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Adjuvants to local anaesthetics for plexus nerve blocks: a systematic review

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Abstract

This article is a systematic review of the effect of different drugs that have been used as local anaesthetic additives for plexus blocks. These adjuvants are used to hasten the onset of nerve block, prolong block duration, increase analgesia or reduce toxicity.

Some of them have been used previously in spinal anaesthesia. The mechanism of action, clinical effectiveness and potential adverse effects are reviewed for hyaluronidase, tramadol, buprenorphine, midazolam, magnesium, clonidine, dexmedetomidine, ketamine and dexamethasone. The different local anaesthetics, doses, route of administration, plexus blocks, surgeries and studies designs make really difficult to evaluate the real impact of the drugs used as perineural adjuvants.

The additions of drugs that improve the blockade with slight benefits possibly are not worth considering the risks of perineural toxicity. The addition of various epineural adjuvants or the combination of different local anaesthetics is not a solution.

After carefully evaluation of these nine drugs, the better results appear to be those related with the addition of buprenorphine, dexmedetomidine and dexamethasone.

In conclusion, further studies are necessary to improve our knowledge of additives used with local anaesthetics for nerve blocks in order to enhance analgesia (with safety) in our patients. *Anestezjologia i Ratownictwo 2015; 9: 186-202.*

Keywords: regional anaesthesia, plexus nerve blocks, local anaesthetics, perineural adjuvants, hyaluronidase, tramadol, buprenorphine, midazolam, magnesium, clonidine, dexmedetomidine, ketamine, dexamethasone

Introduction

Peripheral nerve blocks have increased in popularity in Anaesthesia since nerve-stimulation with ultrasound technologies allow now the correct placement of the needle tip in percutaneous nerve blocks with safety, so a "single-shot" perineural injection may be performed for anaesthesia or postoperative analgesia. Alternatively, if pain is expected to persist postoperatively for more than several hours, an indwelling perineural catheter can be placed, and a continuous infusion of local anaesthetic delivered for up to several days.

Numerous adjuvant medications have been evaluated for their ability to hasten the onset of sensory or motor blockade (i.e. sodium bicarbonate), prolong the duration of the resulting nerve block, or slow the absorption of the local anaesthetic administered, thus reducing the likelihood of local anaesthetic toxicity (i.e. epinephrine). The search strategy in PubMed includes: "name of the drug" AND "plexus block", "nerve block" OR "perineural" AND "add", "additive" OR "adjuvant".

The many adjunct medications currently used do not share a unitary mechanism of action. Many adjunct medications are themselves analgesics (e.g., tramadol,

buprenorphine, ketamine), and recent studies have compared the effect of the same adjuncts given perineurally versus intravenously or intramuscularly in an effort to elucidate whether giving the adjunctive agent peripherally might offer the same benefit while avoiding the risk of neurotoxicity.

One problem (possibly the most important) is that the existing studies are not fully comparable between them because the design of these trials is quite variable, considering various technical approaches (ultrasound guided punction with or without nerve stimulation, or even only paraesthesias in the first studies), distinct outcome measures (such as the time to first non-opioid analgesic requirement, to first morphine analgesia, the total morphine consumption or the time to regression of paraesthesias), different drugs protocols (various local anaesthetics and not uniform doses are used for different surgeries with also distinct postoperative pain and analgesia requirements).

All these differences hinder the adoption of the conclusions of these studies in our clinical practice. The evaluation is easier if we have many published articles regarding the same item, and even better if we have meta-analysis, as it happens, for example, with the use of dexamethasone as adjuvant for nerve plexus block, but there are other studies with drugs that offer incomplete or even contradictory results. In these situations we have to extreme the caution in the clinical adoption of their conclusions. However, these situations can give us a good opportunity to investigate and improve our clinical practice.

We have not reviewed the "classical" drugs used to modify the onset or the duration of local anaesthetics: sodium bicarbonate (recommended only for selected peripheral nerve blocks [1]) and epinephrine. We have tried to resume the data of the different reports in tables following the same methodology, in order to evaluate the results in an easier mode than only text, but nevertheless, the results are sometimes inconclusive.

Hyaluronidase:

HYLENEX ®, *Halozyme Therapeuthics, USA*, (150 USP units of non-preserved recombinant human hyaluronidase per mL in a single-use glass vial) 42.10 €

Hyaluronidase (table I) was largely used for retrobulbar anaesthesia in order to reduce the onset time. It has been described in upper limb surgeries under axillar block with different results: as an adjuvant to ropivacaine hyaluronidase reduces the time to reach complete sensory block and therefore shortens the total anaesthetic time before operation [2]; while the use of hyaluronidase produced a significant reduction in the duration of bupivacaine anaesthesia, neither did it increase the speed of onset of anaesthesia nor reduce the incidence of inadequate nerve block [3].

Tramadol:

ADOLONTA ®, *Grünenthal Pharma, Germany* (100 mg, 5 ampoules 2 ml) 3.26 €

Tramadol (table II) exerts its effect via several mechanisms: serotonin release, weak μ-opioid receptor agonism, inhibition of norepinephrine reuptake, and block voltage-gated sodium channels [4]. In human volunteers perineural tramadol has a brief local anaesthetic-like action when administered to ulnar nerve [5] and blocks sensory nerve conduction of the sural nerve in a dose-dependent manner [6].

As an additive to local anaesthetics for peripheral nerve blocks [7-19], tramadol has been shown to increase the duration of analgesia, albeit inconsistently.

Perineural tramadol used in shoulder arthroscopy for rotator cuff tear under interscalene plexus block with levobupivacaine, provided a longer duration of analgesia compared with placebo and IM tramadol [7], but was less efficient than perineural buprenorphine [8].

