A comparative study on adding Dexmedetomidine versus Clonidine to epidural 0.125% Bupivacaine for postoperative analgesia in patients undergoing upper abdominal surgeries

Swarnalingam Thangavelu[1,*], Shankar Anand Radhakrishnan[2], Nazir Ahmed Mallick[3]

[1,2]Assistant Professor, [3]Professor, Tagore Medical College & Hospital, Tamil Nadu

***Corresponding Author:**
Email: lingamks@gmail.com

Abstract

Background: The pain experienced after upper abdominal surgery leads to a reduction in 70-75% of vital capacity which leads to postoperative pulmonary complications. The ideal adjuvant for epidural analgesia in patients undergoing upper abdominal surgery seems to be every effective for better outcome and early immobilization in the immediate postoperative period. With this background we planned to conduct a study on epidural analgesia by comparing two alpha 2 agonists.

Methods: 50 patients who have planned for elective upper abdominal surgery under general anaesthesia were enrolled in our study. Before induction of general anaesthesia, epidural catheterization was done. The surgical procedure was carried out under routine general anaesthesia with endotracheal controlled ventilation. The patients were given either Dexmedetomidine or Clonidine in the dosage of 2mcg/Kg with 0.125% Bupivacaine via epidural catheter after extubation. Patients were shifted to Post Anaesthesia Care Unit for observation. Sedation and pain were assessed with monitoring of vital parameters. The side effects were also noted.

Results: Statistical analysis showed that the duration of analgesia was prolonged in the patients who received Dexmedetomidine as an adjuvant with local anaesthetic agent (417.32±67.36 minutes, p value < 0.05). The time to first rescue analgesia was comparatively delayed in Dexmedetomidine group while comparing with Clonidine group (425.6±64.27 minutes, p value < 0.05). The incidence of hypotension and bradycardia was greater in Clonidine group. There was no significant statistical difference with respect to side effects in both groups.

Conclusion: From our study we concluded that Dexmedetomidine provides both analgesia and sedation with better hemodynamic status while compared to Clonidine used as adjuvants in epidural analgesia. But needs further study to optimize the dosage of these two adjuvants while giving via epidural route along with local anaesthetic agent.

Keywords: Dexmedetomidine, Clonidine, Epidural analgesia, Alpha 2 agonists

Access this article online	
Quick Response Code:	Website: www.innovativepublication.com
	DOI: 10.5958/2394-4994.2016.00080.9

Introduction

Effective pain control is the mainstay of treatment in patients who have undergone upper abdominal surgery since pain has many adverse effects on various systems of the body. Thoracic epidural analgesia provides not only provides pain relief but also reduces the postoperative stress response. Pain free patients have a shorter duration of stay in the hospital and reduced postoperative pulmonary complications[1,2] To achieve this goal various adjuvants are added to local anaesthetic mixture like fentanyl, morphine, tramadol etc. But opioid related side effects are more common like pruritus, respiratory depression, ileus etc.

To overcome the side effects produced by opioids used along with local anesthetic agent given via epidural route selective alpha2 agonists can be used. The selective alpha 2 agonists clonidine and dexmedetomidine produce sedation as well as analgesia while given via epidural are many studies on epidural clonidine but limited to dexmedetomidine.[3,4,5,6] With this back ground we planned to conduct a study on postoperative epidural analgesia in patients undergoing upper abdominal surgery.

Aim and Objectives

To compare the efficacy and safety profile of two selective alpha 2 agonists namely clonidine and dexmedetomidine given via epidural route in the patients planned for upper abdominal surgery. The primary objective was to provide extended pain relief to the patients and allow them for early mobilisation.

Methodology

After obtaining approval from Institutional ethical committee this study was conducted in our department. The fifty ASA I & II patients aged 18-60 years were selected for whom upper abdominal surgery was planned under general anaesthesia and planned for an epidural analgesia post operatively. The written informed consent was obtained from all patients after explaining about the benefits of epidural analgesia and the details about 10-point Visual Analogue Scale in the preoperative period.

