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Effects of intraoperative i.v. acetaminophen *vs* i.m. meperidine on post-tonsillectomy pain in children

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Background. Enteral acetaminophen, when used alone, is not very effective for postoperative analgesia because of delayed absorption and sub-therapeutic plasma concentrations. In contrast, i.v. acetaminophen is devoid of these shortcomings and could potentially provide adequate postoperative analgesia as a single agent. This randomized double-blind study compared the analgesic effects of i.v. acetaminophen and i.m. meperidine in paediatric patients undergoing tonsillectomy.

Methods. Eighty children undergoing tonsillectomy were randomized to receive either acetaminophen 15 mg kg^{-1} i.v. (acetaminophen group) or meperidine 1 mg kg^{-1} i.m. (meperidine group), intraoperatively. Anaesthesia was induced with either sevoflurane inhalation or propofol, and was maintained with sevoflurane. After operation, the objective pain scale (OPS), Ramsay sedation score and Aldrete score were recorded every 5 min, and nurses' satisfaction was determined on a 7-point scale (1–7).

Results. On admission to the recovery room, OPS scores were 3.1 (SEM 0.3) for the acetaminophen group and 2.1 (SEM 0.3) for the meperidine group (P=0.147); however, Ramsay sedation scores were 3 (SEM 0.2) and 4 (SEM 0.3) for the acetaminophen and meperidine groups, respectively (P<0.05). Patients in the meperidine group continued to be more sedated 5 min after arrival in recovery (P<0.05). Acetaminophen group patients achieved an Aldrete score of 10 min sooner than those in the meperidine group [median (IQR) time: 15 (0–20) min *vs* 25 (15–30) min, respectively, P=0.005]. Adjusted nurse satisfaction scores were similar in both groups [6.1 (SEM 0.2) *vs* 5.7 (SEM 0.2) min, P=0.311].

Conclusion. Compared with i.m. meperidine, i.v. acetaminophen provided adequate analgesia, less sedation and earlier readiness for recovery room discharge among paediatric patients undergoing tonsillectomy.

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Tonsillectomy is a very common paediatric day-case procedure that is associated with significant postoperative pain.[1] This pain has traditionally been treated with opioid analgesics and non-steroidal anti-inflammatory drugs;[2 3] however, these agents are associated with increased risks of respiratory depression and postoperative bleeding, respectively.[2 4] In contrast, acetaminophen is a non-opioid analgesic that is devoid of these risks,[4] and its enteral formulation has been used, alone,[5] and in combination with other agents, in the management of postoperative pain.[6] However, enteral acetaminophen as a stand-alone analgesic is less than ideal in the management of post-tonsillectomy pain in the immediate postoperative period.[4 5] This has been attributed to delayed drug absorption[7] and sub-therapeutic plasma concentrations.[4 8]

Recently, an i.v. formulation of acetaminophen has been introduced, and its safety and pharmacokinetic properties have been established for children as young as 1 yr of age.[9] Although i.v. acetaminophen solves the bioavailability issues associated with the enteral formulation and could potentially provide adequate postoperative analgesia, the analgesic efficacy of i.v. acetaminophen as monotherapy for post-tonsillectomy pain has not been established. This randomized, double-blind, clinical study was, therefore, undertaken to compare the postoperative analgesic effects of intraoperatively administered i.v. acetaminophen as a

stand-alone therapy; with those of preoperative i.m. meperidine in paediatric patients undergoing day-care tonsillectomy.

Methods

After institutional Ethics Committee approval and informed consent from a parent or guardian in each case, 80 patients were randomized using a computer-generated schedule, to double-blind treatment with i.v. acetaminophen (acetaminophen group) or i.m. meperidine (meperidine group). Inclusion criteria were: age 3–16 yr, ASA physical status I or II, and elective tonsillectomy. Patients were excluded from the study if they were developmentally delayed, had neurological dysfunction or renal insufficiency, and/or had allergy to any of the study medications.

