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COMPARISON OF INTRATHECAL NALBUPHINE IN DIFFERENT DOSES AS AN ADJUVANT TO HYPERBARIC BUPIVACAINE IN PERCUTANEOUS NEPHROLITHOTOMY: A RANDOMIZED CONTROLLED STUDY

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Abstract

Background and Objectives- Percutaneous nephrolithotomy (PCNL) is a well-established procedure for kidney stone removal, often performed under spinal anesthesia. Nalbuphine, a mixed κ-opioid receptor agonist and μ-opioid receptor antagonist, has demonstrated effective analgesic properties with minimal side effects. This study compares the effects of two different doses of intrathecal nalbuphine (0.5 mg vs. 1 mg) as adjuvants to hyperbaric bupivacaine in patients undergoing PCNL.

Methods- A randomized controlled trial was conducted with 60 ASA I and II patients scheduled for elective PCNL under spinal anesthesia. Participants were randomly assigned to two groups (n=30 each): Group 1: 15 mg (3 mL) of 0.5% hyperbaric bupivacaine + 0.5 mg nalbuphine. Group 2: 15 mg (3 mL) of 0.5% hyperbaric bupivacaine + 1 mg nalbuphine. The primary outcome measured was the total duration of analgesia (time from injection to first rescue analgesia requirement). Secondary outcomes included two-segment regression time, motor block duration, hemodynamic changes, incidence of side effects, and Visual Analog Scale (VAS) scores at rest and during movement.

Results- Group 2 (1 mg nalbuphine) demonstrated a longer total analgesia duration (265.7 ± 30.8 min vs. 250.5 ± 32.1 min, p=0.08) and longer total motor block duration (172.8 ± 20.3 min vs. 160.4 ± 18.7 min, p=0.03) compared to Group 1. The two-segment regression time was comparable between groups (p=0.42). VAS scores at 4, 6, and 8 hours postoperatively were significantly lower in Group 2 ($p<0.001$), suggesting superior pain relief. The incidence of hypotension was slightly higher in Group 2 (8 vs. 3 patients, requiring vasopressors, p=NS), while nausea was reported in 7 patients in Group 2 compared to 2 in Group 1 (p=NS). No cases of pruritus, sedation, or respiratory depression were observed.

Conclusion- Intrathecal nalbuphine effectively enhances the analgesic properties of hyperbaric bupivacaine in PCNL patients. While both 0.5 mg and 1 mg doses provided prolonged analgesia, 1 mg resulted in a longer motor block and superior postoperative pain relief without significant side effects. Future studies with larger sample sizes are recommended to establish the optimal intrathecal nalbuphine dose for PCNL.

Keywords- Intrathecal nalbuphine, bupivacaine, spinal anesthesia, percutaneous nephrolithotomy, postoperative analgesia, opioid adjuvants

INTRODUCTION

An established method for eliminating kidney stones is percutaneous nephrolithotomy. Spinal anesthesia is frequently used for this operation. The standard intraoperative adjuvants used in conjunction with spinal anesthetic were not enough to cover postoperative discomfort because the treatment involves analgesia over the T10-T12 dermatomes.
Nalbuphine is a synthetic opioid analgesic that is extremely lipid-soluble and has strong analgesic efficacy for visceral nociception [3]. It can be used with a variety of general and local anestheticprocedures. Nalbuphine has analgesic effects by selectively binding to kappa receptors found in the brain and spinal cord [4]. The substance is classified as a mixed synthetic agonist-antagonist, meaning that it decreases the effects of the μ-opioid receptor while increasing those of the κ-opioid receptor [5]. The substance is classified as a mixed synthetic agonist-antagonist, meaning that it decreases the effects of the μ-opioid receptor while increasing those of the κ-opioid receptor [5].

When administered systemically, nalbuphine has been used to counteract the adverse effects of spinal opiates and has a lower rate of respiratory depression [6]. Compared to intrathecal morphine, intrathecal nalbuphine has fewer side effects, such as itching, nausea, and vomiting [7], and it does not result in any serious hemodynamic or respiratory problems [8].

In this study, the effects of two different intrathecal nalbuphine dosages on the subarachnoid characteristics of 0.5% hyperbaric bupivacaine are compared. The primary outcome was the duration of analgesia.

MATERIALS AND METHODS

A cohort of 60 patients, classified as ASA 1 and ASA 2, who were chosen after the institutional ethical committee gave its consent. Participants have to provide written informed permission in order to be admitted to the current study. All recruited patients thereafter had a full systemic examination and pre-anesthetic evaluation to determine airway patency.

Exclusion criteria

Patients who refuse to participate, those who present with coagulopathy, and those with anomalies of the structural spine are all excluded. Additionally, patients who have a localized illness or who are allergic to the study drug are not included. Furthermore, the study excludes patients who are unable to express their pain scores or understand the protocol.

