Original Research Article

Comparative study of bupivacaine-fentanyl versus bupivacaine-clonidine in patients undergoing spinal anaesthesia for lower abdominal surgery

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Abstract

Background: There are many adjuvants used along with bupivacaine for subarachnoid block, but Fentanyl and Clonidine are commonly used as adjuvants to intrathecal bupivacaine for prolonging both sensory and motor blockade as well as postoperative analgesia in patients undergoing lowerabdominal surgery.**AIM**: The present study aimedto compare the effect of intrathecal Clonidine and Fentanyl as adjuvants to Bupivacaine in the subarachnoid block for lower abdominal surgery. **Materials and methods:** 200 patients belonging to the American Society of Anaesthesiologists I or II,scheduled for lower abdominal surgeryunder spinal anaesthesia were randomly allocated to one of the two following groups to receive Bupivacaine 15mg combined with 50μg clonidine (group A; N =100), Bupivacaine 15mg combined with 25μg., fentanyl (groupB; N=100). Parameters like time for an adequate level of analgesia, peak sensory and motor level reached, duration of sensory, motor block, and incidence of complications was noted in this prospective, randomized double-blinded study. **Result:** Both the groups were comparable in demographic data, onset and duration of sensory and motor blockade, and hemodynamic parameters, but the duration of analgesia was significantly longer in the Clonidine group when compared with the Fentanyl group,with a mild increase in sedation score. **Conclusion**: The addition of intrathecal Clonidine in a dose of 50μg provided prolonged postoperative analgesia with minimum side effects compared to Fentanyl and other different doses of Clonidine.

Keywords: Bupivacaine, Clonidine, Fentanyl, spinal anaesthesia, intrathecal.

Introduction

Attenuation of intraoperative anxiety and stress always remains a challenge in the practice of anaesthesia and it also has several detrimental effects on different systems of the human body. Inadequate analgesia leads to elevated plasma catecholamine concentrations, resulting in an adverse effect on all organ systems[1]. Neuraxial analgesia using only local anaesthetic often provides suboptimal analgesia with higher side effects. A localanaesthetic like Bupivacaine is commonly used in spinal anaesthesia, but the duration of spinal anaesthesia may be short and limited, and higher doses of rescue analgesics may be required during the postoperative period. This can be avoided by using higher doses of Bupivacaine which again can produce cardiac toxicity. Many drugs have been used as adjuvants to localanaestheticsto provide optimal analgesia with lower side effects such as opioids, epinephrine, ketamine, midazolam, clonidine, and magnesium[2,3]. Studies have shown that the duration of analgesia due to bupivacaine in spinal anaesthesia can be prolonged by using adjuvants such as midazolam, opioids, neostigmine, dexmedetomidine, and clonidine[4].

The most commonly used opioid in regional anaesthesia is Fentanyl citrate which is a μ_1 and $\mu_2$receptor agonist.Fentanyl is a potent, synthetic opioid analgesic with a rapid onset and short duration of action with minimal cephalic spread[5,6]. Fentanyl exhibits close structural similarities to local anaesthetics and havea demonstrable local anaesthetic effect on sensory C primary afferent nervefibers, which may facilitate analgesic effects[7,8].

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Fentanyl is the least likely of all the intrathecal opioids to cause delayed respiratory depression[8].

However, pruritus, nausea, vomiting, respiratory depression, and urinary retention are other common side effects for which the search for ideal nonopioid adjuvants goes on[9]. It is reported that a single administration of an opioid may also induce a long-lasting increase in threshold pain sensitivity, leading to delayed hyperalgesia[10].

