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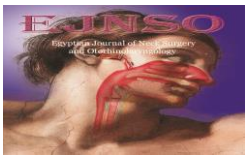

Comparative study between the effect of Diclofenac and Ketorolac in post-tonsillectomy pain management

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Abstract:

Introduction: Tonsillectomy is one of the most common surgical procedures performed in children. It is associated with significant pain Ketorolac and Diclofenac are the commonly used NSAIDS for post-tonsillectomy pain; however, they may cause bleeding .

Objective: To compare between the effect of diclofenac sodium and ketorolac in post-tonsillectomy pain management and bleeding.

Materials and methods: 100 children aged 6-12 years were divided into two groups; Diclofenac group (n=50 patients who received diclofenac sodium analgesia) and Ketorolac group (n= 50 patients who received ketorolac tromethamine analgesia). Intra-operative and postoperative blood loss was assessed using the following scale for bleeding assessment (0 = no bleeding, 1 = bleeding as usual, 2 = bleeding more than usual, 3 = profuse, 4 = excessive, and lastly 5 = excessive and continuous), while postoperative pain was assessed using the verbal rating scale, the total consumption of additional analgesics used in each group and the time needed to restore normal dietary habits

Results: There were no statistical differences between the two groups regarding intraoperative and postoperative bleeding. On the other hand, there was no statistical difference between the two groups regarding postoperative pain management. Forty-eight and forty-six patients returned to their normal dietary habits in the first day post-operative in diclofenac group and ketorolac group respectively .

Conclusions: Both ketorolac and diclofenac administered intraoperatively before the start of surgery and continued postoperatively, both drugs effectively and equally controlled post-tonsillectomy pain with no serious adverse effects.

Key words: Tonsillectomy, Diclofenac, Ketorolac, post tonsillectomy pain

Introduction

Tonsillectomy is the most popular surgery among pediatric population [1, 2]. Post-operative pain is severe and its control usually ineffective [2].

The pain is attributed to exposure of pharyngeal musculature to injury, saliva, bacterial colonization, and subsequent inflammation. Delayed postoperative hemorrhage still occurs in 1% to 3% of patients [3].

Various studies have shown that non-steroidal anti-inflammatory drugs (NSAID) are effective in reducing pain after different types of surgery, Although the mechanism of analgesic action (i.e. inhibition of prostaglandin synthesis) is the same for all presently used NSAID, the analgesic efficacy relative to side effects may vary from agent to agent [4].

NSAID have potential side effects because of derangement of hemostasis caused by decreased platelet function[5]. The effect of some NSAID on platelets is reversible and they inhibit platelet aggregation for a few hours only [6]. Comparative studies of the analgesic potency of various NSAID are rare. As the type of surgery may influence the efficacy of individual NSAID on postoperative pain and side effects [5].

Patients and Methods:

Patients:

This study was a prospective randomized comparative study conducted on 100 patients scheduled for elective tonsillectomy and divided into two groups. Group (A) included 50 patients who received diclofenac sodium at dose of 0.3 mg/kg IV intraoperatively. Group (B) included 50 patients who received ketorolac tromethamine at dose of 0.5 mg/kg intraoperatively.

Then the two groups continued postoperatively on oral analgesic formulation with the same drug ingredient received intraoperatively.

The study had been carried out in the department of otolaryngology at Assiut university hospital. This study was approved by the Institutional Ethics and Research Committee of the Faculty of Medicine, Assiut University, Assiut, Egypt. Dealing with the collected data of the patients and data dissemination were confidential.

The study and all interventions and surgical procedures within it were done by scientifically qualified and trained personnel.

Inclusion criteria: Children aged between 6-12 years who underwent elective tonsillectomy.

Exclusion criteria: Children were excluded from the study if they have:

1. Known hypersensitivity to medication drugs.
2. Coagulation disorders, thrombocytopenia or active bleeding for any cause.
3. Bronchial asthma.
4. Significant cardiac, renal, pulmonary, hepatic disease or peptic ulcer.
5. The use of any medications that interact with diclofenac or ketorolac.
6. The use of any analgesic medications within 24h preoperative or antiplatelet medication within the past 2 weeks.
7. Refusal to participate in the research.

