A comparative study of the effect of caudal dexmedetomidine versus morphine added to bupivacaine in pediatric infra-umbilical surgery

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ABSTRACT

Background: One of the most commonly used regional anesthetic techniques in pediatric surgeries is the caudal epidural block. Its main disadvantage remains the short duration of action. Hence, different additives have been used. Dexmedetomidine is a potent as well as highly selective α2 adrenergic receptor agonist. The aim of this randomized, double-blinded, study was to compare the duration of postoperative analgesia of caudal dexmedetomidine versus morphine in combination with bupivacaine in pediatric patients undergoing lower abdominal or perineal surgery. **Patients and Methods:** A total of 50 pediatric patients 1-5 years old The American Society of Anesthesiologists status I, II scheduled for lower abdominal and perineal surgeries were included in the study. The patients were enrolled into 2 equal groups: Group A patients (n = 25) received dexmedetomidine with bupivacaine while Group B patients (n = 25) received morphine with bupivacaine. Patients were placed in a supine position then inhalational general anesthesia was induced, and laryngeal mask airway (LMA) was placed. Patients were then given caudal epidural analgesia. By the end of surgery reversal of muscle relaxation was done and the LMA was removed. Post-operatively, the sedation as well as pain score were observed and recorded. **Results:** The current study showed that minor complications were recorded in the post-anesthesia care unit; in addition, significantly longer periods of analgesia and sedation were detected in Group A. However, no significant differences in demographic data, as well as in the duration of surgery, and the time of emergence from anesthesia and patient condition during recovery were detected. **Conclusion:** The present study suggested that use of dexmedetomidine, during single dose injection, as an additive to the local anesthetic bupivacaine in caudal epidural analgesia prolongs the duration of post-operative analgesia following lower abdominal as well as perineal surgery compared with caudal morphine with no side-effects on the vital signs. Postoperative side effects were seen with caudal morphine injection rather than with dexmedetomidine.

Key words: *Bupivacaine, caudal block, dexmedetomidine, postoperative analgesia*

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INTRODUCTION

Being unpleasant, pain is a subjective sensation, which in children can only be experienced and not expressed, because they depend on their care-givers for their well-being.[1] Over the recent years, the concept of providing adequate post-operative analgesia in pediatric patients is well established, however, various methods showed side-effects limiting their use such as respiratory depression with IV opioids. With a high success rate, caudal analgesia was proved to be a simple and effective technique in children. In spite of using long acting local anesthetics, the main disadvantage of caudal analgesia remains the relatively short duration of action.[2] The use of caudal epidural catheter was a suggested solution to administer a continuous infusion or repeated top up doses, but concerns are available regarding the risk of infection. Hence different additives have been used in order to improve the duration of action as well as the quality of analgesia of the local anesthetic used in the single shot caudal block technique such as opioids, epinephrine, clonidine, ketamine and neostigmine.[3]

Access this article online	
Quick Response Code:	Website: www.saudija.org
	DOI: 10.4103/1658-354X.130677

Dexmedetomidine is a potent as well as highly selective α2 adrenergic agonist having a sedative, sympatholytic and analgesic effect and have been described as a safe and effective additive in many anesthetic applications and analgesic techniques.[4] Its use was approved by the American food and drug administration at the end of 1999. The physiological response resulting from the stimulation of α2 adrenergic receptors vary and depend on their location, in the nervous system their stimulation decreases calcium entry in the nerve terminals resulting in an inhibitory effect on the neurotransmitter release thus facilitating analgesia.[5] Dexmedetomidine has, as much as, eight folds more stronger affinity to α2 adrenergic receptors and lower affinity to α1 receptors than clonidine, besides its great advantage in having higher selectivity to α_{2A} adrenergic receptors, responsible for the analgesic effect of such drugs, compared with clonidine.[6]

In 1981, Jensen was first to describe the use of epidural morphine, after which several studies provided evidence of profound analgesia with its use, but unfortunately with number of side-effects including nausea and vomiting, urine retention, pruritus and hypoventilation, the most serious of which is the respiratory depression in adults and children.[7] The aim of this randomized, double-blinded, study was to compare the duration of post-operative analgesia, sedation, as well as the incidence of any side effect of single dose caudal dexmedetomidine versus morphine in combination with bupivacaine in pediatric patients undergoing lower abdominal or perineal surgery.

