Egyptian Journal of Anaesthesia 33 (2017) 97–101

HOSTED BY

Contents lists available at ScienceDirect

Egyptian Journal of Anaesthesia

journal homepage: www.sciencedirect.com

Research article

Effect of single dose intraoperative IV acetaminophen in pediatric tonsillectomy or adenotonsillectomy

Christopher A. Roberts [a], Shivani Shah-Becker [b], Jonathan B. Derr [b,1], Khaled Sedeek [c], Michele M. Carr [b,*]

[a] The Pennsylvania State University, College of Medicine, 500 University Drive, Hershey, PA, USA
[b] The Pennsylvania State University, College of Medicine, Department of Surgery, 500 University Drive, Hershey, PA, USA
[c] The Pennsylvania State University, College of Medicine, Department of Anesthiology, 500 University Drive, Hershey, PA, USA

ARTICLE INFO

Article history:
Received 5 July 2016
Revised 20 September 2016
Accepted 8 October 2016
Available online 11 November 2016

Keywords:
Pain management
Tonsillectomy
Acetaminophen
Pediatrics
Postoperative pain
Recovery room

ABSTRACT

Background: A number of different treatment regimens have been described for post-operative pain management for pediatric tonsillectomy following the widespread discontinuation of the use of codeine due to safety concerns. However, the literature is lacking with regard to the relative efficacy of the treatment regimens. This study is designed to determine the effectiveness of an intraoperative dose of intravenous acetaminophen for pediatric tonsillectomy pain management.

Methods: Records were reviewed for pediatric patients undergoing tonsillectomy with a single surgeon between 2012 and 2014. Pain scores, need for narcotic analgesics, and recovery times were reviewed for up to 24 postoperative hours. Patients were grouped based on whether they received an intraoperative dose of intravenous acetaminophen (Group 1) or did not receive it (Group 2). The primary outcome measure was pain score during the 24-h post-operative period. Secondary outcome measures include need for narcotic medications for breakthrough pain in the recovery room and time spent in the recovery room and hospital.

Results: 350 patients were included, of which 116 received an intraoperative dose of intravenous acetaminophen. Patients in Group 1 had lower pain scores during the second postoperative hour (1.27 vs. 2.06, $p = 0.008$). No significant differences were noted for pain scores during postoperative hours 1 or 3–24. Patients in Group 1 spent less time in the Recovery Room (59.08 min vs. 69.5 min, $p = 0.016$) but more time in the hospital (24.54 h vs. 19.66 h, $p = 0.030$). There was no difference between the groups based on whether the patients received narcotics for breakthrough pain in the recovery room (79.3% vs. 70.9%, $p = 0.094$).

Conclusion: Intraoperative intravenous acetaminophen may lead to improved pain scores in the early postoperative period and decreased time in the recovery room, but this group also had a longer hospital stay. This information should instigate randomized controlled trials of this intervention.

© 2016 Publishing services by Elsevier B.V. on behalf of Egyptian Society of Anesthesiologists. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Post-operative pain management for pediatric tonsillectomy operations has historically been achieved using codeine and acetaminophen. There has been a shift away from this strategy, however, due to reports of deaths caused by the administration of codeine following pediatric tonsillectomy. In 2012, Kelly et al., discussed several cases across North America in which administration of codeine to children who were rapid metabolizers of this medication via increased levels of cytochrome P4502D6 led to a greatly increased production of morphine, resulting in respiratory depression, and ultimately proving to be fatal [1]. Consequently, there is great interest in establishing a safe and efficacious alternative to this pain management strategy.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are generally a valued component of any pain control regimen. While they had previously been demonstrated to be effective at controlling postoperative pain following pediatric operations, the use of NSAIDs for this purpose was largely limited by the fear that they may increase the risk of bleeding due to their action on the cyclooxyge-

Peer review under responsibility of Egyptian Society of Anesthesiologists.

* Corresponding author at: The Pennsylvania State University, College of Medicine, Departments of Surgery and Pediatrics, Division of Otolaryngology, 500 University Drive, H091, Hershey, PA 17033, USA.

E-mail addresses: croberts2@hmc.psu.edu (C.A. Roberts), sshah13@hmc.psu.edu (S. Shah-Becker), jonathanbderr@gmail.com (J.B. Derr), ksedeek@hmc.psu.edu (K. Sedeek), mcarr@psu.edu (M.M. Carr).

