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EDITORIALS

Intravenous lidocaine, regional blockade, or both: considerations for multiple interventions involving local anaesthetics

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It is our choices, Harry, that show what we truly are, far more than our abilities.

Professor Dumbledore to Harry Potter

J. K. Rowling, *Harry Potter and the Chamber of Secrets*, 1998

Recently, Foo and colleagues[1] published consensus guidelines on the use of i.v. lidocaine, prompted by a death reported to the Safe Anaesthesia Liaison Group of the Royal College of Anaesthetists. Although the accompanying editorial[2] clarified that these guidelines are not endorsed by Safe Anaesthesia Liaison Group or its parent organisations and should be considered only as expert opinion of the individual authors, the absence of any national or international guidelines puts the onus for safe practice on individual practitioners. One of the recommendations was that 'i.v. lidocaine should not be used at the same time as, or within the period of action of other local anaesthetic interventions'. Specifically, they noted 'do not use within 4 h' as applying to any nerve or fascial plane block, or infiltration of laparoscopic port sites, or epidural use. The clinical implications of this recommendation were not discussed by the guidelines group or in the editorial. Our premise is that this 4 h rule is problematic and limits the usefulness of the proposed guidelines. At the same time, this is an opportunity to recognise the implications of any combination of local anaesthetic interventions, which we refer to using a new term, Multiple Interventions of Local ANAesthetics (MILANA [MILANA in Sanskrit refers to 'mixing' or 'union' or 'coming together']), and an opportunity to consider potential strategies to minimise the risk of local anaesthetic systemic toxicity (LAST).[3]

Why is the 4 h rule a potential problem?

Physicians are currently eager to adopt medications and techniques that might improve pain relief and minimise opioid use, often in the setting of enhanced recovery pathways.[4] For this reason, a variety of locoregional analgesic strategies including i.v. lidocaine infusion therapy have found enthusiasts. However, there is the problem of mismatch between enthusiasm and evidence for many of these interventions.[5] These range from potentially harmful to overtly harmful, such as the use of both NSAIDs and cyclooxygenase-2 (Cox-2) inhibitors on the same patient, leading to acute renal failure.[6]

Recently, there has been an explosive growth in the use of peripheral regional analgesic procedures, especially fascial plane blocks.[7] One can find more than six different regional analgesia techniques currently being used or advocated in

breast surgery,[8] although the relative merits of each are still unclear.[9] At the same time, there is an argument for using i.v. lidocaine in breast surgeries, specifically considering its effect on chronic post-surgical pain.[10,11] Similar observations can be made for other surgical procedures. Despite not being administratively approved, the use of i.v. lidocaine is now widespread, as noted by the Safe Anaesthesia Liaison Group,[2] and also by a 2020 survey of Australian and New Zealand anaesthetists where >50% of respondents reported using it.[12] I.V. lidocaine has also been suggested as part of enhanced recovery after surgery (ERAS) protocols, apart from its use as an adjuvant or supplement to locoregional anaesthesia.[13]

Although a precise measure of the 'combined use of i.v. lidocaine plus locoregional procedures' is not possible, it is likely more common than recognised. We are aware of such practices at many centres and of many variations in their approaches. In a survey of Scottish hospitals 44% had no policy on combined use,[14] and the Australia–New Zealand survey found that only 37% of anaesthesiologists turned off i.v. lidocaine before a regional block, 44% reduced their dose of local anaesthetic for regional block, and 41% had unrestricted use.[12] These observations suggest there could be considerable dissent among practitioners or settings against this 4 h rule. Moreover, what would be the impact of this rule on the legal exposure for an anaesthetist or a perioperative team in the event of a random mishap, such as after i.v. lidocaine and port site infiltration? Similarly, what would be the implications of this rule on the multiple perioperative lidocaine infusion trials that have been approved by ethical committees or medical regulatory authorities,[15] or practices following ERAS-approved protocols? We recognise many practical barriers for implementing the proposed clinical practice advice. These barriers result in part from the myriad variations and nuances in real-world clinical practice.[16] Nevertheless, such barriers must not ignore the fundamental risk of LAST when combining multiple sources of local anaesthetic administration, including i.v. lidocaine by bolus (e.g. at induction of general anaesthesia) or by infusion.