Perineurally administered tramadol in axillary nerve block shows different outputs, ranging from favourable improvement of analgesia [9,12,18] in a dose-dependent mode [16] to small benefit reports [11,17], less than perineural dexamethasone [19] or no differences with placebo [10,13]. These differences could be explained partially by the different surgeries (i.e. hand surgery is less painful than forearm surgery) and local anaesthetics included.

The effect of tramadol in psoas compartment block has been reported as clinically small [14] or not significative [15].

Buprenorphine:

BUPREX ®, *Schering Plough, USA* (0.3 mg, 5 ampoules 1 ml) 3.84 €

Perineural buprenorphine (table III) is more potent than butorphanol [20]. Buprenorphine has been studied as perineural adjuvant for plexus blocks

in upper limb [21-23] and ankle surgery [24], showing a prolongation of analgesia that has been reported as three times more than placebo, whereas the IM route of administration only increases twice the analgesia time. Opioids induce analgesia mainly by inhibiting synaptic transmission via G protein-coupled opioid receptors. In addition to analgesia, buprenorphine induces a pronounced antihyperalgesia and is an effective adjuvant to local anaesthetics. Buprenorphine is a potent local anaesthetic and blocks voltage-gated Na+ channels via the local anaesthetic binding site. This property is likely to be relevant when buprenorphine is used for pain treatment and for local anaesthesia [25].

Midazolam:

DORMICUM ®, *Roche Farma, Spain* (1 mg/ml, 10 ampoules 5 ml) 9.02 €

Midazolam (table IV) enhances the effect of local anaesthetics and also has an analgesic effect via the GABA type A-receptors when administered epidurally or intrathecally. Midazolam (50 μg/kg) in combination with bupivacaine improved analgesia quality in brachial plexus block [26-28].

It is necessary to prove the safety of midazolam as a perineural adjunct before its routine use in clinical practice could be recommended. Animal experimentation indicates that processes underlying midazolam--induced nerve block and neurotoxicity are separable, and suggests that selective activation of the 18-kd translocator protein may facilitate modality-selective nerve block while minimizing the potential for neurotoxicity [29]. As midazolam appears to produce only modest prolongation of sensory blockade (less than clonidine [30] or dexamethasone [31]), its use as an adjunct to peripheral nerve blocks cannot be recommended in the absence of further safety data.

Other consideration is that midazolam can induce sedation. No other adverse effects have been reported.

Magnesium:

MAGNESIUM SULPHATE ®, *Genfarma, Spain* (150 mg (0.3 mEq per mg)/ml 10 ampoules 10 ml) 12.41 €

Magnesium (table V) improves anaesthesia and analgesia when used intravenously and intrathecally. Magnesium has effects on the cellular calcium influx and is also a N-methyl-d-aspartate (NMDA) antagonist. Both effects may potentiate the action of local anaesthetics, but the mechanism is still unclear. The duration of upper limb blocks (interscalene with bupivacaine [32] and axillar with ropivacaine [33]) is prolonged with perineural magnesium in a modest mode (1-2 hr.), so, the risks of administering perineural magnesium (although no side effects had been reported) is not worth it compared with other safer manoeuvres, such as increased dose of plain local anaesthetics. The addition of magnesium to levobupivacaine prolongs the sensory and motor block duration without increasing side effects, enhances the quality of postoperative analgesia, decreases rescue analgesic requirements and increases patient satisfaction but delays the time to first mobilisation in patients undergoing anterior cruciate ligament reconstruction with femoral nerve block [34].

Clonidine:

CATAPRESAN ®, *Boerhinger, Germany* (0,15 mg/ml, 5 ampoules 1 ml)

This α_2-agonist (table VI) has been used as an adjuvant in neuraxial space and peripheral nerve techniques. The effect of clonidine at the nerve appears to be related to the enhancement of activity-dependent hyperpolarization induced by blockade of current through hyperpolarization-activated cyclic nucleotide-gated channels. This current allows neurons to return to their resting potential from a hyperpolarized state after an action potential, and when this current is blocked, neurons are unable to generate subsequent action potentials [35].

Perineural clonidine in doses ranging from 30 to 300 μg (usually 150 μg) prolonged with different local anaesthetics (mepivacaine, lidocaine, prilocaine, bupivacaine, levobupivacaine and ropivacaine) [36-40] the time to the first analgesic request by approximately 2.0-2.5 hours [41] and the sensory block. The motor block was also prolonged with all these local anaesthetics except mepivacaine. Nevertheless, there are some authors that reported no differences with plain levobupivacaine [42] and bupivacaine (in children) [43]. It has also been described that clonidine does not alter the onset of ropivacaine block but prolongs postoperative analgesia [44].

Clonidine has several adverse effects such as arterial hypotension, sedation, bradycardia, and fainting, most likely as the result of systemic clonidine absorp-

tion. There are doubts about the relationship between dose and adverse effects, but nonetheless clonidine doses of 0.5-1.0 mcg/kg are recommended.

Compared with other α_2-agonist, clonidine was worse than dexmedetomidine in terms of duration of action [40], but presented less haemodynamic secondary effects.

Dexmedetomidine:

DEXDOR ®, *Orion Pharma, Spain* (100 mcg/ml 25 ampoules 2 ml) 520.95 €

This α_2-agonist (table VII) has the same adverse effects than clonidine. It has been used as an adjuvant in general anaesthesia (it reduces the requirements of inhaled gases and opioids) and neuraxial anaesthesia (dexmedetomidine increases the sensory and motor blocks). Perineurally administered, it prolongs the duration of block and analgesia [40,45-51]. Compared with other adjuvants, dexmedetomidine is better than clonidine in terms of duration of action [40] and appears to be comparable with buprenorphine and dexamethasone [49].

