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Original Research Article

Comparative study of buprenorphine with bupivacaine and clonidine with bupivacaine in spinal anaesthesia in patients for total abdominal hysterectomy

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Abstract

Background and Objectives: In the present day practice of Anesthesia, bupivacaine is the most commonly used drug for spinal anesthesia. To improve upon the quality of analgesia and prolong the duration of its action, many adjuvants have been tried. Intrathecal clonidine, an α2 adrenergic receptor agonist has potent central anti-nociceptive properties with analgesic effect at spinal level mediated by post synaptically situated adreno receptor in dorsal horn of spinal cord. Buprenorphine, an opioid, has analgesic effect when given in the sub arachnoid space by acting primarily at the μ receptor in the substanstia gelatinosa of the dorsal horn. It suppresses the excitatory neuropeptide release from C fibers. Low doses of clonidine and buprenorphine have shown effectiveness in prolonging the duration of action and improving the quality of analgesia during spinal anesthesia.
This study was designed to evaluate and compare the above mentioned benefits of adding 150μg buprenorphine and 50μg clonidine to bupivacaine for spinal anesthesia.
Methodology: This is a prospective, randomized comparative clinical study involved 60 ASA grade I/II patients aged 35-65 years undergoing elective total abdominal hysterectomy at Dr VRK Womens Medical College from September 2021 to April 2022.
Patients were divided into two groups of 30 each:
Group B (Buprenorphine group) patients received intrathecally 0.5% hyperbaric bupivacaine 3.5 ml + 150μg buprenorphine (Total 4 ml) whereas Group C (Clonidine group) patient received intrathecally 0.5% hyperbaric bupivacaine 3.5 ml + 50μg of clonidine (Total 4 ml).
Parameters:
Onset and duration of sensory block and motor block, highest level of sensory blockade, Duration of postoperative analgesia, sedation, vitals and side effects were assessed.
Results: The onset of sensory and motor blockade was faster in the group B compared to group C. Duration of sensory block, motor block and analgesia was significantly prolonged in group B. There was no significant hemodynamic changes in both the groups.
Conclusion: Buprenorphine and Clonidine potentiates bupivacaine spinal anesthesia by increasing the duration and improving the quality of analgesia without significant

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hemodynamic side effects and with mild sedation.

Keywords: Spinal anesthesia, bupivacaine, buprenorphine, clonidine, postoperative analgesia

Introduction

Spinal anesthesia or sub-arachnoid block (SAB) is a form of regional anesthesia involving injection of a local anesthetic into the subarachnoid space, generally through a fine needle. Spinal anesthesia is a commonly used anesthesia technique, both alone and in combination with either sedation or general anesthesia. It is one of the most popular techniques for both elective and emergency surgical procedures particularly caesarean sections, lower abdominal surgeries like hysterectomy, orthopedic and urological surgeries.

Bupivacaine is the local anesthetic most commonly used. In order to extend intraoperative analgesia into postoperative period a number of adjuvants like opioids are added to the local anesthetic to improve the block and provide post-operative pain relief, examples include morphine, fentanyl, or buprenorphine [5]. Central neuraxial opioids, intra thecal as well as epidural, offer the benefit of analgesia but however the related side effects include sense of dizziness, nausea, vomiting, pruritis, urinary retention and even cases of respiratory depression have been reported [6].

Non-opioids like clonidine may also be added to prolong the duration of analgesia.

Bupivacaine with opioid like buprenorphine and clonidine, which is an α_2 adrenergic agonist have been tried as an adjuvants to prolong the action of local anesthetics [7, 8].

Hence, this study was designed to evaluate and compare the effectiveness of adding 150 µg of buprenorphine with bupivacaine and 50µg clonidine with bupivacaine for spinal anesthesia and to compare its use with that of bupivacaine.

Objectives of the study

Primary objective

The main objective of the study is to compare adjuvants buprenorphine and clonidine intrathecally with bupivacaine and to assess the onset and duration of sensory and motor blockade and postoperative analgesia.