Methods:

I. **Pre-operative evaluation:**

A. History: was taken from the parents of children and from the children themselves (when possible).

B. Clinical examination: Complete ENT examination including examination of ear, nose, throat, neck and oropharyngeal examination.

C. Preoperative Investigations and assessment:

- Complete blood picture.
- Prothrombin time and concentration.
- Preoperative fitness.

II. Operative work up:

All patients had undergone tonsillectomy (by cold knife and limited use of bipolar diathermy for hemostasis in both groups) under general anesthesia using oral endotracheal tube and inhalation anesthesia. Anesthesia was induced with inhalational induction with sevoflurane 8% in 100% oxygen or with intravenous propofol 2–3 mg/kg.

Atracurium besylate 0.5 mg/kg was administered to facilitate endotracheal intubation. Anesthesia was maintained with isoflurane in oxygen/air mixture. Monitoring included electrocardiography, non-invasive blood pressure and peripheral arterial oxygen saturation.

Study drugs were given intravenously after induction of anesthesia and before the start of the surgery.

Patients in group A received diclofenac sodium at dose of 0.3 mg/kg IV while patients in group B received ketorolac tromethamine at dose of 0.5 mg/kg intraoperatively both groups continued postoperatively on oral analgesic formulation with the same drug ingredient received intraoperatively .

Intra-operative blood loss was assessed using the following scale for bleeding assessment (0 = no bleeding, 1 = bleeding as usual, 2 = bleeding more than usual, 3 = profuse, 4 = excessive, and lastly 5 = excessive and continuous). Bleeding score was assessed by the surgeon at the end of the operation using this scale.

III. Postoperative Follow up:

A**. Early Post-operative follow up:**

Patients were admitted in otolaryngology department for the first 24 hours post-operatively for monitoring of the following :

1) **Post-tonsillectomy bleeding assessment**:

Postoperative bleeding was also assessed by the same scale used for assessment of intra-operative blood loss. Bleeding score was recorded immediately postoperative and 3, 6, 12 and 24h postoperatively. Hospital re-operation because of bleeding was also recorded if had occurred.

2) **Post-tonsillectomy pain assessment**:

Pain intensity was assessed postoperatively by the verbal rating scale (VRS; 0 = no pain, 1 = mild pain, 2 = moderate pain, 3= severe pain, and lastly 4= excruciating pain).

VRS assessment was performed immediately postoperative and 3, 6, 12 and 24h postoperatively. Additional analgesia was given if requested or if the VRS≥2.

Patients in group A received diclofenac sodium 0.3 mg/kg IV while patients in group B received ketorolac tromethamine 0.5 mg/kg, both groups continued postoperatively on oral analgesic with the same drug ingredient received intraoperatively,

The total consumption of additional analgesics used in each group in the first 24 h postoperative was calculated and the time of the need for additional analgesia was recorded if VRS ≥2 in spite of adequate oral analgesia.

B. Late Post-operative data:

Patients were asked to come back for follow up at a week and 2 weeks after surgery. In each visit patients were asked and evaluated for:

- Bleeding tendency.
- Time needed to restore normal dietary habits

Statistical analysis:

Data was collected and analyzed using SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York). Continuous data was expressed in form of mean ± SD or median (range) while nominal data

was expressed in form of number and frequency (percentage).

Chi²-test was used to compare the nominal data of different groups in the study while Student-t test and Mann-Whitney tests were used in case of continuous data of both groups. The level of confidence was kept at 95% hence a P value <0.05 indicated a significant association.

Results:

One hundred-twenty-two patients scheduled for tonsillectomy or adenotonsillectomy were eligible for this the study. Eight children were excluded, 4 children their parents refused to participate, and 10 children were lost during follow up because of early postoperative discharge. Finally, 100 children were subjected to statistical analysis and were divided into groups; Diclofenac group (n=50 patients who received diclofenac sodium analgesia) and Ketorolac group (n= 50 patients who received ketorolac tromethamine analgesia), (Figure 1).

Patients' demographic and clinical Characteristics :

No significant differences were recorded between the two studied groups as regards to age (P= 0.214), sex (P=0.273), weight (P=0.205) or type of operation (P=0.112), respectively.

