WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 3, 1458-1469. Research Article ISSN 2277– 7105

CAUDAL NEOSTIGMINE AS AN ADJUNCT TO BUPIVACAINE FOR POST OPERATIVE ANALGESIA IN CHILDREN UNDERGOING INFRA UMBILICAL SURGERY.

Tahira Akhter (MD Anesthesiology SKIMS), Sheikh Irshad Ahmad(Associate Professor Anesthesiology SKIMS), Tanveera Gani(Diploma Anesthesiology), Syed Qazi (Professor Anesthesiology SKIMS), Tantry Tariq Gani (MD Anesthesiology SKIMS)*, Zaffar Malik(MD Anesthesiology SKIMS)

(SKIMS: Sheri Kashmir Institute of Medical Sciences, Srinagar, Kashmir, India).

Article Received on
16 Jan. 2017,

Revised on 06 Feb. 2017,
Accepted on 26 Feb. 2017

DOI: 10.20959/wjpr20173-8032

***Corresponding Author**
Tantry Tariq Gani
(SKIMS: Sheri Kashmir Institute of Medical Sciences, Srinagar, Kashmir, India).

ABSTRACT

Background: Caudal block has evolved to become the most popular regional anesthetic technique for use in children. It provides excellent analgesia during surgery as well as during postoperative period in infra umblical 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. This problem can be circumvented by the use of different adjunct drugs to the local anesthetic solutions. The aim of the present study was to compare the analgesic efficacy and safety of Neostigmine - bupivacaine mixture to that of bupivacaine with saline following caudal administration in children undergoing infra umbilical surgeries ***Methods***: In a prospective, randomized, double blind study, 100 patients of ASA physical status I of either sex in the age range of 1 to 5 years 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). The perioperative hemodynamic effects, post operative pain scores(OPS), supplementary analgesic requirement and side effects were assessed by a blind observer during 24 hour observation 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 B was 4.16±1.687hours while in group BN mean duration of analgesia was 11.87±3.502hours. The duration of analgesia in group BN was longer and the difference was statistically significant ($p< 0.05$). 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. 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 3 patients 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. ***Conclusion***: Caudal neostigmine provides effective and prolonged intra and postoperative analgesia in patients undergoing infra-umbilical surgeries. Neostigmine in the dose of 2µg/kg body weight when added to caudal bupivacaine is safe and without any significant side effects.

KEYWORDS: caudal anesthesia, neostigmine, post operative pain, children, bupivacaine.

INTRODUCTION

The International Association for study of pain has defined pain as “an unpleasant sensory and emotional experience, associated with actual or potential tissue damage”.[1] 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 subumblial 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]

In the present study we studied the analgesic effect of Neostigmine as an adjuvant to caudal bupivacaine.

MATERIALS AND METHODS

This prospective, randomized and double blind study entitled “Neostigmine as an adjunct to Bupivacaine, for caudal block in children undergoing infra-umbilical surgeries” was conducted in the Department of Anesthesiology and Critical Care at Sher-i-Kashmir Institute

of Medical Sciences, Srinagar, Kashmir from June 2013 to May 2015. After taking Institutional Review Board approval, 100 patients belonging to ASA physical status I, in the age range of 1- 5 years of either sex, for infra-umbilical surgeries were recruited. The sample size was divided into two groups B and BN, having 50 patients each. **B group (Study group)** received caudal bupivacaine 0.25% 1ml/kg plus normal saline 0.2ml/kg and **BN group (Control group)** received caudal bupivacaine 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 bupivacaine and normal saline and other containing bupivacaine 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 checkup 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 (SpO_2) were recorded. After securing IV access with 22G iv cannnula patients were induced with inj. fentanyl (1-2µg/kg), inj. Propofol (1-2mg/kg) and inj. Atracurium (0.5mg/kg). Airway was secured with appropriate size endotracheal tube. Maintenance was done with O_2 (33%) + N_2O(67%) + isoflurane 0.6% to 1% and supplementary doses of atracurium. Injection ondansetron 0.1mg/kg i/v was given intraoperatively 30 minutes before the expected extubation. Patients were positioned in lateral position for caudal block. 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, diclofenac suppository (1mg/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]

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

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

RESULTS AND OBSERVATIONS

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 [Table 1].