Ketamine:

KETOLAR ®, *Pfizer Pharmaceuticals, Ireland* (50 mg/ml 1 vial 10 ml) 4.40 €

Ketamine (table VIII) is an NMDA-receptor antagonist that has been used previously in neuraxial anaesthesia. However, there are few reports about its use as an adjuvant for plexus blockades. Ketamine enhances the analgesic action of lidocaine [52] in supraclavicular plexus blocks, articaine [53] and ropivacaine in axillar blocks. Ketamine has a dissociative anaesthetic and potent analgesic effects. Studies have shown that ketamine also has local anaesthetic properties and affects nerve conduction in vitro. Ketamine might increase the binding capacity of local anaesthetic to albumin alpha acid glucoprotein and changes ionic balance. Another mechanism might be due to two isomers (S) and (R): S isomer blocks the opiate receptors and R isomer has hypnotic effects [53].

However, other authors didn't find effect of ketamine on ropivacaine axillar block [54], and the high doses of perineural ketamine (2 mg/kg), close to the IV induction dose, are suspected to be the cause of the enhancement of analgesia in the studies with lidocaine [52] and articaine [53].

Dexamethasone:

FORTECORTIN ®, *Merck, Germany* (4 mg/ml 3 ampoules 1 ml) 2.12 €

It is possibly one of the most popular additives to plexus nerve blocks nowadays. The mechanism by which dexamethasone prolongs sensory and motor blockade when added to local anaesthetics remains unclear. It may act by increasing the activity of inhibitory potassium channels on nociceptive C fibbers via glucocorticoid receptors, thereby decreasing the fibbers' activity.

Perineural dexamethasone (table IX) has been used for different surgeries such as upper limb procedures (under interscalene [55-60], supraclavicular [61-64] and axillar brachial plexus block [19,65-67]), lower limb surgeries (femur fracture with *fascia iliaca* compartment block [68], anterior cruciate ligament reconstruction surgery with femoral block [69] and ankle and foot surgery with sciatic block [70]).

There are several studies using different doses of dexamethasone phosphate, including some meta-analysis, which conclude that perineural dexamethasone improves postoperative pain outcomes and significantly prolongs the duration of analgesia when given as an adjunct to brachial plexus blocks without reports of persistent nerve injury attributed to perineural administration of the drug [71], but the effects of systemic administration of dexamethasone on brachial plexus blocks must be investigated [72]. There were no relationship between the dose of perineural dexamethasone (4-10 mg) and the duration of analgesia [73].

The different studies designs, outcomes measures and methodologies make it difficult to establish the optimal dose of perineural dexamethasone to increase the analgesia period without toxic or adverse nerve or systemic effects.

This effect appears to be effective when using bupivacaine, levobupivacaine, ropivacaine, prilocaine, mepivacaine and lidocaine.

The controversy in the route of administration of dexamethasone (perineural vs. intravenous) still remains, and we can find contradictory publications concluding that perineural but not intravenous administration of dexamethasone significantly prolongs the duration of effective postoperative analgesia [56], both IV and perineural dexamethasone prolongs analgesia [60], preoperative administration of IV dexamethasone prolong analgesic duration [74] or

even that substitution of systemic dexamethasone for perineural dexamethasone has only a minor analgesic enhancing effect [70].

After carefully evaluation of these nine drugs, the better results appear to be those related with the addition of buprenorphine, dexmedetomidine and dexamethasone. The additions of drugs that improve the blockade with slight benefits possibly are not worth considering the risks of perineural toxicity: for example, using midazolam as a plexus blockade adjuvant may be more dangerous than simply slightly increasing the total dose of local anaesthethics.

The addition of various epineural additives or the combination of different local anaesthetics is not a solution. The former option may increase the toxicity. The latter, shows a modest benefit in terms of improved onset of analgesia with combinations of rapid-onset and long-acting agents, but the practitioner should be mindful of a possible decrease in the duration of analgesia.

Other factors should be also considered, such as the physical status, the experience of the anaesthesiologist and even the economic cost. Dexmedetomidine is the most expensive alternative, with a cost of 20.84 € per patient. There are no pharmacoeconomics studies comparing the cost of using adjuvants with other alternatives, such as increased local anaesthetic doses or the cost of NSAID drugs or morphine used as rescue analgesia to treat pain.

Regarding the use of buprenorphine and dexmedetomidine, it is also necessary to remember that both drugs can show adverse effects, possibly related to systemic absorption. Perineural dexamethasone is still in controversy despite the number of studies reported, specially the dose and even the route of administration (IV vs epineural). The Anaesthesia Section for Orthopaedic Surgery and Traumatology of our Hospital use routinely a perineural dose of 4 mg of dexamethasone, finding a significant improvement in the duration of analgesia and postoperative analgesic requirements (not publicated data) in upper and lower limb surgeries.

In conclusion, further studies are necessary to improve our knowledge of additives used with local anaesthetics for nerve blocks in order to enhance analgesia (with safety) in our patients.

Conflict of interest
None

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Table I. Hyaluronidase

Ref.	n	Surg.	PB	LA	Adjuvant	Mode	Suppl. Analg.	Onset	Duration of analgesia	Other comments	Conclusion
[2]	48	UL	AX	ROP 0.5%, 5-7 ml/nerve	HYA 100 IU/ml (dose < 3000 IU)	US+NS	Fentanyl, tramadol, hydromorphone	HYA reduces SB onset	small influence on analgesic duration or the consumption of postoperative analgesics		HYA shortens the total anaesthetic time and the block duration
[3]	22	UL		BUP 2 mg/kg with ADR	HYA 3000 IU			HYA did not shorten onset of SB&MB		HYA: not inadequate nerve block incidence reduction	HYA reduced the duration of anaesthesia

Ref.: reference number; n: number of patients; Surg. (Surgery): UL (upper limb surgeries); PB (Plexus Block): AX (axillar brachial plexus block); LA (Local anaesthetics): ROP (ropivacaine), BUP (bupivacaine); Adjuvant: HYA (hyaluronidase), ADR (adrenaline); Mode: US (ultrasound), NS (nerve stimulation); Suppl. Analg. (Supplemental Analgesia); Onset: SB (Sensory block), MB (motor block)

