Intraoperative administered tramadol reduces the need for piritramide in the immediate postoperative period in children undergoing adenotonsillectomy: A retrospective observational study

A. Teunkens (*), K. Cootjans (*), K. Vermeulen (*), M. Peters (**), M. Van de Velde (*,**) and S. Rex (*,**)

Abstract: Purpose: Adenotonsillectomy is a frequently performed procedure in pediatric day-case surgery causing significant pain for which adequate analgesia is required. Our aim was to investigate if the intraoperative administration of IV tramadol decreases the need for postoperative pain medication in children. Because tramadol has well-known pro-emetic effects, we also assessed the incidence of postoperative nausea and vomiting (PONV).

Methods: We performed a retrospective observational study in 314 children aged 1-13 years undergoing elective adenotonsillectomy. We identified 160 children who had received standard pain medication consisting of IV paracetamol and ketorolac and compared them with a group of 154 children who had received in addition a perioperative infusion of tramadol.

Results: 32.5% of the patients in the tramadol group versus 83.8% of the patients in the standard group required postoperative administration of piritramide (p < 0.0001). Groups did not differ with respect to the postoperative need for anti-emetics but in the tramadol group more patients had received prophylactic therapy with odansetron or dexamethasone (P < 0.0001).

Conclusion: The results of this retrospective study indicate that intraoperative IV tramadol administration in combination with prophylactic antiemetic therapy decreases the need for piritramide in the immediate postoperative period without increasing the incidence of PONV after tonsillectomy in children.

Key words: Adenoidectomy; tonsillectomy; postoperative pain; tramadol; paracetamol; ketorolac; postoperative nausea and vomiting (PONV).

Introduction

Tonsillectomy with or without adenoidectomy is a common and painful procedure in children, frequently performed on an outpatient basis. Effective post-tonsillectomy analgesia is required to increase patients’ comfort, to encourage oral intake for the maintenance of normal hydration and to minimize crying which increases the risk of postoperative bleeding (1). Nonsteroidal anti-inflammatory drugs (NSAID’s) and paracetamol are frequently used for postoperative pain relief after tonsillectomy, but their analgesic effect is often insufficient (2). Moreover, the use of NSAID’s is controversial due to possible increase in the risk of postoperative bleeding (3). Opioids provide efficient analgesia but side effects such as respiratory depression and pro-emetogenic effects may limit their use in day-case surgery (4,5). The latter side effect is of particular concern as children undergoing tonsillectomy carry a high risk for postoperative nausea and vomiting (PONV) (6).

Tramadol is a centrally acting analgesic with agonistic actions at the opiate μ receptor. Moreover, tramadol inhibits the re-uptake of serotonin and norepinephrine in the central nervous system, hereby activating the descending endogenous pain control system (7). Due to its relatively weak potency, tramadol has been considered for a long time as unlikely to depress respiratory function and to cause significant sedation (8). While tramadol has been found by some authors to increase the risk of PONV (9), this has been refuted by others (10). We hypothesized that the intraoperative IV administration of tramadol results in better quality...
of postoperative pain control and decreases the need for postoperative opioids. As a secondary outcome parameter, we assessed the incidence of postoperative nausea and vomiting (PONV).

MATERIALS AND METHODS

After approval of the local ethics committee (ML9427/S55447, approval date 24/06/2013, Ethics Committee of the University Hospitals Leuven, Herestraat 49, 3000 Leuven), a retrospective chart review of all patients undergoing day-case tonsillectomy or adenotonsillectomy from January 2008 to December 2011 was performed. Inclusion criteria were children from 1-13 years old undergoing elective adenotonsillectomy or tonsillectomy. Exclusion criteria included children over 13 years of age and planned hospitalization.

During this period, our perioperative pain management had been modified by supplementing the standard non-opioid based scheme (paracetamol + ketorolac) with a top-up administration of tramadol. The modification of our standard was deemed necessary due to the high postoperative pain scores that we measured in our routine clinical practice. Up to now, this measure had not been checked for effectiveness.

