Open Access Maced J Med Sci **electronic publication ahead of print,**
published on March 29, 2019 as https://doi.org/10.3889/oamjms.2019.243

ID Design Press, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences.
https://doi.org/10.3889/oamjms.2019.243
eISSN: 1857-9655
Clinical Science

Efficacy and Safety of Intravenous Ketorolac versus Nalbuphine in Relieving Postoperative Pain after Tonsillectomy in Children

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Citation: Eladi IA, Mourad KH, Youssef AN, Abdelrazek AA, Ramadan MA. Efficacy and Safety of Intravenous Ketorolac versus Nalbuphine in Relieving Postoperative Pain after Tonsillectomy in Children. Open Access Maced J Med Sci. https://doi.org/10.3889/oamjms.2019.243

Keywords: Ketorolac; Analgesia; Nalbuphine; Postoperative pain; Adenotonsillectomy

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Received: 14-Feb-2019; **Revised:** 22-Mar-2019; **Accepted:** 23-Mar-2019; **Online first:** 29-Mar-2019

Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Pain is a major postoperative complication worldwide, which in turn impairs normal body performance and increases postoperative morbidity, hospitalisation, and the susceptibility to infections which also lead to chronic pain development.

AIM: The purpose of this study was to evaluate the efficacy of intravenous ketorolac versus nalbuphine as analgesia after adenotonsillectomy surgery to determine the optimal procedure for pain control and postoperative reduction of analgesic use.

METHODS: A group of 100 pediatric patients undergoing tonsillectomy or adenotonsillectomy were assigned as follows to two equal groups: Group A: 50 patients received intravenous ketorolac 0.9 mg/Kg. Group B: 50 patients received intravenous nalbuphine 0.25 mg/Kg.

RESULTS: FLACC (Face, Legs, Activity, Cry, Consolability) pain score was measured after recovery from anaesthesia (postoperative). There was a statistically significant difference concerning pain score between group 'A' and group 'B' as pain score in 'A' (ranging from 3.18 ± 0.87 to 4.68 ± 0.74) is lower compared to 'B' (ranging from 3.90 ± 0.76 to 5.54 ± 0.73) and probability value < 0.05 except at 90 & 120 min which was observed statistically insignificant. There was no serious postoperative complication detected in either group.

CONCLUSION: It is concluded that intravenous ketorolac is more effective than intravenous nalbuphine in reducing pain intensity and postoperative analgesic requirements after adenotonsillectomy in children.

Introduction

Adenotonsillectomy is one of the most frequent ENT surgeries performed in children. Postoperative pain can influence the ability of the child to tolerate medication for oral pain and fluid intake, resulting in nausea and dehydration in a considerable number of children postoperatively [1], [2].

The operation involves pain in more than 80 per cent of children on the first day of surgery. It is assumed that pain is not treated adequately in half of all surgical procedures [3].

Although opioids are widely used in postoperative pain management, their side effects, especially respiratory depression, bradycardia, nausea and vomiting, have reduced the use of these analgesics, especially in children. Non-steroidal anti-inflammatory drugs (NSAIDs) have been widely used with very good results in pain reduction and postoperative opioid requirements after adenotonsillectomy in children and adults [4], [5], [6], [7], [8].

Nalbuphine is an opioid agonist-antagonist of the phenanthrene series which was synthesised in an attempt to provide analgesia without the undesirable side effects of the pure agonists. Its

analgesic and possibly certain anti-pruritic effects are mediated via actions on the μ and κ-receptors, and nalbuphine has been indicated for mild to moderate pain [9].

NSAIDs act on prostaglandin synthesis for pain reduction with adverse effects such as bleeding problems in both gastrointestinal tracts and from the surgical site and potential renal dysfunction that have caused some concerns in their widespread application [5], [6], [8], [10].

Ketorolac is a non-steroidal anti-inflammatory drug (NSAID) that has an analgesic efficacy similar to commonly used opioids, and that recently has found wide acceptance in the treatment of postoperative pain in a variety of surgical procedures. Ketorolac is used for moderate pain relief; it may be used to treat severe pain when associated with opioids, reducing the opioid dose. The advantage of this association is the reduction of opioid side effects such as respiratory depression, pruritus, urinary retention, sedation and nausea [11], [12], [13].

This study aimed to evaluate the efficacy of intravenous ketorolac versus nalbuphine as analgesia after adenotonsillectomy surgery to determine the optimal procedure for pain control and postoperative reduction of analgesic use.

