A systematic review of adjuncts for intravenous regional anesthesia for surgical procedures

[Étude méthodique des traitements d'appoint à l'anesthésie régionale intraveineuse pendant les interventions chirurgicales]

Andrew Choyce MBCHB FRCA,* Philip Peng MBBS FRCPC†

Purpose: To review the use of adjuncts to intravenous regional anesthesia (IVRA) for surgical procedures in terms of their intraoperative effects (efficacy of block and tourniquet pain) and postoperative analgesia.

Source: A systematic search (Medline, Embase, reference lists) for randomized, controlled and double-blinded studies using adjuncts to IVRA for surgical procedures was conducted. Data were collected on intraoperative effects (onset/offset and quality of block and tourniquet pain), postoperative effects (pain intensity and analgesic consumption) and side effects recorded. Statistical significance as indicated in the original report and likely clinical relevance were taken into account to arrive at a judgment of overall benefit.

Principal findings: Twenty-nine studies met all inclusion criteria. Data on 1,217 study subjects are included. Adjuncts used were opioids (fentanyl, meperidine, morphine, sufentanil), tramadol, nonsteroidal anti-inflammatory drugs (NSAIDs; ketorolac, tenoxicam, acetyl-salicylate), clonidine, muscle relaxants (atracurium, pancuronium, mivacurium), alkalinization with sodium bicarbonate, potassium and temperature. There is good evidence to recommend NSAIDs in general and ketorolac in particular, for improving postoperative analgesia. Clonidine 1 $\mu g \cdot kg^{-1}$ also appears to improve postoperative analgesia and prolong tourniquet tolerance. Opioids are poor by this route; only meperidine 30 mg or more has substantial postoperative benefit but at the expense of postdeflation nausea, vomiting and dizziness. Muscle relaxants improve intraoperative motor block and aid fracture reduction.

Conclusion: Using NSAIDs or clonidine as adjuncts to IVRA improves postoperative analgesia and muscle relaxant improves motor block.

Objectif : *Passer en revue l'usage des traitements d'appoint à l'anesthésie régionale intraveineuse (ARIV) pour les interventions chirurgicales, en termes des effets peropératoires (efficacité du bloc et douleur du garrot et de l'analgésie postopératoire.*

Source : *Une recherche systématique (bases de données Medline, Embase, listes de références) des études randomisées, contrôlées et à double insu utilisant les traitements d'appoint à l'ARIV pendant les interventions chirurgicales a été réalisée. Les données concernant les effets peropératoires ont été recueillies (début/fin et qualité du bloc et douleur de garrot) ainsi que les effets postopératoires (intensité de la douleur et consommation analgésique) et les effets secondaires. La signification statistique, tel qu'indiqué dans l'article original, et la pertinence clinique possible ont été retenues afin d'en arriver à un jugement sur les bienfaits généraux.*

Constatations principales : *Vingt-neuf études répondaient à tous les critères d'inclusion. Les données sur 1 217 sujets d'étude ont été compilées. Les traitements d'appoint étaient des opioïdes (fentanyl, mépéridine, morphine, sufentanil), le tramadol, les anti-inflammatoires non stéroïdiens (AINS; kétorolac, ténoxicam, acétylsalicylique), la clonidine, les myorelaxants (atracurium, pancuronium, mivacurium), l'alcalinisation avec le bicarbonate de sodium, le potassium et la température. Il existe de bonnes indications pour l'utilisation des AINS en général et du kétorolac en particulier concernant l'analgésie postopératoire. L'administration de 1 $\mu g \cdot kg^{-1}$ de clonidine semble améliorer l'analgésie postopératoire et la tolérance prolongée du garrot. Les opioïdes font piètre figure dans ces circonstances; seule une dose de 30 mg ou plus de mépéridine présente des bienfaits postopératoires substantiels, mais aux dépens de nausées, de vomissements et d'étourdissement au relâchement du garrot. Les myorelaxants améliorent le bloc moteur peropératoire et favorisent la réduction de fracture.*

Conclusion : *L'utilisation de AINS ou de clonidine comme traitement d'appoint de l'ARIV améliore l'analgésie postopératoire tandis que les myorelaxants améliore le bloc moteur.*

From the Departments of Anesthesia, King's College Hospital,* Denmark Hill, London, UK; and the Toronto Western Hospital,† University Health Network, University of Toronto, Toronto, Ontario, Canada.

Address correspondence to: Dr. Philip Peng, Department of Anesthesia, Toronto Western Hospital, University Health Network, University of Toronto, 399 Bathurst Street, Toronto, Ontario M5T 2S8, Canada. Phone: 416-603-5118; Fax: 416-603-6494; E-mail: philip.peng@uhn.on.ca

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INTRAVENOUS regional anesthesia (IVRA) was first described in 1908 for anesthesia of the hand and forearm.[1] The earliest agent injected into the isolated vascular space was procaine. The technique regained popularity in the 1960's when Holmes used lidocaine.[2] Lidocaine remains the standard local anesthetic (LA) agent for surgical procedures in North America[3] and prilocaine is used widely in Europe.[4]

IVRA is simple to administer, reliable and cost-effective.[5] It is ideal for short operative procedures on the extremities performed on an ambulatory basis. Disadvantages include concerns about LA toxicity, slow onset, poor muscle relaxation, tourniquet pain and minimal postoperative pain relief. The ideal IVRA solution should have the following features: rapid onset, reduced dose of LA, reduced tourniquet pain and prolonged postdeflation analgesia. At present, this may only be achieved by the addition of adjuncts to LA.

The purpose of this article is to review the available literature and provide the operator with a guide to the likely benefits of adjuncts added to LA for IVRA for surgical procedures, i.e., improved block efficacy, decreased tourniquet pain or prolonged duration of postdeflation analgesia.