All patients had standard anesthesia monitoring using pulse oxymetry, electrocardiogram and non-invasive blood pressure measurements. After inhalational induction with sevoflurane 8%, an intravenous catheter was placed, followed by the IV-administration of fentanyl 1.0 µg/kg and propofol 2.0-3.0 mg/kg. Endotracheal intubation was performed without the use of neuromuscular blocking agents. Anesthesia was maintained with 1.5 MAC sevoflurane and 50% nitrous oxide in oxygen. Standard pain therapy consisted of a loading dose of IV-paracetamol 15-30 mg/kg over 15 minutes and an IV-ketorolac bolus 0.5 mg/kg at the start of surgery. In the tramadol group, an IV-tramadol bolus of 3 mg/kg – in addition to the standard regimen - had been administered after induction of anesthesia.

The prophylactic administration of antiemetic drugs (ondansetron, dexamethasone and dehydrobenzperidole either alone or in combination) was left at the discretion of the attending anesthesiologist.

All patients underwent tonsillectomy using the blunt dissection technique.

Postoperatively, patients of both groups received ondansetron (0.1 mg/kg) if PONV occurred and piritramide (0.03 mg/kg) if patients complained about pain, repeated if necessary. Piritramide is a synthetic opioid receptor agonist which binds to the µ-receptor in the central nervous system. The analgetic potency of piritramide is 0.7 compared to morphine. The administration of the respective drugs was left at the discretion of the attending physician at the PACU. According to our institutional standard protocol piritramide was only given if pain scores were > 3 on a visual analog scale (VAS score: 0= no pain, 10= maximal pain) and repeated maximal 3 times. Antiemetics were given if PONV scores were > 5 on a numeric rating scale (NRS: 0= no nausea or vomiting PONV, 10= worst nausea and vomiting).

Outcome parameters

Primary outcome parameters were the frequency and dose of postoperative piritramide administration. Secondary outcome parameters included the frequency of intra- and postoperative administration of anti-emetics, and various procedure-related times.

Statistics

Statistical analyses were performed using GraphPad Prism (GraphPad Software Inc., La Jolla, CA, USA). After checking the data for normality with the Shapiro-Wilk test, groups were compared using the Mann-Whitney-U-test for continuous variables and the chi-square test or Fisher's exact test for proportions. A p < 0.05 was considered statistically significant.

RESULTS

We identified 160 pediatric patients that had received our previous standard therapy (standard group). These patients were compared to 154 patients in whom – in addition to the standard regimen - an IV-tramadol bolus of 3 mg/kg had been administered (tramadol group).

There were no statistically significant differences with respect to baseline data (Table 1). Duration of surgery was significantly longer in the tramadol group [median time (percentile 25-percentile 75) 40.5 (31-38) minutes vs 35 (27-45) minutes, p<0.002]. In contrast, emergence-times from anesthesia, defined as the time between end of surgery and end of anesthesia, did not differ between the two groups [median time (percentile 25-percentile 75) 12.5 (8-15) minutes vs
Intraoperatively administered tramadol reduced the need for piritramide

