InScienz Open Access

Journal of Anesthesia and Advanced Research

Research Article | Volume: 1.1 | Open Access

Caudal Nalbuphine versus Fentanyl with Bupivacaine for Postoperative Analgesia in Children Undergoing Lower Abdominal Surgeries: A Randomized Controlled Double Blind Non –Inferiority Study

Gangur B. Sumalatha[1] and Ravichandra R. Dodawad[2*]

[1,2]*Department of Anaesthesiology, ESIC Medical College, Gulbarga, India*

Abstract

Background and Aims: Nalbuphine is an agonist -antagonist opioid having analgesic and sedative effects and ceiling effect to respiratory depression. The aim of this study is to compare the effect of caudal nalbuphine and fentanyl as adjuvant in providing post-operative analgesia.

Methods: One hundred and ninety two patients with the American society of anesthesiologists' physical status I–II, aged 2–7 years enrolled in this study were randomly assigned in to two groups as (n=96), Group BF(bupivacaine – fentanyl) and BN(bupivacaine -nalbuphine). Both groups received caudal bupivacaine (0.125%) 1ml/kg. Pain was evaluated using Wong -Baker FACES scale post-operatively at the time of first rescue analgesia (FACES-R) and at 24hr (FACES-24h). The frequency of rescue analgesics was also noted along with side effects 24 hr postoperatively.

Results: Comparison of pain scores in both groups did not differ significantly. FACES –R and FACES-24h score in Group BN and Group BF was 1.7±1.1 versus 1.8±1.06 and 0.6±1.3versus 0.3±1.0 respectively which was statistically not significant. The frequency of rescue analgesics received was comparable in both groups. Two children had vomiting in group BF whereas none of the children in group BN complained nausea and vomiting. No other side effects were noted in either group.

Conclusion: Caudal nalbuphine 0.2mg/kg added to bupivacaine provides effective post-operative analgesia and is non-inferior to 1µg/kg of fentanyl with no significant side effects.

Keywords: Analgesia; Bupivacaine; Caudal block; Fentanyl; Nalbuphine;

Introduction

Caudal block is useful as an adjunct during general anaesthesia and for providing post-operative analgesia after infraumblical operations [1]. Fentanyl has been widely used as an analgesic adjuvant to epidural analgesia. However it has undesirable side effects as respiratory depression, itching and vomiting [2,3]. Nalbuphine has relatively potent µ-antagonist and κ-agonist activity. The respiratory depression induced by opioids is primarily mediated by the µ-receptor agonist activity. The µ-antagonist properties of the nalbuphine produce fewer µ-mediated side effects such as respiratory depression, pruritus, nausea and vomiting [4-6]. In addition, presently there are no studies reporting the efficacy of caudal nalbuphine versus fentanyl. The aim of this prospective, randomized, double-blind study, therefore, was to investigate the non-inferiority of nalbuphine to fentanyl and to assess efficacy and side-effects of caudal nalbuphine as an adjuvant by single shot technique in children.

Methods

The study was undertaken after obtaining Institutional ethical committee clearance as well as informed consent from all parents. One hundred and ninety two children in the age group of 2-7 years, American society of anaesthesiologists physical status I-II, posted for elective paediatric short surgical procedures below the umbilicus were included in the study The study was conducted from May 2016 to October 2017. Children with co-existing medical illness, coagulation disorders, anatomical abnormalities of the spine, metabolic and endocrine disorders, infection at the local site, known allergy to local anaesthetics and with anticipated difficult intubation were excluded. Thorough pre-anaesthetic evaluation and required investigations were done the day before surgery. General pre-operative fasting guidelines were followed. One hundred and ninety two children were randomly divided into two groups: Bupivacaine-Fentanyl (BF) and Bupivacaine-Nalbuphine (BN) of 96 each as shown in figure 1. Group BF received 1ml/kg of 0.125% bupivacaine (Anawin 0.25%, Neon laboratories, Andheri East Mumbai) plus fentanyl (Fent 50µg/ml, Neon laboratories, Andheri East, Mumbai) 1µg/kg and Group BN received 1ml/kg of 0.125% bupivacaine plus nalbuphine (Nacphin, 10mg/ml, Neon Laboratories, Andheri East, Mumbai) 0.2mg/kg for caudal block. Randomization was done using computer generated random numbers inserted into opaque-concealed envelopes; inside these envelopes was a number, which indicates the group to which the patient was assigned. The drug was prepared by one anaesthesiologist who gave unlabelled syringes to the anaesthesiologist performing the block who was blinded to the solution of bupivacaine and adjuvant, thus ensuring double blindness of the study. After securing intravenous (IV) access with appropriate- sized IV cannula, all children were pre-medicated before induction. Pre-operative heart rate (HR), blood pressure (BP), oxygen saturation (SPO2) and Respiratory Rate (RR) were recorded using routine monitors. After pre-oxygenation with 100% O2 for 3 min, anaesthesia was induced with injection - Propofol 2mg/kg IV, and tracheal intubation (with appropriate-sized endotracheal tube) was facilitated by injection-

