

A COMPARATIVE STUDY OF CLONIDINE VERSUS NALBUPHINE AS INTRATHECAL ADJUVANTS TO 0.5% HYPERBARIC BUPIVACAINE DURING LOWER ABDOMINAL SURGERIES – A RANDOMIZED DOUBLE BLIND INTERVENTIONAL STUDY.

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Article Info: Received 15 February 2020; Accepted 08 March 2020

DOI: <https://doi.org/10.32553/ijmbs.v4i3.1004>

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Conflict of interest: No conflict of interest.

Abstract

Background: Regional anesthesia techniques for gynecological 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 Lower abdominal surgeries in Gynecology.

Methods: With institutional ethics committee clearance No. 193MC/EC/2018, randomized, double blind study was conducted. After obtaining informed written consent total of 84 patients scheduled for lower abdominal surgeries were randomly allocated into two groups:

Group A (n=42) - Inj. 3.5 ml Bupivacaine 0.5% + 0.2 ml Clonidine(30µg) intrathecally.

Group B (n=42) - Inj.3.5 ml Bupivacaine 0.5%+0.2 ml Nalbuphine(2mg) intrathecally.

The characteristics of sensory and motor block, hemodynamic data, side effects were recorded.

Results: The onset of sensory block was earlier in Group B than Group A (3.08±0.52 min vs 4.00±0.54 min, p<0.001). The onset of motor block was also earlier in Group B than Group A (7.78±0.80 min vs 8.80±0.95min, p<0.001). The time to first rescue analgesia in patients receiving intrathecal clonidine was significantly delayed than patients receiving intrathecal nalbuphine (284.95 ± 12.93 min vs 211.52 ± 15.92 min, p<0.001). Intraoperative hemodynamic changes were comparable and none of the patient suffered from respiratory depression except very little cases of shivering which are not significant.

Conclusions: Intrathecal clonidine as adjuvant to bupivacaine provided was clinically more effective than nalbuphine for prolonging the duration of analgesia for gynecological procedures.

Keywords: Bupivacaine, Clonidine, Lower abdominal surgeries in gynecology, Nalbuphine, Subarachnoid block.

Introduction

Subarachnoid block with local anesthetic is a commonly used regional anesthetic technique for Lower abdominal surgeries. 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.

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⁽¹⁾.

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.

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 κ-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.

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 Lower abdominal surgeries.

Methods

After Institutional Ethical Committee approval No. 193MC/EC/2018, this prospective randomized, double blind, interventional study was conducted on 84 female patients of American Society of Anesthesiologist (ASA) physical status I and II aged between 20-60 years, weighing 50-70 kg, scheduled for Lower abdominal surgeries 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. Patients were kept NBM (Nothing By Mouth) for 8 hours pre-operatively. Premedication was done with oral ranitidine 150 mg and alprazolam 0.25 mg a night before surgery.

Randomization and blindness

Patients were divided in a double-blind manner into two equal groups of 42 patients each by sealed envelope method. Patients of Group A were given 3.5 mL of 0.05% hyperbaric bupivacaine with 0.2ml of clonidine (30µg) and patients of Group B were given 3.5 mL of 0.5% hyperbaric bupivacaine with 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 investigator who was unaware of group allocation.

Anesthetic Technique

Monitors were applied and baseline pulse rate, SpO₂, 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 Preloading with Ringer lactate as 10 ml/kg over 20 min. Lumbar puncture was performed at L3-L4 intervertebral space with 25 G Quincke's needle using midline approach in left lateral 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, Following the subarachnoid block,

position of the patient was supine with 15 degree head low tilt. Oxygenation done by face mask at 4 L/min.

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 20 G hypodermic needle until the level was stabilized for 4 consecutive tests. The onset time of sensory blockade at T10 dermatome, The highest level of sensory block, Time to achieve highest level of sensory block was noted from intrathecal injection to achieve highest level of sensory block and time taken to two segment regression of sensory block was assessed for each patient.

