www.jmscr.igmpublication.org
Index Copernicus Value: 79.54
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossrefDOI: https://dx.doi.org/10.18535/jmscr/v7i2.78

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Research Article

Effectiveness of co-administration of neostigmine and ropivacaine in children for caudal block

Authors
Dr Shabir Ahmad Mir[1], Dr Tahira Akhter[2], Prof Syed Mohammad Quazi[3]
Dr Umar Jan[4], Dr Aijaz Ahmad Mir[5], Dr Sumairah Ishaq[6]
[1]Post Graduate SKIMS Soura, [2,4]Senior Resident SKIMS Soura, [3]Prof SKIMS Soura
[5]Post Graduate, GMC Srinagar, [6]Senior Resident, SKIMS Medical College
*Corresponding Author
Dr Tahira Akhter
Senior Resident SKIMS Soura, Pin Code 190011, India
Email: *sheikhtahiraakhter@gmail.com*, Phone number 919697915118

Abstract
Background: *Pain control by various methods, in children is of great concern for the anaesthesiologists. we coadminstered neostigmine with ropivacaine to prolong duration of block due to its synergistic effect. We compared the analgesic efficacy and safety of Neostigmine -Ropivacaine mixture to that of ropivacaine with saline following caudal administration in children undergoing infra umbilical surgeries.*
Methods: *In a prospective, randomized, double blind study, 100 children aged 1-5years of ASA class 1 of either sex, were randomly allocated to one of the groups of 50 patients each to receive caudal injection of either 1ml/kg of 0.25% ropivacaine hydrochloride with saline 0.2ml/kg in group R (Control group) or 2µg/Kg(10 µg/m) of neostigmine added to 1ml/kg of 0.25% ropivacaine hydrochloride in Group RN(Study group). The perioperative hemodynamic effects, post operative pain score, supplementary analgesic requirement and side effects were assessed by a blind observer in all patients during 24 hour post operative period.*
Results: *Both the groups were homogenous with reference to age, sex, weight and duration of anesthesia and duration of surgery. No significant differences with respect to mean heart rate, blood pressure (systolic and diastolic) and oxygen saturation were noted during perioperative period between the two groups. The mean duration of analgesia in group R was8.25±2.229hours while in group RN mean duration of analgesia was 18.00±4.93 hours. The duration of analgesia in group RN was longer and the difference was statistically significant ($p< 0.05$). In the postoperative period rescue analgesia in the form of paracetamol I/V (15mg/kg) was required in 13 patients (26%) in the study group and 28(56%) patients in the control group. Statistically a significant difference ($p<0.001$) was observed between the two groups. In our study 2 patients in study group had nausea and vomiting (4%), while in control group 4patients had nausea and vomiting (4%). The total number of patients who had side effects was less in study group compared to control group. However, the difference was statistically insignificant ($p>0.05$) between the two groups. None of our patient developed any other complication. In our study there was very low incidence of nausea and vomiting which was probably due to i/v ondansetron given intraoperatively.*
Conclusion: *Caudal neostigmine is an effective and prolonged intra and postoperative analgesia in children undergoing infra-umbilical surgeries. Neostigmine in the dose of 2µg/kg body weight when added to caudal ropivacaine is safe and without any significant side effects. KEYWORDS: caudal anesthesia, neostigmine, post operative pain, children, ropivacaine.*