Table II. Tramadol

Ref.	n	Surg.	PB	LA	Adjuvant	Mode	Suppl. Analg.	Onset	Duration of analgesia	Other comments	Side effects	Conclusion
[7]	120	ASS	IS	LBUP 0.5% 0.4 ml/kg	TRA 1.5 mg/kg		TRA i.m.	No difference	Longer with TRA			duration of analgesia: Perineural TRA > i.m TRA
[8]	161	ASS	IS	LBUP 0.75% 0.4 ml/kg	BUPR 0.15 mg, TRA 100 mg				BUPR > TRA			BUPR is more efficacious for analgesia than TRA.
[10]	60	ULS	BR	PRI 1.5% 40 ml	TRA 1.5 mg/kg, CLO 1.5 µg/kg			No differences	No differences	Prolonged SB&MB with CLO	None reported	No differences with placebo
[11]	102	ULS	AX	LID 1.5% (ADR 1/200,000)	TRA 100 mg			Longer onset with TRA	TRA: prolonged SB and time for rescue analgesia			the benefit of block prolongation with TRA is limited by the slow onset
[12]	60	ULS	AX	MEP 1% 40 ml	TRA 100 mg			No difference with placebo	Longer SB&MB with TRA	Specific analgesic effect of TRA on peripheral nerves	No	TRA: pronounced prolongation of blockade without side effects
[13]	45	ULS	AX	ROP 0.75% 40 ml	TRA 100 mg			No differences	No differences		No	TRA no effect on MB, SB and analgesia
[17]	40	ULS	AX	LID 200 mg + LBUP 150 mg	TRA 100 mg	NS		No differences	No differences		No differences	TRA not provide an important clinical effect
[18]	36	ULS	AX	ROP 0.375% 40 ml	TRA 50 mg KET 50 mg	NS		Fastest SB onset with TRA	TRA: longer analgesia	Shortest SB&MB duration with TRA	No side effects with TRA	TRA improves the quality of postoperative analgesia
[19]	60	ULS	BR	BUP	TRA 2 mg/kg DEX 8 mg				DEX (1028 min) TRA (453 min)			DEX improve analgesia more than TRA

Ref.	n	Surg.	PB	LA	Adjuvant	Mode	Suppl. Analg.	Onset	Duration of analgesia	Other comments	Side effects	Conclusion
[9]	80	CTR	AX	ROP 0.75% 20 ml	TRA 100 mg, CLO 1.5 µg/kg or SUF 20 µg			reduction of onset with TRA, CLO and SUF	Greater analgesia with TRA		TRA: lower than CLO and SUF	TRA may be a useful adjuvant with a lower incidence of side effects
[16]	100	CTR	BR	MEP 1.5% 40 ml	TRA 40, 100 or 200 mg			No differences	No differences	TRA: Less requirements of analgesics	acceptable side effects	TRA extends duration and improves analgesia in a dose dependent fashion
[14]	30	LLS	PCB	BUP 0.25%	TRA 100 mg	NS			No differences in rescue analgesic consumption		No differences	TRA does not provide a significant analgesic action
[15]	60	LLS	PCB	LBUP 0.5% 0.4 ml/kg	TRA 1.5 mg/kg	NS		No differences	No differences	No differences in total morphine consume	No differences	TRA is not useful as adjuvant for PCB

Ref.: reference number; n: number of patients; Surg. (Surgery): ASS (arthroscopic shoulder surgery), ULS (upper limb surgery), CTR (carpal tunnel release), LLS (lower limb surgery); PB (Plexus Block): IS (Interscalene plexus block), AX (axillar brachial plexus block), BR (brachial plexus block), PCB (psoas compartment block); LA (Local anaesthetics): LBUP (levo-bupivacaine), ROP (ropivacaine), PRI (prilocaine), LID (lidocaine), MEP (mepivacaine); Adjuvant: TRA (tramadol), BUPR (buprenorphine), CLO (clonidine), SUF (sufentanil), ADR (adrenaline), DEX (dexamethasone), KET (ketamine); Mode: NS (nerve stimulation); Suppl. Analg. (Supplemental Analgesia); Onset: SB (Sensory block), MB (motor block)

Table III. Buprenorphine

Ref.	n	Surg.	PB	LA	Adjuvant	Suppl. Analg.	Onset	Duration of analgesia	Other comments	Side effects	Conclusion
[20]	60	ULS	BR	BUP 0.5% 20 ml + LID 2% 10 ml	Butorphanol 1 mg or BUPR 150 µg	No	delayed SB & MB onset and complete block with BUPR compared to BUT	up to 5-6 hr. with BUT, and up to 8-9 hr. with BUPR		Vomiting Pruritus	BUPR is more potent than BUT
[22]	40	ULS	BR	40 ml	BUPR 0.3 mg			Increased x3 with BUPR	complete analgesia persisting 30 hr. in 75% patients		Benefit inpatients undergoing ambulatory ULS
[23]	60	ULS	IS	MEP 1% 40 ml TET 2.2% 40 ml	BUPR 0.3 mg			BUPR: perineural 22.3 hr., IM 12.5 hr., Placebo 6.6 hr.,	peripherally mediated opioid analgesia by BUPR		BUPR prolongs analgesia x3 (perineural) or x2 (IM)
[21]	150	ASS	IS	LBUP 0.75% 30 ml	BUPR 0.15 mg		Longer SB&MB with BUPR	BUPR: lower pain scores	BUPR: less opioid received	No	Analgesia: Epineural BUPR > i.m. BUPR
[24]	103	AS	SB	BUP 0.5%	BUPR 0.3 mg	GA					BUPR enhances analgesia

