How to Cite:
Vijaya, H. N., Priya, K., & Shivashankar, M. (2022). A study to compare the prolongation of postoperative analgesia between intravenous pethidine and intravenous dexmedetomidine on hyperbaric 0.5% bupivacaine spinal anesthesia. *International Journal of Health Sciences*, *6*(S6), 9574–9582. https://doi.org/10.53730/ijhs.v6nS6.12493

A study to compare the prolongation of postoperative analgesia between intravenous pethidine and intravenous dexmedetomidine on hyperbaric 0.5% bupivacaine spinal anesthesia

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Abstract---Background: Spinal anesthesia is a routinely performed technique used for lower abdominal surgeries. It provides good sensory and motor blockade with single local anesthetic drug. The duration of intrathecal anesthesia with a single bolus dose of local anesthesia is limited [2]. Hence various adjuncts like opioids, alpha-2 agonists, ketamine, have been used to prolong the spinal anesthesia, with the possible advantages of delayed onset of postoperative pain and reduced analgesic requirements. Objectives: To determine whether intravenous pethidine or intravenous dexmedetomidine provides intraoperative hemodynamic stability, sedation and good postoperative analgesia. Methodology : The present prospective randomized control study was done by the department of Anesthesia at K C General Hospital Bengaluru from August 2018 to May 2019. A total of 100 subjects who belonged to ASA status 1 and 2 of age 18yrs to 60yrs who were scheduled to undergo lower extremity surgeries were included in the study .After obtaining the written consent, hundred patients were randomly allocated into one of the following two groups consisting of 50 patients each by using sealed envelope method. Group D: 0.5% hyperbaric Bupivacaine 15mg + Inj. Dexmedetomidine50mcg over 10 min, n=50. Group P: 0.5% hyperbaric Bupivacaine 15mg + Inj. Pethidine 50 mg IV, n=50 Results:

The mean time of regression of sensory block to L1 was 200.38±31.95 in group P and 377.90 ± 52.71 in group D with p value of <0.001. The mean time of regression of motor block was 179.24 30.17 in group P and 356.28 ± 56.06 with p value of < 0.001. The mean time for rescue analgesia was 230.56 ± 30.39 in group P and 417.78 ±48.99 in group D with p value < 0.001. There was statistically significant difference between two groups with regards to regression of sensory block to L1, regression of motor block and time to rescue analgesia respectively Conclusion: Intravenous Dexmedetomidine 50µg given after 15 min of 0.5% hyperbaric bupivacaine spinal anaesthesia, provided better postoperative analgesia, longer duration of motor and sensory blockade, optimal sedation and was safe with regard to the haemodynamic variables and adverse effects, when compared to intravenous pethidine 50mg in lower limb orthopedic surgeries.

***Keywords*---**dexmedetomidine, haemodynamic, analgesia, spinal anasthesia.

Introduction

The international society of pain defines “Pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”[1] Surgery produces tissue injury with consequent release of histamine and inflammatory mediators which activates peripheral nociceptors that initiate transmission of nociceptive information to the central nervous system. Adequate pain control will reduce the incidence of postoperative complications such as myocardial ischemia or infarction, tachycardia or dysrhythmias, atelectasis, thromboembolic events and metabolic acidosis [1]. Spinal anesthesia is a routinely performed technique used for lower abdominal surgeries. It provides good sensory and motor blockade with single local anesthetic drug. The duration of intrathecal anesthesia with a single bolus dose of local anesthesia is limited [2].

Hence various adjuncts like opioids, alpha-2 agonists, ketamine, have been used to prolong the spinal anesthesia, with the possible advantages of delayed onset of postoperative pain and reduced analgesic requirements. [3] Pethidine (Meperidine), a synthetic opioid, is widely used to treat pain. It probably acts directly on the thermoregulatory center or via agonistic effect on µ and κ-opioid receptors. Furthermore, it is reported that only a single administration of an opioid may also induce a long-lasting reduction of threshold of pain sensitivity, which leads to delayed hyperalgesia. Therefore, the potential clinical advantages of other drugs in this setting needs to be evaluated .[4 ,5,6.] Dexmedetomidine is a highly selective alpha2-adrenergic agonist. It has better hypnotic, sedative, and analgesic properties. It decreases sympathetic tone and attenuates the stress responses to anesthesia and surgery with mild cardiovascular adverse effects [3].