LAST with MILANA

The rationale for the 4 h rule is that combining i.v. lidocaine (in any dose and duration) with any additional mode of locoregional local anaesthetic intervention increases the chances of LAST. Unfortunately, objectively quantifying the risk in general or for a specific patient is not possible because it depends on so many factors, both knowable and unknowable. MILANA implies any combination of two or more different regional anaesthetics[17] or regional anaesthesia plus i.v. lidocaine. Conceptually, any MILANA predisposes the patient to LAST when it increases the total dose or duration of local anaesthetic the patient receives. Despite the well-known shortcomings of standard maximum dose recommendations, the simplest clinical approach to reducing the risk of LAST is to estimate the maximum amount of a local anaesthetic that is safe for each given patient.[18] With a combination of local anaesthetic agents, one can estimate the fraction of the estimated limit for each agent and assume a simple, additive effect for each local anaesthetic and route. However, there is greater complexity and challenge when two or more different methods of administration are being used to achieve different clinical effects.[19] Factors contributing to this complexity include differences in absorptive area, the characteristics of surrounding structures, and differences in patient susceptibility.[20,21] Holborow and Hocking[22] reviewed several studies performing bilateral brachial plexus blocks and attempted to reconcile the challenges and provide safer strategies. However, present-day practice requires us to go beyond this scenario and also recognise that there is a dearth of scientific literature discussing these considerations.[23]

Caesarean delivery is a timely example, because of the known susceptibility of parturients to LAST,[23] and the increasing interest in the use of fascial plane blocks in this

Table 1 MILANA strategies. *A more accurate estimate of LAST incidence with lidocaine infusions requires monitoring that is sensitive to such physiological parameters. LAST, local anaesthetic systemic toxicity; MILANA, Multiple Interventions of Local ANAesthetics; TAP, transverse abdominus plane.

Techniques
• Choose techniques where minimum effective dose is small, such as selective root blocks of the brachial plexus, or inguinal nerve blocks.
• Consider alternatives to MILANA when targeting areas with high risk of LAST because of absorption characteristics (e.g. intercostal, paravertebral, or fascial plane blocks).[45]
• Fascial plane blocks are volume dependent.[7] Ensure lower concentrations and minimal doses, especially for midline surgeries needing bilateral blockade.
*Intravenous lidocaine**
• Lidocaine metabolism can be affected by the duration and direct effects of general anaesthesia and surgery on liver blood flow.
• No other continuous infusion of local anaesthetic should be administered when infusing i.v. lidocaine, before, during or after surgery.
• Consider subcutaneous instead of i.v. lidocaine infusion in post-surgical wards to minimise the risk of large inadvertent i.v. injection.
Dosing
• Despite mixed evidence around i.v. lidocaine, there is consensus that doses >2 mg kg^{-1} h^{-1} add little value.[43]
• Avoid excessive total doses and use reduced concentrations of local anaesthetic wherever appropriate, aiming for sensory blockade.
Timing
• Temporally space local anaesthetic administration. For example, if local anaesthetic in higher concentrations (4% lidocaine) is used for an awake intubation,[46] consider avoiding i.v. lidocaine or other locoregional block before, at or after induction.
• Consider using one local anaesthetic approach before surgery with the another at the end of surgery to avoid peak levels of local anaesthetic at the same time. This could affect the choice of locoregional blocks.
• Because of the many known and unknown factors, a specific time frame cannot be provided as safe. Toxicity has been noted even 3 h after a TAP block.[33]

population.[24] There are more than 50 reports, three network meta-analyses, and multiple other reviews on the topic of transverse abdominal plane (TAP) block or quadratus lumborum block for Caesarean delivery, just within the past 3 yr. Results from these meta-analyses suggest uncertain or minimal additional benefit from either block over intrathecal morphine or wound infiltration[24,25]; nevertheless, several variations of regional block continue to be advocated for Caesarean delivery.[26] Among the reported trials, patient convulsion caused by toxicity was reported in two studies,[27,28] with one of them being terminated for that reason, although the overall incidence of LAST in obstetric anaesthesia was low in a recent UK survey.[29] Susceptibility of a given patient population is an important consideration, and the perceived safety of using an average adult dose can be misleading. For example, toxic bupivacaine levels and LAST symptoms were observed in 18% of women receiving bilateral TAP blocks with bupivacaine 100 mg in addition to spinal anaesthesia.[21] In contrast, higher doses of local anaesthetic can be tolerated with no toxic levels in a less susceptible adult population having the same regional technique.[30]

Higher doses, higher risk

The literature consistently shows that higher doses of local anaesthetics pose higher risk,[31–33] even with i.v. lidocaine. Dosing based on actual body weight leads to higher doses and potential toxicity, and hence ideal body weight should be preferred.[34] Furthermore, assuming lidocaine observes first-order kinetics, steady-state concentrations during prolonged infusions are strongly influenced by the dose rate.[1] Studies looking at local anaesthetic plasma concentration in truncal regional blocks highlight similar issues. Among 15 studies with 381 patients having either perioperative TAP or rectus sheath blocks (RSBs), 33 patients (9%) had plasma concentrations above toxic thresholds as defined by the authors, with most being related to the injection of 'high doses'.[32] High doses continue to be used for both TAP and quadratus lumborum blocks in many recent studies, although the literature indicates minimal additional benefit is achieved with doses greater than 15–20 mL per side using a concentration of 0.125–0.25% bupivacaine or ropivacaine.[24,35,36] For example, in a review specifically comparing high-dose *vs* low-dose local anaesthetic for TAP block with Caesarean section, eight of the 14 trials (57%) used a 'high dose' of bupivacaine equivalents (mean, 147 mg), or roughly 60–100 mg per side.[36]