PATIENTS AND METHODS

After obtaining approval from the Clinical Research Ethics Committee of Erfan and Bagedo General Hospital and obtaining informed consent from the parents or guardian. A total of 50 pediatric patients with aged range between 1 and 5 years old, The American Society of Anesthesiologists (ASA) physical status I, II of both sex scheduled for lower abdominal surgeries, e.g., hernia and perineal surgeries, e.g., undescended testis and hypospadius were included in the study. The patients were randomized in a double blinded fashion using closed envelop method to get enrolled into 2 equal groups: Group A patients (n = 25) received single dose caudal epidural analgesia using dexmedetomidine with bupivacaine, whereas Group B patients (n = 25) received single dose caudal epidural analgesia using morphine with bupivacaine. Exclusion criteria included history of mental retardation or delayed development that may interfere with pain intensity assessment, known or suspected coagulopathy, any congenital anomalies of the sacrum, any infection at the site of injection, known or suspected allergy to any of the studied drugs.

All patients were premedicated with ketamine 1 mg/kg and 0.01 mg/kg atropine I.M. 30 min before shifting to OR. Patients were kept fasting according to the ASA guidelines for water 2 h, breast milk 4 h, and infantile formula or light meals for 6 h. On arrival to the operating theatre, the standard monitors were applied including non-invasive blood pressure, electrocardiography and pulse oximetry. Patients were placed in a supine position then inhalational general anesthesia was induced using 8% sevoflurane in 100% oxygen, and a 24 G IV line was inserted. Atracurium 0.5 mg/kg was given IV, and then laryngeal mask airway (LMA) of the appropriate size was placed. Anesthesia was maintained using sevoflurane 1% in 50% nitrous oxide in oxygen with controlled mechanical ventillation. Thereafter, patients were placed in a lateral position and the skin of the back over the sacrum was scrub using povidone iodine solution, and under strict aseptic precautions single dose caudal epidural injection was done using 25 G needle. Proper position of the needle was confirmed by the pop sensed during penetration of the sacro-coccygeal ligament, which was followed by the whoosh test[8] done using 0.5 ml of air. After needle insertion and negative aspiration of blood or cerebrospinal fluid, patients of Group A were given dexmedetomidine (prcedex 100 μg/mL parenteral preparation (Hospira®) 2 μg/kg in 1 ml/kg bupivacaine 0.25%, whereas patients of Group B were given morphine 30 μg/kg in 1 ml/kg bupivacaine 0.25%. Intravenous fluid volume was maintained using lactated ringer solution 4 ml/kg/h. The mean arterial pressure (MAP), heart rate (HR), and peripheral oxygen saturation (SPO_2), as well as end tidal CO_2 were recorded every 5 min all through the surgery and sevoflurane level was adjusted to maintain the baseline MAP and any intraoperative increase of MAP or HR more than 20% of the base line was considered as in adequate analgesia and was managed by fentanyl 1 μg/kg IV. By the end of surgery, all patients were given ondansetron 0.08 mg/kg IV, and then reversal of muscle relaxation was done by atropine 0.02 mg/kg and neostigmine 0.05 mg/kg IV. On return of spontaneous ventilation the LMA was removed and patient was shifted to the post-anesthesia care unit (PACU). The time of surgery was recorded, in addition to the emergence time from anesthesia (defined as the time from end of surgery and closure of sevoflurane until removal of LMA). All physicians, anesthetist and surgeon and pediatrician, as well as patients' parents or guardians were blinded to the caudal medication administered and the master codes were kept with a person that does not share in the collection or analysis of the results.

In the PACU, the patient condition during recovery was assessed by a four point sedation score such that:

1. Alert and calm,
2. Sleepy but verbally arousable,
3. Sleepy but aroused by physical stimulus,

4. Deeply asleep, whereas, the duration of sedation was defined to be the time elapsed between the injection of the test drug until the patient sedation score becomes equal or less than 2. Pain was assessed by the pediatric observational 10-point scale "Face, Leg, Activity, Cry, Consolability (FLACC) pain score[9] [Table 1], and duration of post-operative analgesia was defined to be the elapsed time between drug injection and a patient FLACC score equal or more than 4. Patients with pain score ≥4 were given rescue analgesia of acetaminophen 20 mg/kg suppository. Post-operatively, the sedation as well as pain score were observed and recorded every hour for the first 24 h. Any side-effect including vomiting, itching, respiratory depression (oxygen saturation <95%), hypotension (20% decrease from the baseline) and bradycardia (HR <60 beats/min) were also recorded.

