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Original Research Article

Comparative Analysis of Intrathecal Morphine and Nalbuphine with Bupivacaine in Laparoscopic Gynecological Surgery

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Conflict of interest: Nil

Abstract

Background and Aim: The literature presents conflicting findings regarding the comparative effectiveness and safety of morphine and nalbuphine. The current study aimed to evaluate and compare the pain scores, motor blockade, and side effects associated with the use of intrathecal morphine versus nalbuphine in conjunction with bupivacaine during laparoscopic gynaecological procedures.

Material and Methods: A study was conducted involving 100 patients classified as American Society of Anaesthesiology (ASA) Class I/II, all of whom were scheduled for elective laparoscopic gynaecological procedures. In this study, participants were randomly assigned to one of two groups, each consisting of 50 individuals. The allocation was conducted using a sealed envelope method. Group A received a combination of 100 µg morphine and 2 ml bupivacaine, while Group B was administered 400 µg Nalbuphine along with 2 ml bupivacaine. The main goal of our research was to assess pain intensity using the visual analogue scale (VAS). Post-operative side effects such as hypotension, bradycardia, respiratory depression, nausea, vomiting, and pruritus were documented and categorised as secondary objectives of the study.

Results: The findings indicate that following extubation, the mean motor blockade scores were recorded at 4.20±0.54 for group A and 4.22±0.42 for group B. The mean motor blockade score recorded after 12 hours was 5.94±0.48 for group A and 5.92±0.34 for group B. The analysis revealed no notable difference in motor blockade scores between groups A and B. The mean Visual Analogue Scale (VAS) scores recorded after extubation and at the 3-hour mark were similar across both groups. However, at the 6, 12, and 24-hour intervals, group B exhibited higher scores compared to group A, although these differences were not statistically significant. ($p>0.05$)

Conclusion: Nalbuphine demonstrates analgesic efficacy that is on par with morphine; however, it offers a superior safety profile, particularly concerning the incidence of pruritus.

Key Words: Bupivacaine, Morphine, Nalbuphine, Visual Analogue Scale

Introduction

The evolution of enhanced recovery after surgery highlights a pressing demand for improved postoperative pain management and a decrease in the duration of hospital stays following surgical procedures. Recent advancements in laparoscopic surgical instruments and techniques have made it possible for a wide range of surgically indicated patients in the field of gynaecology to benefit from laparoscopic surgery.[1] Our institution routinely performs total laparoscopic hysterectomy and laparoscopic myomectomy as part of its laparoscopic gynaecological surgery offerings. Recent research indicates that the use of combined spinal and general anaesthesia may offer a safer alternative for patients undergoing laparoscopic hysterectomy compared to the use of general anaesthesia alone.[2] Our institution employs a combined spinal-epidural and general anaesthesia approach for all gynaecological surgical procedures.

Intrathecal morphine (ITM) made its debut in 1979 as a treatment option for individuals suffering from severe intractable pain.[3] ITM offers clear benefits for managing pain during the perioperative period, such as enhanced analgesic quality and reduced reliance on systemic opioids.[4] ITM has gained significant traction in managing postoperative pain associated with caesarean sections, cholecystectomies, and transurethral resections of the prostate.[5-7] A

prior investigation indicated that administering 9 mg/kg of ITM after surgery significantly alleviates postoperative pain in adolescents with idiopathic scoliosis, while also reducing the necessity for standard ICU admission for additional care. Nonetheless, high doses of morphine may lead to side effects such as itching, nausea and vomiting, urinary retention, and respiratory depression.[8] Nalbuphine is a unique opioid that belongs to the phenanthrene class, designed to deliver pain relief while minimising the adverse effects commonly associated with traditional opioid agonists. 4 The analgesic properties, along with likely anti-pruritic effects, are thought to be facilitated through interactions with the mu (μ) and kappa (k) receptors.[5] When utilized for addressing a variety of conditions, including burns, multiple trauma, orthopaedic injuries, gynaecological issues, and intra-abdominal ailments, it has demonstrated safety and reliability.[9]

Research on the effectiveness and safety of morphine versus nalbuphine presents a range of conflicting results across various studies.[10] Consequently, there is minimal evidence to suggest which option is more effective in alleviating pain. Nalbuphine may present advantages over morphine when considering adverse events. This study aimed to evaluate and compare the pain scores, motor blockade, and side effects associated with the use of intrathecal morphine versus nalbuphine in conjunction with bupivacaine during laparoscopic gynaecological procedures.