Patients and Methods

This is a prospective randomised clinical study designed to assess the effect of intravenous ketorolac versus intravenous nalbuphine on postoperative pain after tonsillectomy in children.

The study was carried out in Children Hospital of Cairo University (Abu El Reish) on 100 pediatric patients following the approval of the Ethical committee and obtaining informed consent from parents.

Inclusion criteria:

- ASA physical status I & II.
- Age between 2 years & 10 years old.
- Body weight below 30 Kg.

Exclusion criteria:

- ASA physical status ≥ III.
- Age below 2 years & above 10 years old.
- Body weight above 30 Kg.
- Any contraindications to any drug used.

Methodology in details

One hundred patients meeting the inclusion criteria were randomly assigned into two equal groups:

Group A: 50 patients received intravenous ketorolac 0.9 mg/Kg**.**

Group B: 50 patients received intravenous nalbuphine 0.25 mg/Kg.

The investigators did not know the details of the series and the group assignment was kept in the assets of sealed envelopes with only the case number on the outside.

Anesthetic Management

All patients were visited preoperatively on the day before surgery. The entire procedure has been explained to the patient, and informed consent has been taken. Full history has been taken including diseases, bleeding, drug intake, allergy or drug sensitivity and previous anaesthetic experience. Complete general examination including airway evaluation, chest and cardiac auscultation was conducted. All patients fasted for an appropriate period (6 hours for food, 4 hours for water). Laboratory evaluation: complete blood count (CBC), prothrombin time and concentration (PT&PC), INR, liver function tests, renal function tests. Upon arrival at the operating theatre, IV access was established by 22 G cannula insertion.

Five lead ECG pulse oximeter and non-invasive ABP were monitored. Premedication injection: atropine sulfate intravenously 0.01 mg/kg and dexamethasone intravenously 0.2 mg/kg. Induction of anaesthesia by inhalation sevoflurane and oral endotracheal intubation of appropriate size was done. After induction of anaesthesia, children were randomly allocated to receive 0.9 mg/Kg ketorolac or 0.25 mg/Kg nalbuphine administered as an intravenous injection. Anaesthesia was maintained by isoflurane inhalation. IV fluids according to body weight “Hartmann's solution”, 1st 10 kg 4 ml/kg, 2nd 10 kg 2 ml/kg and for each kg above 20 kg 1 ml/kg fluids.

Data collected

1-patients characteristics and demographic data were collected; age, gender, weight.

2-Postoperative pain, using “FLACC score “(face, legs, activity, cry,consolability) this scale (Table 1) is scored between a range of 0-10 with zero representing no pain. The scale has 5 criteria each assigned a score of 0, 1, 2. Pain was recorded at 15, 30, 45, 60, 90, 120, 180, 240, 300 and 360 minutes postoperatively. Postoperatively intramuscular ketoprofen (1 mg/kg) was used as ‘‘rescue analgesia” if pain score > 5.

Table: 1 FLACC pain score [14]

Criteria	Score 0	Score 1	Score 2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, uninterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs were 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
Consolability	Content, relaxed	Reassured by occasional touching, hugging or being talked to, distractible	Difficult to console or comfort

3-Postoperative sedation, using Ramsay sedation score (Table 2).

Table 2: Ramsay sedation score [15]

Score	Observation
1	Anxious, agitated or restless.
2	Cooperative, oriented and tranquil
3	Responsive to commands.
4	Asleep, but with brisk response to a light glabellar tap or loud auditory stimulus.
5	Asleep, sluggish response to a glabellar tap or auditory Stimulus.
6	Asleep, no response.

4-Postoperative vomiting occurrence.

5-Postoperative side effects: respiratory depression, oedema, rash or itching were also assessed.

Statistical analysis

Data were statistically described, when appropriate, in terms of mean ± standard deviation (± SD), frequencies (number of cases) and relative frequencies (percentages). The student t-test was used to compare quantitative variables among the study groups. For comparing categorical data, Chi-square ($\chi 2$) test was performed. When the expected frequency is less than 5, an exact test was used instead. A probability value (*p*-value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2010 (Microsoft Corporation, NY, and USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 21 for Microsoft Windows.

Results

One hundred (100) patients were included in this study and randomly allocated into 2 groups: group A (ketorolac) and group B (nalbuphine).

Table 3: Demographic data (age & weight)

Demographic data/Groups	A	B
Age	5.18 ± 1.17	5.04 ± 1.26
Weight	17.06 ± 4.2	16.28 ± 4.63

Data expressed as mean ± (SD); P value > 0.05.

