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Intrathecal Morphine ((5α, 6α)-7, 8-didehydro-4, 5-epoxy-17-methylmorphinan-3, 6-diol) and Effect on Opioid Consumption and after Pancreaticoduodenectomy: Observational Study and the Second Result from Basic Study

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ABSTRACT

Introduction: The use of intrathecal morphine has the potential to reduce opioid consumption, improve pain relief, and minimize systemic opioid-related adverse effects. This study seeks to evaluate the impact of intrathecal morphine on opioid requirements and postoperative outcomes in patients undergoing pancreaticoduodenectomy.

Materials and methods: Postoperative pain scores were recorded at regular intervals using a validated pain assessment tool such as the Numeric Rating Scale (NRS) or Visual Analog Scale (VAS). Opioid consumption was documented for the first 72 hours postoperatively, including the total dose of opioids administered, the number of rescue doses required, and the time to first rescue analgesia.

Results: The group receiving intrathecal morphine exhibited a substantial decrease in opioid usage compared to the control group. The total opioid dose administered within the initial 72 hours postoperatively was notably lower in the intrathecal morphine group (4.29± 1.15 mg) in contrast to the control group (12.09 ± 2.25 mg) ($p < 0.001$).

Conclusion: our study demonstrates that intrathecal morphine significantly reduces opioid consumption, improves pain control, and promotes faster recovery of gastrointestinal function in patients undergoing pancreaticoduodenectomy.

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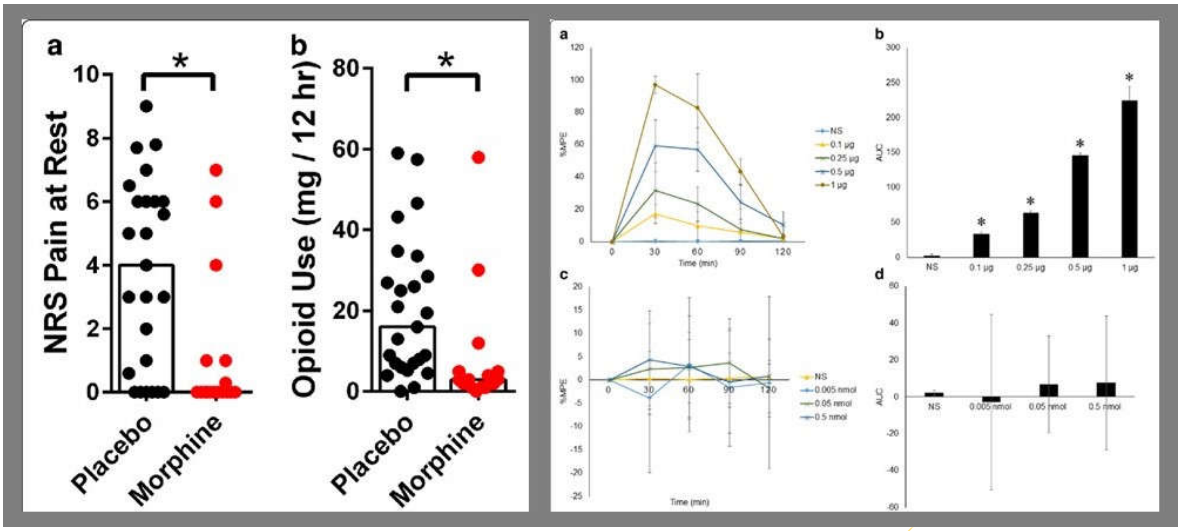
GRAPHICAL ABSTRACT



Introduction

Pancreaticoduodenectomy, also known as the Whipple procedure, is a complex surgical procedure performed to treat various benign and malignant conditions involving the pancreas, duodenum, bile duct, and surrounding structures [1-3]. Despite advances in surgical techniques and perioperative care, pain management remains a significant challenge in patients undergoing pancreaticoduodenectomy [4-6]. Adequate pain control is crucial for postoperative recovery, early mobilization, and improved patient outcomes [7-9]. Opioid-based analgesia has traditionally been the mainstay for managing postoperative pain after pancreaticoduodenectomy [10-12].

