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Using High-Dose Sufentanil Intrathecally For Painless Induction And Postoperative Pain Management In Gastrointestinal Cancer Surgeries

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Abstract

Background: Intrathecal opioids have demonstrated efficacy in pain management during and after surgery, necessitating further exploration across various surgical procedures. This study examines the use of higher doses of intrathecal synthetic opioids (Sufentanil) for pain control in gastrointestinal cancer surgeries, highlighting the need for additional research to establish conclusive outcomes.

Methods: A single-center clinical trial with a control group was conducted, involving adult non-addicted individuals eligible for gastrointestinal cancer surgeries. The intervention group (n=25) received intrathecal Sufentanil (0.2 mcg/kg) before anesthesia induction, while the control group (n=25) received intravenous Sufentanil (0.3 mcg/kg) at induction. The variables between the two groups were compared using chi-square tests, independent t-tests, and exact tests.

Results: The average age in the intrathecal group was 55.1 years ± 9.3, and in the intravenous administration group was 54.2 years ± 13.2, showing no significant difference (p=0.4). A higher proportion of patients in the intrathecal group required three analgesic doses (52%) compared to the IV group, where 44% needed four doses during surgery, with no significant variance observed between groups (p=0.3). Postoperative pain scores were lower in the intrathecal group than in the intravenous administration group (0.8 ± 1.7 vs 0.66 ± 5.12, p<0.001).

Conclusion: Based on our study findings, Intrathecal Sufentanil at a dose of 0.2 mcg/kg reduces postoperative pain by one-third compared to IV administration in gastrointestinal cancer surgeries.

Keywords: Gastrointestinal cancer, Intrathecally, Pain, Sufentanil.

1. Background

Effective pain management is a critical component of care for patients undergoing gastrointestinal cancer surgeries. Inadequate control of perioperative pain can lead to various adverse outcomes, including heightened stress responses, prolonged recovery times, and an increased risk of postoperative complications. Opioids continue

to be a cornerstone of pain management in surgical settings, with intrathecal opioid administration gaining recognition for its ability to provide superior analgesia with fewer systemic side effects compared to intravenous opioids. Among synthetic opioids, Sufentanil—a highly potent, lipophilic μ-opioid receptor agonist—has demonstrated significant potential for perioperative pain relief. Its unique pharmacological profile allows it to act quickly and efficiently, making it an attractive option for pain control in surgeries (1).

The history of spinal and epidural anesthesia parallels the development of general anesthesia. Similar to the use of ether in modern anesthesia pioneered by Morton in 1846, Bier and his assistant made history by using cocaine for intrathecal anesthesia. Romanian surgeon Racoviceanu-Pitesti reported his experience with a mixture of cocaine and morphine in spinal anesthesia in Paris in 1901. He demonstrated that the direct use of morphine in the spinal column produced pain relief. Spinal anesthesia was associated with a myriad of problems until the discovery of opioid receptors in the spinal cord in 1970, proving that the direct use of morphine in the spine resulted in pain relief. This finding was observed when Wang et al. successfully utilized intrathecal bolus doses of morphine in humans and reported pain relief in 10 patients between 6 and 24 h in a groundbreaking article in The Lancet in 1979. This was the first article on the use of epidural morphine doses of 2 mg for acute and chronic pain treatment. Therefore, it took over a century for the practice of administering opioids through the spine for pain relief during and after surgery, in childbirth, as well as for chronic pain, especially cancer-related pain, to become a routine procedure. It is worth mentioning that in the first 50 years of spinal anesthesia history, surgeons played the leading role; however, they became less involved over time, and now this field is exclusively under the domain of anesthesiologists.

Previously, it was somewhat believed that injecting any opioid substances into the epidural or spinal space without causing concerning side effects, such as respiratory depression, would provide more selective spinal pain relief compared to any other method. Unfortunately, this is not true in many cases because these substances can reach higher brain centers through cerebrospinal fluid (CSF) or absorption and redistribution to higher brain centers. The biological availability of these substances at the spinal cord level is very low, leading to supraspinal pain relief (2).