It also provides anesthetic-sparing effects. An intravenous administration of dexmedetomidine before or after spinal anesthesia prolonged the duration of sensory and motor block. Commonly used single dose of intravenous

dexmedetomidine dose ranges between 0.25-1μ\ kg. [7, 8.] Pain is a subjective parameter, which varies with individual perception of pain Intensity. Therefore, the dose of drugs is not individualized to each patient and a standard dose is considered for this study. With this background we compared the effects of intravenous pethidine and intravenous dexmedetomidine on prolongation of spinal analgesia.

Objectives

To determine whether intravenous pethidine or intravenous dexmedetomidine provides intraoperative hemodynamic stability, sedation and good postoperative analgesia.

Materials and Methods

The present prospective randomized control study was done by the department of Anesthesia at K C General Hospital Bengaluru from August 2018 to May 2019. A total of 100 subjects who belonged to ASA status 1 and 2 of age 18yrs to 60yrs who were scheduled to undergo lower extremity surgeries were included in the study. After obtaining the written consent, hundred patients were randomly allocated into one of the following two groups consisting of 50 patients each by using sealed envelope method. Group D: 0.5% hyperbaric Bupivacaine 15mg + Inj. Dexmedetomidine50mcg over 10 min, n=50. Group P: 0.5% hyperbaric Bupivacaine 15mg + Inj. Pethidine 50 mg IV, n=50.

Inclusion Criteria

- 18yrs to 60yrs
- Both male and female
- ASA I and ASA II
- Scheduled for short orthopedic surgeries.
- Stable patients after spinal anaesthesia

Exclusion Criteria

Included patients with contraindications to spinal anesthesia

- International normalized ratio>1.3
- Platelets <75,000
- Use of anticoagulant drug
- Neurologic disease (multiple sclerosis, symptomatic lumbar herniated disc, spinal stenosis),
- Fluid restriction (cardiac or renal insufficiency)
- Allergy or intolerance to local anesthetics

Preoperative assessment was done for each patient and written informed consent also taken. Patients were premedicated on the night before surgery with the tablet Ranitidine 150mg and tablet Alprazolam 0.5mg. On arrival in the operating room Intravenous line was obtained with 18G cannula and preloaded with ringer

lactate at 15 ml/kg body weight. Patients were connected to multichannel monitor for monitoring pulse rate, SPO_2 ECG, NIBP, MAP. Patient was positioned in sitting position. Under aseptic precautions Subarachnoid block was performed at L_3-L_4 inter-space through a midline approach using 25G or 26 G Quincke's spinal needle. After confirming the clear and free flow of CSF, 15mg of 0.5% (heavy) Bupivacaine was injected in to subarachnoid space. As per the group allocation either Intravenous dexmedetomidine 50 μg or intravenous pethidine 50 mg was given. The following parameters were noted:

- Onset of motor and sensory blockade
- Total duration of sensory and motor blockade.
- Sensory blockade was tested using pin prick method with a 27G blunt tip hypodermic needle every 30 seconds for first 2 minutes, every minute for next 5 minutes, and every 5 minutes for next 15 minutes and every 10 minutes for next 30 minutes
- Maximum level of sensory blockade attained and the time taken for the same was noted.
- Two segments sensory regression time was noted.
- Total duration of analgesia was noted.
- Motor level was assessed according to Modified Bromage score.
- Time of motor regression Bromage 0.
- Time of sensory regression to L1.
- Sedation was assessed by a Modified Ramsay Sedation score.

In the postoperative period patients are monitored for postoperative pain by VAS scale initially every 1 hour for 2 hours, then every 2 hours for next 10 hours which will have been explained to the patient's pre operatively. When the VAS is >5 patient was given rescue analgesia of 75mg of Inj Diclofenac intramuscularly. In addition, the overall 24-hr pain VAS will be evaluated by the overall pain impression of the patient for 24 hours postoperatively. The primary outcomes will be to evaluate the time to first requirement of analgesic supplement, total analgesic consumption in the first 24 hours after the surgery.