Methods

Studies were identified in a search of Medline (between July 1966 and January 2001) and Embase (from 1980) by using the following Medical Subject Headings (MeSH) terms: IVRA; intravenous regional analgesia, anesthesia or anaesthesia; Bier's block. The reference sections of eligible and related review articles were then examined for further relevant publications that might have been missed by the computer search.

Articles that were unpublished, abstracts, letters, and non-peer-reviewed or non-English language were excluded from the final systematic review. Of the studies identified, only those that were of a prospective, randomized, controlled and double-blinded design were included. Individual authors were not contacted for further information.

For each study, the concentration and volume of LA and type and dose of adjunct were recorded. Additional data included information on study design, numbers recruited, assessments made, side effects and outcomes. Data are presented in tabulated form. Each type of adjunct is examined for its potential intraoperative benefit (speed of onset and recovery of sensory and motor block, effect on tourniquet pain), postoperative analgesic benefit (visual analogue score (VAS), analgesic consumption (AC), time to first analgesic (TTFA) and side effect profile. The incidence of side effects is given as either "none", "not analyzed" (where no statistical analysis was performed) or the actual side effects if statistically different between groups. Study outcomes were classed as "supportive" if they showed significant benefit in either the intraoperative or postoperative variables examined, or "negative" if they did not.

Both authors using the above criteria reviewed each study independently. The clinical relevance of any differences is considered in the discussion.

Results

A total of 29 studies, all involving adults, met the criteria for inclusion. Two of these studies looked at the use of two adjuncts in combination with LA,[6,7] and one study compared four separate adjuncts to control.[8] Ten studies investigated opioids[6–15] and one tramadol[16] (Table I). Six studies investigated non-steroidal anti-inflammatory drugs (NSAIDs)[8,17–21] and five clonidine[8,22–25] (Table II). Five studies investigated muscle relaxants,[6,7,26–28] three alkalization,[29–31] one potassium[32] and two temperature[33,34] (Table III). None of the studies reported sample size estimation and power analysis.

Opioids

Ten studies involving 412 patients have investigated opioids either as sole adjunct[8–15] or in combination with a muscle relaxant[6,7] (Table I). One of the combination studies also included fentanyl as a sole adjunct.[7] The opioids investigated were fentanyl[6,7,9–11] (five studies), meperidine[13,15] (two studies), morphine[12,14] (two studies) and sufentanil[8] (one study). No study included a systemic control group. Six out of ten studies were supportive of the addition of the adjunct(s)[6–8,13–15] (two with fentanyl plus pancuronium,[6,7] two with meperidine,[13,15] one with morphine[14] and one with sufentanil).[8]

FENTANYL

Four studies on a total 157 subjects (including two volunteer studies), investigated fentanyl as sole adjunct.[6,9–11] The dose range was 50–200 μg.

No study demonstrated any intraoperative advantage in terms of onset (motor or sensory). Tourniquet pain was not investigated and none of the studies looked at postoperative analgesia. Two of the studies reported significant nausea after the deflation of the tourniquet cuff in the fentanyl-treated groups.[9,11]

Two further studies looked at the combination of fentanyl plus pancuronium.[6,7] Abdulla *et al.*[6] found that the combination of fentanyl 50 μg plus pancuronium 0.5 mg to a dilute solution of LA (0.25% lidocaine) provided good or excellent intraoperative analgesia in 100% of cases. No comparison of onset of

anesthesia or postoperative analgesia was made. Sztark *et al.*[7] compared 0.25% lidocaine plus fentanyl 1 $\mu g \cdot kg^{-1}$ and pancuronium 0.5 mg with conventional LA dose (0.5% lidocaine, 0.6 $mL \cdot kg^{-1}$). The plain lidocaine group had complete sensory block four minutes earlier but the overall success rate was similar.

MEPERIDINE

Two studies (one involving volunteers) on a total 80 subjects, investigated meperidine as sole adjunct.[13,15] The dose range was 10–100 mg.

Armstrong *et al.*[13] looked at the intraoperative effect of adding meperidine 100 mg to a dilute solution of LA. The resultant sensory and motor block was faster in onset and slower to recover. Furthermore, forearm pain at 20 min inflation and tourniquet pain at ten minutes (but not at 20 min) inflation were significantly less in the meperidine group than in the control group. Recovery in several of the meperidine-containing groups was complicated by light-headedness or nausea despite giving naloxone at deflation. The authors concluded that postdeflation complications precluded the use of meperidine in routine IVRA.

A dose-response study by Reuben *et al.*[15] looked at the effect of 10 to 50 mg of meperidine on postoperative analgesia. The VAS at one hour and the need for analgesic (acetaminophen/codeine) in the first 24 hr were lower with 30 mg or more. TTFA increased linearly up to 30 mg. Side effects (nausea, vomiting, sedation and dizziness) were more likely with 30 mg or more. The incidence of side effects up to 20 mg meperidine was statistically similar to the control group, but the duration of analgesia significantly less compared to 30 mg (269 ± 67 compared to 419 ± 123 min).

MORPHINE

Two studies on a total 60 subjects, investigated morphine as the sole adjunct.[12,14] The doses studied were 1 and 6 mg.

Erciyes *et al.*[14] added 6 mg morphine to LA and reported a significantly faster onset and slower offset of sensory block but only by approximately one minute each. Gupta *et al.*[12] focussed on the postoperative course and found no benefit from the addition of morphine 1 mg to LA. At the doses studied, there were no significant side effects reported in either study.

