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Original Research Article

Comparative study of analgesic effect of intrathecal nalbuphine and tramadol in patients undergoing vaginal hysterectomy

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Abstract

Aims: To compare the analgesic effect and block characteristics of intrathecal nalbuphine and tramadol in patients undergoing vaginal hysterectomy.
Settings and design: Prospective, double-blind, randomized study on 80 patients of age 20-60 years, undergoing vaginal hysterectomy under spinal anaesthesia.
Methods and Material: Random allocation in two groups, where group T and group N received 25 mg tramdol and 1 mg nalbuphine respectively along with 15 mg 0.5% hyperbaric bupivacine through intrathecal route. Drugs were administered at the L3-4 interspace with the patient in the sitting position. Spinal block was assessed by pin prick and modified bromage scale. In postoperative period time of first request of analgesia, number of rescue analgesia, the duration of motor block from the time of drug administration to the time when patient was able to lift his leg and the adverse effects were recorded. Quantitative variables were compared using Unpaired t-test/Mann-Whitney Test. Qualitative variables were correlated using Chi-Square test /Fisher's exact test. A p value of <0.05 was considered statistically significant.
Results: group N achieved faster onset of sensory block than group T (Group N=2.74±0.46min, Group T= 3.9±0.37min) (p<.0001) Time to reach peak sensory level was lesser in nalbuphine group than tramadol group. (Group T= 8.65 ± 0.86 min, Group N=7.42 ± 0.92min) (p<.0001). Mean peak sensory level was statistically comparable in both groups (Group T= T6.5±0.89, Group N=T6.1±0.53) (p>0.05).
Conclusion: In terms of sensory and motor block characteristics, nalbuphine provides faster onset, faster peak of analgesia than tramadol. In terms of postoperative analgesia nalbuphine and tramadol were statistically similar.
Key message: This study establishes the efficacy of Nalbuphine (1mg) as an intrathecal adjuvant to 15 mg of 0.5% hyperbaric bupivacaine for enhancing the intraoperative sensory block and better haemodynamic stability than Tramadol (25 mg) as an intrathecal adjuvant. In terms of postoperative analgesia and motor block characteristics both the drugs are comparable.
Keywords: Tramadol, Anesthesia, Spinal, Double-Blind Method.

1. Introduction

Intrathecal (IT) opioid administration provides good analgesia for variety of surgical procedures.[1,2] Opioids work in the intrathecal space by activating opioid-receptors in the dorsal gray matter of spinal cord modulating the function of afferent pain fibres[3] prolong the duration of postoperative analgesia.[4-7] Tramadol acts centrally & has minimal respiratory depressant effects[8] with no reported neural toxicity.[9] It provides effective postoperative analgesia with no risk of respiratory depression after neuraxial administration[10] in both adults [11] and children.[12-13] Nalbuphine having mixed μ antagonist and ƙ agonist properties belongs to phenanthrene series.[14,15] Nalbuphine does not cause side effects due to its action at kappa receptors.[16] Hence the present study was undertaken as a randomized double blind controlled study to assess the effect of intrathecally administered tramadol (25mg) or nalbuphine (1mg) when added to hyperbaric bupivacaine (15mg) in patients undergoing vaginal hysterectomy on the duration of postoperative analgesia (time to first rescue) and rescue analgesic consumption in first 24 hours postoperatively as a primary

outcome. Secondary outcome of the study were effect on onset and duration of sensory and motor block, visual analogue scores (VAS) for pain and adverse effects.

2. Material & Methods

It was a Prospective, double-blind, randomized study. After approval from the institutional ethical committee (Letter no. 279/GMC/IEC(2015) reg no.244/IEC/R-16-09-2015) and obtaining a well informed written consent, patients of age 20 - 60 years undergoing vaginal hysterectomy and ASA Physical Status- I & II were enrolled into the study.

Exclusion criteria were Patient refusal, Patients with known history of allergy to nalbuphine or tramadol, Patients with contraindication to spinal anaesthesia, History of any systemic diseases – cardiovasvular, respiratory, hepato-renal, neurological, endocrinal disorders, haematological disorders, drug or alcohol addiction, psychiatric diseases, study drug sensitivity, etc.