The distribution of opioids after spinal administration is complex and follows a multi-compartment pattern (3). The drug is released into the subarachnoid space and moves towards the head through CSF, connecting to non-specific receptors in white matter and specific receptors in gray matter. Lipophilic opioids, such as fentanyl and Sufentanil, can quickly pass through the blood-brain barrier, are absorbed into epidural fat, have good vascular absorption, and connect well to white and gray matter receptors in the spinal cord. Clinically, this results in short delay, limited rostral spread, and consequently spinal pain relief at the injection site, with a short duration of effect and a risk of early respiratory depression due to blood dissemination (4). In contrast, hydrophilic opioids, including morphine, pass more slowly through the blood-brain barrier, connect less to epidural fat and more to specific receptors in gray matter, have slow plasma reabsorption, and maintain higher and longer concentrations in CSF. An intravenous injection of 10 mg of morphine is equivalent to 10 mg of Sufentanil administered intravenously, while only 100 mg of morphine should be used intrathecally to achieve the same degree of pain relief.

Generally, patients undergoing anesthesia induction for surgery require opioids to increase the depth of anesthesia and reduce pain during and after surgery (5). Patients need repeated administration of analgesics

during surgery, and they complain of pain postoperatively, requiring analgesic medication during recovery. The use of intrathecal opioids in some studies has effectively improved pain control during and after surgery. While the efficacy of intrathecal opioids like Sufentanil has been well-documented in a variety of surgeries, there remains a gap in the literature regarding its optimal dosing and long-term safety, particularly in high-risk procedures such as gastrointestinal cancer surgeries (6).

This study aims to investigate the effects of administering higher doses of synthetic opioid Sufentanil (0.2 mcg/kg) intrathecally in patients undergoing gastrointestinal cancer surgeries. By comparing intrathecal Sufentanil to standard intravenous administration, we seek to evaluate its impact on perioperative pain control, analgesic requirements, and potential side effects. The results of this study could provide valuable insights into refining pain management protocols for gastrointestinal cancer surgeries, potentially improving postoperative outcomes and patient satisfaction.

2. Methods

Study design

This study was a clinical trial with a control group. Patients were blinded to the intervention. The study design was parallel arms and a superiority trial.

Adults who were not addicted had no history of sensitivity to the drugs used in the study, provided informed consent, and were candidates for gastrointestinal cancer surgeries were included in the study. The exclusion criteria included addiction, use of beta-blocker medication, contraindications for spinal anesthesia, a history of seizures, and ASA class 4 or higher. Patients hospitalized in the surgical ward and operating room of Imam Reza and Qaem hospitals were studied. Written informed consent was obtained from participants for study participation.

Interventions

Eligible patients were randomized into ten five-member blocks, with the first five assigned to the intervention group and the second to the control group. Each group consisted of 25 individuals. In the intervention group, adult patients undergoing gastrointestinal cancer surgeries received specific medications before and during anesthesia induction to manage cardiovascular responses and pain. They were given medications intrathecally in a seated position after P&D with a 25-gauge spinal needle. They received 0.2 µg/kg of Sufentanil of body weight (from Caspian or Aburaihan Company). Following this, during anesthesia induction, they were administered Midazolam (1-3 mg), Propofol (3-2 mg/kg body weight), Sufentanil (0.1 µg/kg body weight) for suppression of cardiovascular responses to laryngoscopy, and Atracurium (0.5 mg/kg body weight). Anesthesia was then maintained using Propofol.

Vital signs were recorded every 30 minutes during surgery. If the patient experienced a 20% increase in blood pressure compared to baseline at the beginning of surgery and after surgery completion and reported a pain level of 4 based on the Visual Analogue Scale (VAS) checklist, they were given intravenous fentanyl 1 µg/kg body weight.

In the control group, intravenous Sufentanil was injected at a dose of 0.3 µg/kg body weight during anesthesia induction, and the other drugs were administered similarly to the intervention group. The need to repeat anesthesia during and after surgery in these patients was also evaluated using a similar method. The data on pain control and the need for re-administration of analgesics in both groups were then collected and compared.

Outcome Measurements

Patients' Vital signs during surgery were monitored every 30 minutes, and patients'

complaints of pain were assessed every 30 minutes postoperatively, along with the number of patients who needed the first dose of analgesic medication after surgery.

Statistical Analysis

The average pain in two anesthesia methods was calculated based on the article with 80% power and 95% confidence interval, with 25 subjects in each group. Data from demographic observations and patient information were analyzed using Stata software. Comparison of variables between the two groups was performed using the Chi-square tests, independent t-tests, and exact tests. Also, the level of statistical significance was set at P<0.05.