Statistical Analysis

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorial data is represented in the form of frequencies and proportions. Chi-square test is the test of significance. Continuous data is represented as mean and standard deviation. Independent t test is the test of significance to identify the mean difference between two groups. $P<0.05$ is considered as stastically significant.

Results

A total of 50 study subjects were analyzed in each Group P and Group D

Table 1
Age and gender distribution of patients studied

		Group P	Group D	Total
Age in years	<20	3(6%)	2(4%)	P=0.293
	20-30	11(22%)	11(22%)	
	31-40	18(36%)	7(14%)	
	41-50	9(18%)	16(32%)	
	51-60	9(18%)	14(28%)	
	Mean ± SD	39.02±12.00	41.74±13.67	
Gender	Female	16(32%)	14(28%)	0.663
	Male	34(68%)	36(72%)	
Height (cm)	Mean ± SD	160.92±5.90	162.28±5.61	0.240
Weight (kg)	Mean ± SD	68.60±11.00	68.12±14.26	0.851

The mean age in Group P was 39.02 ±12.00 and the mean age in Group D was 41.74 ± 13.67 with a p value of 0.293 and was comparable among two groups. The mean height in group P was 160.92 ± 5.90 and 162.28 ±5.61 in group D with p = 0.240. The mean weight in group P was 68.60 ± 11.00 and 68.12 ± 14.26 in group D with p = 0.851. There was no statistically significant difference between two groups with regards to age, height and weight distribution. There were 16 females in group P and 14 females in group D, 34 males in group P and 36 males in group D with a p value of 0.663. There was no statistically significant difference in gender distribution between two groups.

Table 2
Comparision of study variables in two groups of patients studied

Variables	Group P	Group D	Total	P value
Onset of sensory block (min)	2.14±0.83	2.14±0.67	2.14±0.75	1.000
Onset of motor Block (min)	3.20±1.03	3.50±0.84	3.35±0.95	0.114
Time for max sensory Block	16.40±4.46	17.04±5.01	16.72±4.73	0.501
Time for max motor Block	5.30±1.63	5.54±1.45	5.42±1.54	0.438
Regression of Sensory block to L1	200.38±31.95	377.90±52.71	289.14±99.19	<0.001**
Regression of Motor block	179.24±30.17	356.28±56.06	267.76±99.60	<0.001**
Time to rescue analgesia	230.56±30.39	417.78±48.99	324.17±102.45	<0.001**

There was no statistically significant difference between two groups regards to onset of sensory and motor block, and time for maximum sensory and motor block with p values of 1.000, 0.114, 0501 and 0.01 respectively. However, the mean time of regression of sensory block to L1 was 200.38±31.95 in group P and 377.90 ± 52.71 in group D with p value of <0.001. The mean time of regression of motor block was 179.24 30.17 in group P and 356.28 ± 56.06 in group D with p value of < 0.001. The mean time for rescue analgesia was 230.56 ± 30.39 in group P and 417.78 ±48.99 in group D with p value < 0.001. There was statistically significant difference between two groups with regards to regression of sensory block to L1, regression of motor block and time to rescue analgesia respective.

Table 3
RSS Score distribution in two groups of patients studied

RSS Score	Group P	Group D	Total
1	0(0%)	0(0%)	0(0%)
2	45(90%)	0(0%)	45(45%)
3	5(10%)	0(0%)	5(5%)
4	0(0%)	50(100%)	50(50%)
Total	50(100%)	50(100%)	100(100%)

P<0.001**, Significant, Fisher Exact Test

About 90% of patients had sedation score by Ramsay of 2 and 10 % had sedation score of 3 in group P. Whereas 100 % of patients in group D has sedation score 0f 4 with p value of < 0.001. This indicated that group D has statistically significant sedation scores.

