Local and Regional Anesthesia

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REVIEW

# Intravenous regional anesthesia: a review of common local anesthetic options and the use of opioids and muscle relaxants as adjuncts



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**Purpose:** To provide a review of local anesthetic (LA) agents and adjuncts, opioids and muscle relaxants, and their intraoperative effects and postoperative outcomes in intravenous regional anesthesia (IVRA).

**Source:** A search for prospective, double-blind, randomized controlled trials evaluating LA agents, opioids and muscle relaxants as adjuvants for IVRA, was conducted (MEDLINE®, Embase). Intraoperative benefits (onset/recovery of sensory and motor block, intraoperative analgesia, tourniquet pain), postoperative benefits (pain score, analgesic consumption, time to first analgesia), and side effects were recorded. A conclusion for overall benefit was made based on statistical significance and clinical relevance.

**Findings:** Thirty-one studies were evaluated, with data collected on 1523 subjects. LA agents evaluated were lidocaine, ropivacaine, and prilocaine. Adjuncts evaluated were opioids (morphine, fentanyl, meperidine, sufentanil, tramadol) and muscle relaxants (pancuronium, atracurium, mivacurium, cisatracurium). There was good evidence that ropivacaine provided effective IVRA and improved postoperative analgesia. Lidocaine and prilocaine were effective LA agents, however they lacked postoperative benefits. Morphine, fentanyl, and meperidine as sole adjuncts did not demonstrate clinically significant benefits or result in an increased risk of side effects. Sufentanil data was limited, but appeared to provide faster onset of sensory block. Tramadol provided faster onset of sensory block and tourniquet tolerance, however postoperative benefits were not consistent and the risk of minor side effects increased. Muscle relaxants improved the quality of motor block, but at the expense of delayed motor recovery. The combination of fentanyl and muscle relaxants can achieve an equivalent quality of IVRA with 50% reduction in LA dose, but at the expense of a potentially slower onset of sensory block.

**Conclusion:** Ropivacaine is effective for IVRA and improves postoperative analgesia. Muscle relaxants enhance the motor block and when combined with fentanyl allow for an equivalent quality of IVRA with 50% reduction in LA dose.

**Keywords:** intravenous regional anesthesia, IVRA, adjuncts, local anesthetic, opioid, muscle relaxant

## Introduction

Intravenous regional anesthesia (IVRA) was first described by August Bier in 1908 for anesthesia of the hand and forearm.[1] After losing popularity following the advent of brachial plexus blocks, Holmes revived the technique in 1963 when he substituted lidocaine for the use of procaine.[2] IVRA is suitable for operations of the distal extremities, in situations where it is safe and easy to apply an occlusive tourniquet. It is mainly used for surgical procedures of the upper extremity, but it can also be used for procedures involving the lower extremity.[1] The primary advantages of IVRA

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are its simplicity, reliability, and cost-effectiveness.[3] It is a regional anesthetic technique that is easy to perform, with success rates varying between 94% and 98%.[4] For these reasons, it remains a popular choice among anesthesiologists. Constraints of anesthetic duration and tourniquet time limit the use of this technique to short procedures (approximately 20–60 minutes).[5] The rapid recovery of function make this technique ideally suited for surgeries performed in an ambulatory setting.

There are a few limitations associated with IVRA[4] and those concerns regarding its use must be considered. These concerns include, but are not limited to, local anesthetic (LA) toxicity, delayed onset of action, poor muscle relaxation, tourniquet pain, and minimal postoperative analgesia.[6] Features of an ideal IVRA solution include rapid onset of sensory and motor block, reduced intraoperative and tourniquet pain, prolonged post-deflation analgesia, and minimal side effects. Various LA options and adjuncts for IVRA exist, each possessing its own advantages and disadvantages. Selecting an ideal IVRA solution can be a challenge.

Lidocaine is the most frequently used LA for IVRA in North America.[7] Despite its benefits, it has a relatively brief duration of action which may limit the postoperative analgesia that can be provided.[8] The use of a longer-acting agent may offer an improvement. Bupivacaine, a long-acting agent used in the past, is no longer recommended for IVRA because of its risk of causing irreversible cardiac arrest.[9,10] Ropivacaine, a derivative of bupivacaine and produced as a pure levorotatory enantiomer,[11] causes less depression of cardiac conduction.[12–14] Its use has increased in popularity because of its potential to offer prolonged and improved analgesia compared to lidocaine, with a lower toxicity profile than bupivacaine. Prilocaine is another popular LA for IVRA, and is the most commonly used agent in Europe.[15] It has a relatively short duration of action and is the least toxic of the amino-amide local anesthetics.[16] Various adjuncts added to LA have been investigated in an attempt to improve the quality of IVRA, including opioids, muscle relaxants, nonsteroidal anti-inflammatory drugs (NSAIDs), clonidine, potassium, and alkalizing agents. A systematic review of IVRA adjuncts performed by Choyce and Peng[17] suggested that NSAIDs were most useful for improving postoperative analgesia after IVRA. New studies continue to be published in the search for an ideal adjunct.

The purpose of this article is to provide an updated review of (1) LA agents for IVRA and (2) the efficacy of opioids and muscle relaxants as adjuncts in this technique.

# Methods

## Search strategy

A search was carried out for articles indexed in MEDLINE® and Embase over the past 25 years (January 1986 to July 2011). The following Medical Subject Headings (MeSH) terms were used: anesthesia or anaesthesia, intravenous regional an(a)esthesia, intravenous regional neural block, nerve block, i.v. regional an(a)esthesia, intravenous regional neural block, an(a)esthesia (conduction), an(a)esthesia (intravenous), an(a)esthesia (local), bier block, IVRA, an(a) esthesia (adjuvants), analgesics, narcotic analgesic agent, neuromuscular non-depolarizing agents, neuromuscular blockade, neuromuscular block, neuromuscular blocking, neuromuscular blocking agent, mivacurium, atracurium, ropivacaine, lidocaine, ropivacaine, prilocaine. Articles that were unpublished, abstracts, letters, and non-English studies were not retrieved. Reference sections of included articles and published reviews were searched for relevant publications that may have been missed by the electronic search. Individual authors were contacted on two occasions to facilitate retrieval of articles that were not available in electronic format.

## Inclusion and exclusion criteria

The review was limited to prospective, randomized controlled trials. Of the studies that were identified, only those that were of double-blinded design were included. Studies that were not double-blinded,[18–22] were not able to be retrieved (either electronically or by contacting the study authors or journal of publication),[23] or contained questionable data (all major studies conducted by Reuben et al[24] have been retracted from journals) were excluded from analysis. The search results are presented in Figure 1. Studies of low Jadad[25] score (two or lower) were not excluded as almost half of the literature included were of low score (Table 1).

## Methods of review

Data was abstracted onto data abstraction forms independently by both authors. For each study in part one of this review (evaluation of LA agents), the concentration and volume of LA was recorded. Study design, group allotment, number of subjects, presence of plasma level measurement, outcomes, and side effects were collected. Outcome measurements for each adjunct included an evaluation of its potential intraoperative benefits (speed of onset and recovery of sensory and motor block, intraoperative analgesia, tourniquet pain), postoperative benefits (pain score, analgesic consumption, time to first analgesic), and side effect profile. The statistical significance of potential

