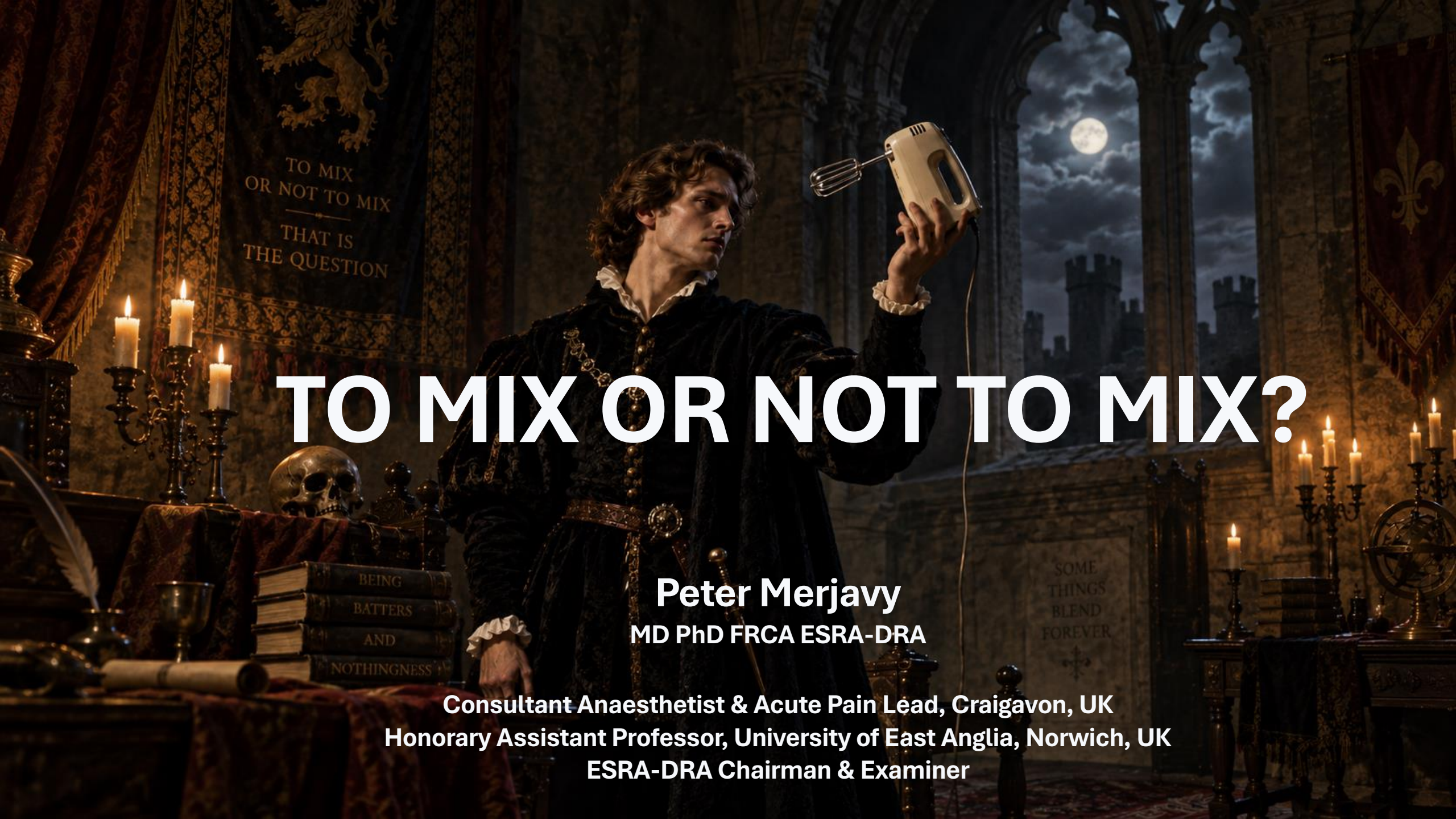


A man with long, wavy brown hair, wearing a dark, ornate historical tunic with a ruffled collar and cuffs, stands in a gothic-style room. He holds a modern white hand mixer in his raised right hand. The room is dimly lit by several candelabras with lit candles. In the background, a large arched window shows a full moon and a castle silhouette. To the left, a banner reads 'TO MIX OR NOT TO MIX THAT IS THE QUESTION'. In the foreground, a table holds a skull, a quill, and books titled 'BEING BATTERS AND NOTHINGNESS'. To the right, a tombstone is inscribed 'SOME THINGS BLEND FOREVER'.

TO MIX OR NOT TO MIX?

Peter Merjavy
MD PhD FRCA ESRA-DRA

Consultant Anaesthetist & Acute Pain Lead, Craigavon, UK
Honorary Assistant Professor, University of East Anglia, Norwich, UK
ESRA-DRA Chairman & Examiner



CONFLICT OF INTEREST – BBRAUN (CONSULTATION / TEACHING)



XXXII

kongres České společnosti anesteziologie, resuscitace a intenzivní medicíny

17.-19. ZÁŘÍ 2026 | BRNO – VÝSTAVIŠTĚ (PAVILON E)
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Why clinicians mix local anaesthetics?



FAST START



**FAST ONSET + LONG
DURATION**



LONG COVER



Conceptual rationale summarised in Fettiplace & Soffin, ASRA Pain Medicine News 2026.

What this presentation will answer

1

Why do we mix?

The intuitive pharmacology and workflow rationale.

2

Does onset improve?

RCTs and meta-analyses: modest overall effect, often absent with ultrasound.

3

What are the consequences?

Shorter sensory and motor block when the long-acting drug is diluted.

4

What about safety?

Additive toxicity and emerging crystallisation/compatibility concerns.

5

When might it still make sense?

Selected cases where a shorter block or faster readiness has value.

Goals in choosing a local anaesthetic

The better question is “what does this patient and pathway need?”

1

**Expedite
operating room
flow**

2

**Minimise
toxicity potential**

3

**Avoid unwanted
side-effects**

4

**Match analgesia
to pain burden**

5

**Reduce chance
for errors**

Choose the single agent first

Mix only if a single agent cannot match the clinical target.

When NOT to mix

**IF YOU WANT YOUR BLOCK TO
LAST AS LONG AS POSSIBLE**

**IF SHORT OPERATION WITH
MINIMAL POSTOP PAIN**

IF USING ROPIVACAINE

**IF YOU HAVE THE BLOCK ROOM &
TIME**

IF USING BLOCK + GA / SPINAL

HOW DO WE MIX?

