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Commentary: Postoperative Use and Early Discontinuation of Intravenous Lidocaine in Spine Patients

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Our author group's publication *Postoperative Use and Early Discontinuation of Intravenous Lidocaine in Spine Patients* published in "Spine Deformity" outlines initial results of an intended line of investigation exploring our experience utilizing intravenous lidocaine for improving perioperative pain in posterior lumbar fusion. The primary aims appear to be met, acknowledging limitations in retrospective design. We contributed adverse outcome data of a unique 48-hr lidocaine infusion protocol in an otherwise minimally-studied population and confirmed our hypothesized comparable discontinuation rate between adult and pediatric populations. However, the implications of these aims (and intended future study) reach deeper.

The opioid pandemic has provided ongoing torment to global society for decades, which is most recognized in adults[1]. Largely underrecognized is the trickle-down effect that is impacting children and adolescents[2]. This includes inpatient impact, where pediatric patients may demonstrate persistent opioid use (beyond 3 months) in trauma[3] and post-surgical populations[4], with resultant outpatient implications on later use[5,6].

Naturally, a movement towards advancing multimodal analgesic strategies and identifying novel opioid-sparing therapies has spawned, however existing trials in adults far outweigh that in pediatrics. This is multi-factorial. The adequacy of pediatric patient volume remains a significant barrier. Brewster and colleagues identified recruitment failure as the predominant reason for early discontinuation of clinical trials, which is over 10%[7]. There is statistically significant discrepancy in funding of drug trials in pediatrics, which are primarily funded by government and nonprofit organizations with limited budgets, as opposed to adult studies primarily sponsored by industry (36.6% peds vs 64.7% adults)[8]. Additionally (and appropriately), a strict emphasis on safety is adherent to pediatrics, both by research regulators such as institutional review boards and the Food & Drug Administration, as well as clinical policing by pediatric practitioners. The latter of those was subtly present within this publication, and likely confounds interpretation of lidocaine safety data and discontinuation rate within this paper.

Systemic lidocaine infusions are, quite frankly, ~not used in pediatric critical care units for adjuvant analgesia. Drug familiarity comes primarily through rare encounters with ventricular arrhythmias. Protocols are therefore underdeveloped on how to

uniformly respond to its' adverse profile. Compounding this, lidocaine side effects include black box warnings including "cardiopulmonary arrest" and "death"[9]. Generally, there is a stepwise progression in lidocaine symptoms from mild to severe[10,11], however children may be less interpretive of early symptoms than adults. And while lidocaine pharmacokinetics have a well-established threshold for toxicity[12], serum levels are not readily obtainable (results often measured in ~days), especially for aiding in acute decisions such as whether to discontinue an infusion. Its' toxic potential and need for continuous cardiac monitoring typically disallow use outside of a pediatric ICU (contradictory to some adult practice). The above are true at our institution and lend towards an [respectable] innate bias for intensivists to more readily discontinue the infusion.

With this background in mind, further reflection on this paper can be supplemented by the following questions:

What is gained by examining the study's primary outcome: 'lidocaine discontinuation rate'?

The comparison of this data in pediatrics vs adults is essentially non-existent, and therefore adds to an otherwise paucity of data. At an intra-institutional level, we were interested in whether pediatric perception of lidocaine's toxic potential was altering the ability to complete the intended 48-hr infusion protocol compared to adults, as well as further understand the overall side effect profile for potential guidance in future protocols. Ultimately, we observed no statistical difference in children vs adults. Although this was hypothesized in the publication, it was surprising to some given the natural tendency towards safety in pediatrics.

While interesting, the question's answer may actually be 'nothing' – the outcome itself does little to guide any clinical decision-making at the bedside. The discontinuation rates (40% pediatric, 52% adult) were also highly discrepant compared to some existing literature of other lidocaine infusion protocols discontinuation rates[13,14,15]. This difference is driven – at least in part – by differences in study design, highlighting a fundamental challenge in clinical pain trials. Working groups have begun attempts at creating unifying sets of study variables[16,17], which will be utilized in future studies.

Is the discontinuation rate interpretable?

We think yes, though within the realm of the design. As acknowledged in the manuscript, the retrospective nature of the study is fundamentally dependent on accurate and comprehensive documentation, especially in deciphering risk profile. Eight pediatric patients (and an additional three adults) did not have a chart-identified reason for discontinuation, which, at least in the pediatric cohort was [anecdotally] suspected secondary to early transfer out of PICU. This alludes to the daily systems-based challenge of navigating patient bed capacity (a national problem)[18] alongside a national nursing shortage (local hospitals with up to 17% nursing vacancy)[19]. The daily manipulation of patient flow through the ICU is a bit akin to "musical chairs", albeit with significantly more weight. Often transferring a non-critical patient out of the PICU trumps the use of an off-label or investigative therapy. This is an inherent confounder which may be difficult to control for in this population with a prolonged infusion.

