Original Research Article

Clinical efficacy of clonidine versus nalbuphine as intrathecal adjuvants to 0.5% hyperbaric bupivacaine for subarachnoid block during gynaecological procedures: a double blind study

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ABSTRACT

Background: Regional anesthesia techniques for gynaecological procedures are on increasing trends due to their advantage of postoperative analgesia owing to intrathecal adjuvants. The present study was aimed to comparatively evaluate the clinical efficacy of clonidine with nalbuphine when co-administered intrathecally with 0.5% hyperbaric bupivacaine for gynaecological procedures.
Methods: Regional anesthesia techniques for gynaecological procedures are on increasing trends due to their advantage of postoperative analgesia owing to intrathecal adjuvants. The present study was aimed to comparatively evaluate the clinical efficacy of clonidine with nalbuphine when co-administered intrathecally with 0.5% hyperbaric bupivacaine for gynaecological procedures.
Results: The onset of sensory block was earlier in patients of Group BN (3.91±2.25 min vs 4.30±0.87 min, p=0.039). The onset of motor block was also earlier in patients of Group BN (p=0.042). The time to first rescue analgesia in patients receiving intrathecal clonidine was significantly delayed (283±14.18 min vs 231.50±26.18 min, p=0.001). Intraoperative hemodynamic changes were comparable and none of the patient suffered from respiratory depression, shivering, nausea or vomiting.
Conclusions: Intrathecal clonidine as adjuvant to bupivacaine provided was clinically more effective than nalbuphine for prolonging the duration of analgesia for gynaecological procedures.

Keywords: Bupivacaine, Clonidine, Gynecological procedures, Nalbuphine, Subarachnoid block

INTRODUCTION

Subarachnoid block with local anesthetic is a commonly used regional anesthetic technique for elective gynecological procedures. If bupivacaine was used alone, patients do experience pain during prolonged procedure due to their limited duration of action. The duration of subarachnoid block may be enhanced by adding intrathecal adjuvants like opioids, α-2 agonist, neostigmine, ketamine and midazolam, but no drug inhibits nociception without its associated adverse effects.[1] The combination of adjuvants to local anesthetic are synergetic for producing the analgesia of prolonged duration without increasing the sympathetic or motor blockade, thus allow early ambulation of patients with reduction in their dosages.[2]

Clonidine, α2 adrenoceptor agonist, is lipid soluble and can easily penetrates the blood-brain barrier to provide effective and extended analgesia by binding to presynaptic C-fibers and postsynaptic dorsal horn neurons, but associated with side effects of hypotension and bradycardia due to decrease sympathetic outflow. The prolongation of sensory and motor block may result from synergism between bupivacaine and clonidine.[3]

Nalbuphine is highly lipid soluble synthetic opioid analgesic with agonist-antagonist activity. It acts as antagonist at μ-receptors and agonist at κ-receptors. Its affinity to k-opioid receptors results in analgesia, sedation, and cardiovascular stability with minimal respiratory depression. Nalbuphine is widely studied as an adjuvant to local anesthetics in central neuraxial techniques to improve the quality of perioperative analgesia as it provides reasonably potent analgesia for visceral nociception.[4,5]

Clonidine and nalbuphine are freely available and absence of neurotoxicity has already been established. Not much studies have been conducted to compare the clonidine with nalbuphine as intrathecal adjuvants to bupivacaine. The present study was designed to compare the duration of sensory and motor block, surgical condition, time to request for first rescue analgesia and any adverse effects of clonidine (30 μg) and nalbuphine (2mg) when used as intrathecal adjuvant to 0.5% hyperbaric bupivacaine for gynecological procedures.

METHODS

After Institutional Ethical Committee approval, this prospective randomized double blind study was conducted on 60 female patients of American Society of Anesthesiologist (ASA) physical status I and II aged between 35-65 years, weighing 50-90 kg and height > 150 cm, scheduled for elective gynecological procedures under subarachnoid block. All patients were subjected to pre-anesthetic assessment prior to enrollment for the study.