Ref.: reference number; n: number of patients; Surg. (Surgery): ASS (arthroscopic shoulder surgery), ULS (upper limb surgery), AS (ankle surgery); PB (Plexus Block): IS (Interscalene plexus block), BR (brachial plexus block), SB (sciatic block); LA (Local anaesthetics): BUP (bupivacaine), LBUP (levo-bupivacaine), TET (tetracaine), MEP (mepivacaine); Adjuvant: BUPR (buprenorphine), BUT (Butorphanol); Suppl. Analg. (Supplemental Analgesia): GA (General Anaesthesia); Onset: SB (Sensory block), MB (motor block)

Table IV. Midazolam

Ref.	n	Surg.	PB	LA	Adjuvant	Mode	Suppl. Analg.	Onset	Duration of analgesia	Side effects	Conclusion
[26]	40	ULS	SC	BUP 0.5% 30 mL	MID 50 µg/kg	PAR		Significantly faster SB&MB	Lower 24 hr. pain scores and less rescue analgesic requirements	No adverse events	MID hastened onset of SB&MB, and improved postoperative analgesia
[27]	50	ULS	SC	BUP 0.5% 30 ml	MID 50 µg/kg			Significantly faster onset and longer duration of SB&MB	Lower 24 hr. pain scores and less demand for rescue analgesic	No adverse events	MID quickened the onset, prolonged SB&MB duration and improved analgesia
[28]	100	ULS	SC	LID 2% 10 ml with ADR and BUP 0.5% 10 ml	MID 50 µg/kg	PAR	Ketamine in some patients	SB: prolonged onset and less duration. MB: less onset and higher duration		Higher sedation score	MID speeds the onset of SB&MB with postoperative analgesia
[30]	60	ULS	SC	BUP 0.5% 20 ml + LID 2% 10 ml	CLO 150 µg MID 5 mg		Diclofenac	No clinically significant difference in onset and duration of SB&MB	More prolonged with CLO	CLO: More sedation	CLO provides better postoperative analgesia and more sedation than MID
[31]	60	ULS	SC	BUP 0.5% 30 ml	DEX 8 mg or MID 50 µg/kg	US		Onset of SB&MB was significantly rapid with DEX and MID	Greater duration of SB&MB and time to rescue analgesia with DEX	Fewer side-effects with DEX	DEX had rapid onset of block and longer time to first analgesic request than MID
[75]	60	ULS	SC	LID 2% + BUP 0.5% with ADR 30 ml	MID 50 µg/kg	PAR		Faster onset of SB&MB	Prolonged duration of post-operative analgesia	Sedation	MID speeds the onset of SB&MB

Ref.: reference number; n: number of patients; Surg. (Surgery): ULS (upper limb surgery); PB (Plexus Block): SC (supraclavicular plexus block); LA (Local anaesthetics): BUP (bupivacaine), LID (lidocaine); Adjuvant: MID (midazolam), DEX (dexamethasone), CLO (clonidine), ADR (adrenaline); Mode: PAR (paraesthesia), US (ultrasound); Suppl. Analg. (Supplemental Analgesia); Onset: SB (Sensory block), MB (motor block)

Table V. Magnesium

Ref.	n	Surg.	PB	Local anaesthetic	Adjuvant	Mode	Suppl. Analg.	Onset	Duration of analgesia	Other comments	Side effects	Conclusion
[32]	66	ASS	IS	0.5% BUP 20 mL + ADR (1:200,000)	10% MAG 2 mL	US+NS	meperidine, zaltoprofen	No differences	Analgesia prolonged 2 hr. with MAG.	No differences in SB & MB durations	No	MAG prolongs analgesia and reduces postoperative pain
[33]	60	ULS	AX	5 mg/kg of 2% PRI	MAG 100-150 mg				MAG prolonged SB & MB about 1-1.5 hr.		No	MAG prolongs SB and MB
[34]	107	ACL	FEM	20 ml 0.25% LBUP	1 ml of 15% MAG		GA	MAG: lower MB	MAG: Lower analgesic requirement and total opioid consumption	MAG: higher time to first mobilisation	No	MAG prolongs SB & MB duration enhances the quality of analgesia

Ref.: reference number; n: number of patients; Surg. (Surgery): ASS (arthroscopic shoulder surgery), ULS (upper limb surgery), ACL (anterior crucial ligament reconstruction); PB (Plexus Block): IS (Interscalene plexus block), AX (axillar brachial plexus block), FEM (femoral block); LA (Local anaesthetics): BUP (bupivacaine), PRI (prilocaine), LBUP (levobupivacaine); Adjuvant: MAG (magnesium), ADR (adrenaline); Mode: US (ultrasound), NS (nerve stimulation); Suppl. Analg. (Supplemental Analgesia): GA (General Anaesthesia) Onset: SB (Sensory block), MB (motor block)

