International Journal of Enhanced Research in Medicines & Dental Care (IJERMDC),
ISSN: 2349-1590, Vol. 5 Issue 4, April-2018, Impact Factor: 1.338

Comparative study of dexmedetomidine and fentanyl with low dose ropivacaine for epidural analgesia in lower limb surgery

Corresponding Author: Dr. R.K. Solanki[3] email id: dr.rajendrasolanki51@gmail.com

Dr Neelam Meena[1], Dr Gayatri Tanwar[2], Dr. R.K. Solanki[3], Dr Shradha Mundra[4]

[1]Associate Professor, Deptt of Anaesthesiology and Critical Care, Dr SN Medical College, Jodhpur
[2,4]Senior Resident, Deptt of Anaesthesiology and Critical Care, Dr SN Medical College, Jodhpur
[3]Professor, Deptt of Anaesthesiology and Critical Care, Dr SN Medical College, Jodhpur

INTRODUCTION

Adequate and timely acute perioperative pain management after major orthopedic surgery is an essential part of perioperative anesthesia to facilitate patient comfort and early mobilization[1]. Epidural anesthesia is commonly used technique for surgical anesthesia as well as postoperative analgesia. It provides good postoperative pain relief lead to early mobilization and rehabilitation with minimum discomfort[2-4]. The newer amide local anesthetic agent ropivacaine shows better alternative for bupivacaine as it has physiochemical properties similar to bupivacaine but has less systemic toxicity and greater margin of safety. It is s-enantiomer form so has less cardiac and neurotoxicity in comparison to bupivacaine. It also has early recovery of motor function lead to early mobilization and shorter stay in hospital which also has benefit as decrease chances of thromboembolism[5-7].

Adjuvants like Ketamine, clonidine, opioids, and midazolam are commonly used to improve the duration and quality of analgesia of neuraxial blockade and decrease risk of systemic toxicity by decreasing the dose of LA[8,9].α-2 agonists are newer adjuvant with high efficacy and less side effects in comparison to traditionally used adjuvants. Dexmedetomidine is newer and highly selective α2 agonist has evolved as an effective alternative adjuvant for various procedure in perioperative care[8-11].

Taking this in mind, wedesignedaprospective, randomized doubleblindedcontrol studyto evaluate andcomparethe efficacy and safetyofdexmedetomidinein comparison to fentanyl as an adjuvant toepidural 0.5% ropivacaineforlowerlimbsurgery. We compared quality of block in view of onset and duration of motor and sensory block, hemodynamic responses and duration of postoperative analgesia.

MATERIAL AND METHOD

The prospective, double blinded, randomized control, comparative study was conducted in tertiary center after approval of institutional ethical committee. A written informed consent was taken from all the patients before inclusion in study.Ninety patients were randomly selected for elective lower limb surgery under epidural anesthesia after confirming inclusion and exclusion criteria.

Patients between 18 to 60 years of age of both gender, American society of anesthesiologists (ASA) grade I and II class, undergoing lower limb surgery, and with normal sensory and motor function of affected limb were enrolled in this study. Patients with hypersensitivity to study drugs, local pathology at the site of injection, ASA Class III or above, pregnant, lactating mothers, patients with chronic pain or on long-term analgesics, patients on anticoagulants or having bleeding disorder, and body mass index (BMI) >30kg/m^2 were excluded from study.

All patients were underwent thorough preanesthetic checkup (PAC) and kept nil per oral as per the fasting guidelines. The patients were randomly divided into three predefined groups of 30 each by using computer generated random numbers.

Group A- 0.5% ropivacaine(13 ml)+ saline 0.9% (2 ml)

Group B- 0.5% ropivacaine(13 ml) + inj. Fentanyl 1 mcg/kg (in 2 ml 0.9% saline)
Group C- 0.5% ropivacaine(13 ml) + inj. dexmedetomidine 1 mcg/kg (in 2 ml 0.9% saline)

To reduce subjective and objective bias, the study was so designed that anesthetist doing the procedure, patient, surgeon and observer were not aware of group allocation.