[1] Present address.

http://dx.doi.org/10.1016/j.egja.2016.10.002
1110-1849/© 2016 Publishing services by Elsevier B.V. on behalf of Egyptian Society of Anesthesiologists.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

nase (COX) enzymes [2]. Recent studies have shown that nonsteroidal anti-inflammatory drugs (NSAIDs) do not cause an increased risk of bleeding following tonsillectomy operations [3]. A meta-analysis by Riggin et al. in 2013 concluded that the use of NSAIDs for analgesia following tonsillectomy in both adult and pediatric populations led to no increased risk of bleeding when compared to opiates or placebo [4]. Therefore, NSAIDs have become more widely accepted as an appropriate option for post-operative pain management.

One emerging strategy employed in the post-operative pain management for pediatric tonsillectomy procedures is to utilize both ibuprofen and acetaminophen. Using this approach, each medication is given according to a standing order, but the dosing schedule is staggered so the patient receives the medications in an alternating fashion. There is some evidence to suggest that a regimen of a combination of acetaminophen and ibuprofen can provide safe and effective pain relief following pediatric tonsillectomy [5].

Furthermore, there is evidence to suggest that the use of a single prophylactic perioperative dose of IV acetaminophen may be effective for pain management following pediatric tonsillectomy. In one study, the administration of a single intraoperative dose of IV acetaminophen improved pain relief and reduced narcotic requirement in the post-operative period when compared to placebo [6]. Another study compared the efficacy of an intraoperative dose of IV acetaminophen with that of an intraoperative dose of IV tramadol and found the two to be similar with regard to all outcome measures [7].

However, there is a gap in the literature regarding the efficacy of a single intraoperative dose of IV acetaminophen when used alongside the emerging combination regimen of acetaminophen and ibuprofen for post-operative pain management. Because there has been some evidence that a single intraoperative dose of IV acetaminophen can improve post-operative pain following pediatric tonsillectomy, as well as separate evidence that the post-operative regimen of alternating ibuprofen and acetaminophen can also be beneficial in this setting, many practitioners have begun to combine these options with the goal of improved pain management. However, while there is evidence supporting the benefit of either of these two pain management options, there is a lack of evidence regarding whether combining them results in any significant improvement in post-operative pain management when compared to using the post-operative strategy of alternating ibuprofen and acetaminophen alone. The goal of this retrospective study was to look for evidence that IV acetaminophen resulted in any outcome improvement, particularly in pain scores, in our population of pediatric tonsillectomy patients receiving the alternating ibuprofen and acetaminophen post-operative pain management regimen.

2. Methods

A retrospective cohort study was performed after receiving approval from the Penn State Milton S. Hershey Medical Center Institutional Review Board. Pediatric patients undergoing tonsillectomy or adenotonsillectomy with a single surgeon between March 2012 and December 2014 at a single academic medical center were included in the study. Chart reviews were performed on these patients to acquire information regarding patient characteristics and outcome variables. Patients were divided into cohorts based on whether they received a single intraoperative dose of IV acetaminophen (Group 1 received intraoperative IV acetaminophen, Group 2 did not receive intraoperative IV acetaminophen). Group 2 received no acetaminophen via any route of administration in the immediate preoperative or intraoperative period. The decision to administer IV acetaminophen was made by the anesthesiologist involved in the case based on their personal preference and practice patterns. Medications administered in the Recovery Room (RR) were also determined by the anesthesia team. Following discharge from the RR, both groups received an alternating regimen of ibuprofen and acetaminophen in the post-operative period which is standard at our institution. Both medications are given every six hours but the administration is staggered so that patients receive one medication every three hours.

The main outcome measure for this study was the level of pain reported for various post-operative time intervals (hours 1, 2, 3, 4, 5–8, 9–12, 13–16, 17–20, and 21–24). Pain scores were recorded using a combination of the Wong-Baker Faces Pain Rating Scale [8], a numeric rating scale (scores 0–10) [9], and the Face, Legs, Activity, Cry, Consolability (FLACC) scale [10]. Choice of scale depended on the age of the patient. Secondary outcome measures in this study included the time spent in the RR, time spent in the hospital, complications, and the need for narcotic pain medications for breakthrough pain in the RR.

A non-parametric test (Wilcoxon Rank-Sum Test) was used to test for differences for ordinal outcome variables such as number of doses of medications [11]. A Chi-square test was used to test for differences in nominal data such as gender, procedure, and indication for surgery. *T*-tests were used to compare groups for outcomes comprised of continuous data such as age, weight, pain scores and durations.