Ethical Committee

This thesis was conducted based on research proposal number 990848, which was approved on 10.3.2020. The Ethics Committee approved the research on 9.18.2020 (IR.MUMS.MEDICAL.REC.1399.580) under the title "The use of high-dose intrathecal Sufentanil for pain management during and after surgery in gastrointestinal cancer surgeries."

3. Results

A total of 50 patients were divided into two groups, with 25 patients in the intrathecal injection group and 25 in the intravenous injection group of Sufentanil. The mean age of individuals in the intrathecal and intravenous groups was 55.1 ± 9.3 and 54.2 ± 13.2 years, respectively, with no significant difference (P=0.4). There was no significant difference in the distribution of gender, weight, ASA score, and duration of surgery between the two groups. The most common gastrointestinal cancer in both groups was colon and rectal cancer, as detailed in Table 1.

Table 1. Background characteristics of subjects in two control and intervention groups at the beginning of the study

Characteristic	(n=25) Intrathecal administration	Intravenous administration (n=25)	p-value
Age (years)	55.1±9.3	54.2±13.2	0.4
Weight (kg)	7.5±65.6	6.8±62.1	0.46
Duration of surgery (minutes)	22.2±243.6	26.3±238.8	0.24
Gender (female)	5 (20.0%)	9 (36.0%)	0.2
Asa Score			*0.96
1	14 (56.0%)	13 (52.0%)	
2	9 (36.0%)	10 (40.0%)	
3	2 (8.0%)	2 (8.0%)	
Type of cancer			*0.69
Colon cancer	9 (36.0%)	9 (36.0%)	
Duodenal mass	0 (0%)	1 (4.0%)	
Rectal cancer	7 (28.0%)	9 (36.0%)	
Rectosigmoid cancer	3 (12.0%)	3 (12.0%)	
Sigmoid cancer	6 (24.0%)	3 (12.0%)	

*The exact test was used to compare the two groups

More patients (52%) in the intrathecal method required three doses of analgesic medication during surgery, while in the intravenous method, 44% needed four doses. The frequency of analgesic injections did not differ significantly between the two groups (P=0.3). The average postoperative pain in patients under anesthesia with the intrathecal method was 1.7 ± 0.8, while it was 5.12 ± 0.66 in patients under anesthesia with the intravenous method, showing a statistically significant difference in average pain between the two groups (P<0.001).

The results of this study indicated that patients' blood pressure mainly increased around minute 60 and reached its peak between minutes 90 and 120. There was no

significant difference in systolic and diastolic blood pressure changes between the intrathecal injection group and the control group during surgery (Figures 1 and 2).

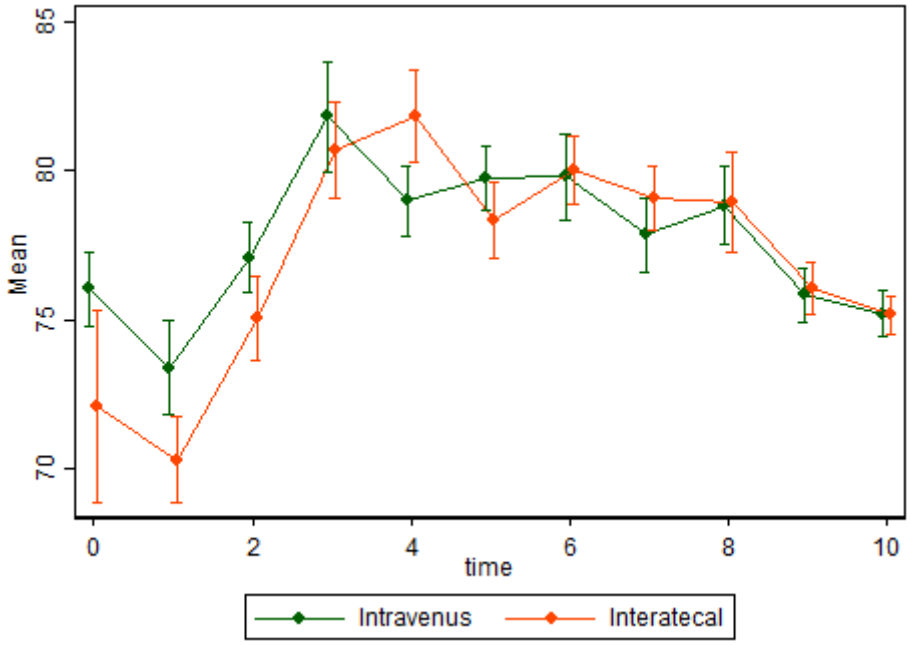

Figure 1: Changes in diastolic blood pressure during surgery between intrathecal and intravenous administration