All study patients were premedicated with oral midazolam 0.5 mg kg^{-1} 30 min before the procedure and received fentanyl 1 μg kg^{-1} i.v. immediately after induction of general anaesthesia, which was done with either sevoflurane inhalation or propofol 2–3 mg kg^{-1} i.v. Before surgery was started, patients in the acetaminophen group received acetaminophen 15 mg kg^{-1} i.v. (premixed with normal saline to a total volume of 70 ml) and normal saline 1 ml i.m., whereas those in the meperidine group received meperidine 1 mg kg^{-1} i.m. (premixed with normal saline to total volume of 1 ml) together with normal saline 70 ml i.v. Anaesthesia was maintained, in both groups with sevoflurane in an oxygen/nitrous oxide mixture at a total fresh gas flow of 1 litre min^{-1}, titrated to keep mean arterial pressure within 20% of baseline values. Other than the single dose of fentanyl that was administered on anaesthesia induction and the study drug, no additional opioids or non-steroidal analgesics were administered intraoperatively. Oxygen saturation (Sp_{O_2}) (Dinamap™ Plus, Critikon Inc., Tampa, FL, USA), Ramsay sedation score (1=anxious, agitated, and restless; 2=cooperative, oriented, and tranquil; 3=responds to commands only; 4=asleep, brisk response to light glabellar tap or loud auditory stimulus; 5=asleep, sluggish response to light glabellar tap or loud auditory stimulus; 6=asleep, no response),[10] the objective pain scale (OPS) score (best to worst: 0–10) (Table 1),[11] and Aldrete score[12] (Table 2) were determined on admission to the post-anaesthesia care unit (PACU) and every 5 min thereafter, until patients were ready for discharge from the unit. Readiness for discharge from PACU was determined by achieving an Aldrete score of 10. Rescue analgesia with morphine 0.05 mg kg^{-1} i.v. was administered, after operation; for OPS score ⩾5 or if the patient requested analgesia during pain assessment. All adverse events including, but not limited to, respiratory depression (ventilatory frequency ⩽10), desaturation (Sp_{O_2}⩽92%), nausea or vomiting, and bleeding requiring assessment by the surgeon, were documented. Upon patient discharge, PACU nurses were asked to rate their satisfaction with patient analgesia on a 7-point scale; 1 being extremely dissatisfied and 7 being extremely satisfied.[13] All patients were prescribed acetaminophen syrup 15 mg kg^{-1} orally 6 hourly and tramadol drops 2 mg kg^{-1} orally 4 hourly as needed for analgesia at home. The anaesthetist who administered the anaesthetic, PACU nurses and the observer who recorded study parameters were all blinded to patients' group assignment.

Table 1 The OPS

Observation	Criteria	Points
Blood pressure	±10% preoperative value	0
	>20% preoperative value	1
	> 30% preoperative value	2
Crying	Not crying	0
	Crying but responds to loving care	1
	Crying and does not respond to loving care	2
Movement	None	0
	Restless	1
	Thrashing	2
Agitation	Asleep or calm	0
	Mild	1
	Hysterical	2
Posture	No special posture	0
	Flexing legs and thighs	1
	Holding scrotum or groin	2

Table 2 The Aldrete score

Observation	Criteria	Points
Activity	Able to move four extremities voluntarily or on command	2
	Able to move two extremities voluntarily or on command	1
	Unable to move extremities voluntarily or on command	0
Respiration	Able to breathe deeply and cough freely	2
	Dyspnoea or limited breathing	1
	Apnoea	0
Circulation	Blood pressure ±20% of preoperative level	2
	Blood pressure ±20–49% of preoperative level	1
	Blood pressure ±50% of preoperative level	0
Consciousness	Fully awake	2
	Arousable on calling	1
	Not responding	0
O_2 saturation	Able to maintain O_2 saturation >92% on air	2
	Needs O_2 supplement to maintain O_2 saturation >90%	1
	O_2 saturation <90% even with O_2 supplement	0

Statistical analysis

Study sample size was calculated using a two-sided value for α of 0.05, a population variance for the OPS score of $(4)^2$, and 90% power to detect a difference of 3 in OPS scores between the study groups. OPS and Ramsay sedation scores were analysed using repeated measures ANOVA, the nurses' satisfaction score was analysed with an unpaired *t*-test, proportions were analysed using the χ^2-test, and Aldrete scores data were analysed using the log-rank test after constructing Kaplan–Meier survival curves for times to

