Original Article

A Comparative Study of Dexmedetomidine and Clonidine as an Adjuvant to Intrathecal Bupivacaine in Lower Abdominal Surgeries

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Abstract

Context: Spinal block is the first choice for lower abdominal surgeries. Bupivacaine is the most common local anesthetic used but has a shorter duration of action. Many adjuvants have been used to improve the quality of analgesia till postoperative period. In this study, we used α_2-agonists. **Aims:** The aim of this study is to compare the effects of intrathecal dexmedetomidine and clonidine as adjuvants to hyperbaric bupivacaine with respect to onset and duration of sensory and motor blockade duration of analgesia and incidence of side effects. **Settings and Design:** This was a prospective randomized double-blind study. **Subjects and Methods:** One hundred and fifty patients of physical status American Society of Anesthesiologists Classes I and II were randomly divided into Groups B, C, and D each administered with bupivacaine with normal saline, clonidine, and dexmedetomidine, respectively. **Statistical Analysis Used:** Data were entered into Microsoft excel data sheet. Analysis software used in this study was SPSS 22 version IBM. Categorical data were represented in the form of frequencies and proportions. Chi-square test was the test of significance. Continuous data were represented as mean and standard deviation. Independent *t*-test was used for mean difference between two groups. $P < 0.05$ was statistically significant. **Results:** Mean sensory onset in Group B was 2.8 ± 0.7 min, in Group C was 1.4 ± 0.5 min, and in Group D was 1.2 ± 0.4 min. Mean sensory regression by two segments in Group B was 78.5 ± 9.9 min, in Group C was 136.7 ± 10.7 min, and in Group D was 136.4 ± 11.7 min. **Conclusions:** α_2-agonists with hyperbaric bupivacaine intrathecally have a faster onset of both motor and sensory block. It also prolongs the duration of analgesia.

Keywords: Bupivacaine, dexmedetomidine, spinal anesthesia

Introduction

Lower abdominal surgeries may be performed under regional (spinal or epidural) or general anesthesia. Spinal block is still the first choice because of its rapid onset, superior blockade, lower risk of infection, lesser failure rates, and cost-effectiveness but has the drawbacks of shorter duration of block and less postoperative analgesia.

Local anesthetic, bupivacaine, is the most common agent used for spinal anesthesia but has relatively short duration of action. Many adjuvants to local anesthetics have been used intrathecally to improve the quality of intraoperative analgesia and prolong it in the postoperative period.[1] Opioids are commonly used as intrathecal adjuvants without significant motor or autonomic blockade. However, side effects such as pruritus, nausea, vomiting, urinary retention, and delayed respiratory depression have prompted further research toward nonopioid analgesics with lesser side effects.[2]

α_2-adrenergic agonists are new neuraxial adjuvants being studied to improve the quality of subarachnoid blockade regarding both sensory and motor blockades. There are many studies supporting their efficacy as adjuvants individually.[3] Among that, dexmedetomidine and clonidine are found to be of use. Their primary mechanism of action is believed to be at the level of spinal cord. This includes pre- and postsynaptic sites of action. Presynaptically, α_2-receptor activation inhibits release

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of substance *P* from afferent "c" fibers within dorsal horn. Postsynaptically, it inhibits the development and subsequent transmission of integrated pain signals within second-order neurons of the substantia gelatinosa.

Clonidine, a selective partial α_2-adrenergic agonist, is being evaluated as an adjuvant to intrathecal local anesthetics without any clinically significant side effects.[4,5]

Dexmedetomidine, a new, highly specific, potent, and selective α_2-adrenergic agonist, is under evaluation as it provides stable hemodynamic conditions and good quality of intraoperative and prolonged postoperative analgesia with minimal side effects.[3]

While clonidine has been in use as an adjuvant to bupivacaine in the subarachnoid block, there are only a few studies available upon intrathecal uses of dexmedetomidine. Therefore, we designed this study to compare the synergistic effect of the addition of clonidine and dexmedetomidine to intrathecal hyperbaric bupivacaine with respect to onset and duration of sensory and motor blockade and associated side effects if any.