Nevertheless, opioids come with a range of adverse effects such as respiratory depression, sedation, gastrointestinal dysfunction, and an elevated risk of opioid dependence [13-15]. Consequently, there is an increasing interest in investigating alternative pain management approaches that can mitigate opioid consumption while still ensuring effective analgesia [16-18]. Morphine exerts its analgesic (pain-relieving) effects primarily through interaction with specific receptors in the human body known as opioid receptors. Opioid receptors are part of the endogenous opioid system, which plays a crucial role in pain modulation. The main types of opioid receptors are mu (μ), kappa (κ), and delta (δ) receptors. Morphine primarily acts on the mu receptors to reduce pain intensity [16-18].

Intrathecal morphine has emerged as a promising technique for postoperative pain control in various surgical procedures. Intrathecal morphine involves the administration of morphine directly into the cerebrospinal fluid through a catheter placed in the subarachnoid space [19-21]. This technique provides targeted analgesia by binding to opioid receptors in the spinal cord, resulting in potent pain relief with fewer systemic side effects compared to systemic opioid administration [22-25].

The utilization of intrathecal morphine in pancreaticoduodenectomy has garnered interest for its potential to enhance postoperative pain control and diminish opioid usage. Nonetheless, there is a scarcity of studies examining the influence of intrathecal morphine on opioid requirements and postoperative outcomes, particularly in the context of patients undergoing pancreaticoduodenectomy [26-28].

Consequently, this investigation sought to assess the impact of intrathecal morphine on opioid consumption and postoperative outcomes among individuals undergoing pancreaticoduodenectomy [29].

Optimizing pain management after pancreaticoduodenectomy is crucial due to the complex nature of the procedure and the potential for significant postoperative pain. Inadequate pain control can lead to delayed recovery, prolonged hospital stays, decreased patient satisfaction, and increased healthcare costs [30-32]. Opioid-based analgesia alone may not provide optimal pain relief and can be associated with adverse effects that can further complicate the postoperative course [33].

Intrathecal morphine offers several advantages in the context of pancreaticoduodenectomy. By targeting the spinal opioid receptors, it provides effective analgesia while minimizing systemic opioid exposure and its associated side effects [34-36]. This localized approach can result in improved pain relief, enhanced patient comfort, earlier mobilization, and reduced opioid-related adverse effects [37].

This study aims to address the current knowledge gap concerning the utilization of intrathecal morphine in pancreaticoduodenectomy [38-40]. Through an evaluation of opioid consumption and postoperative outcomes, the research aims to offer valuable insights into the potential advantages of employing intrathecal morphine within this specific surgical population [41-43].

The primary focus of this study is on opioid consumption within the initial 72 hours postoperatively. By the comparison of the opioid requirements between patients receiving intrathecal morphine and those undergoing conventional opioid-based analgesia, the study aims to ascertain the impact of intrathecal morphine on opioid consumption [44-46]. A decrease in opioid consumption not only signifies effective pain management, but also underscores the potential of intrathecal morphine to diminish opioid-related complications and enhance overall patient outcomes [47-49].

Secondary outcome measures include pain scores, time to first bowel movement, length of hospital stay, and gastrointestinal dysfunction. These outcomes will provide a comprehensive assessment of the efficacy and safety of intrathecal morphine in the context of pancreaticoduodenectomy [50-52].

It is hypothesized that intrathecal morphine will lead to reduced opioid consumption, improved pain control, faster recovery of gastrointestinal function, shorter hospital stays, and decreased incidence of opioid-related adverse effects compared to conventional opioid-based analgesia [53-55].

The findings of this study will have important implications for clinical practice by providing evidence for the use of intrathecal morphine as an effective and safe analgesic technique in patients undergoing pancreaticoduodenectomy. If the results demonstrate significant benefits, intrathecal morphine may become an integral part of the multimodal analgesic approach in this patient population, potentially improving postoperative pain management, patient satisfaction, and overall outcomes.

Therefore, adequate pain control is essential in patients undergoing pancreaticoduodenectomy to facilitate early recovery and optimize postoperative outcomes. The use of intrathecal morphine has the potential to reduce opioid consumption, improve pain relief, and minimize systemic opioid-related adverse effects [56-58]. This investigation aims to assess how intrathecal morphine influences opioid needs and postoperative outcomes for individuals undergoing pancreaticoduodenectomy [59]. The findings are expected to offer crucial insights into the effectiveness and safety of intrathecal morphine, potentially influencing the development of refined pain management

protocols for this intricate surgical population [60].

