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A comparative study of intrathecal morphine v/s nalbuphine along with bupivacaine in laparoscopic gynaecological procedures

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ABSTRACT

Background and Aim: To compare the pain score of intrathecal morphine v/s nalbuphine along with bupivacaine in laparoscopic gynaecological procedures under general anaesthesia.**Materials and Methods:** A prospective, comparative, randomized, double blinded, hospital based study was conducted among patients undergoing elective laparoscopic gynaecological procedures. After explaining the study to the selected patients, they were randomized into two groups of 30 each with the use of sealed envelope method i.e. group M (100 µg morphine + 2 ml bupivacaine) and group N (400 µg Nalbuphine + 2 ml bupivacaine). The primary objective of our study was to compare the pain intensity which was done by visual analogue scale (VAS). Any side-effects in the form of post-operative hypotension, bradycardia, respiratory depression, nausea, vomiting and pruritus were recorded and included as secondary objectives. With the help of SPSS version 24, difference between the continuous and categorical variables was analysed using t and chi square test respectively.**Results:** There was no significant difference among both groups with respect to motor blockade score. Mean VAS after extubation and 3 hour was comparable among both the groups, but at 6, 12 and 24 hour, it was comparatively more in group N as compared to group M, though statistically insignificant. Pruritus was revealed in 10% and 0% of the subjects among group M and N respectively.**Conclusion:** Our results conclude that the analgesic efficacy of nalbuphine is comparable to morphine, but nalbuphine provides a better safety profile than morphine especially related to pruritus.This is an Open Access (OA) journal, and articles are distributed under the terms of the [Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License](https://creativecommons.org/licenses/by-nc-sa/4.0/), which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.For reprints contact: reprint@ipinnovative.com

1. Introduction

Laparoscopic surgery can be used by most surgically indicated patients in the field of gynaecology with recent developments in laparoscopic surgical instruments and techniques.¹ Total laparoscopic hysterectomy and laparoscopic myomectomy are regularly conducted in our institution in laparoscopic gynaecological surgeries. Latest findings suggest that combined spinal (SAB) and general anaesthesia (GA) is safer for laparoscopic hysterectomy

than general anaesthesia alone.² In our institution we follow combined SAB & GA approach for all the gynaecological surgical procedures.

Traditionally, most patients are treated with an injection of epidural morphine for the first 24 hours, accompanied by need based oral analgesia.³ However because of the intolerable adverse effects associated with morphine, alternative opioid like nalbuphine can be used as an option. Nalbuphine is a phenanthrene sequence opioid agonist-antagonist that was synthesized in an effort to provide analgesia without the pure agonists' unwanted side effects.⁴ Its analgesic and probably certain anti-pruritic effects are

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mediated by actions on the mu (μ) and kappa (κ) receptors.⁵ When used for treating conditions ranging from burns, multiple trauma, orthopaedic injuries, gynaecology and intra-abdominal conditions, it has been proven to be safe and reliable.⁶

The comparative effectiveness and safety findings between morphine and nalbuphine are contradictory in different literature.⁷ Therefore, there is little evidence to indicate which one is better at treating pain. In terms of adverse events, nalbuphine may have benefits over morphine.^{4,6} Hence the present study was conducted to compare the pain score, motor blockade and side effects effect of intrathecal morphine v/s nalbuphine along with bupivacaine in laparoscopic gynaecological procedures.

We hypothesize that both nalbuphine and morphine have same analgesic efficacy. Primary objectives of our study was to compare the pain intensity in both the groups which was done by visual analogue scale (VAS). Secondary objective of our study was to compare adverse effects among subjects receiving nalbuphine and morphine.

2. Materials and Methods

A prospective, comparative, randomized, double blinded, hospital based study was conducted over a period of 6 months from April 2020 to September 2020 after taking approval from the Institutional Ethics Committee (reference number MGMCH/IEC/JPR/2020/38). The study was registered prospectively with the Clinical Trials Registry- India (www.ctri.nic.in) with registration no.: CTRI/2020/03/0321. The trial followed the consort guidelines (Diagram 1). A total of 60 patients of American Society of Anaesthesiology (ASA) of Class I/ II, aged 18-65 years undergoing elective laparoscopic gynaecological procedures were recruited for the study. All patients were visited on the day prior to surgery for pre anaesthetic check up and nil by mouth (NBM) orders according to institutional guidelines. Written and informed consent was taken from all the patients.

The sample size was calculated based on the expected difference of 135 min (± 53.70) on comparison of mean duration of analgesia between the study groups as per the pilot study carried out at our tertiary care center. The sample size required was 9 in both the groups at α error 0.05 and with a power of 80%. This sample size was enhanced to 30 in each group to enable adequacy in the assessment of other study variables.