SUFENTANIL

Hoffman *et al.*[8] studied a number of single adjuncts to LA for IVRA. The other agents are discussed elsewhere. The addition of sufentanil 25 µg shortened the onset of complete sensory block compared to control by about three minutes. No postoperative benefit was demonstrated. Light-headedness after tourniquet deflation was reported in 8/15 but this was not analyzed statistically.

TRAMADOL

One study looked at the intraoperative effects of adding tramadol 100 mg to LA (Table I).[16] The resultant sensory (pinprick, touch and temperature) block was faster in onset compared to plain LA. However, only touch sensation was slower to recover compared to plain LA. Onset and recovery of motor block was not affected. Skin rash below the tourniquet that disappeared within one hour of deflation was the only significant side effect when tramadol was added to LA. Possible benefits in terms of tourniquet pain and postoperative course were not investigated.

NSAIDs

Six studies involving 370 patients have investigated various NSAIDs as the sole adjunct[8,17–21] to IVRA (Table II). The agents investigated were ketorolac,[17,19,21] tenoxicam[8,18] and aspirin.[20] One study compared IVRA ketorolac to local infiltration of ketorolac into the wound margin.[19] Three studies had a systemic control group.[17,18,20] All of these studies were supportive in terms of postoperative outcome.

KETOROLAC

Three studies on a total 190 subjects, have investigated ketorolac (5–60 mg) as the sole adjunct to IVRA.[17,19,21]

Only the study by Reuben *et al.*[17] looked at the potential intraoperative benefit of NSAIDs added to LA. They compared tourniquet pain scores and found significantly fewer patients had a pain score of >3/10 during the first 30 min when ketorolac 60 mg was added.

Reuben *et al.*[36] reported a number of significant postoperative benefits from IVRA-ketorolac compared to systemic control. Patients had less pain during the first postoperative hour, required no supplemental analgesia in the postanesthesia care unit (PACU) and consumed fewer analgesics during the first postoperative day when added to standard LA. In a follow-up study, Reuben *et al.*[19] found that ketorolac 60 mg was equally effective either infiltrated into the surgical site before incision or when given as an adjunct to IVRA. Steinberg *et al.*[21] added varying doses of ketorolac to IVRA and found a linear dose-response relationship up to 20 mg. Between 20 and 60 mg, there appeared to be no additional analgesic benefit. Side effects with IVRA ketorolac were not reported, and fears about wound hematoma remained unfounded.

TENOXICAM AND ACETYL-SALICYLATE

Two studies involving 120 patients have looked at 20 mg tenoxicam as an adjunct.[8,18] Both looked at the postoperative effects only. Jones *et al.*[18] found patients had less pain and consumed fewer analgesics during the first 24 hr. Hoffman *et al.*[8] failed to demonstrate significant benefit from tenoxicam beyond 30 min compared to control, but they did not record analgesic intake and follow-up lasted only 45 min.

One study[20] involving 60 patients looked at acetylsalicylate 90 mg as an adjunct. Again, only the postoperative course was investigated. Duration of postoperative analgesia was prolonged by over three hours and significantly less morphine was consumed during the first six hours compared to placebo; between 6–24 hr there was no difference between groups.

Clonidine

Five studies (one with volunteers) involving 246 patients have investigated clonidine as the sole adjunct for IVRA[8,22–25] (Table II). The dose range was 1–2 $\mu g \cdot kg^{-1}$, with one study using 150 μg in all patients. Two out of five studies included a systemic control group.[22,24] Four out of five of these studies were supportive overall.[8,23–25]

No study has demonstrated a difference in terms of onset of block. Two studies have investigated tourniquet pain and tolerance.[23,25] Gentili *et al.*[23] showed that clonidine 150 μg produced a significant increase in tourniquet tolerance (median [range]: 22 [10–50] *vs* 10 [5–10] min). In a study in volunteers, Lurie *et al.*[25] added clonidine 1 $\mu g \cdot kg^{-1}$ and found that the onset of intolerable tourniquet pain from the distal cuff (inflated when the pain score from the proximal cuff reached 6/10) was delayed for over seven minutes.

Results of studies reporting on the postoperative analgesic effects of clonidine have been mixed. Kleinschmidt *et al.*[22] found no difference in VAS and AC when observing regression of the block for 45 min. Hoffmann *et al.*[8] found reduced VAS at 30 and 45 min after tourniquet deflation, at which point recording stopped. Gentili *et al.*[23] were unable to demonstrate any difference in VAS or AC although these were only followed for 60 min and VASs were low in both treatment and control groups.

Reuben *et al.*[24] studied the effect of clonidine 1 $\mu g \cdot kg^{-1}$ on postoperative analgesia and presented a number of significant findings. TTFA was longer in the IVRA-clonidine group compared to control (median [range]: 460 [215–1440] *vs* 115 [14–390] min). VAS was reduced at one and two hours postoperatively in the clonidine group compared to control. Less fentanyl was administered in the PACU and AC (first 24 hr) was less in the clonidine group compared to the control group. *IV* clonidine (systemic control group) conferred no advantage.

Two of five studies reported side effects.[22,23] Both these studies used a larger dose of clonidine (2 $\mu g \cdot kg^{-1}$ or 150 μg) that resulted in sedation or hypotension upon tourniquet deflation. The smaller dose of clonidine (1 $\mu g \cdot kg^{-1}$) used by Reuben *et al.*[24] and Lurie *et al.*[25] appears to be well tolerated.

Muscle relaxants

Five studies involving 186 patients have investigated muscle relaxants either in combination with fentanyl[6,7] or as sole adjuncts[26–28] (Table III). The agents investigated were pancuronium (combined with fentanyl – two studies),[6,7] atracurium[26,27] and mivacurium.[28] Four out of five studies were supportive overall.[6,7,26,27]

Elhakim *et al.*[27] looked at sensory onset and found no difference. No study reported the speed of onset of motor block. Elhakim *et al.*[27] reported a significantly greater degree of muscle relaxation and, in agreement with McGlone *et al.*,[26] reported that the addition of atracurium 2 mg to IVRA significantly improved both intraoperative analgesia and operating conditions for performing closed and open reduction of wrist and hand fractures.