-  **LA + ADDITIVES (DEXA / ADRENALINE / CLONIDINE ...)**
-  **LIDOCAINE TO SKIN + ANOTHER LA FOR BLOCK**
-  **PROXIMAL BLOCK – SHORT ACTING LA**
DISTAL BLOCKS – LONG ACTING LA
-  **2 LA DRUGS IN DIFFERENT SYRINGES IN SAME BLOCK (SEQUENTIAL)**
-  **2 LA DRUGS IN SAME SYRINGE IN SAME BLOCK (SIMULTANEOUS)**

The Voltage-Gated Na⁺ Channel

...And Local Anaesthetics

Extracellular

Na Channel

Only Unionised LA Crosses

Cell Membrane

LA Binding Site

H⁺

Intracellular

PHARMACOLOGICAL PROPERTIES OF LA

SPEED OF ONSET

pKa

POTENCY

LIPID SOLUBILITY

DURATION OF ACTION

PROTEIN BINDING

The pharmacology logic

Short/intermediate-acting agent

- Lower pKa → larger non-ionised fraction near physiological pH
- Faster membrane penetration and clinical onset
- But shorter protein binding / duration time
- Useful when time-to-surgical-readiness is critical

Long-acting agent

- Greater lipid solubility / protein binding → longer effect
- More reliable postoperative sensory analgesia
- Usually slower onset than lidocaine/mepivacaine
- Diluting the dose often dilutes the duration

Plausible mechanism does not guarantee clinically meaningful benefit.

Epidural & skin infiltration examples

Across older models, duration behaves like a dose-fraction problem.

No diff

epidural onset

duration $\approx$ bupi fraction

No diff

skin onset

about 100 seconds

**Lido = mix
« Bupi**

skin duration

not best of both

If you halve the bupivacaine contribution, do not expect full bupivacaine duration.

Anesthesiology
56:177–183, 1982

Lidocaine and Bupivacaine Mixtures for Epidural Blockade

L. T. Seow, F.F.A.R.A.C.S.,* F. J. Lips, F.F.A.R.A.C.S., M.R.C.P. (UK),†
M. J. Cousins, M.D., F.F.A.R.A.C.S.,‡ L. E. Mather, Ph.D.§

The Effect of Mixing 1.5% Mepivacaine and 0.5% Bupivacaine on Duration of Analgesia and Latency of Block Onset in Ultrasound-Guided Interscalene Block

Jeff Gadsden, MD, FRCPC, FANZCA, Admir Hadzic, MD, PhD, Kishor Gandhi, MD, MPH, Ali Shariat, MD, Daquan Xu, MB, MPH, Thomas Maliakal, MD, and Vijay Patel, MD

Anesth Analg 2011;112:471

Study design

64 shoulder arthroscopy patients

US-guided interscalene block

Mepivacaine vs bupivacaine vs 50:50 mixture

similar onset, intermediate duration.

Onset of sensory block



Duration of analgesia



Interscalene: does order matter?

Sequential administration did not show a clinically useful sequence effect.

QUESTION

If mixing works because the short-acting drug reaches the nerve first...

should injection order matter?

RESULT

≈0.2 h

motor duration difference

10.1 vs 10.3 h

≈0.7 h

analgesia difference

9.5 vs 10.2 h

mepi first

bupi first



The Sequence of Administration of 1.5% Mepivacaine and 0.5% Bupivacaine Does Not Affect Latency of Block Onset or Duration of Analgesia in Ultrasound-Guided Interscalene Block

Jeff Gadsden, MD, FRCPC, FANZCA, Ali Shariat, MD, Admir Hadzic, MD, PhD, Daquan Xu, MB, MPH, Vijay Patel, MD, and Thomas Maliakal, MD

Anesth Analg 2012;115:963

Infraclavicular block

Triple-Blind Randomized Clinical Trial of Time
Until Sensory Change Using 1.5% Mepivacaine
With Epinephrine, 0.5% Bupivacaine, or an Equal
Mixture of Both for Infraclavicular Block

John J. Laur, MD, MS, Emine Ozgur Bayman, PhD,*† Peter J. Foldes, MD,* and Richard W. Rosenquist, MD‡*

Reg Anesth Pain Med 2012;37:28

ONSET

3 min

1.5% mepivacaine

fastest

6 min

1.5% mepi + 0.5% bupi

mixture

6 min

0.5% bupivacaine

long-acting

Key interpretation

The mixture did not create a faster block than the long-acting drug.

A clean example: mepivacaine alone was the fastest in this source slide.

Onset times and duration of analgesic effect of various concentrations of local anesthetic solutions in standardized volume used for brachial plexus blocks

Robert Almasi^{a,*}, Barbara Rezman^a, Zsofia Kriszta^a, Balazs Patczai^b, Norbert Wiegand^b, Lajos Bogar^a

Heliyon 2020;6:e04718

17 min

1% LIDO+0.5%
BUPI

duration 6.5 h

13 min

0.66% LIDOCAINE

duration 2.8 h

17 min

0.33%
BUPIVACAINE

duration 9.1 h

DURATION
FOLLOWED
THE LONG-LA
FRACTION

ONSET WAS SIMILAR

Changing the mix ratio changed duration more than onset.

Duration pattern



Axillary block

No onset advantage — and the mixture shortened duration.

No diff

onset

11–14 min

25%

shorter duration

mixture penalty

US-guided

context

less room for rescue

The practical conclusion is simple:

if onset is not faster, then shortening the long-acting component becomes hard to justify.

Comparison of the pharmacological properties of 0.375% bupivacaine with epinephrine, 0.5% ropivacaine and a mixture of bupivacaine with epinephrine and lignocaine – a randomized prospective study

Piotr Bobik^a, Juliusz Kosel^a, Paulina Świryrdo^a, Marcin Tałałaj^b, Igor Czaban^b and Wojciech Radziwon^b

J Plast Surg Hand Surg 2020;54:156

Femoral + parasacral sciatic

A Comparison of the Pharmacodynamics and Pharmacokinetics of Bupivacaine, Ropivacaine (with Epinephrine) and Their Equal Volume Mixtures with Lidocaine Used for Femoral and Sciatic Nerve Blocks: A Double-Blind Randomized Study

Anesth Analg 2009;108:641

Here the mixture may buy readiness — but at a duration cost.

15 min

mix onset

2% lidocaine + 0.5% bupivacaine



13 h

mix duration

shorter

22 h

bupi duration

longer

30 min

bupivacaine onset

0.5% bupivacaine

TRADE-OFF

≈15 minutes saved at onset
≈9 hours lost in duration

Lower-limb contexts are where a real onset gain may be most plausible.

The effect of combining lidocaine and ropivacaine on the duration and onset time of an ultrasound-guided infraclavicular brachial plexus nerve block

A randomised controlled trial

Dec 2025

Sina Yousef, Mathias Therkel Steensbæk, Aurelien-Xuan Rosendal Bahuet,
Rasmus Linnebjerg Knudsen, Cecilie Dupont Harwood, Charlotte Vallentin Rosenstock,



- 74 patients having hand surgery
 - 150 mg Ropivacaine
 - 100mg Ropivacaine + 200mg Lidocaine
- US-guided infraclavicular brachial plexus block as sole anaesthetic

Onset of sensory block

R150		17 min
R100/L200		18 min
R150 /L200		17 min

Duration of analgesia

R150		847 min
R100 / L200		536 min
R150 / L200		671 min

Systematic Review and Meta-Analysis



ANESTHESIA & PAIN MEDICINE

Original Article

Comparative effectiveness of bupivacaine and lidocaine-bupivacaine mixtures in brachial plexus block: a systematic review and meta-analysis

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Background: Combining lidocaine with bupivacaine in brachial plexus blocks seeks to blend rapid onset with extended duration; yet, clinical advantages are uncertain. This systematic review assesses their efficacy against bupivacaine alone in ultrasound-guided brachial plexus blocks.

