Original Article

Role of buprenorphine in prolonging the duration of post-operative analgesia in percutaneous nephrolithotomy: Comparison between bupivacaine versus bupivacaine and buprenorphine combination

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ABSTRACT

Introduction: Percutaneous nephrolithotomy (PCNL) is the treatment of choice for large renal calculi. Pain around the nephrostomy tube is a clinical problem and we have previously reported alleviation of pain by peritubal block with bupivacaine, which lasted for 14 hours. The present study aimed to investigate the role of buprenorphine and bupivacaine combination in prolonging the duration of analgesia in peritubal block.

Materials and Methods: A prospective, randomized controlled study was undertaken in 40 American Society of Anesthesiologists (ASA) grade I and II patients who were scheduled for PCNL. Group I patients received 20 mL of 0.25% bupivacaine and group II patients received 20 mL of 0.25% bupivacaine with 100 μg of buprenorphine. Peritubal infiltration was given under fluoroscopic guidance along the nephrostomy tube from the renal capsule to the skin. Post-operative pain was assessed by Visual Analog Score (VAS), dynamic VAS (DVAS), sedation score, duration of analgesia and number of rescue analgesic demands. Rescue analgesia was inj tramadol 1 mg/kg IV if pain score exceeded 3.

Results: Demographic data were comparable between the groups. Median duration of analgesia was 16 h in group I and 20 h in group II ($P = 0.002$). The maximum median VAS was 4 in group I and 2 in group II ($P = 0.002$). The median area under curve (AUC) for VAS was 7 and 5 in groups I and II, respectively ($P = 0.047$). The median maximum DVAS in group I was 6 and 4 in group II. The median AUC for DVAS in 24 h was 16 in group I and 15 in group II ($P = 0.017$).

Conclusions: Peritubal infiltration of 0.25% bupivacaine with 100 μg buprenorphine around a nephrostomy tube increased the duration of analgesia following PCNL without any side-effects.

Key words: Buprenorphine, percutaneous nephrolithotomy, peritubal block, post-operative analgesia

INTRODUCTION

Percutaneous nephrolithotomy (PCNL) is the treatment of choice for large renal calculi. A nephrostomy tube is placed to drain urine and blood clots, allow reentry for retrieval of residual calculi, and provide tamponade. Pain around the nephrostomy tube may be agonizing and requires analgesia. Post-operative pain management relies on pharmacological agents like opioids and non-steroidal anti-inflammatory drugs with their associated adverse effects, particularly in patients with potential renal complications.[1] Regional techniques offer many advantages: Pain is cured at its origin, close to the damaged tissue area, and when local anesthetics are used, they provide analgesia without opioid-like side-effects. We have reported peritubal infiltration of the nephrostomy tract from the skin to the renal capsule with local anesthetic that alleviated post-operative pain for 14 h with reduced analgesic load.[2] Opioids, when used as an adjuvant to local anesthetics, is known to enhance analgesia. Peripheral opioid receptors that are present along the peripheral sensory nerves, especially after the painful inflammatory conditions, form

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Access this article online	
Quick Response Code:	Website: www.indianjurol.com
	DOI: 10.4103/0970-1591.152815

the basis for peripheral opioid analgesia.[3-5] Buprenorphine, a semisynthetic opioid, has shown to prolong the duration of analgesia when used as an adjuvant in brachial plexus blocks, Biers block and central neuraxial blocks and intraoral nerve blocks.[6-9] There is scant literature on its use in peritubal block. We hypothesized that addition of buprenorphine to local anesthetic prolongs the duration of analgesia in peritubal infiltration. The aim of the present study was to evaluate whether addition of buprenorphine to 0.25% bupivacaine enhances the duration of analgesia in peritubal infiltration following PCNL.

