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Perioperative Pain Control in Patients Receiving Intrathecal Morphine Infusion for Chronic Pain: Does it Matter how we do it?

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Intrathecal opioid infusion therapy has been increasingly utilized since the 1980's, initially in patients with cancer pain, and subsequently in patients with intractable, chronic, nonmaligmant pain. By infusing a small amount of opioid into the cerebrospinal fluid in close proximity to receptor sites in the spinal cord, profound analgesia may be achieved while sparing some side effects due to a systemic opioid route of administration. Morphine is the only FDA approved opioid commonly used for intrathecal infusion therapy. The introduction of intrathecal opioid infusion has been considered one of the most important breakthroughs in pain management in the past three decades. With the ever increasing population of patients having implanted drug infusion pumps for chronic pain, perioperative pain management in this population has been increasingly encountered in clinical practice, as these patients become candidates for surgical procedures such as hip or knee replacement, or spinal fusion, etc. For many years, there has not been any guidelines, recommendations, or even consensus statements from all major pain societies either within or outside the US, pertaining to the utilization of opioids for perioperative pain control [1,2]. Although the Polyanalgesic Consensus Conference (PACC) panel of experts convened in 2000, 2003, 2007, and 2011 to make recommendations on the rational use of intrathecal analgesics based on preclinical and clinical literature to better treat chronic pain, the issue of perioperative pain management in patients with indwelling intrathecal infusion pumps was never addressed [3].

Previous appeals to the leading pain organizations/societies in an attempt to bring about guidelines or consensus statements in guiding utilization of opioid pain management in this problematic setting has been unsuccessful [3]. Due to the paucity of the literature, it is not surprising that quite often; we receive requests for consultation to help manage the perioperative pain in this patient population who undergo major surgeries. Questions most commonly asked are: "What to do with patient's intrathecal opioid infusion during surgery? (go up, come down, or terminate infusion), and "What to do for pos-operative pain control"? and "What about utilizing intrathecal opioid for acute pain management since the patient already has an intrathecal catheter in use for chronic pain"?

There is only one additional reference in the literature that addresses this increasingly encountered complex issue. Grider and colleagues reported their experience of successful perioperative pain control in 3 patients on routine intrathecal opioid infusion for chronic pain having surgical procedures, specifically a rectocele repair, a lumbar fusion revision, and acute burn injury respectively. While maintaining patients' original intrathecal opioid infusion throughout the surgical procedures, intravenous patient-controlled analgesia (IV PCA) hydromorphone was added post surgically, and gradually the patients were transitioned into an oral opioid regimen such as oxycodone or methadone [1]. It seems reasonable to assume that the routine intrathecal opioid infusion satisfies the baseline opioid requirement for the chronic pain component, while the IV opioid PCA (or oral opioid) meets the additional demand for the acute pain due to surgery.

Our clinical approach bears some similarity to that of Grider and colleagues, i.e., maintaining patients' routine intrathecal morphine opioid infusion perioperatively for their chronic pain, while adding another opioid (preferably non morphine) for post-surgical pain. Over the last 10 years, we have had over 100 cases of elective surgery done in patients on intrathecal morphine infusion, while following our recommendations, without experiencing any serious adverse events like respiratory failure, over-sedation, or accidental opioid overdose.

In general, we usually communicate with the corresponding surgical team regarding the postoperative pain control modality, prior to the procedure. If IV PCA is felt to be needed by the surgical team, either oxymorphone, hydromorphone, or morphine can be used. Most hospital staffs are familiar with using hydromorphone or morphine PCA, but not so with using oxymorphone, as it appears that oxymorphone is infrequently present on hospital formularies. However, the parenteral oxymorphone formulation has been available since 1959. Compared with morphine or oxycodone, oxymorphone is more lipophilic and therefore crosses the blood-brain barrier more rapidly [4]. Oxymorphone IV PCA was found to have a quicker onset, less sedation, less itching, better patient satisfaction, in comparison to morphine IV PCA [5]. White conducted a study in 120 patients following major orthopedic, urological, and gynecological surgical procedures, comparing the post-operative analgesia during the 72-hour post-op study period, using either subcutaneous (SC) PCA or IV PCA, when patients were randomized to receive either oxymorphone or morphine [6]. The author concluded that SC PCA is as effective as IV PCA. Further, the author suggested that using this PCA model and comparing the quantitative opioid usage between the two groups, oxymorphone seemed to be 2.9-3.4 times more potent than morphine, rather than 6-10 times more potent than morphine, as suggested by others [7].

