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Intrathecal "Microdosing": Reality or Artifact?

To the Editor,

Hamza and colleagues merit commendation for conducting a prospective study on non-cancer-pain patients receiving intrathecal (IT) therapy [1] using the concept of "microdosing"—the practice of weaning patients off systemic opioids prior to implanting an IT drug delivery system (IDDS) using very low opioid dosage. A number of elements, however, remain unresolved and unexplained in relation to hypothesis, design, and execution of the current study.

The unproven theory of "microdosing" deserves a close look. The premise of placing an IDDS traditionally centered on providing better analgesia with lesser side effects compared with systemic opioids [2]. However, patients who require higher IT opioid doses at the trial stage receive significantly higher IT opioid amounts after implant than patients needing lower IT trial opioid doses [3] and report worse pain scores [4]. A small retrospective study suggested that "microdosing" results in sustained pain relief without the need for supplemental oral opioid dosages [5]. Similar findings were encountered in the current study by Hamza and colleagues [1]. While these findings are significant, it remains unclear why patients who could tolerate being weaned off systemic opioids would need to have an implanted IDDS infusing low-dose IT morphine. Weaned patients may just be managed off opioids or placed on low-dose oral opioids which may be perceived more effective after weaning [6,7]. Certainly, randomizing patients to low-dose systemic opioids or no opioids vs IT "microdosing" would be necessary to answer such questions. This was not accomplished in the current study. Comparative effectiveness research studies are sorely needed in the field of interventional pain medicine and in particular with IT therapies.

The trial methodology is equally intriguing. It is unclear whether patients were trialed in-house or outpatient. Through a percutaneous IT catheter (unspecified gauge and type), patients were administered one of three injectates in a random order: normal saline, 0.25 mg morphine, and 0.5 mg morphine. The injections were performed 24 hours apart and were administered in a single-blinded fashion. Improvement in pain scores and function (both unspecified) and failure to respond to IT saline determined a successful trial. Of 61 trialed patients, three were reported to have had greater relief with the normal saline than the opioid [1]. It is unclear if these saline responses were better than the 0.25 mg or the 0.5 mg IT morphine dose or both doses. In a retrospective study, Dominguez and colleagues employed a similar paradigm using 0.5 mg IT morphine single dose (through lumbar puncture) inpatient IT trial. If a patient had >50% pain relief but suffered excessive side effects, a 0.25 mg dose was administered the next day. If inadequate pain relief was noted, a 1.0 mg IT morphine dose was then administered the next day. A nocebo, such as normal saline was not used, however [3]. Demonstrating a dose–response effect of a pharmacological agent is an important principle in efficacy studies. Hamza and colleagues unfortunately do not describe the relative analgesic effects of the 0.25 mg and 0.5 mg IT morphine doses. If the response to IT morphine reflects analgesic efficacy, greater pain relief is to be expected with the 0.5 mg dose. Using this logic, one should consider an IDDS implant only in patients who do not display an analgesic response to normal saline and respond better to the 0.5 mg IT morphine dose than the 0.25 mg dose. Such a triple-block paradigm has been used successfully in cervical medial branch nerve blocks to diagnose facet-mediated pain [8]. More than three patients would then have to be excluded [1], if this paradigm is applied.

Implanting the IT catheter under general anesthesia, as done in this study, may be controversial especially in previously operated patients [9,10]; the needle entry point being at L4-L5 in all patients is also intriguing (and technically unfeasible in some patients) given previous lumbar spine surgeries and fusions. Additionally, given that 88% of patients had back pain, an additional more specific back pain outcome measure such as the Oswestry Disability Index or the Roland Morris Questionnaire would have provided useful data in this prospective study. Importantly, reporting the opioid dose escalation data starting at 6-month post-implant may be misleading when contrasted to all other studies that describe opioid dose escalation relative to the IT starting dose at implant; not relative to the 6-month mark. Nonetheless, the IT morphine daily dose at 6 months and 1 year post-implant is quite high in this study (1.4 mg/day) compared with the only other "microdosing" study which reported only 335 μg/day IT morphine at 1 year post-implant [5]. The reasons for the discrepancy are unclear and may have to do with trialing methodology and dosage. However, opioid dose escalation did occur in the study by Grider and colleagues from an average dose of 140 μg/day at implant to 335 μg/day [5] and in the study by Hamza and colleagues presumably from 0.5 mg/day to 1.4 mg/day [1].

In summation, the clinical usefulness of IT "microdosing" remains indeterminate. Not unlike oral opioid administration, IT administration is associated with similar problems of tolerance [11,12] and opioid-induced hyperalgesia [13]. Certainly, a lower opioid dosing regimen is better at minimizing side effects and IT "microdosing" appears to accomplish that in patients who are able to wean off systemic opioids prior to the implant. However, weaning may not always be possible, especially in patients with cancer-related pain [12]. Curbing IT opioid dose escalation may be accomplished otherwise by avoiding implants in

younger patients [11] and coadministration of bupivacaine with the opiate from the outset of IT therapy [14]. Both studies available on IT "microdosing" report absence or near absence of oral opioid dose consumption in implanted patients [1,5]. However, Kim and colleagues have reported nil oral opioid doses in IDDS-implanted patients. This was part of the care path protocol for implanted patients, which did not include "microdosing" [4].

More prospective studies are needed to answer many questions related to IT therapies in chronic non-cancer pain. Overcoming limitations of patient recruitment, inadequate study design, and limited U.S. Food and Drug Administration-approved IT analgesics may require multifaceted collaboration among clinicians, industry, and regulatory agencies.

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