Perioperative effect of epidural dexmedetomidine with intrathecal bupivacaine on haemodynamic parameters and quality of analgesia

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Abstract

Background: The present study was a randomised controlled trial designed to evaluate the perioperative effect of epidural dexmedetomidine, in conjunction with intrathecal bupivacaine.

Method: In this trial, 60 male patients of American Society of Anesthesiologists' grades I and II, between 20-50 years of age, and posted for elective lower limb orthopaedic surgery, were selected. After written informed consent was obtained and a thorough preanaesthetic check-up carried out, the patients were randomly divided into two groups using the manual envelope randomisation technique. Group I received 2.5 ml of 0.5% bupivacaine intrathecally, plus 10 ml normal saline (NS) epidurally (control). Group II received 2.5 ml of 0.5% bupivacaine intrathecally, plus 2.0 µg/kg dexmedetomidine epidurally, made up to 10 ml with NS (study).

Results: We observed a significant prolongation in the duration of analgesia to 424.1 minutes (Group II) in patients receiving epidural dexmedetomidine, in comparison to 140.0 minutes in patients receiving saline (Group I). There was a significant fall in the pulse rate and mean arterial pressure five minutes following epidural dexmedetomidine in Group II patients, which lasted throughout the study period. The majority of the patients in Group II were sedated, yet arousable, by verbal commands or light tactile stimulus (sedation scale 3-4) 10 ± 5 minutes following administration of dexmedetomidine in the epidural space. This decrease in the level of consciousness lasted for 45 ± 5 minutes.

Conclusion: The addition of 2 µg/kg dexmedetomidine epidurally to 2.5 ml of intrathecal bupivacaine prolongs the duration of analgesia, and decreases the requirement of rescue analgesics in patients undergoing lower-limb orthopaedic surgery, with a significant fall in pulse rate and mean arterial pressure.

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Introduction

The use of central neuraxial blockade for surgery of the lower extremities is widely acknowledged. To potentiate the quality and duration of the subarachnoid block, a variety of drugs, such as opioids, ketamine, midazolam and alpha-2 agonists, have been tried. In addition, a wide range of opioids have been used epidurally, ranging from epidural morphine to epidural fentanyl.

Dexmedetomidine is a highly selective newer prototype of alpha 2 agonists, with $\alpha 2$:$\alpha 1$ selectivity of approximately eight times more in comparison to clonidine.[1] Dexmedetomidine is being widely used in critical care because of its sedative, analgesic, and sympatholytic properties.

Although the use of dexmedetomidine in neuraxial blockade has been extensively studied in animals, until now, to the best of our knowledge, there have been no studies on epidurally administered dexmedetomidine, in conjunction with intrathecally administered bupivacaine, to aid surgery and enhance postoperative analgesia.

This study was designed to evaluate the effect of epidural dexmedetomidine for potentiating perioperative analgesia in combination with single-dose intrathecal bupivacaine in patients undergoing elective lower-limb (hip or thigh) orthopaedic surgery.

Method

After the study had been approved by the board of studies (equivalent to a hospital ethical committee elsewhere), 60 male patients of American Society of Anesthesiologists' (ASA) grades I and II, between 20-50 years of age, and scheduled for elective lower-limb orthopaedic surgery (hip or thigh), for non-malignant conditions, were selected. Written informed consent was obtained from each patient.

Patients who were hypertensive, or those who had coagulation or neurological disorders, spine deformity, or skin infection, were excluded from the study. Each patient underwent a thorough preanaesthetic check-up. All patients were premedicated with injected metoclopramide 10 mg intravenously, and preloaded with 10 ml/kg of lactated Ringer's solution, 30 minutes prior to the combined spinal epidural (CSE) injection. Patients were randomly divided into two groups of 30 each, using the manual envelope randomisation technique. Sixty mixed envelopes for each of the two groups were kept in a box. After premedication, an envelope was withdrawn from the box and opened by a designated researcher, just prior to taking the patient to the operating room. This researcher prepared the saline or dexmedetomidine solution as per the envelope. The person injecting the drug was unaware of the group allocation.

Group I patients received 2.5 ml of 0.5% bupivacaine intrathecally, plus 10 ml normal saline (NS) epidurally (control). Group II patients received 2.5 ml of 0.5% bupivacaine intrathecally, plus 2 µg/kg dexmedetomidine epidurally, made up to 10 ml with NS (study).