Introduction

Caudal analgesia attenuates the stress response of anaesthesia and surgery and decreases postoperative narcotic use.[1] The International Association for study of pain has defined pain as "an unpleasant sensory and emotional experience, associated with actual or potential tissue damage". Pain is a protective mechanism designed to alert the body to potentially injurious stimuli. Relief of pain is one of the paramount goals of medical science. Pain after surgery is inevitable. Relieving pain is one of the fundamental responsibilities of an anesthesiologist. The concept of pain relief and its utilization in pediatric age group has improved dramatically over the recent years. Till date various methods have evolved for avoiding postoperative pain in pediatric population, nonetheless having some side effects which prohibit their use in children. In children narcotics could cause respiratory depression, oral analgesics cannot be given for some time after general anesthesia due to fear of vomiting, aspiration and fear of needle stick in case of parenteral analgesics. The provision of adequate analgesia is necessary after any surgery and it is all the more important in children. Under-treatment of post operative pain even in the children and newborns may trigger biochemical and physiologic stress response and causes impairments in pulmonary, cardiovascular, neuroendocrine, gastrointestinal, immunological and metabolic functions.[2] Painful surgical incisions involving the upper abdomen result in reflex mediated increase in tone in abdominal muscles during expiration and decrease in diaphragmatic functions. The result is reduced pulmonary compliance, muscle splitting and inability to breathe deeply or cough forcefully and in some cases hypoxia, hypercarbia, retention of secretions, atelectasis and pneumonia.[3] Suprasegmental reflex response to pain results in increased sympathetic tone, hypothalamic stimulation, increased catecholmine and catabolic hormones secretion and decreased secretion of anabolic hormones. All these are responsible for sodium and water retention, hyperglycemia, free fatty acid ketone bodies and lactate production.[4] Caudal block, since its first description in 1993 for pediatric urological interventions, has evolved to become the most popular regional anesthetic technique for use in children.[5] It provides excellent analgesia during surgery as well as during post-operative period in Merskey H, Albe Fessard, Bonica. Pain terms: A list with defenitions and notes on usage. Pain, 1979; 6: 249.subumblical surgeries in children. However, one of the major limitations of the single injection is relative short duration of post-operative analgesia even with long acting local anesthetics such as bupivacaine and supplemental intravenous or intramuscular analgesics are often required.[6] This problem can be circumvented by the use of continuous catheter technique or by the use of different adjunctive drugs to the local anesthetic solutions. However, most standard pediatric operations do not merit the use of continuous catheter technique.[7] Prolongation of caudal analgesia has been achieved by addition of various additives.[8] Opioids like morphine, fentanyl and sufentanyl have been traditionally used to increase the duration of analgesia but they are associated with objectionable side effects such as nausea, respiratory depression, pruritus etc.[9] A number of non-opioid additives have been suggested to increase the quality and duration of analgesia by local anaesthetic. The various non-opioid additives include ketamine[10], midazolam, neostigmine[7], clonidine and more recently dexmedetomidine.[11,12] Ketamine and midazolam further increase the duration of analgesia. However, the potential of neurotoxicity remains of concern.[11]

Materials and Methods

This prospective, randomized and double blind study entitled "Effectiveness of co-adminstration of neostigmine and ropivacaine in children for caudal block." was conducted in the Department of Anesthesiology and Critical Care at Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Kashmir from June 2016 to May 2018. After

taking Institutional Review Board approval, 100 patients having ASA class I, age of 1- 5 years of either sex, for infra-umbilical surgeries were recruited. The sample size was divided into two groups with 50 patients each, R group (Study group) received caudal ropivacaine 0.25% 1ml/kg plus normal saline 0.2ml/kg and RN group (Control group) received caudal ropivacaine 0.25% 1ml/kg plus neostigmine 2µg/kg (10µg/ml) respectively. Patients allergic to local anesthetic, spinal deformity, neurological disease, coagulopathy, bleeding diathesis and infection near the site of injection were excluded from the study. The sterile syringes containing equal volumes of content, one containing Ropivacaine and normal saline and other containing Ropivacaine and neostigmine were loaded by the anaesthesiologist not participating in the study. The intraoperative monitoring and postoperative observation were done by the anaesthesiologist who administered the drug and saline, but were unaware of the contents. All the patients underwent thorough pre-anaesthetic check up pre-operatively and a written consent was taken from the parents/ guardians, explaining all risks and benefits. In the operation room baseline monitoring like heart rate (HR), non- invasive blood pressure (NIBP), ECG and pulse oxymetery (SpO2) were recorded. After securing IV access with 22G iv cannula patients were induced with inj. fentanyl (1-2µg/kg), inj. Propofol (1-2mg/kg). Airway was secured with appropriate size LMA. Maintenance was done with O2 (33%) + N2O(67%) + isoflurane 0.6% to 1%.. Injection ondansetron 0.1mg/kg i/v was given intraoperatively at the end 30 minutes before finishing procedure. Under all aseptic precautions, caudal block was performed by using 22/24G needle with bevel, using loss of resistance technique to saline. After proper identification of caudal space, drug was injected and antiseptic dressing was applied. The duration of analgesia was taken as from onset of caudal block to time of first dose of rescue analgesia. In the intraoperative period the degree of analgesia was analyzed by objective assessment of vitals including heart rate, blood pressure. The parameters were recorded at the following intervals: baseline, before incision, immediately after surgical incision and then every 5 minutes till the end of surgery. Postoperatively patients were assessed at 0 minutes, 30 minutes, 60 minutes, 4, 8, 12 and 24hrs by using FLACC Pain scale. FLACC (Face, Legs, Activity Cry, console ability) pain scale consists of five parameters, each given a score of 0-2. Total score is taken to assess the pain. Score “0” No pain, “1-3” Mild pain, “4-7” Moderate pain, “8-10” Severe pain.[5] Rescue analgesia, PCMI/v (15mg/kg) was given if pain score was ≥4. The time of first rescue analgesia administration and number of doses of rescue medication was noted in both groups. An increase in heart rate within 15 minutes of skin incision more than 15% indicated failure of caudal analgesia and rescue analgesia was given. The data was collected from both the groups and compared for duration and degree of analgesia, complications and need for rescue analgesia. The data thus obtained was analyzed statistically using analysis of variance (ANOVA) and students `t` test. A `p` value of < 0.05 was considered statistically significant.