TABLE 1

Demographic patterns and pre-operative vital parameters

Parameters	Study Group BN (*n*=50)	Control Group B (*n*=50)	*P* value
Age (years)	3.448 ± 1.1357	3.450 ± 1.1573	0.993
Weight (kg)	20.696 ± 13.2502	17.02 ± 4.2502	0.832
Preoperative pulse (bpm)	100.30 ±7.569	101.08±5.096	0.593
Preoperative SBP (mmHg)	97.54±4.886	98.42±5.693	0.414
Preoperative DBP (mmHg)	56.65±4.334	57.38±4.252	0.636
Preoperative SpO2 (%)	98.65	98.60	0.137

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 (SpO_2%), 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 end of surgery. The mean heart rate was (94.688±.452) in BN (study) group and (95.750±.452) in B (control) group. The mean of systolic BP was (95.847±.538) in BN (study) group and (96.788±.527) in B (control) group. The mean DBP was (55.429±.419) in BN (study) group and (55.733±.411) in B (control) 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) [Table 2].

TABLE 2

Parameter	**BN (Study) group Mean ± SD**	**B (Control) Group Mean ± SD**	**P value**
Pulse rate(bpm)	94.688±.452	95.750±0.452	0.101
SBP(mmHg)	95.847±.538	96.788±0.527	0.214
DBP (mmHg)	55.429±.419	55.733±.411	0.605
SPO2 (%)	98.483	98.388	0.575

Quality of postoperative analgesia in PACU(Postanesthesia care unit) was assessed by using FLACC pain scale at 0 minute, 30minutes and 60minutes. A statistically significant difference (p<0.001) was observed in FLACC pain scores between the two groups at

0minute, 30minutes and 60minutes. Mean scores at 0 minutes, 30 minutes and 60 minutes in B (control) group were 2.20±0.585, 2.26±0.573 and 2.62±0.648 respectively. Mean scores at 0minutes, 30minutes and 60 minutes in BN (study) group were 1.63±1.696, 1.88±0.703 and 2.28±0.589 respectively Quality of postoperative analgesia in ward was assessed by using FLACC scale at different time intervals, i.e; 4hr, (after the discharge from PACU) 8hr, 12hr and 24hr. Mean scores at 4hr,8hr,12hr,24hr in control group were 3.35±0.556, 4.06±0.978, 4.71±1.538 & 5.42±2.052 hrs respectively. Mean scores at 4hr, 8hr, 12hr, 24hr in study group were 2.94±0.552, 3.10±0.472, 3.27±0.494 & 3.52±0.899 hrs respectively. There was a statistically significant difference in FLACC scores at various intervals between the two groups, FLACC scores being less in study group compared to control group ($p<0.001$) [Table 3].

Comparison of FLACC Scale between the two groups at different time intervals [Table 3].

Table 3

FLACC Scale between the two groups

Time(min)	BN (Study) group	B (Control) group	P Value
0 min	1.63±1.696	2.20±0.585	0.059
30min	1.88±0.703	2.26±0.573	0.030
60min	2.28±0.589	2.62±0.648	0.004
4hrs	2.94±0.522	3.35±0.556	<0.01
8hrs	3.10±0.472	4.06±0.978	<0.01
12hrs	3.27±0.494	4.71±1.538	<0.01
24hrs	3.52±0.899	5.42±2.052	<0.01

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. Statistically a significant difference ($p<0.001$) was observed between the two groups. In our study the mean time to first rescue analgesia was 11.87±3.502 hours in the study group while it was 4.16±1.687 hours in control group. Statistically a significant difference ($p<0.001$) was observed. In our study 2 patients in BN (group) had nausea and vomiting (4%), while in control group 3 patients had nausea and vomiting (6%). 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 {TABLE 4}.

TABLE 4

Parameters	BN (Study) group	B (control) group	P Value
First dose of rescue analgesia	11.87±3.502	4.16±1.687	0.001
Number of doses of rescue analgesia	5.60±1.682	8.42±1.385	<0.001
Total number of patients receiving rescue analgesia	15 (30%)	31 (62%)	<0.001
Patients with side effects	2(4%)	3(6%)	0.685
Patients with no side effects	48	47	

Data are given as mean±SD. *n*: Number of patient, Test done: Independent sample *t*-test.

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, body weight.
- Hemodynamic parameters (heart rate, systolic BP and Diastolic BP) and oxygen saturation by pulse oxymetry (SpO_2%).
- 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. BN (study) group was having less pain scores as compared to B (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 BN (study) group was more than B (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 caudal administration 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.

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 infra-umbilical surgeries.

BIBLIOGRAPHY

1. Merskey H, Albe Fessard, Bonica. Pain terms: A list with defenitions and notes on usage. *Pain,* 1979; 6: 249.
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.