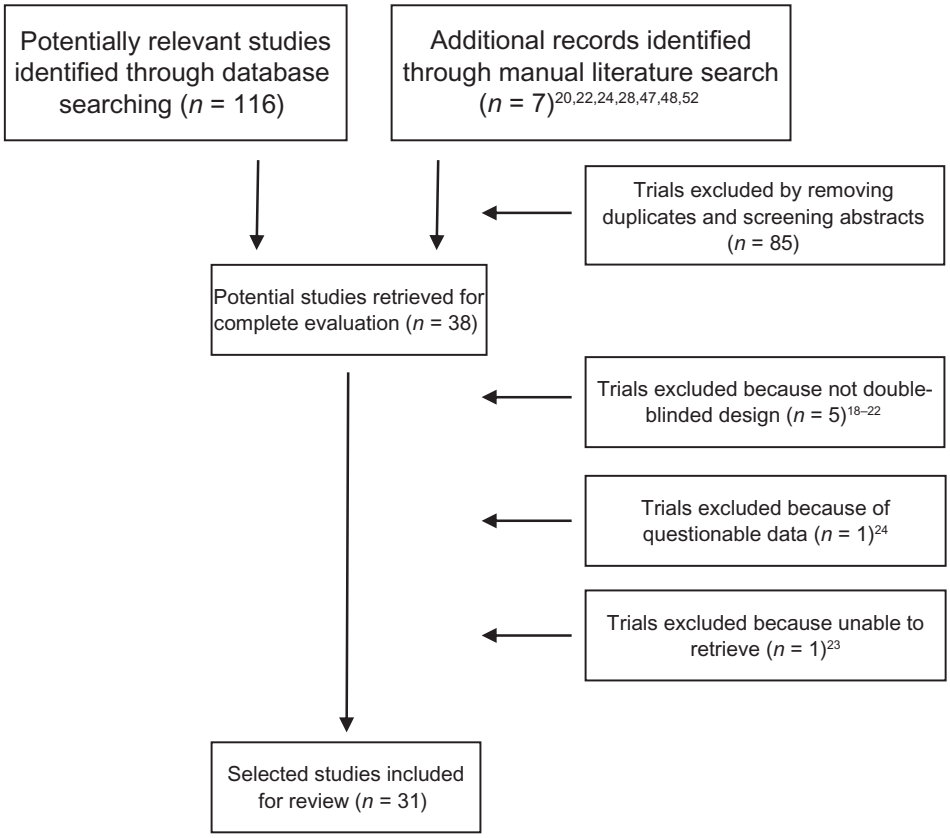


**Figure 1** Search strategy flow diagram.

side effects in each study was provided. If noteworthy side effects existed without any evidence of statistical analysis, this information was provided with the qualifying statement "statistical analysis not performed". For each study in part two (evaluation of adjuncts), the concentration and volume of LA and type and dose of adjunct was recorded. Information including study design and group allotment, number of subjects, presence of systemic control, outcomes, and side effects were collected. Outcome measurements and side effect profile were assessed as in part one. Study outcomes were determined to be "positive" if they demonstrated significant intraoperative or postoperative benefits, or "negative" if they did not.

The reviewers, Flamer and Peng, also independently rated study quality on the basis of the adequacy of randomization, allocation concealment, double-blinding, and description of withdrawals or dropouts (Table 1).[25] Inter-rate agreement was performed, and discrepancies were resolved by consensus.

# Results

## Part one: local anesthetics for IVRA

Nine studies involving 516 patients compared the efficacy of lidocaine, ropivacaine, and prilocaine as local anesthetic agents for IVRA (Table 2).[8,15,26–32] One study evaluated three different LA drugs,[32] with the remaining studies evaluating two LA agents in comparison to one another. Three of the studies reported sample size estimations and power analysis.[15,26,30] Allocation concealment was adequate in two studies[30,32] and unclear in the others (Table 1).

### Local anesthetic

Lidocaine and ropivacaine were the most common LA agents evaluated. Out of nine studies, five compared lidocaine to ropivacaine,[8,26,27,29,31] three compared lidocaine to prilocaine,[28,30,32] and one compared ropivacaine and prilocaine.[15]

### Sensory anesthesia

Overall, there were no significant differences in the onset of sensory block between lidocaine, prilocaine, and ropivacaine.[8,26–29,31,32] One study[15] compared 0.5% prilocaine with 0.2% ropivacaine and found that more patients had pin-prick analgesia in one of the four peripheral nerve distributions (radial nerve) 10 minutes after injection in the prilocaine group compared to the ropivacaine group (90% vs 60%). The clinical significance of this is doubtful.

**Table 1** Quality of studies included in the review

| Study | Randomized/method described | Allocation concealment | Double-blinded | Jadad* score |
|---|---|---|---|---|
| **Local anesthetic** | | | | |
| Bader et al[28] | +/– | – | + | 2 |
| Simon et al[32] | +/+ | + | + | 4 |
| Hartmannsgruber et al[8] | +/– | – | + | 3 |
| Chan et al[29] | +/– | – | + | 4 |
| Atanassoff et al[27] | +/– | – | + | 4 |
| Davidson et al[30] | +/– | + | + | 3 |
| Peng et al[31] | +/+ | – | + | 5 |
| Niemi et al[15] | +/+ | – | + | 4 |
| Asik et al[26] | +/+ | – | + | 5 |
| **Opioid +/– Muscle relaxant** | | | | |
| Armstrong et al[47] | +/+ | – | + | 4 |
| Arthur et al[48] | +/– | – | + | 2 |
| Pitkanen et al[35] | +/– | – | + | 2 |
| Abdulla et al[33] | +/– | – | + | 2 |
| Gupta et al[34] | +/– | – | + | 3 |
| Armstrong et al[36] | +/+ | – | + | 4 |
| Erciyes et al[37] | +/– | – | + | 2 |
| Sztark et al[38] | +/– | – | + | 2 |
| Hoffman et al[40] | +/– | | + | 2 |
| Lim and Ong[41] | +/– | – | + | 2 |
| Acalovschi et al[38] | +/+ | – | + | 4 |
| Tan et al[46] | +/– | – | + | 2 |
| Langlois et al[43] | +/– | – | + | 3 |
| Alayurt et al[42] | +/+ | + | + | 5 |
| Siddiqui et al[45] | +/+ | – | + | 5 |
| Aujla et al[44] | +/+ | – | + | 4 |
| **Muscle relaxant** | | | | |
| McGlone et al[52] | +/– | – | + | 2 |
| Abdulla et al[33,†] | +/– | – | + | 2 |
| Elhakim and Sadek[49] | +/– | – | + | 2 |
| Torrance et al[53] | +/– | – | + | 2 |
| Sztark et al[38,†] | +/– | – | + | 2 |
| Lim and Ong[41,†] | +/– | – | + | 2 |
| Esmaoglu et al[6] | +/+ | – | + | 4 |
| Aujla et al[44,†] | +/+ | – | + | 4 |
| Mizrak et al[50] | +/+ | – | + | 4 |
| Prasad and Anjan[51] | +/+ | – | + | 2 |

**Notes:** *See reference 25; †study involves both opioids and muscle relaxants (repeat); +, information present; –, information absent.

Five studies evaluated offset of sensory block with the use of ropivacaine compared to lidocaine and prilocaine. All five studies found recovery to be prolonged when ropivacaine was used.[8,15,26,27,29] Hartmannsgruber et al[8] found that sensory recovery was prolonged by up to 30 minutes in those who received 0.2% ropivacaine compared to 0.5% lidocaine (but only in the area of the lateral antebrachial cutaneous nerve). Likewise, Chan et al[29] found that sensory recovery in the high-dose ropivacaine group (1.8 $mg \cdot kg^{-1}$) was significantly longer than the low-dose ropivacaine (1.2 $mg \cdot kg^{-1}$) or lidocaine group (3 $mg \cdot kg^{-1}$). Atanassoff et al[27] found a prolonged sensory recovery by approximately 19 minutes, on average, with the use of 0.2% ropivacaine compared to lidocaine. Asik et al[26] demonstrated sensory recovery to be significantly prolonged in both 0.2% and 0.25% ropivacaine groups compared to 0.5% lidocaine (20.5 ± 4.6 minutes and 23.5 ± 4.8 minutes compared to 3.5 ± 1 minute). Only one study compared ropivacaine with prilocaine. In this study, 0.2% ropivacaine was compared with 0.5% prilocaine, and a prolonged recovery was found with the ropivacaine – but only in the area innervated by the median nerve.[15] One study investigated sensory recovery times between lidocaine and prilocaine and did not find a difference.[28]

