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EFFECT OF FENTANYL, HYPERBARIC LIGNOCAINE AND INTRATHECAL BUPIVACAINE DURING SPINAL BLOCKADE

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Abstract:

The effects of volume and baricity of spinal bupivacaine on block onset, height, duration when it's associated with fentanyl and hyperbaric lignocaine are very effective but has many adverse effects. We conducted this review among published studies found in electronic medical databases such as; PubMed, Embase, up to the beginning of 2022. According to studies, the addition of clonidine to intrathecal bupivacaine provides longer-lasting postoperative analgesia than fentanyl, albeit with a greater sedative effect. Clonidine prolongs postoperative analgesia more than fentanyl, hence fentanyl is suggested when sedation is undesirable while clonidine is advised when sedation is acceptable.

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INTRODUCTION:

Spinal anesthetic is often used after cesarean section because it has numerous advantages, including less blood loss, early mother-child contact, and effective intra- and post-operative pain management. Hyperbaric bupivacaine is the most common local anesthetic (LA) given intrathecally during cesarean delivery. Several medications are administered intrathecally, either alone or in combination with bupivacaine, to guarantee an excellent sensory and motor block and prolonged post-operative pain control. It has been demonstrated that the addition of an opioid (e.g., fentanyl) to an intrathecally administered LA produces a synergistic analgesic effect [1] by reducing visceral pain, which improves the quality of the block [2], while also decreasing the required dose of LA, thereby ensuring hemodynamic stability. Additionally, it extends the duration of postoperative analgesia [3].

The growing use of intrathecal (IT) therapies for the treatment of chronic pain problems has necessitated the development of drugs other than morphine (the only commercially available FDA approved IT analgesic). A recent survey [4] revealed that 68% of the 413 pain practitioners who responded use bupivacaine in addition to morphine for intrathecal (IT) administration. This application is off-label and is conducted without regulatory authorisation. The objective of this study is to review and synthesize the key literature on IT bupivacaine's systematic evaluation. A review of bupivacaine stability, microbiology, preclinical toxicity, and pharmacokinetics will be presented in order to establish fundamental safety for the use of IT bupivacaine. A brief review of the literature on epidural bupivacaine is provided due to the abundance of data showing its safe usage and efficacy [5].

Adjuvants to local anesthetic agents, such as midazolam, neostigmine, clonidine, and opioids, might enhance the impact of subarachnoid block and prolong the duration of postoperative analgesia [6]. Wang et al. were the first to demonstrate the successful intrathecal injection of morphine, and practically all opioids have been utilized as adjuncts to local anesthetic agents since then [7]. Among all opioids, fentanyl is the preferred adjuvant due to its strength, fast onset, and short duration of action, as well as its decreased incidence of respiratory depression [8]. However, the inclusion of opioids as a local anesthetic adjuvant is related with adverse effects[9] such as nausea, vomiting, pruritus, urine retention, herpes labialis activation, and respiratory depression. The research in favor of nonopioid adjuvants led to the development of clonidine as a local anesthetic agent adjuvant. It has been proven that intrathecal clonidine enhances the impact of subarachnoid block and reduces the amount of local anesthetic required [10]. Additionally, intrathecal clonidine provides longer postoperative analgesia,[11] reduces shivering associated with subarachnoid block, and is devoid of the adverse effects associated with intrathecal opioids. As a possible adverse effect of this anesthetic approach [12], respiratory and hemodynamic dysfunction may ensue. Bupivacaine is the most often used local anesthetic for subarachnoid blocking in Cesarean section patients. However, intrathecal bupivacaine alone may not be adequate to provide full analgesia, even in the presence of a significant sensory block [13]. Due to the enhancement of subarachnoid block quality, the addition of intrathecal opioids to bupivacaine has been advocated for subarachnoid blockade in parturients undergoing cesarean section [14].

DISCUSSION:

Hildebrand et al. [15] examined the stability of bupivacaine using a fully implanted infusion system. The stability evaluation described in this publication indicates that both drug-material and drug-device stability and compatibility evaluations were performed. The significance of drug-material testing stems from the possibility that the materials of the pump could accelerate the rate of drug degradation or the development of unwanted byproducts. The drug-device stability evaluation verifies that, under the predicted conditions of actual use, the drug does not deteriorate, create byproducts, or adversely influence the operation of the device. The evaluation period used for this report was 90 days at 378C with continuous agitation; a predicted refill interval based on usual dose and flow rate needs. The evaluation duration for the drug-device testing was sixteen weeks. At the conclusion of each evaluation period, the concentration of drug analyzed (HPLC) was within 5% of its initial concentration. The established definition of stability [16] stipulates that at the stated time point, at least 90 percent of the active agent remains. In other words, stating that bupivacaine is stable in an implantable pump for 90 days implies that the amount of medication remaining after 90 days is less than 90 percent, or that testing was terminated at this time because available concentrations and average dosing did not warrant further research. Stability testing supports the use of bupivacaine in external systems with a 90-day refill interval and in implanted systems with a 90-day refill period [16].

