International Journal of Medical and Health Research
ISSN: 2454-9142
Received: 05-04-2019; Accepted: 07-05-2019
www.medicalsciencejournal.com
Volume 5; Issue 6; June 2019; Page No. 29-33

The efficacy and safety of epidural dexmedetomidine and clonidine with 0.5% levobupivacaine in patients undergoing elective lower abdominal gynaecological procedure

Dr. Plabon Hazarika[1], Dr. Prabir Pranjal Das[2]
[1] Registrar, Department of Anesthesiology, Tezpur Medical College & Hospital, Tezpur, Assam, India
[2] Assistant Professor, Department of Anesthesiology, Tezpur Medical College & Hospital, Tezpur, Assam, India

Abstract
The efficacy and safety of epidural dexmedetomidine and clonidine with 0.5% levobupivacaine in patients undergoing elective lower abdominal gynaecological procedure.
Methods: Sixty females of ASA physical status I and II aged 18-65 years weighing after taking due consent were blindly randomized into two treatment groups. Patients received epidural 0.5% levobupivacaine 20 ml either with of 50 µg Dexmedetomidine (Group D) or 100µg Clonidine (Group C) and the total volume of study solution was kept 21ml. Onset and duration of sensory and motor blocks, duration of analgesia, sedation and adverse effects were assessed.
Results: Demographic data, surgical characteristics cardio-respiratory parameters, side-effect profile were comparable and statistically not significant in both the groups. However, sedation scores with Dexmedetomidine were better than Clonidine and turned out to be statistically significant. The onset times for sensory and motor blocks were significantly shorter in Group D as compared to Group C. The duration of analgesia and motor block was significantly longer in Group D as compared to Group C.
Conclusion: Dexmedetomidine was better than Clonidine as an epidural adjuvant for providing early onset of sensory analgesia, adequate sedation with no respiratory depression and prolonged postoperative analgesia.

Keywords: dexmedetomidine, epidural anesthesia, clonidine, levobupivacaine

Introduction
Epidural anesthesia is the most commonly used technique for providing peri-operative surgical anesthesia and postoperative analgesia in lower abdominal and limb surgeries [1]. Many techniques and drug regimens, with partial or greater success, have been tried since long time to calm the patients and to eliminate the anxiety component during regional anesthesia [2, 3, 4]. Epidural anesthesia is a safe and inexpensive technique with the advantage of providing surgical anesthesia and prolonged postoperative pain relief. It has become a common practice to use multidrug approach for the treatment of intra and postoperative pain because no drug has yet been identified that specifically inhibits nociception without associated side effects [5]. Many a time for achieving desired effect, invariably large volumes of local anesthetics are used with deleterious consequences or the impulsive use of large doses of sedation or even general anesthesia defeats the novel purpose of regional anesthesia [6]. Alpha (α-2) adrenergic agonists like Dexmedetomidine and Clonidine have both analgesic and sedative properties when used as an adjuvant in regional anesthesia.

Objectives
The aim of this study will be to compare the effect of dexmedetomidine versus clonidine in combination with levobupivacaine in epidural anesthesia on intraoperative and postoperative analgesia, to find out the better and safe adjuvant for regional anesthesia.

Materials and Methods
The present study was a prospective, randomized control trial study, conducted in a tertiary care centre in north east India where sixty adult patients of age group 18–60 years with American Society of Anesthesiologists (ASA) I/ II grade and undergoing lower abdominal gynaecological procedure after taking due written consent were included in the study. Ethical clearance was duly obtained from the Institute Ethical Committee for conducting the study. The study group was randomized into two groups of 30 patients each. Group D received 20 ml of 0.5% levobupivacaine (100 mg) with 1ml (50 µg) dexmedetomidine and group C received 20 ml of 0.5% levobupivacaine (100 mg) with 1ml (100 µg) clonidine using an epidural catheter.
In the operation theater, an intravenous (IV) access was secured and monitoring devices were attached which included electrocardiograph, pulse oximetry (SpO), noninvasive blood pressure (BP) and the baseline parameters were recorded. Patients were administered epidural block with 18 gauge Tuohy Needle - Portex Continuous Epidural (Smith Med. Inc.) and catheter was secured 3-4 cm into the epidural space. The catheter was then anchored in place on the back of the patient using adhesive tape and a test dose of 3 ml of 2% lignocaine hydrochloride solution containing adrenaline 1:200,000 was injected. After
4-6 min of administering the test dose, patients in Group D received 20 ml of 0.5% levobupivacaine and 1µg/kg of

