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Effects of intrathecal Nalbuphine as an Adjuvant to Ropivacaine in Patients undergoing Transurethral Resection of Prostate

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Abstract

Spinal anaesthesia is commonly used in elderly patients who undergo transurethral resection of prostate (TURP) especially in those with compromised cardiorespiratory functions. *Aims:* To evaluate the efficacy of Nalbuphine when used as an adjuvant to Ropivacaine in spinal anaesthesia for Transurethral resection of prostate in terms of providing adequate sensory and motor blockade along with post operativeanalgesia and to look for any adverse effects. *Methods:* Fifty patients of the American Society of Anaesthesiologists (ASA) physical status II and III within the age group of 60 to 80 years were chosen for a prospective randomized double blinded comparative clinical study. Patients were divided into two groups. Group R received 2.5 ml of 0.75% Ropivacaine and 1 ml of normal saline. Group RN received 2.5 ml of 0.75% Ropivacaine and 1 mg of Nalbuphine (in 1 ml of normal saline). Sensory and motor blockade characteristics,post operative analgesia and adverse effects if any were studied. *Statistical analysis:* The data which was collected was tabulated using Microsoft Excel and analysis was done using SPSS version 16.0.Student t test was used to analyze the demographic and hemodynamic variables. Unpaired t test and chi square test were used to analyze the parameters which included onset, time, duration of sensory and motor blockade and also duration of analgesia. p value <0.05 was takenas statistically significant and p value <0.01 was considered as highly significant. *Results:* Patients in group RN had an early onset of sensory block at T10 (4.46±0.23min v/s 5.39±0.24 min). The duration of sensory (242.31±10.36 min v/s 175.70±9.78 min) and motor blockade(150.72±5.79 v/s 126.98±3.49) along with two segment regression times were prolonged in group RN when compared to group R. Post operative analgesia was also superior in group RN as total analgesic consumption was less in group RN (230.46±10.8 v/s 320.6±13.2). *Conclusion:* Addition of 1 mg of Nalbuphine to 0.75% Ropivacaine provided faster onset of sensory and motor blockade. Sensory and motor blockade was also prolonged. The post operative analgesia was enhanced in group RN with low visual analogue scale score (VAS score). Haemodynamic stability was well maintained without any incidence of adverse effects.

Keywords: Ropivacaine; Nalbuphine; Spinal Anaesthesia; Transurethral Resection of Prostate.

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Introduction

The most common surgical intervention in elderly patients with benign prostatic hyperplasia is transurethral resection of prostate (TURP). Elderly patients are very easily vulnerable to volume overload, water intoxication and bladder perforation. Spinal anaesthesia is commonly used for this procedure as these complications can be identified at the earliest in them. Spinal anaesthesia provides a very good analgesia and increases the venous capacitance thereby preventing sudden absorption of irrigating fluids [1].

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Ropivacaine is an S-enantiomer of Bupivacaine. It was introduced to reduce the cardiotoxic and central nervous system toxicity seen with the use of Bupivacaine. Use of Ropivacaine is preferred as it has a greater degree of differentiation between sensory and motor blockade. Due to the reduced lipid solubility of Ropivacaine, high peak plasma levels are achieved early during epidural anaesthesia and peripheral nerve blocks [2].

Nalbuphineis an agonist-antagonist opioidacting on μ (mu) receptors as antagonist and κ (kappa) receptors as agonist with an analgesic potency equal to morphine. It is one of the opioid with potent preoperative and post operative analgesic properties. It can also be used as an antagonist but when compared to Naloxone, it is about one fourth of its potency. It can be used as an adjuvant to local anaesthetics as it is known to potentiate their onset and duration of sensory and motor blockade [3].

