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ORIGINAL ARTICLE

Evaluation of Nalbuphine with that of Clonidine as an Adjuvant to IntraThecal 0.5% Hyperbaric Bupivacaine

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Abstract

Background and objectives: This study compares the clinical efficacy of nalbuphine and clonidine as adjuvants to 0.5% hyperbaric bupivacaine for Sub arachnoid block. The efficacy is compared in terms of onset of block, duration of block, and quality of sensory and motor blockade, as well as other associated side effects. **Methodology:** Sixty adult patients ranging between 18 to 65 years and having ASA physical status I or II and were scheduled for lower abdominal surgeries from January to December 2020, were enrolled in this randomized type of study. To ensure proper study without any bias, computer-generated randomisation sequence was used to allocate participants evenly into two groups (n=30 each). Group N received an intrathecal dose comprising 2.8 ml of 0.5% hyperbaric bupivacaine combined with 0.2 ml of nalbuphine (0.4 mg), whereas Group C was administered 2.8 ml of 0.5% hyperbaric bupivacaine along with 0.2 ml of clonidine (30 µg). Sensory and motor block assessments were performed using the pinprick method and the Bromage scale, respectively. **Results:** Clonidine had a sensory onset of 3 (0.83) minutes compared to 4.47 (1) minutes of Nalbuphine. Onset of motor blockade of Clonidine was 5.07 (0.86) minutes compared to 6.57(1) minutes of Nalbuphine. Motor blockade in Clonidine was 294.53 (25.93) min as compared to 240.53 (23.45) min of Nalbuphine. Duration of Sensory blockade of clonidine was 323.13 (27.20) as compared to 268.93 (23.67) of Nalbuphine**.** Clonidine demonstrated a quicker initiation and extended duration of both sensory and motor blockade in comparison to nalbuphine. **Conclusion:** Both nalbuphine and clonidine effectively prolong spinal anesthesia duration when used along with bupivacaine, though clonidine shows superior efficacy in terms of onset and duration.

Keywords: Spinal anesthesia, intrathecal nalbuphine, intrathecal clonidine, analgesia duration, bupivacaine.

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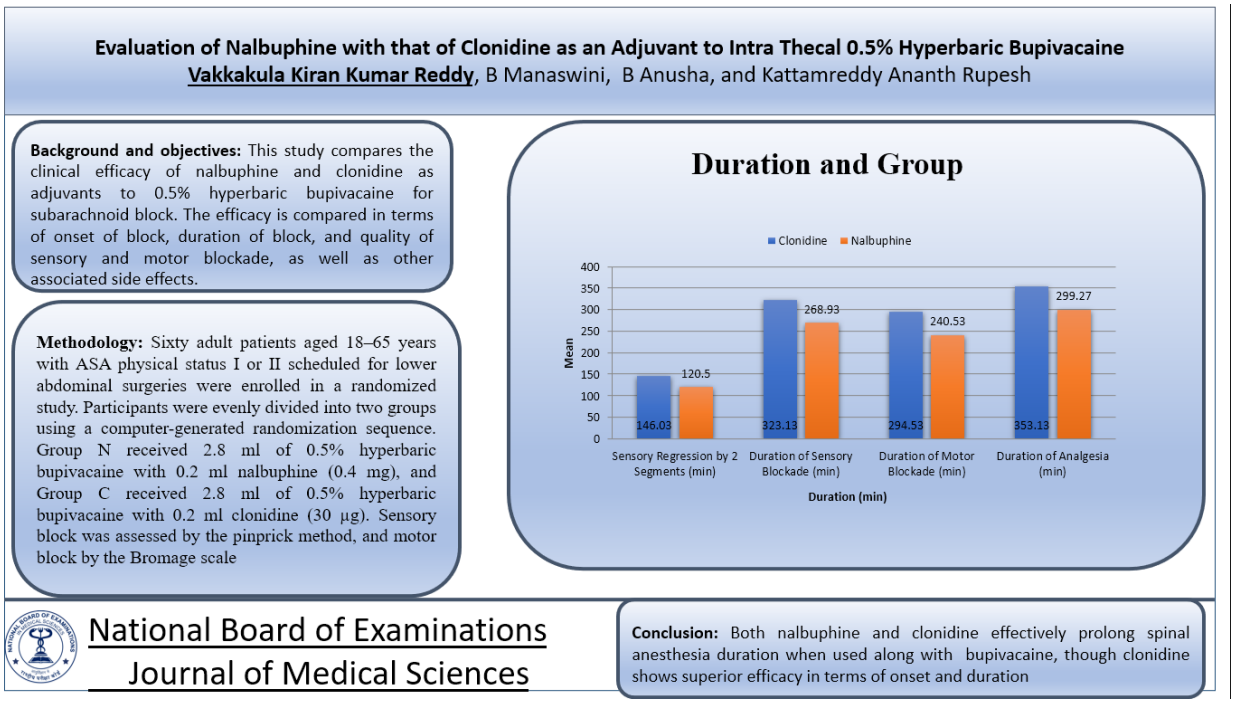
Graphical Abstract