80 ASA Grade I/II patients of 20-60 years undergoing elective vaginal hysterectomy were randomized into one of the two study groups receiving intrathecal tramadol (T) or intrathecal nalbuphine (N).

Group T (n=40): The patients received intrathecal mixture of 15 mg hyperbaric bupivacaine 0.5 % [3 ml] in addition to 25 mg [0.5 ml] of preservative free tramadol hydrochloride (final volume 3.5 ml)[13]

Group N(n=40): The patients received intrathecal mixture of 15mg hyperbaric bupivacaine 0.5 % [3 ml] plus 1 mg of preservative free nalbuphine diluted to 0.5 ml (final volume 3.5 ml)[14]

In operation theatre, patient's nil per oral status and identity was reconfirmed. Patients and anaesthesia providers were blinded to the treatment group. The study drugs were prepared by another investigator not included in the patient care. In all patients electrocardiogram, non invasive arterial blood pressure, and peripheral oxygen saturation were monitored at baseline and every 5 min thereafter until the end of surgery.

A large bore intravenous access was established and patients were preloaded with 15ml/kg of lactated Ringer's solution. Lumber puncture was performed in L3-L4 intervertebral space in sitting position using a 25-gauge Quincke's spinal needle under all aseptic precautions. Injection was given over approximately 10 to 15 seconds. Immediately after intrathecal injection, patient was made to lie down in supine position.

The level of sensory block was checked by loss of pinprick sensation by 23 gauge hypodermic needle and dermatomal levels were tested every 2 minutes until the highest required level i.e. T6 got stabilized for four consecutive tests. Testing was conducted then every 10 minutes until the point of two segment regression of block.

Further testing was performed every 20 minutes intervals until the recovery to S2 dermatome. Simultaneously motor blockade was evaluated by Bromage scale. Haemodynamic parameters were recorded every 3 minutes after spinal administration of selected drug for first 15 minutes and subsequently every 5 minutes for half an hour after spinal anaesthesia then at every 10 minutes till end of surgery. Data regarding the highest dermatomal level of sensory blockade, the time to reach this level from the time of spinal injection, time to S2 sensory regression was recorded). Postoperatively, pain scores were recorded by using Visual Analogue Scale (VAS) between 0-10 (annexure), initially every 1 hour for 2 hours , every 2 hours for next 8 hours and then after every 4 hours till 24 hours [50].

In both groups Injection diclofenac 1 mg/kg (voveron 75 mg) i.v. was started eight hourly in postoperative ward as per routine analgesic protocol being followed in our institution by surgeons, starting from the time when patient had arrived in postsurgical ward from operation theatre. At any point of time if VAS came ≥4, injection tramadol 1 mg/kg body weight 8 hourly was added.

The time of first request of analgesia, number of rescue analgesia, the duration of motor block from the time of drug administration to the time when patient was able to lift his leg, haemodynamic parameters and the adverse effects such as nausea, vomiting, pruritus, respiratory depression (respiratory rate – (8 breaths/min) was recorded.

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non parametric test was used. Quantitative variables were compared using Unpaired t-test/Mann-Whitney Test (when the data sets were not normally distributed) between the two groups. Qualitative variables were correlated using Chi-Square test /Fisher's exact test. A p value of <0.05 was considered statistically significant.

3. Results

The mean age, height as well as weight distribution were statistically similar amongst the both groups ($p>0.05$). Distribution of ASA physical status grades, and duration of surgery were statistically similar amongst both groups ($p>0.05$).