Secondary objectives

1. To evaluate the safety and efficacy of clonidine intrathecally with bupivacaine and to assess the onset and duration of sensory, motor blockade and postoperative analgesia.
2. To study the safety and efficacy of buprenorphine intrathecally with bupivacaine and to assess the onset and duration of sensory, motor blockade and postoperative analgesia.
3. To estimate the incidence of side effects / complications like nausea, vomiting, headache, pruritis, constipation, flushing, sedation, respiratory depression, urinary retention etc.

Methodology

Materials

This clinical study conducted on 60 ASA grade I/II patients aged 35-65 years undergoing elective total abdominal hysterectomy at Dr. VRK Womens Medical College from September 2021 to April 2022. Patients were divided into two groups of 30 each: Group B (Buprenorphine group**)** patients received intrathecally 0.5% hyperbaric bupivacaine 3.5 ml + 150µg buprenorphine (Total 4 ml) whereas Group C (Clonidine group) patient received intrathecally 0.5% hyperbaric bupivacaine 3.5 ml + 50µg clonidine (Total 4 ml).

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Inclusion criteria

1. ASA Grade 1 and 2 patients
2. Age group of 35-65 Years
3. Those patients scheduled to undergo elective total abdominal hysterectomy.

Exclusion criteria

1. Patient refusal.
2. Patients belonging to ASA grade 3 and 4.
3. Patients on opioids and α2 agonist like clonidine.
4. Patient with gross spinal abnormalities, localized skin infection, hemorrhagic diathesis or neurological involvement and diseases.
5. Patient with increased ICP
6. Patient with cardiac, pulmonary, hepatic or renal disorders
7. Patient with epilepsy and acute neurological symptoms
8. Patient with uncontrolled diabetes mellitus and hypertension
9. Patient with allergy to any of the drugs mentioned above
10. Morbidly obese patients

Method of study

Pre-anesthetic assessment was carried out pre-operatively with a detailed history, general physical examination and systemic examination. Airway assessment and spinal column examination were done.
The following laboratory investigations were done in all the selected cases -

Complete Blood Picture

- Urine analysis
- Blood sugar
- Blood urea
- Serum creatinine

a) Coagulation profile
b) Blood grouping and Rh typing
c) ECG-for patients over 40 years of age
d) Chest X- ray

Preoperatively

- Patient's informed consent was taken.
- Nil per oral status was confirmed.
- The procedure and complications of subarachnoid block were explained
- They were pre-medicated with tab diazepam 10 mg and tab ranitidine 150 mg orally 10:00 pm the night before surgery and at 7:00am on the morning of surgery.

The following parameters were observed and recorded

Vital parameters

Heart Rate, Blood Pressure, Respiratory Rate and SpO2 monitoring at 1, 3, 5, 10, 15 minutes

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and thereby every 15 minutes till the end of surgery.
Bradycardia was defined as heart rate less than 50/min (should be treated with inj. Atropine). Hypotension was defined as fall in systolic BP by more than 20% 0f the base line (should be treated with inj. Mephenteramine/Ephedrine).

Modified bromage scale

- **Grade 0:** Full flexion of knees and feet.
- **Grade 1:** Just able to flex knees, full flexion of feet.
- **Grade 2:** Unable to flex knees, but some flexion of feet possible.
- **Grade 3:** Unable to move legs or feet.

Assessment of postoperative analgesia

VAS consists of a 10 cm line anchored at one end by a label such as" No pain'' and at the other end by a label such as the "Worst Pain Imaginable" or "Pain As Bad As Can Be". The patient simply marks the line to indicate the pain intensity and the provider then measures the length of the line to mark a point scale. All the patients were instructed about the VAS and to point out of the intensity of pain on the scale 0- no pain, 10- worst pain.

Table 1: Visual analog score

VAS Score	Intensity of pain
0-1	No pain to slight pain
2-3	Mild pain
4-6	Moderate pain
7-9	Severe pain
10	Worst possible pain

Duration of complete analgesia was defined as the time from the intrathecal injection to VAS >0 - <2 and duration of effective analgesia as the time to VAS >1 - <4.
Analgesics were avoided until demanded by the patient and the time taken for the first pain medication was also noted (i.e., when VAS >5) VAS was also recorded 3, 6, 12 hours postoperatively.

