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MZ EVENTS

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Pharmacological Update: adjuvants in ALR

Antonio Coviello MD

Anesthesia and Intensive Care AOU Federico II Naples
S.O. Contact Person Orthopedics and Traumatology Federico II
ESRA Campania Regional Delegate

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WHY … adjuvants in LRA?

Regional Anesthesia & Pain Medicine
11 August 2022 / Volume 47, Issue Suppl 1

SP30.1 ADJUVANTS OR DEXAMETHASONE AS MULTIMODAL ANALGESICS AT HIGH DOSES?

Pia Jæger. Department of Anesthesia, The Juliane Marie Center, Rigshospitalet, Copenhagen University Hospital, Denmark

It is a common perception that higher concentrations of local anaesthetics will increase the duration of nerve blocks, but the **relationship between concentration and duration is not linear.**

Low volume or concentration → reduced block effectiveness, success rate and duration

Excessive volume or concentration → No linear duration increase but toxicity risk increase

ADJUVANTS HELP INCREASE DURATION AND ANALGESIC COVERAGE

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WHICH … adjuvants in LRA?

DEXMEDETOMIDINE

EPINEPHRINE

DEXAMETHASONE

CLONIDINE

MORPHINE

FENTANYL

MAGNESIUM

KETAMINE

MIDAZOLAM

NEOSTIGMINE

PLOS ONE | September 10, 2015

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Local Anesthetic Peripheral Nerve Block Adjuvants for Prolongation of Analgesia: A Systematic Qualitative Review

Meghan A. Kirksey[1,2], Stephen C. Haskins[1,2], Jennifer Cheng[1], Spencer S. Liu[1,2]*

[1] Department of Anesthesiology, Hospital for Special Surgery, New York, New York, United States of America, [2] Department of Anesthesiology, Weill College of Medicine at Cornell University, New York, NewYork, United States of America

Randomized controlled trials and meta-analyses that were published between **1990 and 2014** were included in the initial bibliographic search. Only studies that were **published in English** and **listed block analgesic duration** as an outcome were included. A total of **61 novel clinical trials and meta-analyses** were included in this systematic qualitative literature review.

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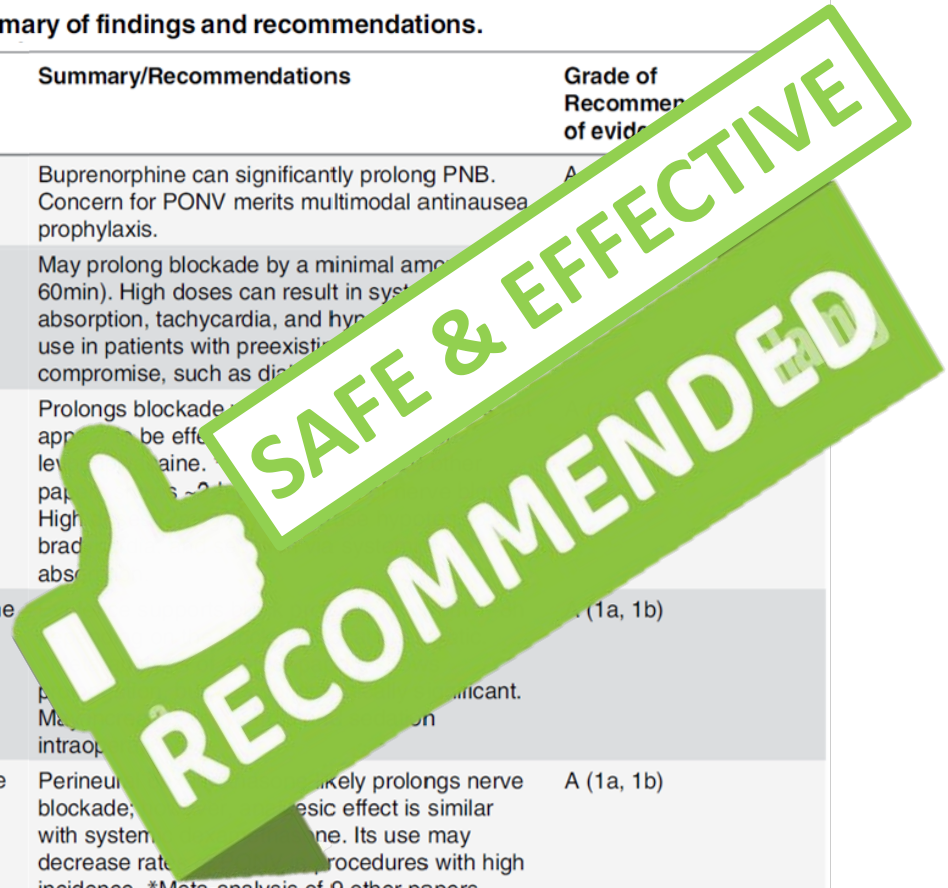
WHAT OUT … WHAT IN?