Methods

Fifty elderly male patients between age group of 60-80 years with benign prostatic hyperplasia posted for transurethral resection of prostate were chosen for the prospective randomized double blinded comparative clinical study after obtaining the institutes' ethical committee approval. Informed consent was taken from all the patients. Patients with ASA grade II and III were chosen for the study. Patients who refused to take part in the study were not included. Patients with history of allergy to local anaesthetics, altered coagulation profile, infection at the site of administration of local anaesthetic, spinal deformities, proven history of neurological deficits, any spinal surgeries in the past,with severe hepatic dysfunction were excluded from this study. The patients were randomly allocated into two groups based on a computer generated code. Group R (25 patients) received 2.5ml of 0.75% Ropivacaine along with 1ml of normal saline. Group RN (25 patients) received 2.5ml of 0.75% Ropivacaine along with 1mg of Nalbuphine (preservative free Nacphin 10 mg in 1 ml, Neon Laboratories) in 1 ml of normal saline.We planned a double blinded study. The drug solutions used for the study were prepared by a resident not involved in the study protocol. Neither the anaesthesiologist who was conducting the procedure nor the patient undergoing the procedure were aware of the study solutions being used.

All the patients were subjected to detailed pre anaesthetic examination and evaluation. A written informed consent was obtained from all the patients. Routine investigations and specific investigations were done as per the patients clinical status. All patients were given information about pain VAS (Visual Analogue Score) scale preoperatively as score of 0 to 10 (0= no pain, 10= worst imaginable pain) during pre anaesthetic evaluation.

Patients were advised to remain nil orally from ten pm onwards on the previous night of surgery. Tablet Alprazolam 0.25mg was administered the previous night to reduce anxiety and to induce a good sleep . On the day of surgery, intravenous access was secured with 18 gauge cannula. Patients were preloaded with 10ml/kg of 0.9% sodium chloride solution. Hemodynamic baseline variables (blood pressure, heart rate and SpO_2) were recorded. Electrocardiogram (ECG) leads were attached.

With patient in sitting position, using all aseptic precautions after injection of 2% lignocaine as a local anaesthetic to the skin and subcutaneous tissues at the level of L4/L5 space, spinal anaesthesia was administered s using 25G Quinke Babcock spinal needle and study drugs were injected as assigned to respective groups as per the study. As soon as the patient was made to lie supine continuous hemodynamic monitoring was commenced. All patients received supplemental Oxygen (4litres/min) through ventimask.

The interval between the end of intrathecal local anaesthetic injection to complete loss of pin prick sensation was taken as onset of sensory block . Sensory block levels were checked every three minutes from the time of drug injection. Maximum sensory block levels attained and the time taken to reach the maximum sensory level was noted. The surgery was started when the block level reached T10 dermatome. The interval from achievement of complete sensory block to the time of the first requirement of analgesia was taken as duration of sensory blockade.

Onset of motor block was the time from end of the local anaesthetic injection until the loss of motor power using the modified Bromage Scale which was as follows;

0= no motor block,

1=hip blocked,

2= hip and knee blocked,

3=hip, knee and foot blocked.

Bromage score was recorded during the beginning as well as at the end of surgery until complete motor blockade recovery. Duration for motor block was taken as time from establishment of motor block to complete

recovery from motor block as observed by a decrease in Bromage Score. Two segment regression time was evaluated.

Postoperative pain was assessed using visual analogue scale (VAS) between 0 and 10. It was initially assessed hourly for 2hours and then every 4hourly for the next 24 hours; Tramadol 50 mg intravenously was kept as rescue analgesic medication in the post operative period, if VAS was 3 or more. Total dose of analgesic used over 24hours was calculated.

Heart rate and mean arterial pressure were recorded in all the patients of both the groups every two minutes for first ten minutes and then every five minutes for 30 minutes followed by every one hour until recovery. In our patients, injection fentanyl 100µ gm was used as rescue analgesic intraoperatively. Episodes of perioperative hypotension was noted as systolic blood pressure of less than 20% of baseline value and a mean arterial pressure of less than 60 mm of hg), bradycardia was considered when heart rate decreased to below 50beats/min. Respiratory depression (<10cycles/min), arterial 02 desaturation (SpO_2 <90%) if occurred were noted.If hypotension did not respond to fluid boluses Injection Ephedrine 5mg was given intravenously in incremental doses and injection Atropine 0.6mg was given intravenously if heart rate dropped to below 50 beats/min. In addition the number of patients experiencing other adverse effects like nausea, vomiting, shivering, respiratory depression, pruritis and urinary retention if any were noted. Injection ondansetron 8mg was given intravenously if patients had nausea and vomiting.