Data were analyzed using computer statistical software system SPSS version 12.0 (SPSS Inc., Chicago, IL, USA). The data was expressed as mean or median ± standard deviation or range as appropriate. Patient characteristics and duration of sedation and analgesia were compared using unpaired *t*-test. Although the incidence of side-effects and other categorical data such as age and sex were compared between the groups using Mann-Whitney U test. $P \leq 0.05$ was considered to be statistically significant. The power analysis was performed on the basis of the duration of analgesia for dexmedetomidine and morphine as the primary outcome, with an expected mean value of 14.5 (4.1) and 10.9 (3.4) respectively, which indicated a sample size of 24 subjects per group to achieve a difference of 4 h, with an α error <0.05 and β error 0.2 and power of 80%.[1,10] Sample size calculation was done by PASS software program (Power Analysis and Sample Size calculation) by NCSS, LLC, USA.

RESULTS

The current study showed no significant differences in demographic data including age, sex; body weight between the two groups, furthermore, no significant differences was detected between Group A and B in the type of surgery as well as the duration of surgery as shown in Table 2. Moreover, no rescue analgesia intra-operatively (fentanyl) or post-operatively (acetaminophen) was given to patients of both groups.

Regarding the vital signs and hemodynamic stability intra-operatively, the recorded MAP, HR as well as the SPO_2 showed no statistically significant difference between both groups as shown in Figure 1. Moreover, the incidence of complications in the PACU after recovery revealed only one patient (4%) of Group A had vomiting, while in Group B, 4 patients (16%) had vomiting, 4 patients (16%) developed itching and 2 patients (8%) developed SPO_2 <95% with no significant difference among Group A and B, and similarly patients revealed no significant difference as regards the time of emergence from anesthesia and patient condition during recovery as indicate in Table 3.

Table 1: Face, leg, activity, cry, consolability pain score

Parameter	Finding	Points
Face	No expression or smile	0
	Occasional grimace or disinterested	1
	Quivering chin or clenched jaw	2
Leg	Normal position or relaxed	0
	Restless tense	1
	Kicking or legs drawn up	2
Activity	Lying quietly, normal position	0
	Shifting back and forth, tense	1
	Arched, rigid or jerking	2
Cry	No cry (awake or asleep)	0
	Moans or whispers occasionally	1
	Crying steadily or screams	2
Consolability	Content relaxed	0
	Reassured by occasional touching or hugging	1
	Difficult to console or comfort	2

Table 2: Demographic and operative data

	Group A (*n* = 25) (%)	Group B (*n* = 25) (%)
Age (year)	3.6±1.3	3.4±1.9
Gender (M/F)	18/7	16/9
Body weight (kg)	13.3±30	13.6±28
Duration of surgery (min)	61±26	63±24
Type of surgery		
Inguinal hernia	12 (48)	10 (40)
Hypospadius	8 (32)	9 (36)
Undescended testis	4 (16)	4 (16)
Urethroplasty	1 (4)	2 (8)

Values are expressed as mean ± SD. No significant differences between the two groups ($P > 0.05$). SD: Standard deviation

Table 3: Patient emergence time, emergence condition and side effects in the PACU

	Group A (*n* = 25) (%)	Group B (*n* = 25) (%)
Emergence score	1.5±0.7	3.6±0.3
Emergence time (min)	5.1±1.6	4.3±1.1
Side-effects in PACU		
Nausea and vomiting	1 (4)	4 (16)
Hypotension	0 (0)	0 (0)
Bradycardia	0 (0)	0 (0)
Itching	0 (0)	4 (16)
Respiratory depression (SPO_2 <95%)	0 (0)	2 (8)

Values are expressed as mean ± SD. No significant differences between the two groups ($P > 0.05$). PACU: Post-anesthesia care unit, SD: Standard deviation

As regards the total duration of postoperative analgesia as indicated by FLACC score which gets equal or more than 4, it was found to be significantly longer in Group A (17.3 ± 1.6) compared with Group B (9.9 ± 1.2) $P < 0.001$, furthermore, patients of Group B showed a shorter sedation time (3.2 ± 0.6) compared with that of Group A (6.2 ± 0.5) which was statistically significantly different $P < 0.001$ [Figure 2].

