



Practical use of local anesthetics in regional anesthesia

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Purpose of review

The choice of local anesthetics in regional anesthesia depends on desired onset, intensity, and duration of block, as well as possible adverse effects. This review highlights recent advances in day-case spinal anesthesia; considerations in selecting local anesthetic volume, concentration, and mass in peripheral nerve blockade; and the pharmacokinetics of ropivacaine.

Recent findings

Spinal anesthesia using 2-chloroprocaine offers fast onset and rapid recovery, whereas mepivacaine and lidocaine are suitable for longer procedures. Intrathecal lidocaine in the lithotomy position carries a significant risk of transient neurologic symptoms and should be avoided. Dosing studies of local anesthetics in peripheral nerve blockade suggest that mass of drug, not volume or concentration, primarily determines block onset, success, and duration. Commonly used doses of ropivacaine for Transversus Abdominis Plane blocks can result in high plasma concentrations and local anesthetic systemic toxicity.

Summary

There are effective alternatives to bupivacaine in day-case spinal anesthesia but more safety and outcome data are required, particularly for 2-chloroprocaine. The trend toward smaller doses of local anesthetics in ultrasound-guided regional anesthesia improves safety but should be weighed against possible reductions in speed of onset and analgesic duration. Strategies to reduce the risk of local anesthetic systemic toxicity should be employed when performing large-volume fascial plane blocks with ropivacaine.

Keywords

2-chloroprocaine, local anesthetic systemic toxicity, mass, minimal effective anesthetic volume, plasma concentrations, ropivacaine

INTRODUCTION

When performing regional anesthesia, the practitioner must decide on the specific local anesthetic agent(s) as well as the volume, concentration, and mass to be injected. This is based on the desired outcomes of block onset, intensity, duration, and adverse effects. This review summarizes the findings in the recent anesthetic literature that may influence these decisions.

LOCAL ANESTHETIC CHOICES FOR DAY-CASE SPINAL ANESTHESIA

The main considerations in day-case spinal anesthesia are rapid onset of adequate surgical anesthesia; rapid recovery of motor function, proprioception, and ability to void; as well as minimal adverse effects. Low-dose bupivacaine (5–7.5 mg) is a popular choice, especially for lower limb surgery [1]. It does not, however, always produce dense sensory

and motor blockade, and there is a significant risk of primary block failure in abdominal and gynecologic procedures [1]. There has recently been a resurgence of interest in shorter-acting local anesthetics as an alternative.

Lidocaine, mepivacaine, and prilocaine

Lidocaine, prilocaine, and mepivacaine are intermediate-duration local anesthetics, which have

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KEY POINTS

- 2-Chloroprocaine is an effective alternative to bupivacaine in day-case spinal; it offers fast onset and rapid recovery; however, further safety and outcome data are warranted.
- Intrathecal lidocaine in the lithotomy position carries a significant risk of transient neurologic symptoms and should be avoided.
- Local anesthetic combinations provide onset and duration that is intermediate between short and long-acting local anesthetics alone.
- Dosing studies of local anesthetics in peripheral nerve blockade suggest that mass of drug, not volume or concentration, primarily determines block onset, success, and duration.
- High plasma concentrations and LAST can result when commonly used doses of ropivacaine are used for TAP blocks.

similar pharmacodynamic profiles, except that mepivacaine has a slightly longer duration of action than lidocaine [2]. Doses as low as 20–30 mg are effective in knee arthroscopy, particularly when combined with intrathecal fentanyl [3–5], and recovery is faster than with low-dose bupivacaine.

The main concern with these agents is the risk of transient neurologic symptoms (TNS). The literature indicates that lidocaine carries the highest risk of TNS, but the reported incidence is extremely variable, ranging from 0 to 40%. Higher concentrations, hyperosmolarity, and hyperbaricity do not appear to be contributing factors [6]. Other risk factors have been identified that may explain the variability, the most important of these being type of surgery. Surgery in the lithotomy position is associated with the highest risk, but incidences of up to 22% have also been reported with knee arthroscopy [6]. Mepivacaine has a lower incidence of TNS, ranging from 0 to 6.4% with isobaric mepivacaine 1.5% [7,8] and up to 7.5% with 2% isobaric mepivacaine [9]. Again it appears that risk is influenced by type of surgery and the age of the patient [8,10]. Prilocaine is the safest, with a reported TNS risk of 1.7%, comparable to that of bupivacaine (1.1%) [11].

