Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

Comparison of Caudal Neostigmine and Clonidine as an Adjuvant for Post-operative Pain Relief in Infraumbilical Pediatric Surgeries

Rajan B Godwin[1], P T Vineeth[2], Ashish Gupta[1], Mayura Setiya[3]

[1]Associate Professor, Department of Anaesthesiology, Netaji Subhash Chandra Bose Medical College, Jabalpur, Madhya Pradesh, India, [2]Ex Resident, Department of Anaesthesiology, Netaji Subhash Chandra Bose Medical College, Jabalpur, Madhya Pradesh, India, [3]Assistant Professor, Department of Anatomy, Netaji Subhash Chandra Bose Medical College, Jabalpur, Madhya Pradesh, India

Abstract

Introduction: Caudal analgesia is the most promising central neuraxial block in pediatric age group for perioperative and post-operative analgesia and decreasing the magnitude of stress response in infraumbilical pediatric surgeries. Inadequate pain relief with single shot caudal block perpetuates the need of use of adjuncts such as clonidine and neostigmine to get a meaningful prolongation of postoperative analgesia with minimal side effects.

Purpose: The purpose of the study was to assess and compare the efficacy of neostigmine and clonidine as an adjunct to caudal bupivacaine in prolonging analgesia.

Materials and Methods: Ninety children aged 2–10 years (American Society of Anesthesiologists physical status I-II) received standardized general anesthesia with inhaled sevoflurane and caudal epidural block with 0.25% bupivacaine 1 ml/kg for infra-umbilical surgeries were randomly allocated in three groups each comprising 30 patients wherein one group received 0.25% bupivacaine 1 ml/kg with neostigmine in dose of 2 μg/kg, second group received 0.25% bupivacaine1 ml/kg with clonidine in dose of 2 μg/kg, and third group received only 0.25% bupivacaine 1 ml/kg as control group.

Results: The mean duration of analgesia in group BN was 7.47 ± 1.4 h while in group BC mean duration of analgesia was 6.83 ± 0.9 h as compared to control Group B in which it was 3.33 ± 0.6 h. The duration of analgesia in BN and BC was comparable and did not differ significantly ($P > 0.05$). However, the duration of analgesia between group BN and BC as compared to B had a statistically highly significant difference ($P < 0.01$). Time for requirement of first analgesic was longest in group BN which was 18.18 ± 3.5 h followed by group BC which was 16.68 ± 3.6 h and Group B was 9.03 ± 3.57.

Conclusion: On the basis of this study, it appears that neostigmine and clonidine have proven to be reliable adjuvants for prolongation of analgesia in caudal block with less requirement of rescue analgesia.

Key words: Bupivacaine and post-operative analgesia, Caudal analgesia, Caudal block, Clonidine, Neostigmine

INTRODUCTION

Caudal block is a universally accepted and promising central neuraxial block in pediatric age group for perioperative and post-operative analgesia and attenuation of stress response in infraumbilical pediatric surgeries.[1] The caudal space is the sacral portion of the epidural space. Caudal anesthesia involves needle penetration of the sacrococcygeal ligament overlying the sacral hiatus that is created by unfused S4 and S5 laminae. The hiatus may be felt as a groove or notch above the coccyx and between the two bony prominences, sacral cornua. Its anatomy is more easily appreciated in infants and children. The posterior superior iliac spines represented by skin dimples and the sacral hiatus define an equilateral triangle. Caudal anesthesia is typically combined with general anesthesia for intraoperative supplementation and post-operative analgesia. The patient is placed in the lateral or prone position with one or both hips flexed and the sacral hiatus is palpated. After initial preparation, a

Access this article online

www.ijss-sn.com

Month of Submission : 04-2021
Month of Peer Review : 04-2021
Month of Acceptance : 05-2021
Month of Publishing : 06-2021

Corresponding Author: Dr. Mayura Setiya, Department of Anatomy, Netaji Subhash Chandra Bose Medical College, Jabalpur, Madhya Pradesh, India.