dexmedetomidine. Patients in Group C were administered 20 ml solution of 0.5% levobupivacaine and 2 µg/kg of clonidine. The drug preparation was done by an anesthesia technician who was unaware of the randomization. The sensory level was assessed by response to pin-prick while the motor weakness was evaluated using a modified Bromage scale (0 = No block, 1 = Inability to raise extended leg, 2 = Inability to flex knee and 3 = Inability to flex ankle and foot). This was assessed every 5 min for 30 min and thenevery 30 min. The patient was prepared for surgery after 25-30 min of epidural administration of the drugs and ensuring effective sensory and motor block. Surgery was performed by one of three consultant surgeons of similar clinical experience; they were blinded to the allocation group. The following variables were observed for and recorded: The time taken for onset of sensory block at T10; the highest dermatomal level of sensory analgesia; the complete establishment of motor blockade (Bromage 3), the time to two segment regressions.

Results

On comparison of initial block characteristic among the two groups which is shown in Table 2, Group D exhibited an earlier onset of sensory analgesia at T10 when compared to Group C which was statistically significant(P < 0.0001). Further Group D also showed achievement of maximum analgesic level in a shorter period compared to Group C which was statistically significant (P < 0.0001). Motor block of Bromage 3 was achieved earlier in Group D than Group C which was statistically significant(P < 0.0001).

Table 1: Comparison of initial block characteristics in both the groups

Variables	Groups	Mean	S.D	P
Onset time for sensory block	Group D	6.85	0.72	P < 0.0001
	Group C	12.17	0.79	
Time to max sensory block	Group D	12	0.77	P < 0.0001
	Group C	17	0.78	
Time in min for bromage-3	Group D	16.33		P < 0.0001
	Group C	26.17		

On comparison of the variable sensory block level as depicted in Table 3,Group D achieved Higher sensory block level(T4) which was 36.67% in GroupD and 26.67% in group C.

Table 2: Comparison of Maximum sensory block level in both groups

Variables Sensory block level	Group D	Group C	Total
T4	11(36.67%)	8(26.67%)	19(31.67%)
T5	3(10%)	9(30%)	12(20%)
T6	16(53.3%)	13(43.3%)	29(48.3%)
Total	30(100%)	30(100%)	60(100%)

Patients in both the groups remained calm (mean sedation score for Group D was 2.53 and that of Group C was 1.56) throughout surgery but mean sedation scores were significantly higher in Group D compared to Group C. Sedation scores were statistically significant at 20 min (*P* = 0.00001), 40 min (*P* = 0.00001), 60 min (*P* = 0.0093) in Group D compared to Group C. More patients Group D achieved sedation scores of 3 when compared to Group C.

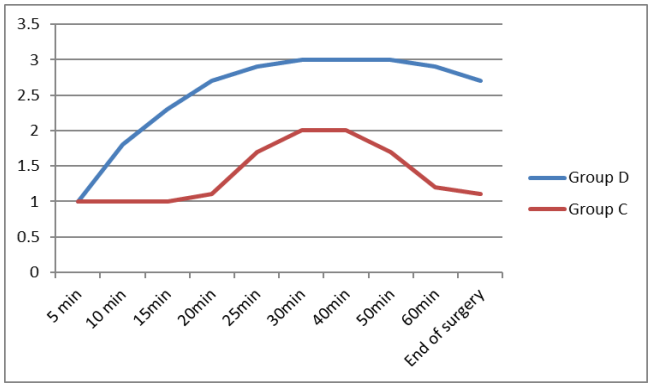

Fig 1: Comparison of intra-operative sedation scores in patients of Group A and Group B

On comparison of postoperative block and analgesic properties like, time for two segment regression, regression of the sensory block to S1, return of motor power to Bromage 1,it showed prolongation in Group D when compared to group C as shown in Table 3.There was statistically significant prolongation in mean time to two segment regression, Mean time to sensory regression to S1 and Mean time to "rescue analgesia" in Group D (P < 0.0001).