On the day of surgery in the operation room, standard 5 leads electrocardiogram (ECG), non-invasive blood pressure (NIBP), end-tidal carbon dioxide (EtCO₂) measurement and pulse oximetry (SpO₂) were attached and base line parameters were noted. Venous access was secured. Equipment and drugs for resuscitation, airway management and ventilation were kept ready.

After explaining the study to the selected patients, they were randomized into two groups with the use of sealed envelope method.

The anaesthesiologists managing the intraoperative and postoperative courses as well as patients were blinded to knowledge of the group to which they belonged.

Subarachnoid Block (SAB) was performed with 2 ml of Bupivacaine with additive in the same syringe injected in L3/4 or L4/5 intervertebral space, using a 25 gauge Quincke's spinal needle, in the sitting position, maintaining all aseptic precautions, according to the standard institutional protocol. Thereafter, patients were placed in supine position.

Group-M: Morphine 100 μ g added Bupivacaine.

Group N: Nalbuphine 400 μ g added to Bupivacaine.

Onset of sensory anesthesia was checked with pin prick sensation, and motor block assessment was carried out with modified Bromage scale. A waiting period of 20 min or time for maximal spinal action, whichever occurred earlier. There was no case of failed SAB.

Before induction patients were premedicated with glycopyrrolate 0.2 mg, midazolam 0.03 mg/kg, and fentanyl 1.5 mcg/kg intravenously. All patients received ondansetron to prevent postoperative nausea and vomiting. Anaesthesia was induced with 2mg/kg body weight propofol. Vecuronium 0.1 mg/kg was given to facilitate endotracheal intubation. Anesthesia was maintained with air and oxygen mixture (50:50), isoflurane, and vecuronium. Isoflurane was used in lowest possible concentration necessary while maintaining mean arterial pressure (MAP) and heart rate (HR) within 20% of baseline.

The changes in HR, systolic and diastolic blood pressure (B.P.) and MAP were recorded at 0, 2, 5, 10 and 15 min and then at 15-min intervals up to 300 min after SAB, or up to the end point of study. Intraoperative fluid replacements were given as necessary depending on the blood loss and hemodynamic parameters. Intraoperative hypotension and bradycardia were managed with colloids and atropine 0.6 mg respectively. At the end of the procedure, neuromuscular blockade was reversed with neostigmine 0.05 mg/kg and glycopyrrolate 80 mcg/kg intravenously. Patients were extubated when they regained spontaneous respiration and started obeying simple verbal commands. Patients were observed for regression of SAB in the postoperative room for the next 2 h.

Any side-effects in the form of post-operative hypotension, bradycardia, respiratory depression, nausea and vomiting (in presence of stable hemodynamic parameters) and pruritus were recorded. Intensity of pain was assessed by VAS at 0, 10, 15, 30 and 60 min and then at 30-min intervals till 24 hr post operatively or until the patient received a rescue analgesic. Patients reporting a VAS score 3.5 or more received rescue analgesics in the form of injection diclofenac 75 mg IV and after that repeated

Diagram 1: Consort diagram

every 6 hourly. Nausea and vomiting were treated with Inj Ondansetron 4 mg i.v. and pruritus with Inj. Hydrocortisone 100 mg i.v.

The outcomes assessed and compared in our study were duration of motor blockade assessed by Modified Bromage score, VAS pain score and the incidence of nausea, vomiting, pruritus, urinary retention and respiratory depression.

The statistical analysis was done using Statistical Package for Social Science evaluation (SPSS) version 24. Results are expressed as mean, standard deviation, and range values. Frequencies expressed as number and percentage. Difference between the continuous and categorical variables was analysed using t and chi square test respectively. P value of 0.05 or less is considered for statistical analysis.

3. Results

In our study mean age of study subjects was 41.78 ± 9.87 and 40.59 ± 10.81 years in group M and N respectively. When

mean age, ASA Grade (1/2) and weight (Kg) was compared among both the groups, it was found to be statistically insignificant as $p > 0.05$ (Table 1).

Complete motor blockade was achieved in group M as well as N after intubation of spinal anesthesia. As shown in Table 2 after extubation mean motor blockade score was 4.17 ± 0.13 and 4.21 ± 0.12 in group M and N respectively. Mean motor blockade score after 12 hours was 5.92 ± 0.39 and 5.91 ± 0.44 in group M and N respectively. There was no significant difference among group M and N with respect to motor blockade score. Mean VAS after extubation and 3 hours was comparable among both the groups, but at 6, 12 and 24 hours, it was comparatively more in group N as compared to group M, though statistically insignificant as $p > 0.05$.