Elhakim *et al.*[27] measured postoperative pain and found it to be reduced at five and 15 min. Two studies reported a delay in return of fine motor control.[26,27] Torrance *et al.*[28] investigated 0.6 mg mivacurium, the shortest acting of the agents investigated, and found a prolonged motor block after cuff deflation (median recovery to 90% control 80 min, range 60 min to more than eight hours).

Four out of five studies did not find any significant side effects.[6,7,26,27] Torrance *et al.*[28] reported signs of LA toxicity (light-headedness, perioral paresthesia, tinnitis, diplopia) in the group given mivacurium 0.6 mg compared to none in the control group given a similar dose of LA. This apparent interaction between mivacurium and prilocaine has not been reported in other studies.

Alkalinization

Three studies involving 131 patients have investigated alkalinization with bicarbonate as an adjunct for IVRA[29–31] (Table III). Two studies were supportive.[30,31]

The three studies have each used different concentrations of LA from 0.5–1.0%. Armstrong *et al.*,[31] in a study in volunteers, demonstrated a slightly faster onset of block when 0.5% prilocaine (pKa=7.9) had bicarbonate added to adjust the pH from 6.40 to 7.75. This pH adjustment theoretically raised the amount of free-base

from 3% to nearly 50%. In a follow-up clinical study, Armstrong *et al.*[30] found no difference in time to establish an adequate block when 0.75% prilocaine underwent similar pH adjustment. However, the more alkaline solution was less painful to inject and produced a denser block (decreased pain reported during surgery). Benlabed *et al.*[29] studied the effect of pH adjustment on 1.0% lidocaine (pKa=7.8) for IVRA. The change in pH of the solution from 6.63 to 7.34 resulted in an increase in the proportion of free base from 5% in the control group to 22% in the study group. Unfortunately, this study failed to demonstrate any difference with respect to sensory and motor onset or offset following alkalinization of LA.

Postoperative outcome following alkalinization of LA has not been well investigated. Armstrong *et al.*[30] noted less pain at five minutes post cuff deflation in the treatment group, after which no further assessments were made. Benlabed *et al.*[29] could find no difference in the time to first report pain after surgery. No side effects were reported in any of these studies.

Other agents

Table III also includes studies investigating the addition of potassium[32] and alteration of temperature.[33,34]

McKeown *et al.*[32] hypothesized that a physiological concentration of potassium added to LA would potentiate IVRA. Yet there was little clinical advantage to this addition. Heavner *et al.*[34] found no advantage from cooling the limb by 5–10°C. Paul *et al.*[33] injected LA solution at three different temperatures in volunteers: 0°C, 22°C and 37°C. The cold solution was significantly more painful and the warmed solution was significantly less painful to inject compared to the room temperature solution. It seems that warming LA solutions may be of practical benefit in reducing the discomfort associated with injection.

Discussion

The results of this systematic review suggest that NSAIDs have the most to offer as adjuncts to IVRA. A dose-response study investigating ketorolac[21] has shown that the optimal dose is 20 mg, beyond which no further postoperative benefit was accrued. Tenoxicam[18] and lysine-acetylsalicylate[20] were also shown to be beneficial for postoperative analgesia but dose-response studies have not been performed, so the ideal dose remains unknown. The results of studies investigating opioids as adjuncts to IVRA have been disappointing. Reuben *et al.*[15] demonstrated prolonged postoperative analgesia with meperidine 30 mg but the side effect profile was much better with 20 mg. Studies investigating the addition of clonidine 1 $\mu g \cdot kg^{-1}$ to LA have demonstrated reduced tourniquet pain[23,25] and improved postoperative pain relief[24] without adverse effects. Improved muscle relaxation during IVRA can be achieved by the addition of a non-depolarizing neuromuscular blocking agent such as atracurium 2 mg. This can facilitate fracture reduction and also improve overall analgesia particularly in young, muscular patients.[26] However there is a risk of residual muscle weakness that can last several hours.[28] A muscle relaxant plus an opioid have been shown to be a useful combination to allow the use of a non-toxic dose of lidocaine ($1.5\ mg \cdot kg^{-1}$) to provide a satisfactory block, albeit with a slower onset of action.[6,7] The alkalinization[31] and warming[33] of LA for IVRA offered little benefit beyond reduced pain during injection.

Drugs selected as potential adjuncts to conventional LA agents could theoretically potentiate a block by either altering nerve conduction or via peripheral nociceptor binding. The observation that some drugs are analgesic at the spinal level has led researchers to examine if the same is true in the periphery. A variety of receptors mediate nociceptor response and, therefore, peripherally administered agents may have an analgesic benefit, perhaps avoiding systemic side effects.[35] IVRA isolates the limb from the rest of the circulation and is a useful model for studying the peripheral actions of a drug in the absence of central effects. Well-designed studies looking at the duration of postdeflation analgesia also included a systemic control group to elucidate if the analgesic effect is local or systemic.

