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A COMPARATIVE STUDY BETWEEN 0.125% BUPIVACAINE WITH DEXMEDETOMIDINE VS 0.125% BUPIVACAINE WITH NALBUPHINE IN THORACIC EPIDURAL PROCEDURE FOR POST OPERATIVE ANALGESIA IN PATIENTS UNDERGOING ELECTIVE UPPER ABDOMINALSURGERY: A RANDOMIZED DOUBLE BLIND CONTROLLED STUDY.

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ABSTRACT **BACKGROUND:** The present study aims to compare analgesic efficacy between dexmedetomidine and nalbuphine as an additive to local anaesthetic for thoracic epidural procedure for postoperative analgesia in patients undergoing upper abdominal surgeries, in a randomised double blinded controlled study design.

MATERIAL AND METHOD: Sixty consented adult patient of ASAI and ASAII grade undergoing elective upper abdominal surgery were randomly allocated into three groups (n=20 each). Group P received 10ml of 0.125% epidural bupivacaine diluted with normal saline to total volume 15ml only(control), Group Q received 10ml of 0.125% bupivacaine with dexmedetomidine 1mcg/kg diluted with normal saline to total volume 15ml, Group R received 10ml of 0.125% bupivacaine with nalbuphine 0.1mg/kg diluted with normal saline to total volume 15ml, postoperatively. Patients in all three groups were assessed for pain, sedation, hemodynamic status, any side effects in postoperative period only. The primary outcome of our study was duration of analgesia while the secondary outcome being pain and sedation score, hemodynamic parameters, side effects if any. VAS (visual analog scale) and MOAA (modified observer's alertness/sedation scale) were used for assessment of pain and sedation respectively. All patient during their pre anaesthetic check-up were explained about the VAS scale and its assessment.

RESULT: The duration of analgesia between the three groups, in GROUP P it was found to be 146 ± 24.7 minutes, while in GROUP Q it was 414±72.6 minutes and in GROUP R it was 338.2 ± 63.2 minutes respectively. Thus, duration of analgesia was found to be comparatively higher in GROUP Q as compared to GROUP P and GROUP R (p value <0.0001, considered extremely significant), the duration of analgesia being the primary objective of our study. Pain score was comparable between the three groups, sedation score better in dexmedetomidine group at early hours as compared with nalbuphine and bupivacaine only group. Side-effects in dexmedetomidine group lesser as compared to nalbuphine group, while in bupivacaine only group no significant side-effects seen.

CONCLUSION: The result of this double blinded randomized controlled study revealed that epidurally administered dexmedetomidine with bupivacaine produced longer duration of postoperative analgesia as compared to epidurally administered nalbuphine with bupivacaine and bupivacaine alone. The side-effects were less and haemodynamic parameters showed much lesser variation with dexmedetomidine when compared to that of nalbuphine.

KEYWORDS : bupivacaine, nalbuphine, dexmedetomidine, duration of analgesia, VAS SCORE, MOAA SCORE, side-effects.

INTRODUCTION

Postoperative pain relief has been a subject receiving increased amount of attention for past few years. The incidence of postoperative pain varies with individual patients. Upper abdominal surgeries are associated with large surgical incision, extensive manipulation and gut handling, as a pathphysiological response to surgical stress there occurs sympathetic activation leading to hemodynamic alteration, a complex cascade of cytokine release that initiate inflammatory response at the site of injury ,thus it demands for both intra and post-operative adequate analgesia.[1]

The nociceptive signal to the central nervous system is transmitted from the site of surgery primarily by small myelinated (A-delta) and unmyelinated (C) sensory afferent fibres. Although the neural stimulus is a major release mechanism for the surgical stress response, various humoral factors also contribute to surgical stress response during major procedures. The macrophage-derived peptides like interleukins and tumour necrosis factor seem to be most important in releasing various component of stress response.[2]