3. Results

Three hundred and sixty-three patients were included in this study. Thirteen patients were excluded because they had not received intra-operative fentanyl, leaving 350 study patients. Of these, 116 patients received a single intraoperative dose of IV acetaminophen (Group 1) and 234 patients did not receive IV acetaminophen (Group 2). Table 1 summarizes the patient characteristics between these two groups. There were no significant differences between Groups 1 and 2 in terms of gender, age, BMI, comorbidities or comorbid syndromes. Twenty patients are listed as "other" regarding presence of comorbidities. Of these twenty patients, six had a congenital heart anomaly (n = 3 Group 1, n = 3 Group 2), two had a coagulation disorder (n = 1 Group 1, n = 1 Group 2), three had a seizure disorder (n = 2 Group 1, n = 1 Group 2), seven patients had asthma alongside a congenital heart anomaly (n = 4 Group 1, n = 3 Group 2), one patient had asthma and a seizure disorder (n = 1 Group 1), and the final patient had a congenital heart anomaly, gastroesophageal reflux, and a coagulation disorder (n = 1 Group 1).

Table 2 summarizes characteristics of the operation(s) performed as well as the indications for the procedure. Seven patients are listed as "other" regarding the indication for the procedure. Of these seven patients, three underwent operation due to asymmetric tonsils (n = 3, Group 1), two patients underwent the procedure for failure to thrive (n = 1 Group 1, n = 1 Group 2), one patient underwent operation due to a combination of Obstructive Sleep Apnea (OSA) and Failure To Thrive (FTT) (n = 1 Group 2), and the final patient of these seven underwent the procedure for a combination of OSA, recurrent tonsillitis, and failure to thrive (n = 1 Group 1).

Table 3 lists intraoperative medications given. Patients in Group 1 received a statistically significantly larger dose of dexamethasone by weight (0.31 mg/kg vs. 0.28 mg/kg, $p = 0.009$). Mean dexamethasone dose per kilogram was 0.29 mg. The study population was divided into low dose (<0.29 mg/kg) and high dose (>0.29 mg/kg) dexamethasone groups, distribution of which was not significantly different between Groups 1 and 2 ($p = 0.112$). No

Table 1
Comparison of patient characteristics.

Patient characteristics	Group 1	Group 2
Number of patients	116	234
Gender		
Male	58 (50.0%)	129 (55.1%)
Female	58 (50.0%)	105 (44.9%)
Average age (years)	6.10	6.59
Average BMI	18.76	18.95
Comorbidities		
Asthma	30 (25.9%)	70 (39.9%)
Reflux	13 (11.2%)	12 (5.2%)
Other	12 (5.2%)	8 (3.4%)
Comorbid syndromes		
Trisomy 21	2 (1.7%)	8 (3.4%)
Other syndromes	5 (4.3%)	10 (4.3%)

Table 2
Characteristics of operation(s) performed and indications.

Characteristics	Group 1 n = 116	Group 2 n = 234
Procedure		
Tonsillectomy	9 (7.8%)	15 (6.4%)
Tonsillectomy + adenoidectomy	107 (92.2%)	219 (93.6%)
Indication		
Obstructive sleep apnea	90 (77.6%)	168 (71.8%)
Recurrent tonsillitis	11 (9.5%)	30 (12.8%)
Sleep-disordered breathing + tonsillitis	11 (9.5%)	33 (14.1%)
Other	4 (3.5%)	3 (0.9%)
Other procedures performed at time of operation		
DLB	6 (5.2%)	18 (7.7%)
BTT	15 (12.9%)	25 (10.5%)
DLB + BTT	1 (0.9%)	1 (0.4%)
Average surgery duration (min)	30.0	30.2

DLB – Direct laryngoscopy and bronchoscopy.
BTT – Bilateral tympanostomy tubes.

Table 3
Comparison of intraoperative medications given.