Introduction

Spinal anesthesia is one of the most routinely performed procedure. Since its introduction by August Bier in 1898, spinal anesthesia has become a very routine, familiar and well used regional anesthesia techniques due to its procedural simplicity and cost-effectiveness. The addition of adjuvants or additives to local anesthetics which are primarily sodium channel blockers can prolong both analgesia and motor block duration, thereby improving anesthetic quality and patient satisfaction.

Nalbuphine is a semisynthetic opioid. The advantage of Nalbuphine is that it has both µ antagonist and k agonist features. Previous studies (Mukherjee et al. and Sapate et al.) demonstrated that nalbuphine, when combined with intrathecal bupivacaine, enhances motor and sensory blockade with minimal adverse effects [1-3].

Clonidine is an alpha-2 adrenergic agonist with a well documented drug kinetics and dynamics. It has long been used as an antihypertensive agent in clinical practice. Motor and sensory blockade can be increased by adding Clonidine to Spinal Anesthesia [4-6].

Addition of Alpha-2 agonists or opiods can minimize the usage of additional Anesthetic and analgesic drugs during peri operative period [7-11].

While the effectiveness of clonidine and nalbuphine as spinal adjuvants has been individually demonstrated in numerous studies, direct comparative evaluations between the two remain limited.". Hence the idea behind conceptualizing the study was to have a direct comparison of the two study drugs Clonidine and Nalbuphine. After going through various previous studies and drug pharmacodynamics and pharmacokinetics, we decided to compare the clinical effects of intrathecal bupivacaine after addition of

nalbuphine or clonidine. 2.8ML (0.5%) of intra thecal bupivacaine was taken and after addition with either nalbuphine 0.4 mg or clonidine 30 µg as adjuvant, was used in lower abdominal surgeries and anesthetic efficacy was compared. Anesthetic efficacy in terms of motor and sensory onset, duration of motor and sensory blockade, 2 segment regression and Anesthetic complications were assessed.

Materials and Methods

The study received prior permission from the Ethics Committee of the Institution in accordance with standard ethical protocols. Before incorporating any patient into the study group, proper written and informed consent was taken from all patients in their own language in which they can understand and apprehend.

Sixty patients, admitted to KAMSRC (Kamineni Academy of Medical Sciences and Research centre) in the year 2020 from January to December belonging to ASA grade I and II were selected. These were the patients who were scheduled for elective lower abdominal surgeries, of duration less than 3 hrs, under spinal anesthesia. After selection the 60 patients were included in one of the two groups after proper randomization through computer software.

Inclusion Criteria

Patients scheduled for elective lower abdominal surgeries, aged 18–65 years, and classified as ASA physical status I or II, were considered. Patients were selected after a thorough Pre anesthesia check up and assessment.

Exclusion Criteria

Exclusion criteria addressed known contraindications to spinal anesthesia such as history of allergic reactions to study drugs, spinal deformities, neurological deficits, and anticipated surgical duration exceeding three hours. Surgeries beyond three hours of duration were not included in the study.