Clonidine (Alpha2-adrenergic agonist) has an analgesic effect at the spinal level mediated by postsynapticallysituatedadrenoreceptors in the dorsal horn of the spinal cord.Clinical studies have suggested that intrathecal clonidine, prolongs sensory and motor block in spinal anaesthesia and provides prolonged postoperative analgesia. Clonidine has beneficial effects such as antiemesis, reduced postspinal shivering, anxiolysis, and sedation, thereby avoiding unwanted opioid-related side effects such as pruritus and respiratory depression[11,12]. It is reported that Clonidine by stimulation of α2 adrenoreceptors beyond the analgesic effects possesses antihyperalgesic properties[13-15]. Clonidine mimics the effects of norepinephrine and its antihyperalgesic mechanisms that partly depend on the fortification of noradrenergic inhibitory controls in the dorsal horn of the spinal cord[16]. The safety of intrathecal clonidine has been extensively evaluated in animals, humans, and obstetrical anesthesia[17,18].

Hence, the present study is being undertaken to evaluate and compare the effects of Clonidine and Fentanyl as intrathecal adjuvants to hyperbaric bupivacaine in patients undergoinglower abdominal surgery. The primary objectives of this study were to compare the effects of Clonidine and Fentanyl on the time of onset and duration of sensory and motor block, hemodynamic status, and side effects. Secondary objectives were to evaluate and compare the effects of Clonidine and Fentanyl on time of request forthe first dose of rescue analgesic.

Materials and methods

This randomized controlled study was carried out, after obtaining approval from the Hospital Ethics Committee and written informed consent from the patients. Eighty patients of the American Society of Anaesthesiologists Classes I or II of either sex and age 20–60 years of age posted for lower abdominal surgery were randomly divided into two groups (n = 100) using a computer-generated program. The assigned random group was enclosed in a sealed envelope to ensure concealment of the allocation sequence. The anaesthesiologist, who was not involved in the study, opened the envelope in the operation theater and prepared the drug accordingly; Bupivacaine 15mg combined with 50μg clonidine (group A; N=100), Bupivacaine 15mg combined with 25μg., Fentanyl (group B; N=100).The observation was done by the anesthesiologist who was blinded to the drug. Patients having severe systemic disorders such as diabetes mellitus, hypertension, heart disease, allergy to Bupivacaine, spine deformity, increased intracranial pressure, neurological disorders, hemorrhagic diathesis, requiring any intraoperative added general anaesthetic aid, deaf, mentally retarded patients, dementia or with psychiatric disorder and infection at the puncture site were excluded from the study.

Preanaesthetic checkup was done, and a visual analogue scale (VAS) was explained to all patients. All the patients were kept nil orally for solid food for at least 8 hours and clear water for 2 hoursbefore surgery. After shifting the patients to the operation theater, an intravenous (IV) cannula was inserted, and preloading was done with Ringer solution (10 ml/kg). Preoperative parameters such as pulse rate, oxygen saturation, and blood pressure were recorded. Under all aseptic precautions, spinal anaesthesia was administered at the level of L3–L4 intervertebral space in a sitting position using a midline approach by a 25-gauge Quincke spinal needle. The anaesthesiologist who administered anaesthesia was blinded to the group allocation. Pulse rate, respiratory rate, electrocardiogram, SpO_2, and blood pressure were monitored. Hypotension was defined as SBP of < 90 mm of Hg or a decrease of more than 30% from baseline mean arterial pressure which was treated with an incremental IV bolus of Mephentermine 6 mg. Bradycardia (heart rate< 60bpm) was treated with IV atropine. Postoperatively, the pain score was recorded by using VAS between 0 and 10 (0 = no pain, 10 = severe pain), for 4 hours postoperatively[28]. Injection Paracetamol infusion was given intravenously at 15mg/ kg body weight dosage over 15 minutes duration as rescue analgesia when VAS was >5(when patient first complained of pain). The time of administering the first dose of rescue analgesia was noted.

Sensory and motor block was monitored at 2, 4, 6, 8, 10, 15 min, and after that at 15 min interval. Sensory block was tested by the pinprick method. Motor block was assessed usinga modified Bromagescale[20].