Patients were allocated into two groups of twenty five each namely Group C (Clonidine) and Group D

(Dexmedetomidine). Randomization was done by lottery method. The exclusion criteria were

- Patients with coagulation abnormalities
- Patients with cardiac or renal disease
- Patients with neurological illness
- Patients with mental illness
- Patients with deformity of spinal column
- Patients with allergy to local anaesthetics
- Patients not fitting into inclusion criteria

In all patients, age, body weight and baseline vital parameters were recorded. All patients were premedicated with T. Alprazolam 0.25-0.5mg, T. Metoclopromide 10 mg and T. Ranitidine 150mg at 6am on the day of surgery. Standard monitors like ECG, Non-invasive BP, Pulse oximetry were connected to the patient. Intravenous access was done using 16 or 18 gauge intravenous cannula and crystalloid infusion was started. Prior to induction of anesthesia under strict aseptic precaution an epidural catheterisation was done in lateral or sitting position using 8-9 cm long, 18 G Tuohy needle. The insertion site of epidural needle was kept in the intervertebral space between T10-T12. The catheter was advanced 3-4cm into the epidural space after ensuring the space with loss of resistance technique. The epidural catheter position was rechecked with a test dose containing 3 ml of 1.5% lignocaine with adrenaline (5mcg/ml) to rule out intravascular or subarachnoid placement of catheter tip.

In all patients routine general anesthesia with controlled ventilation was used. Anaesthesia was induced with Propofol 2mg/kg and fentanyl citrate 2mcg/kg. Tracheal intubation was done with atracurium besylate 0.6mg/kg body weight. Anaesthesia was maintained with atracurium besylate and sevoflurane 1-2% in N2O-O2 mixture to maintain muscle relaxation and depth of anaesthesia respectively. Intraoperative analgesia was achieved with intermittent intravenous bolus dose of fentanyl citrate 25-50 mcg every hour. After the end of procedure, patient was reversed with neostigmine and glycopyyrolate.

After extubation, either dexmedetomidine or clonidine was given via epidural catheter after the negative aspiration for CSF or blood.

Group C: This group received 7ml of 0.125% bupivacaine with 2mcg/kg clonidine made up to 3ml with normal saline (Total volume of 10 ml)

Group D: This group received 7ml of 0.125%b bupivacaine with 2 mcg/kg dexmedetomidine made up to 3ml with normal saline (Total volume of 10ml)

Patients were observed in the theatre for 15 minutes and then shifted to Post Anaesthesia Care Unit (PACU) for monitoring. Various parameters like heart rate, blood pressure (both systolic and diastolic), SpO2 , visual analogue scale and Ramsay sedation score were observed for 24 hours post operatively. Injection Tramadol 50 mg was used as rescue analgesia when pain score was more than 4 (VAS≥4). Sedation was assessed using modified Ramsay scale.

Awake levels

1. Anxious, agitated or both
2. Cooperative oriented, tranquil
3. Response to commands only

Asleep levels

4. Brisk response to loud auditory stimulus
5. Sluggish response to loud auditory stimulus
6. No response to loud auditory stimulus

Vital parameters were monitored continuously and recordings were made every 5 minutes until 1 hour and at every 15 minutes interval for the next hour and finally at 60 minutes interval for next 24 hours. Hypotension (defined as Mean arterial pressure falling than 65 mmHg) was treated with injection Ephedrine 6mg and bradycardia (Heart rate less than 50/min) was treated with 0.3-0.6 mg Inj.Atropine.

During the first 24 hours of postoperative period adverse events like nausea, vomiting, dizziness, pruritus and respiratory depression were noted. Nausea and vomiting were treated with 4 mg of intravenous ondansetron. After 24 hours epidural analgesia was maintained with intermittent bolus dose of 0.125% bupivacaine. The patient was shifted to postoperative ward thereafter and catheter was removed after 48 hours.

Results

Data were analysed using INSTAT 3(Graph pad software, California, USA). Two sided independent student's t test to analyse continuous data, Fisher's exact test and Chi-square test for categorical data were used. $P<0.05$ was considered as statistically significant.