All patients were given 150 mg oral ranitidine and 0.25mg alprazolam as premedication a night prior to surgery. In the operative room, identity of the patient, fasting status, consent and PAC were confirmed. After reassuring the patient, standard ASA monitoring was applied. Base line values of HR, SBP, DBP and MAP, RR, SpO2 were noted. IV cannulation using 18G iv cannula was taken in the contralateral upper limb and Lactate Ringer solution was started. Oxygen was administered at the rate of 4-5 L/min via face mask.

Under strict aseptic precautions and after local infiltration of 2ml (2%) Lidocaine, lumber epidural anesthesia was given in sitting position at the level of L3-L4/L4-L5 interspace by using 18 G Touhy's needle and location of epidural space was confirmed by loss of resistance technique. A test dose of 3 ml of 2% lignocaine with 1:200000 adrenaline solution was administered to exclude intrathecal or intravascular placement of the needle. After 4-6 minutes of test dose and excluding intravascular or intrathecal injection, 15 ml study solution were administered according to study group.

Patients were placed in the supine position immediately after the epidural injection. Time of drug infiltration was noted soon after the needle was out of the injection site after injecting the 15 ml of study drug according to allocated groups. The patients were evaluated for onset of sensory and motor block every 2 min for first 30 min. HR, SBP, DBP, MAP, RR,SPO2 andsedationscorewere documented at every 5min for first 30 min and thereafter every 15min till end of surgery and then every 2hr till 20hrs. Bradycardia defined as heart rate < 60 beats/min and was treated with i.v. atropine 0.6 mg. Hypotension defined as SBP < 20% of baseline value or < 90 mmHg and was treated with intravenous fluid or if needed injMephentermine 3-6 mg in intravenous bolus dose.

Following parameters were noted in study:

1. Onset of sensory block at T10 (time interval between the end of injection of study drug and the complete loss of cutaneous sensation)
2. Maximum sensory level
3. Time to achieve maximum sensory level
4. Time to 2 segment dermatome regression of sensory level
5. Total duration of sensory block
6. Onset of motor block (time interval between the end of injection of study drug and Bromage grade 2)
7. Maximum grade of motor blockade achieved
8. Total duration of motor block (Time interval between injection of study drug and complete resolution of motor blockade to grade 0)
9. Time of requirement of first dose of rescue analgesia (when VAS ≥ 4)
10. Sedation score by Ramsay sedation score
11. Side effects, if any.

The sensory block was assessed by loss of sensation to pin prick in the midline with 25G hypodermic needle every 2 min interval till T10 dermatome was achieved and then every 5 min interval until no change in level occurred. Sensory block was assessed by using a 3-point scale:

Grade 0 – sharp pain on pin prick (normal sensation)
Grade 1- loss of sensation of pinprick (analgesia)
Grade 2- loss of sensation of touch (anesthesia)

Motor block was evaluated every 5 min for first 30 min and then every 15 min till the end of surgery by Modified Bromage scale:

Grade 0 – No block,
Grade 1 –Inability to move the hip but able to move knee and ankle,
Grade 2 –Inability to move hip and knee but can move ankle,
Grade 3 – No movement at all and unable to move hip, knee and ankle.

Sedation was graded every 5 min for first 30 min and then every 15 min till the end of surgery by Ramsay sedation score:

Grade 1- anxious, agitated or restless
Grade 2- cooperative, oriented and tranquil
Grade 3- reports to command only
Grade 4- asleep but basic response to glabellar tap or loud auditory stimuli
Grade 5- asleep but sluggish response to glabellar tap or loud auditory stimuli
Grade 6- no response

Failure of block/Inadequate block was defined by block grade <1 for both sensory and motorblock even after 30 min of LA administration. Such cases were managed by providing GA and were excluded from the study.