Intraoperative and Postoperative Bleeding:

Intra-operative and post-operative bleeding in both groups is shown table 3. Intraoperative bleeding was as usual in 40 (80%) patients of diclofenac group and 37 (74%) patients of ketorolac group while it was more than usual in 10 (20%) and 13 (26%) patients of both groups respectively.

More than usual postoperative bleeding occurred only in 4 (8%) patients in each group. Both groups had insignificant differences as regarding intraoperative and postoperative bleeding, respectively (P= 0.326 and 0.647).

Postoperative Pain Assessment in both Groups:

As regarding the Verbal Rating Pain Scale ''VRS'' immediately postoperative (0 time), pain was absent in 17 (34%) patients of diclofenac group and 22 (44%) patients of ketorolac group while majority of both groups had mild pain immediately postoperative .

It was noticed that majority (64% of diclofenac group and 56% of ketorolac group) had mild pain based on VRS at the 3rd h postoperatively. At the 6th h postoperatively, 24 (48%) and 23 (46%) patients of diclofenac group had no pain and mild pain while 27 (54%) and 21 (42%) patients of ketorolac group had no pain and mild pain respectively.

Also, majority of patients in both groups had no pain at 12 and 24 hours postoperatively (84% and 94% in diclofenace group and 80% and 90% in ketorplac group respectively). Both groups had insignificant differences as regarding VRS at different time of follow up postoperatively (P> 0.05).

Nineteen patients (38%) in diclofenac group required additional analgesia; seven of them required analgesia immediately postoperatively while six, three, two and one patient required analgesia at 3rd hour, 6th hour, 12th hour and 24th hour postoperative respectively. In case of ketorolac group, twelve patients (24%) required additional analgesia; five of them required analgesia immediately postoperative, four patients required analgesia at the 3rd hour postoperative, two patients required it at 12th hour postoperative and one patient required it at 24th hour postoperative.

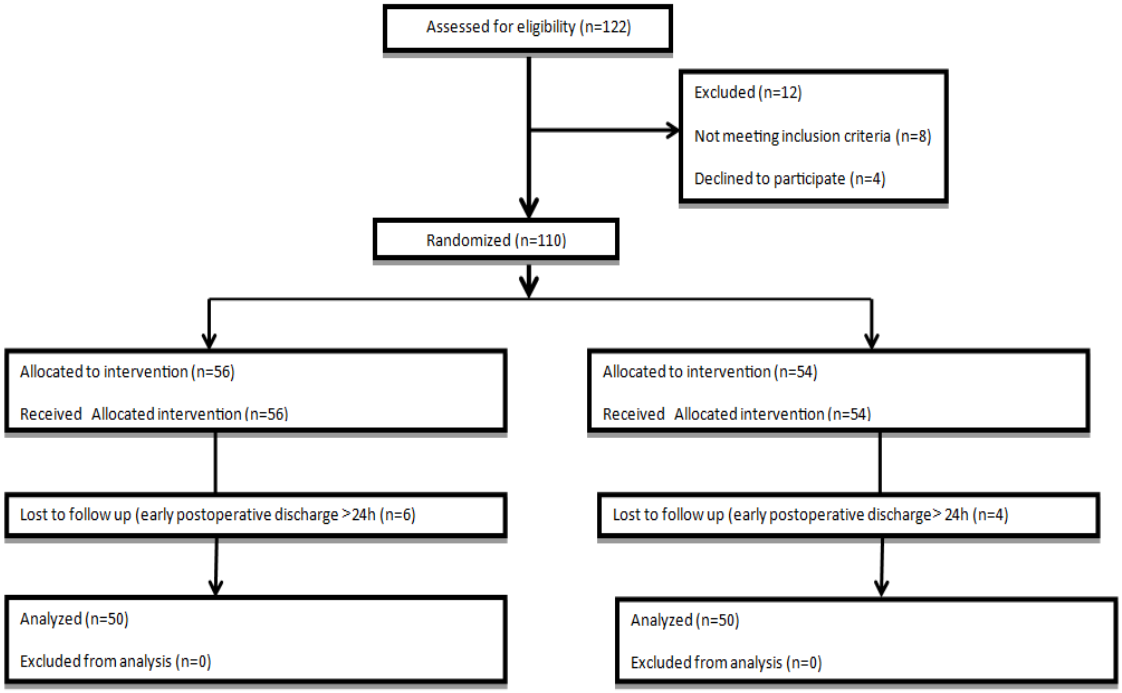

Table 1: Intra-operative and post-operative bleeding in both studied groups:

Bleeding	Diclofenac group	Ketorolac group	*P* value
Intraoperative 0 1 2 3 4 5	0 (0%) 40 (80%) 10(20%) 0 (0%) 0 (0%) 0 (0%)	0 (0%) 37 (74%) 13 (26%) 0 (0%) 0 (0%) 0 (0%)	0.326
Postoperative 0 1 2 3 4 5	46 (92%) 0 (0%) 4 (8%) 0 (0%) 0 (0%) 0 (0%)	46 (92%) 0 (0%) 4 (8%) 0 (0%) 0 (0%) 0 (0%)	0.647

Return to Normal Dietary Habits:

Majority of patients returned to normal dietary habits at the 1st day but it was noticed that only two patients from diclofenac group and four patients from ketorolac group returned to normal dietary habits at the 2nd day (4% vs. 8%; P= 0.335). There is no statistically significant difference between the two groups regarding return to normal dietary habits (P= 0.33).

Adverse effects:

The adverse effects recorded in this study were:

-Vomiting in ten patients (five in each group).

-All the eight cases with post-operative bleeding were re-operated for either a slipped stitch (six patients) or dislodgement of blood clot (two patients).

•There were no serious adverse effects noticed.

Table 2: Postoperative Verbal Rating Pain Scale ‘’VRS’’ in both groups.

VRS	Diclofenac group	Ketorolac group	*P* value
At 0 time:			
0	17 (34%)	22 (44%)	
1	26 (52%)	23 (46%)	
2	7 (14%)	4 (8%)	0.458
3	0 (0%)	1 (2%)	
4	0 (0%)	0 (0%)	
3 h postoperative:			
0	12 (24%)	18 (36%)	
1	32 (64%)	28 (56%)	
2	5 (10%)	3 (6%)	0.575
3	1 (2%)	1 (2%)	
4	0 (0%)	0 (0%)	
6 h postoperative:			
0	24 (48%)	27 (54%)	
1	23 (46%)	21 (42%)	
2	2 (4%)	0(0%)	0.464
3	1 (2%)	2 (4%)	
4	0 (0%)	0 (0%)	
12 h postoperative:			
0	42 (84%)	40 (80%)	
1	6 (12%)	10 (20%)	0.217
2	2 (4%)	0 (0%)	
3	0 (0%)	0 (0%)	
4	0 (0%)	0 (0%)	
24 h postoperative:			
0	47 (94%)	45 (90%)	
1	2 (4%)	4 (8%)	0.711
2	1 (2%)	1 (2%)	
3	0 (0%)	0 (0%)	
4	0 (0%)	0 (0%)	

Data expressed as number and frequency (percentage). VRS, verbal rating score. P< 0.05; significant difference between the two studied groups.

Table 3: Postoperative dysphagia in both studied groups

	Diclofenac group(N=50)	Ketorolac group(N=50)	*P* value
Time return to normal dietary habits			
At 1st day	48 (96%)	46 (92%)	0.335
At 2nd day	2 (4%)	4 (8%)	

Data was expressed as number and frequency (percentage). P value was significant if < 0.05

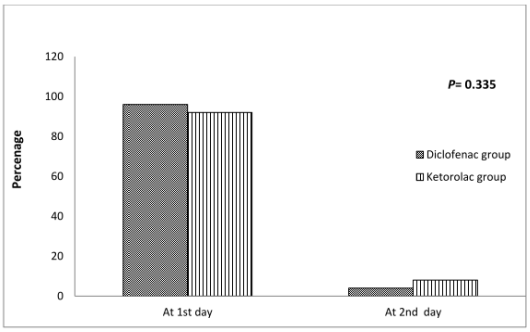

Figure 2: Return to normal dietary habits in both studied groups

Discussion :

Tonsillectomy is a common procedure performed in the pediatric population. It is the second common procedure in USA according to **Philip et al., 2017**[7]. Therefore, post-tonsillectomy pain management is a topic of interest in many publications [8-10]. NSAIDS were found to be effective and safe in management of post-tonsillectomy pain [1,11-12]. Ketorolac and Diclofenac are the commonly used NSAIDS for post tonsillectomy pain.