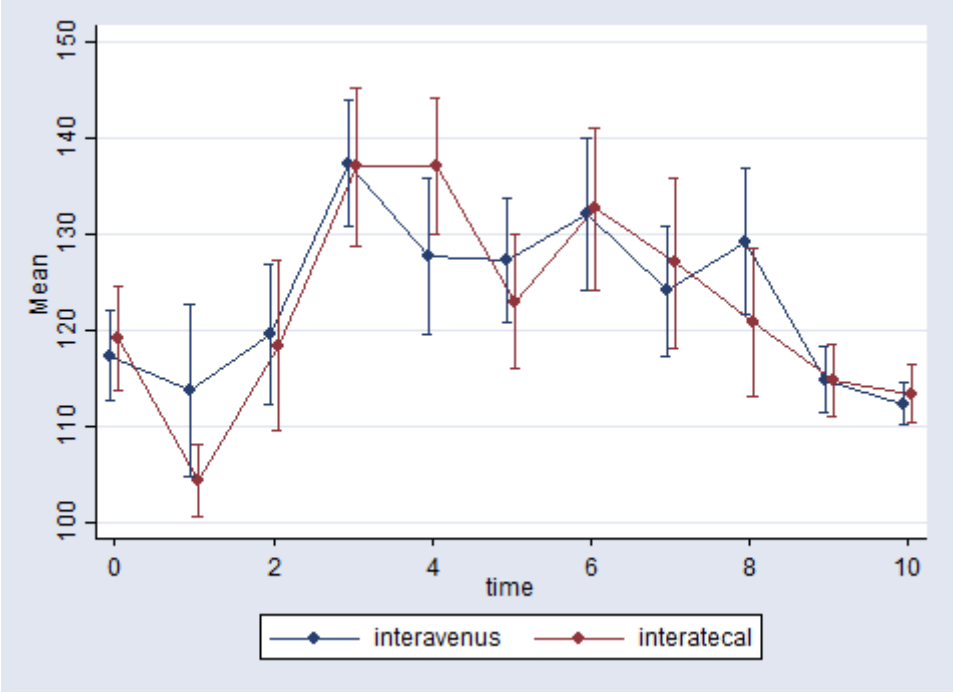

Figure 2: Changes in systolic blood pressure during surgery between intrathecal and intravenous administration

4. Discussion

The findings of this study highlight the potential benefits of using high-dose intrathecal Sufentanil (0.2 mcg/kg) for perioperative pain management in patients undergoing gastrointestinal cancer surgeries. Intrathecal administration of

opioids has long been recognized as a powerful method for controlling surgical pain, and this study supports previous research that demonstrates the superior efficacy of intrathecal opioids in comparison to intravenous administration. The results showed that intrathecal Sufentanil injection led to a one-third reduction in postoperative pain compared to intravenous injection. The clinical difference in pain was also significant, with a 3.4 difference on the VAS. Previous studies have shown that a minimum pain difference of 2 to 3 units is needed to create a clinical difference (7).

Sufentanil is a highly lipophilic drug, allowing it to pass through biological membranes quickly. The lower postoperative pain scores in the intrathecal group (0.8 ± 1.7) compared to the intravenous group (0.66 ± 5.12, $p<0.001$) are consistent with the pharmacokinetic properties of lipophilic opioids such as Sufentanil. As a lipophilic opioid, Sufentanil rapidly penetrates the blood-brain barrier. It acts directly on spinal cord receptors, providing rapid onset of analgesia with limited rostral spread and a decreased risk of delayed respiratory depression compared to more hydrophilic opioids like morphine (8). When injected into the subarachnoid space, Sufentanil must penetrate the spinal cord to reach its site of action in the posterior horn. Sufentanil may also reach supraspinal opioid receptors through the cerebrospinal fluid. Movement towards the upper brain has been observed in humans (9, 10) and animal studies (11) and may be induced by the movement of cerebrospinal fluid. The current study results demonstrated that intrathecal Sufentanil was more potent than intravenous Sufentanil. Intrathecal Sufentanil acts directly on spinal receptors, reaching supra-spinal receptors faster, leading to an additive analgesic effect.