Stress response to surgery produces an increased production of hormones of catabolic function which mobilizes substrate to provide energy. Increase cortisol level is related to intensity of surgical stimulus and is detected few minutes after surgery[3]. It shows metabolic effect and anti-inflammatory effect[4]. Prolactin has little metabolic activity, but it regulates T lymphocyte proliferation[5]. Metabolic responses that occur consist of initial catabolic phase for up to 2 weeks and a final anabolic phase following a major surgery. Increased level of glucocorticoid inhibits protein synthesis, limits inflammatory activity of mononuclear cells and suppresses antibody production.[6,7]

Thoracic epidural analgesia (TEA) provides good postoperative pain relief and facilitates deep breathing exercises and early ambulation. TEA also decreases the sympathetic outflow, prevents ileus, and the incidence of postoperative myocardial infarction by providing favourable redistribution of coronary blood flow, attenuating stress response, endocrine and metabolic responses and hypercoagulability.[8]

Various adjuvants have been used to prolong the duration of action, improve the quality and provide adequate analgesia through epidural route. In the present study we have compared postoperative analgesic effect between nalbuphine and dexmedetomidine in a double-blind controlled study design with 0.125% bupivacaine hydrochloride.

Nalbuphine is a mixed k-agonist and mew antagonist opioid of phenanthrene group, chemical structure is related to opioid antagonist naloxone and oxymorphone. It leads to stimulation of spinal and supraspinal opioid receptors which leads to good analgesia with minimal sedation, minimal nausea vomiting, less respiratory depression and stable cardiovascular function.[9] Dexmedetomidine is a selective alpha2 adrenergic agonist with analgesic and anxiolytic properties, it is a safe and effective adjuvant to many anaesthetic techniques such as intrathecal or epidural. Its effects are resulting from activation of alpha 2 adrenergic receptors and depending on their location; their stimulation in central nervous system result in inhibition of calcium influx in the nerve terminals with subsequent inhibition of neurotransmitter release thus facilitating analgesia[10].

MATERIALAND METHOD

The study was conducted after receiving approval from institutional ethical committee (vide notification no: MC/KOL/IEC/NON-

SPON/454/08/19) and obtaining written informed consent from patient, under the Department of Anaesthesiology, Medical College, Kolkata.

This study included 60 consented adult patients of ASA I and ASA II category who underwent elective upper abdominal surgeries, were randomly allocated into three groups of 20 each (N =20). Group P (control) received epidural bupivacaine 0.125%10ml diluted with normal saline to total volume 15ml only, Group Q received epidural bupivacaine 0.125% 10 ml with inj. Dexmedetomidine 1mcg/kg diluted with normal saline to total volume 15ml, Group R received 10ml of 0.125% bupivacaine, with inj. nalbuphine 0.1mg/kg diluted with normal saline to total volume 15ml via thoracic epidural route, postoperatively.

The inclusion criteria was-ASAI and ASAII, age group-20 to 60years, patient posted for elective upper abdominal surgeries (hepaticojejunostomy, gastrojejunostomy, opencholecystectomy, choledocholithotomy, choledochoduodenostomy/jejunostomy, hemicolectomy, Whipple's procedure). The exclusion criteria was-ASA III and ASA IV, all contraindications to epidural anaesthesia-(noncompliant patient, pre-existing coagulopathy, local site infection, spine deformity), history of opioid abuse, morbidly obese patient, allergy to any of the testing drug, patient high risk for postoperative nausea, vomiting were excluded from study.

Equipment used for study-intra venous cannula 18G, hypodermic syringes-2cc,5cc,10cc, epidural set (18G Tuohy needle, catheter, epidural filter, air syringe), standard monitoring equipment as per ASA standard -pulse oximeter, ECG, non- invasive blood pressure monitor, temperature probe and the study drugs.

On arrival to operating room standard monitors were applied to each patient. NPO status assessed. Baseline vitals (BP, HR, SPO2) obtained. Proper peripheral intravenous access done and intra venous drip commenced. A thoracic epidural catheter was inserted at T8-T9 or T9-T10 intervertebral space, with patient in sitting or lateral decubitus posture with standard aseptic precaution using a 18-G Tuohy needle via a midline approach with a loss resistance method. A test dose of 3ml of 2% lignocaine with 1:200,000 adrenaline was given for intra vascular assessment. Epidural catheter fixed aseptically and patient was then made supine.