The most noteworthy conclusion of this study was that a successful sensory block and a prolonged duration of postoperative analgesia were accomplished using this strategy, and that patients in the rapid sequential group experienced a rapid onset of sensory block and a greater sensory block level. These benefits could be attributable to the quick injection rate of fentanyl, which allowed it to freely mix and circulate with the cerebrospinal fluid, allowing it to reach more distant parts of the spinal cord and so reduce visceral discomfort. Keera and Elnabtity [17] studied the effect of separately injecting intrathecally administered fentanyl and hyperbaric and discovered that separately injecting intrathecal fentanyl allowed it to work at a higher level in the spinal cord, thereby preventing visceral pain, providing superior analgesia, and extending the duration of sensory block. They hypothesized that these results were due to the method by which the intrathecal drugs spread: when the patient is in a supine position, hyperbaric bupivacaine spreads due to gravity down the slope of the lumber curvature, whereas hypobaric fentanyl moves freely with the cerebrospinal fluid and thus achieves a wider range of spread, allowing it to induce sensory block at higher levels of the spinal cord. Moreover, we propose that rapidly administering fentanyl (within 1 second using an insulin syringe) enables it to block even higher levels, which may explain why higher degrees of sensory blockade were achieved in this investigation [17].

Low-dose clonidine and fentanyl extend the postoperative analgesia of intrathecal bupivacaine, and there are few research comparing the safety and effectiveness of these two medications. In our study, we examined the safety and efficacy of intrathecal clonidine and fentanyl. To compare the efficacy, various studies have utilized the effective analgesia duration measured in minutes for the need for rescue analgesia. In accordance with the findings of several other studies[18,19], we discovered that both medications are efficient adjuncts to intrathecal bupivacaine in prolonging the duration of analgesia. (P 0.05) The duration of analgesia was substantially longer in the clonidine group (497.20 139.78 min) than in the fentanyl group (416.87 105.21 min). In our investigation, the duration of enhanced analgesia owing to fentanyl and clonidine was distinct from other studies[18,19], but consistent with the study conducted by Shidhaye et al. [20] This may be due to the use of dosages of clonidine, fentanyl, and bupivacaine comparable to those employed by Shidhaye et al. [20] Small doses of intrathecal clonidine or fentanyl are typically not linked with systemic adverse effects such as bradycardia, hypotension, or sedation, and the hemodynamic stability found in both groups of our investigation verifies this. Only one patient required intravenous atropine therapy for substantial bradycardia. Similarly, Sethi et al.[11] and Shah et al.[21] observed very few incidences of hypotension and bradycardia when using 1 mcg/kg of intrathecal clonidine for nonobstetric surgeries, whereas Kothari et al.[22] observed a higher incidence of both hypotension and bradycardia in the bupivacaine group compared to the bupivacaine with clonidine Bajwa et al.[23] did not find bradycardia when clonidine was added to 9 mg of bupivacaine at concentrations up to 45 g. Biswas et al.[24] and Agrawal et al.[19] showed comparable hemodynamic stability while administering 12.5 g and 25 g of intrathecal fentanyl, respectively. In our investigation, the onset, peak, and duration of sensory and motor block are similar in both groups, but the duration of analgesia is considerably longer in the clonidine group than in the fentanyl group (P 0.05). In our investigation, the clonidine group exhibited more sedation than the fentanyl group (P 0.05). Similarly, Kothari et al.[22] found that 35–45% of patients were drowsy when 50 g of clonidine was added to bupivacaine, although Bajwa et al.[23] did not record any sedation when 45 g of clonidine was added to bupivacaine. The sedation induced by clonidine appears to be dose-dependent based on the preceding evidence. In one trial, there is no sedation in the fentanyl group, which is consistent with the findings of Biswas et al[24] 's investigation.

Epidural Administration of Bupivacaine:

The use of continuous infusion IT Bupivacaine is a relatively recent therapy technique. The use of epidural local anesthetics in the management of pain has a considerably older history. Numerous articles [25,26,27] attest to the application, safety, and effectiveness of epidural infusion of local anesthetics. This approach has been demonstrated to be efficacious in controlling sympathetic hyperactivity, minimizing ventilator time in trauma patients, enhancing postoperative recovery and shortening hospital stay and intensive care unit length of stay [26,27]. It has been demonstrated that epidural bupivacaine is synergistic with epidural opioids such as morphine, fentanyl, sufentanil, hydromorphone, methadone, and meperidine [28,29,30]. In addition to enhancing the reaction to epidural opioids, bupivacaine has provided extremely excellent pain relief for both cancer-related and non-cancerous pain. With the exception of occasional instances of epidural fibrosis and effects of systemic uptake resulting in cardiovascular abnormalities, the safety profile of continuous infusion has been extremely positive. The safe and effective use

of epidural bupivacaine has sparked interest in administering this medication via the Internet.