Haemodynamic monitoring, in the form of pulse and non-invasive blood pressure (NIBP) recording, was conducted every five minutes after CSE injection for the first 30 minutes, and every 15 minutes thereafter, till discharge of the patient from the recovery room. In the wards, pulse and NIBP were recorded every hour for the first 12 hours, and thereafter, four hourly, up to the first 24 hours after the operation.

Level of sedation was monitored during the first 24 hours, using the sedation scale, as follows:

- 5: Fully awake
- 4: Aroused easily with verbal command
- 3: Aroused with light tactile stimuli
- 2: Aroused with vigorous stimuli
- 1: Responsive to painful stimuli
- 0: Unresponsive to all stimuli.

Level of sensory block was assessed 10 minutes after CSE injection of drugs (NS/dexmedetomidine), using the pin-prick method (anaesthetised to nonanaesthetised area), and observing meticulous asepsis, using povidone iodine for cleansing the area. The pain-free period was calculated from the CSE injection to the first rescue analgesic (injected tramadol 2 mg/kg).

Data analysis

We conducted a pilot study of 10 patients in each group, considering duration of analgesia as the primary outcome, with α error of .05 and β error of 0.1. In each recruited group, adequate sample size was calculated to be > 14. Therefore, we included 30 patients in each group.

Statistical analysis

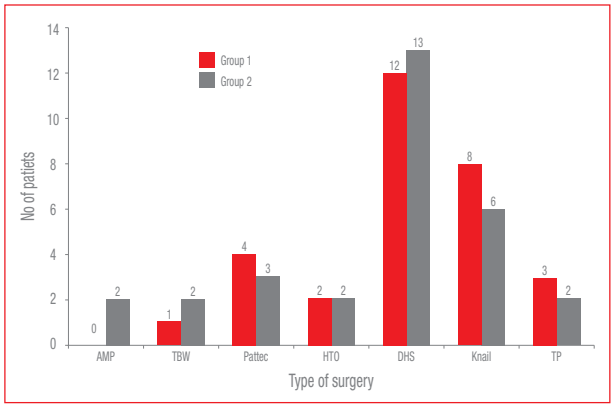
A commercial software package (SPSS version 10, Chicago, IL, USA) was used for statistical analysis. Perioperative data on various parameters in Group I and Group II were expressed in the tables as mean ± standard deviation. The parametric data were analysed statistically using the paired t-test for comparison of within-group data, and the unpaired t-test for comparison of between-group data. Nonparametric data were analysed using the Mann-Whitney U test. P-value < 0.05 was considered significant in this study.

Results

The patients in the two groups were comparable with regard to age, weight, height, duration of surgery, and type of surgery (see Table I and Figure I).

Table I: Demographic data of the groups receiving epidural normal saline/epidural dexmedetomidine, in combination with intrathecal bupivacaine

	Group I	Group II	P-value
Number	30	30	0.000
Age (years)	40	38.87	0.624
Height (cm)	162.4	164.0	0.244
Weight (kg)	64.8	64.5	0.839



AMP = Austin Moore prosthesis, TBW = tension band wiring, Pattec = patellectomy, HTO = high tibial osteotomy, DHS = dynamic hip screw, Knail = K-nailing, TP = tibial plating

Figure 1: Comparison of type of surgery in Group I and Group II

As seen in Table II, a statistically significant fall in the pulse rate was noticed 10 ± 5 minutes following epidural dexmedetomidine injection in Group II patients, and

Table II: Comparison of pulse rate during perioperative procedure in Group I and Group II

Time (minutes)	0	5	10	30	45	60	120	180	360	720	1 440
Group I	87.2	90.1	87.6	84.8	83.2	82.7	82.5	84.4	89.2	88.1	88.2
Group II	90.1	85.1	77.5	74.8	76.4	76.9	78.2	79.7	80.8	82.2	82.5
P-value	0.112	0.015	0.000	0.000	0.000	0.001	0.013	0.003	0.000	0.001	0.003
Significance	NS[a]	S[b]	VS[c]	VS	VS	VS	S	VS	VS	VS	VS

a = not significant, b = significant, c = very significant

Table III: Comparison of blood pressure during perioperative procedure in Group I and Group II

Time (minutes)	0	5	10	30	45	60	120	180	360	720	1 440
Group I	90.5	87.9	88.1	88.4	90.0	89.9	90.4	90.3	90.1	90.6	90.2
Group II	90.8	82.6	82.6	84.4	84.3	83.5	85.0	84.3	84.0	84.0	84.0
P-value	0.852	0.023	0.005	0.14	0.000	0.000	0.000	0.001	0.000	0.000	0.000
Significance	NS[a]	NS	S[b]	S	S	S	S	S	S	S	S

a = not significant, b = significant

Table IV: Comparison of sedation during perioperative procedure in Group I and Group II