needle is advanced at a 45° angle cephalad until a pop is felt as the needle pierces the sacrococcygeal ligament. The angle of the needle is flattened and advanced. Aspiration for blood and cerebrospinal fluid (CSF) is performed, and if negative, injection of local anesthetic proceeds.[2] Most common drugs used in caudal block include local anesthetics and opioids. Caudal epidural block being most commonly employed regional anesthetic technique and is generally contemplated as a simple and safe procedure, but its main pitfall is its relatively short duration of action, even with the use of long acting local anesthetic agent such as bupivacaine.[3,4] It is a well-known fact that pain is highly unpleasant and the most distressful consequence of any surgery.[5,6] In children, utterance of pain and method of pain evaluation is more complex which makes them more vulnerable to post-operative pain.[7] Thus, to compensate this inadequate pain relief with single shot caudal block of local anesthetic, circumstances have compelled to use different adjuvant to local anesthetic drugs to get a meaningful prolongation of post-operative analgesia with minimal side effects and it has become the need of hour. So far, different additives such as opioids, ketamine, and dexmedetomidine have been used to enhance postoperative pain relief but are associated with their limitations and unpleasant side effects. Reports also suggest the use of neostigmine as an adjuvant to local anesthetic agent in caudal block thereby prolonging the duration of analgesia but its use has been limited by unacceptably high incidence of nausea and vomiting.[8-10] Thinking of the reason for the high incidence of nausea and vomiting could be the higher dose; we used the optimal dose of 2 μg/kg of caudal neostigmine in our institution. Neostigmine, like all cholinesterase inhibitors, causes analgesia by preventing the breakdown of acetylcholine in the spinal cord. With the discovery of epidural clonidine, an alpha 2 receptor agonist, producing analgesic effect has made a place and is been increasingly used in anesthetic practice.[11,12] Clonidine has been shown to produce analgesia without causing significant respiratory depression after systemic, epidural, or spinal administration. Although epidural clonidine may cause hypotension, bradycardia, and sedation in higher doses, so to overcome these serious side effects, we have used it in an optimal dose of 2 μg/kg.[13] The present study was carried out to evaluate the analgesic efficacy of clonidine and neostigmine as adjuncts to caudal bupivacaine for post-operative pain relief in children.

MATERIALS AND METHODS

It is a prospective randomized double blinded controls study which after the approval from the Institutional Ethics Committee of N.S.C.B Medical College, Hospital Jabalpur M.P. was conducted in the department of anesthesiology. Written informed parental consent was obtained for each child undergoing infraumbilical surgeries. Ninety children aged 2–10 years (American Society of Anesthesiologists [ASA] physical status I-II) received standardized general anesthesia with inhaled sevoflurane and caudal epidural block with 0.25% bupivacaine 1 ml/kg for infra-umbilical surgeries was randomly allocated in three groups each comprising of 30 patients wherein one group received 0.25% bupivacaine 1 ml/kg with neostigmine in dose of 2 μg/kg, (Group BN) second group received 0.25% bupivacaine1 ml/kg with clonidine in dose of 2 μg/kg (Group BC), and third group received only 0.25% bupivacaine 1 ml/kg as control group (Group B). Exclusion criteria were any contraindication to a caudal block or any sensitivity to the study drug. The random allocation of children into one of the three study groups was done using a random number table. An anaesthesiologist not involved in the patient care prepared the drug solutions by following the standard written instructions. The association of saline was not necessary as the methodology was based on a final caudal volume as it should be similar in all groups. No premedication was prescribed to any child and all procedures were performed under general anesthesia. Induction was done by 8% sevoflurane with 100% oxygen through a face mask. After securing IV access, the child was turned to left lateral decubitus and caudal block was performed. Under all aseptic precaution, caudal block was performed using 22/24G needle. The needle was inserted at a 60° angle and advanced until a "pop" was felt. The needle was then lowered to 20° angle and further advanced 2–3 mm to make sure the bevel was in the caudal epidural space. Gentle test aspiration was done and if no blood or CSF was aspirated then the appropriate amount of study drug was injected. Tracheal intubation was performed after administration of atracurium 0.5 mg/kg. Anesthesia was maintained with O2 40% in nitrous oxide, halothane 0.5–1% with intermittent positive pressure ventilation. No Intraoperative opioids or sedatives were administered. Surgical intervention was started 10–15 min after the injection. The intraoperative monitoring and post-operative observations were done by the anaesthesiologist who has performed the procedure and administered the drugs, but were unaware of the contents. The duration of absolute analgesia was defined as the time from caudal injection until pain score was 2. The rescue analgesic time was the time from caudal injection till the pain score was >4. Oral paracetamol 20 mg/kg was given as rescue analgesia. In the intraoperative period, the degree of analgesia was analyzed by objective assessment of vitals such as heart rate and blood pressure. The parameters were recorded at the baseline and every 5 min after placement of caudal anesthesia. Fluid therapy was standardized during and after surgery: During surgery children received ringer lactate at

6 ml/kg/h whereas 5% dextrose in 0.45% NS was infused at 4 ml/kg/h in the post-operative period. Each patient was observed for 2 h in the recovery room before being shifted to the ward. Heart rate, mean arterial pressure, SpO2, and RR were monitored every 10 min. When the child was awake, pain and sedation scores were assessed every hour for 10 h and then every 4 h for next 24 h.