Table 3. Summary of findings and recommendations.

Agent	Summary/Recommendations	Grade of Recommendation (level of evidence)[3]
Morphine	Not recommended due to lack of quality studies and lack of consistently positive results.	A (1b)
Fentanyl	May prolong bupivacaine PNB. Not recommended due to inconsistent results and	A
Tramadol	7/8 studies showed minimal to no prolongati analgesia or nerve blockade. Not recom due to lack of evidence of clinically efficacy and potential to increas PONV.	
Magnesium	Consistently shown t clinically significa One study of suggeste anal	
Ketamine	ence of ofile sea).	A (1b)
Neostigmine	idence of rabbit model,	A (1b)
Midazolam	Not re established neurot administered with local anesthet animal models, high incidence of sedation, and lack of quality clinical studies.	A (1b)

Table 3. Summary of findings and recommendations.

Agent	Summary/Recommendations	Grade of Recommen of evid
Buprenorphine	Buprenorphine can significantly prolong PNB. Concern for PONV merits multimodal antinausea prophylaxis.	A
Epinephrine	May prolong blockade by a minimal amo 60min). High doses can result in syst absorption, tachycardia, and hyp use in patients with preexisti compromise, such as di	
Clonidine	Prolongs blockade app be effe le aine. pa High brad abs	
Dexmedetomidine		(1a, 1b)
	intraop	licant.
Dexamethasone	Perineu kely prolongs nerve blockade; esic effect is similar with system ne. Its use may decrease rat rocedures with high incidence. *Meta-analysis of 9 other papers supports prolongation of brachial plexus blocks compared to dexamethasone-free controls.	A (1a, 1b)



Buprenorphine

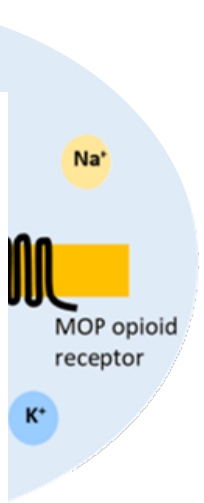
- ✓ Hi
- ✓ Bl
- ✓ Ar
- its
- ✓ Si
- ✓ PC

Table 2. Clinical findings for most extensively studied agents not covered by recent meta-analyses.