Received date: April 21, 2018; **Accepted date:** : May 29, 2018; **Published date:** June 05, 2018.

***Corresponding Author:** Dr. Ravichandra R Dodawad, Assistant Professor, Department of Anaesthesiology, ESIC Medical College, Gulbarga, #3, 1st floor, Yamunadeep apartments, opposite HKE dental college, jayanagar, Gulbarga, Kartnataka, India, 565105, Tel,: 9986514152, E-mail: rdodawad@gmail.com

Citation: Ravichandra R, wad D, Gangur B, Sumalatha, (2018) Caudal Nalbuphine versus Fentanyl with Bupivacaine for Postoperative Analgesia in Children Undergoing Lower Abdominal Surgeries: A Randomized Controlled Double Blind Non –Inferiority Study. J Anesthe Advan Res 1(1)

succinylcholine 1.5 mg/kg iv followed by Intermittent Positive Pressure Ventilation (IPPV). Anaesthesia was maintained with sevoflurane, N2O and oxygen and injection atracurium 0.3 mg/kg was given for maintenance of neuromuscular blockade. IPPV was continued with Jackson Rees modification of Ayre's T-piece. IV fluid administration was done using Holliday and Segar formula. Thereafter, patients were positioned in a lateral decubitus and caudal space was identified under aseptic technique with 25-gauge needle. After negative aspiration for blood or cerebrospinal fluid, appropriate drugs were injected depending on the group to which they were assigned. The patient was handed over to surgeon after 20 min of caudal block. Any increase in the HR or mean arterial pressure within 15 min of skin incision indicated failure of caudal analgesia. If the readings increased by more than 15%, the child received a rescue opioid and the caudal analgesia was considered failure and the patient was excluded from the study. Hypotension (Systolic pressure; mmHg 70+2× age in years) and bradycardia (HR 20% decrease from baseline for that specific age) [7] if any, were noted and treated appropriately. At the end of surgery, neuromuscular blockade was reversed with injection neostigmine 0.05 mg/kg and injection atropine 0.02 mg/kg. Extubation was done once the extubation criteria were fulfilled. Assessment of pain was done by using Wong-Baker FACES scale [10]. It consists of six Cartoon faces ranging from smiling face for "no pain" to tearful face "worst pain". The score is given from 0-5 indicating as: 0 – no hurt; 1 – hurts little bit; 2-hurts little more; 3- hurts even more; 4-hurts whole lot; 5- hurts worst. Rescue analgesic was given if FACES scale score was ≥ 3 with iv tramadol 1mg/kg

Since, the aim of the study was to test the non-inferiority of nalbuphine to fentanyl; FACES score at the time of rescue analgesia was taken as primary end point. To assess the efficacy of nalbuphine, the mean time for rescue analgesia and the total number of rescue analgesics received in 24h was noted down. The two groups were assessed in the post-operative room for sedation, nausea and vomiting and residual motor block for 15 min for the 1st h and then hourly for 6h. HR, BP, RR and SPO2 were also recorded. After 6h, the children were observed and monitored 6 hourly for 24h using the same parameters. Assessment of sedation was done by Ramsay sedation [12]. Side effects such as post-operative nausea and vomiting, pruritis, urinary retention, and respiratory depression (RR < 10 or SPO2<90%) were recorded.