Anaesthesia was induced after proper pre-medication and adequate preoxygenation, induction agent used as per patient's pre-anaesthetic assessment or relevant clinical history (usual drug being injection propofol2ml/kg body weight, succinyl choline 1.5mg/kg or intravenous atracurium 0.5mg/kg). Anaesthesia maintained with Sevoflurane or isoflurane with 60% nitrous oxide in oxygen titrated to maintain a Bispectral- index (BIS) value of 40-60. Maintenance muscle relaxant with top up of injection vecuronium bromide guided by EtCO2monitoring and clinical assessment, BIS value. Patients were mechanically ventilated to maintain a end-tidal carbon-dioxide between 32 and 36 mm hg. At the end of surgery residual neuromuscular blockade was reversed with neostigmine sulphate 50 mcg/kg and glycopylorrate 10 mcg/kg and then endotracheal tube was removed when TOF >0.9(assessed clinically) and BIS>80, with patient breathing adequately. Patient thereafter transferred to post anaesthesia care unit and there assessed for pain, sedation, haemodynamic parameters which were assessed at 0min(on arrival to PACU) ,30 min,1,4,8,12,18,24 hours respectively. In post- operative period patient complaining of pain corelating with VAS score > 3, the study drug was administered by an a anaesthesia resident blinded to patient's group allocation, neither patient or his/her relative nor the care giver knows about the study drug being administered or regarding the allocated patient group, it's a double blinded study carried out.

The primary outcome was duration of analgesia assessed from administration of 1st dose of study drug till the requirement of 2nd dose as assessed from VAS scale and then the study abandoned. All complications such as bradycardia, hypotension, hypoxia (spo2<92%) and respiratory depression (respiratory rate<8) were noted and promptly managed. Other adverse events or side effects like nausea, vomiting, pruritus, urinary retention were also recorded and treated accordingly.

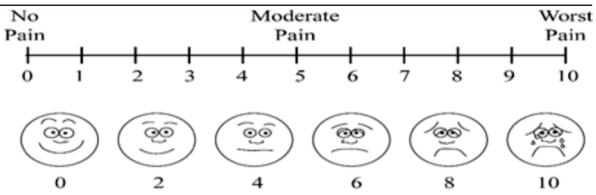

Figure 1: VAS SCORE

Score	Description
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Responds only after painful trapezius squeeze
0	No response after painful trapezius squeeze

Figure2: MOAA SCORE

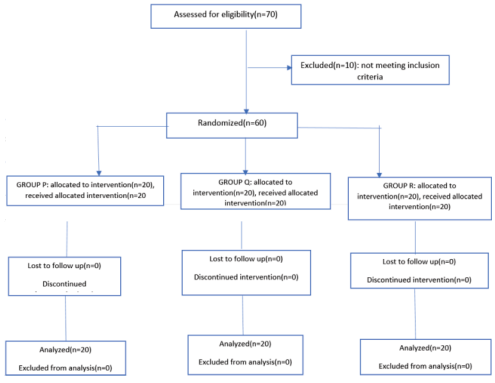

Figure 3: Consort flow chart of participation

All Compiled data were analysed by ***GRAPHPADIN STAT,*** statistical software V3. For qualitative data Fischer's exact test was used. Quantitative data was analysed with student test.

p-value was determined. p>0.05-=not significant, p<0.001=highly significant, p<0.0001 =extremely significant.

RESULTS

The study groups were matched in respect to age and sex distribution, but significant difference found in respect to weight distribution in between the three study groups, p value<0.05. In respect to mean duration of analgesia between the three groups, in GROUP P it was found to be 146 ± 24.7 minutes, while in GROUP Q it was 414±72.6 minutes and in GROUP R it was 338.2± 63.2 minutes respectively.Thus, duration of analgesia was found to be comparatively higher in GROUP Q as compared to GROUP P and GROUP R (p value <0.0001, considered extremely significant), the duration of analgesia being the primary objective of our study.