Post-operative Pain was assessed by a Five Point Verbal Pain Score

1. Asleep
2. Awake but no pain
3. Mild pain
4. Moderate pain
5. Severe pain.

Sedation Score

1. Eyes open spontaneously
2. Eyes open to verbal command
3. Eyes open to physical stimulation
4. Unarousable.

Motor Block was assessed by Using a Modified Bromage Scale

1. Full motor strength (Flexion of knees and feet)
2. Flexion of knees only (inability to lift an outstretched leg)
3. Little movement of feet only (inability to flex knees)
4. No movement of knees and feet (total paralysis of lower limbs).

The incidence of other adverse effects such as nausea, vomiting, hypotension, and bradycardia was also recorded.

RESULTS

The data obtained were analyzed statistically using Student's *t*-test. $P < 0.05$ was considered statistically significant. Data are given as mean ± SD. Test done: Independent sample *t*-test. All the three groups were demographically identical and comparable with respect to age, weight, duration of surgery, heart rate, mean arterial pressure, and SpO2 levels ($P > 0.05$) [Table 1]. The mean duration of analgesia in group BN was 7.47 ± 1.4 h while in group BC mean duration of analgesia was 6.83 ± 0.9 h as compared to control group in which it was 3.33 ± 0.6 h [Figure 1]. The duration of analgesia in BN and BC was comparable and did not differ significantly ($P > 0.05$). However, the duration of analgesia between group BN and BC as compared to B had a statistically highly significant difference ($P < 0.01$). Time for requirement of first analgesic was longest in group BN which was 18.18 ± 3.5 h, followed by group BC which was 16.68 ± 3.6 h and Group B was 9.03 ± 3.57 h [Figure 2]. The incidence of nausea and vomiting was maximum in the BN group as compared to BC and bupivacaine group, but was not statistically significant ($P > 0.05$). In our study, the maximum sedation was found in the BN group which was 5.6 ± 1.25 h closely, followed by BC group which was 5.23 ± 1.26 h and with least sedation in Group B which was 3 h [Figure 3]. Difference was significant among BN and B, and among BC and B ($P < 0.05$) but not between BN and BC ($P > 0.05$). Group BN had 13.3% incidence

Table 1: Demographic and clinical data

Parameters	Group BN	Group BC	Group B
Age (years)	5.78±2.51	5.80±2.55	5.54±2.85
Weight (kg)	13.65±4.32	13.50±4.38	12.3±4.68
Respiratory rate/min	22.90±6.63	23.07±3.92	22.10±5.51
Mean Heart rate/min	110±16.38	112±14.18	114±12.2
MAP (mmHg)	84.67±6.83	83.83±12.8	81.43±11.07
O2 Saturation (%)	97.87±1.19	98.07 ±1.38	98.07±1.28
Duration of surgery (min)	44.37±7.21	46.33±11.27	45.27±4.87