The surgical position was given after attaining sensory blockade to T10 level in every patient. During the surgical procedure, adverse effects like anxiety, nausea, vomiting, pruritis, shivering, etc. were recorded. Nausea and vomiting was treated with 0.1mg/kg of intravenous ondansetron. Intraoperative rescue analgesia was administered with inj ketamine (0.5 mg/kg) intravenously, when required. If pain was not relieved, general anesthesia was given to that patient and then that case was excluded from study.

The patients were shifted to postoperative recovery room (PORU) after completion of surgery. All baseline parameter, level of sensory and motor block, sedation score and analgesia by VAS were evaluated in recovery room. The patients were discharged from recovery room after complete resolution of motor block, had stable vital signs, minimum nausea or vomiting and no severe pain or bleeding. Post operatively, all patients were evaluated for time to requirement of first dose of rescue analgesia. That was the end point of this study. Patients were also assessed for any side effects like confusion, dizziness, nystagmus, nausea, vomiting, or any neurological complications like pain or numbness in the leg, incontinence, urine retention or genital dysaesthesias.

Intensity of postoperative pain was assessed by using verbal analogue scale (VAS):

1- No pain and 10- maximum pain.

Postoperatively, rescue analgesia was provided by inj. Diclofenac 1.5 mg/kg, when patient complaint pain or VAS ≥4.

RESULTS

This study was successfully conducted in 90 patients, who underwent lower limb surgery. All patients were randomly divided into three groups with 30 patients in each group. All groups were comparable in all demographic characteristics and did not show any statistical significant difference with p value >0.5.

All patients were injected study drug after identify epidural space with Touhy's needle. Time of onset of sensory block was taken as time interval between the end of injection of study drug and the complete loss of cutaneous sensation at T10 level. Onset of sensory block was significantly faster in group C (7.63 ±1.07 min) followed by group B (9.63 ±1.03 min) then groupA (12.66±1.15 min). Mostly patients in group C achieved maximum level of block T4 – T6, while in group A and group B, it was T6-T8. Mean of maximum achieved sensory level for groups A, B, C were respectively 6.93 ±1.25, 6.13 ±1.16 and 5.23 ±1.35. Difference was statistical significant between all groups. Time to attain maximum sensory level was also faster in group C followed by group B and then group A. Group C required 13.8 ±1.13 mins while group B needed 14.83 ±1.15 mins and group Aneeded 16.4 ±0.97 mins. Difference between all groups and between every two groups was statistical significant. Group C also had significantly long duration of sensory block followed by group B and then group A. Time required for two segment regression of sensory level for group A, B and was respectively 89.66 ±9.00 mins, 108.66 ±11.44 and 135.16 ±10.86 mins.

Time to onset of motor block were also earlier in group C (18.66 ± 5.77 mins) than group B (23.12 ± 5.27 mins) and group A (28.99 ± 7.67 mins).All groups were also different in terms of density of motor block. Group C achieved most dense motor block then other groups. 28 (93.33 %)patients in group C attained motor blockade grade 3 while 18 (60%) patients in group B attained maximum motor grade 2 while 17 (56.66 %) patients in group A attained maximum motor blockade grade 2. Statistical analysis suggested that difference between group A and B was not significant but difference between all groups and between group A and C and between group B and C was significant. Group C also had longer duration of motor block then other two groups. Time of resolution of motor block to grade 0 in all 3 groups were respectively 131.33 ± 8.50 mins, 176.33 ± 9.82 mins and 257.16 ± 10.64 mins.

All patients were assessed in postoperative period for analgesia and time to first requirement of rescue analgesia. Group C had maximum duration of analgesia as time of requirement of rescue analgesia was longer in this group. Mean time for rescue analgesia in group C was 363.83 ± 10.39 mins followed by group B (240.66 ± 9.16 mins) and in group A was 198.33 ± 8.54 mins. Difference between all three groups was statistical significant with p value < 0.0001.