0 -- No paresis – full movements of lower limbs
1 – Partial paresis – flex knees and ankles
2 – Partial paresis – flex ankles
3 – Partial paresis – flex toes only
4 – Full paresis –no movement

The onset of sensory block was taken from the time ofintrathecal injection till loss of pinprick sensation at T10. Duration of sensory block was taken as time from the maximum height of block till regression to Level 1. The onset of motor block was defined as the time from intrathecal injection to motor blockade Level 2 in the Bromage scale. Duration of motor blockade was taken as time from intrathecalinjection till no motor weakness (Bromage 0). Duration of analgesia was defined as the time from intrathecal injection to administration of the first rescue analgesic. Any side effects such as nausea, vomiting, pain, shivering, pruritus, sedation, hypotension, bradycardia, and respiratory discomfort were noted.

Patients were assessed for degree of sedation, at 30 minutes intervals intraoperatively, at 2 hoursintervals till 6 hours postoperativelyand scoring was done with Campbell sedation score[21] as:

1: Wide awake
2: Awake and comfortable
3: Drowsy and difficult to arouse
4: Not arousable

Results

1. All the statistical analysis was carried out using Microsoft Excel, 2013, and STATA 14 software.
2. The student's t-test was used to test the null hypothesis that the mean of the two groups isthe same at a 5% level of significance. Both groups were comparable concerning their demographic profile, baselinehemodynamic parameters, and duration of surgery. This has also been statistically verified since the mean differences between them among the groups are insignificant at a 5% level of significance.

a) Onset of sensory block

The 'Clonidine' has a mean onset time of sensory block of 5.87 minutes whereas the 'Fentanyl' has an onset time of 5.69 minutes. The mean differenceis of 0.18 minutes which is insignificant at a 5% level of significance with a p-value of 0.41.

b) Onset of motor block

The 'Clonidine' has a mean onset of 8.68 minutes whereas the 'Fentanyl' has an onset of 8.83 minutes. The difference in the mean is of -0.15 minutes which is not significant at a 5% level of significance with a p-value of 0.52. The difference isstatistically insignificant.

c) Time to reach peak sensory level

The 'Clonidine' has a mean time to reach the peak sensory level of 9.34 minutes whereas the 'Fentanyl' has a mean time of 9.24 minutes. The mean difference is of 0.10 minutes which is insignificant at a 5% level of significance with a p-value of 0.49.

d) The duration of sensory block

The 'Clonidine' has a mean duration of 121.78 minutes whereas the 'Fentanyl' has a duration of 96.14 minutes. The mean difference is of 25.64 minutes which is significant at a 5% level of significance with a p-value of 0.00.

e) Duration of motor block

The 'Clonidine' has a mean duration of 209.74 minutes whereas the 'Fentanyl' has a duration of 195.86 minutes. The mean difference is of 13.88 minutes which is significant at a 5% level of significance with a p-value of 0.00.

f) Duration of spinal anaesthesia

The 'Clonidine' has a mean duration of spinal anaesthesia of 246.08 minutes whereas the 'Fentanyl' has a duration of 224.06 minutes. The mean difference is of 21.48 minutes which is significant at a 5% level of significance with a p-value of 0.00.

g) Time when first rescue analgesia was given

The 'Clonidine' dose has a mean time of 400.82 minutes when the first rescue analgesia was given whereas the 'Fentanyl' dose has a duration of 277.8 minutes. The mean difference is of 123.02 minutes which is significant at a 5% level of significance with a p-value of 0.00.

Table 1: Demographic characteristics of the study population

Parameters	Group A: Clonidine	Group B: Fentanyl	p-value
Age (yrs)	46.54 ± 12.26	42.86 ± 13.10	0.15
Height (cms)	63.66 ± 2.39	64.2 ± 2.53	0.27
Weight (kgs)	62.72 ± 5.84	61.46 ± 6.47	0.31
Duration of Surgery (mins.)	93.6 ± 29.47	87.6 ± 26.31	0.28
Male: Female	26:24	28:22	
ASA PS Grade I: II	25:25	28:22	