MAP: Mean arterial pressure

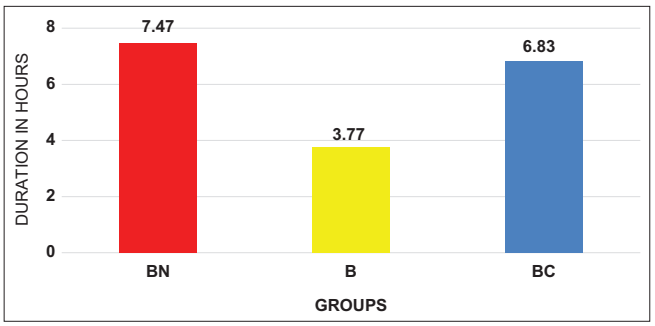

Figure 1: Mean duration of absolute analgesia

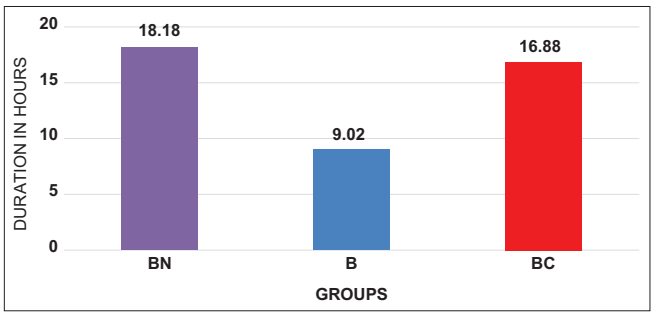

Figure 2: Time of first analgesia

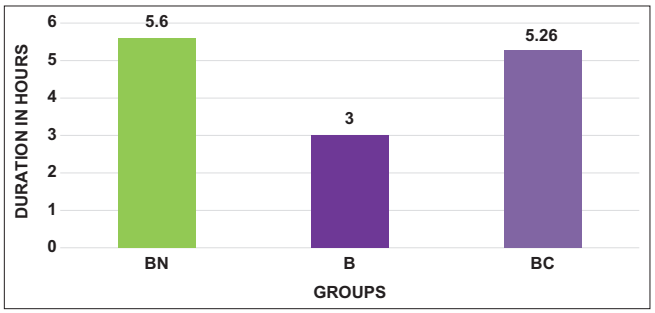

Figure 3: Mean duration of sedation

of Grade 1 motor block which was highest among the three groups and 3.3% incidence of Grade 2 motor block. Group BC had 10% incidence of Grade 1 motor block and 6.7% incidence of Grade 2 motor block. Group BC had the more severe degree of motor block. Group B had 6.7% incidence of Grade 1 motor block and 0% incidence of Grade 2 motor block and had an incidence of least motor block [Figure 4].

DISCUSSION

Caudal analgesia is the most promising central neuraxial block in pediatric age group for perioperative and post-operative analgesia and decreasing the magnitude of stress response in infraumbilical pediatric surgeries. Inadequate pain relief with single shot caudal block perpetuates the need of use of adjuncts such as clonidine and neostigmine to reduce the overall emergence agitation and to get a meaningful prolongation of post-operative analgesia with minimal side effects. This study was carried out to compare the quality and duration of analgesia of caudal bupivacaine with adjuncts neostigmine and clonidine. This was a prospective, double-blind randomized clinical study in which 90 children aged 2–10 years (ASA physical status I-II) received standardized general anesthesia with inhaled sevoflurane and caudal epidural block with 0.25% bupivacaine 1 ml/kg for infra-umbilical surgeries were randomly allocated in three groups each comprising 30 patients wherein one group received 0.25% bupivacaine 1 ml/kg with neostigmine in dose of 2 μg/kg (BN), second group received 0.25% bupivacaine 1 ml/kg with clonidine in dose of 2 μg/kg (BC), and third group received only 0.25% bupivacaine 1 ml/kg (B) as control group. In our study, the addition of neostigmine 2 mcg/kg as adjuvant to 0.25% bupivacaine 1 mL/kg resulted in significant prolongation of analgesia with reduced requirements in post-operative analgesia. Analgesic effect may be explained by transdural diffusion of neostigmine into CSF. Neostigmine, an anticholinesterase drug, inhibits breakdown of acetylcholine, and increases acetylcholine levels at the dorsal horn of spinal cord. Spinal muscarinic