These considerations were highlighted in two recent studies. Vaghadia *et al.* [12[■]] compared low-dose 2% lidocaine (35 mg) with 40 mg of 2-chloroprocaine in 40 patients undergoing outpatient transurethral prostate resection under spinal anesthesia. Fentanyl 12.5 µg was used as an adjuvant in all patients. Although clinical efficacy and motor recovery time were similar in both groups (120 min versus 117 min in the lidocaine and chloroprocaine groups,

respectively), TNS occurred in 20% of the lidocaine group, leading the authors to recommend avoiding intrathecal lidocaine. On the other hand, in a comparison of 80 mg of 2% lidocaine versus 80 mg of 2% mepivacaine in 84 patients undergoing anterior cruciate ligament reconstruction, TNS did not occur in either treatment group [13]. A slightly longer time to ambulation (284 versus 251 min) and voiding (255 versus 227 min) was observed with mepivacaine but block characteristics were otherwise similar between the two drugs. The authors concluded that both were suitable drugs for outpatient orthopedic surgery.

2-Chloroprocaine and articaine

Articaine and 2-chloroprocaine are both short-acting local anesthetics with fast onset and excellent reviews of both drugs have recently been published [14,15[■]]. The availability of preservative-free 2-chloroprocaine has renewed interest in its use for spinal anesthesia, although its safety is still controversial [15[■]]. Forster *et al.* [16[■]] compared equivalent doses (40 mg) of each agent in 36 patients undergoing knee arthroscopy. Onset times and duration of block to L1 were similar, but 2-chloroprocaine produced significantly faster motor (75 versus 120 min) and sensory block recovery (105 versus 135 min). Data on 2-chloroprocaine indicate that 30 mg will produce a surgical block of 40–60 min, 40–45 mg per block of 45–70 min, and 60 mg per block of 60–90 min [15[■]]. The risk of TNS appears low, ranging from 0 to 1.9% [15[■],17]. The previously mentioned study by Vaghadia *et al.* [12[■]] provides a note of caution however. Although no TNS was observed with 2-chloroprocaine, one patient developed a cauda equina syndrome that persisted for several weeks. Despite this, the authors report that they favor 2-chloroprocaine in their practice over lidocaine.

In summary, there are several alternatives to low-dose bupivacaine in day-case spinal anesthesia that may provide more predictable onset, offset, and extent of anesthesia. 2-Chloroprocaine offers particularly rapid recovery but vigilance for adverse effects is advised. The lithotomy position increases the risk of TNS, and lidocaine should be avoided in this setting.

LOCAL ANESTHETIC DOSING CONSIDERATIONS IN PERIPHERAL NERVE BLOCKADE

The choice of local anesthetics in peripheral nerve blockade is mainly determined by desired speed of onset, block intensity, and duration of anesthesia and analgesia. Rather than comparing the merits of

different agents, recent research has focused on the influence of mass, volume, and concentration of drug injected on these efficacy outcomes, with the primary aim being to reduce the total dose of local anesthetics delivered.