Motor block was assessed using the Modified Bromage scale, till achievement of the highest motor level. Onset of motor block was defined as the time taken for motor block to reach Modified Bromage score 1. Offset of motor block was defined as modified Bromage scale 6. [Modified bromage scale score 1 = Complete motor blockade, 2 = Almost complete blockade, the patients is able only to move the feet, 3 = partial motor blockade, the patient is able to move the knees, 4 = detectable weakness of hip flexion the patient is able to raise the leg but is unable to keep it raised, 5 = no detectable weakness of hip flexion, the patient is able to keep the leg raised for 10s at least, 6 = no weakness at all, the patient is able to perform partial knee bend while lying supine.]

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 1. 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=1). 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 30 minutes intervals for 2 hours then 60 minutes for next 2 hours. The severity of postoperative pain was measured visual analogue scale (VAS) (0=no pain, 10=worst possible pain) 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 20 minutes, then every 15 minutes till end of surgery, followed by at every 30 minutes for 2 hours and every 60 minutes for next 2 hours in postoperative room. For the present study, hypotension was defined as systolic blood pressure of less than 20% of base line value. 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 50 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).

Sample size

A sample size of 42 in each group were required at 95 % confidence and 80 % power to verify the expected difference of 52 (± 26.18) minutes in time duration for the requirement of first rescue analgesia in both groups. This sample size was adequate to compare other study variables too.

Statistical analysis

The continuous variables (quantitative data) like age, weight, height, blood pressure, heart rate, time were presented as mean and standard deviation and analyzed by applying one way –ANOVA test. The categorical variables (qualitative data) like ASA grade, sedation score were presented in frequency and percentage and were analyzed with Chi-Square test (for nominal data).

For significance, following at the level of P value will be taken: [$P > 0.05$ = not significant, $P = 0.05$ = just significant, $P < 0.05$ = significant, $P < 0.001$ = highly significant.] A p value of less than 0.05 was considered statistically significant in all the analysis.

All the statistical analysis of data was done with statistical programming software – SPSS (Statistical Package for the Social Science) version 21 for Windows statistical software package (SPSS Inc., Chicago, Illinois, USA).

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 84 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.

Variables	Group A		Group B		P value
	Mean	SD	Mean	SD	
Age (Yrs)	39.52	11.09	38.88	11.04	0.790 (NS)
Weight (kg)	59.58	5.28	60.33	5.19	0.513 (NS)
Height (cm)	162.24	3.82	162.45	3.94	0.800(NS)
ASA Grade (I/ II)	37/5		38/4		0.724(NS)
Duration of Surgery (min)	104.64	12.75	103.21	11.09	0.585(NS)

Sensory and motor blockade profile

The mean onset time was 4.00 ± 0.54 minutes in Group A and 3.08 ± 0.52 in Group B with statistically significant difference ($P < 0.001$), The time required to achieve highest level of sensory blockade was 7.55 ± 0.70 min in patients of Group A and 6.45 ± 0.62 min in patients of Group B with statistically significant difference ($P < 0.001$). Median highest level of sensory block was comparable between both the groups ($P = 0.375$). Mean time for two segment regressions was 208.37 ± 12.09 min in patients of Group A and 161.36 ± 7.39 min in patients of Group B. The duration of two segment regression varied significantly between the groups ($p < 0.001$). Mean duration of analgesia was 284.95 ± 12.95 min with clonidine and 211.52 ± 15.92 min with nalbuphine and it also showed statistically significant difference ($P < 0.001$) (Table 2). Mean time to achieve complete motor block (onset time of motor block) was 8.80 ± 0.95 min in patients of Group A and 7.78 ± 0.80 min in patients of Group B with statistically significant difference ($P < 0.001$). Mean duration of complete motor block was 190.24 ± 13.25 min in patients of Group A and 153.57 ± 12.31 min in patients of Group B with statistically highly significant difference ($P < 0.001$) (Table 2).

Table 2: Sensory and motor blockade profile.