DISCUSSION

In the present study, we found that the use of dexmedetomidine, during single dose injection, as an additive to the local anesthetic bupivacaine in caudal epidural analgesia prolongs the duration of postoperative analgesia following lower abdominal as well as perineal surgery compared with caudal morphine; furthermore, the duration of sedation was found to be longer with dexmedetomidine than with morphine with no side-effects on the vital signs, or rescue analgesia requirement. However, the emergence time from anesthesia and the condition of patients during recovery showed no difference. Postoperative side effects, including vomiting, itching and respiratory depression, were recorded in the PACU with morphine rather than dexmedetomidine.

Caudal epidural analgesia is a widely used technique for providing regional anesthesia and analgesia in children undergoing infra umbilical and lower limb surgeries and to prolong its effect wide range of additives have been used in combination with local anesthetics to promote analgesia.[11] The use of additives during caudal anesthesia have increased in the last decade by 58%,[12] specially with ketamine 38% and clonidine 42%, whereas the use of opioids as additives has decreased from 36% to 18% due to the higher incidence of side-effects as nausea and vomiting, itching and respiratory depression specially in children.[13,14] Dexmedetomidine, potentiates the action of local anesthetics without increasing the incidence of side-effects and compared to clonidine it's a highly selective α2 adrenergic receptor agonist, and this facilitates its use in larger doses for analgesia and sedation without the fear of inadvertent effects on the hemodynamics.[15]

Supporting the results of the present study was the results of El-Hennawy *et al.*,[16] who compared the use of single dose caudal epidural injection of dexmedetomidine or clonidine or placebo (normal saline) added to bupivacaine, and proved that the duration of analgesia was found to be significantly prolonged with dexmedetomidine, and to a lesser extent with clonidine than with plain bupivacaine, without any increase in the incidence of side-effects. Furthermore Demiraran *et al.*[17] in their study on the use of single dose epidural morphine versus tramadol for postoperative analgesia in pediatric surgery showed that the incidence of side effects as respiratory depression, itching, skin rash and vomiting was higher with morphine. Furthermore, in a study of the effect of caudal dexmedetomidine by Xiang *et al.*, they concluded that the supplementation of caudal bupivacaine with dexmedetomidine reduces the response to hernia sac traction in the inguinal hernia repair in paediatric surgery, besides it prolongs the duration of postoperative analgesia.[18] Neogi *et al.* studied the effect of caudal dexmedetomidine added to ropivacaine 0.25% against caudal clonidine with ropivacaine for postoperative analgesia in children and found out that the duration of analgesia was prolonged for both drugs when compared with ropivacaine alone with good hemodynamic stability,

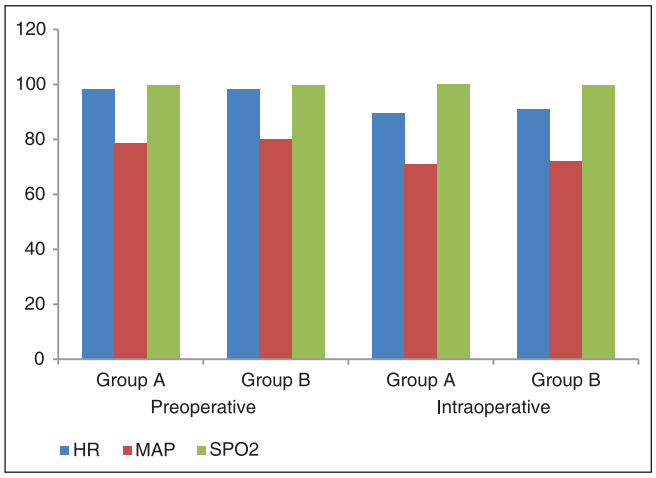

Figure 1: The mean arterial pressure, heart rate, peripheral oxygen saturation recorded pre-operative and intra-operative. •No significant difference ($P > 0.05$)