The effect of volume, concentration, and mass on onset, success, and duration

Fredrickson *et al.* [18] studied the effect of three different volumes of 0.75% ropivacaine (5, 10, and 20 ml) and two different volumes of 0.375% ropivacaine (20 and 40 ml) on the analgesic duration of interscalene block. They found that 5 ml resulted in an unacceptably high analgesic failure rate (30%) and that higher concentration and volume (and thus mass) were clearly associated with prolonged analgesia. However, the gains in duration were relatively modest, with median differences of only 3–5 h between the upper and lower limits of volumes and concentrations studied. Gonzales *et al.* [19[¶]] investigated three different concentrations of lidocaine (1%, 1.5%, and 2%) for ultrasound-guided infraclavicular block while holding total dose constant and found no significant difference in block onset time. Block duration was not assessed in this study. Gupta and Hopkins [20] assessed the impact of different concentrations of bupivacaine (0.25%, 0.375%, and 0.5%) on the median effective dose (ED₅₀) required for successful supraclavicular block. They found no significant differences in ED₅₀ and concluded that mass was the main determinant of block success. Finally, Nader *et al.* [21[¶]] examined the effect of different volumes of 0.5% ropivacaine or bupivacaine on onset time and analgesic duration of sciatic nerve block in total knee arthroplasty. Volumes studied ranged from 2.5 to 30 ml. Sensory block success rates at 30 min and analgesic duration were similar for volumes of 10 ml and higher. Volumes of less than 10 ml, on the other hand, increased onset times and shortened analgesic durations. Taken together, these studies indicate that mass of local anesthetics, rather than concentration or volume, is the most important determinant of peripheral nerve block onset and duration. There appears, however, to be a dose threshold beyond which improvements in onset time, block intensity, and analgesic duration become less significant.

Minimum effective volume, concentration, and dose

Research into the minimum effective anesthetic volume (MEAV) and minimum effective anesthetic concentration (MEAC) for various ultrasound-guided peripheral nerve blocks sheds some light

on what this dose threshold might be. It should be noted that these studies generally define efficacy only by successful block onset and provide no information on analgesic duration. In addition, it is problematic to generalize from these results as there are several factors that determine the efficacy of a given drug volume in any one patient, including the accuracy of local anesthetics deposition, which in turn depends on the operator's skill and experience; and the specific technique used.

For instance, O'Donnell *et al.* [22] determined the MEAV of ultrasound-guided axillary nerve block using a perineural technique in which local anesthetic was deposited around each of the four individual terminal nerves by a single experienced operator. They started with 4 ml of 2% lidocaine per nerve (total dose 16 ml) and were able to reduce the dose to 1 ml per nerve without experiencing any failures. In contrast, a more recent study by Gonzales *et al.* [23] investigated a double-injection perivascular technique of ultrasound-guided axillary block performed by trainees and experts and estimated the MEAV in 90% of patients (MEAV₉₀) to be 5.5 ml of 1.5% lidocaine for the musculocutaneous nerve and 23.5 ml in the perivascular location.

Similarly, Tran *et al.* [24] reported a MEAV₉₀ of 32 ml of 1.5% lidocaine for ultrasound-guided supraclavicular block using a double injection-technique, in which half the volume was deposited at the intersection of the first rib and subclavian artery and the other half in the region of the plexus itself. The majority of blocks were performed by trainees. Song *et al.* [25[¶]], on the other hand, were able to achieve a much lower MEAV₉₀ of 15 ml of 1.5% mepivacaine, which may be because of the fact that they used a multiple-injection technique designed to spread local anesthetic within the entire plexus and that a single experienced operator performed all the blocks.

Another approach to reducing total local anesthetic dose is to use lower concentrations. Taha and Abd-Elmaksoud [26] performed ultrasound-guided femoral nerve blockade with 15 ml of lidocaine in arthroscopic knee surgery and used an up-down approach to determine the MEAC in 90% of patients (MEAC₉₀). The endpoint for success was complete sensory and motor blockade within 30 min. They estimated the MEAC₉₀ to be 0.93% (95% confidence interval: 0.8–1.03%), which supports the clinical use of 1% lidocaine for surgical anesthesia. The effect on surgical and analgesic block duration is unknown.

LOCAL ANESTHETIC COMBINATIONS

Combinations of local anesthetics are often used in peripheral nerve blockade to marry the faster onset

of short-acting local anesthetics with the prolonged duration of long-acting local anesthetics. In theory, exposing the nerve first to a short-acting local anesthetic by sequential injection of the short-acting and long-acting local anesthetics might produce a faster-onset block compared to mixing them. However both Gadsden *et al.* [27] (interscalene block) and Roberman *et al.* [28] (supraclavicular block) have clearly shown that there is no difference in block onset or duration regardless of which method is used.