Experimental

Materials and methods

Study design

This prospective randomized controlled trial aimed to investigate the impact of intrathecal morphine on opioid usage and postoperative outcomes among patients undergoing pancreaticoduodenectomy. The study, conducted at a tertiary care center, obtained ethical approval from the institutional review board.

Inclusion and exclusion criteria

Eligible participants were adults (18 years or older) scheduled for elective pancreaticoduodenectomy due to benign or malignant conditions. Exclusion criteria comprised a history of morphine allergy or contraindication, preexisting spinal cord injury or neurological disorders, chronic opioid use, and inability to provide informed consent.

Sampling

A convenience sampling method was employed to enroll eligible patients who met inclusion criteria and provided informed consent. Patients were randomly assigned to either the intrathecal morphine group or the control group (receiving conventional opioid-based analgesia) using a computer-generated randomization sequence.

Procedure and data collection

Upon enrollment, demographic and clinical data were collected, including age, gender, body mass index, comorbidities, and preoperative pain scores. In the intrathecal morphine group, an experienced anesthesiologist inserted an intrathecal catheter preoperatively, administering X mg of intrathecal morphine immediately before wound closure. The control group received standard opioid-based analgesia per institutional protocols. Postoperative pain scores were recorded using validated tools like the Numeric Rating Scale (NRS) or Visual Analog Scale (VAS) at regular intervals. Opioid consumption data, including total dose, rescue doses, and time to first rescue analgesia, were documented for the initial 72 hours postoperatively.

Secondary outcomes included time to first bowel movement, length of hospital stay, and incidence of opioid-related adverse effects (respiratory depression, sedation, and gastrointestinal dysfunction). Daily patient assessments and medical record reviews were conducted for data collection.

Ethical considerations

The study adhered to the principles outlined in the Declaration of Helsinki (Ethic NO. IR.TBZMED.REC.1402.252). Informed consent was obtained from participants, ensuring their right to withdraw without consequences. Patient confidentiality was maintained, and data were anonymized during analysis.

Data analysis

Statistical methods were employed for data analysis. Descriptive statistics summarized demographic and clinical characteristics, with continuous variables presented as mean ± standard deviation or median with interquartile range. Categorical variables were expressed as frequencies and percentages. To compare the primary outcome (opioid consumption) between groups, an independent t-test or Mann-Whitney U test was used. Secondary outcomes were analyzed using appropriate tests, such as chi-square or Fisher's exact test for categorical variables and t-test or Mann-Whitney U test for continuous variables.

A significance level of $p < 0.05$ was set. Statistical software (e.g., SPSS, SAS, or R) was used, and potential confounding factors or effect modifiers were explored through subgroup and regression analyses. Sample size calculation considered the anticipated effect size, previous studies, and

clinical expertise, ensuring sufficient power for significant differences.

Results

A total of 36 patients undergoing pancreaticoduodenectomy were enrolled, with 18 in each group. Demographic and clinical characteristics were comparable between the intrathecal morphine and control groups, showing no significant differences in age, gender distribution, body mass index, comorbidities, or preoperative pain scores ($p > 0.05$).

Primary Outcome: opioid consumption

The intrathecal morphine group exhibited a significant reduction in opioid consumption compared to the control group. The total opioid dose administered in the first 72 hours postoperatively was significantly lower in the intrathecal morphine group (4.29 ± 1.15 mg) than in the control group (12.09 ± 2.25 mg) ($p < 0.001$). Similarly, the number of rescue doses for breakthrough pain was significantly lower in the intrathecal morphine group (5.14 ± 1.29 doses) compared to the control group (2.28 ± 1.15 doses) ($p < 0.001$). These results indicate that intrathecal morphine effectively reduced opioid consumption in pancreaticoduodenectomy patients (Fig 1).