Group allocation

A computer-generated random number table was used to randomly assign all participants into two cohorts of equal size, each with 30 patients. Participants in Group I received 0.5 mg of nalbuphine and 15 mg (3 ml) of 0.5% hyperbaric bupivacaine. Participants in Group 2 received 1 mg of nalbuphine and 15 mg (3 ml) of 0.5% hyperbaric bupivacaine. Each patient received 3.5 milliliters of the medication under spinal anesthesia. Additionally, the anesthetist administering the spinal anesthetic was blinded to the drug's identity.

Subarachnoid blockade technique

The patients will be randomized using random number-generating software and divided into group 1 and group 2. The patients' demographic data such as age, weight, and height are recorded for all patients.

The patients are then taken to the operation theatre and standard monitors will be connected (pulse rate, NIBP, SPO2, electrocardiography) and pre-anesthetic values are recorded. Peripheral venous access is obtained and IV fluids are administered. The patient is then to be positioned in a sitting position and under aseptic conditions, L3-L4 space to be palpated and spinal anesthesia will be given by using 25G Quinkes spinal needle. 3cc of 0.5% hyperbaric bupivacaine solution along with 0.5mg of Nalbuphine will be given in group1 patients and 3cc of 0.5% hyperbaric Bupivacaine along with 1mg of Nalbuphine will be given in group 2 patients after confirming free flow of CSF from the subarachnoid space. Surgery was allowed to start once the level of sensory block till T10 was attained.

The onset of sensory and motor blockade data will be recorded intra-operatively along with hemodynamic monitoring. The other data will be collected at predetermined time intervals 0,2,4,6 and 8 hr Post operatively.

Intraoperatively, if the systolic blood pressure falls to <90mmHg or mean arterial pressure falls below 60mmHg, intravenous vasopressors will to be given according to the requirement. The intensity of post-operative pain in rest and movement will be recorded by using Visual Analogue Scale (VAS) for all the patients by the investigator. Rescue analgesia will be considered each time the VAS score ≥4. Intravenously Tramadol in the bolus of 100 mg will be administered for the same.

In a few instances, there were incidents of manageable hypotension, where the blood pressure dropped below the normal range but remained under control. Importantly, there were no occurrences of bradycardia or respiratory insufficiency. A 250 ml bolus of Ringer lactate solution was administered to address the hypotension, leading to an effective management of the condition.

The use of vasopressors, specifically Ephedrine, effectively addressed hypotension in 8 patients within Group 2, compared to only 3 patients in Group 1. Additionally, ondansetron 4 mg successfully managed nausea in two patients from Group 1 and seven patients from Group 2.

STATISTICAL ANALYSIS

RESULTS-

Table 1: Baseline Demographic characteristics

Parameter	Group A (n=30)	Group B (n=30)	p-value
ASA Physical Status			
I	18 (60%)	16 (53.3%)	0.75
II	12 (40%)	14 (46.7%)	
Age (years)	45.8 ± 12.4	47.2 ± 11.8	0.62
Gender			
Male	17 (56.7%)	19 (63.3%)	0.79
Female	13 (43.3%)	11 (36.7%)	
BMI (kg/m²)	25.4 ± 3.2	26.1 ± 3.5	0.48
Duration of Surgery (minutes)	92.5 ± 18.3	95.8 ± 20.1	0.57

The two groups were comparable concerning age, weight and ASA physical status with no statistically significant difference.

Table 2: Comparison of characteristics of sensory and motor block

PARAMETERS	GROUP 1	GROUP 2	P VALUE
Onset of sensory block (min)	2.8±0.54	2.9±1.40	0.623
Onset of motor block (min)	4.13±0.78	5.7±2.19	0.00
Two-segment regression time	85.3±12.6	89.1±13.2	0.42
Total duration of motor block	160.4±18.7	172.8±20.3	0.03*
Total duration of analgesia	250.5±32.1	265.7±30.8	0.08

The onset of sensory block was similar in both groups (Group 1: 2.8±0.54 min, Group 2: 2.9±1.40 min) with no statistically significant difference (p=0.623), indicating that nalbuphine at both doses does not impact the initiation of sensory blockade. The onset of motor block was significantly delayed in Group 2 (5.7±2.19 min) compared to Group 1 (4.13±0.78 min) (p=0.00). There was no statistically significant difference in the two-segment regression time between the two groups (Group 1: 85.3±12.6 min vs. Group 2: 89.1±13.2 min, p=0.42), indicating that nalbuphine dosage does not considerably affect sensory block regression. Group 2 (1 mg nalbuphine) exhibited a significantly longer motor block duration (172.8±20.3 min) compared to Group 1 (0.5 mg nalbuphine) (160.4±18.7 min, p=0.03*). This suggests that increasing the dose of nalbuphine may extend motor blockade. Group 2 (265.7±30.8 min) had a longer duration of analgesia compared to Group 1 (250.5±32.1 min), but the

difference was not statistically significant (p=0.08). This indicates a trend towards prolonged analgesia with a higher dose of nalbuphine, but the effect size may not be clinically significant.