Objectives of the study

The objective of this study is to assess the synergistic effect and safety of adding dexmedetomidine to bupivacaine compared with clonidine to bupivacaine in subarachnoid block in lower abdominal surgeries, regarding

1. Time of onset and duration of sensory blockade assessed by pinprick and visual analog score (VAS)
2. Time of onset and duration of motor blockade assessed by modified Bromage scale
3. Changes in vital parameters – heart rate (HR), noninvasive blood pressure (NIBP), and oxygen saturation (SPO_2).

Subjects and Methods

After obtaining permission from the Institutional Ethics Committee, this study was conducted at our institute from January 2016 to January 2017. Patients belonging to physical status American Society of Anesthesiologists (ASA) Classes I and II between 18 and 60 years' age group posted for lower abdominal surgeries were included in the study. One hundred and fifty patients were included and were randomly divided into three groups. The exclusion criteria included patient's refusal, allergic history to local anesthetics, dexmedetomidine and clonidine, spine abnormality, local skin infection, bleeding or clotting disorders, uncontrolled hypertension or diabetes mellitus, raised intracranial pressure, asthma, and epilepsy, thyroid, renal, hepatic, and cerebrovascular disease.

Data were entered into Microsoft Excel data sheet and analyzed using SPSS 22 version software (IBM, USA). Categorical data were represented in the form of frequencies and proportions. Chi-square test was the test of significance. Continuous data were represented as mean and standard deviation. Independent *t*-test was the test of significance to identify the mean difference between two groups. ANOVA test was done to find the mean difference between three groups. $P < 0.05$ was considered as statistically significant.

The sample size was estimated using the mean time to reach T10 sensory block from the study by Kanazi *et al*., using this values at 95% confidence limit, and 80% power sample size of 46 was obtained in each group. With 10% nonresponse, sample size of $46 + 4.6 \approx 50$ cases was included in each group.

A prospective randomized double-blind study was planned. Each patient was visited preoperatively, and the procedure was explained. A written informed consent was obtained. Routine investigations required for preoperative evaluation and the proposed surgery was done. All the patients were premedicated with tablet alprazolam 0.5 mg and tablet ranitidine 150 mg overnight and the morning of surgery. Patients were kept nil per oral for a period of at least 8 h.

On arrival in the operating room, intravenous line was secured with 18-G intravenous cannula and patients were preloaded with lactated Ringer's solution at 15 mg/kg. Monitoring was done using multiparameter monitor having SPO_2, electrocardiogram, and NIBP.

Patients were randomized to three groups of fifty each by computer-generated table to receive one of the followings for the subarachnoid block:

1. Group B ($n = 50$) – 3.5 ml volume of injection bupivacaine 0.5% hyperbaric and 0.5 ml normal saline
2. Group C ($n = 50$) – 3.5 ml volume of injection bupivacaine 0.5% hyperbaric and 0.5 ml of injection clonidine (30 μg)
3. Group D ($n = 50$) – 3.5 ml volume of injection bupivacaine 0.5% hyperbaric and 0.5 ml of injection dexmedetomidine (3 μg).

A patient was placed in lateral position. Under aseptic precautions, lumbar puncture was done between L3 and L4 interspinous space with 25-G Quincke spinal needle and the total volume of 4 ml of drugs was injected intrathecally. The patient will be turned to supine posture immediately and supplemental oxygen given.

Parameters noted were as follows:

1. Time of onset of sensory blockade
2. Time of onset of motor blockade
3. Maximum sensory level
4. Time to achieve that
5. Maximum motor blockade
6. Time to achieve that
7. Two-segment sensory regression time
8. Intraoperative sedation
9. Time for rescue analgesia
10. Total duration of sensory blockade
11. Time for complete motor recovery
12. Adverse events
13. Vital parameters.

- Sensory blockade was achieved by testing the loss of pinprick sensation to 23-G hypodermic needle.