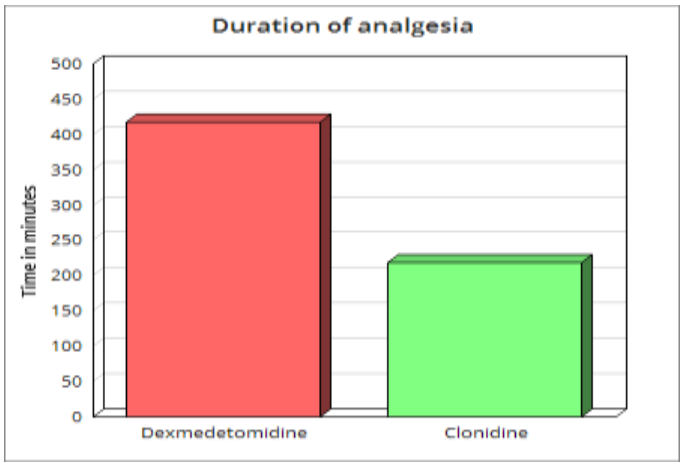
A sample size of 22 patients per group was determined through power analysis ($\alpha = 0.05$; $\beta = 0.90$) needed to detect a decrease in VAS score to ≤ 4 postoperatively with an standard deviation of 1. Therefore twenty five patients were enrolled pre group to account for drop outs.

The two groups were comparable with respect to their age, weight, sex and ASA Physical status. There was no statistically difference among two groups in demographic profile.

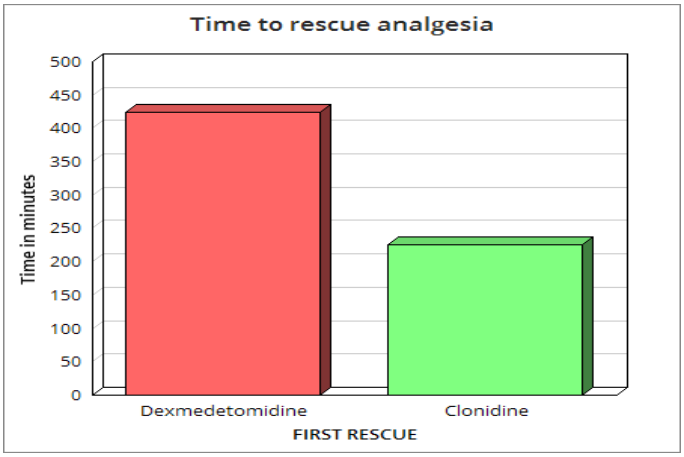
Demographic Data

	Group D	Group C	P value
Age(In years)	42.32±11.657	58.24±8.313	0.3758
Sex(M/F)	16/9	18/7	0.7157
Weight	58.24±6.514	59.2±6.298	0.001
ASA I/II	17/8	17/8	1.000

The mean ±duration of analgesia was 417.32±67.36 minutes in Group D and 217.2±25.32 minutes in Group C. There was statistically difference among two groups in the mean duration of analgesia ($p < 0.05$).



The mean duration for 1st rescue analgesia (defined as the time at which patient demands some mode of pain relief i.e when VAS more than 4) was 425.6±64.27 minutes in group D and 226±24.83 minutes in Group C. There was significant ±difference among two groups duration of time for rescue analgesia.



There was no difference in pain score at 0, 30 and 120 minutes and was found to be statistically not significant ($p > 0.05$). At 360 minutes, the mean VAS score in Group D was 0.84±0.89 and in Group C was 1.76±0.99. There was statistical significant difference in both groups ($p < 0.05$). The mean VAS score in Group D was 2.96±1.01 and in Group C was 2.08±1.07 at 720 minutes which was found to be statistically significant ($p< 0.05$). At 1440 minutes, the mean VAS score in Group D was 3.48±0.82 and in Group C was 3.52±1.04 and was found to be statistically not significant. There was no statistical difference in Ramsay Sedation Score in both groups at 0 and 60 minutes ($p >0.05$).