Methods

Computer software was used to generate randomization to allocate patients to two groups. 2.8 ml of hyperbaric bupivacine (0.5%) + 0.4mg of nalbuphine =(3ml) was given to Group N. 2.8 ml of hyperbaric bupivacine (0.5%) + 30 µg of clonidine =(3ml) was given to Group C.

Monitoring

ECG monitoring was used intra operatively. It was done using three leads and monitoring was done in standard Lead II. Continuous ECG monitoring was performed intraoperatively using lead II, which is sensitive for early detection of myocardial ischemia. Blood pressure monitoring was done using automated Non invasive blood pressure monitoring at regular intervals. Oxygen saturation was monitored using pulse oximeter. Baseline vitals were noted and vitals were monitored at regular intervals.

Procedure

All patients had 20G or 18G IV cannula secured before surgery. A 25-gauge Quincke-type spinal needle, the standard instrument used at our institute, was utilized to administer spinal anesthesia. The intrathecal drug was administered at either the L3–L4 or L4–L5 interspace, chosen based on anatomical

accessibility and ease of lumbar puncture. All spinal procedures were conducted in the lateral decubitus position, using appropriate support and strict aseptic technique. Blood loss and vitals were assessed intra operatively and used as a guide for fluid replacements.

Post-block parameters including onset and duration of sensory and motor blockade, two-segment regression time, and analgesia duration were meticulously recorded. Sensory blockade was assessed using pin prick method and motor blockade was assessed using Bromage scale.

Various essential parameters such as Heart rate, Blood pressures were recorded at baseline, and then at 5, 10, 20, and 30 minutes, followed by every 30 minutes up to 120 minutes post-spinal block.

This included parameters like pulse rate, Blood pressures, oxygen saturations and respiratory rates. Complications and untoward incidents like changes in blood pressure, changes in heart rate, respiratory depression (that is respiratory rate less than 10 or SpO_2 <90%) nausea and vomiting were also documented. Any other surgical or anesthesia complications were also noted during the study.

Pain and sensory block assessments were conducted by employing the Visual Analogue Scale (VAS) at predetermined timings until rescue analgesia was required. Patient comfort and satisfaction was of utmost importance, hence VAS score 4 or more or if the patient complained of pain and demanded analgesia, rescue analgesics were given in the form of Injection Diclofenac 75 milligrams intra muscularly. Injection Emeset (Ondansetron) 4 milligrams intra venous was used for its anti emetic properties to treat peri operative nausea and vomiting. Patient was regularly monitored in the post operative period.

Statistical Methods

Robust statistical analysis was conducted to ensure accurate interpretation of the study findings. Advanced computing methods and computer software was used. Microsoft Excel (Windows 7; Version 2007) was used for data entry. Microsoft excel being easy to use and enter data, it was preferred for data entry. Statistical analyses are very important for proper interpretation and analyses of data. It is for this purpose that for statistical analyses SPSS software for Windows (version 22.0; SPSS Inc, Chicago) was used. Statistics such as mean ± standard deviation for continuous data and frequency distributions for categorical data which are all types of descriptive statistics were analyzed.

The variables were compared using the Chi-Square test for categorical variables. Unpaired t-test was employed to assess the means of variables which are quantitative after verifying normality with the Samuel Sanford Shapiro and Martin Wilk test. Pictorial representation was done to enhance the data.

P values were calculated for all the data we compared. A p-value below 0.05 was regarded as a data which is significant statistically; while a value below 0.001 was considered highly significant in terms of statistics. This is as per the standard statistical guidelines followed everywhere.

Results and Observations

Sixty patients in total were allocated to two groups, that is Group N (nalbuphine 0.4 mg) and Group C (clonidine 30 µg). All the patients were lying in the age group 18 to 65 years. These were non emergency surgeries posted for elective lower abdominal procedures. All the procedure were performed under spinal anesthesia. The relation between age of the patients and the study groups were documented and assessed. Computer-generated randomization yielded comparable demographic distribution between the groups, as indicated by a statistically non-significant p-value (Table 1).