The FLACC Pain Scale[13]

Table 1

Categories	Scoring		
	0	1	2
Face	Smile or no particular expression	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking

Cry	No cry (awake or asleep)	Moans or whimpers occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consol ability	Content, relaxed	Reassured by occasional touching, hugging or talking to, distractable	Difficult to console

Table 2 pain scoring

Severity of pain	**Pain Score**
No pain	0
Mild pain	1-3
Moderate pain	4-7
Severe pain	8-10

Results and Observations

Table 3

	RN group Mean ± SD	**R group Mean ± SD**	P-value
Age (year)	3.430 ±1.078	3.230 ±1.120	1.000
Weight (kg)	20.688 ±5.986	19.158 ±6.691	0.231
Baseline heart rate	101.3800 ±7.62887	102.0000 ±5.51806	.643
Baseline SBP	97.4800 ±4.79898	98.4600 ±5.73286	0.356
BaselineDBP	58.4800 ±4.33420	57.4000 ±4.27618	0.212
BaselineSpo2	98.4000 ±0.63888	98.6200 ±0.69664	0.103
mean Heart rate	95.0608 ±4.123	96.115 ±3.278	0.1602
mean Spo2	98.4517 ± 0.5642	98.5042 ± 0.5092	0.625
mean SBP	95.68 ±4.101	96.72 ±3.968	0.2005
mean DBP	55.583 ±4.901	55.343 ±4.780	0.8047

The study was conducted over a 17-month period (February ’09 to June ’10). Demographic patterns and pre-operative vital parameters were similar when the two groups were compared with no statistical significance. Preoperative pulse (bpm) 101.3800±7.62887 and 102.00±5.51806 Preoperative SBP (mmHg)97.4800±4.79898 and 98.4600±5.73286 Preoperative DBP (mmHg) 58.4800±4.33420 and 57.4000±4.27618 Preoperative SpO2 (%) 98.4000±0.63888 and 98.6200±0.69664 Data are given as mean±SD. Test done: Independent sample t-test, $Pearson Chi square. n: Number of patient; bpm: Beats per minute; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; SpO2 (%): Oxygen Saturation. Heart rate, oxygen saturation by pulse oxymetry (SpO2%), systolic blood pressure and diastolic blood pressure were recorded at 5 minutes of intervals intraoperatively starting from baseline, before skin incision, immediately after

incision, then every 5 minutes till the mean heart rate was 95.0608±4.123in RN (study) group and 96.115 ±3.278 in R group. The mean of systolic BP was (95.68±4.101) in RN group and 96.72±3.968 in R group. The mean DBP was 55.583±4.901in RN group and55.343±4.780 in R group. The groups were compared with reference to mean heart rate, mean oxygen saturation, mean systolic blood pressure and mean diastolic blood pressure intraoperatively and the difference was found to be statistically insignificant (p>0.05) Quality of postoperative analgesia in PACU (Postanesthesia care unit) was assessed by FLACE scale

Table 4

Time	**RN group Mean ± SD**	**R group Mean ± SD**	**p-value**
0hr	1.5000 ±1.54819	1.9600 ±0.57000	.051
1/2hr	1.8600 ±0.70015	2.2800 ±0.49652	0.001
1hr	2.2800 ±0.53605	2.6400 ±0.56279	0.001
4hr	2.9400 ±0.51150	3.3600 ±0.56279	<0.01
8hr	3.1000 ±0.46291	4.1400 ±1.01035	<0.01
12hr	3.2600 ±0.48697	4.8000 ±1.55183	<0.01
24hr	3.5000 ±0.88641	5.4000 ±2.11891	<0.01