Visual Analogue Score (Student's t test)

Time in minutes	No. of cases	Group D Mean±SD	Group C Mean±SD	P value
0	25	0.44±0.65	0.48±0.58	0.820
30	25	0.08±0.27	0.12±0.33	0.644
120	25	0.24±0.59	0.28±0.54	0.805
360	25	0.84±0.89	1.76±0.99	0.001
720	25	2.96±1.01	2.08±1.07	0.004
1440	25	3.48±0.82	3.52±1.04	0.881

The mean sedation score in Group D was 3±0 and in Group C was 2.76±0.43 at 120 and 180 minutes which was found to be statistically significant ($p< 0.05$) At 240 and 300 minutes, the mean sedation score in Group D was 2.84±0.37 and in Group D was 2±0 minutes which was found to be statistically significant. The mean sedation score

in Group D was 2.56±0.50 and in Group C was 2±0 at 360 minutes which was found to be statistically significant (p <0.05)

The mean systolic blood pressure in Group D was 107.32±7.93mmHg and in Group C was 101.4±3.21mmHg. There was significant statistical difference in systolic blood pressure between the two groups (p <0.05). The mean diastolic blood pressure in Group D was 63.12±4.59 mmHg and in Group C was 59.36±5.04 mmHg which was found to be statistically significant (p< 0.05) The mean heart rate in Group D was 62.6±6.04 and in Group C was 58.52±6.04 which was found to be statistically significant.

Hemodynamic Parameters (Student's t test)

Group	No.of cases	Systolic BP (mmHg)	Diastolic BP (mmHg)	HR (per minute)
Group D	25	107.32±7.93	63.12±4.59	62.6±6.04
Group C	25	101.4±3.21	59.36±5.04	58.52±6.04
P value		0.0012	0.008	0.028

The incidence of hypotension in Group D was 8% and in Group C was 24% which was statistically not signifcant (p>0.05). The incidence of bradycardia in Group D was 8% and in Group C was 16% and there was statistically no significant difference in both groups (p>0.05)

The incidence of nausea and vomiting in Group C was 8% and in Group D no patient had nausea and vomiting which was statistically not significant (p>0.05). The incidence of dizziness in Group D was 8% and in Group C was 16% and there was statistically no significant difference in both groups (p>0.05). The incidence of dry mouth in Group C was 16% and in Group D, no patient had reported dry mouth. Statistically there was no significant difference in both groups (p>0.05)

The patient acceptance of the study drug in Group D found to be not satisfied, satisfied, good and excellent were 16%, 56%, 16% and 12% respectively when compared to Group C were 72%, 20%, 8% and 0% respectively. There was significant statistical difference between the two groups in the patient accceptance. (p< 0.05)

Discussion

In human beings, studies using epidural alpha 2 agonists like clonidine and dexmedetomidine have been conducted without any neurological deficit. Epidural administration of aplha 2 agonists is associated with sedation, analgesia, anxiolysis, hypnosis and sympatholysis[4-7] Clonidine has been successfully used over the last decade for the above said purpose and the introduction of dexmedetomidine has further widened the scope of alpha 2 agonists in postoperative epidural analgesia.

In our study 2mcg/kg of dexmedetomidine or 2mcg/kg of clonidine was added to 7ml of 0.125% bupivacaine (made upto 10ml with normal saline) and their efficacy as an adjuvant in postoperative epidural analgesia was studied in 50 patients who underwent upper abdominal surgery.

The demographic profile of our patients in both groups was comparable with respect to mean age, body weight, ASA physical status.

The results of our study have shown that addition of either 2mcg/kg dexmedetomidine or 2 mcg/kg clonidine as an adjuvant to epidural bupivacaine (0.125%) not only prolonged the duration of analgesia but also provided a good sedation level in the post operative period. Dexmedetomidine had a visible edge over clonidine as it enabled an earlier onset and establishment of analgesia. The addition of these two adjuvants promoted faster onset compared to established time of onset of sensory analgesia with bupivacaine alone.