Methods: A systematic search of PubMed, EMBASE, and Cochrane databases was conducted in May 2025. Randomized controlled trials (RCTs) comparing lidocaine-bupivacaine mixtures with bupivacaine alone in ultrasound-guided brachial plexus blocks were included. The primary outcome was sensory block onset time. Secondary outcomes included motor block onset time, sensory and motor block durations, and conversion to general anesthesia. Data were analyzed using a random-effects model, with heterogeneity assessed via I^2 statistics.

Results: Of 1,490 identified articles, 7 RCTs (358 patients) met the inclusion criteria. No significant difference was found in sensory block onset time (mean difference [MD] -1.81 min, 95% confidence interval [CI] -3.92 to 0.29; $P = 0.10$; $I^2 = 98\%$) or motor block onset time (MD 0.02 min, 95% CI -2.34 to 2.39; $P = 0.99$; $I^2 = 95\%$) between groups. The mixture reduced sensory (MD -172.88 min, 95% CI -215.18 to -130.59; $P < 0.001$; $I^2 = 90\%$) and motor block durations (MD -212.13 min, 95% CI -374.99 to -49.28; $P = 0.01$; $I^2 = 93\%$).

Conclusions: No clinical benefit was observed from combining lidocaine with bupivacaine, as there was no improvement in block onset times and a reduction in block durations. Given the very low certainty of evidence, these findings should be interpreted with caution, and further high-quality RCTs are needed.

Keywords: Anesthesia, conduction; Brachial plexus block; Bupivacaine; Lidocaine; Meta-analysis; Systematic review.

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Review

Combination of shorter and longer-acting LA vs. longer-acting LA for brachial plexus block: Systematic review and meta-analysis of randomized clinical trials

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^cDepartment of Anesthesiology, The Ohio State University, Columbus, USA
^dDepartment of Anesthesia, Dalhousie University, Halifax, Nova Scotia, Canada
^eDepartment of Anesthesia, Pain and Perioperative Medicine, Stanford University, Palo Alto, CA, USA

HIGHLIGHTS

- Considerable debate exists regarding benefits of combining short and long acting local anesthetics to speed the onset of blockade in brachial plexus blocks.
- In this systematic review and meta-analysis of randomized clinical trials we aimed to evaluate the block and analgesic profile of utilizing mixtures of short and long acting local anesthetics compared to single long-acting local anesthetic agents when used for brachial plexus blocks.

ARTICLE INFO

Keywords:
Anesthetics, local
Regional anesthesia
Brachial plexus block
Anesthesia, conduction

Abstract
Background: Combining shorter-acting local anesthetics (LA) with longer-acting ones should theoretically ensure a quick-onset block without compromising on the duration of blockade. We wanted to perform a review of literature evaluating combination of shorter-acting and longer-acting LA in comparison to long-acting LA alone when used for brachial plexus blocks in terms of block characteristics and efficacy.
Methods: Primary literature searches were performed in PubMed, Embase, and the Cochrane databases from their inception through October 26, 2023. Randomized clinical trials (RCTs) utilizing any combination of mixtures of a shorter and longer-acting LA (combination LA) compared to any single long-acting LA for brachial plexus block in adults were selected. The primary outcomes of interest were sensory and motor block onset times while secondary outcomes included duration of blockade, duration of analgesia and, the need for conversion to general anesthesia (GA).
Results: A total of 4209 primary references were reviewed and after exclusions, 11 RCTs were included for data extraction. Pooled data showed that compared to long-acting LA, combination of LAs did not reduce the sensory onset time (MD [95 % CI] -0.44 min (-0.89; 0.02)) nor the motor onset (MD [95 % CI] 0.01 (-1.30 to 1.32)). The combination group showed a shorter duration of sensory and motor blockade without differences in other secondary outcomes.
Conclusion: Our meta-analysis of RCTs indicate that combination of shorter and long acting LAs did not provide benefit in terms of onset time while leading to notably shorter durations of sensory and motor blockade compared to longer acting LA alone when used in brachial plexus blocks.
PROSPERO registration no.: CRD42023476579.

Brazilian Journal of Anesthesiology 2025;75(3): 844617

SBA
Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

REVIEW ARTICLE

Comparing block characteristics of mixtures of short/intermediate- and long-acting local anesthetics for peripheral nerve block: a systematic review and meta-analysis

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Available online 28 March 2025



KEYWORDS
Conduction anesthesia;
Local anesthetic;
Nerve block

Abstract
Introduction: Results from Randomized Controlled Trials (RCTs) on mixed Local Anesthetics (LA) are conflicting. We conducted a systematic review and meta-analysis on whether using mixed LA leads to faster onset of surgical block.
Method: We conducted systemic review and meta-analysis of RCTs. Medline and Embase without language restriction from inception to June 15, 2024, were searched. Included RCTs had to compare mixed LA to long-acting LA in adult surgical patients for onset or duration of nerve blocks. Onset time to surgical block was the primary outcome. The Cochrane Risk of Bias Tool with GRADE methodology was utilized to assess evidence quality.
Results: Nineteen trials including 1060 participants met the inclusion criteria. Mixed LA modestly reduced time to surgical block (-4.4 minutes; 95% CI -12.0 to -4.8 minutes; $p = 0.0001$; $I^2 = 0.99$), sensory block duration (-226.2 minutes; 95% CI -352.2 to -100.1 minutes; $p = 0.002$; $I^2 = 0.98$) and motor block duration (-259.2 minutes; 95% CI -399.5 to -119.0 minutes; $p = 0.003$; $I^2 = 0.98$) but not time to analgesic request duration (-130.5 minutes; 95% CI -265.9 to 4.9 minutes; $p = 0.057$; $I^2 = 0.98$). GRADE scoring ranged from low to very low.
Conclusion: The existing evidence showed mixed LA led to a modest reduction in surgical block latency but also shortened block duration. Future studies should evaluate the role of mixed LA in lower limb blocks and optimal dosing of long-acting LA to balance onset latency and analgesic duration.
PROSPERO registration: CRD42024552801.
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Review

Efficacy of long-acting local anesthetics versus their mixture with shorter-acting local anesthetics for peripheral nerve blocks guided by ultrasound: a systematic review with meta-analysis of randomized controlled trials

Natanael Pietroski dos Santos^a,¹ Vanessa de Paula Silva^a,² Guilherme Stefano da Silva Oliveira^a,² Victor Cardoso Musacchio^a,² Vanessa Henriques Carvalho^a,³



Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1186/s12942-024-10050-4>).