Agent	Local Anesthetic	Site/Dose	Prolongation of Analgesia or Sensory Block	Side Effects & Toxicity	Systemic Control (route)	Jadad Scale (I-V)
Buprenorphine	Bupivacaine 0.5% + epi [18]	Sciatic—0.3mg	6h*	PONV events: 7 in control group, 21 in IM buprenorphine group, 19 in PN buprenorphine group	No	V
Buprenorphine	Mepivacaine 1 + tetraca [16]	—	15h**	None	No	III+
Buprenorphine	[	0.3mg		PONV in 2/20 in PN buprenorphine group, 6/20 in IM buprenorphine group, and 3/20 in control group	Yes	V
Buprenorphine	Levo pivacaine 0.75% [19]	ISB—0.15mg	6h***	PONV in 4/50 pts; hypotension in 1/50 pts	No	IV+
Buprenorphine	Lidocaine 1% + bupivacaine 0.5%[15]	SCB- 3mcg/kg	9h*	Pruritus in 4/20 pts; PONV in 10/20 pts	No	II
Buprenorphine	Bupivacaine 0.3%[20]	SCB- 3mcg/kg	6h**	PONV in 2/20 pts in PN buprenorphine group and 2/20 pts in IM buprenorphine group. No buprenorphine-free control group.	Yes (IM)	III

0,3 mcg/kg
0,3 mg

6h - 15h



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Local Anesthetic Peripheral Nerve Block Adjuvants for Prolongation of Analgesia: A Systematic Qualitative Review

Meghan A. Kirksey[1,2], Stephen C. Haskins[1,2], Jennifer Cheng[1], Spencer S. Liu[1,2]*

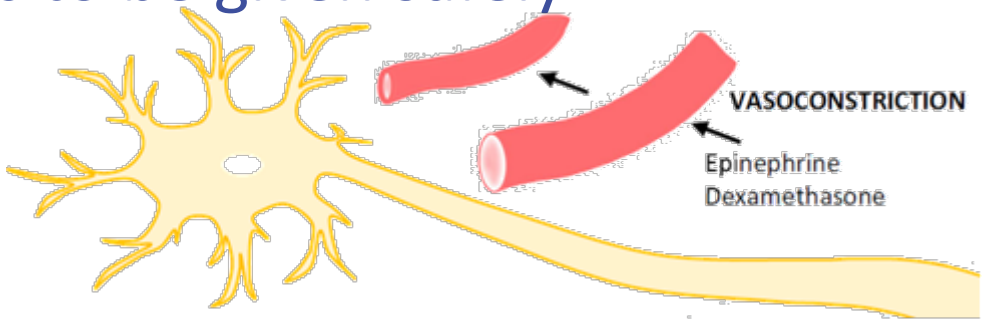
Epinephrine

- ✓ Vaso
  - ✓ p duration
  - ✓ a
  - ✓ allow for larger netic to be given safely
- ✓ Intravascular injection detection
- ✓ Side effects: tachycardia and hypertension.

Agent	Local Anesthetic	Site/Dose	Prolongation of Analgesia or Sensory Block	Side Effects & Toxicity	Systemic Control (route)	Jadad Scale (I-V)
Epinephrine	Lidocaine 1.5%[42]	Axillary-200mcg/ml	45min**	Tachycardia and hypertension with 200mcg	No	IV
Epinephrine	Mepivacaine 1%[43]	Brachial plexus-200mcg	1h***	None	No	III+
Epinephrine	Ropivacaine 0.5% and 0.2%[44]	Fe -	None*	None	No	IV

5-10 mcg/ml

45 – 60 min



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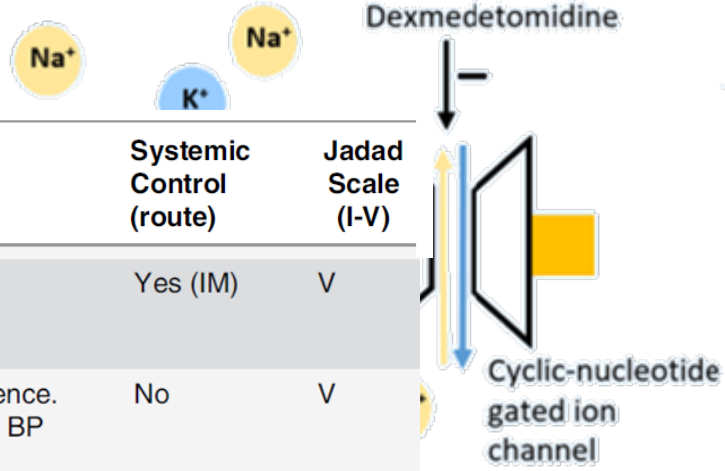
Clonidine