Table VI. Clonidine

Ref.	n	Surg.	PB	LA	Adjuvant	Mode	Suppl. Analg.	Onset	Duration of analgesia	Other comments	Side effects	Conclusion
[40]	80	ULS	SC	BUP 0.25% 35 ml	1µg/kg DEXM Vs. 1 µg/kg CLO	NS	Intraoperative supplements	No data	Greater SB&MB with DEXM		decrease in HR, and BP with DEXM	DEXM is better than CLO in terms of duration of action
[37]	60	ULS	SC	ROP 0.75% 30 ml	CLO 60µg			Almost the same onset for SB&MB	significantly increased by CLO	CLO prolonged time for rescue analgesia	Lower HR statistically insignificant	CLO increases SB&MB
[39]	60	TKA	FB	ROP 0.75% and 0.2%	CLO 1 µg/kg			No-CLO 15 min, CLO 10 min			None reported	CLO slowed the recovery of motor function
[38]	30	HV	SB+FB	ROP 0.75% 30 mL	CLO 1 µg/kg	PAR		No differences	significantly increased by CLO		slight sedation and no hemodynamic adverse effects	CLO prolongs postoperative analgesia by 3 h
[42]	80	ULS	AX	LBUP 0.5% 40 ml, BUP 0.5% 40 ml	CLO 150 µg			No differences		CLO: marked variability of block duration	None	No difference in duration with or without CLO
[36]	30	AV-F	AX	LID 2% 40ml	CLO 150 µg			Longer SB onset with CLO	SB&MB prolonged with CLO	chronic renal failure patients	CLO: lower MAP, HR and higher sedation scores	CLO prolongs blockade, decreases both HR and BP and has sedative effects
[43]	98	H-O	II-IH	BUP 0.25% 0.3 ml/kg	CLO 1 µg/kg		Paracetamol + Fentanyl	No data	No statistical difference in rescue analgesia	Children	No more sedation with clonidine	CLO Addition had no advantages vs. BUP alone.
[41]	1054	Any except eye surg.	BR, FB, SB, II-IH	MEP, PRI, LID, ROP, BUP, LBUP	CLO 30 to 300 µg; usually 150 µg	Various		CLO shortened SB&MB	CLO prolonged SB 74 min and MB 141 min	meta-analysis of randomized trials	CLO increased the hypotension, bradycardia, and sedation	CLO prolonged the postoperative analgesia, SB&MB by about 2 h
[44]	60	ULS	SC	ROP 0.75% 40 mL	CLO 2 µg/kg	PAR	No data	No differences	CLO prolongs postoperative analgesia		Mild short lived intraoperative sedation	CLO does not alter the onset of block but prolongs analgesia

Ref.: reference number; n: number of patients; Surg. (Surgery): SS (shoulder surgery), ULS (upper limb surgery), TKA (total knee arthroplasty), HV (hallux valgus), AV-F (arteriovenous fistula construction); PB (Plexus Block): IS (Interscalene plexus block), SC (supraclavicular plexus block), IC (infraclavicular brachial plexus block), BR (brachial plexus block), AX (axillary plexus block), FB (femoral block), SB (sciatic block), AB (ankle block), II-IH (ilioinguinal–iliohypogastric nerve Block), UNB (ulnar nerve block); LA (Local anaesthetics): BUP (bupivacaine), LBUP (levo-bupivacaine), ROP (ropivacaine), MEP (mepivacaine), LID (lidocaine), PRI (prilocaine); Adjuvant: DEXM (dexmedetomidine), CLO (clonidine), Mode: US (ultrasound), NS (nerve stimulation), PAR (paraesthesia); Suppl. Analg. (Supplemental Analgesia); Onset: SB (Sensory block), MB (motor block)

Table VII. Dexmedetomidine

Ref.	n	Surg.	PB	LA	Adjuvant	Mode	Suppl. Analg.	Onset	Duration of analgesia	Other comments	Side effects	Conclusion
[40]	80	ULS	SC	BUP 0.25% 35 ml	1µg/kg DEXM vs. 1µg/kg CLO	NS	Intraoperative supplements	No data	Greater SB&MB with DEXM		significant decrease in HR, and BP that not required treatment	DEXM is better than CLO in terms of duration of action
[49]	36	none	UNB	ROP 0.75% 3 mL	DEXM 20 µg (perineural or systemic)	US	no	Shorter onset with perineural DEXM	perineural DEXM > systemic DEXM	a volunteer study	No haemodynamic side-effects	prolongation of UNB: perineural DEXM 60%, systemic DEXM 10%
[47]	60	ULS	AX	LBUP 0.5% 40 ml	DEXM 100 µg			1-2 min shorter onset with DEXM	DEXM: 2 hr. of analgesia more		DEXM may lead to bradycardia	DEXM shortens onset and prolongs block duration and analgesia.
[46]	60	ULS	SC	LBUP 0.5% 35 ml	DEXM 100 µg			No data	DEXM: Greater analgesia (196 min)	DEXM: Greater SB (253 min) and MB (328)	Lower BP values with DEXM	DEXM prolongs the duration of block and postoperative analgesia
[48]	62	SS	IS	ROP 0.5% 12 ml	DEXM 150 µg		diclofenac or acetaminophen	significantly faster SB onset with DEXM	DEXM: more block 18 vs 14 hr)	Similar analgesic usage	DEXM: Lower HR, no significant differences in BP or sedation	DEXM increased the duration of IS
[50]	111	ULS	IC	LID 1.5% 25 mL	DEXM 100 µg or KET 5 ml	US		Similar SB onset, less MB onset with DEXM	Time to first analgesic request was longer in KET	DEXM: longer SB&MB than KET	DXM: lowest mean arterial pressure and heart rate	DEXM: better SB & MB duration and worse first time to analgesic request than KET
[51]	14	None	PT	ROP 0.5% 10 ml	1µg/kg DEXM	US	None	Similar onsets, longer SB with DEXM			hypotension, bradycardia, and sedation	DEXM prolongs the duration of SB with similar onset time
[45]	516	Various	Various	Various	DEXM				DEXM prolongs SB & MB	systematic review and meta-analysis	MB prolongation and more likelihood of transient, reversible bradycardia	DEXM appears to be comparable with BUPR and DEX, and exceeds CLO, MAG and MID

Ref.: reference number; n: number of patients; Surg. (Surgery): SS (shoulder surgery), ULS (upper limb surgery); PB (Plexus Block): IS (Interscalene plexus block), SC (supraclavicular plexus block), IC (infraclavicular brachial plexus block), AX (axillary plexus block), PT (posterior tibial nerve block), UNB (ulnar nerve block); LA (Local anaesthetics): BUP (bupivacaine), LBUP (levo-bupivacaine), ROP (ropivacaine), MEP (mepivacaine), LID (lidocaine), PRI (prilocaine); Adjuvant: DEXM (dexmedetomidine), CLO (clonidine), BUPR (buprenorphine), DEX (dexamethasone), MAG (magnesium), MID (midazolam); Mode: US (ultrasound), NS (nerve stimulation), PAR (paraesthesia); Suppl. Analg. (Supplemental Analgesia); Onset: SB (Sensory block), MB (motor block)