TABLE 1:

Demographic parameters Mean± SD	Group P	Group Q	Group R	P value
Age	42.2±12.4	45.9±11	46.4±13.5	0.5156
Weight	58.2±8.3	52.3±6.2	54.6±7.2	0.0427*
sex	Male-25% Female-75%	Male-5% Female-95%	Male-30% Female-70%	>0.9999
Inference: samples are age and sex match with p>0.05, however in term of body weight distribution * p<0.05 which is considered significant.				

Demographic Parameters

GROUP	Mean± standard deviation	p -value
GROUP P	146 ±24.7 minutes	p -value <0.0001 considered extremely significant.
GROUP Q	414.2±72.6 minutes	
GROUP R	338.2±63.2 minutes	

TABLE 2: Mean Duration of Analgesia in minutes

Among the secondary outcome in terms of pain and sedation score, as per VAS score assessment statistically significant difference in pain score were found at 1 hour, 4 hours and 8 hours assessment between the three study groups. At 1 hour and 4 hour assessment GROUP R was found to be at less pain as compared to GROUP Q and GROUP P while at 8 hour and 12 hour assessment GROUP Q was found to be comparatively better in pain score as compared to GROUP P and R, (p<0.0001 and <0.0003). VAS SCORE assessment in farther subsequent time interval was not much difference between the three groups (vide Table 3)

Table 3: (VAS) score

VAS score				
Time	Group P	Group Q	Group R	p value
0 minute	4.7±0.73	4.5±0.60	4.75±0.71	0.4815
30 minutes	3.65 ±0.74	3.4± 0.59	3.2±0.61	0.1035
1 hour	3.35±0.48	2.8±0.52	2.6±0.50	<0.0001*
4 hours	5.45±1.09	3.3±-0.57	2.9±0.44	<0.0001*
8 hours	6.25±0.96	3.15±0.48	3.9±0.85	<0.0001*
12 hours	6.65±0.87	5.3±0.80	6.4±1.39	0.0003*
18 hours	7.25±0.91	7.05±0.75	7.05±0.82	0.6833
24 hours	7.65±0.67	7.35±0.58	7.5±0.51	0.2870
VAS score represented over point of time data represented mean ± SD. *p value<0.05 considered statistically significant.				

In terms of sedation score, significant difference found at 0 minutes and 1-hour assessment. GROUP Q found to be more sedated than GROUP P and GROUP R at both 0 minutes and 1 hour assessment (p-value 0.0089 and 0.0240 respectively, both <0.05 considered significant), subsequent further assessments were not of much difference between the groups.(vide Table 4

MOAA (Modified observer's assessment of alertness and sedation scale)				
Time	Group P	Group Q	Group R	P value
0 minute	3.25± 0.44	2.80± 0.52	2.85±0.48	0.0089*
30 minutes	3.55±0.60	3.20±0.41	3.50±0.51	0.0761
1 hour	4.15±0.48	3.70±0.47	3.90±0.55	0.0240*
4hours	4.30±0.47	4.00±0.45	4.15±0.36	0.1011
8 hours	4.55±0.51	4.20±0.52	4.55±0.51	0.0535
12 hours	4.90±0.30	4.70±0.47	4.85±0.36	0.2444
18 hours	4.95±0.22	4.80±0.41	4.90±0.30	0.3341
24 hours	5.00±0.00	4.85±0.36	4.95±-0.22	0.1589
Post- operative MOAA score over time points, data presented as mean ± SD. *p value<0.05 considered statistically significant.				

