ISSN (O):2395-2822; ISSN (P):2395-2814

A Prospective Randomized Double Blind Study on Efficacy of Dexmedetomidine and Ketamine as Adjuvant to Epidural Ropivacaine in Lower Abdominal and Lower Limb Surgery.

Rajat Kumar Das[1], Amit Pradhan[2], Debasish Debata[3]

[1]Assistant Professor, Department of Anaesthesiology, Pain and Palliative care, Acharya Harihar Regional Cancer Centre. Cuttack, Odisha.
[2]Associate Professor, Kalinga Institute of Medical Sciences. Bhubaneswar, Odisha.
[3]Senior Resident, Kalinga Institute of Medical Sciences. Bhubaneswar, Odisha.

Received: July 2017
Accepted: July 2017

ABSTRACT

Background: Various adjuvants including α-2 adrenergic agonist have been used to prolong the action of local anaesthetics in epidural anaesthesia. Now a days dexmedetomidine is most commonly used adjuvant in epidural anaesthesia but still it may produce side effects like hypotension and bradycardia.There is limited study on efficacy of ketamine as adjuvant in epidural anaesthesia. **Aim:** The aim of the study was to compare the duration of postoperative analgesia and side effects of epidural dexmedetomidine with ropivacaine versus epidural ketamine with ropivacaine in lower abdominal and lower limb surgery. **Methods:** This prospective randomised study was carried out in 100 patients of 20-60 years of age and of ASA classes I/II. All the patients, posted for lower abdominal and lower limb surgery were divided into two groups of 50 each. Group RD received 15ml ropivacaine(0.75%) with dexmedetomidine(1µgm/kg) and group RK received 15ml ropivacaine with ketamine(0.5mg/kg).Time for first rescue analgesia request, sensory and motor block characteristics and side effects were recorded. $p<0.05$ was considered statistically significant. **Results:** Time of first rescue analgesia request was delayed in group RD (360.15±35.23min) than group RK (311.14±32.48min) which was statistically significant. Both onset of sensory and motor block was earlier and duration of sensory and motor block was prolonged in group RD compared to group RK which was statistically significant. Hemodynamic parameters and side effects were comparable in both groups. **Conclusion:** Dexmedetomidine is a superior additive to ropivacaine compared to ketamine. Dexmedetomidine provides prolonged postoperative analgesia, earlier onset of sensory and motor block with minimal side effects.

Keywords: Dexmedetomidine, Ketamine, Ropivacaine, Epidural.

INTRODUCTION

Epidural analgesia is one of the common method of postoperative pain management. It provides hemodynamic stability, reduce perioperative stress response, enables early mobilization and reduce incidence of thromboembolic events.[1] Bupivacaine is the most common local anesthetic agent used in epidural route but due to its cardiac side effects ropivacaine is being used more now a days.Ropivacaine produces lesser motor blockade compared to bupivacaine thus making it suitable for postoperative pain management.[2] Various additives have been used for extending the duration of epidural block to prolong the effect of ropivacaine which helps in reducing total required dose of ropivacaine. These include drugs like opioids, midazolam, neostigmine and α2 adrenergic agonists like clonidine and dexmedetomidine which have their own side effects.[3] Dexmedetomidine is a highly selective α2 adrenergic agonist with analgesic, anxiolytic, sedative, perioperative sympatholytic and anti hypertensive properties. It also enhances action of local anaesthetics and increases the duration of post operative analgesia, but it can produce side effects like bradycardia and hypotension.[4] N-methyl-D-Aspartate (NMDA) receptor antagonist plays a significant role in blocking central hypersensitivity and pain. As an NMDA receptor antagonist, ketamine may be used as additive to local anaesthestic agents for post operative pain relief. Epidural ketamine produces analgesia at spinal cord level without systemic side effects.[5] There is very little information in literature regarding use of ketamine in epidural route. Hence,

Name & Address of Corresponding Author
Dr. Amit Pradhan
Associate Professor,
Kalinga Institute of Medical Sciences,
Bhubaneswar,
Odisha.

we have done this study to compare ropivacaine with dexmedetomidine and ropivacaine with ketamine in epidural anesthesia for lower abdominal and lower limb surgeries. The primary outcome of our study was to find out duration of postoperative analgesia and the secondary outcome of our study was to compare sensory and motor block characteristics, hemodynamics and side effects.