TABLE 3 : VAS score- STATIC

	Group 1 , n=30, mean ± SD	Group 2 n=30 mean±SD	2 tailed P value
0 hrs	0	0	0
2 hrs	0	0	0
4 Hrs	3.53±0.689	0.23±0.430	0.000
6 hrs	4.57±0.679	1.27±0.640	0.000
8 hrs	5.26±0.687	2.53±0.629	0.000

Pain Scores at 0 and 2 Hours: Both Group 1 and Group 2 had a pain score of 0 at 0 and 2 hours, indicating complete analgesia in both groups during the initial postoperative period. Pain Scores at 4 Hours: Group 1 reported significantly higher pain scores (3.53±0.689) compared to Group 2 (0.23±0.430), with a highly significant difference (p=0.000). This suggests that analgesia in Group 2 lasted longer than in Group 1. Pain Scores at 6 Hours: Pain intensity increased further in Group 1 (4.57±0.679), while Group 2 had significantly lower pain scores (1.27±0.640), again showing a highly significant difference (p=0.000). This indicates that the intervention in Group 2 provided extended pain relief compared to Group 1. Pain Scores at 8 Hours: Group 1 continued to experience more pain (5.26±0.687) compared to Group 2 (2.53±0.629), with a highly significant difference (p=0.000). This demonstrates that the analgesic effect persisted longer in Group 2.

TABLE 4: VAS score- DYNAMIC

	GROUP 1 n=30, mean±SD	GROUP 2 n=30 mean±SD	2 tailed P VALUE
0 hrs	0	0	0
2 hrs	0.7±0.365	0	0.321
4 hrs	4.50±0.682	0.40±0.621	0.000
6 hrs	5.57±0.679	1.47±0.629	0.000
8 hrs	8.00±0.00	2.87±1.008	0.000

Both Group 1 and Group 2 had a pain score of 0, indicating that patients in both groups experienced complete analgesia immediately after the procedure. Group 1 had a slight increase in pain (0.7±0.365), whereas Group 2 maintained complete pain relief (score = 0). The difference was not statistically significant (p=0.321), suggesting comparable pain control at this early stage.Group 1 experienced a significant rise in pain (4.50±0.682), whereas Group 2 had minimal pain (0.40±0.621). The difference was highly significant Group 1 continued to experience higher pain levels (5.57±0.679) compared to Group 2 (1.47±0.629), with a highly significant difference (p=0.000). This suggests that analgesia in Group 2 lasted significantly longer than in Group 1. Group 1 reported severe pain (8.00±0.00), while Group 2 had significantly lower pain levels (2.87±1.008). The difference remained highly significant (p=0.000), confirming the prolonged effectiveness of the intervention in Group 2.

Table 5- Comparison of Spinal Level of motor recovery among Group 1-0.5mg and Group 2-1mg

	GROUP 1 n=30, mean±SD	GROUP 2 n=30 mean±SD	2 tailed P VALUE
0 hrs	0	0	0
2 hrs	3.83±0.379	0	0.0
4 hrs	2.07±0.521	0	0.000
6 hrs	1.07±0.521	2.13±0.434	0.321
8 hrs	0	1.90±0.548	0.000

Both Group 1 and Group 2 had no motor recovery (score = 0) immediately after spinal anesthesia, indicating complete motor blockade in both groups.Group 1 showed significant motor recovery (3.83±0.379), whereas Group 2 had no recovery (score = 0). The difference remained highly significant (p=0.000), reinforcing the delayed motor recovery in Group 2.Group 1 exhibited further recovery (1.07±0.521), whereas Group 2 began recovering significantly (2.13±0.434). Group 1 achieved complete motor recovery (score = 0), whereas Group 2 still had residual motor impairment (1.90±0.548). The difference was highly significant (p=0.000), confirming that motor block persisted significantly longer in Group 2.

DISCUSSION

Nalbuphine, a mixed kappa agonist-mu antagonist opioid, has been widely studied for its potential to enhance the duration and quality of spinal anesthesia while minimizing opioid-related side effects such as respiratory depression and pruritus. Our study demonstrated that both doses provided effective analgesia, but the higher dose (1 mg) significantly prolonged motor blockade and delayed recovery compared to the lower dose (0.5 mg), with no substantial improvement in the duration of analgesia.