- ✓ α2-agc
- ✓ α2-ad
- ✓ Mech ation
  chann
- ✓ α1-ad riction
- ✓ Side e

Agent	Local Anesthetic	Site/Dose	Prolongation of Analgesia or Sensory Block	Side Effects & Toxicity	Systemic Control (route)	Jadad Scale (I-V)
Clonidine	Bupivacaine 0.375%[53]	Sciatic popliteal- 100mcg	~3-4h**	None	Yes (IM)	V
Clonidine	Levobupivacaine 0.5% [54]	tic eal- g	None*	50% with clonidine experience. >20% decrease in systolic BP	No	V
Clonidine	Ropiva		None***	None	No	IV+
Clonidine		mcg/kg vs. 2mcg/kg	21h wit	Higher hypotension, bradycardia, and sedation in 2mcg/kg group	No	V
Clonidine		SCB- 30mcg		Sedation	No	V
Clonidine	Li .5% (note: com arison to epinephrine 5mcg/ml) [58]	Cervical plexus- 5mcg/ ml		Increased lidocaine plasma concentrations compared to epinephrine	No	V
Clonidine	Bupivacaine 0.5% and lidocaine 2% (note: comparison to 5mg midazolam)[59]	SCB- 150mcg	None**	None	No	I+

1 mcg/kg
150 mcg

3h - 21h



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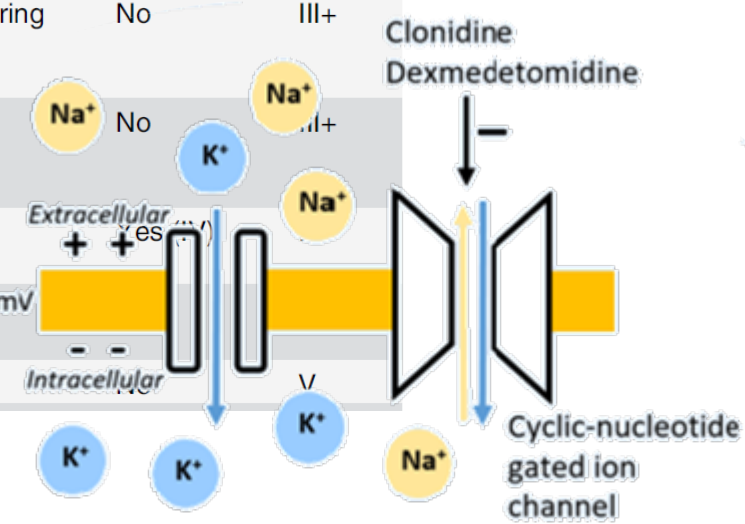
Dexmedetomidine

- ✓ α2-a
- ✓ Prol
  acti
- ✓ No
- ✓ Side

Agent	Local Anesthetic	Site/Dose	Prolongation of Analgesia or Sensory Block	Side Effects & Toxicity	Systemic Control (route)	Jadad Scale (I-V)
Dexmedetomidine	Bupivacaine 0.375%[64]	SCB- 100mcg	~8h*	Bradycardia in one patient	No	III+
Dexmedetomidine	Ropivacaine 0.5%[65]	ISB- 150mcg	~4h**	Lower HR with dexmedetomidine, no neurotoxicity	No	V
Dexmedetomidine	Ropivacaine 0.375%[66]		~50min**	Sedation, bradycardia requiring atropine	No	III+
Dexmedetomidine	Mepiva		~75min**	Bradycardia	No	III+
Dexmedetomidine	Rop	Ulnar nerve block- 20mcg		None		
Dexmedetomidine	Ropiva .5%[68]	Posterior tibial- 1mcg/kg		Hypotension, bradycardia		
Dexmedetomidine	Bupivacaine 0.25%[69]	SCB- 1mcg/kg	~180min*	Bradycardia		V