- Quality of analgesia was assessed by VAS.
  - 0 – No pain
  - 1–3 – Mild pain
  - 4–6 – Moderate pain
  - 7–10 – Severe pain.
- Motor blockade was assessed using modified Bromage scale.
  - 0 – Full flexion of knee and feet
  - 1 – Inability to raise extended leg, able to move knee and feet
  - 2 – Inability to raise extended leg and move knee, able to move feet
  - 3 – Complete block of lower limb.
  - Sedation was assessed by Ramsay sedation scale.

1. Patient anxious, agitated, or restless
2. Patient-cooperative, oriented, and tranquil alert
3. Patient responds to commands
4. Asleep but with brisk response to light glabellar tap or loud auditory stimulus
5. Asleep, sluggish response to light glabellar tap or loud auditory stimulus
6. Asleep, no response to light glabellar tap or loud auditory stimulus.
   - Vitals included HR, mean arterial pressure (MAP), and SPO2 recorded at 0, 2, 5, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, and 90 min
   - Adverse events included hypotension, bradycardia, and nausea.

Results

Table 1 shows that mean sensory onset in Group B was 2.8 ± 0.7 min, in Group C was 1.4 ± 0.5 min, and in Group D was 1.2 ± 0.4 min. This difference in mean duration of sensory onset between three groups was statistically significant. Sensory onset was faster in Group D and slowest in Group B.

Table 2 shows that mean motor onset in Group B was 4 ± 0.7 min, in Group C was 1.6 ± 0.5 min, and in Group D was 1.1 ± 0.4 min. This difference in mean duration of motor onset between three groups was statistically significant. Motor onset was faster in Group D and slowest in Group B.

Table 3 shows that mean sensory regression by two segments in Group B was 78.5 ± 9.9 min, in Group C was 136.7 ± 10.7 min, and in Group D was 136.4 ± 11.7 min. This difference in mean sensory regression by two segments between three groups was statistically significant. Difference between Group C and Group D was not statistically significant. Highest duration of sensory regression by two segments was seen in Group C and lowest in Group B.

Table 4 shows that mean duration of motor blockade in Group B was 167.9 ± 20.6 min, in Group C was 279.2 ± 24.1 min, and in Group D was 302.6 ± 36.6 min. This difference in mean duration of motor blockade between three groups was statistically significant. Highest duration of motor blockade was seen in Group D and lowest in Group B.

Table 5 shows that the mean time for rescue analgesia in Group B was 167.9 ± 20.6 min, in Group C was 344.4 ± 28.9 min, and in Group D was 366.6 ± 37.5 min. This difference in mean time for rescue analgesia between three groups was statistically significant. Highest time for rescue analgesia was seen in Group D and lowest in Group B.

Table 6 shows that mean VAS score in Group B was 5.9 ± 0.8, in Group C was 4.9 ± 0.8, and in Group D was 4.7 ± 0.7. This difference in mean VAS score between three groups was statistically significant. Highest VAS score was seen in Group B and lowest in Group D.

Table 7 shows that in Group B, 6% had bradycardia, 4% had hypotension, 12% had nausea, and 4% had Shivering. In Group C, 2% had bradycardia and 6% had hypotension, and in Group D, 2% had bradycardia, hypotension, and nausea, respectively. This difference in adverse effects between three groups was statistically significant.

As seen in line Figure 1, there was a significant difference in mean HR between three groups at all the intervals of follow-up. Mean HR was highest in Group C and lowest in Group B. Between Group B and Group C, significant difference in mean HR was seen at all the intervals except at 0 min. Between Group B and D, significant difference in mean HR was seen at all the intervals except at 10, 15, and 20 min. Between Group C and D, significant difference in mean HR was observed at 5, 10, and 15 min; at other intervals, there was no significant difference in mean HR between Group C and Group D.