The required number of subjects per group was calculated from the expression:

$$n = \frac{2 \times (z\alpha + z\beta)^2 \times \sigma^2}{(\mu 2 - \mu 1 - \delta)^2}$$ where μ1 was 2.1 (mean FACES score of fentanyl group in a pilot study), μ2 was 2.5, (mean FACES score of nalbuphine group in a pilot study), the non-inferiority margin was 1.5 and α was 0.05, β was fixed at 0.2. The pilot study included 16 patients and based on this calculation and assuming a 10% dropout rate, the study required 100 patients per group. We assessed 200 patients for eligibility, of which 8 did not meet the inclusion criteria, and 192 were recruited. Figure 1

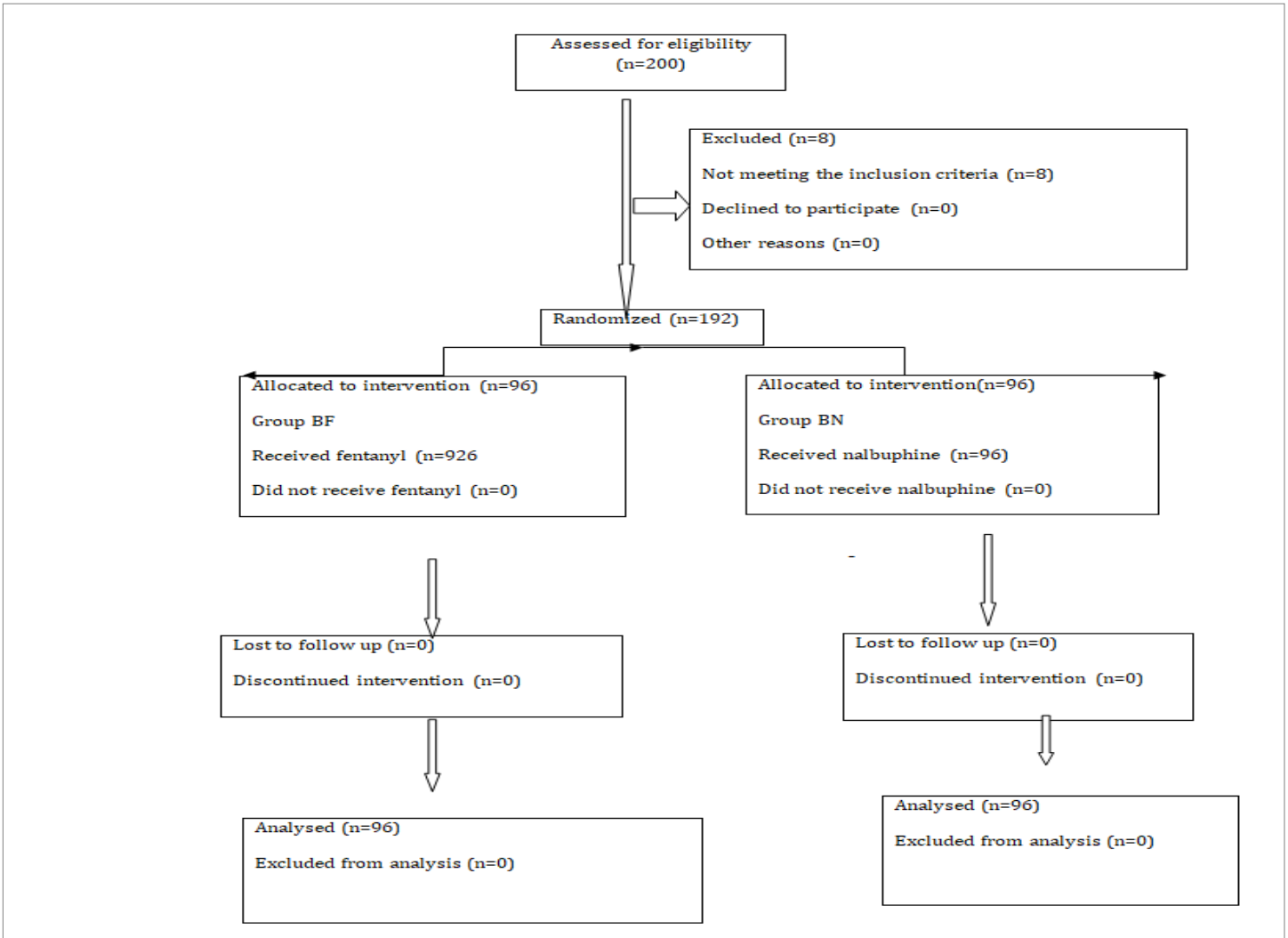


Figure 01: Consort Flow Diagram showing the study phases

depicts the flow diagram of patient progress through the study. All enrolled patients were randomized (group: BN = 96; group BF = 96) and completed the study, and their data were analyzed. All the values were expressed as Mean±SD or percentage. Qualitative data (ASA grade, residual motor block and complications) were compared using Chi-square test incorporating Fishers exact test and quantitative data (age, weight, heart rate, blood pressure, duration of analgesia) were compared using unpaired and paired t-test. A linear mixed model was used to compare simultaneous FACES score, to account for correlations between repeated observations The non inferiority of nalbuphine to fentanyl was analysed using 95% Confidence Intervals (CI) for the difference in FACES score (μ2–μ1, as above). Noninferiority was confirmed when the upper 95% CI was less than the no inferiority margin i.e 1.5(the largest change from the reference value considered to be trivial). All statistical analyses were performed with SPSS® version 17.0 (SPSS Inc., Chicago, IL, USA) for Windows®. P-values <0.05 were considered statistically significant.

Results