1 mcg/kg
150 mcg

1h – 8h



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Dexamethasone

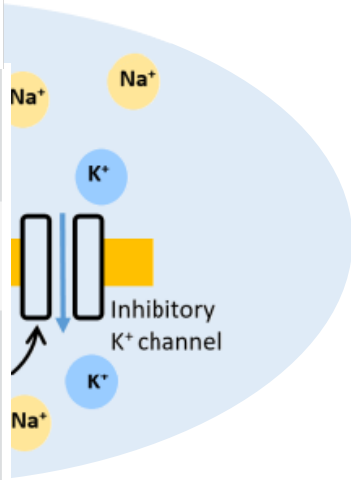
- ✓ Anti-in
- ✓ Stimul
  neuroi
  inhibit
  excitat
- ✓ Systen
- ✓ Inducing localised vasoconstriction

Agent	Local Anesthetic	Site/Dose	Prolongation of Analgesia or Sensory Block	Side Effects & Toxicity	Systemic Control (route)	Jadad Scale (I-V)
Dexamethasone	Lidocaine 1.5% + epi[73]	SCB- 8mg	3h**	None	No	V
Dexamethasone	Prilocaine 2%[76]	Axillary- 8mg	3h**	Not reported	No	IV+
Dexamethasone	Bupivacaine 0.5%[77]	Sciatic/saph- 8mg; ankle- 8mg	Sciatic/saph—13% of patients with pain in first 24hrs vs. 47% in IM group; ankle—none	Not reported	Yes (IM)	V
Dexamethasone	Ropivacaine 0.5%[78]	ISB- 10mg	None	3.8 bloo admi	Yes (IV)	V
Dexamethasone	Bupivacaine [79]	8mg	Non	Statistic significant increase in incidence of numbness and paresthesia at 24 and 48hrs. No symptoms persisted at 8wks in any group.	Yes (IV)	V
Dexamethasone	Bupivacaine 0.25%[74]	TAP- 8mg	1h*	Decreased nausea and vomiting (6/30 with dexamethasone vs. 14/30 with control).	No	IV+
Dexamethasone	Bupivacaine 0.25%[81]	SCB- 1mg, 2mg, 4mg	10h*	One transient paresthesia noted in 2mg group	Yes (IV)	V

1 mg – 10 mg

1h – 24h

No side effects!



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Meghan A. Kirksey[1,2], Stephen C. Haskins[1,2], Jennifer Cheng[1], Spencer S. Liu[1,2]*

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Preclinical Pharmacology
September 2021 • Volume 133 • Number 3