achieving an Aldrete score of 10. *A post hoc* power analysis was performed based on the observed results of the primary outcome measure. Nursing satisfaction data were also analysed with ANCOVA to adjust for the effect of morphine administration. In addition, univariate analyses were performed to determine the association between nursing satisfaction and each of the following variables: study group, occurrence of vomiting, requirement for morphine analgesia, and OPS, Ramsay, and Aldrete scores. OPS, Ramsay, and Aldrete score data were limited to the first 15 min of PACU stay as this is the time of peak nursing activity. Variables with $P<0.25$ on univariate analyses were included in a stepwise-multivariable regression analysis to determine predictors of nurses' satisfaction using $P\leqslant 0.05$ as the threshold for entering variables into the model and $P\geqslant 0.1$ as the threshold for variable removal. Regression diagnostics were performed for all models to ensure the validity of the assumptions of the models used. In addition, OPS and Ramsay scores data met the underlying assumptions for the repeated measures ANOVA. Sample size and power calculations were performed using PS Power and Sample Size Calculations Program®, version 2.1.30 (Copyright © 1997 by WD Dupont and WD Plummer).[14 15] Other statistical procedures were performed using SPSS® statistical software (SPSS Inc., Chicago, IL, USA), version 13.0 for Windows®. Results throughout the text, tables and figures are presented as mean (SEM) unless otherwise indicated, and statistical significance was defined as $P<0.05$.

Results

Both study groups were similar with regard to baseline characteristics, proportion of patients who underwent inhalational induction of anaesthesia, the amounts of midazolam and fentanyl administered, and the duration of anaesthesia (Table 3). In neither group did the OPS scores change significantly over the course of the assessment period; however, the patients in the meperidine group had OPS scores that were consistently one point lower than those in the acetaminophen group ($P=0.147$ for the overall F-test of between-subject effects) (Fig. 1A). This difference in OPS scores did not achieve statistical significance, and

Table 3 Patients characteristics. Patient ages are presented as mean and range. Other data are presented as mean (SD), or absolute numbers

Variable	Acetaminophen group ($n=40$)	Meperidine group ($n=40$)
Age (yr)	7.7 (3–15)	6.8 (3–13)
Weight (kg)	26.3 (14.5)	24.9 (14.4)
Gender (male/female)	19/21	20/20
ASA physical class (I/II)	26/14	26/14
Preoperative midazolam (mg)	8.5 (3.1)	8.7 (2.6)
Inhalational induction (n)	22 (55%)	21 (52.5%)
Propofol dose for i.v. induction (mg)	94.2 (37.5)	85.6 (43.4)
Anaesthesia time (min)	38 (15)	39 (13)
Intraoperative fentanyl (μg)	26.4 (14.9)	24.4 (14.1)

