A COMPARATIVE STUDY OF INTRAVENOUS NALBUPHINE AND FENTANYL GIVEN AT THE TIME OF INDUCTION FOR POST-OPERATIVE PAIN RELIEF IN CHILDREN UNDERGOING ADENOTONSILLECTOMY/ TONSILLECTOMY PROCEDURE

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ABSTRACT

BACKGROUND

Adenotonsillectomy/tonsillectomy is a routinely performed surgery in children and has a very high incidence of postoperative pain. This study was undertaken to compare efficacy of nalbuphine and fentanyl for post-operative pain relief in children following surgery.

MATERIALS AND METHODS

Sixty patients aged 5 - 15 yrs. of ASA grade I and II, scheduled for elective adenotonsillectomy/tonsillectomy were enrolled in this double-blind prospective randomised study. Patients were randomly divided into two: Group N (N= 30) received nalbuphine 0.2 mg/kg and Group F (N= 30) received fentanyl 1.5 mcg/kg respectively at the time of induction of anaesthesia. Patients were observed post-operatively by blinded observer for sedation, pain and nausea/ vomiting at 1 hr, 2 hrs. and 4 hrs. interval.

RESULTS

With statistical analysis using unpaired t-test for all quantitative variables and Z-test, chi-square test for qualitative variables and proportions it was observed that patients who received nalbuphine had significantly lower pain score at 1 hr ($p < 0.0004$), 2 hrs. ($p < 0.0001$) and 4 hrs. ($p < 0.0001$) and significantly less number of patients required additional analgesic supplement (16.6%) as compared to fentanyl group, where more number of children required additional analgesia (76.6%). Duration of post-operative analgesia was also longer in nalbuphine group. On sedation score, nalbuphine group children appeared more calm, tranquil and easily arousable. There was no significant difference observed with regard to nausea and vomiting.

CONCLUSION

Intravenous nalbuphine compared to fentanyl renders extended time of postoperative analgesia without added side-effect. Freedom from controlled drug act regulation makes it better option for day care surgery like tonsillectomy than routinely used fentanyl.

KEYWORDS

Anaesthesia, Adenotonsillectomy, Post-Operative Analgesia, Fentanyl, Nalbuphine.

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BACKGROUND

Many surgeries are being performed on day care basis in children, tonsillectomy/ adenoidectomy is one of them. Tonsillectomy is a very painful procedure with severe postoperative pain. As many as in 20% of children, severe pain has been reported postoperatively. As it is a day care surgery requiring awake, stable patient for early discharge; optimal perioperative pain relief still remains a challenge.[1] To find the ideal one, many techniques and drugs had been tried so far to decrease the postoperative pain. To name the few: Opioids,[2] NSAIDS,[2] local anaesthetic,[3] acetaminophen,[4] dexamethasone[4] and ketamine.[5]

The challenge lies in adequate pain relief balancing with comfortable awake child with no nausea, vomiting and child should be able to accept early oral intake. Opioids traditionally considered the bench mark drugs for acute pain relief but are associated with postoperative excessive sedation, acute respiratory depression, apnoea, nausea, vomiting and pruritus.[6] Many ENT surgeons hesitate to use NSAIDs, because earlier studies were indicative of increased bleeding and re-operation when used NSAIDs,[7] but recent reviews did not support that[8] Ketamine which is NMDA antagonist was also thought to give adequate post-operative analgesia when used in sub-anaesthetic dose with varying results. Some studies find it very effective,[5] while other studies deny its efficacy for postoperative pain relief.[9] Also the known unpleasant emergence and abnormal

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psychological behaviour limits its use in children.[10,11] A systematic review of local anaesthetic infiltration failed to show effective pain relief in postoperative period.[3] Acetaminophen, non-opioid analgesic also failed to provide adequate postoperative analgesia when used as sole agent.[12] Shorter acting opioids like fentanyl, remifentanil, alfentanil, also failed to give adequate post-operative pain relief.[13]

Fentanyl is synthetic opioid agonist related to phenylpiperidine group; it is short acting with ½ life of (10 - 20) mins. and duration of action (30 - 60 mins.). It is routinely used now-a-days in India. As analgesic it is 100 times more potent than gold standard morphine, but associated with increased risk of apnoea and hypoxaemia when used with midazolam.[14] Also post-operative analgesia coverage is limited.[15] These effects are undesirable for children in day care procedure. Also now-a-days fentanyl comes under "controlled drug regulation act," so not easily and freely available which is the real problem.