As seen in line Figure 2, there was a significant difference in mean systolic blood pressure (SBP) between three groups at 20, 30, and from 50 to 90 min intervals of follow-up. Mean SBP was highest in Group B and lowest in Group D. Between Group B and Group C, significant difference in mean SBP was seen from 50 to 90 min intervals. Between Group B and Group C, significant difference in mean SBP was seen at 20

Table 1: Sensory onset duration comparison between three groups

Sensory onset duration (min)	Group			*P* between three groups	B versus C	B versus D	C versus D
	Group B	Group C	Group D				
Mean±SD	2.8±0.7	1.4±0.5	1.2±0.4	<0.001*	<0.001*	<0.001*	0.045*
Minimum	2	1	1				
Maximum	4	2	2				

**P* value statistically significant. SD=Standard deviation

Table 2: Motor onset duration comparison between three groups

Motor onset duration (min)	Group			*P* between three groups	B versus C	B versus D	C versus D
	Group B	Group C	Group D				
Mean±SD	4.0±0.7	1.6±0.5	1.1±0.4	<0.001*	<0.001*	<0.001*	<0.001*
Minimum	3	1	1				
Maximum	5	2	2				

**P* value statistically significant. SD=Standard deviation

Table 3: Sensory regression by two-segment comparison between three groups

Sensory regression by two segments (min)	Group			*P* between three groups	B versus C	B versus D	C versus D
	Group B	Group C	Group D				
Mean±SD	78.5±9.9	136.7±10.7	136.4±11.7	<0.001*	<0.001*	<0.001*	1.000
Minimum	60	120	120				
Maximum	95	155	150				

**P* value statistically significant. SD=Standard deviation

Table 4: Duration of motor blockade comparison between three groups

Duration of motor blockade (min)	Group			*P* between three groups	B versus C	B versus D	C versus D
	Group B	Group C	Group D				
Mean±SD	167.9±20.6	279.2±24.1	302.6±36.6	<0.001*	<0.001*	<0.001*	<0.001*
Minimum	135	240	240				
Maximum	210	330	360				

**P* value statistically significant. SD=Standard deviation

Table 5: Time for rescue analgesia comparison between three groups

Time for rescue analgesia (min)	Group			*P* between three groups	B versus C	B versus D	C versus D
	Group B	Group C	Group D				
Mean±SD	167.9±20.6	344.4±28.9	366.6±37.5	<0.001*	<0.001*	<0.001*	0.001*
Minimum	135	300	300				
Maximum	210	390	420				

**P* value statistically significant. SD=Standard deviation

Table 6: Visual analog score comparison between three groups

VAS score	Group			*P* between three groups	B versus C	B versus D	C versus D
	Group B	Group C	Group D				
Mean±SD	5.9±0.8	4.9±0.8	4.7±0.7	<0.001*	<0.001*	<0.001*	0.907
Minimum	4	4	4				
Maximum	7	7	6				

VAS=Visual analog score, SD=Standard deviation. **P* value statistically significant

Table 7: Adverse effects' comparison between three groups

Adverse effects	Group					
	Group B		Group C		Group D	
	Count	Percentage	Count	Percentage	Count	Percentage
Nil	37	74.0	46	92.0	47	94.0
Bradycardia	3	6.0	1	2.0	1	2.0
Hypotension	2	4.0	3	6.0	1	2.0
Nausea	6	12.0	0	0	1	2.0
Shivering	2	4.0	0	0	0	0
χ^2, df, *P*	16.85, 8, 0.032*					