Patients with cardiac or pulmonary disease, uncontrolled hypertension, relative or absolute contraindications to spinal anesthesia, coagulation disorders, neurological disorders, morbid obesity, anticipated difficult subarachnoid block, allergy to study drug, pregnancy and lactation were excluded from the study. Patients using any drug that modifies pain perception or using anticoagulants were also excluded from study.

Patients were properly explained on the method of sensory and motor assessments. Visual analogue pain scale (VAS) scores were also explained to them. Pre-medication with oral alprazolam 0.25 mg and ranitidine 150 mg, was given, the night before surgery and written informed consent was obtained after explaining the procedure.

Randomization and blindness

Patients were divided in a double-blind manner into two equal groups of 30 patients each according to computer generate random number table. Patients of Group BC were given 3.5 mL of 0.05% hyperbaric bupivacaine with 0.2ml of clonidine (30μg) and patients of Group BN were given 3.5 mL of 0.5% hyperbaric bupivacaine with or 0.2ml of nalbuphine (2mg). To ensure double blindness of the study, intrathecal drugs were prepared by another anaesthesiologist while subarachnoid block was managed by investigator. Perioperative data were recorded by resident who was unaware of group allocation.

Anesthetic Technique

Multipara monitors were applied and baseline pulse rate, non-invasive blood pressure and electrocardiogram of all the patients were recorded. In operation theatre, intravenous line was secured with 18 G cannula and they were preloaded with 500 mL of lactated Ringer solution over 20 min. Lumber puncture was performed at L3-L4 intervertebral space with 24 G Quincke's needle using midline approach in sitting position under all aseptic precautions. After the free flow of CSF, the study drug solution of 3.7 mL was given according to group allocation. Immediately after intrathecal injection, the patients were positioned horizontally in the supine position and 100 Trendelenberg tilt of table was done to achieve the highest level of block.

Sensory and motor blockade characteristics

The sensory and motor block characteristics were assessed at 2 minute interval till the surgical anesthesia was achieved. The segmental level of sensory block was assessed by pin prick method bilaterally along the mid clavicular line using short beveled 25 G hypodermic needle. The onset time of sensory blockade at T10 dermatome, maximum cephalic dermatome level, and time taken to two segment regression of sensory block was assessed for each patient. The motor block of the lower extremities was evaluated bilaterally by modified Bromage Scale (0-3): 0 = full movement and able to raise straight leg against resistance; 1 unable to raise extended leg at the hip but able to flex knee; 2= unable to flex the knee but able to move ankle joint; 3= unable to move hip, knee or ankle (no motor activity). Time taken to achieve complete motor blockade and total recovery time from motor blockade was also recorded.

All time intervals were calculated from the time of end of intrathecal injection. The onset of sensory block was defined as time to reach sensory block at T10. Onset of motor block was defined as time taken to achieve Bromage scale 3. Duration of sensory analgesia was taken from onset of spinal anesthesia to time of administration of first rescue analgesic.

Surgery was initiated when level of sensory block was reached to T10 thoracic dermatome level or above and attainment of complete motor block (Bromage scale=3). All patients were supplemented with 100% oxygen at the rate of 4L/min via the venti face mask. Intravenous fluid and blood volume were administered according to hemodynamic changes and blood loss. No other sedative or analgesic medication was given intraoperatively to the patient. Postoperatively, the sensory and motor block levels were assessed at 15 minutes intervals until normal sensations returned. The severity of postoperative pain was measured using 10 cm visual analogue scale (VAS) (0=no pain, 10=worst possible pain) every hourly till patient requested for rescue analgesia. Rescue analgesia was provided by intramuscular diclofenac sodium 75 mg, if VAS was >3. Time for 1st request for rescue analgesia and total dose of analgesic required in first 24 hour, were noted.