Table 4: Modified observer's assessment of alertness and sedation score

Haemodynamic parameters comparison between the three study groups revealed that heart rate fluctuation between three study groups were not very much significant with incidence of bradycardia occurring in only 1 patient in Group Q and 2 patients in Group R. In terms of mean arterial pressure no significant difference seen between study groups except hypotension developed in only one patient in Group Q (figure 4 and figure 5). Comparison of side effects between the study groups revealed nausea, vomiting incidence higher in GROUP R as compared to GROUP P and GROUP Q, incidence of pruritus 10%(2 out of 20) in GROUP R while the incidence of hypotension 5%(1 out of 20) seen in GROUP Q. Bradycardia occurred in 1 patient in GROUP Q, incidence 5% and in 2 patient in GROUP R, incidence being 10%. No significant respiratory depression or severe degree of adverse effect seen in any group.

Table 5: comparison of side-effects between the study groups

Side effects	Group P		Group Q		Group R	
	No of patients	(%)	No of patients	(%)	No of patients	(%)
Pruritus	0	0	0	0	2	10%
Nausea	0	0	1	5%	2	10%
Vomiting	1	5%	2	10%	4	20%
Hypotension	0	0	1	5%	0	0
Bradycardia	0	0	1	5%	2	10%
Respiratory depression	0	0	0	0	0	0

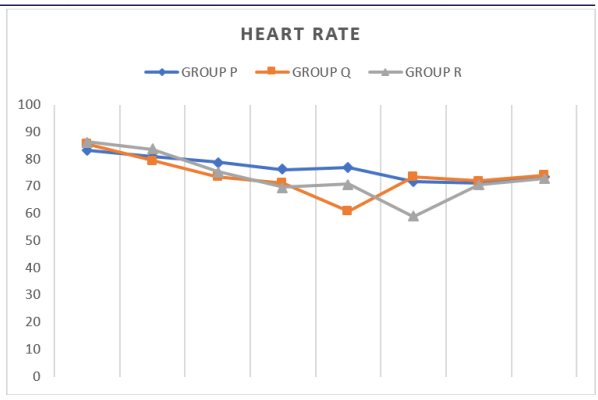

Figure 4: Heart Rate Comparison Between Study Group

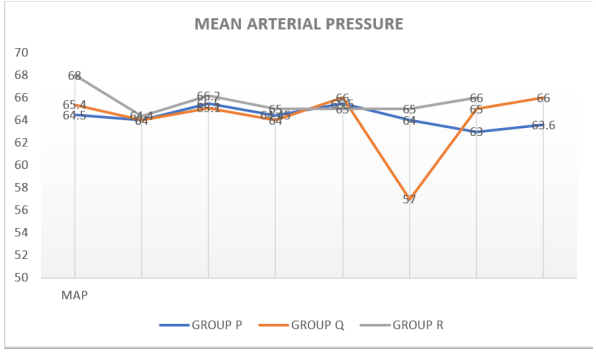

Figure 5: Comparison Of Mean Arterial Pressure Between Study Groups

DISCUSSION

In the present study we have compared the duration of analgesia, primary outcome and secondary outcomes like side effects, pain , sedation score and haemodynamic parameters between three study groups, Group P, Group Q, Group R. Total 60 patients were randomly allocated into three groups of 20 each(n=20).

The same volume of drug was administered in all three groups. Group P received 10ml, 0.125% plain bupivacaine diluted with normal saline to 15ml, Group Q received 10 ml, 0.125% bupivacaine with dexmedetomidine 1mcg/kg dilute with NS to 15ml, Group R received 10 ml 0.125% bupivacaine with nalbuphine 0.1mg/kg diluted with NS to 15ml via epidural route in postoperative period based on pain intensity assessed by VAS score. All the patients were followed up in postoperative period at 0 min, 30 mins, 1,4,8,12,18 and 24 hours and corresponding study parameters were assessed accordingly.

Salama A.K et al studied the effectiveness and duration of postoperative analgesia between caudal dexmedetomidine and nalbuphine in children undergoing hypospadias surgery in a double blind controlled study and found that the duration of analgesia was found to be longer in dexmedetomidine group as compared to nalbuphine group.[11]

In our study the mean duration of analgesia found to be higher in Group Q, received epidural dexmedetomidine (414.2±72.6 minutes) as compared to Group R, received epidural nalbuphine (338.2±-63.2 minutes) and Group P, received plain bupivacaine only.(146 ±-24.7 minutes). So our also yields similar result like that of Salama et al study.