3.1 Sensory and motor block characteristics

Time to reach T10 sensory level was statistically significant in both groups (Group N=2.74±0.46min, Group T= 3.9±0.37min) ($p<.0001$) i.e. group receiving intrathecal nalbuphine achieved T10 sensory level earlier than group receiving tramadol. (Table 1)

Table 1: Time to achieve sensory block at T10

Time (min) to achieve sensory block at T10	N	T	
Sample size	40	40	P value <0.0001
Mean ± SD	2.74±0.46	3.9±0.37	
Median	3	4	
Min-Max	2-3.4	3-5	
Inter quartile Range	2.150 – 3	4 - 4	

Time to reach peak sensory level was lesser in nalbuphine group than tramadol group. (Group T= 8.65 ± 0.86 min, Group N=7.42 ± 0.92min) (p<.0001). (Table 2)

Table 2: Time to achieve maximum sensory block

Time (min) to achieve max. sensory block	N	T	
Sample size	40	40	P value <0.0001
Mean ± SD	7.42 ± 0.92	8.65 ± 0.86	
Median	8	9	
Min-Max	6-9	6-10	
Inter quartile Range	7 - 8	8 - 9	

Median level of peak sensory level was T6 in both groups. Mean peak sensory level was statistically comparable in both groups (Group T= T6.5±0.89, Group N=T6.1±0.53) (p>0.05).

Time to two dermatomal (D2) regression was significantly longer in Group N(124.75 ± 5.79min) as compared to Group T(115.78 ± 4.04min) (P<.0001). (Table 3)

Table 3: Time to 2 dermatomal regressions

Time (min) to 2 dermatomal regression	N	T	
Sample size	40	40	P Value <0.0001
Mean ± SD	124.75±5.79	115.78±4.04	
Median	124.5	115	
Min-Max	118-150	100-124	
Inter quartile Range	120 - 128	114 - 117.500	

Onset of motor block as defined by time to reach Bromage score-3 was statistically comparable in both groups (Group T= 8.50±1.57min, Group N=7.87±1.47 min) (P>0.05).

Time of block regression below S2 was significantly longer in group N than Group T (Group N = 229.78 ± 13.58min, Group T =197.4 ± 9.19min) p value <.0001. (Table 4)

Table 4: Time of block regression below S2

Time (mim) of block regression below S2	N	T	
Sample size	40	40	P value <0.0001
Mean ± SD	229.78±13.58	197.4±9.19	
Median	236	197.5	
Min-Max	180-249	180-210	
Inter quartile Range	220 - 238.500	191 - 208	

Duration of motor block as defined by return of Bromage score to 0 was statistically comparable in both groups (group N=3.58 ± 0.75, group T=3.58 ± 0.75) p value =1.000 (Table 5).

Table 5: Time for bromage 0/1

Time for bromage 0/1	N	T	
Sample size	40	40	P value = 1.000
Mean ± SD	3.58±0.75	3.58±0.75	
Median	3.5	3.5	
Min-Max	2-6	2-6	
Inter quartile Range	3 - 4	3 - 4	

At the end of surgery level of block was T10 in 80% of nalbuphine and 97.5% of tramadol group. It was T11 in 12.5% of nalbuphine group and 2.5% of tramadol group T8 in 7.5% of nalbuphine group and none of the tramadol group. (Table 6)

Table 6: Height of block at the end

		Group		Total
		Nalbuphine	Tramadol	
height of block at the end	T10	80%	97.50%	71 (88.75%)
	T11	12.50%	2.50%	6 (7.50%)
	T8	7.50%	0%	3 (3.75%)
Total		40 (100.00%)	40 (100.00%)	80 (100.00%)

Haemodynamics:-maximum fall in MAP was observed in nalbuphine group was observed at 25 min intraoperative period While maximum fall was observed in tramadol group was at 90 min. Maximum fall in pulse rate was on served at 12 min of intraoperative period in nalbuphine group which was of 12.94 points away from baseline and in tramadol group maximum fall was at 9 minutes which was of 12.15 points away from base line.

Incidence of bradycardia was 5 % in nalbuphine group and 2.5% in tramadol group, which when present was treated with inj. Atropine 0.6 mg i.v.

3.2 Postoperative analgesia

In the postoperative period, fall in mean arterial pressure was more with tramadol being maximum at 15 min postoperative period. Mean of number of times VAS>4 or mean VAS score more than 4 was 2.78± 1.1 min in both nalbuphine and tramadol group. (Table 8, 9) which was statistically insignificant as p value =1.00 meaning postoperative analgesia provided by both tramadol and nalbuphine was same. Requirement of first dose of rescue analgesic was statistically similar in Group N (4.5± 0.82hr) and Group T (4.5 ± 0.82hr), (p=1.00). Thus duration of postoperative analgesia was similar for both Group N and Group T. Requirement of total rescue analgesic in term of total number of doses was statistically comparable in both groups (p=0.207).