**Table 2** Randomized controlled trials evaluating local anesthetic agents for IVRA

| Author | Number/ groups/ setting* | Plasma levels measured | Local anesthetic used | Outcomes | | | Side effects ($P < 0.05$) | Overall |
|---|---|---|---|---|---|---|---|---|
| | | | | Block efficacy | Intraoperative analgesia/ tourniquet pain | Postoperative | | |
| Bader[28] | 21/2/hand surgery | Yes | 50 mL volume:<br>0.5% prilocaine<br>0.5% lidocaine | Sensory onset: equal<br>Sensory recovery: equal<br>Motor onset: N/A<br>Motor recovery: N/A | N/A | N/A | Postdeflation light-headedness in 1/10 lidocaine patients (statistical significance N/A) | Prilocaine, lidocaine equally effective |
| Simon[32] | 30/3/upper limb surgery | Yes | 40 mL volume:<br>0.5% articaine<br>0.5% lidocaine<br>0.5% prilocaine | Sensory onset: no difference between lidocaine, prilocaine<br>Sensory recovery: N/A<br>Motor onset: equal<br>Motor recovery: N/A | N/A | N/A | None | Prilocaine, lidocaine equally effective |
| Hartmannsgruber[8] | 20/2/x-over volunteer | Yes | 40 mL volume:<br>0.5% lidocaine<br>0.2% ropivacaine | Sensory onset: equal<br>Sensory recovery: prolonged in ropivacaine group (lat antebrachial cut nerve only)<br>Motor onset: equal<br>Motor recovery: prolonged in ropivacaine group | IA: N/A<br>TP: equal | N/A | Less dizziness, tinnitus, metallic taste, light headedness at 3 minutes, less tinnitus at 10 minutes in ropivacaine group | Clinical correlation required |
| Chan[29] | 15/3/volunteer subjects | Yes | 40 mL volume:<br>1.2 $mg.kg^{-1}$ ropivacaine<br>1.8 $mg.kg^{-1}$ ropivacaine<br>3 $mg.kg^{-1}$ lidocaine | Sensory onset: equal<br>Sensory recovery: slower in high-dose ropivacaine group<br>Motor onset: equal<br>Motor recovery: slower in high-dose ropivacaine group | IA: N/A<br>TP: equal | N/A | Light-headedness, hearing disturbance postdeflation in lido 5/5, high dose ropivacaine 1/5, low dose ropivacaine 0/5 (statistical significance N/A) | Clinical correlation required |
| Atanassoff[27] | 20/2/upper extremity surgery | No | 40 mL volume:<br>0.2% ropivacaine<br>0.5% lidocaine | Sensory onset: equal<br>Sensory recovery: delayed in ropivacaine group (20 versus 1 minute)<br>Motor onset: N/A<br>Motor recovery: N/A | IA: N/A<br>TP: equal | VNS: lower in ropivacaine group at PACU admission (no difference at PACU discharge or beyond)<br>AC: equal | Lidocaine: 1/10 postdeflation tinnitus (statistical significance N/A) | Supportive for ropivacaine |

(*Continued*)

**Table 2** (*Continued*)

| Author | Number/ groups/ setting* | Plasma levels measured | Local anesthetic used | Outcomes | | | Side effects ($P < 0.05$) | Overall |
|---|---|---|---|---|---|---|---|---|
| | | | | Block efficacy | Intraoperative analgesia/ tourniquet pain | Postoperative | | |
| | | | | | | TTFA: longer in the ropivacaine group (47 versus 34 minutes) | | |
| Davidson[30] | 249 children/2/ forearm fracture reduction | No | 0.5% lidocaine 3 mg.kg$^{-1}$ 0.5% prilocaine 3 mg.kg$^{-1}$ | No difference in successful reduction rate between groups Sensory/motor block N/A | IA: significantly less pain during procedure in lidocaine group (subjective) TP: N/A | N/A | None observed | Lidocaine > prilocaine |
| Peng[31] | 40/2/hand surgery with forearm tourniquet | No | 0.5% lidocaine, 0.4 mL.kg$^{-1}$ (maximum 25 mL) 0.375% ropivacaine, 0.4 ml.kg$^{-1}$ (maximum 25 mL) | Sensory onset: equal Sensory recovery: N/A Motor onset: equal Motor recovery: N/A | IA: N/A TP: equal | VPRS: Significantly lower in ropivacaine group at 60 minutes; more 'pain-free' patients in ropivacaine group through first 90 minutes AC: equal at 24 hours TTFA: request for analgesia in first 2 hours lower in ropivacaine group | None | Supportive for ropivacaine |
| Niemi[15] | 60/2/forearm or hand surgery | Yes | 40 mL volume: 0.2% ropivacaine 0.5% prilocaine | Sensory onset: faster complete sensory onset with prilocaine Sensory recovery: delayed in ropivacaine group (median nerve distribution only, c. 4–10 minutes prolongation) Motor onset: equal Motor recovery: slower recovery in ropivacaine group | IA: equal TP: N/A | VAS: N/A AC: N/A TTFA: equal | Prilocaine: 1 patient with postoperative dizziness, blurred vision (statistical significance N/A) | Supportive for prilocaine |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Asik[26] | 61/3/forearm and hand surgery | No | 40 mL volume:<br>0.2% ropivacaine<br>0.25% ropivacaine<br>0.5% lidocaine | Sensory onset: equal<br>Sensory recovery: slower in 0.2%, 0.25% ropivacaine groups (20.5, 23.5 minutes versus 3.5 minutes lidocaine group)<br>Motor onset: equal<br>Motor recovery: N/A | IA: equal<br>TP: improved distal tourniquet tolerance in 0.25% ropivacaine group (c. 6 minutes) | VNS: significantly lower in both ropivacaine groups during first 20 minutes in PACU<br>AC: decreased 24-hour tramadol consumption in 0.25% ropivacaine group (no difference in 24-hour NSAID consumption between groups)<br>TTFA: longer duration in both ropivacaine groups versus lidocaine (c. 16–18 minutes longer) | Light-headedness, tinnitus, or metallic taste observed in:<br>8/21 lidocaine<br>2/20 0.2% ropivacaine<br>3/20 0.25% ropivacaine<br>(statistical significance N/A) | Supportive for ropivacaine |

**Note:** *The first number shown is the total number of study subjects, second number is the number of groups.
**Abbreviations:** IVRA, intravenous regional anesthesia; LA, local anesthetic; NS, normal saline; N/A, not analyzed or not available; x-over, cross-over study design; VAS, visual analog scale (1 = no pain, 10 = worst imaginable pain); VNS, verbal numerical pain score; VPRS, verbal pain rating score; AC, analgesic consumption; TTFA, time to first analgesia; IA, intraoperative analgesia; TP, tourniquet pain; NSAID, non-steroidal anti-inflammatory drugs; PACU, postanesthetic care unit.

## Motor block

The onset of motor block revealed no significant difference between agents.[8,15,26,29,31,32] When assessing motor block recovery, ropivacaine use was found to cause a delayed recovery in all studies.[8,15,29] Hartmannsgruber et al[8] found that 0.2% ropivacaine resulted in decreased grip strength for up to 30 minutes in comparison to 0.5% lidocaine. Chan et al[29] had similar findings with the high-dose ropivacaine group ($1.8\ mg \cdot kg^{-1}$), where decreased grip strength was found to be sustained for 70 minutes compared to complete recovery in the lidocaine group during the same period. Niemi et al[15] compared 0.2% ropivacaine and 0.5% prilocaine, and had similar findings: 57% of patients in the ropivacaine group had decreased grip strength after 12 minutes compared to complete recovery in the prilocaine group during the same period. Motor recovery times were not assessed in studies comparing lidocaine and prilocaine.

## Tourniquet tolerance and intraoperative analgesia

Similar tourniquet tolerance times were found in four of five studies that compared lidocaine and ropivacaine.[8,27,29,31] Only Asik et al[26] demonstrated contrary findings, in which 0.25% ropivacaine resulted in improved distal tourniquet tolerance compared to the 0.2% ropivacaine or 0.5% lidocaine group (15.3 ± 2.3 minutes vs 9.1 ± 2.6 minutes and 9.0 ± 2.1 minutes). Tourniquet tolerance for prilocaine was not compared with the other agents, but intraoperative analgesia was assessed in two studies. Niemi et al[15] found intraoperative fentanyl requirements to be similar between those receiving 0.5% prilocaine and 0.2% ropivacaine. Davidson et al[30] used an objective scoring system for intraoperative pain, with results suggesting improved pain relief with 0.5% lidocaine compared to 0.5% prilocaine.