ASA status is the same in all patients of both groups “ASA 1”.

There was no statistical difference in age, weight, and sex between the groups (Table 3 and 4).

Table 4: Demographic data (sex)

Sex/Groups	A	B
Male	39/50	36/50
Female	11/50	14/50

Data expressed as count.; P value > 0.05.

FLACC pain score was measured after recovery from anaesthesia (postoperative). There was a statistically significant difference concerning pain score between group ‘A’ and group ‘B’ as pain score in 'A' (ranging from 3.18 ± 0.87 to 4.68 ± 0.74) is lower compared to 'B' (ranging from 3.90 ± 0.76 to 5.54 ± 0.73) and P-value < 0.05 except at 90 & 120 min which was observed statistically insignificant (Table 5) (Figure 1).

Table 5: FLACC score at (6 hours) postoperatively

	Group A	Group B
15 min	3.18 ± 0.87	3.96 ± 0.83*
30 min	3.36 ± 0.80	3.90 ± 0.76*
45 min	3.40 ± 0.67	4.34 ± 0.48*
60 min	3.48 ± 0.65	4.34 ± 0.48*
90 min	3.96 ± 0.61	4.04 ± 0.19
120 min	3.96 ± 0.61	4.04 ± 0.19
180 min	4.28 ± 0.53	4.52 ± 0.51*
240 min	4.48 ± 0.65	5.34 ± 1.00*
300 min	4.68 ± 0.74	5.54 ± 0.73*
360 min	4.52 ± 0.58	5.00 ± 0.49*

Data expressed as mean ± (SD); *P value < 0.05.

A number of patients who needed rescue analgesia (ketoprofen 1 mg/kg I.M.) were recorded. None of the patients required analgesia in the first two hours (as pain score was < 5) postoperatively in both groups.

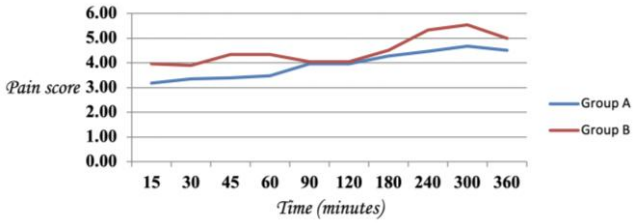

Figure 1: FLACC pain scale 6 hours postoperative

There was a significant difference concerning the analgesic need between the two groups being lower in ‘A’ group compared to ‘B’ group which was statistically significant in 2-4 hours after surgery (group A 8% of cases while group B 32% of cases producing p-value < 0.05) and statistically insignificant in 4-6 hours after end of the surgery, however lower number of cases in group A compared to B (12% and 18% of cases respectively) producing p-value > 0.05 (Table 6).

Ramsay sedation score was significantly higher in group ‘B’ when compared to group ‘A’ at 0 and 30 minutes after recovery. But both groups have the same score (which is 2) from 30 minutes to 6 hours postoperatively (Table 7).

Table 6: Need for rescue analgesia (Ketoprofen) at 6 hours postoperative

		Group A	Group B
1st 2 hours postoperatively	Count	0/50	0/50
	% within gruop	0%	0%
2nd 2 hours postoperatively	Count	4/50	16/50*
	% within gruop	8%	32%*
3rd 2 hours postoperatively	Count	6/50	9/50
	% within gruop	12%	18%
Total	Count	10/50	25/50*
	% within gruop	20%	50%*

* P value < 0.05.

The incidence of vomiting was monitored after surgery and was statistically different and significant between both groups being high in 'B' group compared to 'A' group which required intervention (Table 8).

Table 7: Ramsay sedation score

	Group A	Group B
15 min	1 ± 0	2.08 ± 0.9*
30 min	1 ± 0	2.56 ± 0.541*
30-360 min	2 ± 0	2±0

* P value < 0.05.

Although 6% of cases (3 cases out of 50) in group B developed respiratory depression "which was statistically insignificant as p-value <0.05", it is clinically significant and vitally important required immediate intervention (Table 9).

Table 8: Incidence of vomiting

		Group A	Group B
Vomiting	Count	2/50	8/50*
	% within gruop	4%	16%*

* P value < 0.05.

There was no serious postoperative complication detected in either group.

Table 9: Respiratory depression

		Group A	Group B
Respiratory depression	Count	0/50	3/50
	% within gruop	0%	6%

P value > 0.05.