Material and Methods

A hospital-based study was carried out over six months, following the approval of the Institutional Ethics Committee. This prospective, comparative, randomised, double-blinded research design ensured rigorous methodology throughout the investigation. A total of 100 patients classified as American Society of Anaesthesiology (ASA) Class I/II, aged between 18 and 65 years, were recruited for this study, all of whom were undergoing elective laparoscopic gynaecological procedures. On the day before surgery, all patients underwent a pre-anaesthetic checkup, adhering to institutional guidelines regarding nil by mouth (NBM) orders. All patients provided written and informed consent.

The sample size was determined by the anticipated difference of 135 minutes (±54.10) when comparing the mean duration of analgesia between the study groups, as indicated by the pilot study conducted at our tertiary care centre. The sample size was increased to 50 participants in each group, maintaining an alpha error of 0.05 and achieving a power of 80%, to ensure a thorough evaluation of additional study variables.

On the day of the procedure in the operating room, standard five-lead electrocardiogram (ECG), non-invasive blood pressure (NIBP), end-tidal carbon dioxide (EtCO2) measurement, and pulse oximetry (SpO2) were applied, and baseline parameters were recorded. Access to the venous system has been successfully established. All necessary equipment and medications for resuscitation, airway management, and ventilation were prepared and on standby.

Following a thorough explanation of the study to the chosen participants, they were randomly assigned to two groups utilising the sealed envelope method. The anaesthesiologists overseeing the intraoperative and postoperative phases, along with the patients, were kept unaware of the group assignments to which they were affiliated. A Subarachnoid Block (SAB) was executed utilising 2 ml of Bupivacaine, combined with an additive, administered via a 25-gauge Quincke's spinal needle at the L3/4 or L4/5 intervertebral space. The procedure was conducted in the sitting position while adhering to strict aseptic protocols, in line with established institutional guidelines. Following this, patients were positioned supine.

Group A received a combination of 100μg of morphine with bupivacaine.

Group B: Administration of Nalbuphine 400 μg in conjunction with Bupivacaine

The onset of sensory anaesthesia was evaluated using pin prick sensation, while the assessment of motor block was conducted through the modified Bromage scale. A waiting period of 20 minutes or the duration required for optimal spinal response, whichever came first. No instances of failed SAB were reported.

Prior to induction, patients received premedication consisting of glycopyrrolate at a dose of 0.2 mg, midazolam at 0.03 mg/kg, and fentanyl at 1.5 mcg/kg administered intravenously. All patients were administered ondansetron to mitigate the risk of postoperative nausea and vomiting. The induction of anaesthesia was achieved using propofol at a dosage of 2mg per kilogramme of body weight. Vecuronium at a dosage of 0.1 mg/kg was administered to assist with endotracheal intubation. The anaesthesia protocol involved a balanced mixture of air and oxygen at a ratio of 50:50, alongside the administration of isoflurane and vecuronium to ensure optimal sedation and muscle relaxation during the procedure. Isoflurane was administered at the minimum concentration required to keep mean arterial pressure (MAP) and heart rate (HR) within 20% of baseline levels.

The alterations in heart rate, systolic and diastolic blood pressure, as well as mean arterial pressure, were documented at intervals of 0, 2, 5, 10, and 15 minutes, followed by additional measurements every 15 minutes until 30 minutes post-spinal anaesthesia, or until the study endpoint was reached. Fluid replacements during the operation were

administered as needed, taking into account the extent of blood loss and the haemodynamic indicators. During the procedure, intraoperative hypotension was addressed with colloids, while bradycardia was treated using 0.6 mg of atropine. Upon completion of the procedure, the neuromuscular blockade was effectively reversed using neostigmine at a dosage of 0.05 mg/kg, alongside glycopyrrolate administered at 80 mcg/kg via intravenous route. Patients were extubated upon the return of spontaneous respiration and their ability to follow simple verbal commands. Patients were monitored for the regression of SAB in the postoperative room for the subsequent two hours.

Post-operative side effects such as hypotension, bradycardia, respiratory depression, nausea and vomiting, as well as pruritus, were documented. The intensity of pain was evaluated using the Visual Analogue Scale (VAS) at intervals of 0, 10, 15, 30, and 60 minutes, followed by assessments every 30 minutes until 24 hours post-operatively or until the patient required a rescue analgesic. Patients who indicated a VAS score of 3.5 or higher were administered rescue analgesics, specifically an intravenous injection of diclofenac at a dosage of 75 mg, with subsequent doses given every six hours. The management of nausea and vomiting involved the administration of Inj Ondansetron 4 mg intravenously, while pruritus was addressed with Inj. Hydrocortisone 100 mg intravenously. In our study, we evaluated and compared several key outcomes, including the duration of motor blockade measured by the Modified Bromage score, the Visual Analogue Scale (VAS) for pain, and the occurrence of adverse effects such as nausea, vomiting, pruritus, urinary retention, and respiratory depression.