Statistical analysis

The demographic data were analyzed using either Student's t-test or Chi square test. Quantitative data was analyzed by student 't' test and qualitative data was analyzed by Chi-square test. All values were expressed as mean ± standard deviation. $p< 0.05$ was considered statistically significant.

Results

A total of 60 ASA grade I/II patients aged 35-65 years posted for elective total abdominal hysterectomy were randomly selected as per computer generated randomized numbers. Patients were divided into two groups of 30 patients each:

- Group B (Buprenorphine group) patients received intrathecally 0.5% hyperbaric bupivacaine 3.5 ml + 150µg buprenorphine (Total 4 ml)
- Group C (Clonidine group) patient received intrathecally 0.5% hyperbaric bupivacaine 3. 5 ml + 50µg clonidine (Total 4 ml).

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Table 2: Demographic profile

Parameter	Group B Mean± S.D	Group C Mean± S.D	P-Value	Result
Age (Years)	41.13±5.3	41±4.91	0.69	NS
Sex: Female	30	30	---	--
Height (cm)	158.03±3.66	157.47±2.93	0.306	NS
Weight (Kgs)	54.87±3.16	53.83±3.02	0.887	NS

The mean age of the patients in group B was 41.13 ± 5.3 years and in Group c was 41± 4.91 years. The mean height of the patient in group B was 158.03 ±3.66 CMS and in group c was 157.47±2.93 CMS. The mean weight of the patient in group B was 54.87 ± 3.16 KGS and in group C 53.83 ± 3.02 KGS (Table 3, Graph 1). There was no statistically significant difference between the two groups with regards to age, sex, height and weight (p>0.05).

Table 3: Onset of sensory and motor block

	Group B Mean± S.D	Group C Mean± S.D	P-Value	Result
Sensory block (sec)	122.73±5.36	125.97±5.2	<0.043	Sig
Motor block (sec)	166.93±39.99	240.83±38.89	<0.034	Sig

The mean time for onset of sensory block in group B was 122.73 ± 5.36 seconds and Group C was 125.97±5.2 seconds. The onset of sensory block in Group B was faster compared to Group C and is significant with p<0.043. (Table 4, graph 2)
The mean time for onset of motor block in group B was 166.93 ±39.99 seconds and Group C was 240.83±38.89 seconds. There was statistically significant difference between the groups p< 0.034.

Table 4: Time to peak sensory block

	Group B Mean ±S.D	Group C Mean± S.D	P-Value	Result
Time to peak sensory block (in sec)	421.17±33.57	468.33±37.17	<0.032	Sig

The mean time for peak sensory block in group B was 421.17 ± 33.57 seconds and 468.33±37.17 seconds in Group C with p< 0.032, which was statistically significant.

Table 5: Highest level of sensory block

	Group B N, (%)	Group C N, (%)
T4	19(63.33)	13(43.33)
T6	10(33.33)	14(46.67)
T8	1(3.33)	3(10)

The highest level of sensory block in group B- 3% attained T8 level, 33% attained T6 level and 63% attained T4 level where as in Group C 10% attained T8 level, 47% attained T6 level and 43% attained T4 level.
Group B had a greater proportion of patients who achieved higher level of sensory block compared to group C.

Table 6: Duration of analgesia

	Group B Mean± S.D	Group C Mean± S.D	P-Value	Result
Duration of complete Analgesia	378±63.81	264±85.73	<0.043	Sig
Duration of effective Analgesia	536±92.79	379±101.35	<0.036	Sig

Time to first pain medication(in min)	594.83±96.29	431.33±103.62	<0.026	Sig

Mean duration of complete analgesia in Group B was 378±63.81minute and Group C was 264±85.73 minute which was statistically significant (p<0.043), (table 7, graph 5).The mean duration of effective analgesia in Group B was 536±92.79 minute and in Group C was 379±101.35 minute. The P Value is <0.036, the difference between either group is significant (table 7, graph 5). The time for request for rescue analgesic postoperatively in Group B was 594±96.29 minute and in Group C was 431.33±103.62 minute. This was statistically significant (p<0.026).