## Postoperative analgesia

Three out of four studies found significant postoperative benefits with ropivacaine compared to lidocaine.[26,27,31] Atanassoff et al[27] found lower numerical pain scores at the time of postanesthesia care unit (PACU) admission and a significantly longer time to first analgesia (TTFA) in those receiving 0.2% ropivacaine compared to 0.5% lidocaine (median [range]: 47 [27–340] minutes vs 34 [2–140] minutes). Peng et al[31] demonstrated lower postoperative verbal pain rating scores in subjects receiving 0.375% ropivacaine compared to 0.5% lidocaine after 60 minutes. In addition, this subject group was found to request analgesia less often in the first 2 hours (six patients) compared to the 0.5% lidocaine group (13 patients). Asik et al[26] demonstrated

lower verbal numerical pain scores and longer TTFA in the 0.25% and 0.20% ropivacaine subjects compared to 0.5% lidocaine (29.8 ± 4.9 minutes, 27.5 ± 7.3 minutes vs 11.3 ± 3.9 minutes). Furthermore, the number of patients taking more than two tablets of tramadol within the first 24 hours was lowest in the high-dose ropivacaine group compared to 0.2% ropivacaine and 0.5% lidocaine groups (three vs 18 and 16 patients, respectively). One study examined the use of 0.5% prilocaine and 0.2% ropivacaine. Although the time for the request of first analgesic agents was three times longer in the ropivacaine group (82 minutes vs 25 minutes), this did not achieve statistical significance.[15]

### Side effects

No significant side effects were reported in any study. Several studies demonstrated minor side effects without accompanying statistical analysis.[8,15,26–29] The volunteer patient studies[8,29] both demonstrated an increased incidence of temporary dizziness, tinnitus, and light-headedness in the lidocaine groups; however, these patients were not administered any sedation prior to, or during, the procedure. Asik et al[26] identified an increased incidence of light-headedness, tinnitus, and metallic taste in patients receiving lidocaine. Niemi et al[15] identified one patient with postoperative dizziness and blurry vision after receiving 0.5% prilocaine.

In summary, ropivacaine prolongs the sensory and motor block, which in turn results in superior postdeflation analgesia. Higher dose groups of ropivacaine tend to produce more consistent benefit in postdeflation sensory block and analgesia.

## Part two: IVRA adjuncts

Sixteen studies investigated opioids either as sole adjunct or in combination with a muscle relaxant[33–48] (Table 3), and ten studies investigated muscle relaxants either as sole agents or in combination with another adjunct[6,21,33,34,38,41,44,49–51] (Table 4). Five of the studies reported sample size estimations and power analysis.[6,42,43,45,50] Allocation concealment was adequate in one study,[42] and unclear in the others (Table 1).

### Opioids

Sixteen studies involving 761 patients investigated the use of opioids as IVRA adjuncts, either as a sole agent[34–37,39,40,42,43,45–48] or in combination with a muscle relaxant[33,38,41,44] (Table 3). The opioids investigated were morphine[34,37] (two studies), fentanyl[33,35,38,41,44,47,48] (seven studies), meperidine[36] (one study), sufentanil[40,42] (two studies), and tramadol[39,42,43,45,46] (five studies). One of the above studies involved both a sufentanil and tramadol group compared to control.[42]

### Morphine

Two studies involving a total of 57 subjects investigated morphine as a sole adjunct.[34,37] The doses studied were 1 mg and 6 mg.

Gupta et al[34] investigated potential postoperative benefits, and found no improvement in pain or analgesic requirements when 1 mg morphine was added to LA. Erciyes et al[37] added 6 mg morphine to LA, and noticed a significantly faster onset and slower recovery of sensory block compared to the control group (approximately 1 minute each). Postdeflation analgesia was not assessed. Systemic controls were not used in these studies, and no significant side effects were reported.

### Fentanyl

Seven studies involving a total of 345 subjects investigated fentanyl as an IVRA adjunct.[33,35,38,41,44,47,48] Four studies evaluated it as a sole adjunct,[33,35,47,48] and four studies looked at fentanyl in combination with a muscle relaxant[33,38,41,44] (one study investigated it as both a sole adjunct and in combination with a muscle relaxant). The dose range was 50–200 μg.

Studies evaluating fentanyl as a sole adjunct did not identify any benefits in terms of onset or recovery of sensory or motor block. One study investigated tourniquet pain, identifying no improvement compared to control.[35] Postoperative analgesia was not assessed in any study. Two studies reported a significantly increased incidence of nausea post-tourniquet deflation in the fentanyl-treated groups.[35,47]

Three studies investigated fentanyl plus pancuronium,[33,38,44] and one study investigated fentanyl plus mivacurium.[41] All four studies used a dilute solution of LA (0.25% lidocaine) with the addition of these adjuncts. Sztark et al[38] and Aujla et al[44] both compared fentanyl (1 $\mu g \cdot kg^{-1}$) and pancuronium (0.5 mg) added to 0.25% lidocaine. Sztark et al[38] found a slower onset of block (by approximately 4 minutes) compared to control (0.5% plain lidocaine). Aujla et al[44] had similar findings compared to control (0.75% lidocaine), with a slower onset of sensory block by approximately 6 minutes. One study found no difference in onset of sensory block.[41] Abdulla and Fadhil[33] did not assess onset time specifically, but noted that the combination of fentanyl (50 μg) and pancuronium (0.5 mg) added to dilute LA provided good or excellent intraoperative analgesia in 100% of cases. Onset of motor block was assessed in two studies[38,41] with conflicting results. Sztark et al[38] found that fentanyl (1 $\mu g \cdot kg^{-1}$) and pancuronium (0.5 mg) added to 0.25% lidocaine resulted in

**Table 3** Randomized controlled trials evaluating opioid drugs as IVRA adjuncts

| Author | Numbers/ groups/ setting* | Systemic control | Adjunct | LA used | Outcomes | | | Side effects ($P < 0.05$) | Overall |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Block efficacy | Intraoperative analgesia/ tourniquet pain | Postoperative | | |
| Armstrong[47] | 30/2/x-over volunteer | No | Fentanyl:<br>2 mL NS (0 μg)<br>2 mL (100 μg) | 0.5% prilocaine<br>40 mL | Sensory onset: equal<br>Sensory recovery: equal<br>Motor onset: N/A<br>Motor recovery: N/A | N/A | N/A | Increased incidence of nausea in fentanyl group | Negative |
| Arthur[48] | 30/3/x-over volunteer | No | Fentanyl:<br>2 mL NS (0 μg)<br>2 mL (100 μg)<br>42 mL NS (100 μg) (no LA) | 0.25% lidocaine<br>40 mL | Sensory onset: equal<br>Sensory recovery: equal<br>Motor onset: equal<br>Motor recovery: equal | N/A | N/A | Increased incidence of postdeflation nausea in fentanyl groups (statistical significance N/A) | Negative |
| Pitkanen[35] | 37/3/upper limb surgery | No | Fentanyl:<br>4 mL NS (0 μg)<br>4 mL (100 μg)<br>4 mL (200 μg) | 0.5% prilocaine<br>40 mL | Sensory onset: no difference between groups with onset of analgesia (but faster onset anesthesia at 15 minutes with 0.2 mg fentanyl group)<br>Sensory recovery: equal<br>Motor onset: equal<br>Motor recovery: N/A | IA: N/A<br>TP: Equal | N/A | Increased incidence of nausea, light-headedness, dizziness in both fentanyl groups | Negative |
| Abdulla[33] | 60/4/upper limb surgery | No | Fentanyl<br>0, 50, 0, 50 μg<br>Pancuronium<br>0, 0, 0.5, 0.5 mg | 0.25% lidocaine<br>40 mL | Sensory onset: both adjuncts combined gave better IA<br>Sensory recovery: N/A<br>Motor onset: motor block profound with pancuronium<br>Motor recovery: N/A | N/A | N/A | None | Intraoperative supportive (with adjuncts combined only) |