This was correlated with the study done by

1. Antonio Mauro Vieira, TSA, M.D., et al[5] on epidural dexmedetomidine or clonidine in post cholecystectomy analgesia and sedation. There has been analgesia in both groups, especially at 2 and 6 hours. There has been statistically significant difference at 2, 6 and 24 hours in the dexmedetomidine group.
2. Jain et.al[20] studied the peri-operative effect of epidural dexmedetomidine with intrathecal bupivacaine on hemodynamic parameters and quality of anlgesia. They found that the duration of analgesia (424 min) in dexmedetomidine group was longer than the control group (140 min)
3. El-Henaway AM et. al[17] found that on addition of clonidine or dexmedetomidine to bupivacaine prolonged the duration of caudal analgesia in children. They administered dexmedetomidine or clonidine both in a dose of 2mcg/kg as an adjuvant with 0.125% bupivacaine caudally. They found the duration of analgesia was significantly higher in the group received bupivacaine- dexmedetomidine mixture (median 95% CI) 16 hours versus bupivacaine-clonidine mixture (median 95% CI) 5hours.
4. Neogi et. al[18] did a comparative study between clonidine and dexmedetomidine used as adjuvants to ropivacaine for caudal analgesia in paediatric patients. They compared clonidine 1mcg/kg and dexmedetomidine 1mcg/kg as adjuvants to 0.25%

ropivacaine for caudal analgesia in paediatric patients. The mean duration of analgesia was 6.32±0.46 hours in ropivacaine group, 13.17±0.68 hours in clonidine group and 15.26±0.86 hours in dexmedetomidine group.

The results of our study clearly indicates that the sedation score between the two groups was similar in the first two groups after the study drug administration and they had profund sedation but arousable by gentle tactile stimulation (i.e Ramsay sedation score of 3). After two hours, the percantage of dexmedetomidine group patients who have scored higher sedation scores is more when compared to clonidine group. But the patients remained awake but calm in both groups (Score 2). Overall the sedation score was highly significant with administration of dexmedetomidine

Jain et.al[20] assessed the sedation level following epidural administration of dexmedetomidine in their study. Most of the patients were sedated, yet arousable by verbal commands or light tactile stimulus (RSS 3-4) at 10-15 minutes following administration of dexmedetomidine in the epidural space.

Shahi et.al[19] conducted a study by comparing magnesium sulfate with dexmedetomidine – as an adjunct to epidural bupivacaine. They found that the supplementation of epidural dexmedetomidine seemed to be good alternative to epidural magnesium since it produced significantly prolonged duration of sensory and motor block and arousable sedation Grade 2 or 3 and Grade 4 as per five point scale.

In our study dexmedeomidine group showed comparatively good results over clonidine group in various characteristics like prolonged post-operative analgesia and a lesser amount of rescue anlgesia in the post-operative period. The mean time for rescue analgesia was more in group D (425±64.27 min) when compared to group C (226±24.83 min). This was well correlated with the study done by Sukhminder Jit Singh Bajwa et.al[4] They administered 17ml of 0.75% ropivacaine and 1.5mcg/kg of dexmedetomidine to group RD while group RC received 17 ml of 0.75% epidural ropivacaine and 2mcg/kg of clonidine. The time for rescue analgesia was comparatively shorter (310.76±23.75 min) in the patients who were administered clonidine ($P<0.05$).

The vital parameters remained stable through out the study period which confirms the established effects of alpha 2 agonists in providing hemodynamically stable post-operative period. Although a slight decrease in blood pressure (both systolic and diastolic) was observed in both study groups, it never fell down to more than 20% of baseline values. But hypotension and bradycardia were observed more in clonidine group patients.

Gupta K et. al[21] conducted a study on epidural 0.5% levobupivcaine in patients posted for vaginal hysterectomy. They used dexmedetomidine versus fentanyl as adjuvants to epidural levobupivacaine in their study groups. In their study the heart rate remained stable in range of 57-64 beats/min in both groups. Similarly mean arterial blood pressure decreased from baseline in both groups with maximum decline at 30-35 minutes after the epidural injection but it never went beyond the acceptable physiological limit of 65mmHg. Post-operatively heart rate and blood pressure remained stable in both groups. Jain et. al[20] found that the significant reduction in heart rate and mean arterial blood pressure within 5 minutes following epidural administration of dexmedetomidine in patients.

The side effect profile of both drugs was quiet favorable as none of the patients in either group had profound deep sedation or respiratory depression which correlates well with other studies. We observed a little higher incidence of dry mouth, nausea,vomiting and dizziness in clonidine group than dexmedetomidine group. This was not correlated with the study done by Bajwa et. al[4] on dexmedetomidine and clonidine in epdural anaesthesia-a comparative evaluation. Manal M. Kamal et.al[22] in their study on epidural morphine and dexmedetomidine in patients undergoing major abdominal surgery-as adjuvants to levobupivacaine, the side effect like pruritus was more in morphine group patients. The incidence of dry mouth was greater in levobupivacaine dexmedetomidine group.