Table 1. Relationship between Age and Study Group (N=60)

Age (Years)	**Category**	
	Clonidine (n=30)	**Nalbuphine (n=30)**
≤ 30	3 (10.0)	4 (13.3)
31-40	8 (26.7)	12 (40.0)
41-50	13 (43.3)	7 (23.3)
51-60	5 (16.7)	7 (23.3)
>60	1 (3.3)	
Mean (SD)	42.67 (9.71)	41.30 (9.55)
P Value = 0.396, Not Significant		

The mean age of participants was compared between the two groups and found to be similar (Group C: 42.67 ± 9.71 years; Group N: 41.30 ± 9.55 years), with no statistically significant difference (p = 0.396), indicating age distribution was well balanced. This was very important, as a study with variation in age groups may yield false results.

Table 2 displays the data of male and female distribution in both groups.Gender distribution, that is the distribution of male and female gender across the two groups had a p value which was greater than 0.05 and hence was not statistically significant. Indicative of even distribution of sexes across the two groups.

Table 2. Relationship between Gender and Study Group (N=60)

Gender	Category	
	Clonidine (n=30) n (%)	Nalbuphine (n=30) n (%)
Male	9 (30.0)	10 (33.3)
Female	21 (70.0)	20 (66.7)
P Value = 0.781		

Table 3 shows the patients based on ASA grading in the two groups. In Group N, 19 patients (47.50%) were classified as ASA grade 1, compared to 21 patients (52.50%) in Group C. For ASA grade 2, there were 11 patients (55.00%) in Group N and 9 patients (45.00%) in Group C. The difference in ASA grading across the two groups based on ASA grading is not statistically significant, as the derived p value is not statistically significant. ($p = 0.584$; $p > 0.05$).

Table 3. Relationship between ASA Classification and Study Group (N=60)

ASA	Category	
	Clonidine (n=30) n (%)	Nalbuphine(n=30) n (%)
I	21 (70)	19 (63.3)
II	9 (30.0)	11 (36.7)
P Value = 0.584		

Table 4 illustrates that the mean onset time of sensory blockade was 3.00(0.83) minutes in Group C (Clonidine) and 4.47(1.0) minutes in Group N (Nalbuphine). This indicates a statistically significant difference between the two compared groups ($p < 0.001$). Similarly, the average onset time for motor blockade was 5.07 (0.86) minutes in Group C and 6.57(1.0) minutes in Group N. This data when analyzed shows that there is statistical significance ($p<0.001$). The time taken to reach peak sensory blockade averaged 6.10 (0.75) minutes in the Clonidine group and 7.67(0.88) minutes in the Nalbuphine group. The data when analyzed and compared the peak sensory blockade showed a statistical difference with p value < 0.001. Similarly, the mean time to attain maximum motor blockade was 6.70(0.70) minutes in Group C compared to 8.37(0.76) minutes in Group N, with the difference being statistically significant ($p = 0.000$). In this table data comparison of sensory onset, motor onset, time for peak sensory level as well as maximum motor blockade all showed significant statistical difference.

Table 4. Comparison of Sensory and Motor Blockade Features across the Two Study Groups (N=60)

Parameter	Category		P Value
	Clonidine(n=30) Mean (SD)	Nalbuphine(n=30) Mean (SD)	
Sensory Onset (min)	3.00 (0.83)	4.47 (1.00)	<0.001*
Motor Onset (min)	5.07 (0.86)	6.57 (1.00)	<0.001*
Time for peak sensory level (min)	6.10 (0.75)	7.67 (0.88)	<0.001*
Time for Maximum Motor Blockade (min)	6.70 (0.70)	8.37 (0.76)	<0.001*
Unpaired t Test, P Value *Significant			