3.3 Adverse effects

Out of all patients only 7 patients of tramadol group suffered with vomiting as an adverse effect which was 17.5% of group T and 8.75% of whole study population which came out to be statistically significant (p value =0.012) i.e. significantly more in group T than in group N.

No incidence of hypotension was seen among any of the patients in both groups. Incidence of shivering was also minimal i.e. 7.5% in group N and none in group T which was statistically comparable i.e. p value = 0.241. Incidence of itching was minimal i.e. 2 patients only in nalbuphine group and none in group T which was statistically comparable (p value =0.494).

Respiratory depression occurred in none of the patients among both groups.

4. Discussion

4.1 Sensorimotor block

Onset of sensory block was faster in nalbuphine than tramadol group which was statistically significant (P value <0.0001). The time to achieve sensory block at T 10 was shorter for nalbuphine than tramadol. The time to achieve maximum sensory block was also shorter for nalbuphine group as compared to tramadol group. Median level of peak sensory level was T6 in both groups. Mean peak sensory level was statistically comparable in both groups. In contrast few previous studies have shown that onset time and peak sensory level was not significantly affected after addition of intrathecal tramadol [17,19] or nalbuphine [17-18] .

In our study time to two dermatomal (D2) regressions was significantly longer in Group N (124.75 ± 5.79min) as compared to Group T (115.78 ± 4.04min). This finding corroborated with previous studies which have observed that time to two dermatomal regression was significantly prolonged with nalbuphine [17,20] than tramadol [19]. Though Verma *et al* found that duration of sensory block (time to two dermatomal regression) was significantly increased by addition of nalbuphine and tramadol both.[21]

Duration of motor block as defined by return of Bromage score to 0 was statistically comparable in both groups (group N=3.58 ± 0.75, group T=3.58 ± 0.75) while study by Verma *et al* found out duration of motor blockade was more in group N than group T . But study of other authors corroborated with our study and found no prolongation of motor block.[17-20]

4.2 Haemodynamic stability

However, the fall in blood pressure did occur but it was not of the grade of hypotension, i.e., change in blood pressure of <20% of baseline value and hence, this falling blood pressure is considered as physiological fluctuations only. [22]

No incidence of hyotension was observed in both groups of patients. But on comparing the fall in mean arterial pressure from baseline it can be observed that fall of MAP in intraoperative period in tramadol group was more than nalbuphine group. Hence nalbuphine has major role in maintaining haemodynamic stability during spinal anaesthesia. This was observed in both intraoperative and postoperative period.

Incidence of bradycardia was minimal i.e. Incidence of bradycardia was 5 % in nalbuphine group and 2.5% in tramadol group, which came out to be statistically insignificant. Similarly in postoperative period none of the drug was found to cause bradycardia more than the other.

From study of Jyothi *et al*, they concluded that use of nalbuphine hydrochloride along with bupivacaine causes no gross hemodynamic disturbances even with increasing the dosage from 0.8 to 2.4 mg.[23] Similar findings are seen in the study conducted by Culebras *et al*, [7] Tiwari *et al*, [20] Mostafa *et al*, [18] where there was no gross hemodynamic changes throughout their study. These findings corroborated with our study.

Similarly study conducted by Susmita Chakraborty *et al*, intrathecal tramadol when added to bupivacaine , the incidence of hemodynamic side effects like decreased blood pressure, bradycardia, and other side effects like somnolence and dryness of mouth were minimum and well tolerated by the patients studied. [24] Findings of this study were similar to our study.

4.3 Postoperative analgesia

In our study postoperative analgesia provided by both tramadol and nalbuphine was same as VAS score went above 4 for equal no. of times. Hence postoperative analgesia provided by both drugs came out to be statistically comparable. This finding of our study was inconsistent with study done by other researchers. [20,21,25,26]. Our finding corroborated with study done by Alhashemi *et al* [27] in 2003.