Statistical analysis: The collected data was organised and input into a spreadsheet application (Microsoft Excel 2019) before being exported to the data editor interface of SPSS version 15 (SPSS Inc., Chicago, Illinois, USA). Quantitative variables were characterised using means and standard deviations or medians and interquartile ranges, depending on their distribution patterns. Qualitative variables were reported in terms of counts and percentages. The confidence level for all tests was established at 95%, while the level of significance was set at 5%.

Results

The average age of participants in our study was 42.50 years with a standard deviation of 10.78, while group B had an average age of 41.20 years and a standard deviation of 9.65. The comparison of mean age, ASA Grade, and weight between the two groups revealed no statistically significant differences, with a p-value greater than 0.05 (see Table 1). Both groups A and B experienced complete motor blockade following the intubation of spinal anaesthesia. Following extubation, the mean motor blockade scores were recorded at 4.20±0.54 for group A and 4.22±0.42 for group B, as detailed in Table 2. The mean motor blockade score recorded after 12 hours was 5.94±0.48 for group A and 5.92±0.34 for group B. The analysis revealed no notable differences in motor blockade scores between groups A and B. The mean Visual Analogue Scale (VAS) scores following extubation and at the 3-hour mark were similar across both groups. However, at the 6, 12, and 24-hour intervals, group B exhibited higher scores compared to group A, although these differences were not statistically significant, with p values exceeding 0.05. Table 2

Nausea and vomiting were reported in 43% and 46% of participants in group A, while the incidence was noted in 33% and 40% of subjects in the other group, respectively. Pruritus was observed in 10% of subjects in group A, while none in group B, indicating a statistically significant difference between the two groups.

Table 1: Demographic data among the study groups

Variables	Group A	Group B	P value
Age in years (Mean±SD)	42.50±10.78	41.20±09.65	0.1
ASA Grade (1/2)	23/27	26/24	0.09
Weight in Kg (Mean±SD)	57.90±10.22	56.05±09.65	0.42

Statistically significance at $p \leq 0.05$

Discussion

Postoperative pain has long been a significant issue of concern. In recent years, intrathecal morphine has gained traction as a method for managing pain following laparoscopic surgeries. Numerous studies indicate that patients administered intrathecal morphine face a notably heightened risk of experiencing nausea, vomiting, pruritus, along with a marginal risk of respiratory depression. Nalbuphine demonstrates a superior safety profile compared to morphine regarding specific side effects.[11,12] This study aimed to evaluate the effectiveness and side effects of intrathecal morphine compared to nalbuphine in laparoscopic gynaecological procedures when used alongside bupivacaine.

The baseline characteristics, including mean age, ASA grade, and weight, were found to be comparable between the two groups in our study. In a study conducted by Shiv Akshat and colleagues[13], comparable findings were reported.

Table 2: Comparison of motor blockade and VAS among both the study groups

Variable	Group A	Group B	P value
Motor Blockade (Modified bromage scale)			
After Spinal Anesthesia	1.45±0.2	1.30±0.5	0.9
After Extubation	4.20±0.54	4.22±0.42	0.75
After 3 Hour	5.32±0.10	5.35±0.36	0.64
After 6 Hour	5.85±0.50	5.86±0.48	0.70
After 12 Hour	5.94±0.48	5.92±0.34	0.65
VAS			
After Extubation	2.50±0.92	2.15±0.72	0.42
After 3 Hour	3.20±0.48	3.40±0.54	0.20
After 6 Hour	2.95±0.65	3.2±0.70	0.23
After 12 Hour	2.82±0.75	3.10±0.74	0.15
After 24 Hour	2.70±0.40	2.90±0.55	0.32