Hemodynamic parameters

The hemodynamic parameters of systemic arterial pressure, heart rate, pulse oximetry and electrocardiography (ECG) were monitored preoperatively and then at every 5 minute intervals after initiation of subarachnoid block, till end of surgery and followed by at every 15 minutes interval in postoperative room. For the present study, hypotension was defined as systolic blood pressure of less than 20% of base line value or less than 100 mm Hg. It was treated primarily by increasing the rate of infusion and additionally with bolus of mephenteramine 6 mg intravenously, if required further. Bradycardia was defined as heart rate less than 60 beats per minute and was treated with intravenous atropine 0.6 mg.

After the end of surgery, the patients were shifted to the recovery room and monitored for any changes in vital signs, pruritus, nausea, vomiting, shivering, respiratory depression (defined as respiratory rate less than 10 breaths/ minute), or any other adverse effects. Nausea and vomiting was treated by intravenous ondansetron (4 mg).

Study population size

The sample size was estimated with standard computer programme using the duration of the spinal analgesia as the primary variable, which computed that approximately 25 to 27 patients should be included in each group in order to detect at least clinically significant difference of 30 min in mean duration of spinal analgesia between the groups for type 1 error of 0.05 with power of 80% and confidence limit of 95%. Assuming a 5% drop out rate, the final sample size was set at 60 patients for better validation of results.

Statistical analysis

At the end of study, all data were compiled in a tabulated manner and results were expressed as Mean±Standard Deviation (SD), considering the later as the best predictor for statistical analysis. Results were analyzed using Stat graphic centurion, version 16 (Stat point Technologies INC, Warrenton), by unpaired Student's t-test for parametric data and Chi-square test for categorical data. A p value of <0.05 was considered to indicate statistical significance.

RESULTS

The present study compared the clinical efficacy of clonidine with nalbuphine as intrathecal adjuvant to 0.5% hyperbaric bupivacaine for enhancing the duration of subarachnoid block, on 60 adult female patients. There was no protocol deviation and data of all patients were included for statistical analysis. The demographic data for age, weight, height, BMI, American Society of Anesthesiologist (ASA) physical status classification and duration of surgery were comparable between the groups (Table 1).

Table 1: Showing demographic profile.

Demographic data	Group BC	Group BN	P value
Age (year)	35.83±6.7	39.66±15.09	0.209
Weight (kg)	55.23±10.65	54.06±9.4	0.655
Height(cm)	164.6±5.37	162.2±6.58	0.128
BMI (kg/m^2)	21.35±2.51	20.47±2.88	0.894
ASA(I/II)	23/7	22/8	0.640
Duration of surgery (min)	128.56±9.31	131.51±7.82	0.526

Data are expressed as Mean and Standard deviation (SD) or numbers.

Sensory and motor blockade profile

The mean time required to achieve complete sensory blockade was 8.09±1.06 min in patients of Group BC and 7.24±0.78 min in patients of Group BN with statistically significant difference (P=0.042). Mean maximal cephalic dermatome level was comparable between the groups. Mean time for two segment regressions was 216.33±

12.43 min in patients of Group BC and 157.51±18.25 min in patients of Group BN.

The duration of two segment regression varied significantly between the groups (p=0.000). Mean duration of sensory analgesia was 283.00±14.18 min with clonidine and 231.50±26.18 min with nalbuphine and it also showed statistically significant difference (P=0.001)

(Table 2). Mean time to achieve complete motor block was 9.63±2.43 min in patients of Group BC and 7.97±3.26 min in patients of Group BN with statistically significant difference (P=0.021). Mean duration of complete motor block was 186.24±18.05 min in patients of Group BC and 143.26±29.63 min in patients of Group BN with statistically highly significant difference (P=0.000) (Table 2).

Table 2: Sensory and motor blockade profile.