Mostly patients in group C had sedation score 3-4 while in group B sedation score was 2-3 in most of cases. Patients of group A showed minimum sedation in comparison to other groups with sedation score 1-2. Difference was statistical significant between all three groups.

All patients were assessed for intraoperative side effects which include hypotension, bradycardia, nausea, vomiting, pruritis, dry mouth, excessive sedation and respiratory depression. 33 % patients in group C had hypotension while 17 % in group B and 13 % in group A showed hypotension. Difference was not significant with p value 0.126.

2 (7 %) patients in group A, 8 (27 %) patients in group B and 3 (10 %) patients in group C experienced nausea/vomiting which were treated with injondanseteron 6 mg iv. Difference was not significant.

3 patients in group C and 2 patients in group B experienced bradycardia as compared to only 1 patient in group A which were treated with inj. Atropine 0.6 mg iv. This side effect was also not significant between all three groups.

5 (17%) patients in group B had complaint itching during anesthesia while no patients in other two groups had similar complain. So difference was statistical significant with p value 0.005. Similarly only 8 patients in group C had complaint dry mouth while none of patient in other groups had similar complain. This difference was also significant with p value 0.0002.

None of patients in all the three groups had excessive sedation or respiratory depression.

Table I: Demographic Data

Parameter	Group A	Group B	Group C	P value	F value
Age (years)	32.8±9.27	37.5±11.38	36.7±10.47	0.179	1.7507
Gender (M:F)	20:10	22:8	21:9		
Body weight (kg)	64.7±11.76	70±11.10	65.8±12.13	0.184	1.723
Height (cm)	165.26±7.98	164.73±8.61	163±8.70	0.556	0.589
ASA (I:II)	28:2	26:4	27:3		
Duration of surgery (mins)	120.66±15.12	125.3±14.3	122.66±15.18	0.483	0.7347

Table 2: Sensory and motor block characteristics in all groups:

Parameter	Group A	Group B	Group C	P value
Onset of sensory block to T10 level(mins)	12.66± 1.15	9.63±1.03	7.63±1.07	<0.001
Max. level of sensory block	6.93±1.25	6.13±1.16	5.23±1.35	< 0.0001
Time to achieve max sensory level(mins)	16.4±0.97	14.83±1.15	13.8±1.13	<0.0001
Time for 2 segment regression(mins)	89.66±9.00	108.66±11.44	135.16±10.86	<0.0001
Onset of motor block(mins)	28.99±7.67	23.12±5.27	18.66±5.77	<0.0001
Duration of motor block(mins)	131.33±8.50	176.33±9.82	257.16±10.64	<0.0001
Time of 1st dose of rescue analgesia(mins)	198.33±8.54	240.66±9.16	363.83±10.39	<0.0001

Table 3: Comparison of sedation score in all groups:

Sedation score	Group A	Group B	Group C	P value	Chi-square
1	26(87%)	0	0	<0.00001	73.13
2	4(13%)	24(80%)	5(17%)	<0.00001	36.46
3	0	5(17%)	11(37%)	<0.001	13.83
4	0	1(3%)	14(47%)	<0.00001	29.28
5	0	0	0	NA	NA
6	0	0	0	NA	NA

Table 4: Intraoperative complications:

Parameter	Group A	Group B	Group C	Chi square	P value
Hypotension	4 (13%)	5 (17%)	10 (33%)	4.136	0.126
Bradycardia	1 (3%)	2 (7%)	3 (10%)	1.071	1.071
Nausea/vomiting	2 (7%)	8 (27%)	3 (10%)	5.6	0.0616
Pruritus	0	5 (17%)	0	1	0.005
Dry mouth	0	0	8 (27%)	18	0.0002

DISCUSSION

The use of adjuvants with local anesthetic in neuraxial block is well established. Adjuvants can decrease dose related side effects and increase duration and density of block due to synergistic action[12]. Opioids are most commonly used adjuvants but they are associated with various side effects including nausea, vomiting, pruritus, respiratory depression and urinary retention[13]. Hence other alternatives came in light as adjuvants including α2- agonists. The pharmacological properties of α2- agonist like dexmedetomidine are extensively evaluated to achieve analgesia, anxiolysis, hypnosis, sympatholysis and sedation in neuraxial anesthesia[14,15].