MATERIALS AND METHODS

A study entitled "Attenuation of haemodynamic After obtaining the approval from the hospital ethical committee and written informed consent from the patient, this randomized double blind study was conducted from Oct 2015 to Nov 2016. 100 patients belonging to physical status American society association class I and II, aged 20-60 years, scheduled for lower abdominal and lower limb surgical procedures were included in this study. Patient's refusal for regional anesthesia, pregnancy, coagulopathy, uncontrolled hypertension, diabetes mellitus, local infection and allergy to local anesthetics were excluded from the study.During preanesthetic check up, patients were evaluated for any systemic diseases and their laboratory investigations were checked. The anesthetic procedure and visual analog score (VAS) was explained to the patients. The patients were premedicated with tablet alprazolam 0.5 mg and tablet ranitidine 150 mg orally at bed time on the night before surgery.

Randomization was done by using a computer generated random number sequence and sealed opaque envelops.The study population was randomly divided into 2 groups with 50 patients in each group. Group RD (ropivacaine-dexmedetomidine): 15 ml of 0.75% ropivacaine+0.5µg/kg of dexmedetomidine (diluted to 1ml). Group RK (ropivacaine-ketamine): 15 ml of 0.75% ropivacaine +0.5mg/kg ketamine (diluted to 1ml) Study drug was prepared by the anesthesiologist who was not involved in the study. A peripheral I.V line was secured with an 18 G (gauge) cannula. The patients were preloaded with 10ml/kg of Ringer's Lactate 30 minutes prior to the epidural procedure. Baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) and SpO_2 was recorded. With the patients in sitting position, under all available aseptic precautions, the epidural space was identified by the loss of resistance technique to air using 18 G (gauge) Tuohy needle via midline approach at L_{3-4} space. An epidural catheter was threaded and fixed at 4cm in the epidural space. A test dose of 3ml of 2% lignocaine with 1:200000 adrenaline was injected through the epidural catheter after aspiration. After ruling out the intrathecal and intravascular placement of the tip of the catheter, the study drug (16ml) was injected and the patient was then turned to supine position. The sensory blockade was assessed by pinprick method using a short bevel 22G needle in a 3 point scale at every minute till onset of block at T10.0-normal sensation, 1- loss of sensation to pin prick, 2-loss of sensation of touch.[6] Motor blockade was assessed using Bromage scale at 5 min interval till Bromage grade 3 block was achieved. Bromage scale for motor blockade: 0- No block,1-inability to raise extended leg, 2-inability to flex knee,3-inability to flex ankle and foot.[7] HR, SBP, DBP, MAP and SpO_2 was recorded every 5 minutes till the end of first hour and then every 15 minutes till the end of surgery. After the surgery, patients were referred to the post anesthesia care unit. The parameters like heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP) ,mean arterial pressure (MAP), SpO_2 and VAS were recorded at every 15 minutes. Bradycardia (HR<50/min) was managed by inj atropine and hypotension (MAP<20% of baseline) was managed by inj ephedrine. Epidural rescue analgesic dose was given with 6 ml of 0.5% Inj. ropivacaine added with desired adjuvants (dexmedetomidine or ketamine), when the patient complained of pain(VAS $\geq$ 4).