Background/Importance: Local anesthetic (LA) mixtures are used in peripheral nerve blocks (PNB) to improve onset, though study results remain conflicting. **Objective:** This systematic review and meta-analysis compared the efficacy outcomes of long-acting LA to their mixture with shorter-acting LA in ultrasound-guided PNB. The primary outcome was sensory block onset. **Evidence review:** We searched WoS, Scopus, MEDLINE, EMBASE, BVS/LILACS, and Cochrane databases from 1998 to 2024 for randomized controlled trials (RCTs). We conducted a random-effects meta-analysis, evaluated the risk of bias (RoB) with RoB 2.0, performed sensitivity analyses, assessed non-reporting bias with DOI plots and Luis Furuya-Kanamori index, and evaluated strength of evidence with Grading of Recommendations Assessment, Development and Evaluations. **Findings:** We included 10 RCTs (516 participants). Mixture of LA may have no effect on sensory block onset (mean difference [MD] -1.42 min, 95% CI -4.04 to 0.81; $I^2 = 81.50\%$, 95% CI 62.82% to 90.80%; prediction interval (PI) -7.78 to 4.55; very low certainty) and motor block onset (MD -5.60 min; 95% CI -14.54 to 3.33; $I^2 = 98.89\%$, 95% CI 98.50% to 99.18%; PI -31.90 to 20.69; very low certainty), while it may reduce the duration of sensory block (MD -2.16 hours, 95% CI -4.16 to -0.17; $I^2 = 90.77\%$, 95% CI 84.22% to 94.60%; PI -7.24 to 2.92; very low certainty). **Conclusions:** LA mixtures may not affect sensory and motor block onset in ultrasound-guided PNB but could shorten the duration of sensory blockade.

INTRODUCTION
In several situations, the ideal local anesthetic (LA) should have a pharmacodynamic profile that combines a short block onset time with a long sensory block duration. Because such LA does not exist, combinations of long-acting and shorter-acting LAs have been proposed to improve clinical efficacy in regional anesthesia, though studies present conflicting results. Data from trials guided by nerve stimulation suggest that LA mixtures could both reduce¹ or have no effect² on sensory block

onset, and similar uncertainty extends to their impact on analgesia duration.^{1,4-6}
In recent decades, the adoption of ultrasound guidance for peripheral nerve blocks (PNB) has significantly changed practice.^{7,8} Consequently, data from pre-ultrasound studies may not adequately inform current practice or expectations regarding block onset. To the best of our knowledge, this is the first meta-analysis to evaluate the effects of LA combinations in PNB.
This systematic review with meta-analysis of randomized controlled trials (RCTs) aims to bridge the gap in the evidence of 'to mix or not to mix LAs' according to the onset of the sensory block—our primary objective—and secondary outcomes related to ultrasound-guided (US-guided) regional anesthesia. We hypothesize that the sensory onset of blockade is not affected by the LA mixture.
METHODS
We followed the Cochrane Handbook for Systematic Reviews of Interventions⁹ and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses¹⁰ and PRISMA¹¹ guidelines. The protocol was registered (CRD42024504086; first submitted on January 30, 2024) before data extraction; however, it has not been published in a peer-reviewed journal. The registry was updated once, but we followed the original protocol. Post hoc, we included the evaluation of non-reporting bias using DOI plots and the Luis Furuya-Kanamori (LFK) index.¹² We also estimated post hoc a minimally clinically important difference (MCID) of 5 min for sensory block onset, on the precedent of this value being also considered a margin of non-inferiority for block onset.¹³

Search strategy
We conducted searches across Web of Science, Scopus, MEDLINE (via PubMed), EMBASE (via Elsevier), BVS/LILACS (via Biblioteca Virtual em Saúde), and the Cochrane Database (via Cochrane Library)—includes protocols registered at ClinicalTrials.gov, from 1998 to March 5, 2024. The start year considered the time when adequate

2025

2025

2025

2026

Brachial plexus evidence: no clear onset advantage

Systematic review/meta-analysis

- 7 RCTs, 358 patients
- Ultrasound-guided brachial plexus blocks
- No significant sensory onset improvement
- No significant motor onset improvement

Duration penalty

-173

sensory minutes

95% CI -215 to -131

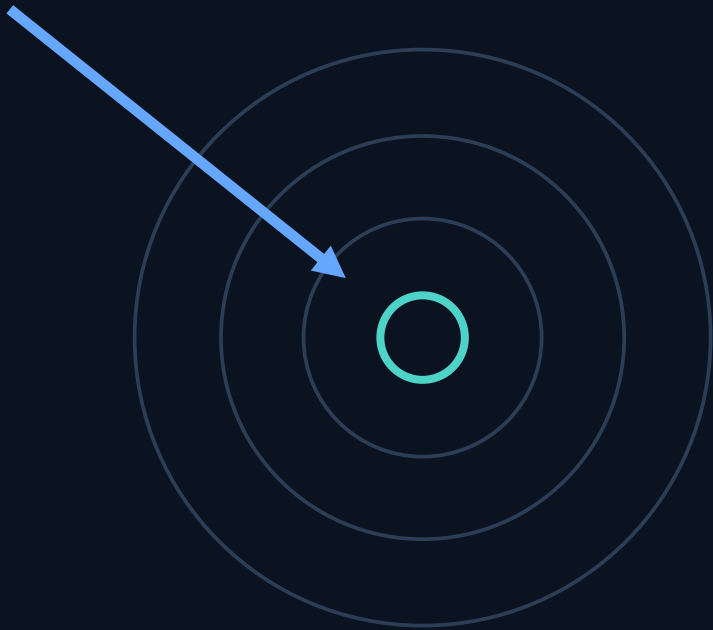
-212

motor minutes

95% CI -375 to -49

This is the same recurring pattern: little or no onset gain, shorter block.

In ultrasound-guided blocks, onset benefit may disappear



Precise deposition reduces the need for pharmacological “rescue”.

RAPM 2025 systematic review

10 RCTs • 516 participants • all ultrasound-guided

**–1.62
min**

**sensory onset difference
not clinically meaningful**

**But sensory block duration may be reduced by
about 2 hours.**

Interpretation: the “onset” argument becomes weakest when ultrasound practice is already efficient.

Largest 2025 meta-analysis: minutes gained, hours lost

–8.4 min

surgical block latency

95% CI –12.0 to –4.8

–226 min

sensory block duration

≈3 h 46 min shorter

–259 min

motor block duration

≈4 h 19 min shorter

NS

analgesic request time

–130.5 min; p=0.057

THE TRADE-OFF

Save ~8 minutes → **Lose ~4 hours of block**

Certainty was low to very low and heterogeneity was high — so use the direction of effect more than the exact minute count.

A 2026 synthesis reaches a pragmatic conclusion

Compared with long-acting LA

-162

analgesia min

≈2½ h shorter

-8.0

onset min

likely small

Compared with short-acting LA

+216

analgesia min

≈3½ h longer

+1.7

onset min

slightly slower

Using either long- or short-acting LA alone may often be sufficient; the need for combination remains unclear.

Temberg S et al. Acta Anaesthesiol Scand 2026; systematic review/meta-analysis with trial sequential analysis.

The common hidden trade-off: dose dilution



Dose dilution explains why duration often lies between the short-acting and long-acting comparators.

SAFETY ARGUMENTS AGAINST MIXING

Nestor CC et al. Anaesthesia. 2022 Mar;77(3):339-350.