4.4 Postoperative adverse effects

In our study, none of patient had respiratory depression (respiratory rate below 10 bpm, SPO2 <90%). Nalbuphine exhibits ceiling effect for respiratory depression. This is proved in studies done by Romagnoli and Keats, [28] Thomas *et al* [29] similarly as that for analgesia [48,71]. Since respiratory depression is predominantly μ receptor-mediated and nalbuphine is a μ receptor antagonist, respiratory depression effect is expected to be attenuated by nalbuphine.

This result correlates that of the studies done by Culebras *et al* [7] Tiwari *et al* [20] and Mustaffa *et al* [18]. Similarly in study by Jyothi *et al* [23] adverse effects like nausea, vomiting, urinary retention, and shivering were statistically insignificant

No significant opioid related adverse effects were observed in our study. Previous studies also documented

intrathecal tramadol and nalbuphine as safer adjuvants [18-21,27].

5. Conclusion

It was concluded in our study that addition of intrathecal Nalbuphine speeds up the onset of sensory block and reduces time to reach maximum sensory block when compared to intrathecal Tramadol. Nalbuphine is also effective in prolonging the duration of sensor motor block but enhancement of the postoperative analgesia following vaginal hysterectomy is equal for both nalbuphine and tramadol with negligible adverse effects. Consumption of total rescue analgesia in first 24 hours of postoperative period was similar for both Nalbuphine and Tramadol groups. Nalbuphine produced a significant haemodynamic stability which was more than tramadol statistically and clinically.

References

[1]. Bhattacharya R, Dutta B. Postoperative analgesia with local anesthetic and Opioid combination using double space CSE technique. *Indian J Anaesth* 2007; 51: 409-14.

[2]. Chakraborty S, Chakrabarti J, Bhattacharya D. Intrathecal tramadol added to bupivacaine as spinal anesthetic increases analgesic effect of the spinal blockade after major gynecological surgeries. *Indian J Pharmacol* 2008; 40: 4180-2.

[3]. Roussel JR, Heindel L. Effect of intrathecal fentanyl on duration of bupivacaine spinal blockade for outpatient knee arthroscopy. *AANA J* 1999; 67(4): 337-43.

[4]. Hindle A. Intrathecal opioids in the management of acute postoperative pain. Continuing Education in Anaesthesia, Critical Care and Pain. *Br J Anaesth* 2008; 8(3):81-85.

[5]. Gandhi K, Viscusi E. Multimodal pain management techniques in hip and knee arthoplasty. *Journal of NYSORA* 2009;13:1-8.

[6]. Gunion MW, Marchionne AM, Anderson TM. Use of the mixed agonist-antagonist nalbuphine in opioid based analgesia. *Acute Pain* 2004; 6:29-39.

[7]. Culebras X, Gaggero G, Zatloukal J, Kern C, Marti RA. Advantages of intrathecal nalbuphine, compared with intrathecal morphine, after cesarean delivery. *Anesth Analg* 2000; 91:601-5.

[8]. Vickers MD, O'Flaherty D, Szekely SM, Read M, Yoshizumi J. Tramadol: pain relief by an opioid without depression of respiration. *Anaesthesia* 1992; 47: 291-296.

[9]. Tsai YC, Chang PJ, Jou IM. Direct tramadol application on sciatic nerve inhibits spinal somatosensory evoked potentials in rats. *Anesth Analg* 2001; 92: 1547-51.

[10]. Alhashemi JA, Kaki AM. Effect of intrathecal tramadol administration on postoperative pain after transurethral resection of prostate. *Br J Anaesth* 2003; 91(4): 536-40.

[11]. Baraka A, Jabbour S, Ghabash M, Nader A,Khour G, Sibai A. A comparison of epidural tramadol and epidural morphine for postoperative analgesia. *Can J Anaesth*. 1993; 40 (4): 308-137.

[12]. Sabbar S, Khan RA, Siddiqui MA, Khan FA. Comparison of caudal bupivacaine with and without tramadol for postoperative analgesia in paediatric inguino scrotal surgeries. *Pak J Surg*. 2010; 26(2): 155-159.