MATERIALS AND METHODS

Forty American Society of Anesthesiologists (ASA) grade I and II patients were recruited for this prospective, randomized controlled study after obtaining Institutional Ethics Committee approval and informed consent from the patients. The patients enrolled were aged between 18 and 60 years, weighing 40–80 kg and belonging to either gender. All patients received standard general anesthesia with fentanyl 2 μg/kg as analgesic. PCNL was performed with single subcostal nephrostomy tract and a nephrostomy tube (size 14/16 F) was placed at the end of the procedure. The average stone size was 2.5 cm (1.8–3.2 cm). The patients were randomized into two groups based on computer-generated random numbers. Group I (n = 21) patients received 20 mL of 0.25% bupivacaine and group II (n = 19) patients received 20 mL of 0.25% bupivacaine with 100 μg of buprenorphine. Exclusion criteria were patients with age more than 60 years, body mass index > 30, renal stones requiring more than a single puncture, surgical procedure extending more than 3 h, excess bleeding, delayed recovery or requiring post-operative ventilation, incomplete data and patient withdrawal from the study. A standard PCNL was performed and, at the end of the procedure, group I patients received 20 mL of 0.25% bupivacaine and group II patients received 20 mL of 0.25% bupivacaine with 100 μg buprenorphine peritubally. Under fluoroscopic guidance, a 23 G spinal needle was introduced along the nephrostomy tube at the 12 O' clock position till it reached the renal capsule, after which the needle was slowly withdrawn by injecting the study drug along the tissue planes, i.e. the renal capsule, muscles, subcutaneous tissue and the skin. The same procedure was repeated at the 6 O' clock position. The patient's trachea was extubated once the extubation criteria were fulfilled by reversing the residual neuromuscular blockade. Post-operative pain was assessed by visual analog scale (VAS) and dynamic VAS (pain on deep breath and cough - D VAS), a 10-point scale ranging from 0 – minimum or no pain to 10 – the maximum pain score perceived by the patient, by an independent observer blinded to the study, every 4th hour for 24 h from the time of extubation. The duration of block was taken from the time the study drug was administered peritubally to the time for first demand of analgesia. Rescue analgesia was provided by inj tramadol 1 mg/kg IV if pain score was 3 or > 3 on VAS. Wilson's Sedation score ranging from 1 to 5 (fully awake to full sedation Appendix 1), duration of analgesia and number of rescue analgesic demands were also noted at four-hourly intervals.

Statistical analysis

Statistical analysis was performed using Minitab-14®. Descriptive data were expressed as median values with interquartile range (IQR) for continuous and ordered categorical variables. Comparison of continuous data and ordered categorical variables was performed between the groups using the Mann–Whitney U-test and comparison of discrete variables between groups was performed using the Chi-square test. To obtain a composite value for the pain score distributed over a period of 24 h, an area under curve (AUC) for the pain score of each patient was determined for VAS and DVAS. AUC was compared between the two groups using the Mann–Whitney U-test as the sample size was small. A *P* value of < 0.05 was considered as being significant

RESULTS

All 40 patients enrolled for the study were analyzed. There were no dropouts or exclusions in the study. Demographic data were comparable between the groups and not statistically significant [Table 1]. The median duration of analgesia was 16 h in group I compared with 20 h in group II ($P = 0.002$). The VAS scores are shown in Table 2. AUCs are shown in Figure 1. There was no statistically significant difference in sedation score between the groups, but, clinically, four patients (21%) in group II were sedated scoring 3 at 8 h. The

Table 1: Demographic data

	Group I (median-IQR)	Group II (median-IQR)	*P*
Age (years)	42 (32-50)	45 (35-51)	0.5245
Weight (kg)	62 (54-72)	62 (54-68)	0.8709
Gender	13:8	13:6	0.666
Duration of surgery (h)	1.89 (1.47-2.5)	1.9 (1.50-2.12)	0.796