SBP (mm Hg)	123.46 ± 5.97	124.76 ± 7.04	0.32
DBP (mm Hg)	78.52 ± 8.24	78.32 ± 6.28	0.89
MAP (mm Hg)	93.44 ± 5.83	93.7 ± 4.72	0.81
HR (bpm)	82.06 ± 9.10	85.58 ± 8.56	0.05

The figures are reported as Mean ± S.D .p-value < 0.05 is considered significant

Table 2: Comparison of different block characteristics

	Group A : Clonidine	Group B : Fentanyl	p - value
Onset of sensory block	5.87 ± 1.21	5.69 ± 0.96	0.41
Onset of motor block	8.68 ± 1.27	8.83 ± 1.09	0.52
Time to reach peak sensory level	9.34 ± 0.73	9.24 ± 0.73	0.49
The duration of sensory block	121.78 ± 8.06	96.14 ± 5.20	0.00
Duration of motor block	209.74 ± 10.12	195.86 ± 9.10	0.00
Time when first rescue analgesia was given	378.28 ± 17.84	277.8 ± 17.73	0.00

The figures are reported as Mean ± S.D; p-value < 0.05 is considered significant

Table 3: Comparison of sedation score

	Group A : Clonidine	Group B: Fentanyl	p - value
Sedation Score at intra-operative 30 mins	1.21 ± 0.41	1.08 ± 0.27	0.01
Sedation Score at intra-operative 60 mins	1.88 ± 0.32	1.08 ± 0.27	0.00
Sedation Score at intra-operative 90 mins	1.93 ± 0.45	1.05 ± 0.22	0.00
Sedation Score at intra-operative 120 mins	1.95 ± 0.43	1.03 ± 0.17	0.00
Sedation Score at post-operative 120 mins	1.88 ± 0.03	1 ± 0.00	0.00
Sedation Score at post-operative 240 mins	1.43 ± 0.02	1 ± 0.00	0.00
Sedation Score at post-operative 360 mins	1 ± 0.00	1 ± 0.00	-