Outcome measure	Group 1 n = 116	Group 2 n = 234
Dexamethasone given in OR	113 (97.4%)	229 (97.9%)
Average dexamethasone dose/kg given in OR*	0.31	0.28
Low dose dexamethasone (<0.29 mg/kg)	47.4%	56.4%
High dose dexamethasone (>0.29 mg/kg)	52.6%	43.6%
Fentanyl given in OR	116 (100%)	234 (100%)
Average fentanyl dose/kg given in OR	1.66	1.69
Morphine given in OR	13 (11.2%)	35 (15.0%)
Average morphine dose/kg given in OR	0.01	0.01

OR – Operating room.
* $p < 0.05$.

statistically significant difference was noted between Groups 1 and 2 based on pain scores reported for the first post-operative hour (2.76 vs. 2.90, $p = 0.624$). However, Group 1 demonstrated significantly lower pain scores than Group 2 for the second postoperative hour (1.27 vs. 2.06, $p = 0.008$). No significant differences were noted for pain scores recorded during post-operative hours 3–24. Comparisons for pain scores recorded for the first 24 postoperative hours are displayed in Table 4. The relationship between the pain scores of Groups 1 and 2 for postoperative hours 1–5 is shown in Fig. 1.

Significant differences were found between Groups 1 and 2 with respect to average time spent in the RR and average time spent in the hospital, with Group 1 requiring less time in the RR (59.1 min vs. 69.5 min, $p = 0.016$) and more time in the hospital

Table 4
Comparison of postoperative pain scores.

Outcome measure	Group 1	Group 2	p-value
RR discharge pain score	1.19	1.16	0.879
Average pain score during 1st hour	2.76	2.90	0.624
Average pain score during 2nd hour*	1.27	2.06	0.008*
Average pain score during 3rd hour	1.49	1.83	0.395
Average pain score during 4th hour	1.14	0.99	0.683
Average pain score during hours 5–8	1.45	1.38	0.554
Average pain score during hours 9–12	1.35	1.37	0.943
Average pain score during hours 13–16	2.07	1.69	0.386
Average pain score during hours 17–20	1.19	1.43	0.637
Average pain score during hours 21–24	1.65	1.23	0.508

* $p < 0.05$.

(24.5 h vs. 19.7 h, $p = 0.030$). Patients in Group 1 were not more likely to receive narcotic analgesics for breakthrough pain while in the RR (79.3% did so versus 70.9%, $p = 0.094$). Patients in Group 1 were significantly more likely to receive ibuprofen in the RR (60.3% of patients in Group 1 vs. 38.9% of patients in Group 2, $p < 0.001$), while patients in Group 2 were significantly more likely to receive acetaminophen in the RR (6.9% of patients in Group 1 vs. 26.5% of patients in Group 2, $p < 0.001$) which reflects the timing on the first acetaminophen dose given in the OR. No significant differences were noted between Groups 1 and 2 with respect to complications. The analyses of outcome measures for the postoperative course are displayed in Table 5.

4. Discussion

This retrospective study examines the use of a single intraoperative dose of IV acetaminophen alongside a post-operative regimen of oral acetaminophen and oral ibuprofen for controlling postoperative pain in a pediatric population undergoing tonsillectomy or adenotonsillectomy. Intraoperative IV acetaminophen was associated with a decrease in the time spent in the RR as well as improvement of pain scores in the early post-operative period, as indicated by the significantly lower pain scores during the second postoperative hour. This is consistent with the pharmacokinetic profile of IV acetaminophen. IV acetaminophen has a quick onset of action, with clinically apparent results within five minutes of administration, as well as a relatively brief half-life of two to four hours [12]. The duration of action of IV acetaminophen has been previously reported to be limited to four to six hours [12], and the manufacturer recommends dosing intervals of every four to six hours depending on the mg/kg dose [13]. This makes any decrease in pain scores beyond the early postoperative period unlikely after a single intraoperative dose of IV acetaminophen.

There were statistically significant differences between the average pain scores for Group 1 and Group 2 during the second postoperative hour (1.27 vs. 2.06, $p = 0.008$). These small differences in pain scores may not be clinically significant. Some have argued that the cost of IV acetaminophen, estimated to be $15.38 for a one gram vial of IV acetaminophen in 2013 US dollars [14], may outweigh this potential benefit. Tonsillectomies are one of the most common procedures performed in the United States, so it is important to establish the efficacy of IV acetaminophen and consider this alongside its cost when deciding to administer it to every patient undergoing tonsillectomy. Importantly, the patients in Group 1 spent an average of 10.42 fewer minutes in the recovery room than patients in group 2. At an estimated cost of $63.70 for every ten minutes spent in the RR [14], this finding of decreased time spent in the RR for patients receiving IV acetaminophen may be favorable in a cost analysis.