Table VIII. Ketamine

Ref.	n	Surg.	PB	LA	Adjuvant	Mode	Onset	Duration of analgesia	Side effects	Conclusion
[52]	60	ULS	SC	LID 1.5% 5 mg/kg	KET 2 mg/kg	US		KET: delayed time of first request for analgesia (8.93 vs. 7.30 hr.)		KET could decrease the postoperative pain and need for analgesic.
[54]	60	ULS	IS	ROP 0.5% 30 ml	KET 30 mg		Similar onset and duration		Yes	Perineural KET not recommended
[18]	36	ULS	AX	ROP 0,375 40 ml	KET 50 mg TRA 50 mg		TRA: shortest SB onset and SB&MB duration	Longer with TRA	No	TRA improves postoperative analgesia
[53]	45	HS	AX	ART 2% 40 ml	KET 2 mg/kg					KET enhance analgesia

Ref.: reference number; n: number of patients; Surg. (Surgery): ULS (upper limb surgery), HS (hand surgery); PB (Plexus Block): SC (supraclavicular plexus block), IS (Interscalene plexus block), AX (axillar brachial plexus block); LA (Local anaesthetics): LID (lidocaine), ROP (ropivacaine), ART (articaine); Adjuvant: KET (ketamine), TRA (tramadol); Mode: US (ultrasound); Onset: SB (Sensory block), MB (motor block)

Table IX. Dexamethasone

Ref.	n	Surg.	PB	LA	Adjuvant	Mode	Suppl. Analg.	Onset	Duration of analgesia	Other comments	Side effects	Conclusion
[19]	60	ULS	SC	BUP	TRA (2 mg/kg) or DEX (8 mg)			Faster onset with DEX	Prolonged with DEX.	Mean analgesia: DEX 1028 min, TRA 453 min		DEX prolongs analgesia more than TRA
[55]	150	ASS	IS	ROP 0.5% 30 ml	DEX 10 mg Perineural or i.v.	NS	GA	Equivalent SB onset: i.v. and perineural DEX	Increased in DEX groups (P < 0.0001).	DEX is not licensed for perineural use		Similar analgesic duration I.V. DEX vs perineural DEX
[56]	39	ASS	IS	ROP 0.75% 20 mL	DEX 4 mg perineural or i.v.	US	GA		Perineural DEX (18 hr.) than IV DEX (14 hr.) or ROP (11.2 hr.)	First analgesic request later with perineural DEX	Redness at the injection site (I.V. DEX)	Perineural but not I.V. DEX prolongs duration of analgesia
[57]	60	ASS	IS	0.5% LBUP 10 mL	DEX 5 mg	US + NS	GA		Longer with DEX	No differences in total analgesic consumption	Without any specific complications	DEX improves postoperative analgesia
[58]	90	ASS	IS	0.5% BUP 40 mL	DEX 4 or 8 mg			Longer MB with DEX (36.7-39.2 hr.) vs. BUP (24.6 hr.)	Prolonged with DEX (21.6-25.2 hr.) vs. BUP (13.3 hr.)	Lower analgesic consumption for the first 48 hr with DEX	Similar duration of analgesia and MB between DEX 4 and 8 mg	DEX prolonged MB duration and improved analgesia
[59]	88	ASS	IS	BUP 0.5% 20 mL + ADR 1:200,000	CLO 75 µg DEX 8 mg		GA	Prolonged SB & MB	DEX: lower pain scores at 24 hr. similar at 48 hr.	DEX: less opioid requirement the first 24 hr		DEX prolongs SB and reduces opioid use.

Ref.	n	Surg.	PB	LA	Adjuvant	Mode	Suppl. Analg.	Onset	Duration of analgesia	Other comments	Side effects	Conclusion
[60]	75	ULS	SC	0.5% LBUP 30 mL	None, Perineural or IV DEX 8 mg	US	None	MB: DexIV (30.1 hr.) DexP (25.5 hr.) and Control (19.7 hr.)	DexIV and DexP reduced pain scores, opioid consumption	DexIV and DexP improved satisfaction		IV DEX prolongs duration of analgesia similar to perineural DEX
[61]	45	ULS	SC	MEP 1,5% 30 mL	DEX 8 mg	US	None	Similar SB & MB onset times	DEX prolonged significantly analgesia			DEX prolongs analgesia and not reduce onset
[62]	70	ULS	SC	0.5% LBUP 25 mL.	DEX 4 mg	US + NS		DEX: longer SB&MB	Lower pain levels with DEX	DEX: less analgesics consumption		DEX prolonged analgesia
[63]	40	ULS	BR		DEX			DEX: faster onset of action	DEX: longer analgesia time		No	DEX significantly prolongs analgesia
[64]	90	ULS	SC	LID with ADR (1.5%)	NEO 0.5 mg or DEX 4 mg			DEX: Better onsets	DEX: Better duration of analgesia	DEX: Less analgesic requirement and lower VAS		DEX: better onsets and analgesia
[65]	60	ULS	SC	1.5% LID (7 mg/kg) with ADR	DEX 8 mg	NS	No	Significantly faster SB&MB with DEX	DEX: lower VAS and MB scores			DEX speeds the onset and prolongs SB&MB
[66]	60	ULS	AX	LID 1.5% 34 mL	DEX 8 mg			Similar onset times of SB&MB	DEX: longer SB&MB			DEX prolongs the duration of SB&MB
[67]	45	ULS	BR	2% PRI 5 mg/kg (G1, G2) or 0.5% LBUP 1.5 mg/kg (G 3)	DEX 8 mg (G 2)	NS		PRI: Similar onsets, LBUP: longer onsets	G1: Similar G3: longer			DEX prolongs the duration of SB&MB
[68]	60	FF	FICB	BUP 0.25% 38 mL	DEX 8 mg	AL	SA	7.85 ± 1.62 in group B and 16.33±5.69 in group BD	Longer with DEX, with less required rescue analgesics	Prolongation of block duration was 1.5 to 2 times with DEX	No	DEX: prolonged block and less requirement of rescue analgesics
[69]	60	ACLRS	FEM	0.5% ROP 20 ml	DEX 8 mg	US + NS	SA		Statistically longer duration of SB with DEX	Similar quality of pain control and analgesic consumption		DEX prolongs SB but does not affect degree of pain control.