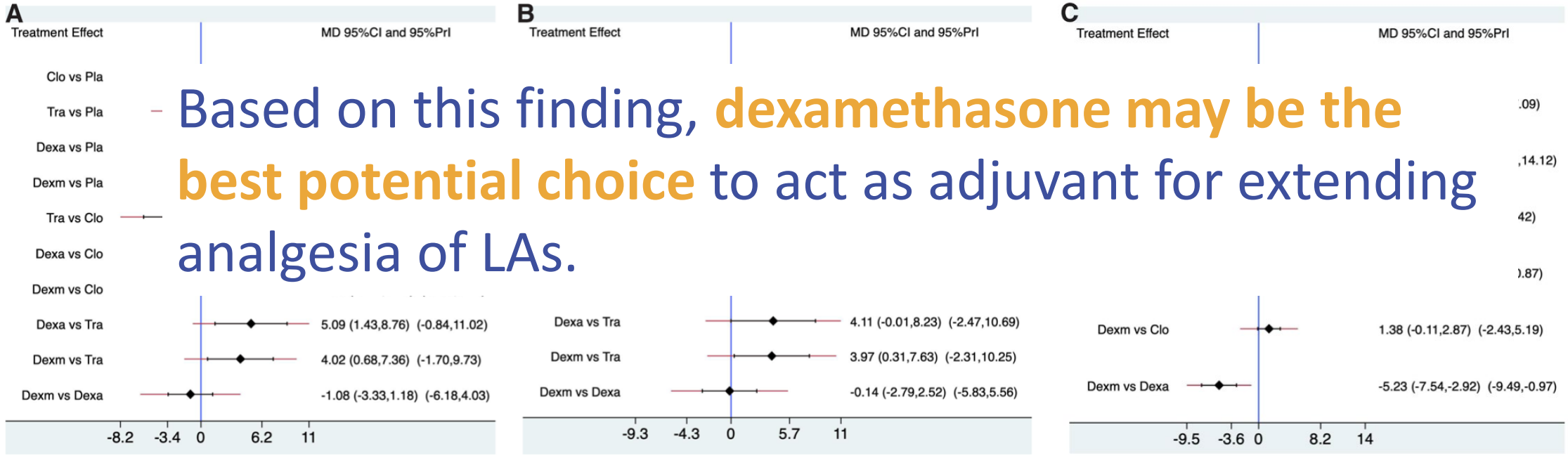
The Facilitatory Effects of Adjuvant Pharmaceutics to Prolong the Duration of Local Anesthetic for Peripheral Nerve Block: A Systematic Review and Network Meta-analysis

C. Xuan*, W. Yan, MD†, D. Wang*, C. Li*, H. Ma*, A. Mueller ‡ and J. Wang‡

From the *Department of Anesthesia, The First Hospital of Jilin University, Jilin, China; †Department of Anesthesia, The Second Hospital of Jilin University, Jilin, China; and ‡Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts.

CONCLUSIONS: **dexmedetomidine, dexamethasone and clonidine**

significantly prolong the duration of Periferical Nerve Block



Based on this finding, **dexamethasone may be the best potential choice** to act as adjuvant for extending analgesia of LAs.

sensory block time (A)

motor block time (B)

time of first analgesia request represent (C)

Preclinical Pharmacology September 2021 • Volume 133 • Number 3

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.... Next publication on Drug Design, Development and Therapy

Dexamethasone versus Dexmedetomidine as Adjuvants in Ultrasound Popliteal Sciatic Nerve Block for Hallux Valgus Surgery: A Mono-Centric Retrospective Comparative Study

A. Coviello[1], C. Iacovazzo[1], D. Cirillo[1], A. Bernasconi[2], A. Marra[1], F. Squillacioti[1], M. Martone[1], E. Garone[1], F. Coppola[1], A. U. de Siena[1], M. Vargas[1], G. Servillo[1]

[1]Department of Neurosciences, Reproductive and Odontostomatological Sciences, University of Naples "Federico II", Via Sergio Pansini, 5, Napoli NA, 80131 Naples, Italy. ; [2]Department of Public Health, School of Medicine, University of Naples "Federico II", Unit of Orthopedics and Traumatology, Naples, Italy.

Dexmedetomidine and dexamethasone as adjuvants were comparable. The satisfaction questionnaire showed that the patients who received dexamethasone reported less pain intensity, less interference with sleep and a minor impact on the affective sphere.

Dexamethasone versus Dexmedetomidine as Adjuvants in Ultrasound Popliteal Sciatic Nerve Block for Hallux Valgus Surgery: A Mono-Centric Retrospective Comparative Study

Table 4. Analysis of questionnaire APS-POQ-R domains.