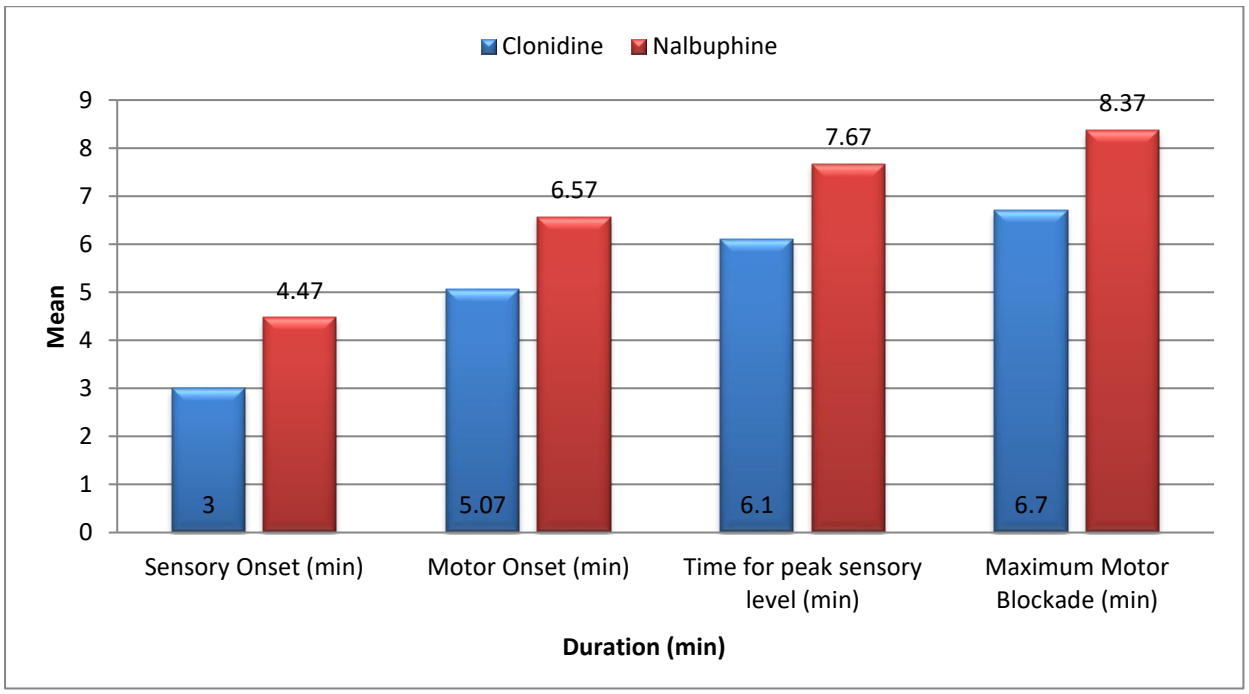


Figure 1. Duration and Group

Table 5 Throughout the study, patients' pulse rates in both groups remained near the baseline values. With ($p > 0.05$), there is no statistical difference between the groups and hence not significant for the outcomes of the study.

Table 5. Comparison of Heart Rate across the Two Study Groups (N=60)

Heart Rate	Category		P Value
	Clonidine(n=30) Mean (SD)	Nalbuphine(n=30) Mean (SD)	
Basal	89.73 (17.27)	84.33 (16.01)	0.214
0 min	94.83 (16.65)	89.03 (11.82)	0.125
2 min	88.90 (18.48)	89.67 (14.74)	0.860
5 min	78.97 (17.39)	86.50 (18.19)	0.107
10 min	74.40 (13.88)	81.67 (19.47)	0.101
20 min	75.40 (11.47)	79.77 (14.01)	0.192
30 min	75.23 (9.24)	76.80 (14.65)	0.622
40 min	76.57 (9.48)	76.93 (12.68)	0.900
50 min	78.33 (11.52)	78.77 (9.35)	0.874
60 min	78.63 (11.86)	79.93 (9.39)	0.640
80 min	80.70 (11.59)	78.77 (9.26)	0.478
100 min	80.07 (11.16)	77.97 (9.89)	0.444
120 min	79.77 (10.40)	79.27 (10.45)	0.853
Unpaired T Test, P Value Not Significant			

Table 6 shows the mean arterial blood pressures across the two groups were assessed and was found to have no statistical difference. ($p > 0.05$).

Throughout the study, hemodynamic parameters—including heart rate and mean arterial pressure—remained stable and showed no statistically significant differences between the groups ($p > 0.05$ for all time points) (Table 7 and Figure 2).

