic by potentiation of muscarinic cholinergic activity. In a literature review of animal and human studies there was no evidence of neurotoxicity with spinal neostigmine (Hodgson et al, 1999).

Intrathecal neostigmine for perioperative and peripartum analgesia resulted in a slight improvement in pain scores and reduced the need for rescue medication; however, it increased nausea and vomiting (OR 5), bradycardia requiring atropine (OR 2.7) and anxiety, agitation and restlessness (OR 10.3) (Ho et al, 2005 **Level I**). The authors concluded that the significant side effects outweighed any clinical benefit.

Epidural neostigmine combined with an opioid reduced the dose of epidural opioid that is required for analgesia but there may not be any decrease in opioid-related side effects compared with the opioid alone (Walker et al, 2002 **Level I**). Epidural neostigmine in the obstetric population improved postoperative analgesia in most studies without increasing the incidence of adverse events (Habib & Gan, 2006 **Level I**). Epidural neostigmine combined with sufentanil or

clonidine, as initial labour analgesia, was without side effects and allowed a 'mobile epidural'; at the doses studied it produced modest analgesia following Caesarean section (Roelants, 2006 **Level II**). The addition of epidural clonidine to bupivacaine reduced hourly patient-controlled epidural bupivacaine requirements during labour (Ross et al, 2009 **Level I**).

Intra-articular administration of neostigmine produced a useful analgesic effect in the postoperative period and was not associated with an increase in the incidence of adverse effects (Habib & Gan, 2006 **Level I**).

Studies investigating the efficacy of adding neostigmine to the local anaesthetics used for brachial plexus block and intravenous regional anaesthesia reported conflicting results indicating the need for further studies (Habib & Gan, 2006 **Level I**).

5.3.6 Magnesium

The long-term effects of perineural or neuraxial magnesium have not been clarified.

In patients undergoing orthopaedic surgery, supplementation of spinal anaesthesia with combined intrathecal and epidural magnesium sulphate significantly reduced patients' postoperative morphine requirements (Arcioni et al, 2007 **Level II**). Addition of magnesium sulphate to lignocaine IVRA improved intra- and postoperative analgesia and tolerance of the tourniquet (Turan et al, 2005 **Level II**; Kashefi et al, 2008 **Level II**). While the addition of magnesium to intrathecal bupivacaine prolonged the times for block regression and first request for analgesia after knee arthroscopy, time to ambulation was longer in the magnesium group (Dayioglu et al, 2009 **Level II**).

Intra-articular magnesium combined with bupivacaine resulted in better pain relief than either drug given alone or placebo (Elsharnouby et al, 2008 **Level II**).

5.3.7 Botulinum toxin A

Following direct IM injection, botulinum toxin acts to irreversibly bind to the acetylcholine receptor and induce a chemical denervation with resultant muscular paralysis. The extent and duration of paralysis depends on the dose administered. Systemic weakness may follow high cumulative doses. Reinnervation may occur over a period of weeks to months.

In treating pain and related muscle spasm in multiple sclerosis, data on the use of botulinum toxin are conflicting and of low quality (Shakespeare et al, 2003). Similarly, the current evidence does not support the use of botulinum toxin injection in trigger points for myofascial pain (Ho & Tan, 2007 **Level I**). In subacute and chronic neck disorders IM botulinum toxin injections have similar effects to saline in improving pain (pooled mean difference: -0.39; CI -1.25 to 0.47) (Peloso et al, 2007 **Level I**); although there is benefit in cervical dystonia (Simpson et al, 2008 **Level I**).

Key messages

1. Intrathecal clonidine improves duration of analgesia and anaesthesia when used as an adjunct to intrathecal local anaesthetics (**N**) (**Level I**).
2. Clonidine improves duration of analgesia and anaesthesia when used as an adjunct to local anaesthetics for peribulbar, peripheral nerve and plexus blocks (**N**) (**Level I**).
3. Intrathecal neostigmine marginally improves perioperative and peripartum analgesia in combination with other spinal medications but is associated with significant side effects (**S**) (**Level I**).