Time (minutes)	0	5	10	30	45	60	120	180	360	720	1 440
Group I	5	5	5	5	5	5	5	5	5	5	5
Group II	5	5	4	3.5	4	5	5	5	5	5	5
P-value	1.000	1.000	0.000	0.000	0.000	1.000	1.000	1.000	1.000	1.000	1.000
Significance	NS[a]	NS	S[b]	S	S	NS	NS	NS	NS	NS	NS

a = not significant, b = significant
Sedation scale: 5 = fully awake, 4 = aroused easily with verbal command, 3 = aroused with light tactile stimuli, 2 = aroused with vigorous stimuli, 1 = responsive to painful stimuli, 0 = unresponsive to all stimuli

Table V: Perioperative variables

	Group I	Group II	P-value
Duration of surgery (minutes)	79.3	80.9	0.524
Maximum level of sensory block	6.5	7	0.747
Duration of analgesia (minutes)	140.0	424.1	0.472
Number of rescue analgesic doses	3.2	1.2	0.000
Postoperative nausea	0	0	0.472
Postoperative emesis	0	2 (6.7%)	
Postoperative shivering	8 (26.4%)	1 (3.3%)	0.03

persisted for all time intervals thereafter, until the end of the study period. However, the pulse rate remained in the normal physiological range throughout the study period.

A statistically significant fall in the mean arterial pressure (MAP) was noticed 10 ± 5 minutes following epidural dexmedetomidine injection in Group II patients at all time intervals thereafter, until the end of the study period. However, like the pulse rate, the MAP remained within the normal physiological range at all time intervals following epidural dexmedetomidine injection (see Table III).

The majority of the patients in Group II were sedated (arousable by verbal commands, or light tactile stimulus, sedation scale 3-4) 10 ± 5 minutes following administration of dexmedetomidine in the epidural space. This decrease in the level of consciousness lasted for 45 ± 5 minutes (see Table IV).

There was an insignificant difference between the maximum dermatomal height of the sensory block achieved in the two groups' patients (see Table V). As seen in Table V, there was a significant prolongation of the mean duration of analgesia to 424.1 minutes in patients receiving epidural dexmedetomidine injection, compared to 140 minutes in patients receiving normal saline (p-value < 0.001).

The mean number of rescue analgesic administration required in patients receiving epidural dexmedetomidine was significantly reduced (1.2 ± 0.8 doses) in comparison to patients receiving NS (3.2 ± 0.3 doses, p-value < 0.05). In the study, there was a significant decrease in the incidence of shivering to 1/30 (3.3%) in patients receiving epidural dexmedetomidine in comparison to 8/30 (26.4%) in patients receiving NS (p-value < 0.05); an interesting finding.

Discussion

Central neuraxial blockade has been the technique of choice for lower-limb surgery. One of the major advantages of subarachnoid block is its high success rate. However, when employing the commonly used local anaesthetic, bupivacaine, the effect lasts for only two to three hours. A variety of drugs has been used to potentiate the effect and quality of analgesia of neuraxial blockade. Epidural opioids, midazolam and ketamine, have all been used for this purpose.[2,3,4] The last two decades have witnessed a dramatic increase in the use of alpha-2 agonists. Epidural clonidine, the most prevalent alpha-2 agonist, was first used by Bonnet et al in 1989 for postoperative analgesia.[5]

In 2003, Jellish et al studied the effect of epidural clonidine to potentiate spinal anaesthesia in patients undergoing lumbar laminectomy.[6] Dexmedetomidine, a newer prototype of alpha-2 agonist, has similar effects to clonidine. The use of dexmedetomidine in regional anaesthesia has been extensively studied in animals by various researchers, such as Sabbe et al in 1994, and Li and Eisench in 2001. However, information on its role in humans is lacking in the literature.[7,8]

The present study was undertaken in 60 ASA groups I and II male patients, undergoing elective orthopaedic surgery of the lower limbs. Epidural analgesia was considered in conjunction with spinal analgesia, as it allows superior postoperative analgesia, leading to early patient mobilisation. Surgeries lasting for a maximum of three hours were selected in an attempt to keep the intensity of postoperative pain nearly constant in both the groups, and thereby avoid bias due to type of surgery. Selection of male patients excluded gender bias from the study.