Table 5

	RN group Mean ±SD	**R group Mean ± SD**	**p-value**
Total number of patients receiving rescue analgesia	**13 (26%)**	**28 (56%)**	<0.01
Time of first rescue analgesia	18.00 ±4.293	8.25 ±2.229	<0.001
Total doses of PCM	2.60 ±1.682	4.00 ±1.322	<0.01
Patients with side effects	2 (4%)	4 (8%)	0.667
Patients with no side effects	48 (96%)	46 (92%)	

In the postoperative period rescue analgesia in the form of paracetamol (15mg/kg) was required in 13 patients (26%) in the study group and 28(56%) patients in the control group, with significant statistical difference (p<0.001. mean time to first rescue analgesia was 18.00±4.293 hours in the study group while it was 8.25±2.229 hours in control group. With significant statistical difference (p<0.001). In our study 2 patients in RN (group) had nausea and vomiting (4%), while in control group 4 patients had nausea and vomiting (8%). The total number of patients who had side effects were less in study group compared to control group. However, the difference was statistically insignificant (p>0.05) between the two groups. None of our patient developed any other complication In our study there was very low incidence of nausea and vomiting (12%) which was probably due to i/v ondansetron given in intraperative period were less from study group as compared to control group due to good analgesia and the difference

was statistically significant (p<0.05). Comparison showed that adding neostigmine with Ropivacaine decreased the overall requirement of rescue analgesia postoperatively. The mean time to first rescue analgesia in RN (study) group was more than R (control). In our study there was a very low incidence of nausea and vomiting (10%) due to i/v ondansetron given intraoperatively, with statistically insignificant inter group variation (P>0.05).

Discussion

Continuous optimization of pain is the concern of the anesthesiologists. Most commonly used procedure to treat pain in children is caudal block. It is simple, safe and effective. It can be used with or without additives. Additives are used to prolong duration of analgesia postoperatively. This study was carried out to compare the quality and duration of analgesia of caudal bupivacaine. When used as single agent and when used as an adjunct to caudal neostigmine on postoperative pain control in pediatric age group (1-5 years) undergoing infra-umbilical surgeries. Two groups of 50 patients each were randomly selected for this study: The following data was collected and analyzed statistically: Age, bodyweight. Hemodynamic parameters (heart rate, systolic BP and Diastolic BP) and oxygen saturation by pulse oxymetry (SpO2%). Quality of analgesia by using FLACC pain scores. Rescue analgesia. Time of first Rescue analgesia (Duration of analgesia). Postoperative complications. Age and weight were comparable in both the group (P>0.05). There were no statistically significant differences in the intraoperative hemodynamic parameters (mean heart rate and mean blood pressure) and oxygen saturation by pulse oxymetry, at various time intervals between the two groups (P>0.05). The pain scores were assessed by FLACC scale postoperatively in PACU and ward. RN (study) group was having less pain scores as compared to R (control) group. The difference was statistically significant (p<0.05). The total number of patients who required rescue analgesia (diclofenac suppository) in postoperative period were less from study group as compared to control group and the difference was statistically significant (p<0.05). Comparison showed that adding neostigmine with bupivacaine decreased the overall requirement of rescue analgesia postoperatively. The mean time to first rescue analgesia in RN (study) group was more than R (control). In our study there was a very low incidence of nausea and vomiting (10%) due to i/v ondansetron given intraoperatively, with statistically insignificant inter group variation (P>0.05).

Turan A et al (2003) in their study "Caudal Ropivacaine and Neostigmine in Pediatric Surgery" studied the comparison of the addition of neostigmine on duration of caudal block produced by 0.2% ropivacaine 0.5ml/kg in control group and 0.2% ropivacaine 0.5ml/kg plus 2mcg/kg neostigmine in study group. They found that there was no difference between the group members in heart rate, mean arterial pressure and spo2 during the study. Severe bradycardia or hypotension was not observed in any patient. The pain scores were significantly lower in group II (study) when compared with group I (control), 7 (31%) children in study group and 18(81%) children in control required rescue analgesia during first 24hrs period. Which was statistically significant (p<0.05).[14]