Statistically significance at $p \leq 0.05$

The similarity in baseline characteristics effectively reduced the potential for bias in the outcomes observed.The preemptive use of an analgesic medication prior to the onset of a pain stimulus has the potential to inhibit the onset of pain hypersensitization. Numerous interventions exist for potential application as preemptive analgesia in lumbar spinal surgery. These include epidural analgesia, local anaesthetic wound infiltration, systemic opioids, and systemic nonsteroidal anti-inflammatory drugs.[14-16]Nalbuphine functions as a partial agonist, in contrast to morphine, which acts as a pure agonist. Morphine acts as an agonist on both opioid receptors, while nalbuphine specifically functions as a kappa agonist. In terms of analgesic effects, morphine operates through both spinal and supraspinal mechanisms, whereas nalbuphine primarily functions through spinal pathways. The current research found no notable differences in motor blockade scores between groups A and B. Shiv Akshat et al[13] conducted an analysis that uncovered comparable findings; however, notable discrepancies were noted across various timeframes between the two groups. The relationship between μ opiates and nalbuphine is intricate. Research indicates that at lower doses, nalbuphine enhances the effects of μ opiates. However, at higher doses, it appears to act as an antagonist to these opiates. Studies have confirmed that a 1:1 ratio of morphine to nalbuphine provides a superior analgesic effect for patient-controlled intravenous analgesia (PCIA) following gynaecologic surgeries compared to other ratio groups. The onset and duration of analgesic action of nalbuphine closely resemble those of morphine. Additionally, nalbuphine boasts a superior safety profile, exhibiting a reduced incidence of adverse reactions such as pruritus and respiratory depression.[17] Research on the effectiveness of nalbuphine in caesarean sections remains sparse, with only a handful of studies conducted to date. Culebras et al[18] have indicated that administering intrathecal nalbuphine at a dosage of 0.8 mg for caesarean sections yields an analgesic effect comparable to that of intrathecal morphine, while also resulting in fewer adverse events.

Nalbuphine exhibits a complex pharmacodynamic profile, acting as an agonist at kappa receptors while simultaneously antagonising mu receptors. The ceiling effect is achieved via analgesia through kappa receptors, leading to unpredictable pain relief during surgical procedures. The analgesic effects of nalbuphine are not easily predictable from a pharmacokinetic standpoint, owing to its varied pharmacodynamic characteristics. Although there were statistically significant variations in VAS scores at various stages of the postoperative cycle, instances of care failure that required rescue analgesia were not observed. It can be suggested that nalbuphine might be suitable for managing pain after surgery. In a study conducted by Yeh et al.,[19] various combinations of morphine and nalbuphine demonstrated comparable outcomes. e. Bindra et al.[20] have shown that the combination of intrathecal nalbuphine at 0.8 mg and fentanyl at 20 μg serves as effective adjuvants to bupivacaine for subarachnoid blocks. Notably, nalbuphine offers prolonged analgesia, making it a viable alternative to fentanyl in the context of caesarean sections. Research conducted by Chen et al. has evaluated the effectiveness of intravenous nalbuphine following a caesarean section.[21] A recent randomized controlled trial revealed that nalbuphine effectively alleviated pruritus induced by intrathecal morphine while also leading to a notable decrease in overall opioid consumption. Despite variations in the methods of drug administration in previous studies, all have consistently demonstrated the effective analgesic properties of nalbuphine, with no corresponding rise in adverse events reported.

Nausea and vomiting were reported in 43% and 46% of participants in group A, while group B showed similar symptoms in 33% and 40% of its subjects, respectively. The study found that pruritus was present in 10% of subjects in group A, while none in group B, highlighting a statistically significant difference between the two groups. Pruritus is a side effect associated with morphine, whereas nalbuphine does not exhibit this particular reaction. Nalbuphine has been shown to be effective in

addressing pruritus caused by morphine use. The side effects and pharmacodynamics profiles of these two drugs exhibit notable similarities. Comparable findings were documented by Shiv Akshat and colleagues[13] in their research. Other authors have also reported the absence of pruritus with nalbuphine. A meta-analysis conducted by Zheng Zeng and colleagues[22] indicated that nalbuphine may offer benefits over morphine in terms of reducing pruritus, nausea, vomiting, and respiratory depression.

The diverse range of gynaecological procedures included in the study may have had an impact on our findings to a certain degree. The VAS score serves as a subjective measure, and its interpretation may vary among patients. Additional research focussing on the limitations mentioned may shed light on the mechanisms behind postoperative pain following laparoscopic gynaecologic surgery and lead to the development of more effective strategies for alleviating pain intensity across various laparoscopic procedures.

Conclusion

The analgesic effectiveness of nalbuphine is on par with that of morphine; however, nalbuphine offers a superior safety profile, particularly concerning the incidence of pruritus. Additional research involving a larger cohort is essential to validate our trial findings and to conduct a more comprehensive assessment of the maternal and neonatal safety profile of nalbuphine.

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