Table 7: Visual analogue scale (VAS) score

Time	Group B Mean± S.D	Group C Mean± S.D	P-Value	Result
3hrs	0.17±0.38	0.53±0.69	<0.041	Sig
6hrs	1.3±0.6	2.87±1.11	0.008	Sig
12hrs	4.2±0.41	5.47±0.57	<0.043	Sig

VAS at the end of three hours was 0.17±0.38 and 0.53±0.69 (p<0.041), at the end of six hours was 1.3±0.6 and 2.87±1.11 (p<0.008), at the end of twelve hours was 4.2±0.41 and 5.47±0.57 (p<0.043) respectively in Group B and Group C. VAS were statistically significant at 3, 6, and 12 hours in both groups but group B had better pain relief (lower VAS) in the postoperative period than in group C.

Table 8: Heart rate (beats per minute)

Time interval (in min)	Group B Mean± S.D	Group C Mean± S.D	P-Value	Result
Base line 0	85.87±11.46	86.87±10.35	0.341	NS
1	91.03±11.26	94.7±10.0	0.405	NS
3	87.43±9.48	92.97±8.74	0.745	NS
5	82.6±8.9	85.2±9.81	0.618	NS
10	79.33±8.82	79.57±7.92	0.593	NS
15	76.6±9.58	71.07±9.83	0.611	NS
30	72.77±8.91	67.5±7.33	0.576	NS
60	70.13±15.38	67.2±6.12	0.236	NS

The two groups did not differ significantly with respect to heart rate at any interval (p>0.05). The fluctuation in heart rate was less in group B patients when compared with group C though negligible. There was no incidence of bradycardia in any patients of either group.

Table 9: Systolic blood pressure (mmHg)

In min	Group B Mean± S.D	Group C Mean± S.D	P-Value	Result
Base line 0	129.57±11.57	129.3±6.18	0.038	Sig
1	127.43±11.7	128.73±6.48	0.027	Sig
3	121.83±9.94	124.43±7.11	0.132	NS
5	114.87±8.79	116.67±7.86	0.3	NS
10	109.2±9.15	108.57±8	0.384	NS
15	106.33±8.1	101.53±9.47	0.586	NS
30	107.17±6.92	101.53±5.36	0.363	NS
60	106.83±21.5	106.23±5.24	0.148	NS

The SBP in group B decreased from base line of 129.57±11.57 mmHg to 109.2±9.15 mmHg at 10 minutes, and 30 minutes 107.17±6.92mmHg. The SBP in group C also decreased from base line value of 129.3±6.18mmHg to 108.57±8 mmHg at 10 minutes, and at 30 minutes

101.53±5.36 mmHg. Hence the changes in mean SBP at any time interval is statistically and clinically insignificant (p>0.05).

Table 10: Diastolic blood pressure (mmHg)

In min	Group B Mean ±S.D	Group C Mean± S.D	P-Value	Result
Base line 0	82.4±9.06	82.37±7.22	0.242	NS
1	81.53±8.29	80.97±6.8	0.123	NS
3	77.07±9.37	77.2±7.02	0.034	Sig
5	71.53±8.11	71.53±6.96	0.225	NS
10	68.23±8.33	67.33±6.68	0.358	NS
15	66.03±8.1	62.1±5.99	0.224	NS
30	64.47±6.92	59.17±4.8	0.046	Sig
60	61.53±14.79	65.53±4.15	0.041	Sig

The DBP in group B decreased from base line of 82.4±9.06 mmHg to 68.23±8.33 mmHg at 10 minutes and 30 minutes 64.47±6.92mmHg. The DBP in group C also decreased from base line value of 82.37±7.22mmHg to 67.33±6.68 mmHg at 10 minutes, at 20 minutes 59.67±6.3 mmHg and at 30 minutes 59.17±4.8 mmHg.
There was a fall in DBP in group C at 10, 15 and 30 minutes was 15-23mmHg when compared to 14-18mmHg fall in group B, which is clinically significant, (as hypotension was defined as fall in systolic BP by more than 20%).