Table 4
Side Effects Distribution in two groups of patients studied

Side Effects	Group P (n=50)	Group D (n=50)	Total (n=100)
No	43(86%)	32(64%)	75(75%)
Yes	7(14%)	18(36%)	25(25%)
• Bradycardia	2(4%)	10(20%)	12(12%)
• Hypotension	5(10%)	6(12%)	11(11%)
• Bradycardia & Hypotension	0(0%)	2(4%)	2(2%)

P=0.011*, Significant, Fisher Exact Test

About 14 % of patients in group P and 18% of patients in group D had side effects. In that, 20 % of patients in group D and 4% of patients in group P had statistically significant bradycardia. About 12 % had hypotension in group D and 10% in group P had hypotension, 4% had both bradycardia and hypotension in group D with p value of 0.011. There was statistically significant difference between both groups with regard to side effects.

Discussion

Spinal anaesthesia is a routinely performed technique used for lower abdominal and lower limb surgeries. It provides good sensory and motor blockade with single local anaesthetic drug. However, the duration of intrathecal anaesthesia with a single bolus dose of local anaesthesia is limited [2]. Hence various adjuncts like opioids, alpha-2 agonists, ketamine, have been used to prolong the spinal anesthesia, with the possible advantages of delayed onset of postoperative pain and reduced analgesic requirements.[3] Pain, one of the most common symptoms experienced by surgical patients, has been historically poorly evaluated and undertreated. The aim of postoperative pain management is to inhibit trauma - induced nociceptive impulses and blunt autonomic and somatic reflexes in response to pain. Adequate postoperative pain management allows better

postoperative recovery and early mobilisation of patients. Pethidine (Meperidine), a synthetic opioid, is widely used to treat pain. It probably acts directly on the thermoregulatory center or via agonistic effect on μ and κ-opioid receptors.

Furthermore, it is reported that only a single administration of an opioid may also induce a long-lasting reduction of threshold of pain sensitivity, which leads to delayed hyperalgesia .Therefore, the potential clinical advantages of other drugs in this setting needs to be evaluated.[4 , 5, 6] Dexmedetomidine is a highly selective alpha2-adrenergic agonist. It has better hypnotic, sedative, and analgesic properties. It decreases sympathetic tone and attenuates the stress responses to anesthesia and surgery with mild cardiovascular adverse effects [3]. It also provides anaesthetic-sparing effects. An intravenous administration of dexmedetomidine before or after spinal anaesthesia prolonged the duration of sensory and motor block. Commonly used single dose of intravenous dexmedetomidine dose ranges between 0.25-1μ\ kg. [7, 8] Jyotsna Kubre et al [2] conducted a study to evaluate the effect of intravenous dexmedetomidine on sensory regression, hemodynamic profile, level of sedation and postoperative analgesia.

They conducted a study on 60 patients of ASA grade I and II posted for elective infraumblical surgeries and randomly allocated into two groups. Group D received intrathecal 0.5% bupivacaine heavy, followed by infusion of intravenous dexmedetomidine 0.5mic/kg over 10 min, patients in group C received intrathecal 0.5% bupivacaine heavy 3ml followed by infusion of same volume of normal saline as placebo.. The study concluded that single dose intravenous dexmedetomidine of prolonged the duration of sensory blockade, as well as it produced satisfactory arousable sedation without causing respiratory depression. These findings correlate with our current study. Madhavi Unmesh Santpur et al [8] conducted a prospective randomized, double blind control study to evaluate the effects of intravenous administration of dexmedetomidine on spinal anesthesia with 0.5% hyperbaric bupivacaine in lower abdominal surgeries. 60 patients of American Society of Anaesthesiologists Grades I and II, 20–60 years age, undergoing lower abdominal surgeries under spinal anesthesia were randomized into two groups by computer-generated table.

Group 1: Bupivacaine and dexmedetomidine group; and Group 2: Bupivacaine and saline group. Spinal anesthesia was given with 15 mg of 0.5% bupivacaine. Patients in Group 1 received dexmedetomidine 1 μg/kg over 20 min followed by 0.5 μg/kg/h, intravenously till the end of surgery. Patients in Group 2 received normal saline. The mean duration of analgesia in group 1 was 219.7 ± 2.55 minutes and in group 2 was 150.2 ± 5.7 minutes. The prolongation in duration of analgesia in dexmedetomidine group was statistically significant. The mean durations of motor blockade in Group 1 and Group 2 were 189.6 ± 2.14 and 158.2 ± 5.31 min, respectively. The study conclude that intravenous dexmedetomidine is useful to maintain hemodynamic stability and prolong spinal analgesia. The findings correlate with our present study. Mi Hyeon Lee et al [7] conducted a study to find out the effects of intravenous dexmedetomidine on spinal anaesthesia.