Supplementation of epidural ropivacaine with dexmedetomidine can prolong the duration of sensory and motor block with improved quality of perioperative analgesia. These effects may be due to additive or synergistic effect secondary to different mechanism of action of local anesthetics. α2- agonists act on pre and post synaptic sympathetic nerve terminals and central nervous system to decrease sympathetic outflow and nor adrenaline release which leads to sedation, analgesia and sympatholytic effects[16,17]. Whereas opioids act on substensiagelatinosa in dorsal horn of spinal cord and blocks the neural fibers carrying pain impulse both pre and post synaptic level.

In present study, we compared effects of fentanyl and dexmedetomidine as an adjuvant of ropivacaine in epidural anesthesia. The demographic profile in this study was comparable and did not show any significant difference. We found that addition of dexmedetomidine and fentanyl to ropivacaine can decrease the onset and time to achieve maximum sensory block in comparison to ropivacaine alone. Onset of sensory block was earlier in dexmedetomidine group than fentanyl group followed by ropivacaine alone group. These results are in concordance with other studies. Salgado et al[18] also noticed the onset of sensory block with dexmedetomidine was earlier than plain ropivacaine. Bajwa et al[19] suggested that mean onset of sensory block with dexmedetomidine was 7.12 ± 2.44 mins which was earlier than fentanyl group (9.14 ± 2.94). Maximum level of sensory block achieved by dexmedetomidine group was T4- T6 which was comparatively higher than other 2 groups. These results were also similar to other studies[18,19].

Bajwa et al[19] observed in their clinical study that onset of sensory block with dexmedetomidine was significantly earlier than ropivacaine alone group. They also found that dexmedetomidine had earlier onset than fentanyl in another study[20]. Onset of sensory block with dexmedetomidine was 7.12 ±2.44 mins while with fentanyl 9.14±2.99 mins which was quite similar to our study. Time to achieve maximum sensory level was also earlier in dexmedetomidine group than fentanyl group.

Kaur et al[21] compared dexmedetomidine as an adjuvant to ropivacaine to ropivacaine alone in epidural anesthesia in lower limb surgery. Time of onset of sensory block, maximum level of sensory level and time to achieve maximum sensory level was significant earlier in dexmedetomidine group similar to our study.

In present study, there was significant earlier onset of motor block with significant prolonged duration in dexmedetomidine group followed by fentanyl and then ropivacaine alone group. Similar results were documented by Bajwa et al[19] and Kaur et al[21]. Onset of motor block in our study was 18.66 ± 5.77 mins in dexmedetomidine group which has similar with results of Bajwa et al[19] (18.16±4.52). Onset time for fentanyl group was 23.12±5.27 mins in our study while 22.98± 4.78 mins in study of Bajwa et al[19]. Similar results were found with duration of motor block.

Epidural use of dexmedetomidine with ropivacaine in present study result in significantly delayed requirement of rescue analgesia in compared to fentanyl and ropivacaine alone group (198.33 ± 8.54 mins in group A, 240.66 ± 9.16 mins in group B and 363.83±10.39 mins in group C). Similar results were also observed by Salgado et al[18] and Kaur et al[21].

Sedative effect of dexmedetomidine is mediated by inhibition of norepinephrine release from locus coeruleus due to activation of presynaptic α-2 adrenoceptors along with inhibition of adenylate cyclase lead to hypnotic response[22,23]. Our

study resulted that dexmedetomidine group has higher sedation score in comparison to other 2 groups which are similar with results of study by Bajwa et al[19].