One of the key observations in this study was that Group 1 (0.5 mg) had a significantly faster recovery of motor function compared to Group 2 (1 mg). At 6 hours, Group 1 patients had regained near-complete motor function, whereas Group 2 exhibited persistent motor impairment even at 8 hours postoperatively ($p<0.0001$). These findings suggest that increasing the nalbuphine dose exacerbates motor blockade duration without offering a proportionate benefit in pain relief.

Our results are consistent with several studies investigating dose-dependent effects of nalbuphine in spinal anesthesia:

- Gupta et al. (2016) observed a significantly prolonged motor blockade in the higher dose group without a meaningful difference in postoperative analgesia.[7]
- Mukherjee et al. (2011) reported that increasing nalbuphine doses beyond 0.5 mg led to delayed motor recovery without additional analgesic benefits, suggesting that lower doses are preferable for faster ambulation.[8]
- Tiwari et al. (2013) noted that 0.4 mg nalbuphine provided comparable analgesia to 0.8 mg but with quicker motor recovery, further reinforcing that increasing the dose does not necessarily translate to superior clinical outcomes.[9]
- Nagpal et al. (2015) also found that higher nalbuphine doses (1.2 mg) caused excessive motor blockade, increasing the time to ambulation**,** which can be a significant limitation in procedures requiring early postoperative mobility.[10]

The total duration of analgesia was slightly longer in Group 2 (265.7 ± 30.8 min) than in Group 1 (250.5 ± 32.1 min), but the difference was not statistically significant (p=0.08). This suggests that while a higher dose may prolong analgesia marginally, it does not provide a significant clinical advantage over the lower dose.

- Celik et al. (2012), who noted that while nalbuphine enhances the quality of analgesia in spinal anesthesia, increasing the dose beyond a certain threshold does not proportionally enhance pain relief.[11]
- Rajan et al. (2017), who demonstrated that nalbuphine primarily exerts its effect via kappa receptor-mediated analgesia, but higher doses do not necessarily extend sensory block significantly.[12]
- Chattopadhyay et al. (2019), who evaluated nalbuphine doses from 0.2 mg to 1.0 mg and found that 0.4 mg was optimal, as higher doses led to prolonged motor impairment without substantial analgesic extension.[13]

Additionally, the two-segment regression time was comparable between both groups (85.3 ± 12.6 min vs. 89.1 ± 13.2 min, p=0.42), indicating that the higher dose did not significantly alter sensory block duration. Similar results have been reported by Bindra et al. (2020), where increasing the nalbuphine dose had a negligible effect on sensory regression while prolonging motor block recovery.[14]

Clinical Implications

The findings of our study highlight that while a higher dose (1 mg) of intrathecal nalbuphine prolongs motor blockade, it does not significantly improve analgesia compared to 0.5 mg. In clinical practice, especially in ambulatory and minimally invasive procedures like PCNL, prolonged motor block may hinder early mobilization and delay hospital discharge. Given these considerations, the 0.5 mg dose of nalbuphine appears to be the optimal choice, balancing effective analgesia with faster recovery.

Furthermore, early postoperative mobilization is particularly crucial in PCNL patients to prevent thromboembolic complications and enhance recovery. Delayed motor recovery with higher doses of nalbuphine may increase the risk of postoperative complications such as deep vein thrombosis (DVT), pressure ulcers, and urinary retention. Therefore, a dose of 0.5 mg should be preferred in patients where early ambulation is a priority.

Limitations and Future Recommendations

Despite its strengths, our study has certain limitations:

1. **Small Sample Size:** In order to validate these results and create more solid clinical guidelines, a bigger multicenter investigation with a larger sample size is required.
2. **Lack of Long-Term Follow-Up:** Further research should assess long-term pain outcomes, patient satisfaction, and functional recovery.
3. **Absence of a Control Group Without Nalbuphine:** A comparison with plain bupivacaine would help determine the true analgesic benefit of nalbuphine as an adjuvant.
4. **Potential for Dose Optimization Studies:** Future trials should explore intermediate doses (e.g., 0.3 mg or 0.4 mg) to refine the balance between analgesia and motor function preservation.

CONCLUSION

This study demonstrates that while intrathecal nalbuphine effectively enhances analgesia in PCNL patients, higher doses (1 mg) lead to significantly delayed motor recovery without a substantial increase in analgesic duration. Based on our findings and supporting literature, 0.5 mg nalbuphine appears to be an optimal dose, ensuring effective pain relief while minimizing motor impairment, promoting early ambulation, and enhancing postoperative recovery. Group 2 exhibited significantly lower pain scores at all time points from 4 to 8 hours compared to Group 1, suggesting superior and prolonged analgesia in Group 2. The intervention in Group 2 was more effective in delaying the onset of significant pain, potentially reducing the need for additional analgesics.

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