Parameters	Group BC	Group BN	P value
Onset time of Sensory block at T 10 level (min)	4.30±0.87	3.91±2.25	0.039*
Median cephalic sensory level	T6 (4-8)	T6 (4-7)	0.076
Time taken to achieve sensory blockade at most cephalic level (min)	8.09±1.06	7.24±0.78	0.042*
Time taken to achieve complete motor block (min)	9.63±2.43	7.97±3.29	0.021*
Time taken for two regression of sensory block (min)	216.3 ±12.43	157.51±18.25	0.000**
Duration of motor block (min)	186.24±18.05	143.26 ±29.63	0.003*
Time to administer first rescue analgesia (min)	283.00±14.18	231.50±26.18	0.001**

Data are presented as mean ± SD; *P value is statistically significant; ** P value is statistically highly significant.

Table 3: Hemodynamic profile.

Parameters	Heart rate (beats/min)		SBP (mm Hg)	
Groups	Group BC	Group BN	Group BC	Group BC
Preoperative	89.3±8.16	94.5±3.95	135.2±1.92	129.5±3.97
5min after SA	71.7±6.34	83.3±4.78	118.5±2.72	117.2±4.78
10 min	70.8±7.21	81.5±2.43	115.6±3.71	117.3±2.75
15 min	68.4±4.28	81.2±3.45	110.4±2.64	114.4±4.70
20 min	66.5±3.45	77.6±1.98	112.3±1.68	112.7±3.76
25 min	63.2±4.67	74.4±1.76	106.8±1.60	111.9 ± 2.74
30 min	68.5±2.38	72.7±2.57	103.7±3.60	107.3 ± 4.73
45 min	67.1±3.47	71.2±5.21	103.3±4.61	109.2 ± 5.67
60 min	65.3±3.61	73.6±3.89	108.9±2.93	108.4 ± 6.62
75 min	67.4±6.36	72.4±6.38	104.4±1.65	110.7 ± 3.68
90 min	68.7±4.93	71.3±4.78	106.5±1.76	118.1 ± 8.72
Postoperative	66.9±5.69	72.4±5.18	109.3±2.67	112.5±9.75

Data are presented as mean±SD; SA- Spinal anesthesia; SBP- systolic blood pressure,; * p value <0.05 significant

Hemodynamic Profile

The hemodynamic parameters of mean blood pressure, mean heart rate, respiratory rate and oxygen saturation at baseline were comparable. After 5 min of subarachnoid block, the mean heart rate and mean systolic blood pressure showed gradual decline in patients of both group till 15 min with comparable values. Later on, the mean heat rate and mean blood pressure became stable in patients of both groups with no statistically significant difference. Incidence of hypotension and bradycardia during the intraoperative period was minimal and did not require any medical intervention (Table-3). No clinically significant incidence of respiratory depression, shivering, nausea or vomiting was observed in any patient during

the study period. None of the patient needed supplemented analgesia during surgery.

Visual analogue scale

Visual Analogue Scale (VAS) was recorded every 30 min. As soon as patients experienced pain score higher than 3 on visual analogue scale (VAS, 0-10 cm), inj. Diclofenac Sodium 75mg was given intramuscularly. In patients of Group BC, the rescue analgesia was given at 7th hour, 15th hour and 24th hour postoperatively while in patients of Group BN, the rescue analgesia was given at 5th hour, 10th hour, 18th hour and 24th hour postoperatively. Rescue analgesia needed were more in patients of nalbuphine group as compared to clonidine group. The total amount of fluids administered following

subarachnoid block, the duration of surgery, and blood transfusion were comparable between the two groups. Surgical condition showed adequate muscle relaxation with comparable bleeding at surgical site.

DISCUSSION

Neuraxial anesthetic techniques are preferred for gynecological procedures due to their rapid onset of surgical anesthesia with complete muscular relaxation. It is also beneficial in patients of anticipated difficult airway or who are suffering from comorbid conditions. These advantages are sometimes offset by a relatively short duration of action of local anesthetics.