In this study we compared the effect of Diclofenac and Ketorolac in the management of post-tonsillectomy pain. According to our knowledge and review of the literature there are no publications comparing the effect of both drugs (Diclofenac and Ketorolac) in management of post tonsillectomy pain in pediatric populations; however, **Tarkkila et al (1999)** compared the effect of Ketorolac and Diclofenac in adults[13].

There are many authors compared the effect of one of our studied drugs with drugs rather than NSAIDs. **Sutters et al.,1995** compared the effect of single dose of intramuscular ketorolac with saline placebo and concluded that there was a statistically significant decrease in pre-fentanyl CHEOPS scores in the Post-Anesthesia Care Unit (PACU) in the ketorolac group whose children were discharged significantly earlier [14]. While **Romsing**

et al.,1998 compared a single dose of intravenous ketorolac administered before or immediately after surgery with saline placebo. They found that intramuscular administration of ketorolac at the end of surgery significantly reduced opioid requirements and shortened length of hospital stay without any increase in the incidence of bleeding [15].

On the other hand, **Watters et al.,1988** compared the effect of Diclofenac and Pethidine and concluded that there was no statistical difference between the two drugs regarding analgesic efficacy. Although patients who received diclofenac tended to be less drowsy postoperatively than those who received pethidine, there were no significant differences between the two drugs in respect of time to awaken from anesthesia [16].

Romsing et al in 2000 compared the analgesic effect of Diclofenac and high doses of Acetaminophen and found that Diclofenac given for the first three days after tonsillectomy did not demonstrate improved analgesia compared to high-dose acetaminophen [17].

In many studies NSAIDs rather than diclofenac and ketorolac were compared with non NSAIDs. In 2014 a multi-centric, placebo-controlled study in USA analyzed the safety and efficacy of intravenous Ibuprofen for treatment of pain in pediatric patients undergoing tonsillectomy and found that Administration of intravenous ibuprofen significantly reduced fentanyl use in pediatric tonsillectomy patients [18]. While Liu et al. compared alternating ibuprofen and acetaminophen regimen for pain relief after tonsillectomy in children and concluded that alternating doses of ibuprofen and acetaminophen provided an effective treatment for post-tonsillectomy pain in the majority of children and did not increase rate of bleeding [11].

Other authors compared the effect of drugs other than NSAIDs in post tonsillectomy pain. **Yenigun et al.,2015** compared ketamine and tramadol hydrochloride for post-operative pain relief and sedation after pediatric tonsillectomy and stated that perioperative low-dose intravenous, rectal, or peritonsillar ketamine infiltration provides efficient pain relief without any adverse effects in children who would undergo adeno-tonsillectomy [19]. While **Safavi et al.,2012** assessed the effect of administration of intravenous Ketamine and intravenous Dexamethasone separately and in combination in pediatric tonsillectomy and reported that a prophylactic preoperative single dose of intravenous 0.5 mg/kg dexamethasone in combination with a single dose of intravenous 0.5 mg/kg ketamine significantly decreased post-tonsillectomy pain compare with using intravenous ketamine or intravenous dexamethasone separately [20].

On the other hand, some authors studied the effect of non-pharmaceutical materials in management of post tonsillectomy pain. **Boroumand et al.,2013** studied the use of honey and found that post-operative honey administration reduces post-operative pain and analgesic requirements in patients after tonsillectomy [21]. While **Horri et al.,2011** reported that rinsing the tonsillar fossae with physiological saline at 4◦c for 10 minutes at end of surgery significantly reduced immediate post-operative pain [22]. Likewise, **Sylvester et al.,2011** reported that drinking iced water immediately after surgery reduced pain scores between 15 minutes and 1 hour post-operatively [23].