The demographic data and types of surgeries between the two groups were comparable as shown in table 1 and figure 2 respectively. There was no statistically significant difference among the two groups as regards to HR, BP and SPO2. The mean FACES score at the time of first rescue analgesia and at 24hr was comparable in both groups and the analgesic effect of nalbuphine was not significantly inferior to that of fentanyl at 24 h after surgery as shown in table 2. Post-operative pain as assessed by FACES scale was comparable in both groups as shown in table 3. In group BF, 92(95.8%) children and in group BN ,90(93.7%) children received 2-times rescue analgesia whereas 4(4.1%) and 6(6.2%) children in group BF and group BN respectively, received 3-times rescue analgesia which was statistically not significant as depicted in table 4. Anaesthetic recovery was not delayed in any child in both the groups. There was no incidence of residual motor block observed in both the groups. The patients in Group BF were significantly more sedated than the ones in Group BN, till 1h postoperatively. The median values of sedation score at 30 min and 60 min are shown in table 5. Beyond this time, the sedation scores were not significantly different amongst the two groups. All the children in the study groups were wide awake and alert by 2h postoperatively. Two children had nausea and vomiting in group BF whereas none of the children in group BN complained nausea and vomiting. No other side effects were observed in either of the group.

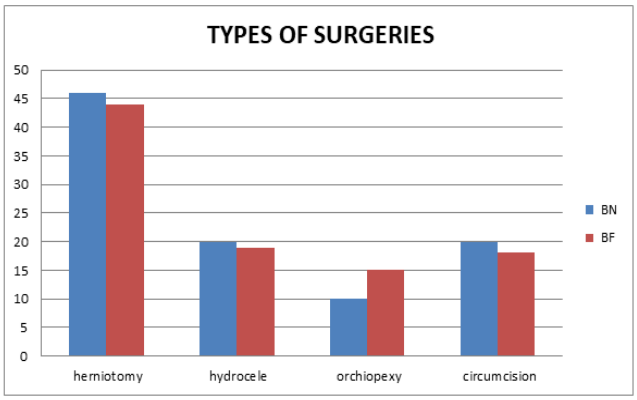


Figure 02: Types of surgeries among the two groups

Table 1: Demographic data

DATA	Mean±SD		*P*
	Group BN	Group BF	
Age (years)	2.9±1.46	3.8±2.31	0.83
Sex (male/female)	93/3	94/2	0.64
Weight (kg)	12±2.88	12.5±2.89	0.29
Duration of surgery (min)	8.33±4.10	8.33±5.77	0.55

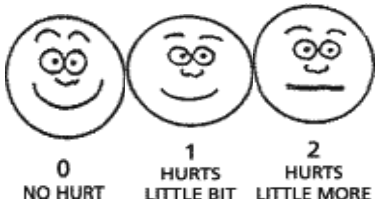
BN – Bupivacaine nalbuphine; BF – Bupivacaine fentanyl; SD – Standard deviation; NS – Not significant