	Dexamethasone group (N=30)	**Dexmedetomidine group (N=32)**			
	Mean (SD)	*Mean (SD)*	*dF*	*t-test*	*p-value*
Pain severity and sleep interference	17.41±11.47	25.12±15.18	57.468	-2.267	**0.027**
Activity interference	0.87±10.74	3.69±4.68	39.858	-3.184	**0.002**
Activities in bed	0.07±0.25	1.19±2.10	31.963	-2.994	**0.005**
Activities out of bed	0.80±1.64	2.50±2.87	48.083	-2.927	**0.005**
	Mean (SD)	*Mean (SD)*	*dF*	*t-test*	*p-value*
Affective sphere	0.00±0.00	2.94±6.50	31.000	-2.556	**0.015**
Quality of postoperative pain management	82.13±28.46	107.88±26.42	58.855	-3.684	**<0.001**

Data are expressed in Mean ± SD or number (percentage). SD (standard deviation); dF (degrees of freedom); N (number).

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Anaesthesia
Peri-operative medicine, critical care and pain
Association of Anaesthetists
Review Article | 10 January 2021

Local anaesthetic adjuncts for peripheral regional anaesthesia: a narrative review

N. Desai,[1,2] K. R. Kirkh
[1] Consultant, Department of K
[2] Honorary Senior Clinical Lec
[3] Assistant Professor, Departr al, University of Toronto, CA
[4] Program Director, Departme Lausanne, Lausanne, SZ

Table 3. Comparison of the characteristics of an ideal local anaesthetic adjunct with perineural dexmedetomidine and dexamethasone.

Characteristics of an ideal local anaesthetic adjunct	Dexmedetomidine	Dexamethasone
Available as a preservative-free preparation	+	+
Chemically compatible with local anaesthetics	+	+*
Plausible mechanism of action	+	+
Effective for all nerve blocks	+	+
No chrondrotoxic, myotoxic and neurotoxic effects	?	+
Evidence of dose-response relationship	–	+
Increase in the duration of analgesia	+	+
Increase in the duration of sensory block	+	+
No prolongation of motor block	–	–
No significant systemic side-effects	–	+

Journal of Clinical Medicine Review

Published: 15 February 2023

MDPI

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Peripheral Regional Anesthesia Using Local Anesthetics: OldWine in New Bottles?

Lukas Gasteiger [1] , Lukas Kirchmair [2], Elisabeth Hoerner [1,*], Ottokar Stundner [1] and Markus W. Hollmann [3]

[1] Department of Anesthesia and Critical Care Medicine, Medical University of Innsbruck,6020 Innsbruck, Austria
[2] Department of Anesthesia and Critical Care Medicine, Hospital Schwaz, 6130 Schwaz, Austria
[3] Department of Anesthesiology, Amsterdam University Medical Center, University of Amsterdam, 1100 Amsterdam, Netherlands

- ✓ Extended-Release Formulations: Liposomal bupivacaine approved by FDA
- ✓ No short- and long-acting anesthetics mixture to reduce onset time (US-PNB)
- ✓ Continuous Peripherical Nerve Block
- ✓ More Adjuvants (MMPNA)

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ASRA News, November 2020

Curb Your Enthusiasm: Local Anesthetic Adjuvants for Peripheral Nerve Blocks

by Yatish S. Ranganath, MD; Melinda S. Seering, MD; and Anil A. Marian, MD, FRCA Leave

Conclusion: Despite their drawbacks, continuous catheter techniques may still **represent a superior option** in situations where prolonged regional analgesia is indicated.

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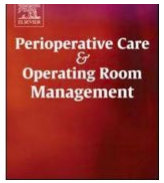
Perioperative Care and Operating Room Management
2022

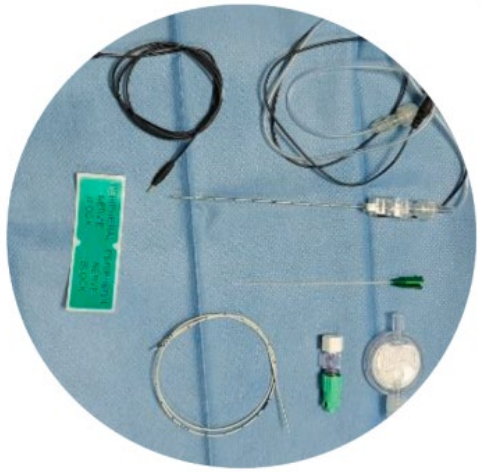


Intra-procedural catheter displacement for continuous adductor canal block: Catheter-through-needle method vs catheter-through-split-cannula method.