The time of onset of sensory blockade was taken from time of injection of the drug under study into the epidural space to loss of pin prick sensation at T10.Onset of motor block was taken as the time from the completion of the injection of the study drug till the patient developed grade 3 motor blockade in Bromage scale. The highest level of sensory block was noted as loss of pinprick sensation at highest dermatomal level. Time of maximum level of sensory block was taken as time from injection of study drug to time of highest level of block achieved. Time to two dermatome regression was defined as time from sensory block at highest dermatome to regression by two dermatome. Duration of sensory block was recorded as the interval from the time of onset of sensory blockade till regression to S1 dermatome. Duration of motor block was recorded from onset of motor block to time when the patient was able to lift the extended leg (Bromage -1).Time to first rescue analgesic requirement was time taken from onset of sensory block at T10 to patient complaining of pain at surgical site(VAS≥4). Grading of sedation was evaluated by Ramsay five point scale:1-alert and wide awake, 2-arousable to verbal command, 3-arousable with gentle tactile stimulation, 4-arousable with vigorous shaking, 5-unarousable.[8] Sedation score was recorded just before initiation of surgery and every 5 minutes till start of surgery and then every 15 minutes throughout the surgical procedure. During the surgical procedure, adverse events like anxiety, nausea, vomiting, pruritus and shivering were noted. Nausea and vomiting was treated with Inj Ondansetron 4mg IV. Sample size calculation was done taking the time of rescue analgesic request

as the primary aim of the study. Assuming the mean difference of 1 hr, 30 patients per group was considered necessary to detect alpha error of 0.05 with power 0.8(1-β=80%). At the end of the study, all the data was compiled systematically and analysed using unpaired student's t-test, chi-square test. All the values were expressed as mean ± standard deviation. Statistical Package for Social Sciences Version 21.0 for Windows was used to compare the variables between two groups. P<0.05 was considered significant and P< 0.001 was considered as highly significant.

RESULTS

The demographic profile of our patients was comparable with respect to age, sex, height, body weight, body mass index, ASA status and duration of surgery [Table 1]. Addition of dexmedetomidine to epidural ropivacaine produced an earlier onset (8.65±2.14min) of sensory block at T10 in group RD compared to group RK (11.3±2.5min) which was statistically significant .Maximum height of block achieved was earlier in group RD compared to group RK, but there was no statistical difference in height of block achieved. Complete motor blockade was achieved earlier in group RD compared to group RK which was statistically significant [Table 2]. Time to two segment regression was earlier in group RD compared to group RK which was statistically significant. Duration of sensory and motor block was prolonged in group RD compared to group RK which was statistically significant. Time to rescue analgesic was earlier in group RK compared to group RD which was statistically significant [Table 3]. Changes in hemodynamic parameters like HR,SBP,DBP and MAP between the two groups was statistically not significant. There was no statistically significant difference regarding side effects in both groups.

Table 1: Demographic profile of patients of both group.

Demographic characteristics	RD group (n-30) Mean ±SD	RK group(n-30) Mean ±SD	P value
Age (yrs)	45.5±10.6	48.2±11.4	0.36
Sex (m:f)	35:15	38:12	0.79
Weight (kg)	55.64.±12.8	56.20±10.85	0.53
Height (cm)	150.4±8.25	152.65±8.4	0.30
BMI(Kg/m^2)	27.5±2.82	28.45±2.92	0.28
ASA (I/II)	40/10	37/13	1.0
Mean duration of surgery (min)	90.35±15.6	95.4±15.8	0.33

There was no significant difference in sedation scores in both RD and RK group.

The incidence of dry mouth was higher in group RD as compared to group RK. The other side effects like nausea and shivering were comparable. No incidence of vomiting, dizziness or respiratory depression was seen in either group [Figure 1].

Table 2: Comparison of preoperative block characteristics.

Block characteristics	RD group (n-30)	RK group(n-30)	P Value
Onset time of sensory block at T 10(min)	8.65±2.14	11.3±2.5	0.02
Max sensory block level	T7-T8	T7-T8	0.04
Time to max level of sensory block(min)	13.75±4.28	17.24±3.32	0.01
Time for onset of motor block(min)	17.8±4.55	24.15±4.94	0.02

Table 3: Comparisons of post op block characteristics.