[13]. Laiq N, Khan MN, Tahmeedullah, Gandapur YK and Khan S. Comparison of Caudal Bupivacaine and Bupivacaine-Tramadol for Postoperative Analgesia in Children Undergoing Hypospadias Surgery. *J Coll Physicians Surg Pak.* 2009 Nov; 19(11): 678-81.

[14]. Chen JC, Smith ER, Cahill M, Cohen R, Fishman JB. The opioid receptor binding of dezocine, morphine, fentanyl, butorphanol and nalbuphine. *Life Sci* 1993; 52: 389-96.

[15]. Pick CG, Paul D, Pasternak GW. Nalbuphine, a mixed kappa 1and kappa 3 analgesic in mice. *J Pharmacol Exp Ther* 1992; 262:1044-50.

[16]. Fournier R, Van Gessel E, Macksay M, Gamulin Z. Onset and offset of intrathecal morphine versus nalbuphine for postoperative pain relief after total hip replacement. *Acta Anaesthesiol Scand* 2000; 44:940-5.

[17]. Mukherjee A, Pal A, Agrawal J, Mehrotra A, Dawar N. Intrathecal nalbuphine as an adjuvant to subarachnoid block. *Anesthesia Essays and Researches* 2011; 5(2):171-175.

[18]. Mostafa MG, Mostafa MF, Farrag WSH. Which has greater effect, intrathecal nalbuphine or intrathecal tramadol. *J Am Sci* 2011; 7(7): 480-84.

[19]. Mankeshwar HJ, Ganesh S. Pre-emptive analgesia with intrathecal tramadol for postoperative analgesia. *J Clin Epidemil* 1997; 50(1):7S-7S(1).

[20]. Tiwari AK, Tomar GS, Agrawal J. Intrathecal Bupivacaine in comparison with a combination of nalbuphine and bupivacaine for subarachnoid block. *Am J Ther* 2013; 20(6): 592-5.

[21]. Verma D, Naithani U, Jain D C, Singh A. Postoperative analgesic efficacy of intrathecal tramadol versus nalbuphine added to bupivacaine in spinal anaesthesia for lower limb orthopaedic surgery. *J Evolut of Med and Dent Scie* 2013; 2(33): 6196-6206.

[22]. Chattopadhyay A, Maitra S, Sen S, Bhattacharjee S, Layek A, Pal S, *et al.* A study to compare the analgesic efficacy of intrathecal bupivacaine alone with intrathecal bupivacaine midazolam combination

in patients undergoing elective infraumbilical surgery. *Anesthesiol Res Pract* 2013; 2013: 567134.

[23]. Jyothi B, Gowda S, Shaikh L. A Comparison of analgesic effect of different doses of intrathecal nalbuphine hydrochloride with bupivacaine and bupivacaine alone for lower abdominal orthopaedic surgeries. *Indian J Pain* 2014; 28:18-23.

[24]. Chakraborty S, Chakrabarti J, and Bhattacharya D, Intrathecal tramadol added to bupivacaine as spinal anesthetic increases analgesic effect of the spinal blockade after major gynecological surgeries *Indian J Pharmacol*. 2008 Aug; 40(4): 180–182.

[25]. Sapate M, Sahu P, Thatte WS, Dubey R. A randomized, double blind, control study of the effects of adding nalbuphine to spinal bupivacaine for lower abdominal surgeries in elderly patients. *Anaesth Pain & intensive Care* 2013; 17(2):145-148.

[26]. Ahmed F, Narula H, Khandelwal M, Dutta D. A comparative study of three different doses of nalbuphine as an adjuvant to intrathecal bupivacaine for postoperative analgesia in abdominal hysterectomy. *Indian J Pain* 2016; 30: 238.

[27]. Alhashemi JA, Kaki AM. Effect of intrathecal tramadol administration on postoperative pain after transurethral resection of prostate. *Br J Anaesth* 2003; 91(4):536-40.

[28]. Romagnoli A, Keats AS. Ceiling effect for respiratory depression by nalbuphine. *Clin Pharmacol Ther* 1980; 27:478-85.

[29]. Gal TJ, DiFazio CA, Moscicki J. Analgesic and respiratory depressant activity of nalbuphine: A comparison with morphine. *Anesthesiology* 1982; 57:36774.