In this study, there was no statistically significant difference between the effect of diclofenac and ketorolac in post tonsillectomy pain management. In accordance, **Tarkkila et al (1999)** found that there is no statistically significant difference between the two drugs regarding analgesia. In view of the above, we can say that there is no statistically significant difference between diclofenac and ketorolac in post tonsillectomy pain management in both children and adult population. In our study, there was no difference between diclofenac and ketorolac in number of patients who required additional analgesia (VRS≥2).

Similarly, **Tarkkila et al (1999**) found that additional analgesia was required after using both drugs with no statistical difference in adults. In contrast, in our study we used the same drugs as additional analgesia while **Tarkkila** in his study used opioids as additional analgesia [13].

In this study we used verbal rating scale (VRS) in assessment of post-operative pain in our children (aged 6-12 years). The validity of this scale in this age group was confirmed. **Tarkkila et al (1999)** used both (VRS) and Visual analogue scale (VAS) in assessment of post tonsillectomy pain; he used VAS also in assessment of nausea and satisfaction [13]. **Abdel-Ghaffar et al.,2015** used VRS in assessment of post-operative pain [1]. While **Sutters et al.,1995** used Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) and the photographic scale of the Oucher [14].

Romsing et al in 2000 used the Poker Chip Tool (PCT) in assessment of post-operative pain [17]. In conclusion, many pain scales are developed for pain assessment in children depending on the maturity of intellectual functions of the child and how he/she can describe their pain. The VRS is suitable to children older than 6 years as in our study. In this study, postoperative bleeding occurred in 4 (8%) patients in each group. All the eight cases were re-operated because of a slipped stitch (six patients) or dislodgement of blood clot (two patients).

NSAIDs act by inhibiting cyclooxygenase enzymes that mediate inflammation and pain. This also results in inhibition of thromboxane, an important component in platelet aggregation, potentially resulting in an increased risk of bleeding. Consequently, many surgeons are reluctant to use NSAIDs to treat pain in their postoperative patients and many centers prescribe opioids for post-tonsillectomy pain. However, several high-quality systematic reviews and meta-analyses have failed to prove a statistically significant difference in the frequency of bleeding post-tonsillectomy when comparing NSAIDs to other analgesics [10].

For assessment of intra-operative and post-operative bleeding we used the bleeding scale commonly used in the literature [1]. We found that there was no statistical difference between the two drugs. In accordance, **Tarkkila** mentioned that neither ketorolac nor Diclofenac increased the incidence of post-operative bleeding in adults [13]. A meta-analysis conducted in 2014 studied post tonsillectomy hemorrhage rates in patients receiving perioperative Ketorolac, stated that ketorolac increases the risk of post tonsillectomy bleeding by five times in adults but not in children [24].

Thiagrjan et al.,1993 stated that Diclofenac has little, if any, effect on blood loss during tonsillectomy operation in children [25]. Future studies of larger sample size are needed to confirm or declare the role of NSAIDS in the development and severity of post-tonsillectomy bleeding.

Regarding post tonsillectomy dysphagia, there was no statistically significant difference between Diclofenac and Ketorolac regarding the return to normal dietary habits as 96% and 92% of patients returned to normal dietary habits in the first day post-operatively in Diclofenac and Ketorolac groups, respectively.

In 1995 Gallagher et al. concluded that the time needed to return to adequate oral intake in patients who received ketorolac was shorter than the time in patients who didn't receive [26].

Tawalbeh et al (2001) was found that diclofenac resulted in more oral intake and started drinking significantly sooner than the paracetamol [27].

In this study, 10% of patients reported having nausea and vomiting (five patients in each group), while **Tarkkila et al (1999)** reported that the incidence of nausea was 44–54% in adults [13].

Watters et al in 1988 found that there was no significant difference between Diclofenac and pethidine in the incidence of postoperative vomiting [16].

Romsing et al in 2000 stated that diclofenac has lower incidence of nausea and vomiting in pediatric tonsillectomy than high doses of Acetaminophen [17]. **Tawalbeh et al.** reported that diclofenac resulted in a lower incidence of nausea and vomiting than paracetamol [28].

Conclusion:

This study showed that both ketorolac and diclofenac administered intraoperatively before the start of surgery and continued postoperatively, both drugs effectively and equally controlled post-tonsillectomy pain with no serious adverse effects.

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Conflicts of interest:

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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