(*Continued*)

**Table 3** (*Continued*)

| Author | Numbers/ groups/ setting* | Systemic control | Adjunct | LA used | Outcomes | | | Side effects ($P < 0.05$) | Overall |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Block efficacy | Intraoperative analgesia/ tourniquet pain | Postoperative | | |
| Gupta[34] | 37/2/hand surgery | No | Morphine<br>4 mL 5% glucose + 1 mL saline (0 mg)<br>4 mL 5% glucose + 1 mL (1 mg) | 0.5% prilocaine<br>3 $mg.kg^{-1}$ | Sensory: N/A<br>Motor: N/A | N/A | VAS: equal<br>AC: equal<br>TTFA: N/A | None | Negative |
| Armstrong[36] | 20/2/x-over volunteer | No | Meperidine:<br>2 mL NS (0 mg)<br>2 mL (100 mg) | 0.25% prilocaine<br>40 mL | Sensory onset: faster onset in meperidine group<br>Sensory recovery: slower recovery in meperidine group<br>Motor onset: faster onset in meperidine group<br>Motor recovery: slower in meperidine group | Forearm pain: less with meperidine at 20 minutes<br>TP: less in meperidine group at 10 minutes | N/A | Increased incidence of light-headed, nausea with meperidine | Intraoperative supportive |
| Erciyes[37] | 20/2/upper limb surgery | No | Morphine:<br>10 mL NS (0 mg)<br>10 mL (6 mg) | 1% prilocaine<br>30 mL | Sensory onset: faster (c. 1 minute only)<br>Sensory recovery: slower (c. 1 minute only)<br>Motor onset: N/A<br>Motor recovery: N/A | N/A | N/A | None | Intraoperative supportive |
| Sztark[38] | 40/2/upper limb surgery | No | Fentanyl<br>1 $\mu g.kg^{-1}$<br>Pancuronium<br>0.5 mg | Lidocaine<br>0.6 $ml.kg^{-1}$ 0.5% + no adjunct<br>Lidocaine<br>0.6 $mg.kg^{-1}$<br>0.25% + adjunct | Sensory onset: faster in plain lidocaine group (c. 4 minutes)<br>Sensory recovery: N/A<br>Motor onset: faster in plain lidocaine group (c. 6 minutes)<br>Motor recovery: N/A | IA: N/A<br>TP: equal | VAS: N/A<br>AC: N/A<br>TTFA: equal | 1 patient with transient diplopia postdeflation in adjunct group (statistical significance N/A) | Intraoperative supportive |
| Hoffman[40] | 75/5/upper limb surgery | No | Sufentanil:<br>5 mL NS<br>5 mL 0.25% bupivacaine<br>5 mL clonidine (150 $\mu g$) | 1% prilocaine<br>30 mL | Sensory onset: faster in sufentanil group compared to control (c. 2.7 minutes faster)<br>Sensory recovery: equal | N/A | VAS: no difference in sufentanil group<br>AC: N/A<br>TTFA: N/A | Light-headedness postdeflation in 8/15 receiving sufentanil (statistical significance N/A) | Intraoperative supportive |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | 5 mL sufentanil (25 μg)<br>5 mL tenoxicam (20 μg) | | Motor onset: equal<br>Motor recovery: equal | | | | |
| Lim[41] | 48/2/forearm or hand surgery | No | Fentanyl: 1 μg . kg$^{-1}$<br>Mivacurium: 1 mg | 0.5% lidocaine 30 mL + no adjunct<br>0.25% lidocaine 40 mL + adjuncts | Sensory onset: equal<br>Sensory recovery: N/A<br>Motor onset: faster in adjuncts group (11.1 min versus 3.0 minutes)<br>Motor recovery: N/A | N/A | VAS: lower in adjuncts group at 45 minutes, 1 hour postoperative<br>AC: N/A<br>TTFA: N/A | 11 patients in adjunct group experienced post-deflation "giddiness", 5 in control (and 1 with tinnitus) (statistical significance N/A) | Intraoperative and postoperative supportive |
| Acalovschi[39] | 60/4/volunteer | No | Tramadol:<br>40 mL NS/0 mg tramadol (no LA)<br>100 mg tramadol in 40 mL NS (no LA)<br>0 mg tramadol (and LA)<br>100 mg tramadol (and LA) | 0 mL 0.5% lidocaine<br>0 mL 0.5% lidocaine<br>40 mL 0.5% lidocaine<br>40 mL 0.5% lidocaine | Sensory onset: faster onset sensory block to pinprick, touch, and cold with tramadol/LA<br>Sensory recovery: slower recovery to touch sensation (not cold or pinprick) in tramadol/LA group<br>Motor onset: equal<br>Motor recovery: N/A | N/A | N/A | Significant increased incidence of skin rash below tourniquet level in tramadol/LA group | Intraoperative supportive |
| Tan[46] | 54/2/upper limb surgery | No | Tramadol:<br>– 1 mL NS<br>– 1 mL tramadol (50 mg) | 0.5% lidocaine, 30 mL | Sensory onset: no difference between groups<br>Sensory recovery: N/A<br>Motor onset: no difference between groups<br>Motor recovery: N/A | IA: N/A<br>TP: less tourniquet pain at 30 minutes and after change to distal tourniquet | VAS: equal<br>AC: N/A<br>TTFA: equal | Skin rash in 2 patients receiving tramadol (statistical significance N/A) | Intraoperative supportive |
| Langlois[43] | 30/2/carpal tunnel sx | No | Tramadol:<br>– 2 mL NS (0 mg)<br>– 2 mL tramadol (100 mg) | 0.5% lidocaine, 3 mg . kg$^{-1}$ | Sensory: N/A<br>Motor: N/A | IA: equal<br>TP: equal | VAS: equal<br>AC: N/A<br>TTFA: equal | None | Negative |

(*Continued*)

**Table 3** (*Continued*)

| Author | Numbers/ groups/ setting* | Systemic control | Adjunct | LA used | Outcomes | | | Side effects ($P < 0.05$) | Overall |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Block efficacy | Intraoperative analgesia/ tourniquet pain | Postoperative | | |
| Alayurt[42] | 60/4/hand or forearm surgery | No | 5 mL saline<br>5 mL sufentanil (25 μg)<br>5 mL tramadol (100 mg)<br>5 mL clonidine (1 μg /kg) | 0.5% lidocaine, 35 mL | Sensory onset: faster with sufentanil (4 min versus 7 minutes) and tramadol (5 minutes versus 7 minutes)<br>Sensory recovery: no difference in sufentanil or tramadol groups compared to control<br>Motor onset: equal<br>Motor recovery: equal | IA: less intraoperative fentanyl in sufentanil and tramadol groups<br>TP: Less with sufentanil and tramadol at 20 and 40 minutes | VAS: equal<br>AC: equal<br>TTFA: N/A | None significant | Intraoperative supportive (both tramadol and sufentanil) |
| Siddiqui[45] | 60/3/hand surgery | No | Tramadol:<br>2 mL saline<br>2 mL tramadol (50 mg)<br>2 mL tramadol (100 mg) | 0.5% lidocaine 40 mL | Sensory onset: earlier onset with tramadol (50, 100 mg groups) compared to control (4.9, 5.2 minutes compared to 7.6 minutes)<br>Sensory recovery: equal<br>Motor onset: equal<br>Motor recovery: equal | IA: less intraoperative fentanyl required in 100 mg tramadol group<br>TP: improved in 100 mg tramadol group | VAS: N/A<br>AC: equals<br>TTFA: longer in 100 mg tramadol group | 3 patients in each tramadol group had PONV, compared to 1 patient in control group (statistical significance N/A) | Supportive for tramadol (100 mg dose) |
| Aujla[44] | 100/2/upper limb surgery | No | Fentanyl:<br>1 $\mu g.kg^{-1}$<br>Pancuronium:<br>0.5 mg | 0.75% lidocaine, 0.6 $ml.kg^{-1}$ + no adjunct<br>0.25% lidocaine, 0.6 $ml.kg^{-1}$ + adjunct | Sensory onset: slower in adjunct group (9.9 minutes versus 3.4 minutes)<br>Sensory recovery: N/A<br>Motor onset: N/A<br>Motor recovery: N/A | IA: equal<br>TP: N/A | N/A | None significant | Negative |

**Notes:** *The first number shown is the total number of study subjects, second number is the number of groups.

**Abbreviations:** IVRA, intravenous regional anesthesia; LA, local anesthetic; NS, normal saline; N/A, not analyzed or not available; x-over, cross-over study design; VAS, visual analog scale (1 = no pain, 10 = worst imaginable pain); VNS, verbal numerical pain score; VPRS, verbal pain rating score; AC, analgesic consumption; TTFA, time to first analgesia; IA, intraoperative analgesia; TP, tourniquet pain; PONV, postoperative nausea and vomiting.