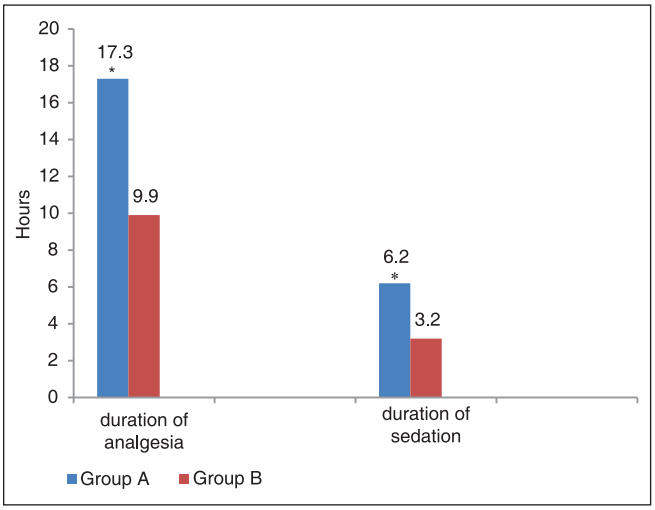

Figure 2: The duration of analgesia, as well as the duration of sedation of both groups. *Indicates significant difference ($P < 0.001$)

moreover, they detected no side-effects for both drugs.[19] In addition, in another study performed by Anand *et al.* they studied the effect of adding dexmedetomidine to caudally injected ropivacaine on the intensity of post-operative analgesia, and its safety in the children performing abdominal surgeries, and their results indicated that dexmedetomidine achieved a remarkable relief of post-operative analgesia leading to better quality of sleep and minimal agitation during recovery from anesthesia, but unlike the present study, they reported a prolonged postoperative sedation.[1]

On the contrary to our study, Singh *et al.* compared the use of caudal clonidine versus morphine with bupivacaine, and showed a longer duration of analgesia as well as sedation with morphine in pediatric patients undergoing upper abdominal surgery than the duration in the present study, in addition to, a lower incidence of post-operative complications than the results of the present study.[10] Moreover, Luz *et al.* in their study of the effect of clonidine versus morphine added to bupivacaine when given caudally to improve postoperative analgesia in children undergoing lower abdominal surgery as orchidopexy, they suggested that the duration of analgesia achieved postoperatively was comparable between both drugs with no significant difference, and this may be explained by the use of the higher selective α2 agonist dexmedetomidine in the present study beside using it in a higher dose (2 μg/kg).[20] Furthermore unlike the results of the current study, Vetter *et al.* compared single dose injection of morphine, clonidine or hydromorphone combined with ropivacaine caudally in pediatric surgery, and concluded that caudal morphine produced a better quality and sustained analgesia with no difference in the pain scores among the patients.[21] However supporting the results of the current study was that of Nasr and Abdelhamid who studied the effect of caudal dexmedetomidine versus fentanyl with bupivacaine on the stress response and post-operative analgesia in pediatric cardiac surgery, and found that dexmedetomidine attenuated the stress response and produced better analgesia, yet in their study they used lower dose of dexmedetomidine and the shorter acting opioid, fentanyl, compared with the current study, furthermore they showed a significant drop in the MAP and HR after caudal injection unlike in the results of the current study.[22] Likely to our study, Saadawy *et al.*, who studied the effect of dexmedetomidine on bupivacaine characteristics in caudal block, found no significant changes in the hemodynamics among their groups and prolonged postoperative analgesia with dexmedetomidine compared to bupivacaine alone.[23]

CONCLUSION

The results of this clinical study showed that the addition of dexmedetomidine to local anesthetic bupivacaine for single dose caudal analgesia produced longer postoperative analgesia with fewer side-effects in children undergoing lower abdominal surgery when compared with morphine, with better emergence from anesthesia and hemodynamic stability. However, further studies are still required to evaluate the effect of dexmedetomidine with other local anesthetics, and compared with other opioids, as well as, its use in infusion or different concentration for a longer duration of time.