Table 1

Baseline and intraoperative variables

<table>
<thead>
<tr>
<th></th>
<th>Tramadol group (n= 154)</th>
<th>Standard group (n= 160)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>years</td>
<td>4 (3-6)</td>
<td>4 (3-6)</td>
</tr>
<tr>
<td>Weight</td>
<td>kg</td>
<td>17 (17-21)</td>
<td>17 (14-23)</td>
</tr>
<tr>
<td>Height</td>
<td>cm</td>
<td>106 (97-121)</td>
<td>105 (97-117)</td>
</tr>
<tr>
<td>ASA 1</td>
<td></td>
<td>143 (92.8)</td>
<td>146 (91.2)</td>
</tr>
<tr>
<td>ASA 2</td>
<td></td>
<td>10 (0.06)</td>
<td>10 (0.06)</td>
</tr>
<tr>
<td>ASA 3</td>
<td></td>
<td>1 (0.006)</td>
<td>4 (0.025)</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>92 (59.7)</td>
<td>100 (62.5)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>62 (40.3)</td>
<td>60 (37.5)</td>
</tr>
<tr>
<td>Tonsillectomy</td>
<td>n (%)</td>
<td>37 (24)</td>
<td>51 (31.8)</td>
</tr>
<tr>
<td>Adenotonsillectomy</td>
<td>n (%)</td>
<td>117 (75.9)</td>
<td>109 (68.1)</td>
</tr>
<tr>
<td>Duration of surgery</td>
<td>min</td>
<td>40.5 (31-46)</td>
<td>35 (27-45)</td>
</tr>
<tr>
<td>Emergence time</td>
<td>min</td>
<td>12.5 (8-15)</td>
<td>10 (7-15)</td>
</tr>
<tr>
<td>Discharge time</td>
<td>min</td>
<td>375 (357-395)</td>
<td>368.5 (350-393)</td>
</tr>
<tr>
<td>Intraoperative dose of</td>
<td>paracetamol</td>
<td>300 (250-452)</td>
<td>300 (250-400)</td>
</tr>
</tbody>
</table>

Data are presented as median (Percentile 25-Percentile 75) or absolute numbers (with the percentage of the whole). ASA= American Society of Anesthesiologists’ physical status

Table 2

Intra-operative anti-emetic prophylaxis

<table>
<thead>
<tr>
<th></th>
<th>Tramadol group (n=154)</th>
<th>Standard group (n=160)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients receiving mono-prophylaxis</td>
<td></td>
<td>25 (16)</td>
<td>26 (16)</td>
</tr>
<tr>
<td>Patients receiving dual prophylaxis</td>
<td></td>
<td>62 (40)</td>
<td>28 (17)</td>
</tr>
<tr>
<td>Patients receiving triple prophylaxis</td>
<td></td>
<td>5 (3)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>n (%)</td>
<td>75 (49)</td>
<td>39 (24)</td>
</tr>
<tr>
<td>Odansetron</td>
<td>n (%)</td>
<td>50 (33)</td>
<td>13 (8)</td>
</tr>
<tr>
<td>Dehydrobenzperidol</td>
<td>n (%)</td>
<td>28 (18)</td>
<td>32 (20)</td>
</tr>
<tr>
<td>Alizapride</td>
<td>n (%)</td>
<td>1 (0.006)</td>
<td>1 (0.006)</td>
</tr>
</tbody>
</table>

Data are presented as absolute numbers (with the percentage of the whole)

Postoperatively, significantly less patients in the tramadol group required piritramide than in the standard group [50 (32%) vs 134 (84%), p<0.0001] (Fig. 1). Moreover, patients in the tramadol group that were still in need of postoperative opioid therapy received significantly lower piritramide doses in the postoperative period than children in the standard group [median dose (range) 0.03 (0.02-0.1) mg/kg vs 0.06 (0.02-0.14) mg/kg, p < 0.0001] (Fig. 1). A subgroup analysis showed that this difference was not affected whether patients had been concomitantly administered dexamethasone or not. In patients that had not been given dexamethasone intraoperatively, there was still a significant difference in number of patients [tramadol group: 28/79 (40%) vs standard group: 102/121 (84%), p < 0.0001] and the postoperatively administered piritramide dose

10 (7-15) minutes, p<0.07]. Likewise, discharge times, defined as the time between end of surgery and discharge from the hospital, were not different between the two groups [median time (percentile 25-percentile 75) 375 (357-395) minutes vs 368.5 (350-393) minutes, p<0.1].