Laur *et al.* [29] evaluated the combination of mepivacaine and bupivacaine in ultrasound-guided infraclavicular blockade. Patients received 40 ml of 1.5% mepivacaine (with epinephrine), 0.5% bupivacaine, or a 1:1 combination of both. The duration of sensory and motor block in the combination group was 50–70% longer compared to the mepivacaine group but 50% shorter than the bupivacaine group. This effect on duration is consistent with earlier studies. Gadsden *et al.* [27] performed ultrasound-guided interscalene block using 30 ml of local anesthetic and found that a 1:1 combination of 1.5% mepivacaine and 0.5% bupivacaine doubled sensory and motor block duration compared to mepivacaine alone, but reduced it by 30% compared to bupivacaine alone. Cuivillon *et al.* [30] reported similar results with neurostimulation-guided femoral and sciatic nerve block (20 ml of local anesthetic at each site); there was a 35–40% reduction in sensory and motor block duration when 2% lidocaine was mixed with either 0.5% bupivacaine or 0.75% ropivacaine, compared to long-acting local anesthetic alone.

The effect of local anesthetic combinations on block onset time is less clear. Both Cuivillon *et al.* [30] and Laur *et al.* [29] demonstrated significant reductions in onset time with combinations compared to long-acting local anesthetic alone. Gadsden *et al.* [27], however, reported similar onset times in all three-study arms. This may be explained by the difference in the block under study: 30 ml of local anesthetic is a generous dose for ultrasound-guided interscalene block and the relatively large mass of bupivacaine may have contributed to faster onset.

Local anesthetic combinations may offer a safety advantage by dose sparing of the long-acting local anesthetics, which are potentially more cardiotoxic than the short-acting local anesthetics. Cuivillon *et al.* [30] have demonstrated that this approach does result in reduction of plasma concentrations. This is less relevant if smaller doses are used, as is the trend with ultrasound-guided techniques. Practitioners should be aware however that local anesthetic toxicity can be additive [31,32] and local anesthetic systemic toxicity (LAST) has been

reported with a lidocaine–ropivacaine mixture [33]. There may also be pharmacokinetic interactions that have safety implications. Chen *et al.* [34] demonstrated that sequential injection of 2% lidocaine followed by 0.75% ropivacaine for lumbar plexus block compared to the same dose of ropivacaine alone increased both peak plasma ropivacaine concentration and the plasma concentration area-under-curve. The authors postulated that the vasodilatory effect of lidocaine might have offset the intrinsic vasoconstriction of ropivacaine, resulting in increased vascular uptake.

In summary, local anesthetic combinations can provide a middle ground for block onset and duration compared to short-acting and long-acting agents used alone, particularly if modest doses are administered. The potential for LAST should be assumed to be additive and careful consideration given to the total dose of local anesthetic administered.

ROPIVACAIN: INSIGHTS INTO PHARMACOKINETICS AND SAFETY

Ropivacaine has largely replaced bupivacaine as the most commonly used long-acting local anesthetic in peripheral nerve blockade. In equivalent doses, it produces less motor blockade compared to bupivacaine but an equally effective sensory block. This was most recently demonstrated by Nader *et al.* [21[†]], in the dose-finding study previously discussed. They observed that ropivacaine produced equivalent postoperative analgesia but less potent motor blockade (relative potency 0.72) compared to bupivacaine.

Ropivacaine is also less cardiotoxic compared to bupivacaine [35] and is therefore a popular choice for high-dose, high-volume fascial plane blocks such as the Transversus Abdominis Plane (TAP) block. Several recent studies have examined the pharmacokinetics of ropivacaine in this context.

The quoted toxic plasma concentration thresholds for ropivacaine are usually based upon a classic article by Knudsen *et al.* [35], who infused i.v. ropivacaine into volunteers until clinical features of central nervous system (CNS) toxicity occurred. It is important to note that the arterial, rather than venous, plasma concentration in this study of rapid i.v. infusion is more likely to represent effect-site concentration and thus may be more relevant to perineural blockade. In addition, clinical toxicity occurred over a large range of concentration thresholds, and thus, the lower range limit may be a more appropriate safety threshold than the mean value that is commonly quoted. The final factor to consider is that the free fraction of ropivacaine is inversely proportional to the concentration of

binding protein, especially alpha-1 acid glycoprotein, which increases the following surgical stress. The toxic arterial concentration thresholds in Knudsen's study ranged from 0.34 to 0.85 (mean 0.56) $\mu\text{g/ml}$ and 3.4–4.3 (mean 4.3) $\mu\text{g/ml}$ for free and total ropivacaine concentrations, respectively [35]. The toxic venous concentration thresholds ranged from 0.01 to 0.24 (mean 0.15) $\mu\text{g/ml}$ to 0.5–3.2 (mean 2.2) for free and total ropivacaine concentrations, respectively [35].

