Brief Commentary

Reinstituting the Bolus – New Reasoning for an Existing Technique

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Improved intrathecal (IT) pump technology is increasing the accuracy of IT opioid bolus dosing and promising advances in pain therapy. Opioid bolus dosing can be used with a minimal continuous infusion or it can function as the sole therapy. Bolus-only dosing is characterized by minimal use of opioid (often less than 1 mg of IT morphine). It achieves adequate pain control while reducing tolerance and possibly opioid-induced hyperalgesia. It may prevent receptor saturation, and provide a "washing out" of the opioid receptor that prevents the observed dose escalation resulting from continuous infusions. With new bolus dosing possibilities, IT pumps can be used earlier in the treatment algorithm instead of being a late-stage treatment for patients who responded poorly to conservative treatments. We hypothesize that morphine bolus-only IT dosing will have comparable adverse effect rates, and possibly increased safety as compared to the more conservative continuous delivery method. We further predict that bolus-only delivery will provide better therapy satisfaction, improved functional scores, lower 24 hour opioid dose, and less dose escalation.

Key words: Intrathecal morphine, patient-controlled analgesia, microdosing, decreased tolerance, bolus only - no continuous dosing

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Intrathecal (IT) patient-controlled bolus dosing, with a minimal or no continuous infusion, is surfacing as a promising therapy for chronic pain. Advanced imaging of cerebrospinal fluid (CSF) pulsatile motion provides improved models of drug distribution in the spinal cord (1). In parallel, recent advances in IT pump technology allow precise bolus administration (2) and provide novel uses for IT pumps earlier in the treatment continuum. Bolusing, with dramatic diminution in constant drug administration, may allow lower IT medication dose and decrease opioid-induced side effects while concomitantly lowering the incidence of tolerance and hyperalgesia. We are currently examining IT bolus dosing strategies that promise to reduce opioid dose escalation, reduce the complications of continuous infusions, and dramatically increase the safety and long-term viability of the therapy.

Historically, IT pumps were reserved as a late-stage treatment for patients who responded poorly to physical therapy, injections, and other conservative treatments. If these patients had a good response to oral or transdermal opioids but could not tolerate their side effects, IT delivery offered the advantage of decreased systemic dosing and potentially reduced side effects (3). Reduced reliance on systemic medications also decreased opioid diversion and the potential for intentional overdose (4).

Despite the advantages of IT drug delivery, limited knowledge of cerebrospinal fluid (CSF) flow dynamics poses a challenge to achieving a constant drug concentration at the spinal cord level. Recent radiographic and mathematical modeling suggests that the IT space is a non-homogenous, poorly mixed system (5). In addition to bulk flow, there is pulsatile CSF flow that results from

changes of blood volume in the craniospinal cavity (6). Due to a renaissance in technological imaging, pulsatile flow can be visualized and studied by phase-contrast magnetic resonance imaging (PC MRI) (1). Pulsatile flow is believed to be the main determinant of drug concentrations in different regions of the spine. Studies on continuous drug distribution in the spinal cord of ambulatory pigs show that, contrary to common belief, a pulsatile CSF does not widely circulate within the subarachnoid space. Morphine distribution remains limited and nonuniform even after prolonged (14 days) continuous IT infusion (5).

Existing models of IT pharmacokinetics and pharmacodynamics suggest that drug spread depends on the rate and volume delivered and is affected by the physiochemical properties of the drug. The historically preferred method employs a low volume, slow and continuous infusion of opioid. However, these findings lack prospective investigative support (7,8). Animal studies and recent models of CSF flow indicate that bolus IT administration results in greater drug distribution than a continuous infusion, due to the kinetic energy imparted to the injected solution. Bolusing may also eliminate the risk of granuloma formation that results from high concentrations of opioids at the tip of continuous flow catheters where there is poor dilution into the CSF (5).

A patient-controlled bolus dosing technique is a variant of microdosing, characterized by minimal use of opioid (less than 1 mg of IT morphine) to achieve adequate pain control while reducing tolerance and opioid-induced hyperalgesia (4). It may prevent receptor saturation and provide a "washing out" of the opioid receptor that prevents the observed dose escalation resulting from continuous infusions. The concept has been used successfully in intravenous patient controlled analgesia (IV PCA) and has resulted in improved analgesia at smaller total opioid doses (9). Bolus-only dosing, employing a combination of local anesthetic and opioid, has also been used in the epidural space for parturients during labor (10).

While a bolus-only technique is applicable to patients with intermittent pain, it may not benefit patients who have constant and severe pain, such as cancer patients. It is not an appropriate technique for patients with altered mental status who may not be able to understand the bolus feature on their pump. There is an increased risk of respiratory depression and sedation in patients with moderate to severe lung disease, obesity, or advanced age. Smaller bolus doses have to be used in these patients. There is a risk of overdose and increased sedation if patients use the bolus feature infrequently and become opioid naive between administrations. To counter this risk, the programming protocols of the newer pump systems with bolus capacity prohibit patient-administered blouses in the setting of infrequent use. If the patient does not use the pump for several days, the bolus option is blocked and can only be unlocked by the physician.

IT bolus therapy of smaller opioid volumes with higher potency requires great pump accuracy. With recent advances in technology, some of the newer pump systems boast a 97.1% level of accuracy, as measured by DP ratio (the ratio of delivered drug volume to programmed drug volume) and a 90% confidence interval of 96.2 – 98.0%. Unintentional pump overdoses are eliminated in newer pumps that have double-gated micro valves (2). With these advances, and those noted above, the IT candidate can be positioned earlier in the pain treatment algorithm (11). IT opioid therapy is no longer reserved only for candidates that failed conservative treatment and can move to more opioid naive patients. Another advantage of the newer pumps is that drugs with narrow therapeutic windows, such as ziconotide, can be administered as a bolus, with improved safety margin and the possibility of fewer side effects (12). The complications associated with the implant of newer pump systems are similar to those of older pump models: procedural pain, nausea, and implant site pain (2). However, the newer pumps with bolus-only capacity are magnetic resonance (MR) conditional (13). If the reservoir volume is ≤ 1 mL at the time of the MRI scan, the safety valve will not close and the entire contents of the reservoir will be bolused to the patient. To avoid this, the reservoir must be emptied prior to the MRI procedure. The physician needs to determine if the patient will need alternate (intravenous) analgesics in order to be comfortable during the MRI. After completion of the MRI, an inquiry is necessary to verify proper pump function and a refill procedure may be required.

Advances in our understanding of drug distribution in the CSF and improved delivery systems facilitate new therapeutic techniques that reduce the chance of withdrawal and overdose. Through ongoing prospective studies, we are investigating the effects of bolus IT dosing in the treatment of non-cancer chronic pain. We hypothesize that morphine bolus-only IT dosing will have similar adverse effects, and possibly increased safety as compared to the more conservative continuous delivery method. We further predict that bolus-

only delivery will provide better therapy satisfaction, improved functional scores, lower 24-hour opioid dose, and less dose escalation over a period of one to 2 years. Our IT bolusing will be limited to FDA approved agents, specifically morphine. Arguably, neuraxial administration of combined synergistic agents may further reduce opioid requirements (14) and prove to be cost efficient (15). Whether improving the safety profile of existing medications or facilitating administration of new medications as they appear on the market, bolus IT therapy is surfacing as a viable solution for chronic pain.

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