On the other hand, our study drug nalbuphine is a synthetic partial kappa (ka) agonist and mu (mu) receptor antagonist; of phenanthrene series with half-life of 0.9 - 1.9 hrs. and duration of action 240 - 300 mins. in children.[16] Drug was synthesised in an attempt to produce analgesia without undesirable side-effect like respiratory depression, pruritus and drug dependence, as these are mu receptor mediated. Thus it exhibits ceiling effect to respiratory depression, drug dependence and analgesia.[17] Nalbuphine shows lower incidence of nausea, vomiting and pruritus than morphine.[18,19,20] Nalbuphine has been shown to be safe and effective in paediatric age group.[21] It is used mainly for moderate-to-severe pain. Studies have shown it to be superior over fentanyl[22,23] /morphine[24] /NSAIDS[2] /pethidine[25] in adults. Also it has been shown to provide satisfactory post-operative analgesia following open surgery,[26] orthopaedic surgeries.[2] Studies have shown its safety even in medically compromised patients.[15] There are many studies to show its effectiveness in children undergoing thoracotomy, abdominal procedures and cardiac surgeries.[27,28] Thus, it has been widely used drug for day care surgeries in adults and children. It is free from controlled drug act regulation and its free availability made us try to use it and compare it with fentanyl for tonsillectomy/ adenotonsillectomy surgeries on hypothesis that its long duration of action and ability to give postoperative calm and tranquil child will be beneficial to increase patient satisfaction, to decrease postoperative analgesic requirement and thus to decrease overall morbidity.

MATERIALS AND METHODS

After approval from Institutional Ethical Committee, a total 60 children of ASA I and II, aged between 5 to 15 years of either sex scheduled for elective tonsillectomy/ adenotonsillectomy under general anaesthesia were selected. Written informed consent was obtained from parents of all children. Children giving history of asthma or allergy to any drug were not included. Children with any other systemic illnesses were not included. Each child was assessed properly for fitness of anaesthesia and was kept NBM for at least 6 hrs. pre-operatively and 4 hrs. post-operatively. Patients were divided randomly into two groups by computer generated random number allocation. N group (N= 30) which received nalbuphine 0.2 mg/kg[21] and F group (N= 30) which received fentanyl 1.5 mcg/kg.[2]

Patient was taken inside operation theatre, 22 no. intravenous cannula inserted on dorsum of the hand. Standard multipara (SP02, ECG, NIBP, etCO2) monitor attached, baseline readings noted and patient given premedication in the form of midazolam 0.04 mg/kg and glycopyrrolate 0.004 mg/kg. Then N group received Inj. Nalbuphine 0.2 mg/kg and F group received Inj. fentanyl 1.5 mcg/kg before induction of anaesthesia. Patients were preoxygenated with 100% oxygen and induced with Inj. propofol 2 - 3 mg/kg followed by atracurium 0.5 mg/kg and intubated with proper size endotracheal tube and maintained on 02:N20: 33:66 and Isoflurane 1 - 1.2% on IPPV. Towards end of surgery ondansetron was given in dose of 0.1 mg/kg. And after seeing good respiratory attempts and TOF of 2 - 3 patient was reversed with neostigmine 0.04 mg/kg and glycopyrrolate 0.008 mg/kg. Patient was extubated after confirming good tone, power, blast and reflexes and TOF of 4. Operative time was noted.

Patient was shifted to recovery room and monitor was attached.

In recovery room, nurse was asked to observe and note the following at 1 hr., 2 hrs., 4 hrs. interval (she was unaware of drug used inside operation theatre).

i) Sedation (According to Ramsay sedation scale).
   - Asleep.
   - Awake, calm and comfortable.
   - Awake, restless and/or crying.

ii) Pain Score (According to VAS and facial expression chart)[29]
   - Mild 1 (VAS 1-3)
   - Moderate 2 (VAS 4-6)
   - Severe 3 (VAS >= 7)

iii) Nausea and vomiting scale.[30]
   - No 0
   - Mild nausea 1
   - Moderate/ Severe nausea 2
   - Vomiting 3

iv) Time when supplementary analgesia was required.

Supplementary analgesia was provided to patients with severe pain or on demand for pain relief or continuous cry for more than 5 mins. in the form of intramuscular Inj. Diclofenac Na 1.5 mg/kg,[31] Inj. metoclopramide 0.2 mg/kg was given to patient with vomiting/severe nausea. Any other side effect like dizziness, headache, pruritus, respiratory depression (RR < 8/min or SpO2 < 90%) and bleeding were noted.

v) Discharge time was also noted.