Opioids

Anesthesiologists have been striving for many years to improve the efficacy and duration of regional anesthesia by injecting opioids close to nerve trunks or nerve endings.[36] A peripheral action of opioids could theoretically be mediated via either a peripheral opioid receptor[37] or by a LA action of their own.[38] It has been suggested that previously inactive neuronal opioid receptors may become active in painful inflammatory conditions resulting in reduced neuronal excitability, inhibited propagation of action potentials, and the release of excitatory, pro-inflammatory neuropeptides.[39]

Clinical evidence for the efficacy of peripherally administered opioids is mixed. A recent systematic review of opioids added to brachial plexus blocks exposed a lack of well-conducted trials employing a systemic control group, making overall evidence equivocal.[40] There appears to be better evidence for the use of intraarticular morphine[41] than for opioids given by other peripheral routes.[36]

TABLE I Randomized, controlled, double-blinded studies using opioid drugs and tramadol as adjuncts to IVRA

Author/ year	*Numbers*/groups/ setting*	*Systemic control*	*Adjunct*	*LA used*	*Outcomes: block efficacy*	*Outcomes: tourniquet pain*	*Outcomes: postoperative*	*Side effects ($P < 0.05$)*	*Overall*
Armstrong[9] 1991	30/2 X-over volunteer	no	Fentanyl: 2 mL saline (0 μg) 2 mL (100 μg)	0.5% prilocaine 40 mL	Sensory - onset and recovery equal Motor - N/R	N/A	VAS - N/A AC-N/A T'TFA - N/A	nausea	negative
Arthur[10] 1992	30/3 X-over volunteer	no	Fentanyl: 2 mL saline (0 μg) 2 mL (100 μg) 40 mL saline (100 μg)	0.25% lidocaine 40 mL	Sensory - onset and recovery equal Motor - equal 40 mL 0 mL	N/A	VAS - N/A AC- N/A T'TFA - N/A	N/A	negative
Pitkanen[11] 1992	37/3 (upper limb surgery)	no	Fentanyl: 4 mL saline (0 μg) 4 mL (100 μg) 4 mL (200 μg)	0.5% prilocaine 40 mL	Sensory - faster onset anesthesia (not analgesia); recovery equal; Motor - N/R	N/A	VAS - N/A AC- N/A T'TFA - N/A	light-headed, dizziness, nausea	negative
Abdulla[6] 1992	60/4 (upper limb surgery)	no	Fentanyl: 0, 50, 0, 50μg Pancuronium 0, 0, 0.5, 0.5 mg	0.25% lidocaine 40 mL	Sensory - both adjuncts combined gave better perop analgesia; Motor block profound with pancuronium	N/A	VAS - N/A AC- N/A T'TFA - N/A	none	intraop supportive
Gupta[12] 1993	40/2 (hand surgery)	no	Morphine: 5 mL saline 5 mL (1 mg)	0.5% prilocaine 3 $mg \cdot kg^{-1}$	Sensory - N/R Motor - N/R	N/A	VAS - no difference AC- no difference T'TFA - N/A	none	negative
Armstrong[13] 1993	20/2 X-over volunteer deflation)	no	Meperidine: 2 mL saline (0 mg) 2 mL (100 mg)	0.25% prilocaine 40 mL	Sensory - faster onset, slower recovery; Motor - faster onset, slower recovery	reduced tourniquet & forearm pain at 10 & 20 min respectively in meperidine group	VAS - N/A AC- N/A T'TFA - N/A	light-headed, nausea (naloxone 0.2 mg *iv* + 0.2 mg *im* given on	intra-op supportive
Erciyes[14] 1995	20/2 (upper limb surgery)	no	Morphine: 10 mL saline (0 mg)	1% prilocaine 30 mL 10 mL (6 mg) Motor - N/R	Sensory - significantly faster onset and slower recovery (only approx. 1 min)	N/A	VAS - N/A AC - N/A T'TFA - N/A	none	intra-op supportive
Sztark[7] 1997	40/2 (upper limb surgery)	no	Fentanyl: 0.1 $\mu g \cdot kg^{-1}$ Pancuronium 0.05 mg	lidocaine 0.6 $mL \cdot kg^{-1}$ 0.5% + no adjunct, 0.25% + adjunct	Sensory - Plain lido - faster onset; Motor - Plain lido - faster onset; Equivalent block at 20 min and post-op	N/A T'TFA - no difference	VAS - N/A AC- N/A	none	intra-op supportive

TABLE I *Continued*

Author/ year	*Numbers*/groups/ setting*	*Systemic control*	*Adjunct*	*LA used*	*Outcomes: block efficacy*	*Outcomes: tourniquet pain*	*Outcomes: postoperative*	*Side effects ($P < 0.05$)*	*Overall*
Hoffmann[8] 1997	75/5 (upper limb surgery)	no	Saline 5 mL 0.25% Bupivacaine 5 mL Clonidine 150 μ 5 mL Sufentanil 25 μ 5 mL Tenoxicam 20 mg 5 mL	1% prilocaine 30 mL	Sensory - Sufentanil - faster complete sensory block; recovery - no difference; Motor - not significant	N/A	VAS - tenoxicam (first 30 min), clonidine (after 30 min)- better pain scores AC - N/A TTFA - N/A	N/A	intra-op supportive
Reuben[15] 1999	60/6 (hand surgery)	no	Meperidine: 0, 10, 20, 30, 40, 50 mg	0.5% lidocaine 40 mL	Sensory - N/R Motor - N/R	N/A	VAS - at 1 hr lower with 30 mg or more AC - 24 hr intake less with 30 mg or more; TTFA - dose dependent up to 30 mg	30 mg or more: nausea and vomiting, sedation, dizziness	post-op supportive
Acalovschi[16] 2001	60/4 X-over volunteer	no	Tramadol: 40 mL saline (0 mg) 40 mL saline (100 mg) 0 mg 100 mg	0.5% lidocaine 0 mL 0 mL 40 mL 40 mL	Sensory - tramadol/lidocaine combination - faster onset and slower recovery of touch sensation; Motor - not significant	N/A	VAS - N/A AC - N/A TTFA - N/A	tramadol/ lidocaine combination - skin rash	intra-op supportive

IVRA=intravenous regional anesthesia; *The number shown is the total number of study subjects (in X-over studies, volunteers may be investigated on *n* occasion, the number of study subjects=number of volunteers × *n*); LA=local anesthetic; N/A=not available or not analyzed; X-over=crossover design; VAS=visual analogue score (0=no pain; 10=worst imaginable pain); AC=analgesic consumption; TTFA=time to first analgesia.