Post op block characteristics	RD group (n=30)	RK group(n=30)	P Value
Mean time to two segment regression (min)	135.76±10.54	126.22±9.98	<0.001
Mean time to regression to Bromage 1(min)	261.15±25.47	220.34±26.55	<0.001
Mean time to sensory regression at S 1(min)	320.50±36.74	285.62±35.16	<0.001
Time to first rescue top up(min)	360.15±35.23	311.14±32.48	<0.001

DISCUSSION

Nowadays, a lot of adjuvants are used with local anesthetics in the epidural anesthesia. Primary aim of these adjuvants is to fasten the onset and prolong the sensory and motor block and produce adequate sedation, analgesia and patient satisfaction without any side effect. The pharmacologic properties of α-2 agonists like dexmedetomidine have been used extensively in various routes. Epidural administration of these drugs is associated with sedation, analgesia, anxiolysis, hypnosis and sympatholysis. The faster onset of action and prolonged duration of analgesia make it a very effective adjuvant to local anesthetics in regional anesthesia. But it can produce side effects like bradycardia and hypotension in some patients.[9] Ketamine a (NMDA antagonist)can cause hypertension and tachycardia when used intravenously.[10] We have compared epidural ketamine with dexmedetomidine to study the efficacy in prolonging the duration of analgesia and found that duration of analgesia was prolonged in group RD compared to group RK which was also supported by few other studies.

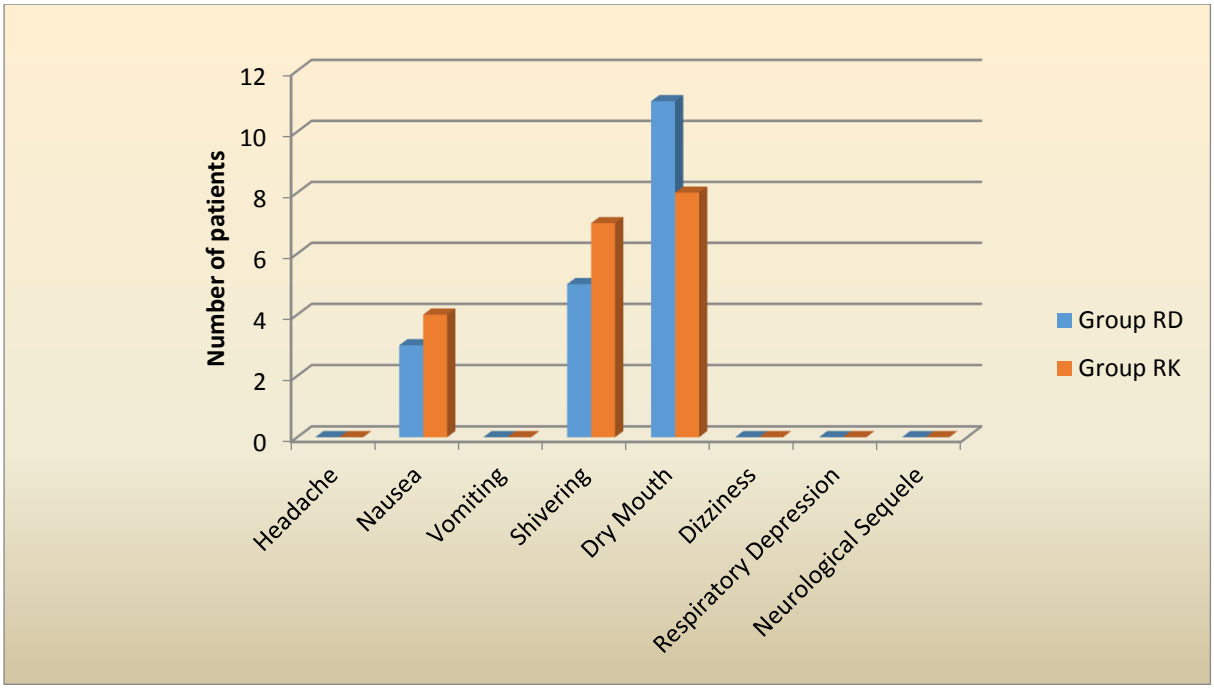

Figure 1: Comparison of side effects.