OBSERVATIONS AND RESULTS

All the descriptive statistics and master-chart is prepared by using MS-Excel 2007. All quantitative variables are compared by using unpaired t-test. Qualitative variables are compared by using Z-test for proportions and chi-square test wherever

applicable. Probability ($p < 0.05$) is considered as statistically significant at % level of significance. For data analysis GraphPad, QuickCal and GraphPad InStat software were used.

Table 1 show the two groups of children were similar with respect to age, sex, ASA grade, type of surgery and duration of surgery. Also basal haemodynamic parameters remained within normal limits in both the groups.

Parameter	Nalbuphine (N= 30)	Fentanyl (N= 30)	P value
Age	9.16 ± 2.79	9 ± 2.62	0.81 (NS)
Weight	23.96 ± 5.16	23.06 ± 5.14	0.46 (NS)
Sex M/F	16/14	17/13	NS
Surgery Type Adenotonsil/ tonsil	16/14	17/13	NS
Time for surgery in min	33.6 ± 5.14	32.83 ± 5.24	0.56 (NS)
ASA Grade 1	30	30	0 (NS)

Table 1. Demography of Children Expressed as Mean (SEM)

NS= Not Significant.

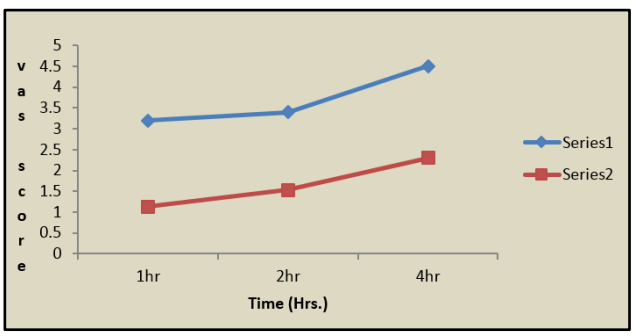
Table 2 shows there was significantly less pain postoperatively in Nalbuphine group at 1 hour (P= 0.0004), 2 hrs. (P< 0.0001) and 4 hrs. (p< 0.0001) as compared to Fentanyl group. Out of 30, only 5 children i.e. 16% required supplementary analgesia and average time to give that was 3 hrs. While in fentanyl group, out of 30 children 23 i.e. 77% which is significantly high number (p< 0.005) required supplementary analgesia and average time to give was 1.5 hrs. which is early and significant ($p < 0.005$) as compared to nalbuphine group.

	Nalbuphine (N= 30)	Fentanyl (N= 30)	P value
VAS at 1 Hr.	1.13 ± 1.59	3.2 ± 2.49	0.0004**
VAS at 2 Hrs.	1.53 ± 1.75	3.4 ± 1.67	<0.0001**
VAS at 4 Hrs.	2.3 ± 1.76	4.5 ± 1.67	<0.0001**

Table 2. VAS Score at Various Interval in Recovery (Mean and Std. Deviation)

**=Very Very Significant.

VAS Score Graph



Graph Diagram of VAS Score

Horizontal is 'X' axis representing time in hours.

Vertical is 'Y' axis representing VAS score.

Series 1= fentanyl F group, Series 2= nalbuphine N group.

According to Table 3, it was observed that at the end of 1st hr. postoperatively in nalbuphine group 18 out of 30 i.e. 60% children were quiet and asleep, while only 6 i.e. 20% were asleep in fentanyl group. This difference is highly significant ($p < 0.0016$) amongst awake children, 2 out of 12 i.e. 16.6% were restless in nalbuphine group, while 8 out of 24 i.e. 33.3% were restless in fentanyl group.

Time	Nalbuphine (N= 30)	Fentanyl (N= 30)
1 hour Asleep Awake and calm Awake and restless	18 10 (out of 12 awake, i.e. 83.4%) 2 (out of 12 awake, i.e. 16.6%)	6 16 (out of 24 awake, i.e. 66.6%) 8 (out of 24 awake, i.e. 33.3%)
2 hours Asleep Awake and calm Awake and restless	10 15 (out of 20 awake, i.e. 75%) 5 (out of 20 awake, i.e. 25%)	2 18 (out of 28 awake, i.e. 64%) 10 (out of 28 awake, i.e. 36%)
4 hours Asleep Awake and calm Awake and restless	0 26 (87% of awake) 4 (13% of awake)	0 22 (74% of awake) 8 (26% of awake)

Table 3. Postoperative Sedation Score

At 2 hrs. postoperatively, we found that out of 20 awake children 75% i.e. 15 were calm and comfortable and 25% i.e. 5 were restless in nalbuphine group. In fentanyl group, our observation was 64% were calm and comfortable and 36% were restless.