Some of the outcome measures included in this study yielded results that were inconsistent with results from prior studies on

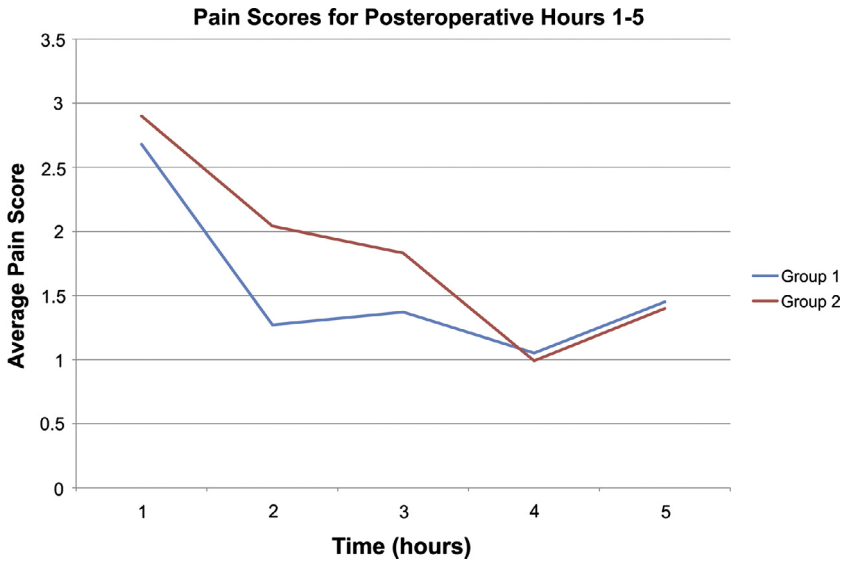

Fig. 1. Average pain scores recorded for Groups 1 and 2 during postoperative hours one through five. There was a significant difference between scores at hour 2 ($p = 0.008$).

Table 5
Comparison of postoperative outcome measures.

Outcome measure	Group 1	Group 2
Average time in RR (min)*	59.08	69.50
Average time in hospital (h)*	24.54	19.66
Acetaminophen given in RR*	8 (6.9%)	62 (26.5%)
Ibuprofen given in RR*	70 (60.3%)	91 (38.9%)
Narcotic given in RR	92 (79.4%)	166 (71.0%)
Mental status on post-operative anesthesia assessment		
Awake	90 (77.6%)	187 (79.9%)
Arousable	25 (21.6%)	47 (20.1%)
Sedated	1 (0.9%)	0 (0.0%)
Complications during admission		
Hemorrhage	3 (2.6%)	1 (0.4%)
Failure to drink	3 (2.5%)	3 (1.3%)
Total	6 (5.2%)	4 (1.7%)
Post-operative hemorrhage	7 (6.0%)	13 (5.6%)

RR – Recovery room.
* $p < 0.05$.

this topic. We expected patients receiving intraoperative IV acetaminophen to require less narcotic analgesic for breakthrough pain in the RR [6], but we did not find that. There is no standard analgesic regimen for our patients in the RR; nurses are typically given the option of oral acetaminophen, oral ibuprofen, or IV narcotics depending on the severity of pain. Group 1 patients did not have the option of oral acetaminophen for 6 h following administration of IV acetaminophen so more received ibuprofen in the RR. Ibuprofen administration in the recovery room could impact the amount of narcotics given in the recovery room if ibuprofen is more effective at this stage of recovery, as has been previously reported [15].

Patients who received intraoperative IV acetaminophen spent, on average, an extra 4.88 h in the hospital compared to the patients who did not receive intraoperative IV acetaminophen. Because of the short duration of action of IV acetaminophen, it is unlikely that this contributed to the increased length of hospitalization.

A confounding factor for this retrospective study is that no standardized protocol was in place for the intraoperative and post-operative management from the perspective of anesthesiology. The use of intraoperative IV acetaminophen was at the discretion of the anesthesiologists, as was the post-operative pain management for these patients. The lack of a standardized protocol resulted in statistically significant differences between the two groups regarding intraoperative dexamethasone dosing, with Group 1 receiving a larger dose by weight. There is evidence to suggest that dexamethasone may lead to decreased pain following pediatric tonsillectomy [16], so the variation in dosing discovered in our study may be a confounding factor when analyzing post-operative pain. However, while the difference in dexamethasone dosing might have been statistically significant, the clinical significance of the small difference – an average difference of 0.03 mg/kg between the groups - is questionable. As well, when patients were classified as having received a high dose (greater than the mean dose) or low dose (less than the mean dose) of dexamethasone, there was no difference between the groups.