El Hennawy et al studied analgesic effects and side-effects of caudal dexmedetomidine and clonidine added to bupivacaine in paediatric patients undergoing lower abdominal surgeries and concluded that addition of dexmedetomidine to caudal bupivacaine significantly prolonged analgesia compared to clonidine.[11] Gupta et al in their study concluded that the onset of sensory analgesia and time to achieve complete motor blockade in epidural anaesthesia was significantly earlier and duration of sensory and motor block was prolonged in patients of dexmetomidine group compared to fentanyl group.[12] Shaikh et al opined that dexmedetomidine is a superior neuraxial adjuvant to bupivacaine when compared to clonidine for early onset of analgesia,stable cardio-respiratory parameters and prolonged postoperative analgesia.[13] Bajwa et al studied dexmedetomidine and clonidine, in epidural anaesthesia and concluded that dexmedetomidine is a better neuraxial adjuvant compared to clonidine for providing early onset of sensory analgesia, prolonged post operative analgesia and adequate sedation.[14] The above studies supports our finding that dexmedetomidine as adjuvant to local anesthetics provides both early onset of block and prolongs the duration of analgesia.Vaidya et al carried out a prospective double blind study to see whether the sympathomimetic effect of intrathecal ketamine attenuates bupivacaine induced hypotension and bradycardia. They concluded that intrathecal addition of ketamine with bupivacaine gives better hemodynamic stability and minimize requirement of fluids and vasopressors.[15] Waleed et al carried out a study to compare the analgesic efficacy and safety of ketamine and magnesium sulfate in combination with bupivacaine for caudal block in pediatric patients for inguinoscrotal operations They observed that caudal administration of ketamine is efficient and safe for pediatric inguinoscrotal operations with longer postoperative analgesia than magnesium sulfate.[16] Kamali et al carried out a study to compare the addition of neostigmine and ketamine to bupivacaine for epidural analgesia and opined that ketamine with bupivacaine in epidural anesthesia increased the duration of analgesia and reduced analgesic consumption compared to ketamine.[17] Shobary HM et al compared epidural ketamine with epidural morphine and concluded that ketamine is associated with less sedation and lesser risk of postoperative nausea and vomiting. but morphine provided prolonged analgesia in elderly patients.[18] Sethi et al studied ketamine in patient controlled epidural analgesia after abdominal surgery and concluded that ketamine reduces postoperative morphine consumption and is an effective adjuvant to local anesthetics.[19] Krishna T et al in their study opined that combined uses of ketamine and midazolam with intrathevcal bupivacaine provided prolonged analgesia compared to either ketamin or midazolam.[20] BGet al studied analgesic efficacy of ketamine with caudal levobupivacaine and concluded that addition of 0.5mg/kg of ketamine to levobupivacaine for caudal block provides effective postoperative analgesia than levobupivacaine alne.[21] Naguib et al in his study concluded that administration of 30 mg of ketamine epidurally was a better method of pain relief without any side effects compared to epidural ketamine 10mg.[22] Ghaffer ME et al in their study concluded that epidural ketamine 30mg reduces post hysterectomy pain and reduces requirement of

fentanyl/bupivacaine.[23] Mihaljevic et al concluded that low dose of S-(+)-ketamine administered epidurally had no sympathomimetic effects; it did not change blood pressure, pulse, serum hormones or pulse transit time. Low dose of S-(+)-ketamine administered epidurally did not deepen sympathetic block.[24] The above studies supports our finding that epidural ketamine is a potent adjuvant to local anesthetics which prolong the duration of analgesia.