Nausea and vomiting was found among 43.33%, 46.67% of group M, while the same was reported among 33.33% and 40% of the subjects in group N respectively. Pruritus was revealed in 10% and 0% of the subjects among group M and N respectively with statistically significant difference.

Table 1: Demographic data among the study groups

Variables	Group M	Group N	p value
Age in years (Mean±SD)	41.78±9.87	40.59±10.81	0.79 ^g
ASA Grade (1/2)	13/17	16/14	0.47 ^l
Weight in Kg (Mean±SD)	58.19±9.91	56.71±10.08	0.14 ^g

^g:t test, ^l:Chi Square test**Table 2:** Comparison of motor blockade and VAS among both the study groups

Variables	Group M Mean± SD	Group N Mean±SD	95% CI (Lower – Upper Bound)	p value ^g
Motor Blockade (Modified bromage scale)				
After Spinal Anesthesia	1.3±0.02	1.27±0.01	0.022-0.038	0.88
After Extubation	4.17±0.13	4.21±0.12	-0.11-0.025	0.84
After 3 Hour	5.24±0.27	5.32±0.22	-0.21-0.047	0.83
After 6 Hour	5.79±0.42	5.80±0.36	-0.21-0.19	0.91
After 12 Hour	5.92±0.39	5.91±0.44	-0.21-0.23	0.92
VAS				
After Extubation	2.4±0.93	2.1±0.74	-0.13-0.73	0.35
After 3 Hour	3.1±0.62	3.46±0.59	-0.67-0.05	0.19
After 6 Hour	2.93±0.61	3.3±0.68	-0.70-0.04	0.11
After 12 Hour	2.81±0.64	3.08±0.68	-0.61-0.07	0.14
After 24 Hour	2.69±0.56	2.93±0.54	-0.52-0.04	0.23

^g:t test**Table 3:** Incidence of nausea, vomiting, pruritus, urinary retention and respiratory depression

Variables	Group M		Group N		p value ^l
	N	%	N	%	
Nausea	13	43.33	10	33.33	0.37
Vomiting	4	13.33	3	10	0.81
Pruritus	4	10	0	0	0.04*
Urinary Retention	0	0	0	0	1
Respiratory Depression	0	0	0	0	1

*: statistically significant, ^l:Chi Square test

(Table 3)

4. Discussion

Postoperative pain, historically, is a matter of concern.^{8,9} Intrathecal morphine has become popular in recent years for pain control after laparoscopic surgeries.³ But, many studies have shown that patients receiving intrathecal morphine showed a significantly increased risk of nausea, vomiting, pruritus, and a slight risk of respiratory depression. Nalbuphine provides better safety profile than morphine in the aspect of certain side-effects.^{4,5} The present research was carried out to determine the effectiveness vis-à-vis side effects of intrathecal morphine v/s nalbuphine in laparoscopic gynaecological procedures in combination with bupivacaine.

In our study baseline characteristics viz mean age, ASA grade and weight was comparable in both the groups. Shiv Akshat et al¹⁰ in their study reported similar results. As the baseline characteristics are same, so chances of bias on outcome was also minimized.

Nalbuphine is a partial agonist, whereas morphine is a pure agonist. On both opioid receptors, morphine has an agonist effect, whereas nalbuphine is a kappa agonist. Therefore in its analgesic effect, morphine has both spinal and supraspinal components, while nalbuphine mainly has spinal components. In the present study, there was no significant difference among group M and N with respect to motor blockade score. Similar findings were revealed by Shiv Akshat et al¹⁰ in their analysis, but substantial variations were observed at different periods between the two classes.

In their meta-analysis, Zheng Zeng et al⁷ observed that there was no substantial difference in pain relief in pooled analyses between nalbuphine and morphine (pooled RRs, 1.01; 95% confidence interval [CI], 0.91 to 1.11; P = 0.90). Baxter et al¹¹ in their study revealed that pain levels were lowest in the morphine community (P < 0.01), suggesting an analgesic efficacy benefit for morphine.

Nalbuphine has diverse pharmacodynamics of kappa receptor agonism and mu receptor antagonisms. The

ceiling effect is accomplished by analgesia through kappa receptors and thus provides unpredictable analgesia for surgical procedures. The analgesic activity of nalbuphine is therefore not pharmacokinetically predictable due to diverse pharmacodynamic profile of nalbuphine.⁷ Despite statistically meaningful variations in VAS scores observed at different points in the postoperative cycle; care failure, necessitating rescue analgesia, was never seen. It may thus be postulated that nalbuphine could be appropriate for postoperative regulation of pain. Yeh et al¹² in a study using different combinations of morphine and nalbuphine, revealed similar result.