Table 3: Comparison of postoperative block characteristics in both the group

Variables	Groups	Mean	S.D	P
Mean time to two segment regression	Group D	134.5	3.25	P < 0.0001
	Group C	118.7	3.51	
Mean time to regression to Bromage 1	Group D	212	73.03	P = 0.0338
	Group C	179	39.77	
Mean time to sensory regression to S1	Group D	315	4.20	P < 0.0001
	Group C	290	7.06	
Mean time to first rescue analgesia	Group D	340	27.67	P < 0.0001
	Group C	289	21.55	

In both groups, the VRS followed a decreasing trend from 0 to 15 min after epidural administration. From 15 to 220 min (4 h) scores were stable and this period totally pain free. The mean VRS score was higher in the clonidine group
at each time interval after 220 min (*P* = 0.0001). In Group D 13% patients needed rescue analgesia at 310 min, 40% at 340 min and 47% at 370 min (*P* = 0.0057). In Group C, 3% patients needed analgesia at 220 min, 67% at 310 min and 27% patients at 340 min. The duration of analgesia also prolonged in the Dexmedetomidine group compared to Clonidine group.

The cardio-respiratory parameters remained stable throughout the procedure. There was no significant difference of heart rate and mean arterial BP in both the groups at the time of administration of drugs.

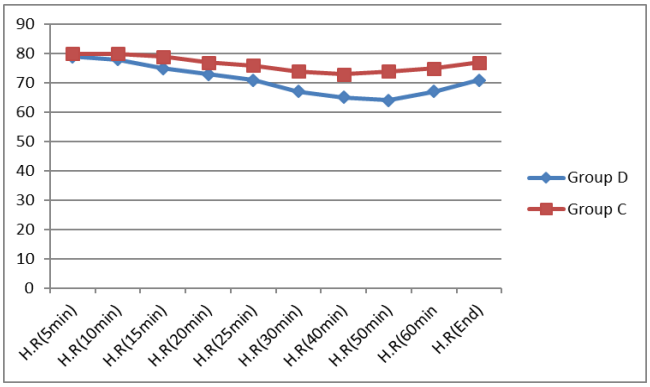

Fig 1: Comparison of Group D and Group C with respect to heart rate beats/min

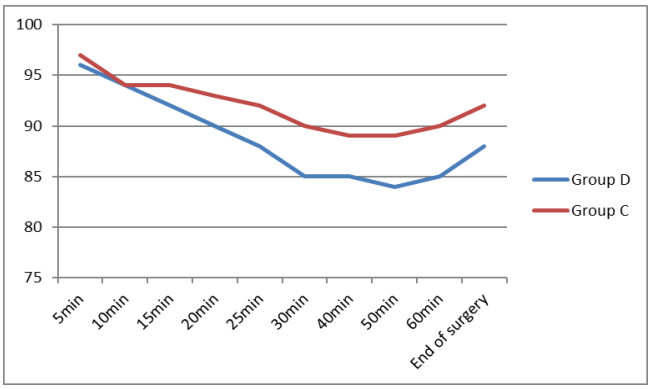

Fig 3: Comaparison of Mean Arterial pressure among Group D and Group C

There was a decreasing trend of heart rate and mean arterial pressure post injection in both groups and this decrease at 20 min post injection was not statistically significant. None of the patient showed significant bradycardia or hypotension at any time.

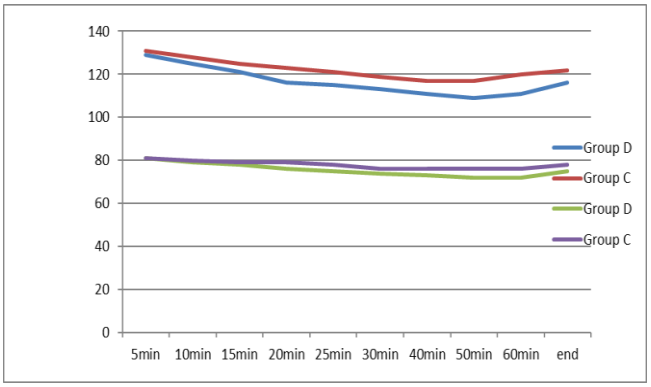

Fig : Comparison of Group D and Group C with respect to systolic and diastolic blood pressure (mm Hg)

Mean respiratory rate in both the groups decreased after giving the drug, the difference between the groups was statistically not significant at different time intervals. Respiratory depression (<10/min) was not observed any group. The comparative incidence of various side-effects in both groups was observed in the intra-operative and postoperative period as shown in Table 4. The most common side-effect in both the groups was dryness of the mouth (21.67%) followed by bradycardia (13.3%) and nausea (11.67%). The incidence of side-effects were comparable in both groups.