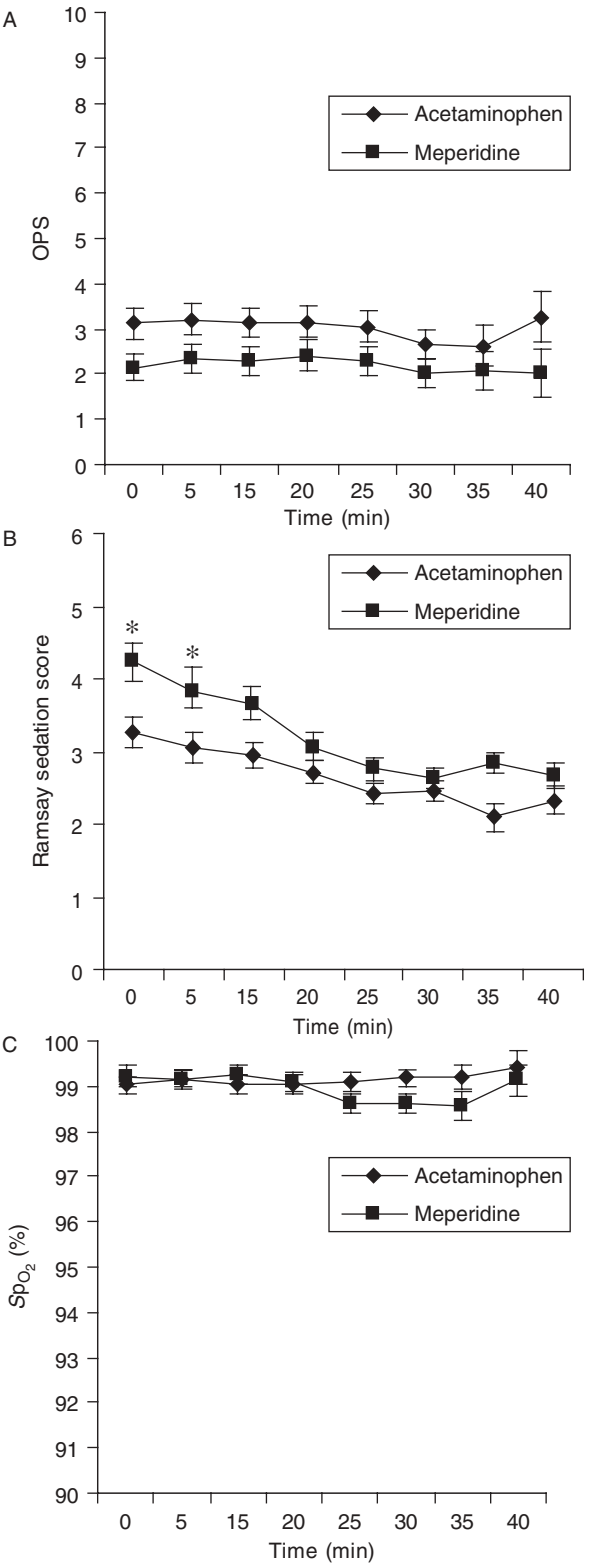

Fig 1 OPS scores did not change significantly over the course of the assessment period in either study group (A). Ramsay sedation scores were higher on admission to recovery room and for 5 min thereafter in meperidine group (B). Sp_{O_2} was similar between study groups during recovery room stay (C). OPS, objective pain scale; Sp_{O_2}, oxygen saturation. Data presented as mean (SEM). *$P<0.05$, pairwise comparison between groups.

these results did not change after adjusting for the type of anaesthesia induction used. Seven (17.5%) patients in the acetaminophen group required a single dose of rescue morphine 0.3 mg (SD 0.8) in PACU compared with none in the meperidine group ($P<0.01$). The median (IQR) time to administering rescue morphine analgesia was 18 (5–25) min after admission to PACU. Based on Ramsay sedation scores, meperidine group patients were more sedated on arrival to PACU and for 5 min thereafter when compared with those in the acetaminophen group ($P=0.031$ for the overall F-statistic of between-subjects effects) (Fig. 1B). Eleven (27.5%) patients in the acetaminophen group had an Aldrete score of 10 on arrival at PACU compared with only 4 (10%) in the meperidine group ($P=0.045$). Furthermore, Kaplan–Meier survival curves demonstrated that acetaminophen group patients achieved an Aldrete score of 10 earlier than those in the meperidine group ($P=0.005$) (Fig. 2) and, therefore, the median (IQR) time to readiness for PACU discharge was shorter in the acetaminophen group compared with that in meperidine group [15 (0–20) min *vs* 25 (15–30) min, respectively, $P=0.005$]. There were no differences in postoperative Sp_{O_2} between study groups during PACU stay ($P=0.712$ for the overall F-statistic of between-subjects effects) (Fig. 1C). In addition, there was no respiratory depression or other major adverse effects, including bleeding from the operation site, in either group. Postoperative nausea and vomiting in PACU occurred in three (7.5%) patients in each study group, but none of the children experienced delayed discharge or unplanned hospital admission. Unadjusted analysis showed that nurses were more satisfied with patients' analgesia in the meperidine group compared with the acetaminophen group 5 (0.3) *vs* 6 (0.1), respectively ($P=0.009$). However, after adjusting for the effect of morphine administration in PACU there was no difference in nurses' satisfaction scores between groups 5.7 (0.2) *vs* 6.1 (0.2) for the acetaminophen and meperidine groups, respectively ($P=0.311$). Moreover, postoperative morphine administration, PACU length of stay, and OPS score at 15 min after entry into recovery were all independent predictors of nurses' satisfaction.