Based on the previous study by Verma et al. [4], we calculated the sample size using Epi Info 6 software. The confidence interval was 95% and the power of the study was 80%with an alpha error of 0.05. Thus keeping the percentage prolongation time of analgesia (62%) in their group which received Nalbuphine, we enrolled 25 patients in each group. The obtained data was collected and entered in MS excel . The analysis of data was done using SPSS version 16.0. The student t test was used to evaluate demographic and hemodynamic variables. For statistical analysis of onset, time, duration of sensory and motor blockade and duration of analgesia, unpaired t test and chi square test were applied. p value <0.05 was considered as statistically significant and p<0.001 as highly significant.

Results

Among the 50 patients who were included in the study, none of them were excluded. The demographic characteristics (age, weight, height and ASA grading) of both the groups were comparable (Table 1). There was no significant differences in mean blood pressure and heart rate values between both groups.

Time taken to reach T10 sensory block was lower in group RN (4.46±0.23min) when compared to group R (5.39±0.24min). p value was <0.001 (Table 2). Peak sensory levels reached were similar in both the groups(p=0.123) (Table 3). T9 was the peak level of sensory block in both the groups. Fifteen patients reached T10 level in group RN and twenty patients reached T10 level in group R. The 2 segment regression time was 86.6±2.35min in group

Table 1: Demographic data

	Mean	±	S.D	P value
Age (YRS)				
Group R	69.36	±	1.52	0.18
Group RN	69.96	±	1.59	
Weight (KG)				
Group R	62.16	±	2.34	0.19
Group RN	61.28	±	2.34	
Height (CM)				
Group R	166.16	±	1.32	0.36
Group RN	166.21	±	1.09	
Duration of Surgery (min)				
Group R	62.12	±	3.82	0.342
Group RN	63.12	±	3.54	
ASA II/III				
Group R	21/4			1
Group RN	21/4			

Group R-ropivacaine, Group RN-ropivacaine+nalbuphine, SD-standard deviation

Table 2: Sensory block characteristics

		Mean	±	S.D	p value
Onset of t10 Sensory block (min)	Group R	5.39	±	0.24	<0.001
	Group RN	4.46	±	0.23	
2 segment Regression Time (min)	Group R	74.64	±	2.43	<0.001
	Group RN	86.60	±	2.35	
Duration of Sensory block (min)	Group R	175.70	±	9.78	<0.001
	Group RN	242.31	±	10.36	
Time to first postoperative analgesic requirement (min)	Group R	200.18	±	12.67	<0.001
	Group RN	260.20	±	10.52	

Table 3: Peak sensory block level

Peak sensory block level	Group R	Group RN	
T9	5	10	P=0.123
T10	20	15	
Total	25	25	

Group R-ropivacaine, Group RN-ropivacaine+ nalbuphine, p=0.123,not significant, chi square test

Table 4: Motor block characteristics

		Mean	±	S.D	P value
Onset of motor block (min)	Group R	3.94	±	0.19	<0.001
	Group RN	3.22	±	0.13	
Duration of motor block (min)	Group R	126.98	±	3.49	<0.001
	Group RN	150.72	±	5.79	

Group R-ropivacaine, Group RNropivacaine+ nalbuphine, SD-standard deviation, p<0.001 significant