Table 4: Comparison of side-effects observed in both the groups during and after the operative period

Side effects	Gp D	%	Gp C	%	Total	%
Dizziness	2	6.67	2	6.67	4	6.67
Headache	1	3.3	1	3.33	2	3.33
Nausea	4	13.33	3	10	7	11.67
Dry mouth	6	20	7	23.33	13	21.67
Vomitting	2	6.67	2	6.67	4	6.67
Respiratory depression	0	0	0	0	0	0
Bradycardia	6	30	2	6.67	8	13.33

Discussions

Levobupivacaine, the pure S (−)enantiomer of bupivacaine, has strongly emerged as a safer alternative for regional anesthesia than its racemic sibling, bupivacaine. Levobupivacaine has been found to be equally efficacious as bupivacaine, but with a superior pharmacokinetic profile.In epidural anesthesia equal doses of levobupivacaine and bupivacaine (15 mL of 0.5%) provide similar onset of sensory block (8-30 min), maximum cephalic spread (T7-T8) and duration of analgesia (4-6 h) [11, 12]. Though, the onset of motor block is delayed with levobupivacaine [26] it is less dense as compared to bupivacaine but with a similar duration [11-14]. Higher concentration of levobupivacaine (i.e., 0.75% vs. 0.5%) provides a longer duration of sensory and motor block without any increase in the incidence of adverse side effects [11]. An increase in both volume and concentration of levobupivacaine is however associated with a higher incidence of hypotension (82%) and delayed block regression [13].

The use of neuraxial opioids is associated with quite a few side effects, so various options including alpha-2 agonists are being extensively evaluated as an alternative with an emphasis on opioid-related side effects such as respiratory depression, nausea, urinary retention, and pruritus [5, 6, 7]. Alpha-2 receptor agonists have been found to have an antinociceptive action for both somatic and visceral pain [3]. Epidural administration of these drugs is associated with sedation, analgesia, anxiolysis, hypnosis and sympatholysis [15, 16]. α-2 agonists may provide an attractive alternative to anesthetic adjunctive agents now in use because of their anesthetic-sparing and hemodynamic-stabilizing effects [17, 18]. α-2 adrenoreceptor agonists produce analgesia by depressing release of C - Fiber transmitters and by hyperpolarization of postsynaptic dorsal horn neurons [19, 20, 21]. The prolongation of the motor block of local anesthetics may be the result of binding of α-2 adrenoreceptor agonists to the motor neurons in the dorsal horn [8]. Dexmedetomidine is eight times more specific and highly selective α-2 adrenoreceptor agonist compared to clonidine [17, 22]. Addition of either 1 µg/kg dexmedetomidine or 2 µg/kg clonidine as adjuvant to epidural bupivacaine leads to early [8, 23, 24]. onset of analgesia, faster achievement of maximum sensory level and motor blockade. It not only prolonged the duration of analgesia but also provided a good sedation level during the surgical procedure without significant hemodynamic effects. Our data support previous studies that used dexmedetomidine and clonidine as additive to regional anesthetics [8, 23, 24].

We found no statistical significance in the peak levels of analgesia provided by both drugs. Our findings were in concordance with Salgado *et al.* [21] Like our study Bajwa *et al.* [8] found that dexmedetomidine provided a significantly

higher dermatomal spread compared to clonidine when added as adjuvant to epidural ropivacaine. Although patients in both groups remained hemodynamically stable perioperatively but fall in pulse rate, and MAP was maximum in Group C patients followed by Group D but it was statistically insignificant. These findings correlate well with a study by Bajwa *et al*. [8].

The hypnotic and supraspinal analgesic effects of dexmedetomidine are mediated by the hyperpolarization of noradrenergic neurons, which suppresses neuronal firing in the locus coeruleus along with inhibition of norepinephrine release and activity in the descending medulla spinalis noradrenergic pathway. The results of our study clearly indicate the effectiveness of epidural dexmedetomidine as adjuvant to levobupivacaine in providing sedation, more patients in Group D had sedation score 3 and were arousable by gentle tactile stimulation as compared to Group C. Similar results were seen in study done by [23].

Avoidance of respiratory depression in the patients who were administered dexmedetomidine and clonidine was one of the most remarkable observation in our study [Table 4] and the evidence is similar to the earlier studies where researchers have found complete absence of clinically detectable respiratory depression in the previous multiple human studies.