**PHARMACOLOGICAL
COMPATIBILITY NOT
PROVEN**

**RECOMMENDATIONS
ON DOSING ARE
LACKING**

**RISK OF
PRECIPITATION &
CRYSTALLISATION**

**ADDITIVES /
PRESERVATIVES &
NEUROTOXICITY**

**MIXTURES OF LA ARE
“OFF LABEL” & VARIABLE
PH**

**LACK OF CLEAR &
PROVEN BENEFIT**

CRYSTALLISATION STUDIES

Original research

Crystallization of ropivacaine and bupivacaine when mixed with different adjuvants: a semiquantitative light microscopy analysis

Elisabeth Hoerner,¹ Ottokar Stundner¹ ,^{1,2} Guenther Putz,¹ Thorsten Steinfeld,³ Simon Mathis,¹ Lukas Gasteiger¹

► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/ragm-2022-103610>).

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Check for updates

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ABSTRACT

Introduction Amino-amide local anesthetics precipitate when mixed with some commonly used adjuvants, carrying the risk of perineural or vascular crystal deposition. The aim of this study was to evaluate whether crystallization occurs with routinely used local anesthetic–adjuvant combinations and if a relation with the solution's pH exists.

Methods All substances used in this trial were first visually investigated undiluted under tenfold magnification. Grade of crystallization was assessed using a 6-point grading system. Ropivacaine (0.2%, 0.75% and 1%) and bupivacaine (0.25% and 0.5%) were mixed in a 1:1 solution with the following adjuvants: dexmedetomidine, dexmedetomidine, clonidine, fentanyl, sodium bicarbonate 8.4% and sodium chloride 0.9%. Subsequently, ropivacaine (0.2% and 0.75%) and bupivacaine (0.25% and 0.5%) were mixed with adjuvants in concentrations commonly used in clinical practice and then serially assessed at several time points up to 1 hour: pH of all substances/ combinations was assessed and correlated with crystallization grade.

Results All pure substances—except the reference standards sterile water and triamcinolone—showed crystallization grades ranging from grade 1 to grade 4. Addition of adjuvants lead to variable, unpredictable changes in crystal densities. Addition of sodium bicarbonate 8.4% produced heavy crystallization in all combinations. Grade of crystallization was weakly positively related to the pH of the solution in 1:1 mixtures and clinically relevant concentrations, but not in pure substances.

Discussion Our study showed that crystallization is present in pure local anesthetics and may be increased or decreased by admixture of adjuvants. Higher pH of mixtures was weakly associated with more crystallization. Further research is necessary to translate these findings into clinical practice.

INTRODUCTION

Local anesthetic (LA) drugs have been used for over a century and are widely accepted as a central element in the prevention and treatment of perioperative pain. However, many regional anesthetic techniques are limited in their utility by short duration and/or slow onset of action of the LA applied. Several strategies are available to circumvent these limitations, including continuous infusion of LA

WHAT IS ALREADY KNOWN ON THIS TOPIC

→ Local anesthetics can precipitate with chemically incompatible adjuvants. pH incompatibility was thought to invoke precipitation.

WHAT THIS STUDY ADDS

→ This experimental study found that crystal precipitation in local anesthetic–adjuvant mixtures appeared in pure substances as well as clinically relevant concentrations. Sodium bicarbonate 8.4% led to massive crystallization in all combinations.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

→ This study found crystallization in pure local anesthetics and local anesthetic–adjuvant mixtures, even when used in clinical concentrations, and might serve as a primer for further research into the clinical relevance of perineural crystal deposition.

through catheters, or the use of adjuvants like sodium bicarbonate, dexmedetomidine, dexmedetomidine, clonidine or opioids.¹ Their chemical characteristics presuppose some LAs to precipitate when mixed with incompatible adjuvants.² While the clinical relevance of perineural deposition of crystal precipitates remains unclear, it has been established that unintended intravascular injection can lead to catastrophic neurological injury.^{3–5} However, little is known about the pH dependency, magnitude, or timing of crystal precipitation effects for various LA–adjuvant combinations. Existing studies are limited by examining impractical concentrations of LA storage times which are unrealistically long in clinical practice, adjuvants that are not used clinically or by their focus on neurotoxicity.^{1–5}

The aim of this study was to quantify the crystallization effect with commonly used adjuvants, (2) to evaluate whether crystallization is pH-dependent and/or dose-dependent and whether it occurs in clinically relevant concentrations, and (3) to assess whether crystallization grade changes over time.

MATERIALS AND METHODS

The LAs and adjuvants tested in this study were ropivacaine 0.2%, ropivacaine 0.75%, and

Original research

Crystallization of short-acting and intermediate-acting local anesthetics when mixed with adjuvants: a semiquantitative light microscopy analysis

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► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/ragm-2023-104398>).

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ABSTRACT

Introduction The addition of adjuvants to short-acting local anesthetics (LA) is common practice in clinical routine to speed up block onset and decrease pain on injection. In a previous study, we observed the development of microscopic crystal precipitations after bupivacaine or ropivacaine were mixed with adjuvants; this follow-up study is intended to clarify whether crystallization (A) also occurs in short-acting or intermediate-acting LA–adjuvant mixtures. (B) changes over time, and (C) is associated with the solutions' pH. **Methods** Lidocaine 2%, prilocaine 2%, mepivacaine 2%, procaine 2% and chlorprocaine 2% were individually mixed with clonidine, dexmedetomidine, dexmedetomidine, epinephrine, fentanyl, morphine or sodium bicarbonate 8.4% in clinically established ratios. For each mixture, we measured initial pH and recorded crystallization patterns at 0, 15, 30 and 60 min using a standardized, semiquantitative light microscopy approach.

Results Lidocaine 2% and mepivacaine 2% plus sodium bicarbonate 8.4%, and mepivacaine 2% plus dexmedetomidine developed delayed grade 5 crystallization over 1 hour. Prilocaine-based, procaine-based and chlorprocaine-based mixtures showed much less pronounced crystallization, with a maximum of grade 2. Initial pH and grade of crystallization showed weak monotonic relationships at time points t_0 , t_{15} and t_{30} ($p=0.17$, $p=0.31$ and 0.32 , all $p>0.05$) and a moderate relationship time point t_0 ($p=0.57$ ($p=0.0003$)).

Conclusions Our study revealed high grades of crystallization in lidocaine/mepivacaine–bicarbonate and mepivacaine–dexmedetomidine mixtures, although these were previously considered safe for local, perineural or neuraxial use. Our findings cast particular doubt on the safety of preparing these formulations for later use.

INTRODUCTION

The addition of various adjuvants to local anesthetics (LAs) is common practice in clinical routine.^{1–4} For long-acting LAs, the reasoning behind this practice is to prolong block duration. For short and intermediate acting LAs, speed of onset, analgesic efficacy, or prevention of pain on injection are targeted. The most frequently used adjuvants are alpha-2-receptor agonists, opioids, vasoconstrictors, corticosteroids and sodium bicarbonate.^{1–5}

Most LA–adjuvant mixtures are not approved by governing bodies such as the Food and Drug Administration or European Medicines Agency; their use is thus considered off-label. Moreover, the

WHAT IS ALREADY KNOWN ON THIS TOPIC

→ Long-acting local anesthetics form crystal precipitations when mixed with commonly used adjuvants.