The side effects profile of dexmedetomidine was quite favorable and correlates with other studies. Dexmedetomidine does not decrease gut motility, hence it prevents intraoperative and postoperative nausea and vomiting while it is a common side effect of opioids like fentanyl[24]. In present study, commonly noted side effects were hypotension, bradycardia, nausea / vomiting, dry mouth and pruritis. There were no significant difference in side effects between all groups except in pruritis and dry mouth. 17 % patients in fentanyl group showed pruritis (p=0.005) while 27% patients in dexmedetomidine group presented with dry mouth (p= 0.0002). This was in accordance with the study done by Bajwa et al[19].

In the present study all patients remained hemodynamically stable in all three groups and incidence of bradycardia and hypotension was comparable at all measured intervals which confirms the effects of α-2 agonists in providing a hemodynamically stable perioperative period.

CONCLUSION

We conclude that epidural dexmedetomidine seems to be a better alternative adjuvant to ropivacaine in comparison to fentanyl and ropivacaine alone as it produces synergistic effects which lead to earlier onset time of motor and sensory block, earlier achievement of maximum and complete blockade, prolonged sensory and motor blockade with good sedation score and postoperative analgesia. It also provides better hemodynamically stability with less side effects.

REFERENCES

[1] Nowicki PD, Vanderhave KL, Gibbons K, Haydar B, Seeley M, Kozlow K, *et al*. Perioperative pain control in pediatric patients undergoing orthopaedic surgery. J Am Acad Orthop Surg. 2012 Dec;20(12):755-65. PubMed PMID: 23203935.
[2] Schultz AM, Werba A, Ulbing S, Gollmann G, Lehofer F. Peri-operative thoracic epidural analgesia for thoracotomy. Eur J Anaesthesiol. 1997 Nov;14(6):600-3. PubMed PMID: 9466095.
[3] Kehlet H. Acute pain control and accelerated postoperative surgical recovery. Surg Clin North Am. 1999 Apr;79(2):431-43. PubMed PMID: 10352662.
[4] Bradshaw BG, Liu SS, Thirlby RC. Standardized perioperative care protocols and reduced length of stay after colon surgery. J Am Coll Surg. 1998 May;186(5):501-6. PubMed PMID: 9583689.
[5] Zaric D, Nydahl PA, Philipson L, Samuelsson L, Heierson A, Axelsson K. The effect of continuous lumbar epidural infusion of ropivacaine (0.1%, 0.2%, and 0.3%) and 0.25% bupivacaine on sensory and motor block in volunteers: a double-blind study. Reg Anesth. 1996 Jan-Feb;21(1):14-25. PubMed PMID: 8826020.
[6] McClellan KJ, Faulds D. Ropivacaine: an update of its use in regional anaesthesia. Drugs. 2000 Nov;60(5):1065-93. PubMed PMID: 11129123.
[7] Stienstra R. The place of ropivacaine in anesthesia. Acta Anaesthesiol Belg. 2003;54(2):141-8. PubMed PMID: 12872430.
[8] Tong Y, Ren H, Ding X, Jin S, Chen Z, Li Q. Analgesic effect and adverse events of dexmedetomidine as additive for pediatric caudal anesthesia: a meta-analysis. Paediatr Anaesth. 2014 Dec;24(12):1224-30. PubMed PMID: 25203847.
[9] Mahmoud M, Mason KP. Dexmedetomidine: review, update, and future considerations of paediatric perioperative and periprocedural applications and limitations. Br J Anaesth. 2015 Aug;115(2):171-82. PubMed PMID: 26170346.
[10] Wu HH, Wang HT, Jin JJ, Cui GB, Zhou KC, Chen Y, *et al.* Does dexmedetomidine as a neuraxial adjuvant facilitate better anesthesia and analgesia? A systematic review and meta-analysis. PLoS One. 2014;9(3):e93114. PubMed PMID: 24671181. Pubmed Central PMCID: 3966844.
[11] Wu X, Hang LH, Wang H, Shao DH, Xu YG, Cui W, *et al.* Intranasally Administered Adjunctive Dexmedetomidine Reduces Perioperative Anesthetic Requirements in General Anesthesia. Yonsei Med J. 2016 Jul;57(4):998-1005. PubMed PMID: 27189297. Pubmed Central PMCID: 4951480.
[12] Soto RG, Fu ES. Acute pain management for patients undergoing thoracotomy. Ann Thorac Surg. 2003 Apr;75(4):1349-57. PubMed PMID: 12683601.
[13] Arain SR, Ruehlow RM, Uhrich TD, Ebert TJ. The efficacy of dexmedetomidine versus morphine for postoperative analgesia after major inpatient surgery. Anesth Analg. 2004 Jan;98(1):153-8, table of contents. PubMed PMID: 14693611.
[14] Gabriel JS, Gordin V. Alpha 2 agonists in regional anesthesia and analgesia. Curr Opin Anaesthesiol. 2001 Dec;14(6):751-3. PubMed PMID: 17019175.
[15] Vieira AM, Schnaider TB, Brandao AC, Pereira FA, Costa ED, Fonseca CE. [Epidural clonidine or dexmedetomidine for post-cholecystectomy analgesia and sedation.]. Rev Bras Anestesiol. 2004 Aug;54(4):473-8. PubMed PMID: 19471755. Clonidina e dexmedetomidina por via peridural para analgesia e sedacao pos-operatoria de colecistectomia.
[16] 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 Feb;50(2):222-7. PubMed PMID: 16430546.
[17] Lawhead RG, Blaxall HS, Bylund DB. Alpha-2A is the predominant alpha-2 adrenergic receptor subtype in human spinal cord. Anesthesiology. 1992 Nov;77(5):983-91. PubMed PMID: 1359811.