Table 6. Mean Arterial Pressure Comparison across the two study groups - Group C and Group N (N=60)

MAP	Group		P Value
	Clonidine (n=30) Mean (SD)	Nalbuphine (n=30) Mean (SD)	
Basal	96.03 (9.05)	96.60 (8.45)	0.803
0 min	94.27 (8.32)	94.07 (6.37)	0.917
2 min	89.50 (8.49)	90.07 (6.38)	0.771
5 min	84.23 (10.57)	87.37 (7.76)	0.196
10 min	82.53 (10.45)	86.00 (7.06)	0.138
20 min	84.23 (10.57)	84.57 (6.11)	0.882

30 min	82.80 (8.76)	83.97 (6.93)	0.570
40 min	84.50 (8.02)	84.93 (11.08)	0.863
50 min	85.27 (7.36)	85.80 (9.46)	0.808
60 min	85.30 (6.22)	86.47 (8.43)	0.544
80 min	86.27 (6.56)	85.60 (7.06)	0.706
100 min	86.13 (5.61)	85.67 (8.84)	0.808
120 min	86.80 (5.16)	85.63 (8.97)	0.540
Unpaired T Test, P Value Not Significant			

Table 7. Timings of Sensory blockade and Motor Blockade Features across the given Two Study Groups (N=60)

Parameter	**Category**		**P Value**
	Clonidine(n=30) Mean (SD)	**Nalbuphine(n=30) Mean (SD)**	
Sensory Regression by 2 Segments (min)	146.03 (20.23)	120.50 (19.39)	<0.001*
Duration of Sensory Blockade (min)	323.13 (27.20)	268.93 (23.67)	<0.001*
Duration of Motor Blockade (min)	294.53 (25.93)	240.53 (23.45)	<0.001*
Duration of Analgesia (min)	353.13 (26.39)	299.27 (23.26)	<0.001*