REFERENCES

1. Anand VG, Kannan M, Thavamani A, Bridgit MJ. Effects of dexmedetomidine added to caudal ropivacaine in paediatric lower abdominal surgeries. Indian J Anaesth 2011;55:340-6.
2. Cook B, Doyle E. The use of additives to local anesthetic solutions for caudal epidural blockade. Paediatr Anaesth 1996;6:353-9.
3. Abdulatif M, El-Sanabary M. Caudal neostigmine, bupivacaine, and their combination for postoperative pain management after hypospadias surgery in children. Anesth Analg 2002;95:1215-8, table of contents.
4. Carollo DS, Nossaman BD, Ramadhyani U. Dexmedetomidine: A review of clinical applications. Curr Opin Anaesthesiol 2008;21:457-61.
5. Haselman MA. Dexmedetomidine: A useful adjunct to consider in some high-risk situations. AANA J 2008;76:335-9.
6. Asano T, Dohi S, Ohta S, Shimonaka H, Iida H. Antinociception by epidural and systemic alpha(2)-adrenoceptor agonists and their binding affinity in rat spinal cord and brain. Anesth Analg 2000;90:400-7.
7. Semsroth M, Gabriel A, Sauberer A, Wuppinger G. Regional anesthetic procedures in pediatric anesthesia. Anaesthesist 1994;43:55-72.
8. Lewis MP, Thomas P, Wilson LF, Mulholland RC. The 'whoosh' test. A clinical test to confirm correct needle placement in caudal epidural injections. Anesthesia 1992;47:57-8.
9. Merkel SI, Voepel-Lewis T, Shayevitz JR, Malviya S. The FLACC: A behavioral scale for scoring postoperative pain in young children. Pediatr Nurs 1997;23:293-7.
10. Singh R, Kumar N, Singh P. Randomized controlled trial comparing morphine or clonidine with bupivacaine for caudal analgesia in children undergoing upper abdominal surgery. Br J Anaesth 2011;106:96-100.
11. Peutrell JM, Mather SJ. Regional anesthesia for babies and children. Oxford: oxford university press 1997; 187-233.
12. Menzies R, Congreve K, Herodes V, Berg S, Mason DG. A survey of pediatric caudal extradural anesthesia practice. Paediatr Anaesth 2009;19:829-36.
13. Lönnqvist PA, Ivani G, Moriarty T. Use of caudal-epidural opioids in children: Still state of the art or the beginning of the end? Paediatr Anaesth 2002;12:747-9.
14. Lönnqvist PA. Adjuncts to caudal block in children — Quo vadis? Br J Anaesth 2005;95:431-3.
15. Yoshitomi T, Kohjitani A, Maeda S, Higuchi H, Shimada M, Miyawaki T. Dexmedetomidine enhances the local anesthetic action of lidocaine via an alpha-2A adrenoceptor. Anesth Analg 2008;107:96-101.
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. Demiraran Y, Kocaman B, Akman RY. A comparison of the postoperative analgesic efficacy of single-dose epidural tramadol versus morphine in children. Br J Anaesth 2005;95:510-3.
18. Xiang Q, Huang DY, Zhao YL, Wang GH, Liu YX, Zhong L, *et al*. Caudal dexmedetomidine combined with bupivacaine inhibit the response to hernial sac traction in children undergoing inguinal hernia repair. Br J Anaesth 2013;110:420-4.
19. Neogi M, Bhattacharjee DP, Dawn S, Chatterjee N. A comparative study between clonidine and dexmedetomidine used as adjuncts to ropivacaine for caudal analgesia in paediatric patients. J Anaesthesiol Clin Pharmacol 2010;26:149-53.
20. Luz G, Innerhofer P, Oswald E, Salner E, Hager J, Sparr H. Comparison of clonidine 1 microgram kg-1 with morphine 30 micrograms kg-1 for post-operative caudal analgesia in children. Eur J Anaesthesiol 1999;16:42-6.
21. Vetter TR, Carvallo D, Johnson JL, Mazurek MS, Presson RG Jr. A comparison of single-dose caudal clonidine, morphine, or hydromorphone combined with ropivacaine in pediatric patients undergoing ureteral reimplantation. Anesth Analg 2007;104:1356-63, table of contents.
22. Nasr DA, Abdelhamid HM. The efficacy of caudal dexmedetomidine on stress response and postoperative pain in pediatric cardiac surgery. Ann Card Anaesth 2013;16:109-14.
23. Saadawy 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 pediatrics. Acta Anaesthesiol Scand 2009;53:251-6.

How to cite this article: El Shamaa HA, Ibrahim M. A comparative study of the effect of caudal dexmedetomidine versus morphine added to bupivacaine in pediatric infra-umbilical surgery. Saudi J Anaesth 2014;8:155-60.
Source of Support: Nil, **Conflict of Interest:** None declared.