Table 5: Bromage score at the beginning of surgery

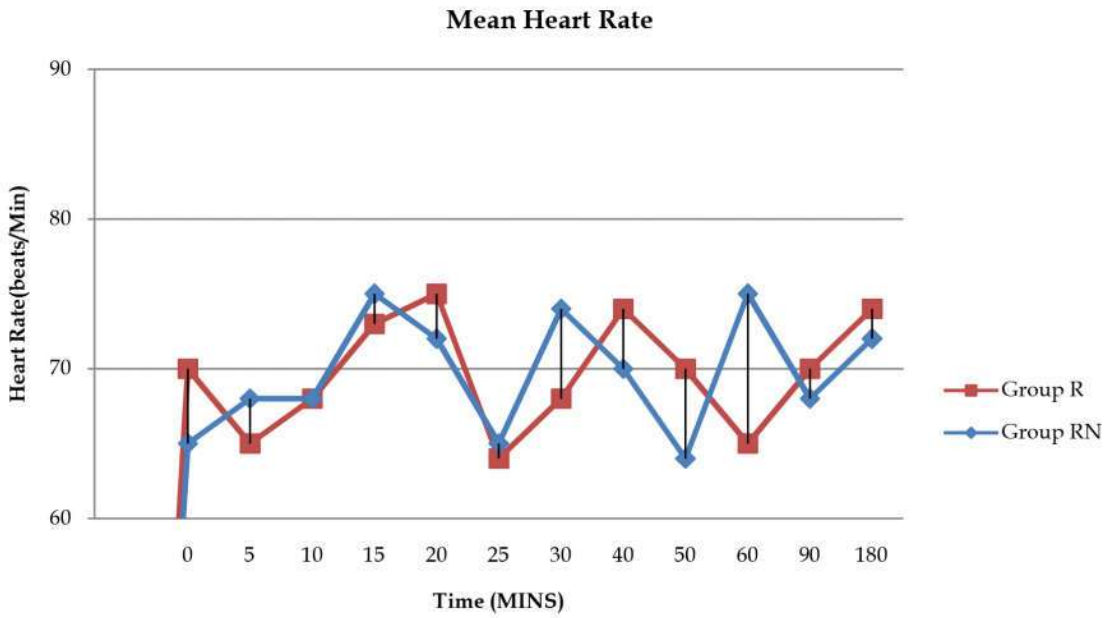
Bromage score at the beginning of surgery	Group R	Group RN	P value
0	0	0	P <0.05
1	8(32%)	0	
2	4(16%)	7(28%)	
3	13(52%)	18(72%)	

Group R-ropivacaine, Group RN-ropivacaine+nalbuphine, p<0.05, significant, chi-square test

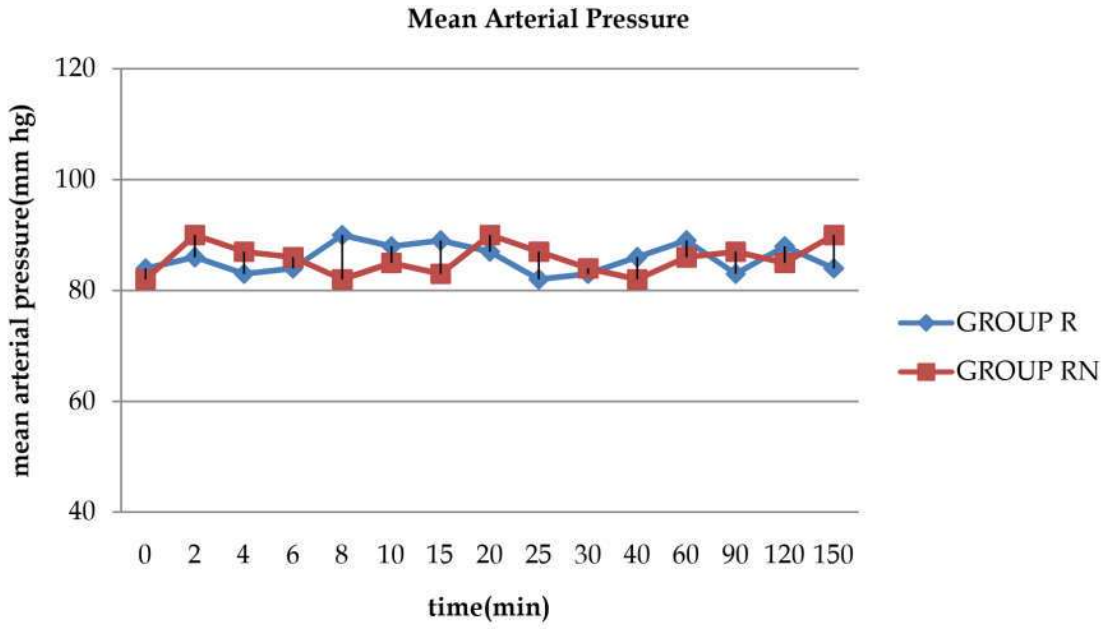
RN as compared to 74.64±2.43min in group R (p value < 0.001) which was statistically very significant.