Other factors

Other determinants such as the type and time of the block performed are critical in establishing peak local anaesthetic plasma levels and the development of symptoms. For example, plasma levels with RSBs consistently peak later than with TAP blocks.[32] Other sources of local anaesthetics that are often unaccounted for include the use of topical anaesthetic for securing the airway or preventing airway complications,[37,38] i.v. lidocaine at induction of general anaesthesia, and local infiltration analgesia performed by the surgical team,[39] sometimes without informing the anaesthetist.[40] Local infiltration analgesia has been used to support multimodal analgesia.[41,42] In comparison with other methods, local infiltration analgesia is technically easy, does not require image guidance, and can be performed either before or at the end of surgery. There are also many variations in its dosing and approach: single injection, continuous catheter infusion, and tumescent local infiltration analgesia.[42] These may involve very high volumes and doses of long-acting local anaesthetics for efficient wound infiltration.[41] The same patients could receive other local anaesthetic interventions, such as peripheral nerve blocks. The use of i.v. lidocaine in MILANA further complicates matters because local anaesthetic is introduced directly into the vascular compartment and requires close monitoring for safe administration often over a long period.

Strategies to prevent LAST with MILANA

I.V. lidocaine is commonly given as a bolus before incision, then often as an infusion during surgery.[43] Adhering to the 4 h rule limits subsequent analgesic choices to either i.v. lidocaine or locoregional options, and may be difficult to reconcile with many ongoing clinical practice strategies. Including dose limits for MILANA techniques has been considered in some recent trials,[11] but they cannot establish safety because of varying determinants and small-sized trials. Therefore, it is important to identify strategies to minimise LAST in MILANA. It is instructive to consider the following examples: knee arthroplasty under spinal anaesthesia with adductor canal block performed before surgery and high volume periarticular infiltration at the end of surgery[17]; mastectomy with two different fascial plane blocks administered before surgery[20,44]; and subtotal colectomy with i.v. lidocaine at incision and during surgery plus TAP block performed at the end of surgery.[13] All of these reflect real-world practice and fall under MILANA, but each presents a different risk of LAST because of the different pharmacokinetic variables. Therefore, defining one set of local anaesthetic doses, approaches for administration, and timing such as the 1 h gap suggested by Holborow and Hocking[22] between two brachial plexus blocks cannot suffice for all MILANA variants. We should ensure that detailed and open communication with the surgeon and the perioperative care team about the planned total local anaesthetic dose and anaesthetic approaches, is included for all cases during the preoperative surgical checklist verification. The general procedures to minimise LAST still apply (e.g. ultrasound guidance when possible; frequent aspiration and incremental dosing); educating perioperative physicians to recognise and treat LAST is equally important. As an approach, avoid MILANA as much as possible in susceptible populations (e.g. older individuals, lower weight or small muscle mass, pregnancy, organ [especially cardiac] dysfunction, hypoxaemia, acidaemia, and possibly epilepsy).[45] We propose the strategies in Table 1 for MILANA.

As physicians, we all try to do our best by implementing practices and interventions that improve patient outcomes. However, performance of multiple interventions, under the assumption of additional benefit, may translate into incremental risk rather than value for many patients. It is not always about 'knowing' how to do an intervention, but more importantly about 'knowing how much' to do, or 'knowing when not' to do something at all. Procedure-specific and patient-specific considerations should help us to make better decisions. We suggest that future studies and reviews including combined local anaesthetic interventions consider implications of MILANA and assess assessing both safety and effectiveness.

Declarations of interest

GW is an officer and shareholder of ResQ Pharma, Inc. (Chicago. IL. USA). HS declares that they have no conflicts of interest.

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Evidence-based guidance for use of intrathecal morphine as an alternative to diamorphine for Caesarean delivery analgesia

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Summary

Intrathecal morphine in combination with fentanyl is an effective and safe alternative to diamorphine for Caesarean delivery analgesia. Evidence suggests minimal differences in clinical efficacy and side-effects between intrathecal morphine and diamorphine. Recommended intrathecal morphine doses for Caesarean delivery analgesia are 100–150 ug.

Keywords: analgesia; Caesarean delivery; diamorphine; intrathecal; morphine; neuraxial; opioid

There is nothing permanent except change.

Heraclitus

Pain after Caesarean delivery is a leading concern for women, and inadequately controlled pain may increase opioid consumption, delay functional recovery, and negatively impact maternal–neonatal bonding and breastfeeding.[1,2] Spinal anaesthesia is the most common technique for elective Caesarean delivery, and as such readily facilitates intrathecal opioid administration. Neuraxial opioids (such as morphine or diamorphine) are considered an essential part of a multimodal post-Caesarean delivery analgesic strategy.[2–5]

In the UK, single-dose diamorphine is the recommended neuraxial opioid for Caesarean delivery[4]; however, outside the UK, intrathecal morphine is the most commonly administered neuraxial analgesic in this setting.[2,3,6] Recent drug shortages