The figures are reported as Mean ± S.D; p-value < 0.05 is considered significant

Pre-operative comparison

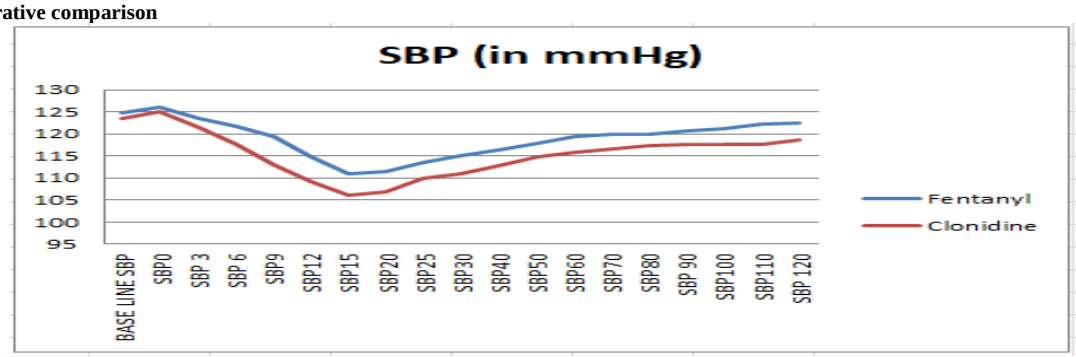

Figure 1: Change in systolic blood pressure

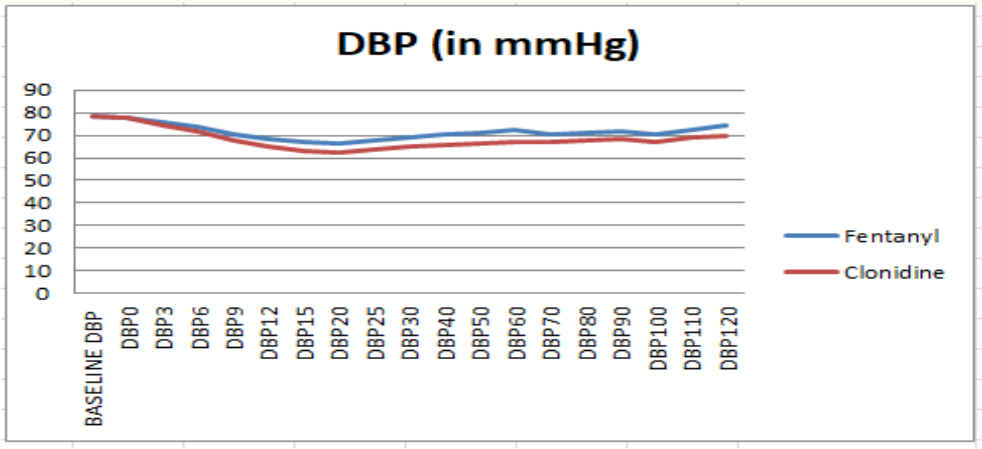

Figure 2: Change in diastolic blood pressure

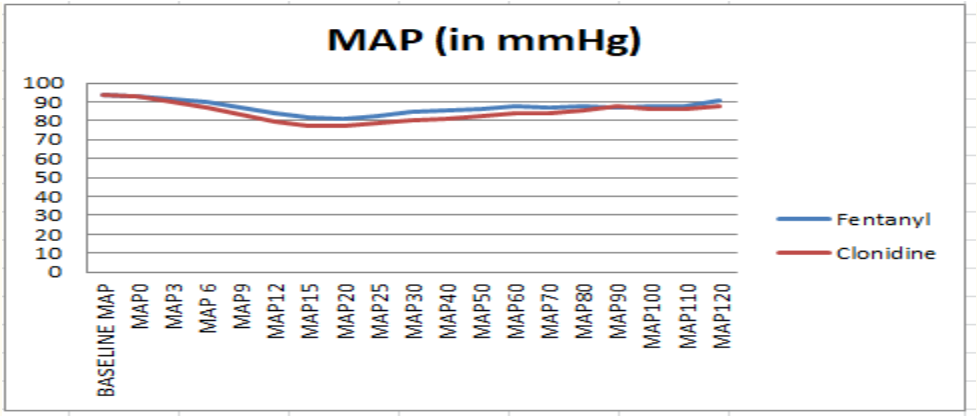

Figure 3 : Change in mean arterial blood pressure

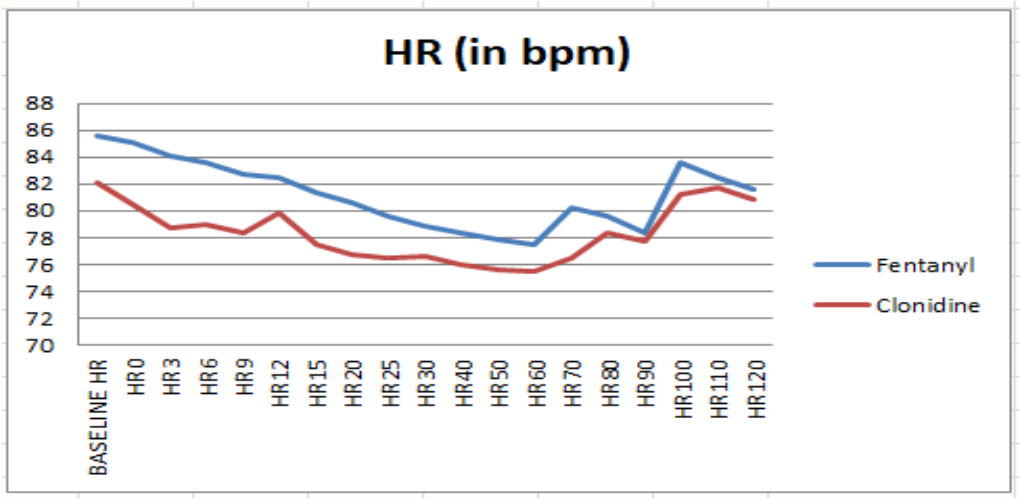

Figure 4: Change in heart rate

Post-operative comparison

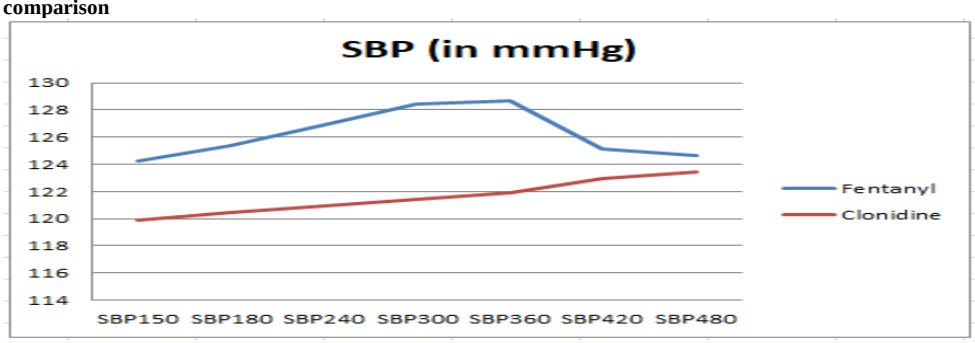

Figure 5: Change in systolic blood pressure

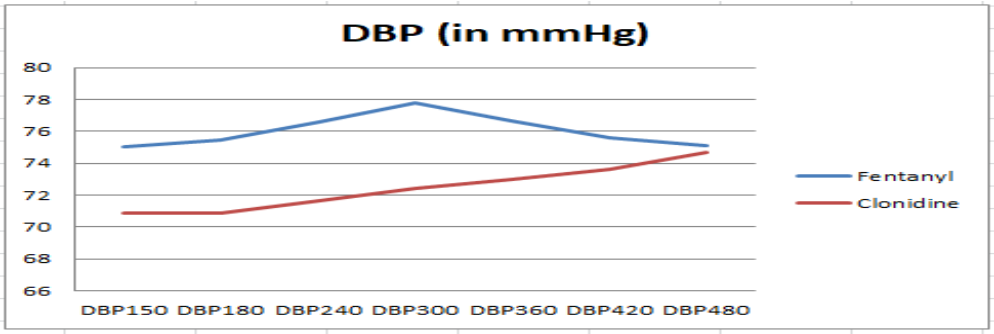

Figure 6: Change in diastolic blood pressure

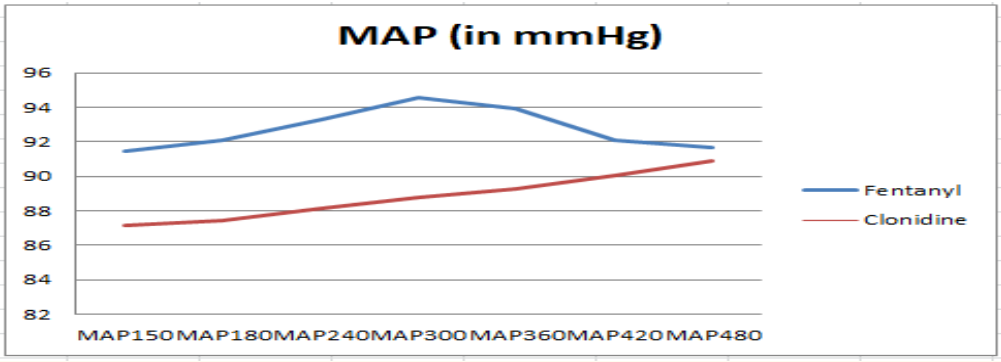

Figure 7: Change in mean arterial blood pressure

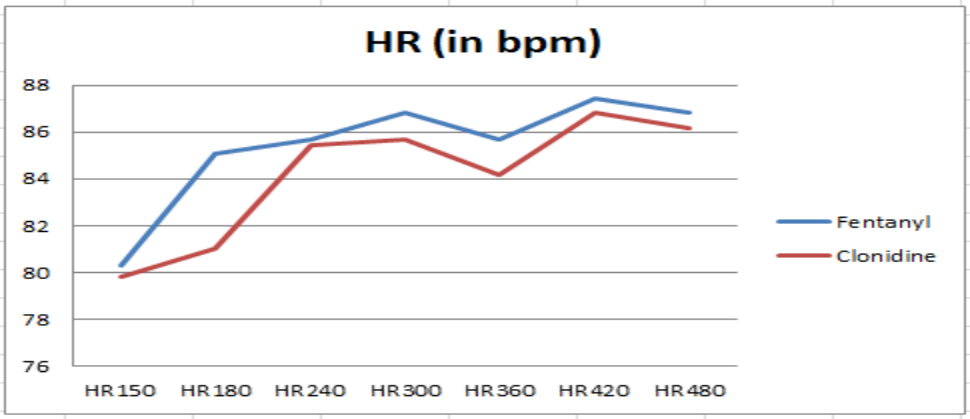

Figure 8: Change in heart rate