IQR = Interquartile range

Table 2: Visual analogue scores

Variables	Group I (median-IQR)	Group II (median-IQR)	*P*
Duration of analgesia (h)	16 (12-16)	20 (16-24)	0.002
Max VAS	4 (4-4)	2 (2-4)	0.002
Time to max VAS (h)	5 (5-6.5)	7 (5-7)	0.061
AUC for VAS in 24 h	7 (6-9)	5 (3-7)	0.047
Max DVAS	6 (5.5-6)	4 (2-6)	0.001
Time to max DVAS (h)	5 (4-5.5)	7 (5-7)	0.007
AUC for DVAS in 24 h	16 (15-17)	15 (12-16)	0.017

AUC = Area under curve, VAS = Visual analog score, DVAS = Dynamic VAS, IQR = Interquartile range

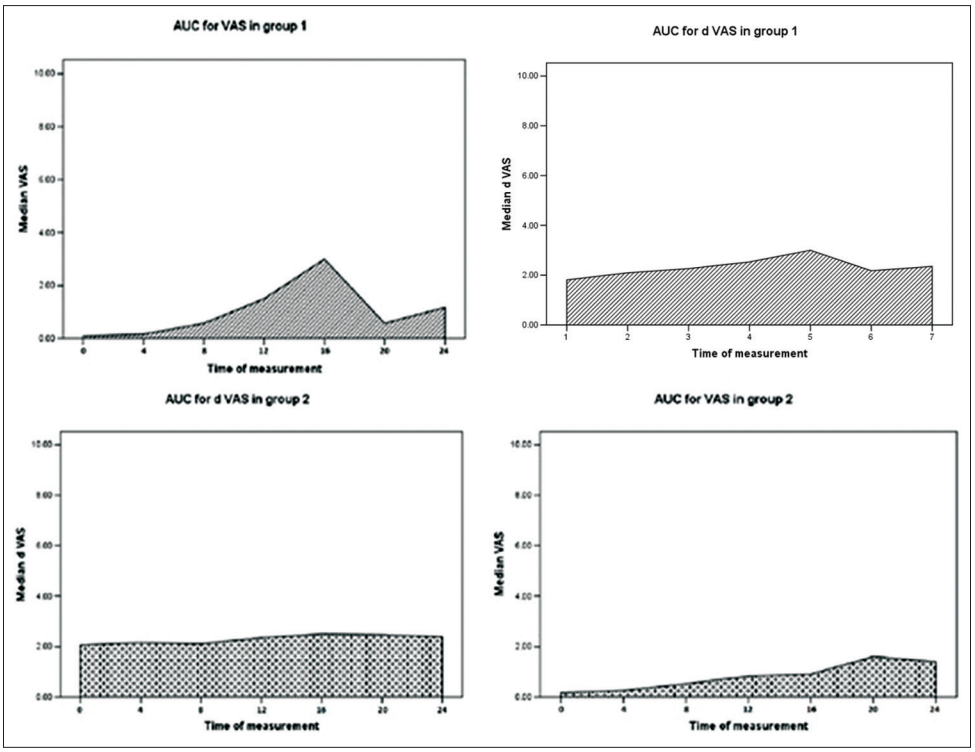

Figure 1: Area under curve

rescue analgesic demands were higher in group I ($P = 0.007$), but the overall analgesic consumption was not statistically different [Table 3].

Power analysis

Because sample size estimation was not performed in this study, we present the power analysis with the result obtained. Using a difference of 5.81 h in the analgesia duration between the study and control groups, and using a pooled standard deviation of 4.72 h, the power of this study was 0.998 and 0.8738 for alpha values of 0.05 and 0.01, respectively.