In a study performed by Murthy K.S et al between caudal dexmedetomidine with ropivacaine and caudal nalbuphine with ropivacaine, they found that there was prolongation of duration as well as quality of analgesia with caudal dexmedetomidine with ropivacaine as compared to caudal nalbuphine with ropivacaine without any significant difference in haemodynamic parameters.[12]

In our study similar result obtained with thoracic epidural administration of dexmedetomidine with 0.125% bupivacaine and nalbuphine with 0.125% and plain bupivacaine 0.125%. The haemodynamic alteration was also not much significant difference

with minor incidence of hypotension in 1 patient in Group Q and incidence of bradycardia in 2 patients of Group R respectively.

A study conducted by Sateesh P.K et al on duration of analgesia between epidural dexmedetomidine with 0.5% bupivacaine and 0.5% bupivacaine with normal saline found that the onset of analgesia early as well as prolongation of duration of analgesia in dexmedetomidine group as compared to 0.5% bupivacaine with normal saline only[13]. Result of this study is in line with the result of our present study.

In a study done on postoperative analgesia with three different doses of injection nalbuphine hydrochloride 10,20,30 mg via epidural route in patient undergoing caesarean delivery under epidural anaesthesia with lidocaine 2% with adrenaline vs 3% chloroprocaine, the duration of analgesia following lidocaine anaesthesia with nalbuphine post op epidural 10,20 ,30 mg were 77min,205 min,185 min respectively while in chloroprocaine anaesthesia group VAS remain elevated , with mean duration of analgesia 30-40 min and did not differ among three doses of nalbuphine[14]. In our present study we found the mean duration of analgesia with 0.1 mg/kg nalbuphine with 0.125% bupivacaine to be 338.2±-63.2 minutes.

In a meta-analysis of 15 randomized control trial for comparison of analgesic effect of nalbuphine with morphine by Zheng et al found that the analgesic efficacy of nalbuphine comparable to morphine but with lesser side effects than morphine[15]. In our study the quality of analgesia of nalbuphine was comparable to dexmedetomidine but in term of duration of analgesia dexmedetomidine offers an upper hand over nalbuphine. In term of side effects dexmedetomidine has lesser adverse effect as compared to nalbuphine like pruritus, nausea, vomiting, bradycardia.

In a RCT study by Fatemah et al between dexmedetomidine vs morphine as adjuvant to epidural bupivacaine in orthopaedic surgery, dexmedetomidine offered a longer duration of analgesia along with faster sensory and motor blockade as compared to morphine[16]. However, in our study, pain score of nalbuphine was comparable to that of dexmedetomidine but in terms of duration of analgesia dexmedetomidine found to be superior to nalbuphine.

Another randomized prospective study on epidural bupivacaine with fentanyl and epidural bupivacaine with dexmedetomidine revealed dexmedetomidine associated with faster onset of and prolonged sensory and motor blockade with less requirement of rescue analgesia as compared to fentanyl.[17]In our study similar effect of prolonged analgesia obtained with dexmedetomidine when compared to nalbuphine and plain bupivacaine only.

CONCLUSION

The result of this double blinded randomized controlled study revealed that epidurally administered dexmedetomidine with bupivacaine produced longer duration of postoperative analgesia as compared to epidurally administered nalbuphine with bupivacaine and bupivacaine alone. The side-effects were less and haemodynamic parameters showed much lesser variation with dexmedetomidine when compared to that of nalbuphine. So we can say epidurally administered dexmedetomidine offers more advantage over nalbuphine in terms of duration of analgesia and safety profile of patient.