**Table 4** Randomized controlled trials evaluating muscle relaxants as IVRA adjuncts

| Author | Numbers/ groups/ setting* | Systemic control | Adjunct | LA used | Outcomes | | | Side effects ($P < 0.05$) | Overall |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Block efficacy | Intraoperative analgesia/ tourniquet pain | Postoperative | | |
| McGlone[52] | 36/2/closed reduction of wrist fractures | No | Atracurium 2 mg | 0.5% prilocaine, 40 mL | Sensory onset: N/A<br>Sensory recovery: N/A<br>Motor onset: N/A, but easier reduction in atracurium group<br>Motor recovery: delayed in atracurium group (25.8 versus 4.8 minutes) | IA: Reduced pain during reduction in atracurium group<br>TP: N/A | N/A | 3//18 in atracurium group with diplopia postdeflation (statistical significance N/A) | Intraoperative supportive |
| Abdulla[33] | 60/4/upper limb surgery | No | Fentanyl 0, 50, 0, 50 μg<br>Pancuronium 0, 0, 0.5, 0.5 mg | 0.25% lidocaine 40 mL | Sensory onset: both adjuncts combined gave better intra-op analgesia<br>Sensory recovery: N/A<br>Motor onset: motor block profound with pancuronium<br>Motor recovery: N/A | N/A | N/A | None | Intraoperative supportive (with adjuncts combined) |
| Elhakim[49] | 40/2/hand fractures – open surgery | No | Atracurium 0 mg<br>2 mg | 0.5% lidocaine, 40 mL | Sensory onset: equal<br>Sensory recovery: N/A<br>Motor onset: equal onset between groups, but improved muscle relaxation in treatment group<br>Motor recovery: slower return in atracurium group (22 minutes versus 3 minutes) | IA: VAS scores significantly less in atracurium group<br>TP: N/A | VAS: less pain in atracurium group at 5 and 15 minutes postoperative<br>AC: N/A<br>TTFA: N/A | None | Intraoperative and postoperative supportive |
| Torrance[53] | 10/2/volunteer | No | Mivacurium 0.6 mg | 0.5% prilocaine, 40 mL | Sensory onset: N/A<br>Sensory recovery: N/A<br>Motor onset: equal quality of paralysis<br>Motor recovery: prolonged in mivacurium group | N/A | N/A | 5/5 patients in mivacurium group with signs of LA toxicity<br>2/5 in mivacurium group developed transient uritcarial wheals postdeflation (statistical significance N/A) | Negative |

(*Continued*)

**Table 4** (*Continued*)

| Author | Numbers/ groups/ setting* | Systemic control | Adjunct | LA used | Outcomes | | | Side effects ($P < 0.05$) | Overall |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Block efficacy | Intraoperative analgesia/ tourniquet pain | Postoperative | | |
| Sztark[38] | 40/2/upper limb surgery | No | Fentanyl 1 μg .kg$^{-1}$ Pancuronium 0.5 mg | Lidocaine 0.6 ml.kg$^{-1}$ 0.5% + no adjunct Lidocaine 0.6 mg.kg$^{-1}$ 0.25% + adjunct | Sensory onset: faster in plain lidocaine group (c. 4 minutes) Sensory recovery: N/A Motor onset: faster in plain lidocaine group (c. 6 minutes) Motor recovery: N/A | IA: N/A TP: equal | VAS: N/A AC: N/A TTFA: equal | 1 patient with transient diplopia after tourniquet release in adjunct group (statistical significance N/A) | Intraoperative supportive |
| Lim[41] | 48/2/forearm or hand surgery | No | Fentanyl: 1 μg.kg$^{-1}$ Mivacurium: 1 mg | 0.5% lidocaine 30 mL + no adjunct 0.25% lidocaine 40 mL + adjuncts | Sensory onset: equal Sensory recovery: N/A Motor onset: faster in adjuncts group (11.1 minutes versus 3.0 minutes) Motor recovery: N/A | N/A | VAS: lower in adjuncts group at 45 minutes, 1 hour postoperative AC: N/A TTFA: N/A | 11 patients in adjunct group experienced postdeflation "giddiness", 5 in control (and 1 with tinnitus) (statistical significance N/A) | Intraoperative and postoperative supportive |
| Esmaoglu[6] | 40/2/elective hand surgery | No | Cisatracurium 0 mg 0.01 mg·kg$^{-1}$ | 3 mg.kg$^{-1}$ lidocaine, diluted with NS to a total volume 40 mL | Sensory onset: shorter in cisatracurium group (c. 1.8 minutes faster) Sensory recovery: equal Motor onset: shorter in cisatracurium group (c. 7 minutes faster) Motor recovery: longer in cisatracurium group (c. 13 minutes longer) | IA: Improved "quality" of analgesia and less intraoperative fentanyl in cisatracurium group TP: N/A | VAS: N/A AC: lower fentanyl requirements in cisatracurium group TTFA: N/A | None | Intraoperative and postoperative supportive |
| Aujla[44] | 100/2/upper limb surgery | No | Fentanyl: 1 μg.kg$^{-1}$ Pancuronium: 0.5 mg | 0.75% lidocaine, 0.6 ml.kg$^{-1}$ + no adjunct 0.25% lidocaine, 0.6 ml.kg$^{-1}$ + adjunct | Sensory onset: slower in adjunct group (9.9 minutes versus 3.4 minutes) Sensory recovery: N/A Motor onset: N/A Motor recovery: N/A | IA: equal TP: N/A | N/A | None significant | Negative |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Mizrak[50] | 60/2/carpal tunnel release | No | Mivacurium 0 mg 0.6 mg | 3 mg · kg$^{-1}$ lidocaine, diluted with NS to a total volume 40 mL | Sensory onset: shorter in mivacurium group (0.9 minutes faster) Sensory recovery: equal Motor onset: shorter in mivacurium group (c. 2 minutes shorter) Motor recovery: longer in mivacurium group (c. 13 minutes longer) | IA: equal TP: equal | VAS: equal AC: decreased fentanyl requirements during 24-hour period in mivacurium group TTFA: N/A | None | Intraoperative and postoperative supportive |
| Prasad[51] | 60/3/upper limb surgery | No | Atracurium 0 mg (control) 2 mg 0 mg (30 mg ketorolac) | 2% lidocaine (10 mL) diluted to 40 mL with NS +/− adjunct | Sensory onset: equal Sensory recovery: N/A Motor onset: equal onset, equal quality of muscle relaxation Motor recovery: equal | IA: N/A TP: equal | VAS: no difference in atracurium group AC: no difference in atracurium group TTFA: N/A | None | Negative |

**Notes:** *The first number shown is the total number of study subjects, second number is the number of groups.
**Abbreviations:** IVRA, intravenous regional anesthesia; LA, local anesthetic; NS, normal saline; N/A, not analyzed or not available; x-over, cross-over study design; VAS, visual analog scale (1 = no pain, 10 = worst imaginable pain); VNS, verbal numerical pain score; VPRS, verbal pain rating score; AC, analgesic consumption; TTFA, time to first analgesia; IA, intraoperative analgesia; TP, tourniquet pain.

a slower time to motor block by approximately 6 minutes. However, Lim and Ong[41] added fentanyl (1 μg · kg$^{-1}$) and mivacurium (1 mg) to a 0.25% lidocaine and found a faster onset (3 minutes) of complete motor block compared to 0.5% plain lidocaine (11.1 minutes). Tourniquet pain was not investigated.