Table 11: Perioperative complications

Adverse effects	Group B N,%	Group C N,%
Nausea/vomiting	4(13.3)	0(0)
Sedation	0(0)	5(16.67)
Dryness of mouth	0(0)	0(0)
Bradycardia	0(0)	4(13.2)
Hypotension	2(6.6)	6(19.8)
Urinary retention	0(0)	0(0)
Respiratory depression	0(0)	0(0)

In group C, 17% patients experienced mild sedation with no other side effects. Whereas group B, none have sedation. In group B 13% had nausea and vomiting where as in group C none had nausea and vomiting. In group C 20% had hypotension 7% in group B.13% bradycardia in group C whereas none had bradycardia in group B.

Discussion

The present study was carried out to assess and compare the efficacy of buprenorphine and clonidine with bupivacaine in spinal anesthesia in patients for total abdominal hysterectomy. Our study design consisted of 60 patients aged between 35-65 years, ASA physical status I / II who were scheduled for elective total abdominal hysterectomy were randomly assigned into two groups of 30 each after taking informed consent.
Group B (Buprenorphine group) patients will received intrathecally 0.5% hyperbaric bupivacaine 3.5 ml + 150µg buprenorphine (Total 4 ml) whereas Group C (Clonidine group) patient will received intrathecally 0.5% hyperbaric bupivacaine 3.5 ml + 50µg clonidine (Total 4 ml).
The study has demonstrated that the combination of bupivacaine with buprenorphine in spinal anaesthesia significantly decreases the onset time, prolongs the duration of sensory blockade, motor blockade and postoperative analgesia than the bupivacaine with clonidine group.

Demographic profile across the group

In our study, majority of patients were middle aged in both the groups i.e. between 35-65 years. The group B mean age was 41.13±5.3 years and in group C 41±4.91 years. The mean weight in group B was 54.87±3.16 kg and in group C 53.83±3.02 kg. The mean height of two groups were 168.03±3.66 and 167.47±2.93 respectively. These parameters were kept identical in both the groups to avoid variations in intraoperative and postoperative outcome of patients.

Onset of sensory and motor blockade

In our study, the mean time for onset of sensory block in group B was 122.73±5.36 seconds and 125.97±5.2 seconds in group C. The mean time for onset of motor block in group B was166.93±39.99 seconds and in group C was 240.83±38.89 seconds. There was statistically significant difference with regard to onset of sensory and motor block between the groups with faster onset in group B compared to group C. Thomas W *et al*. [9] in their study showed that the onset of sensory analgesia in the Buprenorphine group was about 157 seconds with a range of 30-306 seconds and in the control group the onset time was 373 seconds with a range of 240-666 seconds. The result of this study shows that there is a statistical difference in the onset of analgesia and that addition of buprenorphine hastens the onset of action of bupivacaine. Gurudatta *et al*. [10], in a prospective randomized controlled study conducted on 50 patients concluded that the mean time for onset of sensory blockade was faster in group BC (Clonidine group) 1.62±0.85 min compared to group B (bupivacaine group) 2.24±1.04 min which was highly significant with p value<0.001. The mean time for onset of motor blockade was faster with 1.96 ±1.55 min in BC group compared to 2.44±1.16min in group B which was significant with P value<0.017.

Time for peak sensory level and highest sensory level blockade

The mean time to achieve peak sensory level in group B compared to group C was 421.17±33.57 seconds vs 468.33±37.17 seconds. (p<0.05) by unpaired t-test. This implied that group B achieved highest level of sensory block early. In patients of group B, 63.33% attained T4 level, 33.33% achieved T6 level and 3.33% achieved T8 level. Whereas in group C, 43.33% achieved T4 level followed by 46.67% T6 level and10% T8 level.
LippM *et al*. [11] in 1987 showed in his study that 29 patients undergoing orthopedic surgery, addition of buprenorphine elevated the sensory blockade by 2-3 segments both during spread and regression of anesthesia.
Dobrydnjov *et al*. [12], in his comparative study of different doses of clonidine of 15µ (BC15) and 30µ (BC30) combined with small dose of bupivacaine during spinal anaesthesia concluded that the highest level of sensory analgesia wasT10 in bupivacaine group, T6 in group BC15 and T8 in group BC30, Which was clinically and statistically significant among the clonidine group.