4. Epidural neostigmine combined with an opioid reduces the dose of epidural opioid that is required for analgesia (**U**) (**Level I**).
5. Epidural ketamine (without preservative) added to opioid-based epidural analgesia regimens improves pain relief without reducing side effects (**U**) (**Level I**).
6. Intrathecal midazolam combined with a local anaesthetic prolongs the time to first analgesia and reduces postoperative nausea and vomiting (**N**) (**Level I**).
7. Following Caesarean section, intrathecal morphine provides improved analgesia compared with placebo (**N**) (**Level I**) and more prolonged analgesia compared with more lipophilic opioids (**N**) (**Level II**).
8. Intrathecal clonidine added to intrathecal morphine improves and prolongs analgesia (**N**) (**Level II**).
9. Epidural clonidine reduces postoperative systemic opioid requirements (**N**) (**Level II**).
10. Epidural adrenaline (epinephrine) in combination with a local anaesthetic improves the quality of postoperative thoracic epidural analgesia (**U**) (**Level II**).
11. In obstetrics, epidural neostigmine improves postoperative analgesia without increasing the incidence of adverse events (**N**) (**Level II**).
12. Addition of either clonidine or dexmedetomidine to intrathecal bupivacaine increases the speed of onset and duration of motor and sensory block without additional side effects (**N**) (**Level II**).

5.4 ANTI-INFLAMMATORY DRUGS

5.4.1 Corticosteroids

Neuraxial

Use of epidural methylprednisolone resulted in no difference in morphine requirements or pain scores following thoracotomy compared with epidural saline (Blanloeil et al, 2001 **Level II**). Following lumbar disc surgery, the combination of wound infiltration with bupivacaine and epidural/ perineural methylprednisolone improved analgesia and decreased opioid consumption compared with placebo (Mirzai et al, 2002 **Level II**; Jirarattanaphochai et al, 2007 **Level II**). However, epidural administration of either drug on its own was not superior to placebo (Loffinia et al, 2007 **Level II**). Preoperative single dose epidural administration of dexamethasone, with or without bupivacaine, was shown to reduce postoperative pain and morphine consumption following laparoscopic cholecystectomy (Thomas & Beevi, 2006 **Level II**).

Peripheral sites

Intra-articular corticosteroid injections would be expected to have an analgesic effect in inflammatory arthropathies. Following knee joint arthroscopy, intra-articular steroids were more effective than placebo in reducing pain, analgesic consumption and duration of immobilisation either alone (Wang et al, 1998 **Level II**), in conjunction with opioids (Kizilkaya et al, 2004 **Level II**; Kizilkaya et al, 2005 **Level II**) and/or local anaesthetics (Rasmussen et al, 2002 **Level II**). Dexamethasone on its own was less effective than pethidine or fentanyl (Saryazdi et al, 2006 **Level II**). There may be a higher risk of septic arthritis with intra-articular steroids (Armstrong et al, 1992 **Level IV**). Subacromial injections of corticosteroids have been shown to be effective in treating rotator cuff tendonitis for up to 9 months, and were superior to oral NSAIDs (NNT 2.5; CI 1 to 9]) (Arroll & Goodyear-Smith, 2005 **Level I**).

In patients having hand surgery, IVRA using a combination of lignocaine and dexamethasone resulted in lower pain scores and lower analgesic requirements for 24 hours compared with lignocaine alone or lignocaine IVRA with dexamethasone in the non-operative arm (Bigat et al, 2006 **Level II**).

The addition of dexamethasone to lignocaine for axillary brachial plexus block prolonged the duration of sensory and motor blockade compared with lignocaine alone (Movafegh et al, 2006 **Level II**).

There is insufficient evidence to support the use of injection therapy, including corticosteroids, in subacute and chronic low-back pain. However, it cannot be ruled out that specific subgroups of patients may respond to a specific type of injection therapy (Staal et al, 2009 **Level I**). Lumbar epidural steroid injections may provide short-term relief from acute radicular pain but did not impact on function, need for surgery, or provide long-term pain relief beyond 3 months (Armon et al, 2007 **Level I**).