Postoperative analgesia demonstrated conflicting results. Lim and Ong[41] found postoperative visual analog scale (VAS) scores to be significantly reduced at 45 minutes and 60 minutes in patients receiving fentanyl (1 μg · kg$^{-1}$) and mivacurium (1 mg) added to 0.25% lidocaine, while Sztark et al[38] did not identify any postoperative benefits in those receiving fentanyl (1 μg · kg$^{-1}$) and pancuronium (0.5 mg). No significant side effects were reported in any studies.

## Meperidine

One study involving 20 volunteers investigated the use of meperidine as a sole adjunct.[36] The dose was 100 mg.

Armstrong et al[36] demonstrated a faster onset and slower to recover sensory and motor block with the addition of 100 mg meperidine to 0.25% prilocaine. Tourniquet pain at 10 minutes (but not 20 minutes) and forearm pain at 20 minutes was significantly less in the meperidine group compared to the control group. Postoperative analgesia was not assessed, but postdeflation recovery in the tourniquet group was complicated by light-headedness and nausea. It was the authors' conclusion that these side effects would preclude the use of meperidine in normal clinical IVRA.

## Sufentanil

Two studies involving 125 subjects investigated the use of sufentanil as a sole adjunct in IVRA.[40,42] Sufentanil was one of several agents investigated in each of these studies; the other agents are discussed elsewhere. For each study the dose was 25 μg.

Sensory onset was found to be faster in each study. Hoffman et al[40] added 25 μg sufentanil to LA (1% prilocaine) and Alayurt et al[42] added 25 μg sufentanil to LA (0.5% lidocaine). Both studies demonstrated a faster onset of sensory block by approximately 3 minutes. Recovery of sensory anesthesia was not assessed, and both studies did not find any difference in onset or recovery of motor block. Alayurt et al[42] found the addition of sufentanil to LA decreased intraoperative fentanyl requirements compared to the control group (44 ± 29 μg vs 56 ± 54 μg), and improved tourniquet pain VAS scores at 20 minutes and 40 minutes. No postoperative benefits were found in either study. Hoffman et al[40] described an increased incidence

of light-headedness in eight of 15 subjects, however this was not statistically analyzed.

### Tramadol

Five studies involving a total of 264 subjects looked at the use of tramadol as a sole adjunct for IVRA.[39,42,43,45,46] In one study, tramadol was analyzed in comparison to a number of single adjuncts.[42] The dose range was 50–100 mg.

Three out of four studies demonstrated a faster onset of sensory block with the addition of tramadol to LA.[39,42,45] Siddiqui et al[45] investigated two doses of tramadol, and found a faster onset of sensory block with both 50 mg and 100 mg doses added to 0.5% lidocaine (5.2 ± 1.2 minutes and 4.9 ± 1.2 minutes vs 7.6 ± 1.4 minutes). Alayurt et al[42] found a faster onset of sensory block by approximately 2 minutes if tramadol (100 mg) was added to 0.5% lidocaine. Acalovschi et al[39] demonstrated a faster onset of sensory block (pin-prick, touch, and temperature) with 100 mg tramadol added to 0.5% lidocaine. However, this study found only touch sensation to be slower to recover; the remaining studies did not find a difference in sensory recovery.[42] No study demonstrated a significant difference in onset or recovery of motor block.

Tourniquet pain was decreased by the addition of tramadol in three of four studies that investigated this outcome.[42,45,46] Tan et al[46] found that a 50 mg dose decreased tourniquet pain at 30 minutes (not at 10 minutes or 20 minutes) and after changeover to the distal tourniquet. Alayurt et al[42] found that 100 mg tramadol added to LA decreased intraoperative fentanyl requirements (44 ± 54 μg vs 56 ± 54 μg), and decreased tourniquet pain at 20 minutes and 40 minutes compared to control. Siddiqui et al[45] found no difference in intraoperative analgesia with 50 mg tramadol, but identified a decrease in intraoperative fentanyl requirements (32.8 ± 35.2 μg vs 63.3 ± 39.5 μg) and tourniquet pain with the 100 mg dose. One study did not find any improvement in tourniquet pain.[43]

Siddiqui et al[45] found a significantly longer TTFA with 100 mg tramadol (but not 50 mg) added to LA (215 ± 85 minutes vs 125 ± 54 minutes). No other studies found postoperative advantages with the addition of tramadol.[42,43,46] Acalovschi et al[39] reported a significantly increased incidence of skin rash below the tourniquet site in the tramadol group (nine of 15 patients) compared to the control group (zero of 15 patients). A nonsignificant number of patients in this group (five of 15 patients) also complained of burning or pain at the injection site compared to the control group (one in 15 patients). Tan et al[46] found a skin rash in two of 27 patients who received tramadol, however this was not analyzed statistically (both rashes resolved after tourniquet release). Siddiqui et al[45] encountered postoperative nausea or vomiting necessitating treatment with granisetron in three of 20 patients in both the 50 mg and 100 mg tramadol groups; the significance of this was not assessed.

In summary, morphine, meperidine, and fentanyl (as a sole adjunct) do not demonstrate clinically significant benefits as adjuncts or their side effects preclude their clinical use. The combination of fentanyl with a muscle relaxant can achieve an equivalent quality of IVRA with a 50% reduction in LA dose, but at the expense of a potentially slower sensory block. Sufentanil provides a faster onset of sensory block, but does not demonstrate postdeflation analgesia. Tramadol provides a faster onset of sensory block and improved tourniquet tolerance, but lacks consistent postdeflation analgesia and poses an increased risk of minor side effects.

## Muscle relaxants

Ten studies involving 494 patients investigated muscle relaxants, either in combination with fentanyl,[33,38,41,44] or as sole adjuncts[6,33,49–53] (Table 4). The muscle relaxants investigated were pancuronium,[33,38,44] atracurium,[49,51,52] mivacurium,[41,50,53] and cisatracurium.[6]

### Sensory anesthesia

Two out of six studies evaluating muscle relaxants as sole adjuncts reported a faster onset of sensory block with the addition of muscle relaxant to LA. Esamaoglu et al[6] found sensory blockade to be on average 1.8 minutes faster with the addition of cisatracurium (0.01 $mg \cdot kg^{-1}$) to plain lidocaine (3 $mg \cdot kg^{-1}$). Mizrak et al[50] found similar results to the previous studies, demonstrating a faster onset of sensory block by adding mivacurium (0.6 mg) to plain lidocaine (3.1 ± 0.5 minutes vs 2.2 ± 0.8 minutes). No study identified a difference in sensory recovery compared to control.[6,50]

### Motor block

Two studies evaluating muscle relaxants as sole adjuncts to LA found a faster onset of motor block.[6,50] With the addition of mivacurium (0.6 mg) to lidocaine (3 $mg \cdot kg^{-1}$), Mizrak et al[50] found a faster onset of motor block by approximately 2 minutes. Esmaoglu et al[6] found that the addition of cisatracurium (0.01 $mg \cdot kg^{-1}$) to plain lidocaine (3 $mg \cdot kg^{-1}$) resulted in a faster onset of motor block by approximately 7 minutes. Three studies did not report a faster onset of block, yet described a significantly greater degree of muscle relaxation with the addition of 0.5 mg pancuronium[33] or 2 mg atracurium[33,49,52] to IVRA. Five out

of six studies evaluating the recovery of motor block found it to be significantly prolonged in patients receiving muscle relaxant.[6,49,50,52,53]

### Tourniquet tolerance and intraoperative analgesia

Two studies investigating tourniquet pain found no improvement with the addition of muscle relaxant to LA.[50,51] Elhakim and Sadek[49] described significantly improved intraoperative VAS scores unrelated to the tourniquet site. Likewise, Esmaoglu et al[6] described an improved quality of analgesia requiring less intraoperative supplemental opioids.