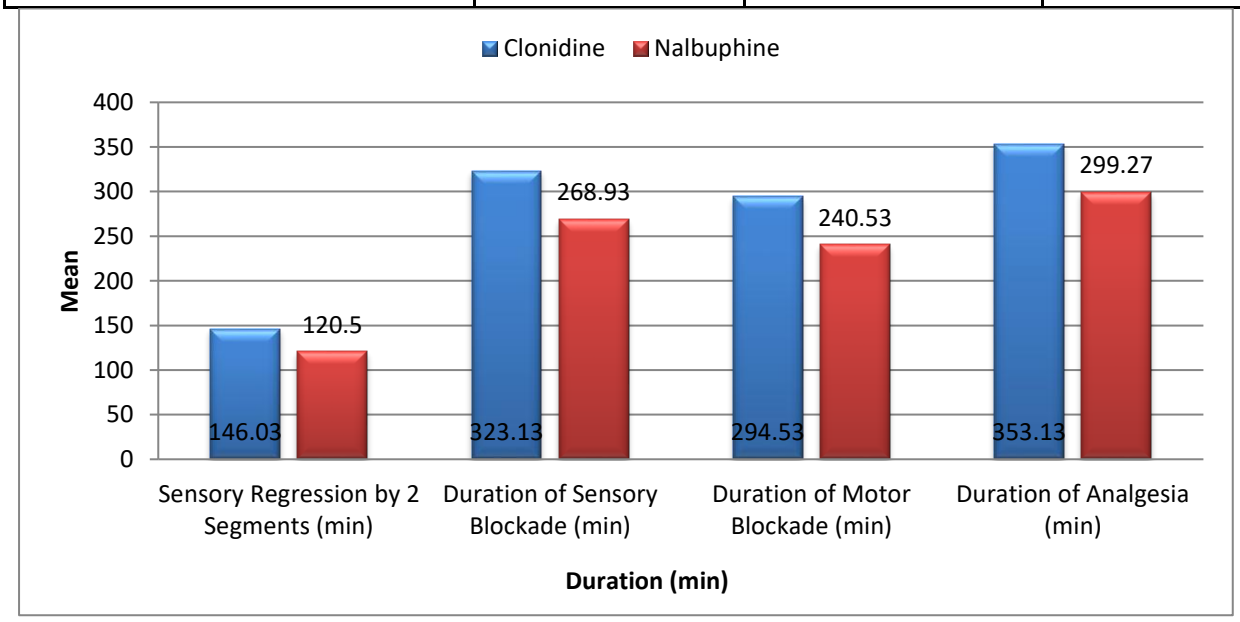


Figure 2. Duration and Group

The calculated mean time for two-segment regression of the sensory blockade was 146.03 ± 20.23 minutes in Group C and 120.50 ± 19.39 minutes in Group N. This when analyzed demonstrated a statistically highly significant difference ($p < 0.001$). Also the average duration of sensory blockade was significantly longer in Group C (Clonidine), at 323.13 ± 27.20 minutes, compared to 268.93 ± 23.67 minutes in Group N (Nalbuphine), with a p-value of < 0.001. The duration of motor blockade also differed significantly between the groups, with Group C showing a mean of 294.53 ± 25.9 minutes and Group N showing 240.53 ± 23.4 minutes ($p = 0.000$). Additionally, the average duration of analgesia was 353.13 ± 26.3 minutes in the Clonidine group and 299.27 ± 23.2 minutes in the Nalbuphine group, again indicating a highly significant statistical difference ($p < 0.001$).

Discussion

Neuraxial anesthesia that is spinal anesthesia or epidural anesthesia techniques are commonly preferred for lower abdominal surgeries. Good analgesia and proper muscle relaxation are the pillars of proper regional anesthesia. Neuraxial techniques have the advantage of being able to provide faster onset of surgical anesthesia (sensory loss) along with complete muscle relaxation.

Nalbuphine is an opioid. It's a partial agonist- antagonist drug. Nalbuphine is semi synthetic drug and belongs to phenanthrene class. It is structurally similar to drugs like oxymorphone and naloxone and interacts with μ-, κ-, and δ-opioid receptors.

Nalbuphine is a potent opioid and has been used for both Intra venous and Intra thecal administration. A lot of studies have documented its efficacy and safe usage in both forms. We went through a lot of online research to find the optimal/ required dose of Nalbuphine for usage and comparison. Tiwari et al. [12]. compared intrathecal administration of 0.2 mg and 0.4 mg Nalbuphine with bupivacaine and found that 0.4 mg offered a longer duration of postoperative analgesia. Based on these findings, in the present study we used 0.4 mg of Nalbuphine to compare its effects with 30 μg of Clonidine as an intrathecal additive.

Clonidine as a drug is a potent Alpha 2 adrenergic agonist and its being used in clinical purpose for a long time for various purposes. Clonidine also has been used in both Intravenous and Intra thecal route. Clonidine produces its analgesic/ sensory effect at the spinal level by activating presynaptic α2-adrenergic receptors. These are primarily located in the substantia gelatinosa of the spinal cord. It enhances both sensory and motor blockade of bupivacaine without increasing the risk of respiratory depression. Enhancing both sensory and motor blockade is a very useful trait in spinal anesthesia. In contrast, intrathecal nalbuphine exerts its action by stimulating opioid receptors in the dorsal grey matter (substantia gelatinosa) of the spinal cord. By stimulating opioid receptors it modulates afferent pain signal transmission, hence enhancing the quality of sensory blockade as well as duration of sensory lockade.

We have gone through a lot of online research to find studies which are comparable to our findings. The findings

which we found out are comparable to those of H. Saxena et al. [13], who reported a mean onset time of motor block of 2.30 minutes using 30 μg of clonidine. However, their study has a drawback as they did not clearly define the criteria for motor block onset.

Bupivacaine is a local anesthetic drug. Its primary action is by blocking voltage gated sodium channel. It is used in various regional anesthesia procedures such as Blocks, local infiltrations, Spinal and Epidural anesthesia procedures. Because of favorable kinetics and pharmaco dynamics, Hyperbaric bupivacaine is the commonly used drug in spinal anesthesia. Bupivacaine has a very safe profile as drug and is very effective in its sensory and motor blockades. Bupivacaine primarily functions by blocking voltage-gated sodium channels on axonal membranes and by presynaptic inhibition of calcium channels.

