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EDITORIAL

Double trouble? The pharmacological pitfalls of mixing local anaesthetics

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Yousef and colleagues present a rigorously designed randomised controlled trial that re-evaluates a longstanding but pharmacologically questionable practice in regional anaesthesia: the admixture of amide-type local anaesthetics (LAs) to purportedly optimise block characteristics. Their study, published in this issue of the *European Journal of Anaesthesiology*, challenges clinical assumptions that combining lidocaine with ropivacaine improves sensory onset without compromising block duration or safety.[1]

In a three-arm, blinded, active-controlled trial, the investigators compared a standard ropivacaine-alone regimen with two admixtures: a fixed dose of ropivacaine plus lidocaine-epinephrine, and a diluted ropivacaine dose plus lidocaine-epinephrine. Their principal finding – that admixture significantly shortened the duration of analgesia without improving sensory onset – carries both practical and theoretical implications, particularly regarding pharmacological interaction and systemic safety.

Pharmacodynamics and competitive channel binding: an unstable alliance

At a molecular level, both ropivacaine and lidocaine act as voltage-gated sodium channel blockers, but their pharmacokinetic profiles differ markedly. Lidocaine, with its relatively short half-life, moderate lipid solubility, and lower sodium channel affinity, is often used for rapid-onset infiltration and short blocks. Ropivacaine, in contrast, is a long-acting S(-)-enantiomer with reduced lipid solubility and lower cardiotoxicity relative to bupivacaine yet still displays dose-dependent and site-dependent systemic risk.

When these agents are co-administered, they compete for identical binding sites in the inactivated state of the sodium channel, potentially interfering with each other's ion channel dynamics. This nonlinear interaction may delay dissociation or alter channel affinity, affecting both efficacy and systemic toxicity. As noted by Nestor *et al.*,[2] such combinations do not behave as simple additive mixtures; rather, they form complex pharmacological interactions that can unpredictably reduce duration and exacerbate toxicity.

In the current trial, although the lidocaine admixture did not accelerate sensory onset, it clearly reduced the duration of ropivacaine action, even when the total dose of ropivacaine remained unchanged. This supports the hypothesis that admixture introduces competitive or dilutional effects that undermine block longevity, likely via faster systemic uptake or altered tissue binding kinetics.

Dilution, dose, and duration: the misconception of equivalence

A key strength of the study by Yousef *et al.* is its methodological clarity in differentiating between dilutional and dose-related effects. By comparing a fixed-dose and a reduced-dose admixture, they disentangle whether observed reductions in duration stem from total dose reduction or from the pharmacodynamic interaction between agents. Both admixture regimens shortened analgesia by several hours compared to ropivacaine alone, confirming that the mere act of mixing – independent of dose – modifies clinical effect.

This result is clinically relevant. In peripheral nerve blocks, where prolonged analgesia is often desirable, the rationale for admixture becomes tenuous if it neither accelerates onset nor sustains duration. The traditional belief that 'fast plus long equals best' appears outdated considering both empirical evidence and pharmacological principles.

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Systemic toxicity and the myth of safe mixtures

Local anaesthetic systemic toxicity, while rare, remains a life-threatening complication with central nervous system and cardiovascular manifestations. The literature increasingly discourages the practice of mixing amide-type LAs due to unclear metabolic interaction and dosing uncertainty.[3] Unlike ester-type agents, which undergo rapid plasma hydrolysis, amide-type LAs share hepatic metabolic pathways – mainly via CYP1A2 and CYP3A4 – introducing a risk of enzymatic competition and accumulation, especially in vulnerable populations (e.g. liver dysfunction, extremes of age, pregnancy and obesity).[4]

Yousef *et al.*[5] adhered to Danish dosing guidelines (ropivacaine ≤4 mg/kg; lidocaine with epinephrine ≤7 mg/kg) and appropriately excluded low-weight and high-BMI individuals to reduce risk. Still, international variation in maximal permissible doses highlights the lack of harmonised, evidence-based standards. For example, ropivacaine's maximum allowable dose varies between 200 mg in some countries in Europe and 300 mg in the United States. Moreover, dosing based on actual body weight is increasingly considered pharmacologically unsound – particularly in obese or pregnant patients where plasma protein binding and volume of distribution are substantially altered.

Site-specific absorption and the role of epinephrine

The infraclavicular region is relatively low in vascular absorption compared to intercostal or epidural sites, but systemic uptake can still occur – especially when vasodilatory agents are used. Ropivacaine possesses intrinsic vasoconstrictive properties, which slow systemic uptake and extend duration. Lidocaine, in contrast, is a vasodilator; hence, the addition of epinephrine in this trial was pharmacologically prudent.

Epinephrine reduces peak plasma concentrations and modestly prolongs block duration – typically by approximately 1 h – through its vasoconstrictive effects.[6] However, this mechanism is not always sufficient to counteract the pharmacodynamic and metabolic consequences of mixing local anaesthetics. The findings of the study reinforce that even with epinephrine, the admixture failed to achieve a block duration equivalent to that of ropivacaine alone.

Precision over tradition: a modern framework for regional anaesthesia practice

This trial contributes to the growing body of literature calling for a rational, evidence-based approach to LA use. While admixture may appear intuitive, it fails under scrutiny. In contrast, the trend in modern regional anaesthesia favours individualised dosing (based on ideal body weight, attention to hepatic clearance capacity and consideration of α_1-acid glycoprotein fluctuations)[7] and the use of regional anaesthesia adjuvants. Different drugs (clonidine, dexmedetomidine, buprenorphine, ketamine, magnesium and dexamethasone) and application routes (perineural and intravenous) have been investigated to increase the duration of analgesia, decrease the incidence of rebound pain and to shorten the onset time.[6] It has to be emphasised that the perineural route of all adjuvants is 'off-label' use. Based on moderate-quality evidence, intravenous dexamethasone offers currently the best efficacy[8] – 8 mg intravenous is equally effective compared to 4 mg perineural dexamethasone[9] – is not 'off-label' use and has only a low number of adverse events (e.g. compared to dexmedetomidine).[10]

Finaly, ultrasound-guided regional anaesthesia now allows for lower volumes, targeted deposition and safer block execution – all of which minimise systemic absorption and the need for pharmacologically complex mixtures. Nevertheless, any LA administration should be performed with full resuscitative preparedness, including immediate access to lipid emulsion therapy for LAST management.

Conclusion

Yousef *et al.* deliver an elegant and clinically relevant reminder that not all traditions in anaesthesia withstand pharmacological interrogation. Their trial provides robust evidence that admixture of lidocaine with ropivacaine in infraclavicular blocks reduces analgesic duration without improving onset – a result consistent with known pharmacodynamic principles and toxicity mechanisms.

Safe dosing of LAs in regional anaesthesia requires a careful balance between analgesic efficacy and toxicity risk, informed by pharmacology, patient physiology, and precise technique. Practices like mixing multiple amide-type LAs – despite lacking evidence – introduce unnecessary complexity, unpredictable interactions and a heightened risk of systemic toxicity. These pharmacologically irrational combinations offer no proven benefit and may undermine both safety and efficacy. As regional anaesthesia advances, abandoning such outdated habits in favour of evidence-based, individualised strategies is essential to delivering safe, high-quality care. In an era where regional anaesthesia is increasingly central to perioperative care, Yousef *et al.* underscore the importance of simplicity, safety and scientific rigor in LA selection. The message is clear: rational monotherapy – appropriately dosed and guided by physiology – in combination with an intravenous adjuvant (like dexamethasone) should remain the foundation of safe and effective regional anaesthesia.

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