Duration of sensory block in group RN was 242.31± 10.36 minutes as compared to 175.70±9.78 minutes in group R which was very significant (p value < 0.001) (Table 2). When comparing the onset of motor blockade among both the groups, group RN had an early onset motor blockade (3.22±0.13min) when compared to group R (3.94±0.19min) (p value < 0.001)(Table 4).

The motor blockade lasted for a long time in patients of group RN(150.72±5.79 min) as compared to group R (126.98±3.49) which was also significant (p value <0.001)(Table 4). In the beginning of surgery, more number of patients in group RN attained higher Bromage score when compared to patients in group R (p value<0.05) (Table 5). Peak sensory level attained was comparable in both the groups and was statistically insignificant (p=0.123) (Table 3). Modified bromage score at the end of surgery also was significant favoring group RN, with increased number of patients having a score of 3 when compared to group R (p=0.04) (Table 6). There were no much changes in the heart rate and mean arterial pressure among both the groups (graph 1 and graph 2). Three patients of group R were given injection Fentanyl 100µgm intraoperatively as a rescue analgesic (p<0.005) (Table 7). Group RN patients had low VAS scores and reduced analgesic requirements in the post operative period when compared to group R (Table 10). The total analgesic requirement in group R (320.6±13.2) were significantly higher when compared to group RN (230.46±10.8) (p<0.001) (Table 8).



Graph 1: Mean heart rate



Graph 2: Mean arterial pressure

Table 6: Modified bromage score at the end of surgery

Modified bromage score at the end of surgery	Group R	Group RN	P value
0	0	0	P=0.04
1	6(24)	3(12)	
2	14(56)	8(32)	
3	5(20)	14(56)	

Group R-ropivacaine, Group RN-ropivacaine+nalbuphine, p=0.040, significant, chi-square test

In this study,there was no significant differences regarding intraoperative and post operative adverse effects in between these two groups (Table 9). Two patients in group RN had vomiting. Only one patient in group R had vomiting (p=0.55). Injection Ondensetron 8mg i.v was administered We did not notice any other adverse effects very significantly like hypotension, bradycardia, sedation, respiratory depression,urinary retention shivering and pruritis.

Discussion

One of the age related conditions is benign hyperplasia of prostate. More commonly the patients undergoing TURP are elderly, with co existing cardiac, pulmonary and metabolic disorders with compromised reserves. Spinal anaesthesia is the most widely used technique for this procedure as the elderly patients tolerate regional anaesthesia better, with minimal physiological disturbances. Relaxation of pelvic floor muscles is very adequate. Signs and symptoms of fluid overload and bladder perforation can be recognized very early [5].

Due to age related changes in spinal anatomy, nerve physiology and cardiovascular reflexes in elderly, it is important to limit the distribution of the spinal block to reduce the adverse hemodynamic effects and maintenance of adequate levels of anaesthesia [6]. The aim of using neuraxial opioids is to achieve good analgesia as with systemic administration but in small doses and in concentrations without the risk of systemic side effects. With the use of these adjuvants the dose of the local anaesthetics can be reduced to avoid further adverse effects.

Ropivacaine is a long acting amide local anaesthetic agent and was first synthesized as an enantiomer. It produces effects similar to other local anaesthetics via reversible inhibition of sodium ion entry in nerve fibers. Ropivacaine is less lipophilic when compared to bupivacaine and thus it minimally penetrates large myelinated motor fibers. This results in a relatively less motor blockade. This is beneficial when motor blockade is not desired. Due to its reduced lipophilicity, the incidence of cardiovascular and central system toxicity is very minimal [7].