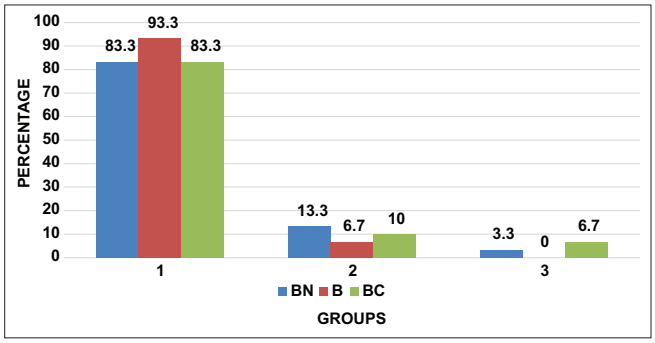

Figure 4: Incidence and duration of motor block

receptors play the important role in analgesia of spinal or epidural neostigmine.[14] Clonidine, an alpha 2 agonist has extensively been used in neuraxial blocks and peripheral nerve blocks to prolong the action of bupivacaine.[13,15-17] It is one of the most commonly used additives with bupivacaine for caudal analgesia in children.[18] Several mechanisms have been suggested for the clonidine-induced prolongation of caudal analgesia with bupivacaine. The anti-nociceptive action is due to the direct suppression of the spinal cord nociceptive neurons by epidural clonidine. Another mechanism is that clonidine crosses the blood brain barrier and interacts with alpha 2 adrenoceptors at spinal and supraspinal sites to produce analgesia. Clonidine also suppresses neurotransmission in peripheral sensory A δ and C nerve fibers. The final mechanism suggested is pharmacokinetically mediated: Clonidine induces vasoconstriction through α-2b adrenoceptors located at the peripheral vascular smooth muscles.[19] The data were collected and analyzed statistically with reference to age, body weight, hemodynamic parameters (Heart rate and Mean arterial pressure) and SpO2 by pulse oximeter, quality of analgesia using five points verbal pain score, rescue analgesia, time of first rescue analgesia, and post-operative complication. All the three groups were homogeneous with reference to age, sex, weight, and both duration of anesthesia and surgery. No significant difference was observed with respect to mean heart rate and mean arterial pressure and oxygen saturation during perioperative period between all three study groups. The mean duration of analgesia in group BN was 7.47 ± 1.4 h while in group BC mean duration of analgesia was 6.83 ± 0.9 h as compared to control group in which it was 3.33 ± 0.6 h. The duration of analgesia in BN and BC was comparable and did not differ significantly ($P > 0.05$). However, the duration of analgesia between group BN and BC as compared to B had a statistically highly significant difference ($P < 0.01$). The duration of absolute analgesia found in our study in group BN was 7.47 ± 1.4 h and was much less as compared to Rajesh *et al.*[7] which was 16.6 h and the duration of absolute analgesia in group BC in our study was 6.83 ± 0.9 h which was less than that reported by Yildiz *et al.* which was 10 h 50 min.[17] These differences could be attributed to the fact that pain scales used were different. The values of absolute analgesia in group BC were 6.83 ± 0.9 h which was comparable to that recorded by Klimscha *et al.* was 6 h,[20] by Cook *et al.*[21] was 5.8 h, and by Tripi and Palmer was 8 h.[16] Time for requirement of first analgesic was longest in group BN which was 18.18 ± 3.5 h, followed by group BC which was 16.68 ± 3.6 h and Group B was 9.03 ± 3.57 h. The time required for first analgesic in group BN was 18.18 ± 3.5 h in our study was comparable to that observed by Abdulatif and El-Sanabary which were 22.8 ± 2.9 h.[8] The time required for first analgesic in group BC in our study was 16.68 ±

3.6 h which was near to that observed by EL-Hennawy *et al.* which was 12 h.[22] From these findings it is clear that addition of neostigmine and clonidine prolong the duration of analgesia when compared with bupivacaine alone. The incidence of nausea and vomiting was maximum in the BN group as compared to BC and bupivacaine group, but was not statistically significant ($P > 0.05$). In our study, the maximum sedation was found in the BN group which was 5.6 ± 1.25 h closely, followed by BC group which was 5.23 ± 1.26 h and with least sedation in Group B which was 3 h. Difference was significant among BN and B, and among BC and B ($P < 0.05$) but not between BN and BC ($P > 0.05$). The incidence and severity of motor block were assessed by modified Bromage scale. Group BN had 13.3% incidence of Grade 1 motor block which was highest among the three groups and 3.3% incidence of Grade 2 motor block. Group BC had 10% incidence of Grade 1 motor block and 6.7% incidence of Grade 2 motor block. Group BC had the more severe degree of motor block. Group B had 6.7% incidence of Grade 1 motor block and 0% incidence of Grade 2 motor block and had a incidence of least motor block.

CONCLUSION

On the basis of this study it is concluded that Neostigmine and clonidine have proven to be reliable adjuvants for prolongation of analgesia in caudal block with less requirement of rescue analgesia and without any significant side effects in paediatric population undergoing infraumbilical surgeries.