Table 2: Test of non-inferiority between nalbuphine and fentanyl

Parameter value	Group BN n-96	Group BF n-96	*p*
FACES -R	1.7±1.1	1.8±1.06	0.317(NS)
TIME OF 1ST Rq Analgesia	400.5±44.8min	390.5±32.36	0.476(NS)
FACES – 24h	0.6±1.3	0.3± 1.0	0.322(NS)

Data presented as mean±SD, FACES-R – FACES score at the time of first rescue analgesia; Rq – rescue analgesia; min-minutes;FACES -24h- FACES score at 24 h postoperatively; BN – Bupivacaine –nalbuphine, BF-Bupivacaine-fentanyl, NS- not significant

Table 3: Wong–Baker FACES Pain Rating Scale at the time of the first complaint of pain

FACES scale	Group BF		Group BN		*P*
	Cases	Percentage	Cases	Percentage	
	44	45.8	45	46.8	0.510(NS)
	52	43.7	51	53.1	0.437(NS)
Total	96	100	96	100	

BF – Bupivacaine -fentanyl; BN – Bupivacaine nalbuphine; NS – Not significant

Table 4: Frequency of rescue analgesics in 24 hour

Number of rescue analgesics	Group BF		Group BN		P value
	Cases	%	Cases	%	
2 times	92	95.8	90	93.7	0.306(NS)
3 times	4	4.1	6	6.2	0.251(NS)

Group BF- Bupivacaine fentanyl;BN-Bupivacaine –nalbuphine; NS – not significant

Table 5: Median (interquartile range) of sedation score

Sedation scores	Group BN	Group BF	P value
After 30 min	1(1-2)	3(2-3)	0.027*
After 60 min	1(1-2)	3(2-3)	0.015*
After 120 min	1(1-2)	2(1-2)	0.66(NS)

Group BN – Bupivacaine-nalbuphine; Group BF – Bupivacaine-fentanyl; * - significant ;NS-not significant

Discussion

The result of our study showed that addition of 0.2mg/kg as adjuvant to bupivacaine for postoperative analgesia in children undergoing elective lower abdominal surgeries is effective and non-inferior to fentanyl with reduced postoperative FACES pain scores. Nalbuphine is a mixed K-agonist and μ-antagonist opioid of the phenanthrene group and its structure is similar to those of naloxone and oxymorphone. The drug is used for managing slight and moderate pain. Its affinity to K-opioid receptors results in analgesia, sedation and cardiovascular stability with minimal respiratory depression. The analgesic effect of nalbuphine has been found to be equal to the analgesic effect of morphine but unlike it has a ceiling effect on respiration [13]. The drug used in recommended doses is believed not to induce respiratory depression in children. Many authors consider that the profile of its action is safe [14]. The safety and efficacy of nalbuphine is established through the epidural route [15]. The pharmacokinetic profile of epidural nalbuphine was similar to that seen with rapid intravenous injection. The dose of maximum analgesic action of nalbuphine is 0.3-0.4mg/kg. Higher doses neither increase the analgesic effects nor substantially increase the risk of respiratory failure Nalbuphine for post-operative management in children can be used in boluses at a dose of 0.2mg/kg [16].