TABLE II Randomized, controlled, double-blinded studies using non-steroidal anti-inflammatory drugs or clonidine as adjuncts to IVRA

Author/ year	*Number*/ groups/ setting*	*Systemic control*	*Adjunct*	*LA used block efficacy*	*Outcomes: tourniquet pain*	*Outcomes: postoperative*	*Outcomes: (P <0.05)*	*Side effects*	*Overall*
Reuben[16] 1995	60/3 (hand surgery)	2 mL *iv* saline Ketorolac (60 mg) saline	Ketorolac: 2 mL saline (0 mg) 2 mL saline (0 mg) 2 mL (60 mg)	0.5% lidocaine 38 mL	Sensory - N/A Motor - N/A IVRA-K group at 15 & 30 min cf. both other groups	significantly less tourniquet pain in AC - less in treatment group in PACA and in first 24 hr cf. both other groups TTFA - longer in treatment group cf. both other groups	VAS - lower at 30 & 60 min in treatment group cf. both other groups;	none post-op supportive	intra-op supportive
Jones[18] 1996	45/3 (reduction of Colles' fracture)	2 mL *iv*: saline tenoxicam (20 mg) saline	Tenoxicam: 2 mL saline (0 mg) 2 mL saline (0 mg) 2 mL (20 mg)	0.5% prilocaine 0.5 mL·kg^{-1}	Sensory - N/A Motor - N/A	N/A	NRS - treatment group lower pain scores cf. both other groups first 24 hr; AC - treatment group less than both other groups first 24 hr; TTFA - treatment group longer cf. placebo group	none	post-op supportive
Reuben[19] 1996	60/3 (hand surgery)	no	Ketorolac: 0 mg 60 mg IVRA 60 mg wound infiltration	0.5% lidocaine 40 mL + 5mL 1% lidocaine for wound infiltration	Sensory - N/A Motor - N/A	N/A	IVRA-K equivalent to infiltration: VAS - reduced pain scores at 1 & 2 hr cf. placebo; AC - reduced 24 hr analgesic intake cf. placebo; TTFA - prolonged time to first analgesic cf. placebo	none	post-op supportive
Corpataux[20] 1997	60/3 (foot surgery)	1 mL *iv* saline lysine-ASA (90 mg) saline	ASA 1 mL (as lysine-ASA) (1 mL saline) (1 mL saline) 90 mg IVRA	0.5% prilocaine 4 mg·kg^{-1}	Sensory - N/A Motor - N/A	N/A	VAS - reduced pain scores for 3 hr cf. placebo; AC - reduced for 3 hr cf. placebo; TTFA - prolonged time to first analgesic in treatment group	none	post-op supportive

TABLE II *Continued*

Author/ year	*Number*/ groups/ setting*	*Systemic control*	*Adjunct*	*LA used block efficacy*	*Outcome: tourniquet pain*	*Outcome: postoperative*	*Outcome: (P <0.05)*	*Side effects*	*Overall*
Kleinschmidt[22] 1997	56/3 (upper limb surgery)	Clonidine: 2 mL saline (0 µg) 2 mL saline (0 µg) 2 mL (2 µg·kg^{-1})	Clonidine: 2 mL saline (0 µg) 2 mL (2 µg·kg^{-1}) 2 mL saline (0 µg)	0.5% prilocaine 3.5 mg·kg^{-1}	Sensory - no difference in onset or offset; Motor - no difference in onset or offset	N/A	PRS - no difference in postop pain scale; AC - no difference; TTFA - N/A	moderate hypotension in both clonidine groups from 12–45 min (end of observation period)	negative
Hoffmann[8] 1997	75/5 (upper limb surgery)	no	Saline 5 mL 0.25% Bupivacaine 5 mL Clonidine 150 µ 5 mL Sufentanil 25 µ 5 mL Tenoxicam 20 mg 5 mL	1% prilocaine 30 mL	Sensory - Sufentanil - faster complete sensory block; Offset - no difference; Motor - not significant	N/A	VAS - tenoxicam (first 30 min), clonidine (after 30 min) - better pain scores AC - N/A TTFA - N/A	N/A	post-op supportive
Steinberg[21] 1998	70/7 (hand surgery)	no	Ketorolac: 0, 5, 10, 15, 20, 30, 60 mg	0.5% lidocaine 40 mL	Sensory - N/A Motor - N/A	N/A	VAS - lower scores for 20 mg or more at 1 & 2 hr; AC - linear dose-response up to 20 mg; TTFA - linear dose-response up to 20 mg	none	post-op supportive
Gentili[23] 1999	40/2 (upper limb surgery)	no	Clonidine: 1 mL saline (0 µg) 1 mL (150 µg)	0.5% lidocaine 40 mL	Sensory - N/A Motor - no difference	reduced tourniquet pain	VAS - no difference AC - no difference TTFA- no difference	sedation	intra-op supportive
Reuben[24] 1999	45/3 (hand surgery)	Clonidine: 1 mL saline (0 µg) 1 mL (1 µg·kg^{-1}) 1 mL saline (0 µg)	Clonidine: 1 mL saline (0 µg) 1 mL saline (0 µg) 1 mL (1 µg·kg^{-1})	0.5% lidocaine 40 mL	Sensory - N/A Motor - N/A	N/A	VAS - less in treatment group at 1 & 2 hr cf. both other groups; AC - less in treatment group cf. both other groups; TTFA - longer in treatment group cf. both other groups	none	post-op supportive
Lurie[25] 2000	30/2 X-over volunteer	no	Clonidine: 0 µg 1 µ·kg^{-1}	0.5% lidocaine 40 mL	Sensory - N/A Motor - N/A	reduced tourniquet pain and increased tolerance	VAS - N/A AC - N/A TTFA - N/A	none	intra-op supportive