**P* value statistically significant

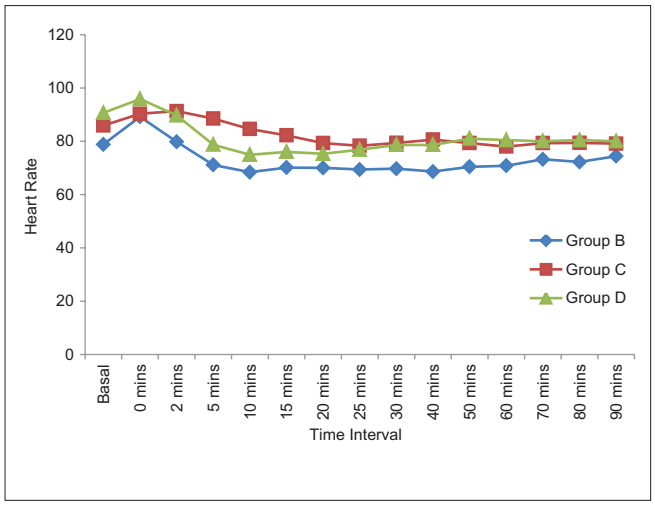

Figure 1: The heart rate

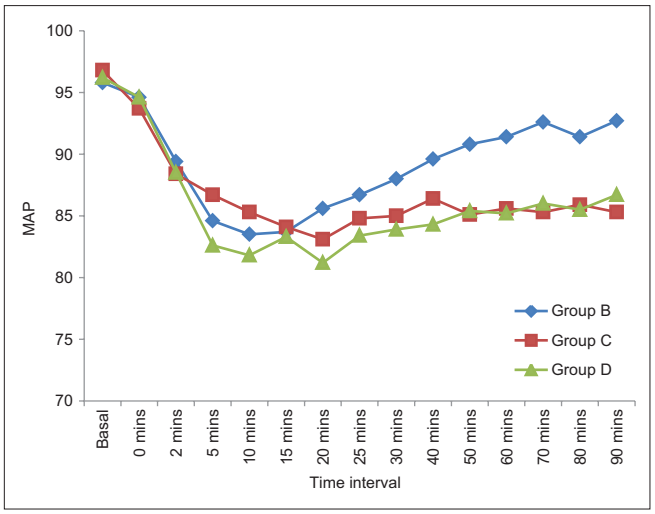

Figure 2: Mean arterial pressure

and from 50 to 90 min intervals. Between Group C and D, significant difference in mean SBP was observed at 50 min; at other intervals, there was no significant difference in mean SBP between Group C and Group D.

In our study, there was no significant variation in the SPO_2 at various intervals. It was between 96% and 99%.

Discussion

Postoperative analgesia must be long-lasting, effective with minimum side effects. For spinal anesthesia, bupivacaine 0.5% hyperbaric is most common local anesthetic used. However, its postoperative analgesic duration is limited. Hence, an additive to these local anesthetics is a reliable method to prolong the duration of anesthesia. A simpler technique has been widely accepted.

Many drugs such as opioids (fentanyl, nalbuphine, pethidine, and buprenorphine), benzodiazepines (midazolam), ketamine, and neostigmine have been used.

The most common are opioids, and they have been the mainstay for postoperative pain.[3] Opioids intrathecally prolong the duration of analgesia but can have late and unpredictable respiratory depression, pruritus, nausea, vomiting, and urinary retention.[6-8] Hence, there was a requirement for better adjuvants which prolongs analgesia without the above side effects of opioids.

Intrathecal α_2-agonists are found to have antinociceptive action for both somatic and visceral pain.[9] Hence, these are used as adjuvants to bupivacaine for spinal anesthesia.[3]

Clonidine being a partial α_2-adrenergic agonist potentiates both sensory and motor block of local anesthetics. Its analgesic effect is mediated through activation of postsynaptic α_2-receptors in the substantia gelatinosa of the spinal cord. It decreases the release of nociceptive substances from substantia gelatinosa by activating the descending inhibitory medullospinal pathways.[1]

Many studies are there regarding clonidine when used intrathecally. It has been found to be a definitive adjuvant to prolong the duration of analgesia.

Dexmedetomidine is also an α_2-receptor agonist more specific than clonidine. It is commonly used as a premedicant in general anesthesia. It reduces opioid and inhalational anesthetic requirements.[10]

There are very few studies available for dexmedetomidine and its intrathecal efficacy. Hence, there is a need to compare its effectiveness as a spinal adjuvant to bupivacaine.

Hence, we undertook this study to evaluate and compare the effect of adding clonidine versus dexmedetomidine with hyperbaric 0.5% bupivacaine in spinal anesthesia for elective lower abdominal surgeries. In this study, we compared dexmedetomidine and clonidine both α_2-agonists. This was intended not just to know the efficacy of α_2-agonists group on a whole but also to identify which among the two were more efficient.