The limitation of our study was the epidural analgesia was commenced at the end of surgery and followed up post-operatively. It would have been started before the skin incision. The peri-operative hemodynamics, surgical relaxation and requirement of other anesthetic agents can be monitored along with post-operative follow up in the future study.

Conclusion

From our study we found that 2mcg/kg of dexmedetomidine given along with 0.125% bupivacaine via epidural catheter significantly prolonged the duration of anlagesia with safety hemodynamic profile. The arousable sedation- hall mark of dexmedetomidine seemed to be better adjuvant in epidural analgesia while comparing with other agents. But further studies need to be done in the optimisation of dosage of alpha 2 agonists while via epidural route.

Source of support: Nil

Conflicts of interest: None declared

References

1. Simpson, B.R., Parkhouse, J., Marshall, R., and Lambrechts, W.(1961). Extradural analgesia and the prevention of post operative pulmonary complications.Br.J.Anaesthesia.,268.
2. Vassilakopoulos et. al 2000. Pain following upper abdominal surgery produces inspiratory muscle dysfunction Scafati A. Analgesia and alpha 2 agonists. Medens Rev 2004;4-7.

3. Sukhminder Jit Singh Bajwa et.al. Dexmedetomidine and clonidine in epidural anaesthesia. A comparative evaluation. Indian J Anaesth 2011;55(2):116-121.
4. Mauro VA, Brandao ST. Clonidine and dexmedetomidine through epidural route for post operative analgesia and sedation in Cholecystectomy. Rev Bras Anestesiol 2004;4:1-10.
5. Gabriel JS, Gordin V Alpha 2 agonists in regional anaesthesia and analgesia. Curr Opin Anaesthesiol 2001;14:751-3.
6. Hall JE, Urich TD, Barney JA, Arain SR, Ebert TJ. Sedative, amnesic and analgesic properties of small dose dexmedetomidine infusions. Anesth Analg 2000;90:699-705.
7. Hall JE, Urich TD, Ebert TJ. Sedative, analgesic and cognitive effects of clonidine infusion in humans. Br J Anaesth 2001;86:5-11.
8. Bucklin B, Eisenach JC, Tucker B. Pharmacokinetics and dynamic studies of intrathecal, epidural and intravenous dexmedetomidine. Anaesthesiology 1991;75(suppl):662.
9. Riberio RN, Nascimento JP. The use of dexmedtomidine in anaesthesiology. Rev Bras Anestesiol 2003;53:97-113.
10. Linde H e Mo. The clincal use of dexmedtomidine. Rev Bras Anestesiol 2004;54:1-4.
11. Schnaider TB,Vieira AM, Brandao AC, Lobo MV.Intraoperative analgesic effect of ketamine,clonidine and dexmedtomidine through epidural route in surgery of the upper abdomen. Rev Bras Anestesiol 2005;55:525-31.
12. Mauro VA, Brandao ST, et. al Clonidine and dexmedetomidine through epidural route for post-operative analgesia and sedation in cholecystecctomy. Rev Bras Anestesiol 2004;4:1-10.
13. Brandao ST, Mauro VA, Aguiar BA, Tontane LM. Intra-operative analgesic effect of ketamine, clonidine and dexmedetomidine, administered through epidural route in surgery of upper abdomen. Rev Bras Anestesiol 2005;55:5,525-531.
14. SA Oriol-Lopez, MD; KA Maldonado-Sanchez et.al. Epidural dexmedetomidine in regional anesthesia to reduce anxiety. Revista Mexicana de Anestesiologia 2008;31:4;271-277.
15. Milligan KR, Convey PN, Weir P. The efficacy and safety of epidural infusions of levobupivacaine with and without clonidine for post operative pain relief in patients undergoing total hip replacement. Anesth Analog 2000;91:393-7.
16. 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.