Our study showed mean onset of sensory block was 6.85 ± 0.72 min for Group D and 12.17 ± 0.79 min for Group C. The statistical analysis showed a significant difference between both the groups which suggest that the addition of dexmedetomidine leads to faster onset of sensory blockade in comparison to clonidine. The onset of motor block was also hastened by the addition of dexmedetomidine and clonidine, but it was faster with dexmedetomidine than clonidine. Mean time for onset of motor block was 16.33 ± 1.6, and 26.17 ± 2.2 min for Groups D, and C, respectively which is also statistically significant among the groups. In a study by Bajwa *et al*. showed that addition of dexmedetomidine to ropivacaine as an adjuvant resulted in statistically significant earlier onset (8.5 ± 2.4 min) of sensory analgesia at T10 as compared to the addition of clonidine (9.7 ± 3.4 min) and also early complete motor block [8].

Intensity of postoperative pain and quality of relief of pain was assessed using VRS and analgesia was provided when VRS was >4. We found significantly higher verbal analogue scores in dexmedetomidine group. Our results were similar to studies conducted by Saravana Babu *et al*., Schnaider *et al*., El-Hennawy *et al*. who found significant differences in the visual analog scores in clonidine group compared to dexmedetomidine group. Unlike this study, Salgado *et al*. found no difference in the scores of pain, assessed in the postanesthesia care unit.

The incidence of side-effects like vomiting, headache, shivering and dizziness were comparable in both the groups and statistically nonsignificant. The incidence of nausea (four patients in Group D and three patients in Group C) and dry mouth (six patients in Group D and seven patients in Group C) was significantly higher in both the groups but it was statistically nonsignificant on comparison. Similar to this study, Bajwa *et al*. and El-Hennawy *et al*. also found the incidence side-effects to be statistically nonsignificant on comparison.

Bajwa *et al*. [8] and El-Hennawy *et al*. [10] in their study also showed the comparable incidence of side effects in both dexmedetomidine and clonidine group and did not observe the respiratory depression in any patient from either group. However, Salgado *et al*. in their study showed there was the insignificant difference in the incidence of hypotension and bradycardia ($P > 0.05$) between ropivacaine group and ropivacaine with dexmedetomidine group [9].

Most of the previous studies have used a higher dexmedetomidine dose and found superior results to clonidine [8, 23, 24]. This study clearly shows the superiority of lower dose of dexmedetomidine (1μg/kg) when compared to clonidine (2 μg/kg).

Conclusion

This study concluded that the patients receiving the addition of dexmedetomidine to levobupivacaine during epidural anesthesia had a faster onset and longer duration of sensory and motor blockade with acceptable hemodynamic stability, superior sedation levels and prolonged postoperative analgesia in comparison to clonidine and makes dexmedetomidine very effective adjuvant in epidural anesthesia with comparable side effects. The clinical experience with dexmedetomidine was suitable for surgery under regional anesthesia, for the patient, the anesthetist, and the surgeon as compared to clonidine because of its superior sedative and block characteristics during the surgical procedure.

References

1. Höhener D, Blumenthal S, Borgeat A. Sedation and regional anaesthesia in the adult patient. Br J Anaesth. 2008; 100:8-16.
2. Sirvinskas E, Laurinaitis R. Use of magnesium sulfate in anesthesiology. Medicina (Kaunas). 2002; 38:695-8.
3. Kamibayashi T, Maze M. Clinical uses of alpha2 - adrenergic agonists. Anesthesiology. 2000; 93:1345-9.
4. Fukushima K, Nishimi Y, Mori K. The effect of epidural administered dexmeditomidine on central and peripheral nervous system in man. Anesth Analg. 1997; 84:S292.
5. Filos KS, Goudas LC, Patroni O, Polyzou V. Hemodynamic and analgesic profile after intrathecal clonidine in humans. A dose-response study. Anesthesiology. 1994; 81:591-601.
6. Chiari A, Lorber C, Eisenach JC, Wildling E, Krenn C, Zavrsky A, *et al*. Analgesic and hemodynamic effects of intrathecal clonidine as the sole analgesic agent during first stage of labor: a dose-response study. Anesthesiology. 1999; 91:388-96.
7. Arain SR, Ruehlow RM, Uhrich TD, Ebert TJ. The efficacy of dexmedetomidine versus morphine for postoperative analgesia after major inpatient surgery. Anesth Analg. 2004; 98:153-8.
8. Bajwa SJ, Bajwa SK, Kaur J, Singh G, Arora V, Gupta S, *et al*. Dexmedetomidine and clonidine in epidural anaesthesia: A comparative evaluation. Indian J Anaesth. 2011; 55:116-21.
9. Salgado PF, Sabbag AT, Silva PC, Brienze SL, Dalto HP, Módolo NS, *et al*. Synergistic effect between dexmedetomidine and 0.75% ropivacaine in epidural anesthesia. Rev Assoc Med Bras. 2008; 54:110-5.
10. El-Hennawy AM, Abd-Elwahab AM, Abd-Elmaksoud AM, El-Ozairy HS, Boulis SR. Addition of clonidine or dexmedetomidine to bupivacaine prolongs caudal analgesia in children. Br J Anaesth. 2009; 103:268-74.