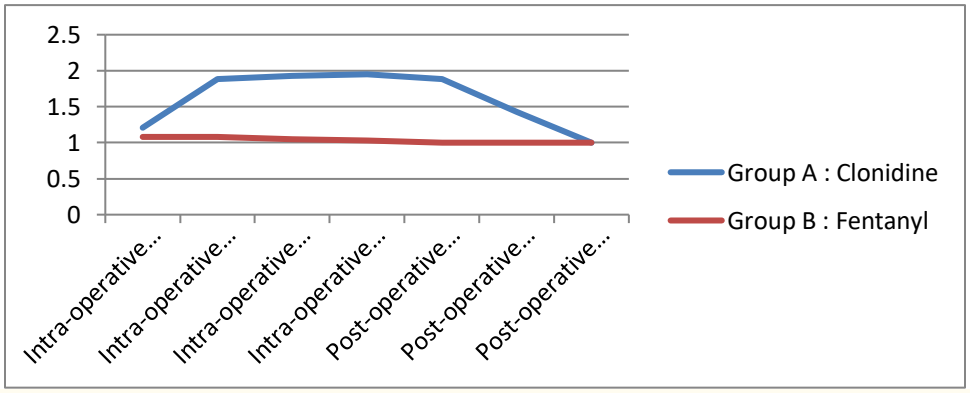

Figure 9: Change in sedation score

Table 4: Comparison of VAS Score

	Group A : Clonidine	Group B : Fentanyl	p - value
VAS at post-operative 120 mins	-	-	-
VAS at post-operative 180 mins	0	1.74 ± 0.08	0.00
VAS at post-operative 240 mins	1.52 ± 0.50	3.48 ± 0.61	0.00
VAS at post-operative 300 mins	2.6 ± 0.64	4.94 ± 0.47	0.00
VAS at post-operative 360 mins	4.14 ± 0.45	4.28 ± 0.57	0.00
VAS at post-operative 420 mins	3.76 ± 0.62	4.46 ± 0.50	0.00
VAS at post-operative 480 mins	3.84 ± 0.50	3.42 ± 0.50	0.00

The figures are reported as Mean ± S.D. p-value < 0.05 is considered significant

Discussion

Maintenance of body physiology as near normal as possible during anesthesia is one of the primary goals of the anesthesiologist. Marked hemodynamic derangements are often seen following subarachnoid block, especially in pregnant, trauma, and elderly patients. Based on the data found in our study,it was concluded that administration of intrathecal Clonidine 50μg with Bupivacaine prolonged intraoperative anesthesia and first analgesic request after lower limb orthopedic surgery compared to Fentanyl and control groups. These findings were consistent with previous studies[22].

Clonidine is an α_2-agonist thatblocks the conduction of Aδ and C fibers, thereby prolonging the action of local anesthetics. When used intrathecally, it activates the postsynaptic α_2-receptors in substantia gelatinosa of the spinal cord and produces analgesia[23]. Khezri et al. in their study concluded that intrathecal Clonidine 75µg with bupivacaine prolonged the time to first analgesia request compared to Fentanyl which was similar to our study[24].