DISCUSSION

The main finding of this prospective study was that addition of 100 μg buprenorphine to 0.25% bupivacaine in peritubal block prolonged the duration of analgesia. The median duration of analgesia was 16 (12–16) h in group I and 20 (16–24) h in group II ($P = 0.002$), which was statistically significant. This finding is consistent with our previous study in which peritubal infiltration of the nephrostomy track provided effective post-operative analgesia for 14 h.[2] Addition of buprenorphine to bupivacaine has prolonged the analgesic duration both statistically and clinically. Candido and coauthors[4] used 300 μg of buprenorphine with local anesthetic for brachial plexus block and found post-operative analgesia for 17.5 ± 1.26 h (control 5.3 ± 0.15 h) that was statistically and clinically significant ($P < 0.0001$). In our study, the duration of analgesia was 20 h. This difference in the duration of analgesia may be because of the type of surgical procedures that the patients had undergone. In another study,[5] 300 μg of buprenorphine was added to local anesthetic (1% mepivacaine and 0.2% tetracaine with 1:200,000 epinephrine) in the axillary approach of brachial plexus block, and the mean duration of analgesia was found to be 22.3 h, which is slightly higher than that in the present study. This may probably be because of the addition of epinephrine to the local anesthetic and also to the usage of a high dose of buprenorphine. Capogna and coworkers[6] in their study of intrathecal buprenorphine for suprapuic prostatectomy in elderly patients reported post-operative analgesia persisting more than 7 h. Similar results were reported when buprenorphine was used in intraoral nerve blocks for minor dental procedures in outpatient procedures.[7] Addition of buprenorphine not only prolonged the duration but also the quality of analgesia because the time to achieve max VAS was 7 h in group II and 5 h in group I. The pain scores, both VAS and DVAS, were low in both the groups; however, the number of analgesic demands and total analgesic consumed in group II was significantly low ($P = 0.007$). The AUC that represents the composite value for VAS and DVAS pain scores distributed

Table 3: Analgesic requirement

No. of demands	Group I	Group II	*P*
0 demand	1 (4.8%)	9 (47.4%)	0.007
1 demand	17 (81%)	9 (47.4%)	
2 demands	3 (14.3%)	1 (5.3%)	
Total amount required (mg)	50 (50-50)	50 (0-50)	0.14

over a period of 24 h was significantly low in group II, 9, than in group I ($P = 0.047$ and 0.017), respectively.

An increasing number of studies recently reported the existence of opioid receptors outside the central nervous system, and the demonstration that opioid receptors exist in the peripheral nervous system offers the possibility of providing post-operative analgesia[3-5] Opioids when administered peripherally act on peripheral opioid receptors without central action and eliminate unwanted central side-effects, mainly like respiratory and cardiac depression, sedation and pruiritus. Sedation score was not statistically or clinically significant in the present study.

Buprenorphine is a synthetic partial μ-receptor agonist derived from thebain, one of the opioid alkaloids.[10] It was chosen because of its physicochemical properties like rapid onset and prolonged duration of action, high lipid solubility, potency (33 times more potent than morphine) and high affinity for μ receptors than morphine, long half-life (mean 30 h), a low abuse potential and ceiling effect for respiratory depression. Therefore, it can safely be used and, in case of any side-effects, inj naloxone (0.01–0.1 mg/kg SC) can be used to reverse the cardiac or respiratory depression. Local analgesic techniques are of increasing interest in the recent years because they are simple and safe and provide effective analgesia without any adverse effects; they are more suitable in patients with potential compromised renal functions. Peritubal block provided effective post-operative analgesia, and addition of buprenorphine further added the duration of analgesia.

CONCLUSION

Peritubal infiltration of 0.25% bupivacaine with 100 μg buprenorphine is a simple and safe method that has significantly increased the duration of analgesia without any adverse effects and with reduced requirement of analgesics.

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How to cite this article: Nirmala J, Kumar A, Devraj R, Vidyasagar S, Ramachandraiah G, Murthy PV. Role of buprenorphine in prolonging the duration of post-operative analgesia in percutaneous nephrolithotomy: Comparison between bupivacaine versus bupivacaine and buprenorphine combination. Indian J Urol 2015;31:132-5.

Source of Support: Nil, **Conflict of Interest:** None declared.

ANNEXURE I

The Wilson Sedation Score

1. Fully awake and oriented
2. Drowsy
3. Eyes closed but rousable to command
4. Eyes closed but rousable to mild physical stimulation (ear lobe tug)
5. Eyes closed but unrousable to mild physical stimulation