One hundred and fifty patients of ASA physical Status I and II between 18 and 60 years' age group of either sex scheduled for elective lower abdominal surgeries were included in the study. The patients were divided into three groups after randomization which was done using simple sealed envelope technique.

Various authors have used different doses of clonidine for intrathecal blockade starting from 15 to 300 μg and dexmedetomidine for intrathecal blockade starting from 3 to 15 μg along with local anesthetics.

Asano *et al*. also told that binding affinity to spinal α_2-receptors of dexmedetomidine compared with clonidine is approximately 1:10. Hence, dexmedetomidine dose was taken as 30 μg.[11]

We found that the difference in mean duration of sensory onset between the three groups was statistically significant. Sensory onset was faster in Group D and slowest in Group B.

Saxena *et al*. observed in their study that the onset of sensory blockade was faster in clonidine group in a dose dependent.[12]

Our study showed a statistically significant difference in mean duration of sensory blockade between the three groups. Highest duration of sensory blockade was seen in Group B and lowest in Group D.

Shukla *et al*. also saw a significant decrease in the meantime taken for the maximum sensory blockade in the dexmedetomidine group.[8]

Mean sensory regression by two segments showed statistically significant difference. Difference between Group C and Group D was not statistically significant. Highest duration of sensory regression by two segments was seen in Group C and lowest in Group B.

Kanazi *et al*. in 2006 did a study where they compared the effects of low-dose dexmedetomidine or clonidine with bupivacaine in spinal anesthesia.[3] They observed that the time taken for two-segment regression of sensory block was prolonged with dexmedetomidine group then clonidine group than the control group which compares with our study. From the study, the authors concluded that addition of low-dose dexmedetomidine or clonidine intrathecally with bupivacaine produced significantly shorter onset of motor block and a significantly longer sensory and motor block than bupivacaine alone.

Meantime for rescue analgesia in our study had a difference that was statistically significant. Highest time was seen in Group D and lowest in Group B. Our study concurs with the study conducted by Grandhe *et al*., and here, the authors observed that the mean duration of analgesia is 3.8 ± 0.7 h in the control group and 6.3 ± 0.8 h when using clonidine of 1 μg/kg with a mean weight of 60.6 ± 19.4 kg. Mean motor onset was faster in Group D and slowest in Group B and difference was statistically significant.[13]

In studies by Al-Mustafa *et al*. in the dexmedetomidine group and Al-Ghanem *et al*. in the clonidine group, authors saw that there was a significant decrease in the meantime for onset of motor blockade.[14,15]

In the study, there was a significant difference in mean HR between three groups at all the intervals of follow-up. Mean HR was highest in Group C and lowest in Group B. Kaabachi *et al*. observed bradycardia to be 30% in clonidine (2 μg/kg) group.

In the study, there was a significant difference in MAP between three groups at 20, 30, and from 50 to 90 min intervals of follow-up. MAP was highest in Group B and lowest in Group D.[16]

Sethi *et al*. observed that the lowest mean MAP was 70 mmHg in clonidine group (1 μg/kg, mean weight 57.93 ± 4.75 kg).[4]

There was no clinically significant difference that we found between clonidine and dexmedetomidine on spinal block characteristics. Cost of dexmedetomidine is 5 times the cost of clonidine. To reduce the total cost, the use of clonidine as an adjunct along with bupivacaine intrathecally is more cost effective.

Strength and limitations of our study

The strength of our study is that α_2-agonists can replace intrathecal opioids which have respiratory depression as their main side effects limiting their use. Furthermore, the postoperative analgesia was prolonged with a lesser dose of the drugs that we used. The limitation is that there was unexpected change in hemodynamics in few participants.

Conclusions

We concluded from our study that dexmedetomidine and clonidine in 3 and 30 μg, respectively, with bupivacaine hyperbaric when used intrathecally have a faster onset of both motor and sensory block. It also prolongs the duration of analgesia.

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Conflicts of interest

There are no conflicts of interest.

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