Sfyra E et al (2007), who in their study "caudal administration of levobupivacaine and neostigmine for postoperative analgesia in children" studied the caudal administration of levobupivacaine plain or in combination with neostigmine for postoperative analgesia in children. They studied the comparison of the addition of neostigmine on duration of caudal block produced by 0.25% Levobupivacaine 1ml/kg in control group and 0.25% Levobupivacaine 1ml/kg plus 2µg/kg neostigmine in study group. They found that pain scores recorded over 24hrs period were lower in study group than in control group.[15]

Emil Batarseh MD et al (2015), in their study "Caudal Bupivacaine–Neostigmine Effect on

Post-operative Pain Relief in children" administered caudal bupivacaine 0.25% 0.5ml/kg (group I), bupivacaine 0.25% 0.5ml/kg plus 1.5mcg/kg neostigmine (group II), bupivacaine 0.25% 0.5ml/kg plus 3mcg/kg neostigmine (group III) and bupivacaine 0.25% 0.5ml/kg plus 6mcg/kg neostigmine (group III). They found that significantly more patients of plain bupivacaine group received postoperative rescue analgesics than Bupivacaine –Neostigmine groups.[16]

Mohamed Abdulatif et al (2002), in their study "Caudal Neostigmine, bupivacaine and Their Combination for Postoperative Pain Management After Hypospadias Surgery in Children" found that caudala dministration of bupivacaine with the addition of neostigmine resulted in superior analgesia as compared with other two groups. Time to first rescue analgesia was 22.8±2.9hrs, 8.1±5.9hrs and 5.2±2.1hrs in the bupivacaine/ neostigmine, bupivacaine and neostigmine groups respectively ($p<0.01$).[17]

Dr Rudra et al (2005), in their study "scope of caudal neostigmine with bupivacaine for post-operative analgesia in children: comparison with bupivacaine" studied the comparison of the addition of neostigmine on duration of caudal block produced by 0.25% bupivacaine 1ml/kg and 0.25% bupivacaine 1ml/kg plus 2mcg/kg neostigmine. They found that the mean time to first rescue analgesia was 7.6±5.4 hours in the study group while it was 19.0±4.2 hours in control group. Statistically a significant difference ($p<0.001$) was observed in both the groups.[18] In our study 3 patients in BN (group) had nausea and vomiting (6%), while in control group 2 patients had nausea and vomiting (4%). The total number of patients who had side effects were less in study group compared to control group. However, the difference was statistically insignificant ($p>0.05$) between the two groups. None of our patient developed any other complication. In our study there was very low incidence of nausea and vomiting (10%) which was probably due to i/v ondansetron given intraperatively.

Dr Pramod Gupta et al (2011), found that there were no incidence of nausea vomiting in their study.[19] "Neostigmine as an adjunct to Bupivacaine, for caudal block in burned children, undergoing skin grafting of the lower extremities" in which they used 0.125% & 0.25% bupivacaine, along with fixed dose of neostigmine (6mcg/kg). The results were due to preoperative i/v ondansetron administration.

Dr Tahira et al 2016, in their study "Neostigmine as an adjunct to Bupivacaine, for caudal block in children undergoing infra-umbilical surgeries." Studied 100 children scheduled for elective infra-umbilical surgical procedures were randomly allocated to one of the groups of 50 patients each to receive caudal injection of either 1ml/kg of 0.25% bupivacaine hydrochloride with saline 0.2ml/kg in group B (Control group) or 2µg/Kg(10 µg/m) of neostigmine added to 1ml/kg of 0.25% bupivacaine hydrochloride in Group BN(Study group).Supplementary analgesic requirement and side effects were assessed by a blind observer during 24 hour observation period. The mean duration of analgesia in group B was 4.16±1.687 hours while in group BN mean duration of analgesia was 11.87±3.502 hours. In the postoperative period rescue analgesia in the form of diclofenac suppository (1mg/kg) was required in 15 patients (30%) in the study group and 31 (62%) patients in the control group. 2 patients in study group had nausea and vomiting (4%), while in control group 3patients had nausea and vomiting (6%). The total number of patients who had side effects was less in study group compared to control group. However, the difference was statistically insignificant ($p>0.05$) between the two groups. None of our patient developed any other complication. In our study there was very low incidence of nausea and vomiting (10%) which was probably due to i/v ondansetron given intraoperatively. Caudal neostigmine is an adjunct to bupivacaine provides effective and prolonged intra and postoperative analgesia in patients undergoing infra-umbilical surgeries.[20]

Conclusion

Thus we concluded that neostigmine as an adjunct to caudal block with bupivacaine increases the intensity and duration of postoperative analgesia in pediatric patients undergoing infraumbilical surgeries.