Is the infusion protocol optimized for study purpose?

Another intriguing finding was the number of patients who experienced lidocaine side effects but did NOT have their infusion discontinued. This at least to a degree combats the theory that enhanced anxiety driven by lidocaine infusions resulted in early discontinuation. To a higher degree, though, it likely speaks to a non-uniform decision-making model of the clinician team regarding lidocaine use, and the overall difficulty in the interpretation of side effects. As is outlined in the paper's table 1 (modified from Beecham et al. and Hall et al.)[11,20], a number of side effects overlap with those that can be seen with opioids, including some encountered in table 2 of our study: nausea/vomiting, hypotension, lethargy, confusion, obtundation, respiratory failure. Attributability of these side effects specifically to lidocaine [or any study drug in acute pain trials] is therefore extremely difficult and often subjective in critically ill patients with complex problem lists. This is one limitation that challenges the justification of trialing exploratory medications for decreasing opioids, especially given some of the severe side effects that can (coma) and were (respiratory failure, arrhythmia, hypotension) observed.

Some suggested highlights of a future pediatric protocol are provided below (aimed at evaluating effect on opioid), though a retrospective review of opioid usage is underway:

- **Population:** age <18 years receiving a posterior spinal infusion consenting to study; exclude if hypersensitivity to lidocaine or other amide-type anesthetic or corn, known arrhythmia.
- **Dosing**: *IV Lidocaine 1 mg/kg/hr infusion (per ideal body weight) for duration of OR analgesia through AM of POD2 randomized 1:1 vs control normal saline infusion* – emphasis on ability to maintain infusion without external reasons for discontinuation.
- **Standardized Decision when encountering potential lidocaine side effect**: *stop infusion, do not restart* – would prioritize safety until better opioid-sparing efficacy is established, though could

consider restarts or dose-decreases; this requires some discretion to physician (anesthesiologist or intensivist) given that a number of side effects WILL be encountered (hypotension in OR, nausea, etc.).

- **Variables**: opioid use during lidocaine infusion (oral morphine equivalents according to Nielsen et al.[21]), pain scores at 1 hour and every 6 hours during infusion, lidocaine total dosage, side effect prevalence and relation to lidocaine, PICU length of stay, Hospital length of stay, considerations of others.

Are post-operative spinal fusion recipients the 'right' population for this infusion protocol?

On one hand, these patients do not have as significant an opioid burden (0.45 ME/kg/d first 48 hrs)[22] as some other ICU populations, for example [arbitrarily] total pancreatectomy with islet autotransplantation (1.76 ME/kg/d first 7 days)[23], thereby lending less potential impact on sparing opioid use. On the other hand, this population is isolated specifically to analgesic need. There is no confounding sedative need [generally], as is the case in many post-operative ICU populations requiring mechanical ventilation, at least in their early course where opioid burden tends to be the highest. For perspective, dexmedetomidine and fentanyl (or other opioid) regimens are mainstays for early sedative agents in intubated children, both which have at minimum concurrent adjuvant analgesic properties. These countering points contribute to the significant challenge of designing acute pain studies for identifying novel opioid-sparing therapies in the critical care unit.

On a simpler level, though, the 'right' population may be reframed as any patient(s) that experiences improved pain while minimizing iatrogenic side effect. Lidocaine infusions in some studies site NO toxicity[22]. Opioids have a noteworthy host of meaningful side effects including pediatric delirium[24] constipation[25], and risk of withdrawal[26], particularly at higher doses and duration. They have nonetheless remained a staple postoperative analgesic, and comparing downstream clinical effects of them vs other study drugs in acute pain remains a topic of interest. Unfortunately, this study did not look at lidocaine infusion's effect on patient pain experience or opioid burden. Though this is a current next step, determining clinical confidence of an adjuvant medication's beneficial effect on pain is inherently difficult. Pain is extremely complex by both physiologic and psychologic mechanisms. Studies frequently defend conclusions based on statistical significance of pain score changes, however these are difficult to interpret, subjective/personal to the individual patient, and not uniformly obtained or documented[27,28]. The consensus panel of PROMPT and IMI-Care provided recommended variables to determine clinical benefit from acute pain studies, though include some measures that are not routine or easily collected for study, and interestingly exclude opioid dosing consumption, which, similarly to our own vantage, is refuted by some[29]. This should be rudimentary in studies targeting opioid-sparing modalities.

The future line of this study will benefit from optimization and uniformity of protocol, prospective randomization, and evaluation of efficacy, all with potential obstacles. Research challenges aside, stop the opioid crisis.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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