Parameters	Group A		Group B		P value
	Mean	SD	Mean	SD	
Onset time of Sensory block at T10 level (min)	4.00	0.54	3.08	0.52	$P < .001$ (HS)
Median highest level of sensory block	T6		T6		$P = 0.375$ (NS)
Time taken to achieve highest level of sensory block (min)	7.55	0.70	6.45	0.62	$P < 0.001$ (HS)
Onset time of Motor block (minutes)	8.80	0.95	7.78	0.80	$P < 0.001$ (HS)
Time taken for two segment regression of sensory block (min)	208.37	12.09	161.36	7.39	$P < 0.001$ (HS)
Duration of motor block (min)	190.24	13.25	153.57	12.31	$P < 0.001$ (HS)
Time to administer first rescue analgesia (min)	284.95	12.93	211.52	15.92	$P < 0.001$ (HS)
Total doses of analgesic in 24 hrs (3/4)	37/5		9/33		$P < 0.001$ (HS)

Visual analogue scale

Visual Analogue Scale (VAS) was recorded every 30 min. post operatively 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. Rescue analgesia needed were more in patients of nalbuphine group as compared to clonidine group (Table 2). There is no statistically significant difference in the incidence of adverse effects among the both groups.

Hemodynamic Profile

The hemodynamic parameters of mean blood pressure, mean heart 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 heart 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 which was statistically comparable in both groups. Post operative hemodynamic parameters were also comparable between both groups.

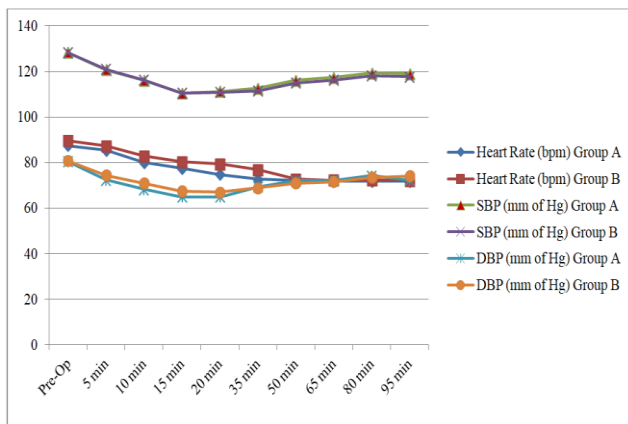


Figure 1: Hemodynamic profile.

Discussion

Regional anesthesia is now more popular than general anesthesia for lower abdominal surgeries because of the increased mortality rate associated with general anesthesia and due to rapid onset of surgical anesthesia with complete muscular relaxation of spinal anaesthesia. 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.

In the present study, the clonidine and nalbuphine were used as intrathecal adjuvant to hyperbaric bupivacaine, which revealed that statistically highly significant difference for onset of sensory block ($p < 0.001$) and onset of motor block ($p < 0.001$) between both the groups. The onset of sensory and motor blockade was earlier with intrathecal nalbuphine while duration of motor blockade was more prolonged by intrathecal clonidine as compared to intrathecal nalbuphine which was statistically highly significant ($p < 0.001$), these results were also similar found by Bansal M. et al.⁽⁹⁾ These effects showed synergism between bupivacaine and intrathecal adjuvants.

The analgesic effect of clonidine is mediated spinally through activation of post synaptic α_2 -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. Bupivacaine acts mainly by blockade of voltage gated sodium ion 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 in present study that highest level of sensory block was comparable between both the groups which was also similar with studies done by Chetty D.K. et al.⁽¹⁰⁾ and Bansal M. et al.⁽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 Bansal M. et al.⁽⁹⁾ and Chetty D.K. et al.⁽¹⁰⁾ This was also in accordance to the study of Tilker Y et al.⁽⁵⁾, Elia N et al.⁽²⁾ and Stebral S et al.⁽⁴⁾ who also reported that the time taken for regression of sensory block and time of first rescue analgesia were statistically more in patients of clonidine group than 0.5% bupivacaine alone and to the study of Clubras X et al.⁽³⁾ and Fareed A. et al.⁽⁷⁾ who were found that the time of two segment regression and time of first rescue analgesia also prolonged with intrathecal nalbuphine as compared to control group.

Gupta K et al.⁽⁶⁾ 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. Their findings are similar to the present study.

Sapate et al.⁽⁸⁾ 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.

Thus our study demonstrated that clonidine produce longer duration of post-operative analgesia when compared to nalbuphine with comparable minimal hemodynamic changes and adverse effects which was supported by Bansal M. et al⁽⁹⁾ and Chetty D.K. et al.⁽¹⁰⁾

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 Lower abdominal surgeries.

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