WHAT THIS STUDY ADDS

→ Heavy crystal precipitation also appeared in lidocaine-based and mepivacaine-based mixtures with a delay of up to 60 min; crystallization appeared to a much lesser degree in prilocaine-based, procaine-based and chlorprocaine-based mixtures.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

→ This study casts doubt on the safety of using bicarbonate-buffered lidocaine and mepivacaine formulations for local, regional or neuraxial anesthesia—particularly in premed formulations—and points out the urgent need to evaluate the behavior of crystal depositions after perineural injection in vivo.

safety and utility of LA adjuvants has recently been discussed controversially.⁶ Admixture of substances can lead to unpredictable chemical and pharmacological effects. In a recently published *in vitro* study, we demonstrated that considerable precipitation occurred after admixture of the long-acting LAs ropivacaine or bupivacaine with various adjuvants in ratios frequently used in routine practice.⁷ Although the clinical relevance of crystallization and subsequent perineural injection of crystalline deposits is not fully elucidated, doubts regarding safety and justification of such off-label uses arise. This follow-up study focuses on short-acting and intermediate-acting LAs. A special emphasis was placed on changes in crystal precipitation pattern over time, as it is common in some practices to prepare LA–adjuvant mixtures ahead for later use. Given the widespread application of LA–adjuvant admixture and its perceived safety, we hypothesized that short-acting and intermediate-acting LAs have a lower aptitude to form crystal precipitates when mixed with adjuvants, compared with their long-acting counterparts.

MATERIALS AND METHODS

This study was performed in a certified analytical laboratory facility under clean air conditions and

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Brief technical report

Crystallization of mixtures of local anesthetics with and without select adjuvants: a semiquantitative light microscopy analysis

Elisabeth Hoerner,¹ Ottokar Stundner¹ ,^{1,2} Anna Seis,¹ Heidi Fiegl,³ Lukas Gasteiger¹

ABSTRACT

Introduction Injecting mixtures of local anesthetics with or without adjuvants is a common practice in regional and particularly obstetric anesthesia to decrease block onset time and/or augment epidural analgesia for cesarean section. While evidence on the efficacy of this practice is equivocal, little is known about its safety in terms of the pharmacologic compatibility of local anesthetics.

Methods We assessed the grade of crystallization in individual mixtures of seven local anesthetics (bupivacaine, ropivacaine, lidocaine, procaine, chlorprocaine, mepivacaine, prilocaine) with or without four adjuvants (sodium bicarbonate, dexmedetomidine, clonidine, fentanyl) using a semiquantitative light microscopy scale (ranging from 0 to 5), repeatedly for up to 60 min and performed correlation analysis between grade of crystallization and initial solution pH.

Results Of the 50 mixtures tested, 26 showed grades of crystallization ≥4 at admixture and 41 showed grades of crystallization ≥4 after 60 min. The addition of adjuvants to local anesthetic mixtures did not substantially change the grades of crystallization. Bupivacaine has a slightly lower precipitation tendency, compared with ropivacaine. A moderate relationship was found between initial pH and grade of crystallization after 15 min for the adjuvant mixtures ($R=0.33$, $p=0.04$), but not at other time points.

Discussion The preparation of local anesthetic (LA)-adjuvant mixtures leads to high grades of crystallization, which increase over 60 min and appear independent of solution pH. The risk of mixing medications with unknown physical or chemical compatibility profiles in regional anesthesia should be critically appraised and its clinical significance elucidated in future translational research.

INTRODUCTION

Injecting two local anesthetics (LA) for neuraxial anesthesia (NA) or peripheral nerve blocks (PNB)—either concomitantly or sequentially—is commonly done to combine fast onset with long block action.^{1–10} The physicochemical safety of this practice is contested, as little is known about the pharmacological compatibility of individual LAs when mixed with other pharmaceuticals.¹¹ This is in line with earlier publications, reporting a broader lack of studies assessing the compatibility of commonly mixed medications, for instance, in the intensive care unit (ICU) setting.¹² In two recent studies, we found that both short-acting and long-acting LA yield crystal precipitates when they are individually

WHAT IS ALREADY KNOWN ON THIS TOPIC

→ Local anesthetics form crystal precipitations when mixed with some commonly used adjuvants.

WHAT THIS STUDY ADDS

→ This study found that the mixture of most pure short-acting, intermediate-acting or long-acting local anesthetics leads to heavy crystal precipitation. The addition of the described adjuvants to these mixtures does not substantially change the level of crystallization.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

→ This study raises questions about the safety of injecting mixtures of local anesthetics, as crystal precipitations form and their behavior in tissue is unclear.

mixed with select adjuvants (LA–adjuvant mixtures), which increased in intensity over 60 min in many cases.^{13–15} In any case, the behavior of such precipitates after perineural or neuraxial deposition is not clear. In this follow-up study, we aimed to assess whether LA–LA mixtures and LA–LA–adjuvant mixtures¹⁶ lead to similar crystallization patterns and whether their crystallization grade is time-dependent, and/or pH-dependent. We hypothesized that moderate crystallization appears in LA–LA mixtures, increasing in intensity when select adjuvants are added as a third component.

MATERIALS AND METHODS

The analysis technique used for this study was repeated according to our previous studies under clean air conditions in a certified laboratory facility at room temperature (20–22°C) at the Medical University of Innsbruck, Austria.^{13–16} The substances used in this trial are seven LAs (bupivacaine 0.5%, ropivacaine 0.75%, lidocaine 2%, procaine 2%, chlorprocaine 2%, mepivacaine 2%, prilocaine 2%) and four adjuvants (dexmedetomidine, clonidine, fentanyl, sodium bicarbonate). As reference standards (ruler standard), distilled water (grade 0) and triamcinolone (grade 5) were used. All formulations used in the studies were freshly purchased from wholesalers through our institutional pharmacy and were used for analyses well before their expiration date. The same preparations as in clinical practice

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BMJ Group

Brief technical report

Crystallization of local anesthetic mixtures with adjuvants and the effect of micropore filtration

Chan Su Park,¹ Min Kyoung Kim¹ ,^{2,3} Geun Joo Choi,^{1,4} Chong Wha Baek,^{1,4} Oh Joo Kwon^{5,6}

ABSTRACT

Background Regional anesthesia is widely used in pain management to reduce opioid requirements, enable early mobilization and improve postoperative outcomes. However, commonly used combinations of local anesthetics and adjuvants can crystallize under clinical conditions, which generates concerns regarding neurotoxicity and embolization complications.

Purpose This study aimed to determine whether microporous filters can effectively eliminate crystals formed by mixing local anesthetics and adjuvants.

Method Commonly used local anesthetics (lidocaine, mepivacaine and ropivacaine) and adjuvants (dexmedetomidine, dexmedetomidine and sodium bicarbonate) were combined and tested. The mixture was passed through 5 µm and 0.2 µm filters, and the presence of crystals before and after filtration at specific time points and volumes was assessed microscopically.