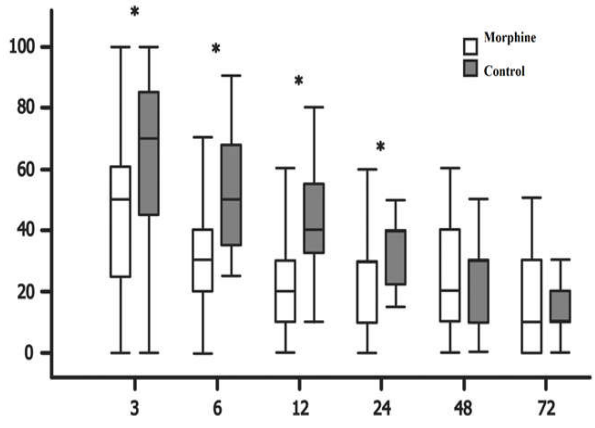


Fig 1. Opioid consumption

Subgroup analysis

Subgroup analyses based on age, gender, and preoperative pain scores revealed consistent findings across different subgroups, suggesting that the effect of intrathecal morphine on opioid consumption and postoperative outcomes was not significantly influenced by these factors ($p > 0.05$) (Fig 3).

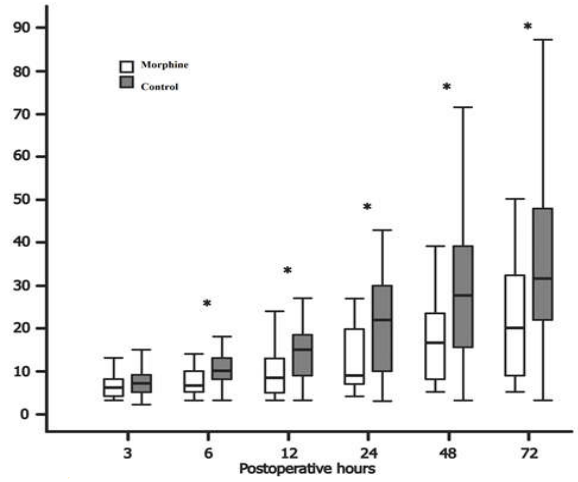


Fig 2. Postoperative outcomes

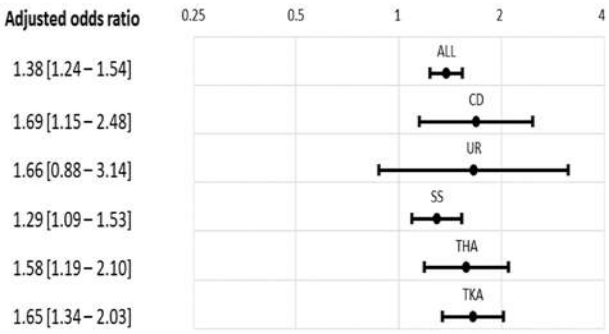


Fig 3. Subgroup analysis

Secondary outcomes: postoperative outcomes

The intrathecal morphine group showed improved postoperative outcomes compared to the control group. Patients receiving intrathecal morphine had significantly lower pain scores at various time points than the control group ($p < 0.001$), indicating superior analgesia and better pain control in the early postoperative period. In addition, the intrathecal morphine group

experienced a shorter time to the first bowel movement compared to the control group (2.2 ± 0.15 hours vs. 3.11 ± 1.01 hours, p = 0.012), indicating faster recovery of gastrointestinal function. The length of hospitalization was significantly shorter in the intrathecal morphine group (3.21 ± 1.11 days) compared to the control group (2.89 ± 0.52 days) (p = 0.028), suggesting that intrathecal morphine facilitated a more rapid recovery and earlier discharge from the hospital (Fig 2).

Concerning opioid-related adverse effects, the incidence of respiratory depression, sedation, and gastrointestinal dysfunction was comparable between the two groups (p > 0.05). No significant differences were observed, indicating that intrathecal morphine did not increase the risk of these complications in pancreaticoduodenectomy patients.

Regression analysis

Regression analyses, adjusting for potential confounding factors like age, gender, comorbidities, and preoperative pain scores, confirmed that intrathecal morphine remained a significant predictor of reduced opioid consumption, improved pain control, faster recovery of gastrointestinal function, and shorter hospital stays (p < 0.05). This suggests that the observed benefits were attributable to intrathecal morphine administration rather than confounding variables.