REFERENCES

1. Triin Jakobson , Juri Karjagin , Liisa Vipp , Martin Padar , Ants-Hendrik Parik , Liis Starkopf , Hartmut Kern , Olavi Tammik , Joel Starkopf: Postoperative complications and mortality after major gastrointestinal surgery, Volume 50, Issue 2, 2014, Pages 111-117.
2. H. KEHLET: SURGICAL STRESS THE ROLE OF PAIN AND ANALGESIA, Br. J. Anaesth. (1989), 63, 189-195.
3. Desborough, J.P., The stress response to trauma and surgery. Br J Anaesth, 2000. 85(1): p. 109-17.
4. Nicholson, G., J.M. Burrin, and G.M. Hall, Peri-operative steroid supplementation. Anaesthesia, 1998. 53(11): p. 1091-104.
5. Clevenger, C.V., et al., Regulation of interleukin 2-driven T-lymphocyte proliferation by prolactin. Proc Natl Acad Sci U S A, 1990. 87(16): p. 6460-4
6. Singer, M., et al., Multiorgan failure is an adaptive, endocrine-mediated, metabolic response to overwhelming systemic inflammation. Lancet, 2004. 364(9433): p. 545-8.
7. Hill, A.G. and G.L. Hill, Metabolic response to severe injury. Br J Surg, 1998. 85(7): p. 884-90
8. Siriussawakul A, Suwanpratheep A. Epidural Analgesia for Perioperative Upper Abdominal Surgery. In: Fyneface-Ogan S, editor Epidural analgesia - Current views and approaches. Croatia: InTech; 2012. P. 43–54.
9. Pouzeratte Y, Delay JM, Brunat G, Boccara G, Vergne C, Jaber S, et al. Patientcontrolled epidural analgesia after abdominal surgery: ropivacaine versus bupivacaine. Anesthesia & Analgesia 2001;93: 1587–92.
10. Salama et al. Comparison between caudal dexmedetomidine and nalbuphine: Pediatric Anesthesia and Critical Care Journal 2016;4(1):48-54
11. A. K. Salama, D. Galante, N. M. Abdallah: Comparison between caudal dexmedetomidine and nalbuphine: Pediatric Anesthesia and Critical Care Journal 2016;4(1):48-54
12. Shiva Keshava Murthy, Geeta Bhandari, Kedar S. Shahi2 and Gyan Chand Comparative study between Nalbuphine and Dexmedetomidine as an adjuvant to Ropivacaine for Caudal Block in children undergoing infra umbilical surgeries, International Journal of Biomedical and Advance Research 2018; 9(4): 157-161.
13. P. Sateesh Kumar, B. Annapurna Sarma, D. B. V. Madhusudhana Rao, K. Aparanji COMPARISON OF NALBUPHINE WITH 0.5% BUPIVACAINE AND NORMAL SALINE WITH 0.5% BUPIVACAINE FOR POST-OPERATIVE EPIDURAL ANALGESIA, J of Evolution of Med and Dent Sci/ eISSN- 2278-4802, pISSN- 2278-4748/ Vol. 4/ Issue 48/ June 15, 2015
14. William R et al : Epidural nalbuphine following caesarean delivery; Canadian journal Anaesthesia 1991/38 :6/ pp 728-732.
15. Zheng Zeng, Jianhua Lu1, Chang Shu, Yuanli Chen, Tong Guo, Qing-ping Wu, Shang-long Yao & Ping Yin: A Comparision of Nalbuphine with Morphine for Analgesic Effects and Safety : Meta-Analysis of Randomized Controlled Trials, Scientific Reports | 5:10927 | DOI: 10.1038/srep10927
16. Fatemeh Moftakhar et al : Comparison of Dexmedetomidine and Morphine as Adjuvants to Bupivacaine for Epidural Anesthesia in Leg Fracture Surgery: Randomized Clinical Trial, Anesth Pain Med. 2019; 9(4):e91480.
17. Neha Nupoor , Anand T Talikoti , Ramesh Kumar PB , Dinesh :Epidural Bupivacaine with Dexmedetomidine or Fentanyl for Lower Abdominal and Lower Limb Surgeries - A Randomized Prospective Study, J Clin Biomed Sci 2016; 6(1):14-19.