Ref.	n	Surg.	PB	LA	Adjuvant	Mode	Suppl. Analg.	Onset	Duration of analgesia	Other comments	Side effects	Conclusion
[70]	126	F/AS	SB or AB	BUP 0.5%	DEX 8 mg				Fewer DEX SB patients had pain at 24 hr. No benefit at 48 hr or at any time for AB	No differences in pain-free survival curves for the first 48 hours between groups		BUP-DEX SB and AB had only a minor analgesic enhancing effect
[71]	760	Various	Various	Various	DEX	Various		DEX: no benefit on SB or MB onset.	DEX prolongs analgesia (264 to 682) min.		no reports of persistent nerve injury	DEX improves postoperative pain outcomes.
[72]	801	ULS	BR	Various	DEX (4-10 mg)	Various	Various		Prolonged with DEX for long-acting (730 to 1306 min) and intermediate LA (168 to 343).	DEX prolonged MB from 664 to 1102 min	no observed adverse events.	Perineural DEX with LA prolongs BPB effects.
[73]	1695	Various	BR: no in 6 studies		DEX 4, 5, 8 mg or 10 mg	US +/- NS or AL	GA (7 trials) or SA (1 trial)	DEX shortened the onset of SB&MB.	DEX prolonged the duration of analgesia or SB.	Meta-regression did not show an interaction between dose of perineural DEX (4–10 mg) and analgesia duration	DEX: A single case of superficial wound infection and increased serum glucose concentrations	DEX prolonged the durations of analgesia and MB from short-, medium- and long-term action LA
[74]	78	F/AS	SB	0.5% BUP with ADR 1:300,000 (0.45 mL/kg)	Perineural DEX 8 mg, I.V. DEX 8 mg or saline	US			DEXp prolonged analgesia and MB and DEXiv prolonged MB but not analgesia	Postoperative opioid consumption was not different among groups	Self-reported neurologic symptoms at 24 hr were not different among groups	DEXp and DEXiv did not improve quality of recovery or decrease opioid consumption but prolong analgesia
[76]	953	ULS	BR	Various	DEX (4-10 mg)			DEX: Variable effect on onset with clinical benefit unclear	Prolonged (1.5 to 4.0 times) regardless of LA kind	DEX reduced pain scores and 48 hr (but not total) opioid consumption	Numbness or tingling in the hand.	DEX significantly prolongs the duration of analgesia
[77]	60	ULS	SC	ROP (0.5%) 30 ml	DEX 8 mg	NS	No	No differences in onset of SB&MB	DEX: longer SB & MB duration	Prolonged post-operative pain relief	No	Prolonged duration of anaesthesia and pain relief
[78]	1040	ULS LLS	UEPNB or LEPNB	ROP 0,5%	DEX and/ or ADR (1:400,000)		No		DEX increases median block duration by 37% in all body regions and block types	DEX reduces pain scores 48 hr No difference in duration of nerve blocks with ADR		DEX prolongs the duration of peripheral nerve blocks of upper and lower extremity

Ref.	n	Surg.	PB	LA	Adjuvant	Mode	Suppl. Analg.	Onset	Duration of analgesia	Other comments	Side effects	Conclusion
[79]	100	ASS	SC	BUP 0.25% 30 ml	DEX 1, 2 or 4 mg	US	GA		Analgesia duration was 15,7; 22,4; 23,4 and 22,2 hours for BUP and DEX 1 mg, 2 mg or 4 mg respectively	The average durations of MB showed similar trend. No dose response effect of DEX as an adjuvant to LA for BR		DEX significantly prolonged the duration of SB&MB, with shorter MB duration than SB increase.
[80]	218	SS	IS	0.5% ROP or 0.5% BUP	DEX 8 mg	NS, US, or both	GA	DEX prolongs analgesia ROP > BUP. However, block duration was longer with BUP than ROP		The choice of technique (US or NS) had no appreciable effect on the block duration		DEX prolonged the action of ROP more than BUP, but produced nearly the same 22 h of analgesia

Ref.: reference number; n: number of patients; Surg. (Surgery): ASS (arthroscopic shoulder surgery), SS (shoulder surgery), ULS (upper limb surgery), LLS (lower limb surgery), FF (femur fracture), ACLRS (Anterior cruciate ligament reconstruction surgery), F/AS (foot/ankle surgery); PB (Plexus Block): IS (Interscalene plexus block), SC (supraclavicular plexus block), BR (brachial plexus block), AX (axillary plexus block), FICB (Fascia iliaca compartment block), SB (sciatic block), AB (ankle block), UEPNB (Upper extremity peripheral nerve block), LEPNB (Lower extremity peripheral nerve block); LA (Local anaesthetics): BUP (bupivacaine), LBUP (levo-bupivacaine), ROP (ropivacaine), MEP (mepivacaine), LID (lidocaine), PRI (prilocaine); Adjuvant: DEX (dexamethasone), CLO (clonidine), TRA (tramadol), NEO (neostigmine), ADR (adrenaline); Mode: US (ultrasound), NS (nerve stimulation), AL (Anatomy Landmarks); Suppl. Analg. (Supplemental Analgesia): GA (General Anaesthesia), SA (Spinal Anaesthesia); Onset: SB (Sensory block), MB (motor block)

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