Topical

Topical corticosteroids have not been shown to have consistent efficacy in acute herpes zoster (Hempenstall et al, 2005 **Level I**).

Key messages

1. Subacromial injections of corticosteroids are superior to oral NSAIDs in treating rotator cuff tendonitis (**N**) (**Level I**).
2. Lumbar epidural steroid administration is effective for short-term relief of acute radicular pain (**N**) (**Level I**).
3. Following knee joint arthroscopy, intra-articular steroids in combination with either local anaesthetic or opioids reduce pain, analgesic consumption and duration of immobilisation (**N**) (**Level II**).
4. Intravenous regional anaesthesia combining dexamethasone with lignocaine improves analgesia for up to 24 hours (**N**) (**Level II**).
5. There is a risk of septic arthritis with intra-articular steroids (**N**) (**Level IV**).

5.4.2 Non-steroidal anti-inflammatory drugs

Peripheral sites

Intra-articular nsNSAIDs such as tenoxicam and ketorolac resulted in improved pain relief after surgery (Elhakim et al, 1996 **Level II**; Cook et al, 1997 **Level II**; Convery et al, 1998 **Level II**; Colbert et al, 1999 **Level II**; Gupta et al, 1999 **Level II**); no long-term follow-up looking at any effect on bone healing has been undertaken.

Topical

With topical application of diclofenac, tissue levels are higher and plasma levels lower than following oral administration (Zacher et al, 2008). Topical diclofenac significantly reduced pain and inflammation in a range of sports, traumatic and inflammatory acute and chronic conditions compared with placebo and was comparable to other topical NSAIDs (although there were no direct comparisons) and oral diclofenac, ibuprofen and naproxen. (Zacher et al, 2008 **Level I**). Topical ketoprofen used for up to one week in acute painful conditions (sprains, sprains or sports injuries) had a NNT of 3.8, which was significantly better than other topical NSAIDs, although in non-comparative (head-to-head) trials. (Mason et al, 2004 **Level I**). Topical indomethacin did not have proven efficacy (Moore RA et al, 1998 **Level I**).

There was a small but significant reduction of pain with the use of topical NSAIDs for traumatic corneal abrasions (Calder et al, 2005 **Level I**).

Use of topical ketoprofen patches showed mild clinical benefit over placebo in tendinitis and ankle sprain (NNT 5 to 6) (Mazieres, Rouanet, Guillon et al, 2005 **Level II**; Mazieres, Rouanet, Velicy et al, 2005 **Level II**).

Topical NSAIDs were of limited efficacy in lateral elbow pain providing short-term functional improvement for up to 2 weeks. They resulted in fewer GI side effects compared with oral NSAIDs (Green et al, 2001 **Level I**).

Overall, there are insufficient data to support the use of topical NSAID analgesia in acute and chronic Achilles tendinitis (McLauchlan & Handoll, 2001 **Level I**) or in superficial venous thrombosis of the leg (Di Nisio et al, 2007 **Level I**).

There is insufficient evidence to differentiate between routes of administration of NSAIDs in the treatment of low back pain (Roelofs et al, 2008 **Level I**).

Key messages

1. Topical NSAIDs are of limited efficacy in lateral elbow pain and provide short-term functional improvement; they result in fewer gastrointestinal side effects compared with oral NSAIDs (**N**) (**Level I** [Cochrane Review]).
2. Non-selective NSAIDs added to local anaesthetic solutions for IVRA improve postoperative analgesia (**N**) (**Level I**).
3. Topical NSAIDs are effective in treating acute strains, sprains or sports injuries for up to 1 week with ketoprofen being significantly better than all other topical NSAIDs, and indomethacin similar to placebo (**N**) (**Level I**).
4. Topical diclofenac significantly reduces pain and inflammation in a range of sports, traumatic and inflammatory conditions and in acute musculoskeletal injuries is at least comparable to oral naproxen (**N**) (**Level I**).
5. Topical NSAIDs are effective analgesics for traumatic corneal abrasions (**N**) (**Level I**).

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