17. Mausumi Neogi et. al- A comparative study between clonidine and dexmeddetomidine used as adjuncts to ropivacaine for caudal analgesia in paediatric patients. J Anaesth Clin Pharmacol 2010;26(2):149-153.
18. Shahi.V et. al- A comparative study of magnesium sulfate vs dexmedetomidine as an adjunct to epidural bupivacaine. J Anaesthesiol Clin Pharmacol 2014;30:538-42.
19. Jain et. al- Perioperative effects of epidural dexmedetomidine with intrathecal bupivacaine on hemodynamic parameters and quality of analgesia. South Afr J Anaesth Analg 2012;18(1):105-109.
20. Gupta K et. al- Epidural 0.5% bupivacaine with dexmedetomidine versus fentanyl for vaginal hysterectomy-A prospective study. Indian J Pain 2014;28:149-154.
21. Manal M.Kamal et. al- A comparative study of eidural morphine and epidural dexmedetomidine used as adjunct to levobupivacaine in major abdominal surgery. Egyptian Journal of Anaesthesia(2014),30,137-141.
22. Saadaway I, Boker A, Elshahawy MA, Almazrooa A, Melibary S, Abdellatif AA, et.al Effect of dexmedetomidine on the characteristics of bupivacaine in a caudal block in paediatrics.Acta Anaesthesiol Scand 2009;53:251-6.
23. Rigg. J, Jamrozikk K, Myles P, et al. Epidural anaesthesia and analgesia and ooutcome of major surgery; a randomised trail. Lancet 2001;359:1276-1282.
24. Williams B, Wheatley R. Epidural analgesia for post opera/tive pain relief. Royl college of Anaesthetists Bulletin July 2000.
25. Klimscha W, Chiari, Krafft P. Hemodynamic and analgesic effects of clonidine added repetitively to contiuous epidural and spinal blocks. Anesth Analog 1997;80:322-7.
26. Fukushima K, Nishimi Y, Mori K. The effect of epidurally administered dexmedtomidine on central and peripheral nervous system in man. Anesth Analg 1997;84:S292.
27. Coskuner I, Tetkin M, Kati I. Effects of dexmedetomidine on the duration of anaesthesia and wakefulness in bupivacaaine epidural block.Eur J Anaesthesiol 2007;24:535-40.
28. Liu SS, Carpenter RL, Neal JM. Epidural anaesthesia and analgesia: their role in postoperative outcome. Anaesthesiology 1995;82:1474-506.
29. Taittonen MT, Kirvelä OA, Aantaa R, Kanto JH. Effect of clonidine and dexmedetomidine premedication on perioperative oxygen consumption and haemodynamic state. Br J Anaesth. 1997;78:400–6.
30. Veering BT. Cardiovascular and pulmonary effects of epidural anaesthesia. Minerva Anesthesiol 2003;69:433-7.
31. Kamibayashi T, Maze M. Clinical uses of alpha -2 adrenergic agonists. Anaesthesiology 2000;93:1345-9.
32. Scheininn M, Pihlavisto M. Molecular pharmacology of alpha 2 agonists. Bailliere's Clin Anaesth 2000;14:247-60.
33. Correa –Sales C. A hynpotic response to dexmedetomidine, an alpha 2 agonist, is mediated in the locus coreleus in rats.Anesthesiology 1992;76:948-52.
34. Sia AT. Optimal dose of intrathecal clonidine added to sufentanil plus bupivacaine for labour analgesia. Can J Anesth 2000;47:875-80.
35. Mato M, Perez A, Otero J, Torres LM. Dexmedetomidine, a promising drug.Rev Esp Anesthesiol Reanim 2002;49:407-20.
36. Bhana N,Goa KL. Mc Cellan KJ. Dexmedetomidine. Drugs 2000;59:263-8.
37. Wu CL. Fleisher LA: Outcomes research in regional anaesthesia and analgesia. Anesth Analg 91;1232,200.
38. Hodgson PS, Liu SS: Thoracic epidural anaesthesia and analgesia for abdominal surgery. Effects on gastrointestinal function and perfusion. Baillieres Clin Anaesthesiol 13:9,1999.
39. Wu CL,Naqibuddin M, Fleisher LA: Measurement of patient satisfaction as an outcome of regional anaesthesia and analgesia Reg Anesth Pain Med 26:196,2001.