The present study was undertaken to compare onset of sensory and motor blockade, sedation and hemodynamic profiles of dexmedetomidine with ketamine as an adjuvant to ropivacaine. Addition of dexmedetomidine to epidural ropivacaine produced an earlier onset of sensory block at T10 compared to ketamine. Complete motor blockade was achieved earlier in group RD compared to group RK. Duration of sensory and motor block was prolonged in group RD compared to group RK. Time to first rescue analgesic request was earlier in group RK compared to group RD. Changes in hemodynamic parameters like HR,SBP,DBP and MAP between the two groups was statistically not significant. There was no statistically significant difference regarding side effects in both groups. Sonawane et al in a pilot study of 60 patients compared epidural infusion of bupivacaine plus dexmedetomidine or ketamine and concluded that dexmedetomidine with epidural bupivacaine reduced pain for longer period compared to epidural ketamine. Receding time for sensory block and receding time for motor block was delayed en dexmedetomidine group compared to ketamine group. But they have opined that a large randomized multicenter study is required to draw definite conclusion.[25]We have found similar result in our study.

EI-Aziz A et al in their study concluded that use of dexmedetomidine with bupivacaine in caudal epidural route provides prolonged analgesia when compared with ketamine. But ketamine produced less sedation compared to dexmedetomidine.[26] This in similarity to our study. Dexmedetomidine can cause hypotension and bradycardia but ketamine can cause hypotension and tachycardia. In our study blood pressure and heart rate was stable and comparable in both groups.

CONCLUSION

Dexmedetomidine is a better adjuvant to ketamine when used with epidural ropivacaine. It provides early onset of sensory and motor block and prolonged postoperative analgesia. Hemodynamics was stable in both groups. Side effects including sedation were comparable in both groups.

REFERENCES

1. Nimmo SM. Benefit and outcome after epidural analgesia. Contin Educ Anaesth Crit Care Pain.2004;4(2):44-7.
2. 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;8(4):463-469.
3. Richards JT, Read JR, Chambers WA. Epidural anaesthesia as a method of pre-emptive analgesia for abdominal hysterectomy. Anaesthesia 1998;53(3):296-8.
4. Arunkumar S, Hemanth Kumar V, Krishnaveni N, Ravishankar M, Jaya V, Aruloli M. Comparison of dexmedetomidine and clonidine as an adjuvant to ropivacaine for epidural anesthesia in lower abdominal and lower limb surgeries. Saudi J Anaesth. 2015;9(4):404-408.
5. Moyse DW, Kaye AD, Diaz JH, Qadri MY, Lindsay D, Pyati S,et al.Perioperative Ketamine Administration for Thoracotomy Pain. Pain Physician. 2017 Mar; 20(3):173-184.
6. Rigg JR, Jamrozik K, Myles PS, Silbert BS, Peyton PJ, Parsons RW, et al. Epidural anesthesia and analgesia and outcome of major surgery:A randomised trial. Lancet 2002;359(9314):1276-82.
7. Sharma A, Kumar NJ, Azharuddin M, Mohan LC, Ramachandran G. Evaluation of low-dose dexmedetomidine and neostigmine with bupivacaine for postoperative analgesia in orthopedic surgeries: A prospective randomized double-blind study. J Anaesthesiol Clin Pharmacol 2016;32(2):187-91.
8. Karhade SS, Acharya SA, Harnagale K. Comparative analysis of epidural bupivacaine versus bupivacaine with dexmedetomidine for vaginal hysterectomy. Anesth Essays Res. 2015;9(3):310-313.
9. Hanoura SE, Hassanin R, Singh R. Intraoperative conditions and quality of postoperative analgesia after adding dexmedetomidine to epidural bupivacaine and fentanyl in elective cesarean section using combined spinal-epidural anesthesia. Anesth Essays Res 2013;7(2):168-172.
10. Kaur D, Anand S. Comparison between caudal bupivacaine and bupivacaine with ketamine for postoperative analgesia in children: A prospective randomized clinical study. Anesth Essays Res 2016 ;10(3):488-492
11. EI-Hennawy, A. M., Abd-Elwahab, A. M., Abd-Elmaksoud, A. M., EI-Ozairy, H. S., & Boulis S. R. Addition of Clonidine or Dexmedetomidine to Bupivacaine prolongs caudal analgesia in children. British J Anaesth 2009; 103(2):268-274.
12. Gupta K, Rastogi B,Gupta PK,Jain M,Gupta S,Mangla D. Epidural 0.5% levobupivacaine with dexmedetomidine versus fentanyl for vaginal hysterectomy: A prospective study. Indian J Pain.2014 ;28(3): 149-54
13. Shaikh SI, Mahesh SB. The efficacy and safety of epidural dexmedetomidine and clonidine with bupivacaine in patients undergoing lower limb orthopedic surgeries. J Anaesthesiol Clin Pharmacol 2016;32(2):203-9.
14. 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(2):116-21.
15. Vaidya PR, Jha BD, Shrestha S. Comparative Study of Hemodynamic Changes of Intrathecal Bupivacaine with or without Ketamine for Lower Limb Surgeries. Postgraduate Medical Journal of NAMS.2012 ; 12(1):1-4
16. Farrag WSH, Ibrahim AS, Mostafa MG, Kurkar A, Elderwy AA. Ketamine versus magnesium sulfate with caudal bupivacaine block in pediatric inguinoscrotal surgery: A prospective randomized observer-blinded study. Urol Ann.2015;7 (3):325-329.
17. Kamali A, Zareei A,Moshiri E, Farokhi F.Comparing the Effect of Adding Ketamine and Neostigmine to Bupivacaine 0.25 % for Epidural Analgesia among Patients Candidated for Elective Femoral Fracture Surgery.International J Med Res & Health Sci. 2016; 5(11):63-67.
18. EI Shobary HM,Sonbul ZM,Schricker TP.Epidural ketamine for postoperative analgesia in the elderly.Middle East J A naesthsiol.2008Oct;19(6):1369-78.