In one of their study by Salama et al, compared 0.2 mg/kg caudal nalbuphine added to levo-bupivacaine in pediatric infraumblical surgeries and concluded that 0.2mg/kg nalbuphine as an adjuvant was associated with prolonged duration of analgesia and reduced analgesic requirements with no side effects when compared to levo-bupivacaine alone [17]. In another study, caudal nalbuphine at a dose of 0.1mg/kg was compared with caudal dexmedetomidine in which the authors concluded that dexmedetomidine prolonged the duration of analgesia when compared to nalbuphine [18]. Based on these references we decided the dose of nalbuphine as 0.2mg/kg in our study. The dose of the fentanyl 1μg/kg was based on our routine institutional practice. The current study compared the caudal nalbuphine 0.2mg/kg and fentanyl1μg/kg in paediatric population who underwent lower abdominal surgeries in terms of, post operative pain score, sedation score and side effects. As regards to the primary outcome, post-operative pain FACES score caudal nalbuphine and fentanyl did not show statistically significant difference. The mean post –operative FACES score at the time of first rescue analgesic (Group BN 1.7±1.1 versus Group BF 1.8±1.06) and at 24 hr (0.6±1.3 versus 0.3±1.0) were comparable in both groups. Similarly there was no statistically significant difference in the Faces scale. The mean duration of analgesia in nalbuphine and fentanyl groups was comparable. In a study assessing nalbuphine at a dose of 0.2 mg/ kg as adjuvant to levo-bupivacaine, nalbuphine delayed the time for the first analgesic requirement [17]. Similar observation was reported in another study with 0.1mg/kg of caudal nalbuphine [19,20]. These results were consistent with the results of the current study in the effectiveness of nalbuphine in post-operative analgesia but differ in using the concentration of bupivacaine. A study by shin et al, evaluated the postoperative analgesic efficacy of different doses of caudal nalbuphine (3,5 and10mg) with 1.5% lidocaine, in which10 mg of nalbuphine significantly reduced the use of systemic analgesics in the first 24h [21]. Similarly two other studies showed that 10mg of epidural nalbuphine compared to morphine and tramadol provided better quality of analgesia with lesser incidence of side effects and complications with better patient satisfaction score [22,23]. In contrast to these studies, another study compared epidural butorphanol, nalbuphine and fentanyl for postoperative analgesia in lower limb surgeries and the authors concluded that butarphanol has longer duration of analgesia compared to nalbuphine and fentanyl [24].

On note in our study the sedation score was significantly higher in fentanyl group (4 children) and children responded for stimuli till 30 min postoperatively. However at 2h postoperatively, all children were awake and alert. Taking into account the incidence of nausea and vomiting, two children in fentanyl group had nausea and vomiting. However none of the children in nalbuphine group had nausea and vomiting. Compared with other opioids, the nalbuphine-induced incidence of nausea and vomiting is lower [16,21]. The side effects are observed in our study may not reflect the accurate results as our study sample is intended only to find the analgesic efficacy of nalbuphine.

Limitation of this study is the dose of nalbuphine which was comparable to those used for IV analgesic therapy based on various references. Thus our results may reflect systemic effects which needs estimation of blood levels of nalbuphine in future studies. The other limitation includes the small follow up duration of the patients and the lack of important outcomes such as length of hospital stay. Till date no studies have compared the efficacy of caudal fentanyl and nalbuphine in post-operative analgesia especially in paediatric population; therefore further studies are recommended on this aspect.

Conclusion

Nalbuphine 0.2mg/kg in caudal block is non-inferior to 1μg/kg fentanyl in providing efficient analgesia with no significant side effects in the post-operative pain management of children undergoing lower abdominal surgeries.

References

1. Johr M, Berger TM. Caudal blocks. Paediatr Anaesth. 2012;22(1):44-50. doi: 10.1111/j.1460-9592.2011.03669.x

2. Ahuja S, Yadav S, Joshi N, Chaudhary S, Madhu SV. Efficacy of Caudal Fentanyl and Ketamine on Postoperative Pain and Neuroendocrine Stress Response in Children Undergoing Infraumblical and Perineal Surgery –A Pilot Study. J Anaesthesiol Clin Pharmacol. 2015;31;104-109. doi: 10.4103/0970-9185.150558

3. Cousins M. J. & Mather L. E. Intrathecal and epidural administration of opioids. Anesthesiology. 1984;61(3):276–310.

4. J Fioramonti, L Bueno . Centrally acting agents and visceral sensitivity. Gut. 2002;51 Suppl 1:i91-5.

5. Tkacz J, Pesa J, Vo L, Kardel P, Un H, Volpicelli J, et al. Opioid analgesic treated chronic pain patients at risk for problematic use. Am J Manag Care. 2013;19:871-880.

6. Gunion M, MarchionneA, Corrie T. Use of the mixed agonist-antagonist nalbuphine in opioid based analgesia. Acute Pain. 2004;6(1):29-39.

7. Elham M. El-Feky, Ahmed A.abd El Aziz. Fentanyl, dexmedetomidine, dexamethasone as adjuvant to local anesthetics in caudal analgesia in pediatrics: A comparative study. Egyptian journal of anaesthesia. 2015;31(2):175-180.