Results Lidocaine mixtures showed no detectable crystallization under any condition. In contrast, crystallization occurred in most combinations containing mepivacaine or ropivacaine, with the highest grades observed in ropivacaine–bicarbonate mixtures (grade 5). Filtration reduced crystallization grades by 1–3 points depending on the mixtures, but did not eliminate crystals in most mixtures. Crystals also persisted after longer intervals and with larger filtration volumes. No meaningful difference was observed between the 5 µm and 0.2 µm filters.

Conclusion Crystallization can occur in anesthetic–adjuvant mixtures that are commonly used for regional anesthesia. Although filtration reduces these crystals, it does not eliminate crystals, especially those with large volumes or unstable compositions.

INTRODUCTION

Local anesthetics are weak bases that are commercially formulated in acidic solutions to enhance their stability, solubility and an extended shelf life.^{1–3} However, the acidity can delay their onset of action because the ionized form predominates in solution.^{2–3} To compensate for this, clinicians frequently add adjuvants to adjust pH and optimize block characteristics, including faster onset and prolonged analgesia.^{4–10} However, such modifications may lead to crystallization.^{7–11}

Crystallization may raise safety concerns because precipitated particles could irritate tissues or potentially affect neural structures.¹² If a mixed solution is inadvertently injected into blood vessels, especially if the size of the crystals exceeds that of red

blood cells, it can obstruct vital vessels, leading to life-threatening complications, such as paralysis, stroke or myocardial infarction.^{13–15} Despite these concerns, adjuvants are frequently combined with local anesthetics in clinical practice to enhance block effect.

Therefore, we assessed the ability of 5 µm and 0.2 µm micropore filters to remove crystals from anesthetic–adjuvant mixtures using microscopic evaluation.

METHOD

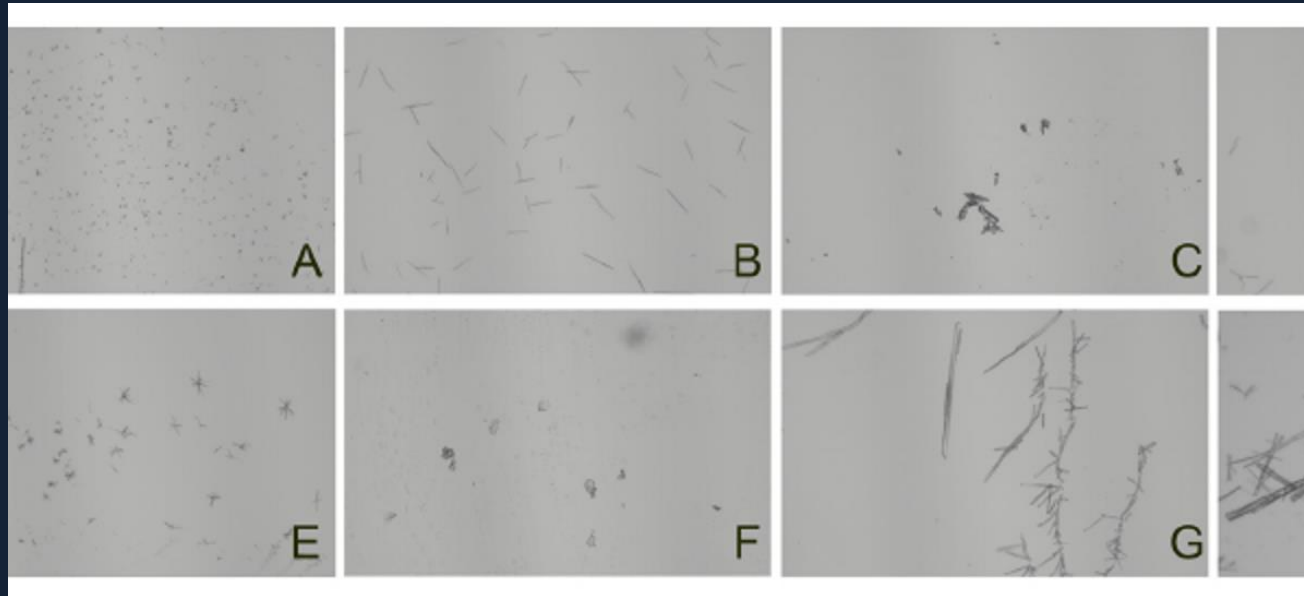
The local anesthetics used in this study included 2% lidocaine (Jell Pharm.), 2% mepivacaine (Reyon Pharm.), 0.2% ropivacaine (Reyon Pharm.) and 0.75% ropivacaine (Reyon Pharm.). All local anesthetic solutions were preservative-free. The adjuvants included dexmedetomidine sodium phosphate (5 mg/mL, Jell Pharm.), dexmedetomidine (100 µg/mL, Kyongho Pharm.) and 8.4% sodium bicarbonate (Huns Co). Normal saline was selected as the reference material because crystallization does not usually occur. All agents were stored at room temperatures of 20°C–22°C. Two types of filters were used to compare filtering capabilities: an EX-CARE filter (EX Healthcare) with a 5 µm micropore and an epidural filter (Accimedical Co) with a 0.2 µm micropore.

The primary outcome of this experiment was the change in the crystallization grade before and after filtration. Secondary outcomes included the pH value of each mixture, impact on crystallization and filtration efficacy with increasing mixture volumes. All experiments were conducted in a certified analytical laboratory under clean air conditions and at room temperature (20°C–22°C).

To avoid bias from the ampule glass fragments and contaminants appearing as crystals on the slide, a filter-needle syringe was used to extract the agent. The mixture was passed through a filter by pushing the plunger of the syringe at a pressure of 0.2 mL per second. One drop of each mixture was placed on a glass slide and covered with a cover glass. Microscopic examination was conducted using a light microscope Axiolab 5 (ZEISS, Oberkochen, Baden-Württemberg) with an Axiocam 208 color camera module (ZEISS) at a total magnification of 200×. The experiment was conducted in a double-blind manner, with slide preparation and grading performed by independent investigators. For the grading of detectable crystallizations, a scale from 0 to 5 was used,

Park CS, et al. *Reg Anesth Pain Med* 2026;50:1–6. doi:10.1136/ragm-2026-107700

The crystallisation signal is visible under microscopy



Microscopy images from LA-LA ± adjuvant mixtures show a spectrum from fine particles to larger crystal structures.

Why it matters

- Particles may irritate tissues or neural structures
- Accidental intravascular injection creates theoretical embolic concern
- Behaviour after perineural deposition remains uncertain
- Immediate use is preferable to premade mixtures for later use

Compatibility evidence: a second reason for caution

2022



**Ropivacaine / bupivacaine +
adjuvants**

Bicarbonate
produced heavy
crystallisation in all
tested combinations.

2023



**Short/intermediate LAs +
adjuvants**

Delayed grade 5
crystallisation in
lido/mepi-
bicarbonate and
mepi-dexamethasone

2025



LA–LA ± adjuvant mixtures

High grades of
crystallisation
common; increased
over 60 min.