Both the groups were comparable with regard to age, weight, height, and duration of surgery, so the cause-and-effect relationship with analgesia was not considered. The maximum dermatomal height of sensory block was comparable in both groups. Because 10 ml of NS, with, or without, dexmedetomidine, was administered in both the groups, the compressive effect of increasing the height of the block remained constant, and was not considered for further analysis.

In our study, we noticed a significant fall in the MAP and the pulse rate 5-10 minutes following administration of dexmedetomidine, in comparison to epidural saline, at all time intervals. This result concurs with the results of other studies on the use of epidural dexmedetomidine.[9,10] The fall in pulse rate and MAP is due to the postsynaptic activation of the alpha-2 adrenoceptors in the central nervous system, resulting in decreased sympathetic activity, both centrally and peripherally. [9] This hypotension and bradycardia can be reversed by epinephrine and atropine, respectively.[11]

Fukushima et al were the first to report the use of epidural dexmedetomidine in patients undergoing surgery under general anaesthesia.[10] They found that an epidural injection of 2 µg/kg dexmedetomidine resulted in the depression of the total electroencephalogram pattern. At 10 minutes, decreased blood pressure (80/65 mmHg), and heart rate (50-70) beats/minute), were observed (p-value < 0.05). Dexmedetomidine reduced the requirement of analgesic drugs by 70% for 24 hours, and duration of analgesia lasted for four to six hours postoperatively.

In the present study, the majority of patients were sedated after five to 10 minutes of receiving an epidural dexmedetomidine injection. Oriol-Lopez et al studied the sedative effects of epidural dexmedetomidine in a dose of 1 µg/kg with lidocaine and epinephrine.[12] These sedative effects are mediated by the activation of presynaptic alpha-2 adrenoreceptors in the locus coeruleus, which inhibit the release of norepinephrine.[13] Inhibition of adenylate cyclase may also be implicated in the hypnotic response of dexmedetomidine.[14]

In the present trial, the mean duration of analgesia in patients receiving epidural dexmedetomidine was 424.1 minutes, in comparison to 140 minutes in the control group. Since the use of dexmedetomidine in the study group was the only difference in the methodology between the two groups in the study, it could be implied that this prolongation of postoperative analgesia could be attributed to dexmedetomidine in the epidural space. In 1996, Fukushima et al demonstrated four to six hours of postoperative analgesia of epidural dexmedetomidine, following culmination of surgery under general anaesthesia. This difference in the duration of the postoperative analgesia could be attributed to the difference in anaesthetic technique in the two trials.

Salgado et al studied the synergistic effect of dexmedetomidine with 0.75% ropivacaine, and observed that epidural dexmedetomidine 1 mg/kg enhances motor and sensory blockade, and prolongs analgesia duration.[15] The analgesic effect of dexmedetomidine is produced by the stimulation of the drug at spinal cord level.[16] At the dorsal root neuron, alpha-2 agonists inhibit the release of substance P in the nociceptive pathway.[17] By inhibiting the release of norepinephrine, the alpha-2 receptors located at the nerve endings play a possible role in analgesia. Even though there is evidence of both the supraspinal and peripheral sites of action of dexmedetomidine, the spinal mechanism is considered to be mainly responsible for the analgesic effects.[18]

An interesting finding that was noted in the present study was a decrease in the incidence of shivering in the patients receiving epidural dexmedetomidine: 1/30 (3.3%), in comparison to 8/30 (26.4%) in the control group. There is a paucity of literature showing the effect of epidural dexmedetomidine in shivering. Douflas et al have reported the successful use of intravenous dexmedetomidine in reducing shivering during the perioperative period.[19]

In the present trial, one patient had a motor blockade lasting for more than 12 hours. The possibility of any complication such as epidural haematoma and neurological injury was ruled out by magnetic resonance imaging and neurological consultation. The patient was kept under observation until his recovery was complete, and discharged without any neurological sequelae. The inherent local anaesthetic property of dexmedetomidine could be one of the contributing causes. This is the first clinical study demonstrating that the addition of 2 µg/kg, made to 10 ml with normal saline, helps in potentiating the effect of intrathecal bupivacaine with minimal haemodynamic fluctuations.

A major limitation of our study is that it was a placebo control study, without a group assigned to receive the same dose of dexmedetomidine intramuscularly. As such, the authors cannot rule out that all, or part of, the effects seen in the treatment group, may have been due to systemic absorption. A second limitation of this study is that it did not include female patients, making the results less generalisable in this population group. Not much contemporary data are available in the literature for comparative analysis. More randomised trials are required to validate the use of epidural dexmedetomidine.