Primary outcome parameters

Postoperatively, significantly less patients in the tramadol group required piritramide than in the standard group [50 (32%) vs 134 (84%), p<0.0001] (Fig. 1). Moreover, patients in the tramadol group that were still in need of postoperative opioid therapy received significantly lower piritramide doses in the postoperative period than children in the standard group [median dose (range) 0.03 (0.02-0.1) mg/kg vs 0.06 (0.02-0.14) mg/kg, p < 0.0001] (Fig. 1). A subgroup analysis showed that this difference was not affected whether patients had been concomitantly administered dexamethasone or not. In patients that had not been given dexamethasone intraoperatively, there was still a significant difference in number of patients [tramadol group: 28/79 (40%) vs standard group: 102/121 (84%), p < 0.0001] and the postoperatively administered piritramide dose
complementary and synergistic actions of these two enantiomers result in an improved analgesic efficacy and tolerability profile of the racemate (12).

The analgesic effect of tramadol has been reported to be ten times less potent than that of morphine (13). Due to its wide therapeutic window, tramadol is often used in children, at least for pain of minor to intermediate severity (8,14).

A recent meta-analysis could demonstrate the superiority of tramadol vs. placebo by revealing (similar to the findings of our study) a reduced need for rescue analgesics when children were treated with tramadol (14). In contrast, Uysal et al. could not demonstrate any difference between the analgesic effects of paracetamol and tramadol after adenotonsillectomy. However, these investigators used much lower tramadol doses (1 mg/kg) than those administered in our study (3 mg/kg) (15).

Unfortunately, there is a paucity of high-quality data on the comparative efficacy of tramadol vs. other opioids in children (14). Van den Berg et al. compared the efficacy and safety of pre-emptively
administered tramadol, pethidine and nalbuphine (3 mg/kg, 1.5 mg/kg, and 0.3 mg/kg, respectively) during adenotonsillectomy, and reported that nalbuphine and tramadol were safe regarding the timely recovery of spontaneous respiration (16). Our findings are in accordance with these observations, demonstrating that the intraoperative administration of tramadol in children undergoing tonsillectomy is associated with significantly less requirements of postoperative opioids without prolonging emergence from anesthesia and discharge from the hospital.

Unfortunately, PONV is frequently observed in pediatric anesthesia (6,17), in particular after (adeno)tonsillectomy which predisposes children to an enhanced PONV-risk (18). During this procedure, swallowing of blood causes gastrointestinal irritation, and stimulation of emetogenic nerve afferents by electrocauterization of the tonsil bed elicits nausea and vomiting (19). PONV has been reported to be the most common cause of delayed discharge or overnight admission in daycare tonsillectomies. It is also associated with an increased risk of bleeding, aspiration of gastric contents and electrolyte disturbance (6). Without prophylaxis, more than 70% of children undergoing tonsillectomy will experience at least one episode of vomiting in the postoperative period (17). Therefore, prevention of PONV represents one of the cornerstones in the perioperative management of outpatient tonsillectomy. Unfortunately, while being effective analgesics, opioids are a well-known trigger for PONV. In fact, Van den Berg et al. observed an increased PONV-incidence with tramadol when compared to placebo (9).

Because of the well-known pro-emetogenic effect of tramadol, significantly more patients in the tramadol group received prophylactic antiemetic therapy. But in patients of the tramadol group without prophylactic therapy (n= 68) we – in contrast - could not observe an increased need for anti-emetics postoperatively. Our findings are in accordance with the results of Ozkose et al. who demonstrated in children undergoing tonsillectomy with or without adenoidectomy that intravenous administration of tramadol at induction of anesthesia provided sufficient analgesia without increasing the PONV-incidence (10). They attributed their findings to the low doses of tramadol used in their study (1 or 0.5 mg/kg) and to the low speed of tramadol-injection. Based on the findings of Radbruch et al. who observed that incidences of PONV increased when tramadol was injected in less than 2-3 minutes (20), Ozkose et al. injected tramadol in > 3 minutes. Although our patients received significantly higher tramadol-doses (3 mg/kg) and injection times were not controlled, we could not observe a higher incidence of PONV. The reasons for this are speculative. It has been postulated that administering tramadol immediately after induction of anesthesia may be associated with lower PONV-incidences (21). It appears that tramadol-induced nausea and vomiting is primarily linked to the peak blood concentrations of tramadol that are achieved immediately after injection.(21) When injecting tramadol during induction of anesthesia, patients are hence unable to experience nausea.