IVRA=intravenous regional anesthesia; *The number shown is the total number of study subjects (in X-over studies, each volunteer may be investigated on *n* occasions, the number of study subjects=number of volunteers × *n*); LA=local anesthetic; N/A=not available or not analyzed; VAS=visual analogue score (0=no pain; 10=worst imaginable pain); PRS=pain ranking scale (0–3); AC=analgesic consumption; NRS=numeric rating scale; TTFA=time to first analgesia.

TABLE III Randomized, controlled, double-blinded studies using muscle relaxants, alkalinization or miscellaneous agents as adjuncts to IVRA

Author/ year	*Number*/ groups/ setting*	*Systemic control*	*Adjunct*	*LA used*	*Outcomes: block efficacy*	*Outcomes: tourniquet pain*	*Outcomes: postoperative*	*Side effects ($P < 0.05$)*	*Overall*
McKeown[32] 1984	12/2 X-over volunteer	no	Potassium 0.4 $mmol \cdot L^{-1}$	0.5% prilocaine 40 mL	Sensory - no Motor - no difference	N/A	VAS - N/A AC - N/A TTFA - N/A	none	negative
McGlone[26] 1988	36/2 (closed reduction of wrist fractures)	no	Atracurium 0.2 mg	0.5% prilocaine 40 mL	Sensory - N/A Motor - delay in fine motor recovery; VAS - reduced pain in treatment group; Easier reduction in treatment group	N/A	VAS - N/A AC - N/A TTFA - N/A	none	intra-op supportive
Paul[33] 1988	30/3 X-over volunteer	no	LA temp 0, 22, 37°C	0.5% prilocaine 40 mL	Sensory - equal onset/offset; Motor - equal onset/offset warm solution most comfortable to inject	N/A	VAS - N/A AC - N/A TTFA - N/A	none	intra-op supportive
Heavner[34] 1989	20/4 X-over volunteer	no	Arm temp 33/22°C	0.5% lidocaine 0.6 $mL \cdot kg^{-1}$	Sensory - 5–10C decrease - no change in anesthetic effect	N/A	VAS - N/A AC - N/A TTFA - N/A	none	negative
Benlabed[29] 1990	31/2 (hand surgery) or normal saline 0.3 $mL \cdot kg^{-1}$ (pH 7.34, 6.63)	no	$NaHCO_3$ 1.4% 0.3 $mL \cdot kg^{-1}$ 3 $mg \cdot kg^{-1}$	1% lidocaine	Sensory - equal onset Motor - equal onset	N/A	VAS - N/A AC - N/A TTFA - N/A time to apearance of pain - equal	none	negative
Armstrong[30] 1990	20 X-over volunteer	no	$NaHCO_3$ 8.4% 5 mL or saline 5 mL (pH 7.75, 6.40)	0.5% prilocaine 40 mL	Sensory - faster onset, slower offset Motor - faster onset (no stats quoted)	N/A	VAS - N/A AC - N/A TTFA - N/A	none	intra-op supportive
Armstrong[31] 1990	80/2 (hand surgery)	no	$NaHCO_3$ 8.4% 5 mL or saline 5 mL (pH 7.75, 6,40)	0.75% prilocaine 40 mL	Less pain on injection, sensory - onset equal, Less pain reported during surgery ("denser block"), Motor - N/A	N/A	VAS - less pain at 5 min in treatment group, AC - N/A TTFA - N/A	none	intra-op supportive

TABLE III *Continued*

Author/ year setting	*Number*/ groups/*	*Systemic control*	*Adjunct*	*LA used*	*Outcome: block efficacy*	*Outcome: tourniquet pain*	*Outcome: postoperative*	*Side effects (P <0.05)*	*Overall*
Abdulla[6] 1992	60/4 (upper limb surgery)	no	Fentanyl 0, 50, 0, 50 µg Pancuronium 0, 0, 0.5, 0.5 mg	0.25% lidocaine 40 mL	Sensory - both adjuncts combined gave better perop analgesia; Fentanyl better than contol; Motor - block profound with pancuronium	N/A	VAS - N/A AC - N/A TTFA - N/A	none	intra-op supportive
Elhalcim[27] 1994	40/2 (hand fractures - open surgery)	no	Atracurium 0.2 mg	0.5% lidocaine 40 mL	Sensory - no difference; Motor - better relaxation in treatment group & delayed return of motor; reduced pain of surgery in treatment group	N/A	VAS - reduced in treatment group at 5 & 15 min AC - N/A TTFA - N/A	none	intra-op supportive post-op supportive
Torrance[28] 1997	10/2 volunteer	no	Mivacurium 0.06 mg	0.5% prilocaine 40 mL	Sensory - N/A Motor - slower return in treatment group	N/A	VAS - N/A AC - N/A TTFA - N/A	mivacurium + prilocaine - signs of LA toxicity in 100%	negative
Szturic[7] 1997	40/2 (upper limb surgery)	no	Fentanyl: 0.1 µg·kg^{-1} Pancuronium: 0.05 mg	0.5 & 0.25% lidocaine 0.6 mL·kg^{-1}	Sensory - Plain lidocaine - faster onset; Motor - Plain lidocaine - faster onset; Equivalent block at 20 min and postop	N/A	VAS - N/A AC - N/A TTFA - no difference	none	intra-op supportive

IVRA=intravenous regional anesthesia; *The number shown is the total number of study subjects (in X-over studies, each volunteer may be investigated on *n* occasions, the number of study subjects=number of volunteers × *n*); LA=local anesthetic; N/A=not available or not analyzed; X-over=crossover design; VAS=visual analogue score (0=no pain; 10=worst imaginable pain); AC=analgesic consumption; TTFA=time to first analgesia.