Duration of analgesia

Analgesia

We found that the duration of complete analgesia in group B was 378±63.81 min and 264±85.73 min in group C. Effective analgesia was 536±92.79 minutes in group B and 379±101.35 minutes in group C. The time for first request of rescue analgesic postoperatively was considerably delayed in group B by 150-165 minutes compared to group C (594.83±96.29 vs 431.33±103.62 minutes), thereby reducing the requirement of analgesics in

the early postoperative period. The quality of analgesia was better as the VAS was lower in group B than in group C.
Dobrydnjov *et al*. [12] reported the surgeon rating of the operating conditions as excellent or good in 93%-100% of patients receiving 50µg clonidine with bupivacaine. Quality of intraoperative analgesia as assessed by modified Belzarena scale was better in clonidine group when compared to Bupivacaine group (p<0.005) by chi square test.

Postoperative analgesia

In our study also there was significant reduction in the VAS scores of the patients receiving buprenorphine in comparison with higher VAS scores in patients receiving clonidine. It was 0.17±0.38 and 0.53±0.69 in the first three hours, 1.3±0.6 and 2.87±1.11 in six hours, 4.2±0.41 and 5.47±0.57 in twelve hours post operatively respectively. This implies better quality of analgesia postoperatively, and reduced the need for analgesia with the use of intrathecal buprenorphine.
Rudra A. *et al*. [13] in the year 1991 in his study using the VAS scale from 0-10 for assessment of pain demonstrated that in the study group receiving 100 µg of intrathecal buprenorphine the mean score remained below 5 for up to 10 hours whereas in study group receiving 150µg of intrathecal buprenorphine the mean pain score did not go beyond 5 for up to 16 hours.

Vital parameters

Haemodynamics– Heart rate & blood pressure

In our study, the two groups did not differ significantly with respect to heart rate at any interval. But there were a 13.2% of patients in whom bradycardia was seen in group C. This was statistically insignificant when compared in both groups. The changes in mean systolic and diastolic blood pressure at any time interval was statistically insignificant. Changes in mean systolic and diastolic blood pressure were noticed at 15 minutes and 30 minutes interval. Hypotension was observed in 6.6%, patients in buprenorphine group and in 19.8% patients of the clonidine group. Hypotension was easily corrected with Inj. Mephentermine / Ephedrine.
Thus, the cardiovascular profile of our patients was found to be remarkably stable throughout the intraoperative period in both the groups.

Side effects

In our study, 17% patients of group C experienced mild sedation with no other side effects, whereas in group B none had sedation. In group B 13% patients had nausea and vomiting where as in group C none had nausea and vomiting. In group C 20% patients had hypotension and 7% patients in group B. In group C 13% patients had bradycardia in group C whereas none had bradycardia in group B. There was no dryness of mouth and urinary retention in either group. Since there was mild sedation during peri-operative period, Respiratory rate was monitored to detect respiratory depression and there was no evidence of respiratory depression in either group.
Dobrydnjov *et al*. [12] in their study concluded that small dose of intrathecal clonidine is not usually associated with systemic side effects such as bradycardia, hypotension or sedation.
Many studies are being conducted with bupivacaine for prolonging the postoperative analgesia. The aim of these studies has been to optimize the dose of intrathecal buprenorphine and clonidine for prolonging the duration of postoperative analgesia with least side effects.
The combined effects of mild sedation and analgesia of buprenorphine and clonidine keeps

patients' pain free and comfortable.

Conclusion

On the basis of our clinical comparative study, we conclude that the addition of 150µg buprenorphine to 0.5% hyperbaric bupivacaine 3.5mL (Total 4ml) in spinal anesthesia significantly decreases the onset time, prolongs the duration of both sensory and motor blockade than addition of clonidine 50µg to 0.5% hyperbaric bupivacaine 3.5ml (Total 4ml). Group B Buprenorphine prolongs the duration and improves the quality of postoperative analgesia with better hemodynamic stability and good sedation as compared to Clonidine.
Thus, the study concluded that the addition of buprenorphine and clonidine potentiates bupivacaine spinal anesthesia but between them buprenorphine is more effective than clonidine.

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Conflict of Interest
None

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