If a parenteral PCA is not deemed necessary by the surgeon, then an oral opioid can be utilized. In our practice we usually start with oxycodone. Oxycodone is a semi-synthetic opioid with unique pharmacology (see below). Oral oxycodone for postoperative analgesia has been found to be more favorable than oral morphine in terms of better bioavailability, faster onset of analgesia, longer duration of action, less sedation, and less itching [8]. Oxycodone is a μ-opioid receptor agonist, despite some previous studies done in rat or mouse

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suggesting that the anti-nociception was mediated via κ-opioid receptors. It was later shown by others that the anti-nociceptive effects of oxycodone could be reversed by μ-receptor antagonists, not by κ-opioid receptor antagonists—indicating μ-opioid receptor activation rather than κ-opioid receptor activation during oxycodone analgesia [8,9]. In humans, κ-opioid receptor activation has been associated with psychotomimesis, such as disturbance in the perception of space and time, abnormal visual experience, depersonalization, and loss of self-control [10]. Our clinical observation of many patients who have been on oxycodone for variable length of time (but without psychotomimesis) does not support κ-opioid receptor activation in humans (personal observation).

It is rather intriguing when one considers that it has been shown that the central μ-opioid receptor affinity of oxycodone is 20 times less than that of morphine, and the concentration of oxycodone needed to activate the G-protein as measured by the (^{35}S) GTPγS agonist-stimulated binding is 3-8 times higher than that of morphine [11-13], yet oxycodone is at least equally potent or may be more potent than morphine following systemic administration [11,14]. This paradox has puzzled many researchers for many years, and as of yet, it is still poorly understood [8]. We speculate that peripheral μ-opioid receptors may be more involved in oxycodone analgesia than it is generally believed (our speculation only). Peripheral μ-opioid receptors have been found in the musculoskeletal system, visceral organs, peripheral sensory neurons, and the gastrointestinal tract [15-17]. Systemically administered centrally penetrating opioids may produce a substantial part of analgesia through peripheral opioid receptors [18]. There might be regional differences in oxycodone-induced analgesic responses via peripheral opioid receptors that contribute to the overall oxycodone analgesia. That would help to explain why systemic oxycodone has been found to be much more efficacious than centrally administered oxycodone [19,20]. Further, we believe oxycodone analgesia, especially in the setting of the patient already receiving intrathecal morphine infusion, might be most advantageous since there will be less central μ stimulation with using oxycodone than with using oral morphine, which may translate into less central μ-opioid receptor mediated side effects. Others have reported less hallucination and less itching with oxycodone as compared with morphine [21].

For many years, we have been quite satisfied with the result of post- surgical pain control in those patients who underwent surgical procedures while receiving intrathecal morphine infusion for their chronic pain, using the aforementioned approach. However, we have also encountered situations when oral oxycodone failed to provide satisfactory analgesia, despite deliberate dose titration; and the oral agent needed to be switched to hydromorphone, or oxymorphone, or other opioid in order to achieve effective analgesia.

The lack of literature, guidelines, recommendations, or consensus statements have resulted in physicians including pain specialists, anesthesiologists, and surgeons having much confusion regarding post-op analgesia, in the patient already established on intrathecal opioid analgeisia for chronic pain. We propose that specialists in analgesia/anesthesia work towards a "standard of care."

In our opinion, the field of perioperative pain management in patients on intrathecal opioid infusion for chronic pain, has been neglected and is sorely in need of attention, in view of the increasing popularity of intrathecal pain pumps currently in use for a variety of chronic pain situations. This is especially important from the medical-legal point-of-view, in order to minimize the potential for complications/adverse events, in our efforts to strive for the practice of good medicine. We urge pain specialists to rise to the challenge, working together, to develop practical "guidelines" to better treat our patients, and practice safe and effective evidence-based medicine.

It is for this purpose that this letter is written. It is our sincere hope that this correspondence will draw the attention of the national and international pain experts to develop guidelines for this increasingly encountered clinical dilemma, and hopefully lead to a collaborative effort among pain management experts so as to fill this "gap" in perioperative pain management.

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