Conclusion

Epidural dexmedetomidine, in a dose of 2 mcg/kg, given along with intrathecal bupivacaine, causes significant prolongation in the duration of analgesia. The number of administered rescue analgesic doses are significantly less in patients receiving epidural dexmedetomidine. A statistically significant fall in pulse rate and MAP was noticed five minutes following epidural injection of dexmedetomidine. This lasted throughout the study period. There was a decrease in the level of consciousness 10 ± 5 minutes following epidural dexmedetomidine, which lasted for 45 ± 5 minutes.

References

1. Kamibayashi T, Maze M. Clinical uses of alpha-2 adrenergic agonists. Anaesthesiology. 2000;93(5):1345-1349.
2. De LeonCasola OA, Lema MJ. Postoperative epidural opioids analgesia: what are the choices? Anesth Analg. 1996;83(4):867-875.
3. Nishiyama T, Hirasaki A, Odaka Y, et al. Epidural midazolam with saline: optimal dose for postoperative pain. Masui. 1992;41(1):49-54.
4. Naguib M, Adu-Gyamfi Y, Absood GH, et al. Epidural ketamine for postoperative analgesia. Can J Anaesth. 1986;33(1):16-21.
5. Bonnet F, Boico O, Rostaing S. Postoperative analgesia with extradural clonidine. Br J Anaesth. 1989;63(4):465-469.
6. Jellish W, Aboodley A, Fluder E, Shea J. The effect of spinal bupivacaine in combination with either epidural clonidine and/or 0.5% bupivacaine administered at the incision site on postoperative outcome in patients undergoing lumbar laminectomy. Anesth Analg. 2003;96(3):874-880.
7. Sabbe M, Penning J, Ozaki G, Yaksh T. Spinal and systemic action of alpha 2 receptor agonist dexmedetomidine in dogs. Antinociception and carbon dioxide response. Anesthesiology. 1994;80(5):1057-1072.
8. Li X, Eisenach J. Alpha 2 adrenoreceptor stimulation reduces capsaicin-induced glutamate release from spinal cord synaptosomes. J Pharmacol Exp Ther. 2001;299(3):939-944.
9. Fukushima K, Nishini Y, Mori K, Takeda J. The effect of epidurally administered dexmedetomidine on central and peripheral nervous system in man. Anesth Analg. 1997;84:S292.
10. Hogue CW, Jalke P, Stein PK, et al. Autonomic nervous system responses during sedative infusions of dexmedetomidine. Anesthesiology. 2002;97(3):592-598.
11. Fukushima K, Nishini Y, Mori K, Takeda J. Effect of epidurally administered dexmedetomidine on sympathetic activity and postoperative pain in man. Anesth Analg. 1996;82:S121.
12. Oriol-Lopez SA, Maldondo-Sanchez KA, Hennandez-Bernal CE, et al. Epidural dexmedetomidine in regional anaesthesia to reduce anxiety. Anesthesiology. 2008;31:271-277.
13. Maze M, Regan JW. Role of signal transduction in anaesthetic action: alpha 2 adrenergic agonists. Ann NY Acad Sci. 1991;625:409-422.
14. Memis D, Turan A, Karamanlioglu B, et al. Adding dexmedetomidine to lidocaine for intravenous regional anaesthesia. Anesth Analg. 2004;98(3):835-840.
15. Salgado PF, Sabbage AT, Silva P. Synergistic effect between dexmedetomidine and 0.75% ropivacaine in epidural anaesthesia. Rev Assoc Med Bras. 2008;54(2):110-115.
16. Kalso EA, Poyhia R, Rosenberg PH. Spinal antinociceptors by dexmedetomidine, a highly selective alpha 2 agonists. Pharmacol Toxicol. 1991;68(2):140-143.
17. Kuraishi Y, Hirota N, Sato Y. Noradrenergic inhibition of the release of substance P from the primary afferents in the rabbit spinal dorsal horn. Brain Res. 1985;359(1-2):177-182.
18. Jaokala ML, Salonem M, Lentinem M, Scheinin H. The analgesic action of dexmedetomidine : a novel alpha 2 adrenoceptor agonist in healthy volunteers. Pain. 1991;46(3):281-285.
19. Douflas AG, Lin CM, Suleman MI, et al. Dexmedetomidine and meperidine additively reduce the shivering threshold in humans. Stroke. 2003;34(5):1218.