At 4 hrs. postoperatively our findings were in both the groups all children were widely awake and 13% were in pain in nalbuphine group, while 26% were in pain in fentanyl group.

We observed that supplementary analgesia required in 16.6% of children in nalbuphine group as compared to fentanyl group where 76.6% children required it. Duration of analgesia was prolonged in nalbuphine group as evident by mean time to give supplementary analgesia, it was 3 hrs. in nalbuphine group as compared to 1.5 hrs. in fentanyl group.

Table 4 showed that there was no significant difference in both the groups with regard to side effects like nausea and

vomiting. Also not a single patient in any group had headache, dizziness, pruritus or respiratory depression.

Nausea Vomiting Score	Nalbuphine (N= 30)	Fentanyl (N= 30)	P Value
No (0)	14	13	0.75 (NS)
Mild (1)	10	10	-
Severe (2)	3	5	0.42 (NS)
Vomiting (3)	3	2	0.67 (NS)

Table 4. Postoperative Nausea and Vomiting Score

NS= Not Significant.

All children did meet discharge criteria in time and were discharged without delay.

DISCUSSION

This study was undertaken to compare efficacy of nalbuphine and most commonly used fentanyl for postoperative pain relief in children undergoing tonsillectomy procedure. We found that incidence of postoperative moderate-to-severe pain was significantly less in nalbuphine group. Similar results were obtained in other studies, where nalbuphine was compared to fentanyl.[22,23] Here author compared these drugs for day care procedure of termination of pregnancy in first trimester. In other study[32,33] tramadol was compared to nalbuphine in children, given as postoperative infusion. Analgesia profile of nalbuphine was better than morphine in adults with less side effects.[19,20] Nalbuphine has advantage of ceiling effect on respiratory depression, which we are worried all the time in paediatric patients and specially in day care surgeries. It has been found that even in doses as high as 0.8 mg/kg, it has no respiratory depression.[34] Pharmacokinetics of nalbuphine in children allowed us to use it in day care setup with analgesia up to 300 mins.[35] In our study, we found that supplementary analgesia required was significantly less (16.6%) in nalbuphine group as compared to fentanyl group (76.6%). Duration of analgesia is calculated by the time for which children were pain-free comfortable not demanding additional pain relief, after which supplementary analgesia was administered in the form of injection diclofenac intramuscularly. This duration was prolonged in nalbuphine group. We found it advantageous with regard to risk involved in giving parenteral diclofenac and many times ENT surgeons are also not willing to give it for fear of bleeding. It was found with sedation score that nalbuphine group children were more calm, tranquil and thus comfortable. Though they were sleeping they were easily arousable and even could answer properly, so we were not worried about bleeding that might go unnoticed. It is well known that crying, agitated restless children have directly proportional impact on postoperative bleeding.[1,2,30] So we want children to be more calm and comfortable. Also comfortable pain-free child accepts early oral intake which is added advantage. Though nalbuphine is long acting drug with ½ life of 1.9 hrs. in children, it is observed that with given dose of 0.2 mg/kg children were fully awake and comfortable within 2 hrs. So they met discharge criteria in time after 4 hrs.

There was no significant difference in side effect of nausea and vomiting in both the groups. Also no other side effects like dizziness, headache, pruritus and respiratory depression was observed in any group and these findings were similar to other studies.[2,23,22]

We thought of using nalbuphine, as its analgesic potency is comparable to morphine with added advantage of prolonged duration of action and ceiling effect on respiratory depression[19,20,28] with no pruritus and minimal nausea and vomiting. With chosen dose of 0.2 mg/kg, recovery is fast with full wakefulness. The most advantage is unlike fentanyl it is free from Controlled Drug Act (Misuse of Drugs Act) regulation. That means it does not have any restriction for its use and is readily and freely available even in peripheral unit. On the other hand fentanyl which is actually 100 times more potent than morphine has failed to provide adequate postoperative analgesia for more than one hr. With fentanyl there are concerns about postoperative respiratory depression, hypoxaemia and apnoea, mainly in children when used with benzodiazepines. Another issue is fentanyl comes under controlled drug act regulation, so not easily available everywhere.

CONCLUSION

Nalbuphine produces significant reduction in incidence of postoperative pain in first 4 hrs. after tonsillectomy as compared to fentanyl without any added side effect. Also nalbuphine group children were calmer and comfortable, which is a desirable advantage. Freedom from controlled drug act regulation and improved quality of analgesia makes it safer and superior alternative to more commonly used fentanyl. We recommend nalbuphine for day care tonsillectomy/ adenotonsillectomy procedures in children.

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