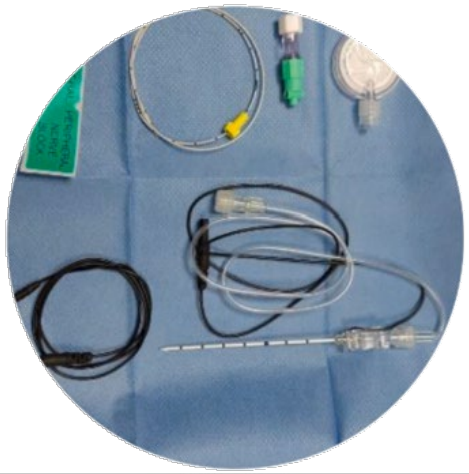
A. Coviello [a,*], E. Spasari[a], M. Ianniello[a], M. Mariconda[b], M. Vargas[a], G. Balato[b], A. Bernasconi[b], C. Iacovazzo[a], A. Marra[a], P. Buonanno[a], G. Servillo[a]

[a] Department of Neurosciences, Reproductive and Odontostomatological Sciences, University of Naples "Federico II", Italy
[b] Department of Public Health, School of Medicine, University of Naples "Federico II", Unit of Orthopedics and Traumatology, Naples, Italy

CTSC SET



CTN SET



… And Over the needle???

MMPNA: Multimodal Perineural Analgesia

- ✓ The evidence for MMPNA efficacy is very heterogeneous, no conclusion on the safety
- ✓ Recent data on the chemical compatibility of some substance mixtures, particularly regarding their aptitude for crystallizing after admixture, raise additional concerns.

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WHERE … adjuvants in LRA?

BJA
British Journal of Anaesthesia, 119 (2): 183–91 (2017)

REVIEW ARTICLE

Efficacy of perineural vs systemic dexamethasone to prolong analgesia after peripheral nerve block: a systematic review and meta-analysis

M. Baeriswyl[1], K. R. Kirkham[2], A. Jacot-Guillarmod[1] and E. Albrecht[1],*
[1]Department of Anaesthesia, Lausanne University Hospital, Lausanne, Switzerland and [2]Department of Anaesthesia, Toronto Western Hospital, University of Toronto, Toronto, Ontario, Canada

Ropivacaine, but not bupivacaine, combined with dexamethasone , crystallizes in vitro

studies, crystallization may occur (pH incompatibility)

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Meghan A. Kirksey[1,2], Stephen C. Haskins[1,2], Jennifer Cheng[1], Spencer S. Liu[1,2]*

Using lidocaine with **epinephrine** prolonged motor block by 10 minutes and sensory block by 30 minutes. When added to **mepivacaine** prolonged motor and sensory block duration by approximately 60 minutes.

Clonidine was shown to prolong block by approximately 3–4 hours with **bupivacaine** added, but did not prolong blockade with levobupivacaine.

Dexamethasone with **Levobupivacaine** shows synergistic action.

Each adjuvant … Own anaesthetic

Take Home Message

- ✓ In UK → The General Medical Council has advised that the prescription of an off-label drug can be appropriate in the presence of adequate evidence or experience of using the drug and when no alternative and licensed drug meets the patient's need.
- ✓ In USA → the Food and Drug Administration in the USA has recommended that the use of an unlicensed drug can be indicated in the presence of reasonable scientific rationale and when sound clinical judgement is exercised.
- ✓ In Italy?

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