In research [31] involving 16 patients without cancer, the addition of bupivacaine to intrathecal opioids was much more effective than opioids alone. In a separate study [32] with 53 patients with a history of cancer-related pain, a combination of morphine and bupivacaine at a ratio of 1:10 (0.5:4.75 mg/ml) was more effective than a high dose of bupivacaine alone in treating intractable pain. In this study, both groups reported urine retention, paresthesia, and orthostatic hypotension as complications. The combination of medicines resulted in a lower rate of complications than high-dose intrathecal bupivacaine alone [32].

Comparison of Epidural Versus Intrathecal Administration of Bupivacaine:

Dahm and colleagues [33] conducted a comprehensive study of opioid alone versus opioid plus bupivacaine via various methods of administration. A retrospective analysis was conducted on 90 patients with external IT catheters, 330 patients with internal IT catheters, 565 patients with external epidural short-term catheters, 50 patients with external long-term epidural catheters, and 111 patients with internal long-term epidural catheters. The study found external intrathecal catheters to be 95% effective and internal intrathecal catheters to be 89% effective. These outcomes were significantly (p 0.0001) superior than internalized and externalized epidural catheters. Over the course of the study, 95% of patients receiving externalized IT had sufficient pain relief, compared to 42.5% receiving externalized epidurals. During the duration of the research, the internalized IT technique gave alleviation to 89% of patients, compared to 59% for the internalized epidural catheters. Externalized epidural catheters were also associated with higher rates of treatment failure compared to internalized IT catheters. In the externalized epidural catheter group, the rate of complications was 51%, compared to 11% in the internalized IT group. Internalized IT catheters were associated with lower rates of treatment failure compared to internalized epidural catheters. The corresponding failure rates for these groups were 11% and 38%. With internalized IT catheters, fewer system replacements have been documented. 72% of the systems in the epidural group were replaced, compared to 12% in the IT group. Overall, 10% of catheter-related problems were recorded in the epidural group against 4% in the IT group for catheter dislodgement, and 10% versus 0.9% for catheter system leakage. Both results were deemed statistically significant (p 0.05). The researchers determined that the IT method was superior than the epidural method in terms of pain alleviation, treatment failure, and the rate of complications. When the completely implanted SynchroMed Infusion System (Medtronic Inc., Minneapolis, MN) was utilized, it indicated that overall patient satisfaction was higher in the IT group. Length of therapy varied across these groups, with the longest treatment periods lasting 1706 days with long-term externalized IT catheters and 1320 days with internalized IT catheters. The average duration of treatment with internalized epidural catheters was reported to be 575 days [33].

Efficacy:

Clinical Performance Several publications have documented the use of intrathecal bupivacaine alone or in conjunction with opioids for the treatment of severe intractable pain. Between 1985 and 1993, Appelgren and colleagues [34] reported a 100 percent success rate in relieving pain in 201 consecutive cancer patients. This retrospective investigation found that epidural metastases affected both the overall outcome and the rate of complications. The advancement of the disease had a further impact on the catheter insertion complication rate, the amount of medicine required, and the IT pain management difficulties. Sjoberg and colleagues [32] reported an 85% effectiveness rate in prospective research with bupivacaine and morphine IT dosage in 52 non-cancer patients. Based on daily dosage, ratings of nonopiate analgesic and sedative use, gait and daily activities, sleep patterns, and visual analog scales, the treatment's efficacy was estimated. Following six months of treatment, pain alleviation was rated as "excellent" in 13.5% of patients, "very good" in 59.6% of patients, and "good" in 23.1% of patients. When doses of intrathecal bupivacaine were between 2.5 and 3 mg/h, there were no adverse effects. However, when doses exceeded this range, additional adverse effects were observed. In a prospective, cohort, nonrandomized consecutive trial [33] of persistent noncancer pain, 90 patients were monitored following placement of an externalized IT catheter via which opioids and bupivacaine were given. 95% of patients experienced satisfactory pain reduction, defined as 60% to 100% on a visual analog scale, for a mean period of 60 days. In addition, there was a notable improvement in the decrease of other sedatives and analgesics, the ability to walk and sleep, and the quality of life.

CONCLUSION:

IT bupivacaine, with or without opioid, appears to be a safe and effective approach for relieving pain in both cancer and non-cancer patients, according to the existing literature. Stability and bacterial tests validate the use of bupivacaine in external and implanted drug

delivery systems. Studies on the toxicity of IT in laboratory animals reveal difficulties only at plasma levels that would not be observed at therapeutically relevant doses. IT opioids are clinically enhanced by the addition of bupivacaine. The intrathecal administration of bupivacaine is more efficacious than the epidural administration. Infrequently are complications reported. Additional research is required to define the usage of intrathecal bupivacaine, including studies of long-term toxicity, neuropathology, and compatibility with other medicines. In addition, specialized outcome studies are required to differentiate the usage of IT bupivacaine based on the types of pain being treated.
Rapid intrathecal injection of fentanyl followed by slow intrathecal injection of hyperbaric bupivacaine provided adequate and prolonged postoperative analgesia while ensuring optimal spinal anesthesia during cesarean delivery; it was also associated with low incidences of intraoperative hypotension and vasopressor requirements.

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