In our study, the distribution of patients based on age, gender, and ASA classification was similar across the two given groups, with no statistically significant differences ($p > 0.05$). This is very important as variations across the study groups in terms of age, gender and ASA classification may impact the study outcome and results will be not completely correct.

Onset of sensory blockade is of prime importance in Anesthesia as a drug with shorter onset will help in faster starting of surgery which in turn reduces the cost of Operation theatre. This is of lot of significance when the cumulative times of a good number of cases are done. The start of sensory blockade occurred significantly earlier in Group C, as compared to Group N ($p < 0.001$). Specifically, the mean onset time of sensory block was 3.00 ± 0.83 minutes in the clonidine group and 4.47 ± 1.00 minutes in the nalbuphine group. This when compared statistically indicated a significant difference between the two groups. A faster sensory onset which is statistically significant is of lot significance in a hospital setting and also more comfortable for the patient as it reduces the anxiety levels.

In the present given study, the mean onset time of motor block was 5.07 ± 0.86 minutes in the clonidine group and 6.57 ± 1.00 minutes in the nalbuphine group. This showed a statistically significant difference upon calculation. A shorter onset of motor blockade is very useful, especially in emergency scenarios where there is a need to start a surgery urgently.

A faster sensory onset and motor onset of clonidine over nalbuphine makes it a very useful attribute which will make clonidine to be preferred over nalbuphine. The duration required for two-segment regression of the sensory blockade was 146.03 ± 20.23 minutes in the clonidine group and 120.50 ± 19.39 minutes in the nalbuphine group. This on comparing the data showed statistical significance. Two segment regression implies the waning off of the effect of the spinal drug. Hence any drug which increases the two segment regression will have a longer sensory and motor duration and will be useful to the patient. In this case the longer two segment regression time of clonidine makes it a drug of longer duration for anesthetic usage.

Sapate et al. [14] compared a Nalbuphine group (0.5 mg) with a control group and reported a two-segment

regression time of 116.23 ± 9.17 minutes, which is closely comparable to the findings in our study. Sapate et al. as well as our study emphasizes the importance of two segment regression time and effectives of clonidine due to better two segment regression time.

In the present given study, the time elapsed for complete sensory recovery was 323.13 ± 27.20 minutes in the clonidine group which was longer in comparison to nalbuphine group at 268.93 ± 23.67 minutes. This difference in time was significant and with a p value of < 0.001 it had statistical significance.

The mean duration of motor blockade that was calculated during the study was 294.53 ± 25.93 minutes in the clonidine group and 240.53 ± 23.45 minutes in the nalbuphine group. This on comparison showed a highly significant statistical difference ($p < 0.001$). Similarly, the total duration of analgesia was significantly longer in the clonidine group (353.13 ± 26.39 minutes) compared to the nalbuphine group (299.27 ± 23.26 minutes). Statistical analysis of total duration of analgesia showed a p value <0.001, which is of statistical importance. There were no statistically significant differences between the two groups with respect to heart rate and blood pressure.

Throughout surgery duration in the operation theatre and after that in post op recovery room, no instances of nausea or vomiting were reported in either group. Additionally, none of the patients experienced any Apnoea or bradyapnoea episodes and all maintained peripheral oxygen saturation levels above 95% without the need for supplemental oxygen.

Conclusion

In our study we compared the efficacy of two drugs clonidine and nalbuphine as an additive/adjuvant to hyperbaric bupivacaine for sub arachnoid block. Based on various previous studies the doses of 30 microgm of clonidine and 0.4 mg of nalbuphine was finalized. Based on the comparison in patients aged between 18 to 65 undergoing lower abdominal surgeries, it can be concluded that both agents are clinically effective in providing adequate surgical conditions with similar hemodynamic stability.

However, intrathecal clonidine offers a longer duration of analgesia as well as extended sensory and motor blockade in comparison to nalbuphine. Hence in lower abdominal surgeries clonidine can be a better modality over nalbuphine as an adjuvant with hyperbaric bupivacaine, as it achieves superior outcomes without notable side effects.

Conflict of interest

The authors declare that they do not have conflict of interest.

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Ethics committee approval

Approved by IEC, KAMSRC, Hyderabad dated 29/10/2019

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