2026



Micropore filtration study

Filtration reduced but
did not reliably
eliminate crystals; no
meaningful 5 µm vs
0.2 µm difference.

Clinical relevance in vivo is still uncertain — but physical incompatibility is no longer a theoretical concern.

Why do studies sometimes disagree?

Example: lidocaine

- 2023 report: lidocaine + bicarbonate developed delayed grade 5 crystallisation
- 2026 report: lidocaine mixtures showed no detectable crystallisation
- Different products, concentrations, ratios, methods and grading thresholds may explain divergence
- Ropivacaine-bicarbonate: highest grade crystallisation

How to present it fairly

- Do not overstate in-vitro microscopy as proven clinical harm
- Do not dismiss physical incompatibility as irrelevant
- Avoid unstable or premade mixtures when a single-agent strategy can achieve the same clinical goal
- Point-of-care preparation is preferable when mixing is chosen

Hoerner et al. RAPM 2023; Park et al. RAPM 2026; discrepancy highlighted deliberately for balanced interpretation.



TOXICITY OF LA MIXTURES IS ADDITIVE, NOT SYNERGISTIC

WE CAN'T MIX 100% MAX DOSE OF EACH LA

**50% OF SHORT-ACTING LA + 50% LONG-ACTING LA = 100% MAX
RECOMMENDED DOSE**

LA	Plain		With Epinephrine	
	Max Dose	Max Dose	Max Dose	Max Dose
Lidocaine	3mg/Kg 5mg/Kg	350mg	7mg/Kg	500mg
Mepivacaine	5mg/Kg	350mg	7mg/Kg	500mg
Bupivacaine	2mg/Kg	175mg	2mg/Kg 3mg/Kg	225mg
Ropivacaine	4mg/Kg 3mg/Kg	200mg	3mg/Kg	250mg

Regional Variations Exist

Use Ideal Body Weight



SafeLocal

For safe dosing calculations

Open

Johns Hopkins Mobile m... Medical



21:21

5G 96



Safe Local

Search



When might mixing still make sense?

Intermediate-duration block

ambulatory surgery where prolonged motor block is undesirable

Lower-limb or slower-onset context

a genuine 10–15 min readiness gain could change flow

Limited ultrasound access

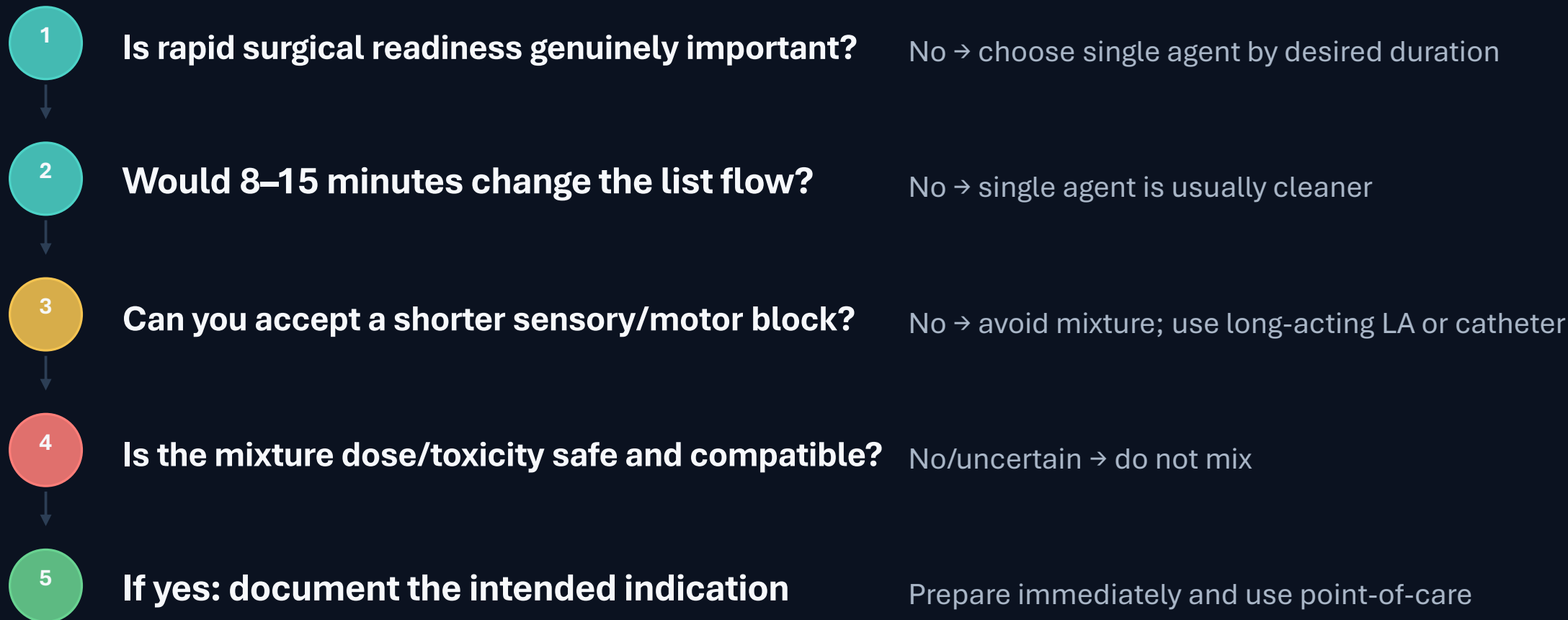
less precise deposition may increase pharmacology value

Clear dose and compatibility logic

avoid full-dose + full-dose “cocktails”

Use selected, explicit indications — not routine recipes.

A practical decision algorithm



Default position: use a single agent unless the mixture solves a specific, patient-centred problem.

Decision frame based on the evidence pattern: modest onset advantage, consistent duration penalty, additive toxicity and compatibility uncertainty.

MYTHBUSTERS

Myth 1

“Mixing gives the best of both worlds.”

Usually: intermediate duration, not magic.

Myth 2

“Onset is always faster.”

In ultrasound-guided upper-limb blocks, often no meaningful gain.

Myth 3

“Safety is just the same.”

Toxicity is additive and physical compatibility is not guaranteed.

Myth 4

“Filters solve crystallisation.”

They may reduce burden, but do not reliably clear unstable mixtures.

**“Mixing local anaesthetics may buy you few minutes,
but often for the price of many hours.”**



SAME
SKILLS
DIFFERENT
BAR



SLEEP
BREATHE
HEAL
REPEAT



GOOD
Anaesthesia
BETTER
Days



Lidocaine
2%
(20 mg/mL)
Local Anaesthetic

Bupivacaine
0.5%
(5 mg/mL)
Local Anaesthetic

Levobupivacaine
0.5%
(5 mg/mL)
Local Anaesthetic

Ropivacaine
0.5%
(5 mg/mL)
Local Anaesthetic

Mepivacaine
2%
(20 mg/mL)
Local Anaesthetic

Prilocaine
2%
(20 mg/mL)
Local Anaesthetic

Chloroprocaine
3%
(30 mg/mL)
Local Anaesthetic

STERILE
INGREDIENTS
BRIGHTER
TOMORROWS