Nausea and vomiting was found among 43.33%, 46.67% in group M, while the same was reported among 33.33% and 40% of the subjects in group N respectively. Pruritus was revealed in 10% and 0% of the subjects among group M and N respectively with statistically significant difference in the present study. Pruritus is caused by morphine, although nalbuphine does not share this side effect. Nalbuphine can actually be used in the treatment of morphine-induced pruritus.⁷ Other side effects and pharmacodynamics profile are similar between these two drugs. Similar results were reported by Shiv Akshat et al¹⁰ in their study. Absence of pruritus with nalbuphine has also been reported by other authors. In a meta-analysis by Zheng Zeng et al,⁷ the results suggested an advantage of nalbuphine over morphine regarding pruritus, nausea, vomiting and respiratory depression.

Therefore, nalbuphine, which has almost similar analgesia effect with morphine but has an advantage over morphine related to some side effects, is another option for pain control.

Due to smaller sample size we could not observe the outcome parameters in similar operation. Study conducted in varied gynaecological procedures might have influenced our results to some extent. VAS score is a subjective indicator, which may not be so precisely appreciated by patients. Further studies addressing the limitations highlighted above may clarify the mechanism of postoperative pain after laparoscopic gynecologic surgery and develop more effective methods to reduce the intensity of pain in different laparoscopic surgery.

The strength of our study is in its design. To the best of our knowledge, this study is one of the few studies conducted to compare the impact of intrathecal morphine v/s nalbuphine along with bupivacaine in laparoscopic gynaecological procedures under general anaesthesia.

5. Conclusion

Our results conclude that the analgesic efficacy of nalbuphine is comparable to morphine, but nalbuphine provides a better safety profile than morphine especially related to pruritus.

6. Source of Funding

None.

7. Conflict of Interest

The authors declare no conflict of interest.

References

1. Dargent D, Martin X, Sacchetti A, Mathevet P. Laparoscopic vaginal radical trachelectomy. *Cancer*. 2000;88:1877–82.
2. O'Malley C, Cunningham AJ. Physiologic changes during laparoscopy. *Anesthesiol Clin North Am*. 2001;19(1):1–19.
3. Kong SK, Onsiong SM, Chiu WK, Li MK. Use of intrathecal morphine for postoperative pain relief after elective laparoscopic colorectal surgery. *Anaesthesia*. 2002;57(12):1168–73.
4. Pinnock CA, Bell A, Smith G. A comparison of nalbuphine and morphine as premedication agents for minor gynaecological surgery. *Anaesthesia*. 1985;40(11):1078–81.
5. Zacny JP, Conley K, Marks S. Comparing the subjective, psychomotor and physiological effects of intravenous nalbuphine and morphine in healthy volunteers. *J Pharmacol Exp Ther*. 1997;280(3):1159–69.
6. Stene JK, Stofberg L, Macdonald G, Myers RA, Ramzy A, Burns B. Nalbuphine analgesia in the prehospital setting. *Am J Emerg Med*. 1988;6(6):634–9.
7. Zeng Z, Lu J, Shu C, Chen Y, Guo T, Wu QP. A comparison of nalbuphine with morphine for analgesic effects and safety : meta-analysis of randomized controlled trials. *Sci Rep*. 2015;5:10927.
8. Chambers JA, Guly HR. Prehospital intravenous nalbuphine administered by paramedics. *Resuscitation*. 1994;27(2):153–8.
9. Gear RW, Miaskowski C, Gordon NC, Paul SM, Heller PH, Levine JD. The kappa opioid nalbuphine produces gender- and dose-dependent analgesia and antianalgesia in patients with postoperative pain. *Pain*. 1999;83(2):339–45.
10. Akshat S, Ramachandran R, Rewari V, Chandralekhya, Trikhya A, Sinha R. Morphine versus Nalbuphine for Open Gynaecological Surgery: A Randomized Controlled Double Blinded Trial. *Pain Res Treat*. 2014;2014:727952.
11. Baxter AD, Samson B, Penning J, Doran R, Dube LM. Prevention of epidural morphine-induced respiratory depression with intravenous nalbuphine infusion in post-thoracotomy patients. *Can J Anaesth*. 1989;36(5):503–9.
12. Yeh YC, Lin TF, Lin FS, Wang YP, Lin CJ, Sun WZ. Combination of opioid agonist and agonist-antagonist: patient-controlled analgesia requirement and adverse events among different-ratio morphine and nalbuphine admixtures for postoperative pain. *Br J Anaesth*. 2008;101(4):542–8.

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