NSAIDs

Surgical trauma results in release of intracellular contents from damaged and inflammatory cells. Nociceptor stimulation causes a neurogenic response with release of mediators such as substance P and neurokinin A. This results in an "inflammatory soup" containing histamine, serotonin, bradykinin and metabolites of the cyclooxygenase and lipooxygenase pathways.[42] NSAIDs inhibit the production of prostaglandins from arachidonic acid in phospholipid membranes. The result is decreased afferent nociceptive signals arising from the site of surgery. Whether interfering with the synthesis of inflammatory mediators has a preemptive analgesic role in preventing sensitization of nociceptors remains controversial.[43]

The role of NSAIDs in the management of postoperative pain is well established.[44] Clinical studies have demonstrated an enhanced analgesic effect from NSAIDs when concentrated at a peripheral site compared to the systemic administration of the same drug.[45,46] This would suggest a predominantly peripheral site of action.

It is interesting to note that the plasma half-life of ketorolac is four to six hours yet the duration of analgesia reached a plateau at over ten hours.[17] It may be that by concentrating the dose of NSAID at the site of surgery, either as part of IVRA or wound infiltration,[19] the resulting analgesic benefit is longer lasting than the same dose administered parenterally. Presumably there is a persistent drug level in the tissues, and this coupled to the lower dosage could result in reduced systemic side effects.

Clonidine

$_2$-adrenoceptors are located on primary afferent terminals (both at peripheral and spinal endings), on neurons in the superficial laminae of the spinal cord and within several brainstem nuclei implicated in analgesia.[47] The mechanism by which clonidine, an agonist at these receptors, produces analgesia is not fully understood but is likely to be by a number of mechanisms.[47] Peripherally, reduced release of norepinephrine may contribute to analgesia[48] and there is an inhibitory effect on nerve-fibre action potentials that is not mediated by the $_2$-receptor.[49]

In clinical studies, clonidine-containing LA solutions have been shown to prolong and intensify analgesia, compared to plain solutions, when used for spinal, epidural or peripheral nerve blocks.[40,47] In a recent systematic review, clonidine was reported to be the most promising analgesic adjunct for brachial plexus block, with minimal risk of adverse effects in doses up to 150 μg.[40]

There is no evidence that clonidine affects the speed of onset or quality of IVRA. However, two studies suggested that clonidine improved tourniquet pain tolerance.[23,25] Previous studies have demonstrated that clonidine prolongs tourniquet tolerance under spinal anesthesia via the intrathecal route[50] and orally.[51] The mechanism of action is unclear because Gentili *et al.*[23] kept the distal tourniquet inflated throughout, deflating only the proximal cuff, whereas Lurie *et al.*[25] inflated the distal cuff and deflated the proximal cuff when pain from the proximal cuff became moderate.

There are conflicting results for the postoperative benefit of clonidine and it is difficult to reconcile the contradictory results. The study by Reuben *et al.*[19] demonstrated improved postoperative analgesia for two hours and reduced analgesic intake for 24 hr. This was not shown by Gentili *et al.*,[23] but the pain scores they quoted were low making it difficult to detect a difference from a small sample size. Kleinschmidt *et al.*[22] also failed to demonstrate any postoperative benefit, this may be due to the use of a relatively insensitive four-point pain scale and the lack of a well defined analgesic protocol. A smaller dose of clonidine (1 $\mu g \cdot kg^{-1}$) is well tolerated.

Muscle relaxants

Both LA and muscle relaxants exert an effect at the neuromuscular junction. In addition, muscle relaxants probably interfere with the muscle spindle activity resulting in loss of muscle tone and spasm.[27] The spindle is the sensory end-organ of skeletal muscles, sending information about fibre length to the brain. The resulting loss of tone and spasm may improve both intraoperative pain and operating conditions.

Alkalinization

LA exist in two forms: the non-ionized, lipid-soluble free base and the water-soluble ionized form. The relative proportions of each depend upon the pKa of the drug and the pH of the environment. The pKa of a LA is fixed but, by increasing the pH of a solution, it is possible to increase the percentage of free base and thus improve the nerve penetration and the rate of onset of blockade. Unfortunately, raising the pH too high will result in precipitation of the drug.

Several mechanisms are thought to be involved in the potentiation of LA by alkalinization with bicarbonate.[52] Firstly, bicarbonate reduces the net inward current (decreased sodium influx, increased potassium efflux) by a direct effect on membrane channels. Secondly, ion trapping occurs when membrane-permeable CO_2 combines with axoplasmic water to pro-

duce carbonic acid that releases protons. The neutral form of LA that has crossed the membrane will then accept these protons and become a charged, active channel-blocking molecule. Thirdly, affinity of the LA molecule for the sodium channel increases. This is well demonstrated by the substantial potentiation of benzocaine, an unionizable, uncharged LA.[52]

Conclusion

There is good evidence to recommend NSAIDs in general, and ketorolac in particular, for improving postoperative analgesia after IVRA. Clonidine also appears to improve postoperative analgesia and prolong tourniquet tolerance. Opioids are disappointing by this route; only 30 mg meperidine has substantial postoperative benefit but at the expense of postdeflation side effects. Muscle relaxants improve motor block and aid fracture reduction.

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