Bibliography

1. Khahil SN, Hanna F, Farag A, et al. Presurgical caudal block attenuates stress response in children. Middle East J Anaesthesiol. 2005; 18(2): 391-400.
2. Duggan J, Drummond GBF. Activity of lower intercostals and abdominal muscles after surgery in humans. Anesth-Analgesia 1987; 66-252
3. Ford GT, whitelaw WA, Rosenel TW. Diaphragm function after upper abdominal surgery in humans. Am. Rev respire Dis. 1983; 127-143.
4. Kehlet H. Pain relief and modifications of the stress response. P.49 in cousins MJ, Philips GD (ed); Acute pain management: Churchill living stone. New York. 1986.
5. Campbell MF. Caudal anaesthesia in children. Am J Urol 1933; 30: 245-1.
6. Wolf AR, Hughes D, Mather SJ. Postoperative analgesia after pediatric orchidopexy: Evaluation of bupivacaine – morphine mixture. British Journal of Anaesthesia 1990; 64: 430-5.
7. Lonnqvist PA, Morten NS. Postoperative analgesia infants and children. British Journal of Anaesthesia 2005; 95: 59-68.
8. De Beer DAH, Thomas M. Caudal additives in children-Solution or problems? Br J Anaesth 2003; 90(4): 487-98.
9. Krane EJ, Jacobson LE, Lynn AM, et al. Caudal Morphine for postoperative analgesia in children. A comparison with caudal bupivacaine and intravenons morphine. Anesthesia Analgesia 1989; 66: 647-53.
10. Malinovsky JM. Lepage JY, Cozain A, et al. Is ketamine or its preservative responsible for neurotoxcity in the rabbit? Anaesthesiology 1993; 78: 109-15.
11. Ansermino M, Basu R, Vandebeek C, et al. Nonopioid additives to local anaesthetics for caudal blockade in children: a systemic revive. Paediatr. Anaesth 2003; 13: 501-73.
12. Kumar P, Rudra A, Pan AK, Achariya A. caudal additives in pediatrics. A comparison among midazolam, Ketamine and Neostigmine co-administered with bupivacaine. Anesth-Analgesia 2005; 10: 69-73.
13. Merkel SI, Voepel-Lewis, T Shayevitz JR, Malviyas. The FLACC, a behavioral scale for scoring postoperative pain in young children. Paediatr Nurs 1997; 23: 293-7.
14. Turan A, Memis D, Basaran U, Karamanlioglu B, Sut N. Caudal ropivacaine and neostigmine in pediatric surgery. Anesthesiology 2003; 98: 719-22.
15. Sfyra E, Georgiadou Th, Svirkos M, Georgiou M, Soubasis I, Zavitsanakis A, Kanakoudis F. Caudal administration of levobupivacaine and neostigmine for postoperative analgesia in children. The Greek E-Journal of Perioperative Medicine, 2007; 5: 44-9.
16. Emil Batarseh, Zahi Majli, Nariuman Nsour, Mohammad Dajja, Oksana Nabukhotna. Caudal Bupivacaine – Neostigmine Effect on Post-opeative Pain Relief in children. Journal of the Royal Medical Services Mar. 2015; 22: 1.
17. Mohamed Abdulatif, Mohga El-Sanabary. Caudal neostigmine, bupivacaine, and their combination for postoperative pain management after hypospadias surgery in children.Anesth Analg. 2002 Nov; 95(5): 1215-8.
18. Dr. Rudra A. Dr. Pan A.K. Dr. Acharya A. Dr Ahmad A.Dr Ghosh M.K. Scope of caudal neostigmine with bupivacaine for post-operative analgesia in children: comparison with bupivacaine. Indian J. Anaesth. 2005; 49(3): 191-194.

19. Dr. Pramod Gupta, Dr Amy Grace MD. Neostigmine as an adjunct to Bupivacaine, for caudal block in burned children, undergoing skin grafting of the lower extremities. Anestesia Pediatricae Neonatale 2011; 9(1): 1-16.
20. Dr Tahira at al Neostigmine in the dose of 2µg/kg body weight when added to caudal bupivacaine is safe and without any significant side effects WJPR Volume 6, Issue 3, 1458-1469.