Our results also align with previous studies suggesting that intrathecal opioid administration can reduce the need for additional analgesic doses during surgery. In this study, 52% of patients in the intrathecal group required three doses of analgesics during surgery, compared to 44% in the intravenous group who needed four doses. Although this difference was not statistically significant ($p=0.3$), it points to a trend toward reduced analgesic consumption with intrathecal administration. These findings mirror those of other clinical trials where intrathecal opioids, including Sufentanil, have been shown to reduce the overall requirement for systemic analgesics during both the intraoperative and postoperative periods (12).

The excellent pain relief observed in patients receiving intrathecal Sufentanil can be attributed to its direct effect on spinal receptors. These results are consistent with those reported by Camann et al. (13), who found better pain relief with 10 mcg of intrathecal Sufentanil compared to the same dose administered intravenously during labor. However, the effects of supra-spinal administration of intrathecal Sufentanil should be considered. Frouz et al. (10) reported rapid spread of hypoalgesia to upper chest or neck dermatomes in women during labor after intrathecal sufentanil injection. On the other hand, Hansdottir et al. (14) stated that after intrathecal injection in humans, Sufentanil is quickly cleared from the cerebrospinal fluid and absorbed by plasma, with a longer half-life in plasma (7 hours) compared to cerebrospinal fluid (1 hour).

Fournier et al. (2005) compared the analgesic effect of Sufentanil in intravenous and intrathecal methods in patients undergoing total hip replacement in a clinical trial involving 40 patients (15). The results showed significantly greater pain relief 20 minutes after intrathecal administration than intravenous. Additionally, the time to the first analgesic

dose and the average analgesic dose used were higher and lower in the intrathecal group compared to the intravenous group. The authors concluded that intrathecal administration provided better analgesic effects postoperatively than intravenous. Another study in 2012 investigated the effect of intrathecal sufentanil injection on postoperative pain following coronary artery bypass grafting surgery. In this study, 40 patients were divided into two groups: one group received intrathecal Sufentanil, while the other did not. The results showed that patients in the intrathecal group required less remifentanil than the control group and had more stable hemodynamic status (16).

The average pain difference in patients after surgery was 3.4 units based on the VAS, which was statistically and clinically significant. However, the optimal dosing of intrathecal Sufentanil remains an area of active investigation. While the 0.2 mcg/kg dose in this study improved pain control, the ideal dose for balancing efficacy and safety has yet to be definitively established. Previous research has suggested that higher doses of intrathecal Sufentanil may increase the risk of opioid-related side effects, including respiratory depression and nausea, though these were not significant issues in our study (17).

One of the strengths of our study is its contribution to the limited body of literature examining the use of high-dose intrathecal Sufentanil, specifically in gastrointestinal cancer surgeries. While intrathecal opioids have been widely studied in other types of surgeries, their use in abdominal cancer surgeries has been less thoroughly investigated. Our findings indicate that intrathecal Sufentanil may be a valuable addition to multimodal analgesia strategies for these complex and often painful procedures, reducing both intraoperative and postoperative pain and potentially improving patient outcomes.

Despite these promising results, our study has several limitations. First, it was conducted at a single center with a relatively small sample size (n=50), which may limit the generalizability of our findings. Future studies with larger, multicenter cohorts are needed to confirm our results and explore the long-term outcomes associated with intrathecal opioid use in this patient population.

5. Conclusion

Our study showed that intrathecal administration of Sufentanil at a dose of 0.2 µg/kg reduced postoperative pain in patients undergoing gastrointestinal cancer surgery by one-third compared to intravenous injection. When administered as an anesthetic drug in the subarachnoid space, drugs can significantly decrease postoperative pain in patients undergoing gastrointestinal cancer surgery after surgery. This method can lead to accelerated recovery and mobilization of the patient, ultimately resulting in greater patient satisfaction with surgical outcomes and a reduction in their hospital stay.

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Consent for publication: Not Applicable

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