Table 7: Patients requiring intraoperative rescue analgesic fentanyl (%)

	Group R	Group RN	P value
Patients requiring intraoperative rescue analgesic fentanyl (%)	3(12%)	0	0.003

Group R-ropivacaine, Group RN-ropivacaine+nalbuphine, p=0.003, significant

Table 8: Total dose of consumption of analgesia(mg) used over 24hr in both groups

Total dose of consumption of analgesia(tramadol)(mg)	Group R	Group RN
Mean ± S.D	320.6 ± 13.2	230.46 ± 10.8
P value	<0.001	

Table 9: Intraoperative side effects

Side Effects	Group R (N=25)	Group RN (n=25)	P
Nausea	1	1	1.000
Hypotension	0	0	
Bradycardia	0	0	
Vomiting	1	2	0.55
Respiratory depression	0	0	
Pruritis	0	0	
Shivering	0	0	

Group R-ropivacaine, Group RN-ropivacaine+nalbuphine, n-no of patients

Table 10: Comparison of visual analogue scale score

Vas Score	Group R	Group RN	P
1 hour after surgery	2.2± 0.78	2.1± 0.36	0.32
2 hours after surgery	3.2± 0.62	2.1± 0.46	<0.05
4 hours after surgery	3.6± 0.82	2.6± 0.28	<0.05
6 hours after surgery	4.5±0.62	3.6±0.18	<0.05

Group R-ropivacaine, Group RN-ropivacaine+nalbuphine, p<0.05, significant

Though studies are limited when considering Nalbuphine as an adjuvant to Ropivacaine, it is being used as an adjuvant to local anaesthetics intrathecally. As it has an agonistic action at 8 opioid receptors and an antagonistic property at μ receptors, its analgesic profile is better without much adverse effects. Nalbuphine has the potential to maintain or even enhance μ opioid based analgesia while simultaneously mitigating the μ side effects. Nalbuphine has the onset of action between 2 and 3 minutes and the duration of action is between 3-6 hours .In the dose of 0.2 to 0.4 mg/kg cardiovascular stability is well documented and the side effects are negligible [8]. Nalbuphine has been used as an adjuvant in several other clinical studies intrathecally along with other local anaesthetics.

Various studies have compared different doses of Nalbuphineas an adjuvant to local anaesthetics and convincing results were obtained with use of increased dose of Nalbuphine during spinal anaesthesia without incidence of adverse effects.

We have used 1mg of Nalbuphine as an additive to 0.75% Ropivacaine in our study and a similar study was conducted by using 1mg of Nalbuphine along with 7.5mg of 0.5% Levobupivacaine by Osama Rehab et al. [9]. They have concluded that addition of 1mg Nalbuphine to Levobupivacaine provided superior sensory and motor block characteristics. The duration of post operative analgesia was significantly prolonged.Nalbuphine when added to Levobupivacaine had better results in terms of sensory block quality and analgesia without any adverse effects. This is in agreement with our study as we also used 1mg of Nalbuphine as an adjuvant to Ropivacaine and found that this resulted in good intraoperative and postoperative analgesia without any side effects.

In a study conducted in pregnant women who underwent caesarian section under subarachnoid block by Yoon et al. [10], Nalbuphine 1mg and 0.1mg of morphine were used as adjuvants to 0.5% Bupivacaine in a comparative study. They contemplated that Nalbuphine in the dose of 1mg prolonged the analgesic duration. Patients in morphine group had high incidence of pruritis and other adverse effects when compared to Nalbuphine group which did not have any adverse effects. This is in agreement with our study as we also did not note any adverse effects in the group for which we used 1mg of Nalbuphine. This was attributed to its agonist effects towards 8 receptors and antagonistic effects on the μ receptors which produces analgesia without mediating any adverse effects.

In one of the study conducted by Gupta K et al. [11], they have found out thatintrathecal Nalbuphine 2 mg when used as adjuvant to 0.5% Bupivacaine was more efficient than fentanyl in prolonging both duration of sensory and motor blockade with better enhancement of post operative analgesia. Side effects like pruritis were noted in patients of fentanyl group.