Finally, this study was limited by variability in the frequency of pain score documentation as well as variability in the pain scales used to document these scores. Because of the retrospective nature of this study and the variation in patient age, pain scores were not recorded using a uniform pain rating scale. Instead, they were documented using a combination of Wong-Baker Faces Pain Rating Scale, the numeric rating scale, as well as FLACC. These variations may have implications regarding the validity of the pain score recordings due to possible variation in pain scale agreement. Additionally, while all three of these pain scales allow for scores between zero and ten, the Wong-Baker scale only allows for even numbers between zero and ten while the others allow for even and odd numbers between zero and ten.

With the widespread discontinued use of codeine for pediatric tonsillectomy pain management, many new strategies have been employed for this purpose. One of these strategies involves alternating acetaminophen and ibuprofen postoperatively, as described in this study. An additional pain management technique that may be a useful addition to regimens involves the use of intraoperative IV acetaminophen. The use of a single intraoperative dose of intravenous acetaminophen appears safe with respect to post-operative hemorrhage risk and complications during admission. It may improve pain in the early post-operative period and decrease the length of time spent in the post-anesthesia care unit. This study provides evidence that prospective, randomized studies are a necessary next step in order to clarify the role of IV acetaminophen in managing children undergoing tonsillectomy.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors have no conflict of interest to disclose.

References

[1] Kelly LE, Rieder M, van den Anker J, et al. More codeine fatalities after tonsillectomy in North American children. Pediatrics 2012;129:e1343–7.
[2] Botting RM. Vane's discovery of the mechanism of action of aspirin changed our understanding of its clinical pharmacology. Pharmacol Rep 2010;62:518–25.
[3] Jeyakumar A, Brickman TM, Williamson ME, et al. Nonsteroidal anti-inflammatory drugs and postoperative bleeding following adenotonsillectomy in pediatric patients. Arch Otolaryngol Head Neck Surg 2008;134:24–7.
[4] Riggin L, Ramakrishna J, Sommer DD, Koren G. A 2013 updated systematic review & meta-analysis of 36 randomized controlled trials; no apparent effects of nonsteroidal anti-inflammatory agents on the risk of bleeding after tonsillectomy. Clin Otolaryngol 2013;38:115–29.
[5] Liu C, Ulualp SO. Outcomes of an alternating ibuprofen and acetaminophen regimen for pain relief after tonsillectomy in children. Ann Otol Rhinol Laryngol 2015;124:777–81.
[6] Kocum AI, Sener M, Caliskan E, et al. Intravenous paracetamol and dipyrone for postoperative analgesia after day-case tonsillectomy in children: a prospective, randomized, double blind, placebo controlled study. Braz J Otorhinolaryngol 2013;79:89–94.
[7] Uysal HY, Takmaz SA, Yaman F, et al. The efficacy of intravenous paracetamol versus tramadol for postoperative analgesia after adenotonsillectomy in children. J Clin Anesth 2011;23:53–7.
[8] Hockenberg MJ, Wilson D, Winkelstein ML. Wong's essentials of pediatric nursing. 7th ed. St. Louis, MO: Mosby; 2005. p. 1259.
[9] Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods. Pain 1986;27:117–26.
[10] Merkel SI, Voepel-Lewis T, Shayevitz JR, Malviya S. The FLACC: a behavioral scale for scoring postoperative pain in young children. Pediat Nurs 1997;23:293–7.
[11] Sheskin D. Handbook of parametric and nonparametric statistical procedures. Boca Raton, Fla: CRC; 1997.
[12] Jahr JS, Lee VK. Intravenous acetaminophen. Anesthesiol Clin 2010;28:619–45.
[13] OFIRMEV [package insert]. Hazelwood, MO: Mallinckrodt Hospital Products, Inc; 2014.
[14] Subramanyam R, Varughese A, Kurth CD, Eckman MH. Cost-effectiveness of intravenous acetaminophen for pediatric tonsillectomy. Paediatr Anaesth 2014;24:467–75.
[15] Bailey E, Worthington H, Coulthard P. Ibuprofen and/or paracetamol (acetaminophen) for pain relief after surgical removal of lower wisdom teeth, a Cochrane systematic review. Br Dent J 2014;216:451–5.
[16] Hermans V, De Pooter F, De Groote F, et al. Effect of dexamethasone on nausea, vomiting, and pain in paediatric tonsillectomy. Br J Anaesth 2012;109:427–31.