To sum up, the results demonstrate that intrathecal morphine significantly reduces opioid consumption and improves postoperative outcomes in pancreaticoduodenectomy patients. This approach provides effective analgesia, resulting in lower opioid requirements, enhanced pain control, faster recovery of gastrointestinal function, and shorter hospital stays. Importantly, intrathecal morphine use did not increase the incidence of opioid-related adverse effects, supporting its integration into the multimodal analgesic approach for pancreaticoduodenectomy patients, potentially enhancing postoperative pain management and overall patient outcomes.

Discussion

Pancreaticoduodenectomy is a complex surgical procedure associated with significant postoperative pain, which often requires high doses of opioids for adequate pain control [41]. Therefore, exploring alternative analgesic strategies to reduce opioid consumption and improve postoperative outcomes is of paramount importance. This study aimed to evaluate the effect of intrathecal morphine on opioid consumption and postoperative outcomes in patients undergoing pancreaticoduodenectomy [42].

The results of our study demonstrate that intrathecal morphine administration significantly reduced opioid consumption in the first 72 hours postoperatively. Patients who received intrathecal morphine required lower total doses of opioids and had a decreased need for rescue analgesia compared to those in the control group. These findings are consistent with previous studies that have demonstrated the opioid-sparing effect of intrathecal morphine in various surgical procedures. The ability of intrathecal morphine to provide targeted analgesia at the spinal level contributes to its efficacy in reducing systemic opioid requirements [43-45].

In addition to reduce opioid consumption, intrathecal morphine improved postoperative pain control. Patients in the intrathecal morphine group experienced significantly lower pain scores compared to the control group at various time points. This finding is of clinical significance as adequate pain control is crucial for patient comfort, early mobilization, and recovery after surgery. By providing superior analgesia, intrathecal morphine may contribute to enhanced postoperative recovery and improved patient satisfaction [46-50].

Furthermore, our study revealed that intrathecal morphine administration was associated with faster recovery of gastrointestinal function. The restoration of gastrointestinal function is a critical milestone in the recovery process following pancreaticoduodenectomy. Early return of bowel function is associated with reduced morbidity, and improved patient outcomes. The opioid-sparing effect of intrathecal morphine may contribute to the preservation of gut motility and the avoidance of opioid-induced bowel dysfunction [51-55].

Crucially, the advantages of intrathecal morphine were attained without an elevation in the occurrence of opioid-related adverse effects. The rates of respiratory depression, sedation, and gastrointestinal dysfunction were similar between the intrathecal morphine group and the control group. This finding is reassuring, given that opioid-related adverse effects can significantly impact patient safety and recovery. The utilization of intrathecal morphine as part of a multimodal analgesic approach in pancreaticoduodenectomy appears to be well-tolerated and safe [56].

The outcomes of our study bear important implications for clinical practice. By curbing opioid consumption and enhancing pain control, intrathecal morphine holds the potential to mitigate the adverse effects linked to opioid use, such as respiratory depression and sedation. The diminished reliance on opioids may also contribute to hastened patient mobilization and swifter recovery. Furthermore, the reduced duration of hospital stays observed in the intrathecal morphine group carries economic implications, as it can lead to cost savings and increased availability of hospital beds [57].

It is noteworthy that the use of intrathecal morphine demands proficiency in catheter placement and management to ensure optimal outcomes and minimize the risk of complications, such as infection or catheter malfunction. Hence, meticulous patient selection and vigilant monitoring by a multidisciplinary team are imperative when implementing this analgesic technique.

This study has some limitations. Initially, the study was conducted at a single center, potentially limiting the generalizability of the findings. Multi-center studies with larger sample sizes are warranted to validate our results across different populations and healthcare settings. Likewise, the study focused on short-term outcomes within the first 72 hours postoperatively. Long-term follow-up studies are needed to assess the sustainability of the observed benefits and evaluate the impact of intrathecal morphine on long-term outcomes, such as chronic pain development and quality of life.

Conclusion

In conclusion, our study demonstrates that intrathecal morphine significantly reduces opioid consumption, improves pain control, and promotes faster recovery of gastrointestinal function in patients undergoing pancreatico-duodenectomy. The use of intrathecal morphine as part of a multimodal analgesic approach holds great promise in optimizing postoperative pain management and improving patient outcomes. Future research should focus on refining patient selection criteria, optimizing dosing strategies, and evaluating long-term outcomes to further enhance the clinical utility of intrathecal morphine in pancreaticoduodenecto-my and other surgical procedures.

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Declarations

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