19. Sethi M, Sethi N, Jain P, Sood J. Role of epidural ketamine for postoperative analgesia after upper abdominal surgery. Indian J Anaesth. 2011;55(2):141-145.
20. Murali Krishna T,Panda NB,Batra YK,Rajeev S.Combination of low doses of intrathecal ketamine and midazolam with bupivacaine improves postoperative analgesia in orthopaedic surgery.Eur J Anaesthesiol.2008Apr; 25(4):299-306.
21. Locatelli BJ,Frawley G,Spotti A,Ingelmo P.Analgesic effectiveness of caudal levobupivacaine and ketamine.Br J Anaesth.2008May;100(5):701-6.
22. Naguib M,Gyamfi Y,Absood G,Frag H,Gyasi H.Epidural ketamine for postoperative analgesia.Can Anaesth Soc J. 1986;33(1):16-21.
23. Abdel-Ghaffar ME, Abdulatif MA, al-Ghamdi A, Mowafi H, Anwar A.Epidural ketamine reduces postoperative epidural PCA consumption of fentanyl/bupivacaine.Can J A naesth.1998 Feb;45(2):103-9.
24. Mihaljevic S, Mihaljevic L, Cacic M. Sympathetic activity of S-(+)-ketamine low doses in the epidural space;Rev. Bras. Anestesiol.2014; 64 (4) : 227-335.
25. Sonawane NB, Balavenkatasubramanian J, Gurumoorthi P, Jadhav PA. Quality of post-operative analgesia after epidural dexmedetomidine and ketamine: A comparative pilot study. Indian J of Anaesth. 2016;60(10):766-768.
26. Abd EI-Aziz AAA, Alla AA. Comparative study between caudal dexmedetomidine with bupivacaine versus ketamine with bupivacaine for postoperative analgesia after inguinoscrotal surgery in pediatric patients.Ain-Shams J of Anaesthesiol.2015 ;08:634-638.

How to cite this article: Das RK, Pradhan A, Debata D. A Prospective Randomized Double Blind Study on Efficacy of Dexmedetomidine and Ketamine as Adjuvant to Epidural Ropivacaine in Lower Abdominal and Lower Limb Surgery. Ann. Int. Med. Den. Res. 2017; 3(5):AN18-AN23.

Source of Support: Nil, **Conflict of Interest:** None declared