REFERENCES

1. Morton N. Pain assessment in children. Pediatr Anesth 1997;7:267-72.
2. Morgan GE, Mikhail MS, Murray MJ. Clinical Anaesthesiology. New York: Lange Medical Books/McGraw Hill Medical; 2006;314-315.
3. Rowney DA, Doyle E. Epidural and subarachnoid blockade in children. Anaesthesia 1998;53:980-1001.
4. Gani TT, Manzoor S, Trumboo ON, Hassan N, Sofi K. Caudal neostigmine and clonidine as adjuncts to bupivacaine for post operative analgesia in children undergoing sub umbilical surgery. J Med Sci Clin Res 2017;5:25844-51.
5. Mrugesh P, Shah TD, Chadha I, Shah BJ. Caudal neostigmine with bupivacaine for postoperative analgesia in pediatric patient comparison with bupivacaine alone. IJBAMR 2016;5:239-47.
6. Warren M, Mark F, David L, Zapol WM, Mackey SC. Anesthesiology and Critical Care. United States: McGraw-Hill Medical; 2008. p. 485.
7. Rajesh M, Grover VK, Chari P. Caudal neostigmine with bupivacaine produces a dose-independent analgesic effect in children. Can J Anesth 2004;53:702-6.
8. 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.
9. Almenrader N, Passariello M, D'Amico G, Haiberger R, Pietropaoli P. Caudal additives for postoperative pain management in children: S(+)-ketamine and neostigmine. Paediatr Anaesth 2005;15:143-7.
10. Kumar P, Rudra A, Pan AK, Acharya A. Caudal additives in pediatrics: A comparison among midazolam, ketamine, and neostigmine coadministered with bupivacaine. Anesth Analg 2005;101:69-73.
11. Tamsen A, Gordh T. Epidural clonidine produces analgesia (letter). Lancet 1984;2:231-2.
12. Eisenach JC, De Kock M, Klimscha W. Alpha agonists for regional anesthesia: A clinical review of clonidine (1984-1995). Anaesthesiology 1996;85:655-74.
13. Jamali S, Monin S, Begon C, Dubousset AM, Ecoffey C. Clonidine in pediatric caudal anesthesia. Anesth Analg 1994;78:663-6.
14. Lauretti GR, Mattos AL, Reis MP, Prado WA. Intrathecal neostigmine for postoperative analgesia after orthopedic surgery. J Clin Anesth 1997; 9:473-7.
15. Lee JJ, Rubin AP. Comparison of a bupivacaine-clonidine mixture with plain bupivacaine for caudal analgesia in children. Br J Anaesth 1994;72:258-62.
16. Tripi PA, Palmer JS. Clonidine increases duration of bupivacaine caudal analgesia for ureteroneocystostomy: A double blind prospective trial. J Urol 2005;174:1081-3.
17. Yildiz TS, Korkmaz F, Solak M, Toker K. Clonidine addition prolongs the duration of caudal analgesia. Acta Anaesthesiol Scand 2006;50:501-4.
18. Menzies R, Congreve K, Herodes V, Berg S, Mason D. A survey of pediatric caudal extradural anesthesia practice. Paediatr Anaesth 2009;19:829-36.
19. Nishina K, Mikawa K. Clonidine in paediatric anaesthesia. Curr Opin Anaesthesiol 2002;15:309-16.
20. Klimscha W, Chiari A, Michalek-Sauberer A, Wildling E, Lerche A, Lorber C, *et al.* The efficacy and safety of a clonidine/bupivacaine combination in caudal blockade for pediatric hernia repair. Anesth Analg 1998;86:54-61.
21. Cook B, Grubb DJ, Aldridge LA, Doyle E. Comparison of the effects of adrenaline, clonidine and ketamine on the duration of caudal analgesia produced by bupivacaine in children. Br J Anaesth 1995;75:698-701.
22. EL-Hennawy AM, Abd-Elwahab AM, Abd-Elmaksoud AM, El-Ozairy HS. Addition of clonidine or dexmedetomidine to Bupivacaine prolongs caudal analgesia in children. Br J Anaesth 2009;103:268-74.

How to cite this article: Godwin RB, Vineeth PT, Gupta A, Setiya M. Comparison of Caudal Neostigmine and Clonidine as an Adjuvant for Post-operative Pain Relief in Infraumbilical Pediatric Surgeries. Int J Sci Stud 2021;9(3):47-51.

Source of Support: Nil, **Conflicts of Interest:** None declared.