The duration of subarachnoid block can be improved by using intrathecal adjuvants in form of opioid analgesics or non-opioid drugs, which act synergistically with local anesthetic agents to intensifying the sensory block without increasing the level of sympathetic block as they act independently via different mechanism. Several clinical studies have shown that opioids and α2-adrenergic agonist are able to do so.

In the present study, the clonidine and nalbuphine were used as intrathecal adjuvant to hyperbaric bupivacaine, which revealed statistically significant difference for onset of sensory block (p=0.039) and duration of sensory blockade (p=0.000) between the groups. The onset of sensory and motor blockade was earlier with intrathecal nalbuphine while duration of sensory and motor blockade was prolonged by intrathecal clonidine. These effects showed synergism between bupivacaine and intrathecal adjuvants.

The analgesic effect of clonidine is mediated spinally through activation of post synaptic α2-adrenergic receptors in substantia gelatinosa of the spinal cord to enhance the sensory and motor blocks of bupivacaine without increasing the incidence of respiratory depression while intrathecal nalbuphine activates opioids receptors in the dorsal grey matter of spinal cord (substantia gelatinosa) to modulate the function of afferent pain fibers.[6,7] Bupivacaine acts mainly by blockade of voltage gate Na+ channels in the axonal membranes and presynaptic inhibition of calcium channels. Synergism is characterized by enhance somatic analgesia without affecting the cephalic spread of bupivacaine. We observed that maximal cephalic sensory level was comparable between the groups.

It was observed in previous studies with clonidine that 30 µg of clonidine was the minimum dose to provide significant increase in the duration of sensory and motor block, without increasing the incidence of side effects. Only few studies are available to conclude that minimum dose of intrathecal nalbuphine was 2 mg to increase the duration of sensory block without its side effects.[8,9]

In present study, the mean time to two segment regression and time to first rescue analgesic request was significantly delayed in patients of clonidine group when compared to nalbuphine group. Similar results were also observed by Strebel et al and Gecaj-Gashi et al .[10,11] This was also in accordance to the study of Tilker et al who also reported that the time taken for regression of sensory block was statistically more in patients of clonidine group.[12]

Gupta K et al compared the analgesic efficacy of intrathecal clonidine, 30 µg with butorphanol 0.20 mg during orthopedic surgeries. They considered that spinal clonidine was better than butorphanol clinically though both drugs could be intensified the sensory block.[13] Their findings are similar to the present study.

Intrathecal clonidine significantly potentiated the duration of motor block, possibly may be due to α2 adrenoreceptors agonistic effect on the motor neurons in the dorsal horn. It is also supported by the studies of Elia et al and Jain et al, who reported 0 pain score in clonidine with bupivacaine as compared to 0.5% bupivacaine alone.[3,14]

Fareed Ahmed et al evaluated the potentiating effect of intrathecal nalbuphine with bupivacaine for postoperative analgesia in three different doses (0.8, 1.6 and 2.4 mg) and concluded that the combination of intrathecal bupivacaine with nalbuphine significantly prolonged the postoperative analgesia as compared to control group.[15]

Sapate et al also stated that nalbuphine provided better quality of subarachnoid block as compared to bupivacaine alone with enhancement of postoperative analgesia for lower abdominal surgeries in elderly patients.[16] No significant hemodynamic changes or any other side effects of nausea, vomiting, pruritus, and shivering were observed in any patient of study groups.

Limitations

The primary limitation of the present study was relatively small sample size and was conducted on patients with stable cardiopulmonary status (ASA I and II). Moreover, the patient's variations of genetic factors which can alter the sensitivity to pain and response to analgesia were also not considered.

CONCLUSION

Clonidine, 30µg and nalbuphine, 2mg as intrathecal adjuvant to 0.5% hyperbaric bupivacaine for subarachnoid blockade, were clinically effective for providing adequate surgical condition with comparable hemodynamic effects. Clonidine was more efficient than nalbuphine for extending the duration of sensory and motor block and enhancing the postoperative analgesia following gynaecological procedures.

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