### Postoperative analgesia

Elhakim and Sadek[49] measured postoperative pain and described a reduction at 5 minutes and 15 minutes with the addition of 2 mg atracurium to LA. Esmaoglu et al[6] described minimally decreased postoperative fentanyl requirements in those receiving 0.01 mg · kg$^{-1}$ cisatracurium added to LA compared to control (median [range]: 0 [0–50] μg vs 0 [0–150] μg). Mizrak et al[50] did not find a significant difference in pain scores, but reported a small but significant decrease in the amount of fentanyl consumption within a 24-hour period with the addition of 0.6 mg mivacurium to LA (10 ± 20.3 μg vs 25 ± 34.1 μg). Prasad and Anjan[51] did not discover any improvement in postoperative analgesia with the use of muscle relaxants.

### Side effects

Nine out of ten studies did not find any significant side effects.[6,33,38,41,44,49–52] Torrance et al[53] described signs of LA toxicity (light-headedness, tinnitus, diplopia, perioral paresthesia) in all volunteers in the group receiving 0.6 mg mivacaurium, compared to none in the control group. McGlone et al[52] reported postdeflation diplopia in three of 18 patients receiving 2 mg atracurium; the significance of this was not assessed.

In summary, muscle relaxants provide an improved quality of motor block, but at the expense of a delay in motor recovery. There are no postdeflation benefits with the use of these adjuncts.

## Discussion

Part one of this review suggests that ropivacaine has the most to offer in terms of postoperative benefits for IVRA. The second part of this review, as discussed below, suggests that opioids and muscle relaxants as IVRA adjuncts have potential benefits, but are overall not recommended for routine use.

## Local anesthetic

With regards to LA, the intraoperative outcomes (onset of sensory and motor block, tourniquet pain) appear to be equivalent with all three agents. When assessing postoperative outcomes the differences between these agents become more evident. One of the major concerns with IVRA is limited postoperative pain relief following tourniquet deflation, and evidence from this review suggests that ropivacaine has the most to offer for improving postoperative analgesia. The prolonged residual anesthesia of ropivacaine may be due to the slow release of the drug from tissue binding sites with subsequent slow increase in plasma concentrations.[54] This benefit was most evident when ropivacaine was compared to lidocaine. One study comparing it to prilocaine did not demonstrate an improvement, and further studies are needed to investigate this comparison. The improvement in postoperative analgesia must be weighed against a prolonged recovery for return of motor function in comparison to other LA agents. Furthermore, although no significant side effects were reported in these studies, LA toxicity remains a concern. Prilocaine has fallen out of favor in the past because of concerns regarding risk of methemoglobinemia, but evidence has shown that this is very unlikely to occur at doses appropriate for IVRA.[55] Data records from 1963–1989 indicated that prilocaine was not responsible for any deaths from all modes of use, not just IVRA.[55] Ropivacaine is devoid of the potential toxic dextrorotatory version of racemic LA anesthetic mixtures, but in high doses may still cause CNS and cardiac toxicity.[26] When considering its use, an unanswered question remains regarding its potency ratio compared to other LA agents.

## Opioids

Using basic concepts of peripheral opioid activity, anesthesiologists have attempted to capitalize on the presence of peripheral opioid receptors to improve the quality of intraoperative and/or postoperative regional anesthesia.[56] The scientific basis for this theory was based on the presence of opioid receptors and their endogenous ligands in the peripheral nervous system, and their effect on modulation of inflammatory pain.[57] However, recent systematic reviews have concluded that, in fact, opioids lack significant effect in this setting.[56] As outlined by Choyce and Peng[17] in a systemic review on IVRA adjuncts in 2002, results of early studies evaluating morphine, fentanyl, meperidine, sufentanil, and tramadol as adjuncts were disappointing. Since this time, however, new studies have continued to assess the benefits of several opioids, with a

focus on sufentanil and tramadol, as well as the combination of opioids with muscle relaxants in an attempt to decrease the required dose of LA. Evidence from this review indicated that morphine did not demonstrate a clinically significant benefit as an adjunct. Fentanyl (as a sole adjunct) failed to demonstrate any benefits, and had an increased risk of minor side effects. Meperidine demonstrated positive findings, but an increased incidence of light-headedness and nausea was a significant disadvantage.

More recent studies focused on the potential benefits of tramadol (and sufentanil). Both tramadol and sufentanil have gained interest because of a demonstrated local anesthetic-type quality, in addition to their affinity for mu receptors. Gissen et al[58] have shown sufentanil to have a depressant effect on the A and C fiber action potentials of peripheral mammalian nerves. Sufentanil was evaluated in two studies, and while showing a faster onset of sensory block, lacked intraoperative and postoperative analgesia. Tramadol is known to have both opioid and non-opioid modes of action; it agonizes the mu receptor, inhibits the uptake of 5-hydroxytryptamine (5-HT) and norepinpephrine, and stimulates 5-HT release.[59] Like sufentanil, Pang et al[60] have demonstrated that tramadol also has local anesthetic effects following intradermal injection, and one study has shown that its local anesthetic effect can prolong duration of an axillary brachial plexus block when added to mepivacaine.[61] Tramadol has shown a faster onset of sensory block and improved tourniquet tolerance, but a lack of consistent postoperative benefits and an increased risk of minor side effects (such as localized skin rash) have been found.

## Muscle relaxants

Evidence indicates that non-depolarizing neuromuscular blocking agents can be of benefit in hastening the onset of motor block and creating a more profound muscle relaxation state.

These benefits have been found to facilitate fracture reduction and also improve overall analgesia in young, muscular patients.[52] However, evidence shows that this comes at the cost of prolonged recovery of motor function. The late return of fine motor control after tourniquet release in these studies is probably an effect of residual receptor blockade at the neuromuscular junction.[62] Muscle relaxants act at the level of the muscle spindle and reduce the central input from these structures. It is hypothesized that the relaxants interfere with their activity resulting in loss of muscle tone and control of voluntary movement, with a decrease in nervous input to the CNS.[49] In addition to making the surgery easier, blockade of the spindles may theoretically alleviate muscle spasm and reduce pain during and after surgery. However, existing evidence from this review does not support a benefit for intraoperative or postoperative analgesia.

In an effort to reduce the dose of LA to a nontoxic range, three studies evaluated the combination of a muscle relaxant and opioid (fentanyl) as adjuncts to a dilute solution of LA. Results have been conflicting. Evidence indicates that an equivalent quality of block can be achieved with the addition of these adjuncts to a dilute solution of LA, but at the expense of a potentially slower onset of sensory block.

## Implications for further research

Further research is needed to investigate the safety of LA options for IVRA. There is currently no recommended dose for ropivacaine in IVRA, and comparison trials should be completed with full knowledge of the relative LA potencies.[26] More clinical studies are required to examine the safety of the use of ropivacaine. Furthermore, one of the major limitations of IVRA continues to be the lack of postoperative analgesia following tourniquet deflation. Trials to date have failed to identify an adjunct that provides consistent postoperative analgesia without an increase in minor side effects. Future studies should focus their investigations on novel adjuncts that can provide effective post-deflation analgesia.

# Conclusion

There is good evidence that ropivacaine provides effective IVRA and improved postoperative analgesia. Lidocaine and prilocaine are effective LA agents, however, they lack postoperative benefits. Morphine, fentanyl, and meperidine as sole adjuncts do not demonstrate clinically significant benefits or result in an increased risk of side effects. Sufentanil data is limited, but appears to provide faster onset of sensory block. Tramadol provides faster onset of sensory block and tourniquet tolerance, but lacks consistent postoperative benefits with an increased risk of minor side effects. Muscle relaxants improve the quality of motor block, but at the expense of delayed motor recovery. The combination of fentanyl and muscle relaxants can achieve an equivalent quality of IVRA with 50% reduction in LA dose, but at the expense of a potentially slower onset of sensory block.

## Disclosure

The authors report no conflicts of interest in this work.

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