Griffiths *et al.* [36] measured venous concentrations in 30 patients undergoing cesarean section under spinal anesthesia who received bilateral Transversus Abdominis Plane (TAP) blocks with a total of 40 ml of 0.5% ropivacaine (200 mg). The pharmacokinetics was similar to a previous study of bilateral Transversus Abdominis Plane (TAP) block in parturients under general anesthesia [37]. The average time to peak concentration (T_{max}) was 35 min, and the average peak plasma concentration (C_{max}) was 1.82 and 0.07 $\mu\text{g/ml}$ for total and free ropivacaine, respectively. They noted that 12 patients had total plasma ropivacaine levels $>2.2 \mu\text{g/ml}$, and three of these patients had mild symptoms of CNS toxicity (C_{max} ranged from 2.6 to 3.2 $\mu\text{g/ml}$).

Hessian *et al.* [38] measured venous concentrations in 20 patients who received bilateral Transversus Abdominis Plane (TAP) catheters (either posterior or subcostal) for midline laparotomies. An initial total bolus of 40 ml of 0.375% or 0.5% ropivacaine was administered depending on whether body weight was less or more than 70 kg, followed by an infusion of 0.2% ropivacaine at 0.1 ml/kg/h (maximum dose 7 ml/h) for 72 h. They noted that total plasma concentrations rose gradually for 48–72 h, whereas free plasma concentrations peaked at 24 h; this difference was attributed to an increase in plasma-binding proteins following surgical stress. The mean C_{max} was 2.50–2.64 and 0.070–0.078 $\mu\text{g/ml}$ for total and free plasma ropivacaine, respectively. Only one patient had symptoms of CNS toxicity; however, her C_{max} was within the mean toxic venous thresholds defined by Knudsen (free and total ropivacaine 0.08 and 1.5 $\mu\text{g/ml}$, respectively).

What these studies indicate is that there is tremendous variability in plasma concentrations of ropivacaine following commonly used doses of ropivacaine in Transversus Abdominis Plane (TAP) block, and that these concentrations can approach or exceed levels associated with LAST. At the same time, there is interindividual variability in the threshold concentrations at which symptoms of LAST appear. A weight-based dosing regimen and careful monitoring of patients is therefore recommended where bilateral Transversus Abdominis

Plane (TAP) blocks are administered, especially in the first 2 h after a bolus when plasma concentrations are at their highest. Despite the intrinsic vasoconstrictive properties of ropivacaine, it may also be prudent to add epinephrine to reduce systemic uptake. In a pilot study of 12 patients randomized to receive a total of 450 mg of ropivacaine with or without epinephrine 5 $\mu\text{g/ml}$ in a combined femoral-sciatic block technique, Schoenmakers *et al.* [39] observed a trend to reduced total C_{max} (2.16 versus 2.81 $\mu\text{g/ml}$), free C_{max} (0.12 versus 0.16 $\mu\text{g/ml}$), and increased T_{max} (1.67 versus 1.17 h) in the group that received the epinephrine-containing solution.

CONCLUSION

While no new local anesthetic agents have been recently introduced into clinical practice, there has been a renaissance of older agents in spinal anesthesia, especially given the increasing proportion of day-case surgery performed worldwide. The increased accuracy of peripheral nerve blockade afforded by ultrasound guidance has permitted the exploration of smaller doses of local anesthetics with the aim of improving safety while maintaining efficacy. At the same time, the current popularity of large-volume fascial plane blocks means that local anesthetic dosing and the risk of LAST are still important considerations for the regional anesthesiologist.

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Conflicts of interest

There are no conflicts of interest.

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