The next finding which should be considered is that intrathecal Clonidine increases the duration of both sensory block and motor block as well as postoperative pain relief. This finding is also consistent with the previous studies[25]. The mechanism of Clonidine-induced potentiation of sensory block in spinal anesthesia is reported to be dependent on presynaptic (decrease in transmitter release) and postsynaptic (increase in hyperpolarization) action[26]. Bajwa et al. in their study concluded that the addition of clonidine (50μg) to intrathecal bupivacaine provided prolonged postoperative analgesia in comparison to Fentanyl (25μg)[20]. Chhabra et al. in their study concluded that Clonidine 60 µg has an advantage over Fentanyl and it prolonged the duration of the subarachnoid block and postoperative analgesia, similar to our study[19]. The findings were similar in our study.Sharan et al. compared intrathecal clonidine 30μg with fentanyl 25μg and concluded that clonidine had an advantage over Fentanyl which is in agreement with our study. Sharan et al.compared intrathecal Clonidine30μgwith Fentanyl 25μgand concluded that clonidine had an advantage over fentanyl which is in agreement with our study[27].

The next finding which should be considered is that intrathecal Clonidine increases the duration of both sensory block and motor block as well as postoperative pain relief. This finding is also consistent with the previous studies[21].

Bhure et al. demonstrated that the addition of clonidine, fentanyl, and midazolam to bupivacaine significantly improves the onset and duration of sensory and motor block with relative hemodynamic stability, prolongs the duration of analgesia, and reduces the consumption of systemic analgesics in comparison to bupivacaine alone. They concluded that clonidine is an excellent additive to bupivacaine in spinal anesthesia and provides a prolonged duration of analgesia without any deleterious effects on the mother and baby[28]. Tilkar et al. conducted a prospective study to differentiate between the effects of fentanyl versus clonidine when added to intrathecal bupivacaine in spinal anesthesia. They concluded that the addition of intrathecal clonidine to hyperbaric bupivacaine was more advantageous than fentanyl with special regard to its analgesic properties[29]. Singh et al. evaluated the effect of the addition of intrathecal clonidine to hyperbaric bupivacaine on postoperative pain after cesarean section and have shown that the duration of postoperative analgesia increases significantly on adding 75 µg clonidine to 2 ml of hyperbaric bupivacaine without any increase in maternal side effects. There was no effect on neonatal outcome[30]. Shidhaye et al. concluded that the intrathecal addition of 25 µg fentanyl to bupivacaine provides good analgesia with less sedation and is a better option when sedation is not desirable. However, intrathecal addition of 60 µg clonidine to bupivacaine provides a longer duration of postoperative analgesia than 25 µg of fentanyl and is a preferred option when sedation is acceptable[31].

The next finding which should be taken into account is that transient hypotension episodes and vasopressor requirement in Clonidine (Group A) were significantly greater than in Fentanyl(Group B), a finding in agreement with the previous studies.Thesympatholytic action of Clonidine and profound analgesia which also reduces sympathetic activity is the onlyexplanation. Lavanda Homme et al. showed a higher incidence of hypotension and sedation with intrathecal Clonidine 150μg than clonidine 75μg[32]. The use of intrathecal Clonidine in a dose of 50μg provided prolonged postoperative analgesia with minimum side effects compared to Fentanyl and other different doses of Clonidine.

Conclusion

Intrathecal Clonidine(50μg) when added to bupivacaine in spinal anesthesia provides a prolonged duration of sensory block, motor block as well as postoperative analgesia. The time to the first analgesic requirement was significantly prolonged with Clonidine (50μg) as compared to Fentanyl (25μg) but with a higher degree of sedation. Fentanyl (25μg) may be recommended as an option when sedation is not desirable.Further studies are needed to evaluate the analgesic efficacy of different doses of Clonidine and Fentanyl with other neuraxial drug combinations.

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