[18] Salgado PF, Sabbag AT, Silva PC, Brienze SL, Dalto HP, Modolo NS, *et al*. [Synergistic effect between dexmedetomidine and 0.75% ropivacaine in epidural anesthesia]. Rev Assoc Med Bras (1992). 2008 Mar-Apr;54(2):110-5. PubMed PMID: 18506317. Efeito sinergico entre a dexmedetomidina e a ropivacaina 0,75% na anestesia peridural.

[19] Bajwa SJ, Arora V, Kaur J, Singh A, Parmar SS. Comparative evaluation of dexmedetomidine and fentanyl for epidural analgesia in lower limb orthopedic surgeries. Saudi J Anaesth. 2011 Oct;5(4):365-70. PubMed PMID: 22144922. Pubmed Central PMCID: 3227304.

[20] 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 Mar;55(2):116-21. PubMed PMID: 21712865. Pubmed Central PMCID: 3106381.

[21] Kaur S, Attri JP, Kaur G, Singh TP. Comparative evaluation of ropivacaine versus dexmedetomidine and ropivacaine in epidural anesthesia in lower limb orthopedic surgeries. Saudi J Anaesth. 2014 Oct;8(4):463-9. PubMed PMID: 25422602. Pubmed Central PMCID: 4236931.

[22] Memis D, Turan A, Karamanlioglu B, Pamukcu Z, Kurt I. Adding dexmedetomidine to lidocaine for intravenous regional anesthesia. Anesth Analg. 2004 Mar;98(3):835-40, table of contents. PubMed PMID: 14980948.

[23] Maze M, Regan JW. Role of signal transduction in anesthetic action. Alpha 2 adrenergic agonists. Ann N Y Acad Sci. 1991;625:409-22. PubMed PMID: 1711813.

[24] Venn RM, Bradshaw CJ, Spencer R, Brealey D, Caudwell E, Naughton C, *et al*. Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. Anaesthesia. 1999 Dec;54(12):1136-42. PubMed PMID: 10594409.