11. Cox CR, Faccenda KA, Gilhooly C, Bannister J, Scott NB, Morrison LM. Extradural S(-)-bupivacaine: Comparison with racemic RS-bupivacaine. Br J Anaesth. 1998; 80:289-93.
12. Casati A, Santorsola R, Aldegheri G, Ravasi F, Fanelli G, Berti M, *et al*. Intraoperative epidural anesthesia and postoperative analgesia with levobupivacaine for major orthopedic surgery: A double-blind, randomized comparison of racemic bupivacaine and ropivacaine. J Clin Anesth. 2003; 15:126-31.
13. Kopacz DJ, Allen HW, Thompson GE. A comparison of epidural levobupivacaine 0.75% with racemic bupivacaine for lower abdominal surgery. Anesth Analg. 2000; 90:642-8.
14. Peduto VA, Baroncini S, Montanini S, Proietti R, Rosignoli L, Tufano R, *et al*. A prospective, randomized, double-blind comparison of epidural levobupivacaine 0.5% with epidural ropivacaine 0.75% for lower limb procedures. Eur J Anaesthesiol. 2003; 20:979-83.
15. Mauro VA, Brandão ST. Clonidine and dexmedetomidine through epidural route for post-operative analgesia and sedation in a colecistectomy. Rev Bras Anestesiol. 2004; 4:1-10.
16. Gabriel JS, Gordin V. Alpha 2 agonists in regional anesthesia and analgesia. Curr Opin Anaesthesiol. 2001; 14:751-3.
17. Gertler R, Brown HC, Mitchell DH, Silvius EN. Dexmedetomidine: A novel sedative-analgesic agent. Proc (Bayl Univ Med Cent). 2001; 14:13-21.
18. Paris A, Tonner PH. Dexmedetomidine in anaesthesia. Curr Opin Anaesthesiol. 2005; 18:412-8.
19. Kanazi GE, Aouad MT, Jabbour-Khoury SI, Al Jazzar MD, Alameddine MM, Al-Yaman R, *et al*. Effect of low-dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block. Acta Anaesthesiol Scand. 2006; 50:222-7.
20. Al Ghanem SM, Massad IM, Al-Mustafa MM, Al-Zaben KR, Qudaisat IY, Qatawneh AM, *et al*. Effect of adding dexmedetomidine versus fentanyl to intrathecal bupivacaine on spinal block characteristics in gynecological procedures: A double blind study. American journal of applied sciences. 2009; 1:882-887.
21. Lawhead RG, Blaxall HS, Bylund DB. Alpha-2A is the predominant alpha-2 adrenergic receptor subtype in human spinal cord. Anesthesiology. 1992; 77:983-91.
22. Murthy TV, Singh R. Alpha 2 adrenoceptor agonist-dexmedetomidine role in anaesthesia and intensive care: A clinical review. J Anaesth Clin Pharmacol. 2009; 25:267-72.
23. Saravana Babu M, Verma AK, Agarwal A, Tyagi CM, Upadhyay M, Tripathi S. A comparative study in the post-operative spine surgeries: Epidural ropivacaine with dexmedetomidine and ropivacaine with clonidine for post-operative analgesia. Indian J Anaesth. 2013; 57:371-6.
24. Salgado PF, Sabbag AT, Silva PC, Brienze SL, Dalto HP, Módolo NS, *et al*. Synergistic effect between dexmedetomidine and 0.75% ropivacaine in epidural anesthesia. Rev Assoc Med Bras. 2008; 54:110-5.