In this prospective, randomized, double-blind, placebo-controlled trial, 60 patients who were scheduled for unilateral lower limb surgery under spinal

anesthesia were randomized into three groups receiving normal saline (control group, n = 20) or 0.5 or 1.0 ug/kg dexmedetomidine (D-0.5 group, n = 20; D-1, n = 20) intravenously prior to spinal anesthesia with 12 mg of bupivacaine. The two-dermatome pinprick sensory regression time, duration of the motor block, Ramsay sedation score (RSS), and side effects of dexmedetomidine were assessed. The two-dermatome pinprick sensory regression time (57.6 ± 23.2 vs 86.5 ± 24.3 vs 92.5 ± 30.7, P = 0.0002) and duration of the motor block (98.8 ± 34.1 vs 132.9 ± 43.4 vs 130.4 ± 50.4, P = 0.0261) were significantly increased in the D-0.5 and D-1 groups than in the control group. The RSS were significantly higher in the D-0.5 and D-1 groups than in the control group.

However, there were no patients with oxygen desaturation in dexmedetomidine groups. The incidences of hypotension and bradycardia showed no differences among the three groups. The study concluded that both 0.5 and 1ug/kg of dexmedetomidine administered as isolated boluses in the absence of maintenance infusions prolonged the duration of spinal anaesthesia. These findings are in congruence with our study. Chilkunda N Dinesh et al [9] studied the effect of intravenous dexmedetomidine on bupivacaine spinal anesthesia. One hundred American Society of Anesthesiologists (ASA) physical status I/II patients undergoing elective surgeries under spinal anesthesia were randomized into two groups of 50 each. Immediately after subarachnoid block with 3 ml of 0.5% hyperbaric bupivacaine, patients in group D received a loading dose of 1 μg/kg of dexmedetomidine intravenously by infusion pump over 10 min followed by a maintenance dose of 0.5 μg/kg/h till the end of surgery, whereas patients in group C received an equivalent quantity of normal saline. The time taken for regression of motor blockade to modifi ed Bromage scale 0 was significantly prolonged in group D (220.7 ± 16.5 min) compared to group C (131 ± 10.5 min) (P < 0.001).

The level of sensory block was higher in group D (T 6.88 ± 1.1) than group C (T 7.66 ± 0.8) (P < 0.001). The duration for two-dermatomal regression of sensory blockade (137.4 ± 10.9 min vs. 102.8 ± 14.8 min) and the duration of sensory block (269.8 ± 20.7 min vs. 169.2 ± 12.1 min) were signifi cantly prolonged in group D compared to group C (P < 0.001). Intraoperative Ramsay sedation scores were higher in group D (4.4 ± 0.7) compared to group C (2 ± 0.1) (P < 0.001). Higher proportion of patients in group D had bradycardia (33% vs. 4%) (P < 0.001), as compared to group C. The 24-h mean analgesic requirement was less and the time to firrst request for postoperative analgesic was prolonged in group D than in group C (P < 0.001) The study concluded that intravenous dexmedetomidine significantly prolonged the duration of sensory and motor block of bupivacaine spinal anesthesia. Dexmedetomidine provides excellent intraoperative sedation and postoperative analgesia. These findings correlate with our present study.

Conclusion

Our study revealed that, that intravenous dexmedetomidine 50 μg compared to intravenous pethidine 50 mg, given 15 min after 0.5% hyperbaric bupivacaine spinal anaesthesia for lower limb orthopedic surgeries, prolonged the sensory and motor block, prolonged the duration of analgesia, provided intraoperative good

sedation, better hemodynamic profile and is safe with regard to the adverse events. Adequate postoperative pain management allows better postoperative recovery and early mobilisation of patients.

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