Discussion

Many studies were concerned with the post-tonsillectomy pain management. These studies studied different routes, drugs and mechanisms for that pain management, e.g. I.V, I.M, rectal, local infiltration, etc. [16]. In this study, we found that patients had less pain in 'group A' with FLACC pain score (ranging from 3.18 ± 0.87 to 4.68 ± 0.741) compared to 'group B' with FLACC pain score (ranging from 3.90 ± 0.763 to 5.54 ± 0.734) six hours postoperatively and rescue analgesia was needed in less number of patients at 2-4 and 4-6 hours in 'group A' (20%) compared to 'group B' (50%) which was statistically significant. So intravenous ketorolac 'group A' reduces pain intensity and postoperative analgesic requirements compared to nalbuphine 'group B' group after adenotonsillectomy in children.

In consistency with this study, Forrest et al. reported that ketorolac was more advantageous compared to opioid analgesics in the control of post-tonsillectomy pain. This was due to lower rates of sedation, nausea, vomiting, and respiratory depression and a similar level of analgesia when using ketorolac, compared to commonly used opioids [17]. In agreement of the study, Tarkkila and Saarnivaara compared ketorolac, ketoprofen, and diclofenac postoperatively following elective tonsillectomy, and reported lower use of opioids, improved pain control, and a similar complication rate compared to placebo. These findings are similar to those we found in our trial [18]. According to Carney et al., ketorolac reduced the use of opioids and lowered the morbidity during the first 48 hours after pediatric surgery. Furthermore, patients receiving ketorolac did not present increased bleeding or kidney toxicity compared to the group that received morphine only. Shende and Das reported a lower rate of vomiting and pain when using ketorolac postoperatively after strabismus surgery in children compared to the placebo group [19], [20].

In this study, we found that patients in 'group B' were significantly more sedated compared to patients in 'group A' using the Ramsay sedation score at 15 and 30 minutes after recovery. Sedation score was (2.08 ± 0.9 at 15 min. and 2.56 ± 0.541 at 30 min.) in 'group B' and was (1 ± 0 at 15 & 30 min.) in 'group A' which was statistically significant. Sedation score was the same in the remaining observational hours after recovery in both groups and was statistically insignificant. So nalbuphine produces more sedation and less agitation during the early postoperative period which not preferred in ENT operations in general and pediatric surgeries in specific.

In this study, we found that the incidence of postoperative vomiting was significantly higher in 'group B' (16%) compared to that of 'group A' (4%). This is explained as opioids alter lower oesophagal sphincter activity, resulting in sphincter relaxation. Gastric emptying is delayed by opioids via supraspinal (vagus nerve-mediated), spinal and peripheral mechanisms [21]. Also, the study revealed that incidence of postoperative respiratory depression occurred in 'group B' (6%) compared to that of 'group A' in which no patient developed respiratory depression (0%) which was statistically insignificant but clinically vital as it required immediate intervention [22].

In agreement with that Hamza et al., 2012 who compared the efficacy of ketorolac and pethidine for postoperative pain relief in the first 24 hours after tonsillectomy? One hundred patients age 5-12 years under going tonsillectomy were divided into group A

and B randomly, who received either inj. ketorolac 0.5 mg/kg or inj. Pethidine 1 mg/kg I.M respectively postoperatively on 6 hourly bases. Patients were assessed in the recovery room and ENT ward for pain according to faces pain scale and for any side effects. Amount of rescue analgesia required by both groups was also recorded. They concluded that ketorolac provides similar analgesic effects as pethidine in the doses mentioned above with much less incidence of nausea, vomiting and drowsiness in the first 24 hours after adenotonsillectomy [23].

Limitation to the study was that patients were not followed up more than six “6” hours, as adequate acute pain management should be controlled and followed up in the first three “3” months as regarding the definition of acute pain of IASP “International Association for the Study of Pain” for better health care service and reducing a lot of morbidities which is an important issue for future studies. This was because tonsillectomy was performed on an ambulatory basis and most of the patients came from rural areas, where it would have been very difficult to track them after they had left the hospital.

It was concluded that intravenous ketorolac is effective in reducing pain intensity and postoperative analgesic requirements after adenotonsillectomy in children. Also, it is generally safe as absent respiratory depression and a very low incidence of postoperative complications. It is recommended that the use of multimodal analgesia is the best way for acute postoperative pain management after adenotonsillectomy surgery.

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