In a study conducted by Mostafa et al. [12] 2mg Nalbuphine was added to intrathecal 0.5% Bupivacaine for transurethral resection of bladder tumour for pain relief and they have found out that addition of Nalbuphineto 3ml of 0.5%Bupivacaine provided prolonged post operative analgesia.They also documented that the first rescue analgesic requirement in the post operative period was delayed and any other side effects like nausea, vomiting, pruritis and respiratory depression were not noted.This study was also supplemented with similar results by our study where in we did not note any significant adverse effects with the use of 1mg of Nalbuphine.

A comparative study was performed by Ahmed et al. [13] using three different doses of Nalbuphine (0.8 mg , 1.6mg, 2.4mg) and they showed that addition of 1.6 mg of Nalbuphine to intrathecal Bupivacaine showed better results in terms of duration of analgesia in patients undergoing abdominal hysterectomy.

Culebras et al. [14] and Gomaa et al. [15] suggested that intrathecal Nalbuphine in the dose of 0.8mg provided good intraoperative and early postoperative analgesia without side effects such as pruritis, nausea and vomiting. Culebras et al. suggested that no much benefit was obtained with use of 1.6mg of Nalbuphine and side effects were more. This was not in agreement with Ahmed et al where in they concluded that 1.6mg of Nalbuphine produced increased duration of analgesia. This may be attributed to involvement of different group of patients (pregnant patients) by Culebras et al in their study.

In our study, the group in which Nalbuphine was used had better and superior post operative analgesia with minimal analgesic requirements and almost devoid of any adverse effects in agreement with the study conducted by Ahmed et al.

Mukherjee et al. [16] used different doses of Nalbuphine intrathecally added to 0.5% hyperbaric Bupivacaine and they found that duration of sensory block and analgesia were prolonged with use of Nalbuphine. Our study also showed that the use of Nalbuphine prolonged sensory and motor blockade along with a superior post operative analgesic profile. Bhosle et al. [17] who added 0.8mg

Nalbuphine to hyperbaric Bupivacaine intrathecally have also opined in a similar fashion.

Lin et al. [18] and Fournier et al. [19] also demonstrated superior post operative analgesic property with Nalbuphine when used with other local anaesthetics. The time to first analgesic requirement was prolonged. This is in in accordance with our study to the group which received Nalbuphine. Even though the desired sensory level was attained among all the patients in both the groups, three patients in group R had to be given injection fentanyl 100μg for abdominal discomfort intraoperatively.

Hemodynamic stability was maintained in both the groups. In our current study, we have found out that Nalbuphine is a very good adjuvant to Ropivacaine for transurethral resection of prostate as onset of sensory and motor blockade was faster when compared to the group which received only Ropivacaine. Duration of sensory and motor blockade was also significantly prolonged in Nalbuphine group. A superior post operative analgesia was also obtained in the same group with low VAS scores. Total analgesic requirements were very less in Group RN as Nalbuphine acted as a good additive to Ropivacaine.Thus by calculating the total dosage of tramadol used in both the groups postoperatively it was observed that Nalbuphine when used was very cost effective to the patients of RN group. Hypotension and bradycardia was not seen significantly among any of the patients in both the groups. Two patients of group RN and one patient in group R had vomiting. (p=0.55) which was statistically insignificant. We did not observe any other adverse effects like pruritis, sedation, respiratory depression and urinary retention in any of the patients. There are few limitations in our study. Although Nalbuphine has emerged as a widely used opioid due to its better analgesic effects and negligible adverse effects with a superior safety profile when compared to other opioids, further studies may be warranted with larger samples to validate these observations including the appropriate dosage protocols to be used in various situations as there are limited clinical human studies.

Conclusion

From the present study we conclude that 1mg ofNalbuphine prolongs the duration of sensory and motor blockade along with superior perioperative analgesia when used as adjuvant to 0.75% Ropivacaine in spinal anaesthesia for transurethral resection of prostate without significant adverse effects.

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