There was a small difference between the two groups with respect to the duration of surgery which was mainly due to one single patient in

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**Table 3**

Frequency of post-operative administration of antiemetics

<table>
<thead>
<tr>
<th></th>
<th>Tramadol group (n=154)</th>
<th>Standard group (n=160)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansetron n (%)</td>
<td>6 (0.039)</td>
<td>5 (0.031)</td>
<td>0.77</td>
</tr>
<tr>
<td>Alizapride n (%)</td>
<td>1 (0.006)</td>
<td>0 (0)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Data are presented as absolute numbers (with the percentage of the whole).

**Table 4**

Frequency of postoperative administration of rescue anti-emetics in patients that had not received any intraoperative PONV-prophylaxis

<table>
<thead>
<tr>
<th></th>
<th>Tramadol group (n=68)</th>
<th>Standard group (n=107)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansetron n (%)</td>
<td>4 (5.9)</td>
<td>3 (2.8)</td>
<td>0.43</td>
</tr>
<tr>
<td>Alizapride n (%)</td>
<td>1 (1.47)</td>
<td>0 (0)</td>
<td>0.39</td>
</tr>
</tbody>
</table>

Data are presented as absolute numbers (with the percentage of the whole).

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which hemostasis was extremely difficult to achieve resulting in an operation time of 140 min.

While tramadol has been long thought to have only negligible effects on central respiratory control, there is now increasing concern about the use of tramadol in children because of the risk of respiratory depression (4). These concerns are based mainly upon a case report of a child with the CYP2D6 genotype who - after adenotonsillectomy - received po 1mg/kg tramadol at home which resulted in severe respiratory depression (22). Therefore, Marzuillo et al. concluded in their review that the use of tramadol should be limited to monitored settings in children with risk factors for respiratory depression (23). Unfortunately, a Cochrane review and meta-analysis of tramadol for pain treatment in children had to remain inconclusive concerning the risk of respiratory depression owing to the poor reporting of adverse events in the published studies (14). In our retrospective study, we did not observe any respiratory depression after IV tramadol. However, we administered tramadol only after induction of anesthesia prior to endotracheal intubation and mechanical ventilation and did not repeat tramadol treatment in the postoperative care unit.

We acknowledge that our study is subject to several limitations. First, the indication to administer postoperative piritramide or ondansetron was based on visual analog or numeric rating scales according to the standard protocol of our hospital for the postoperative evaluation of pain and PONV. Unfortunately these scores were not consistently noted on the anesthesia chart. Hence, a treatment bias cannot be excluded. Second, significantly more tramadol-patients received prophylactic antiemetics already intraoperatively. This was probably done because the attending anesthesiologists were in fear of a probably higher PONV-incident after tramadol. Of note, in the patients that had not received an intraoperative PONV-prophylaxis, the incidence of PONV did not differ between the tramadol and the standard-group. However, owing to the small number of patients without PONV-prophylaxis that were postoperatively in need of rescue medication, this observation might be due to a type-II error. Third, we are unable to report the effects of tramadol on post discharge outcome parameters, including pain or nausea and vomiting. Last, given the retrospective character of our study, our observations and interpretations are limited to the variables that were collected during routine clinical documentation. Our findings should be validated in a prospective way to make final conclusions.

Conclusion

The results of our retrospective study indicate that the intraoperative administration of tramadol significantly decreases the need for postoperative opioids without increasing emergence or discharge times. Using an appropriate intraoperative PONV-prophylaxis, 3 mg/ kg tramadol is not associated with an increased need for postoperative antiemetics after adenotonsillectomy in children.

References