8. Aldrete JA, Kroulik DA. Post Anaesthetic recovery score. Anesth Analg. 1970;49:924-934.

9. International association for study of pain, Subcommittee on Taxonomy. Pain terms: a list with definitions and notes on usage. Pain. 1979;6:249-252.

10. Chambers CT, Giesbercht K, Craig KD, Bennett SM, Huntsman E. A comparison of facies scales for the measurement of paediatric Children's and parents' ratings. Pain. 1999;83:25-35.

11. Gehdoo RP. Postoperative pain management in paediatric patients. Indian Journal of Anaesthesia. 2004;48:406-414.

12. Mason KP, Lubisch BN, Robinson F, Roskos R. Intramuscular Dexmedetomidine Sedation for Pediatric MRI and CT. American Journal of Roentgenology. 2011;197:720-725. doi: 10.2214/AJR.10.6134.

13. Gear R.W, Miaskowski, C. and Gorden, N.C. The Kappa Opioid Nalbuphine Produces Gender and Dose Dependent Analgesia and Antianalgesia in Patients with Postoperative Pain. Pain. 1999;83(2):339-45.

14. Berg AA ,Honjol NM, Prabhu NV , Datta S, Rozario J, Muraleedaran R, et al. Analgesics and ENT surgery. A clinical comparison of the intraoperative, recovery and postoperative effects of buprenorphine, diclofenac, fentanyl, morphine, nalbuphine, pethidine and placebo given intravenously with induction of anaesthesia. Br J Clin Pharmacol. 1994;38:533–543.

15. Baxter AD, LaganièreS, Samson B, Hull K. A dose-response study of nalbuphine for post-thoracotomy epidural analgesia. Canadian Journal of Anaesthesia. 1991;38(2):175-182.

16. Anna Kubica-Cielińska, Marzena Zielińska. The use of nalbuphine in paediatric anaesthesia. Anaesthesiology Intensive Therapy. 2015:47(3);252–256. doi: 10.5603/AIT.2015.0036

17. Salama AK. Comparison between caudal levobupivacaine versus levobupivacaine–nalbuphine for postoperative analgesia in children undergoing hernia repair: A randomized controlled double blind study. Egyptian Journal of Anaesthesia. 2016;32:83–87.

18. Salama AK, Galante D, Abdallah NM. Comparison between caudal dexmedetomidine and nalbuphine in children undergoing hypospadias surgery: a prospective randomized double blind controlled study. Pediatric Anesthesia and Critical Care Journal. 2016;4(1):48-54. doi:10.14587/paccj.2016.10

19. Mohamed MF, Husein RM, El Sonbaty MI, Khattab SM. A comparative study of caudal epidural bupivacaine and bupivacaine plus nalbuphine in postoperative analgesia in children. Ain-Shams J Anaesthesiol. 2015;8:628-633.

20. Saleh RH, Mohammad FY, Heba Mohammad Nassar, Tamer Fathy Younes. Effect of nalbuphine as an adjuvant on levobupivacaine induced caudal analgesia in children undergoing surgical procedures, controlled randomized double blinded study. Egyptian Journal of Anaesthesia. 2016;32:97-102.

21. Shin JS, Yoon DM, Lee KM, Oh HK. Postoperative analgesia by caudal nalbuphine HCL. J Kor Pain Soc. 1990;3(1):44–50.

22. Mok MS, Lippmann M, Wang JJ, Chan KH, Lee TY. Efficacy of epidural nalbuphine in postoperative pain control. Anesthesiology. 1984;61(3A).

23. Chatrath V, Attri J P, Bala A, Ranjana Khetarpal, DeeptiAhuja, and Sawinder Kaur. Epidural nalbuphine for postoperative analgesia in orthopedic surgery. Anesth Essays Res. 2015;9(3):326–330. doi: 10.4103/0259-1162.158004

24. Banerjee S, Pattnaik SK. A Comparative study between epidural butorphanol, nalbuphine and fentanyl for post-operative analgesia in lower abdominal susrgeries. Asian J Pharm Clin Res. 2017;10(5):383-388.