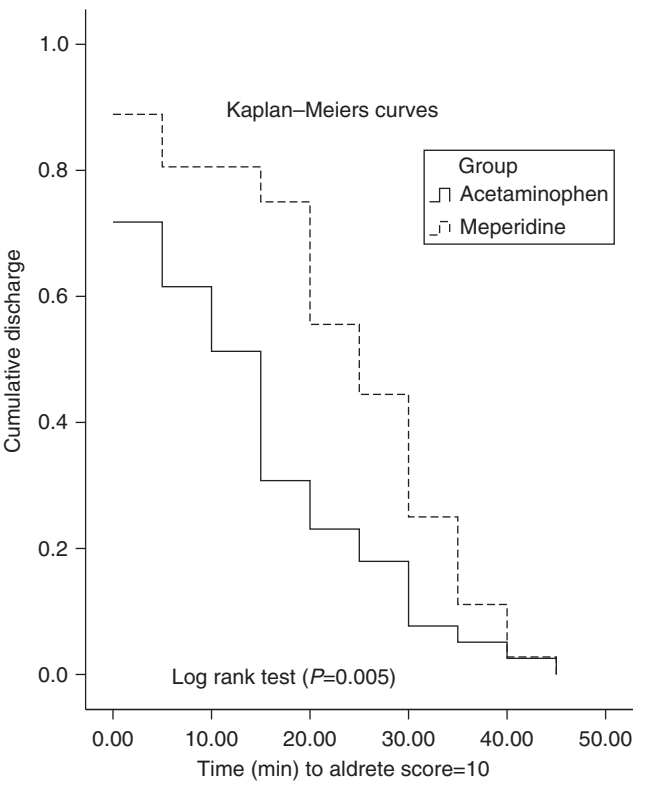

Fig 2 Kaplan–Meier survival curves of times to achieving an Aldrete score of 10. Acetaminophen group patients achieved an Aldrete score of 10 earlier and were thus ready for recovery room discharge sooner than those in the meperidine group ($P=0.005$).

Discussion

This is the first randomized, double-blind study to compare the postoperative analgesic effects of intraoperatively administered i.v. acetaminophen and i.m. meperidine in paediatric patients undergoing day-care tonsillectomy. The study failed to demonstrate a significant difference in postoperative OPS scores between the study groups despite the fact that OPS scores were consistently one point lower in the meperidine group. *Post hoc* power analysis indicated that this study had a 69% power to detect the observed difference in OPS scores, and that a total of 138 patients would have had to be included in the trial to demonstrate statistical significance. As the clinical importance of this small difference is relatively minor, it was not considered appropriate to extend the trial to recruit the re-calculated sample size obtained from the *post hoc* power analysis. The study was underpowered as a result of the smaller than expected difference in OPS scores between the groups. This could be attributed, in part, to the deeper level of sedation observed in the meperidine group in early recovery which in turn could have contributed to the lower OPS scores in this group, and in part, to the fact that treatments usually perform better in clinical trials than in every day clinical practice.[16] Nevertheless, both study drugs provided adequate postoperative analgesia based on the observation that OPS scores were less than 4 in both study groups (Fig. 1A).

The requirement for rescue morphine analgesia among 17.5% of patients in the acetaminophen group suggests that these patients had severe pain, low pain threshold, or both that required treatment with an opioid as opposed to a non-opioid analgesic. Similar findings have been reported by other investigators when propacetamol (an i.v. pro-drug of acetaminophen) and diclofenac have been used alone or in combination to treat post-tonsillectomy pain.[17] In addition, Mather and Peutrell[18] have demonstrated that postoperative supplemental morphine analgesia may also be required amongst those who receive preoperative

acetaminophen or i.v. morphine on induction of anaesthesia for tonsillectomy.

Ramsey sedation scores, on the other hand, were consistently lower throughout the observation period amongst patients in the acetaminophen group compared with those in the meperidine group (Fig. 1B). However, statistical significance could only be demonstrated in the early recovery period. This was probably because of the smaller differences in sedation scores between groups later in recovery and the smaller number of acetaminophen group patients remaining in PACU after 15 min into recovery. The observed differences in sedation scores between groups in the early recovery period could be attributed, at least in part, to the inherent sedative effects of meperidine and their lack thereof in acetaminophen and, in part, to the combination of midazolam premedication and meperidine administration in the meperidine group patients. It is unlikely that these differences were related to the anaesthetic technique itself; as patients in both groups were managed identically intraoperatively, and had received similar amounts of preoperative midazolam and intraoperative fentanyl (Table 3).

An important finding of this study is the earlier readiness for PACU discharge among patients who received i.v. acetaminophen. This could be attributed to the lighter levels of sedation observed in the acetaminophen group compared with the meperidine group. Based on these results and the observation that 27.5% of patients in the acetaminophen group were ready for discharge on admission to PACU, there might be an economic benefit if such patients could bypass PACU and be admitted straight from the operating room to a level II recovery area. However, the safety of this practice would have to be determined first before its economic benefit is explored. Postoperative adverse events were rare in this study. The occurrence of nausea and vomiting in PACU was in keeping with previous reports,[19] and the absence of postoperative bleeding in this cohort was anticipated based on its reported incidence of 1.5% in a population of 15 218 patients.[20]

An interesting finding was the results of the unadjusted analysis that showed higher nursing satisfaction scores in the meperidine group compared with the acetaminophen group, despite the fact that pain scores were not statistically different between the groups. However, this difference in nursing satisfaction was no longer present after adjusting for the effect of morphine administration. The observation that OPS score at 15 min into recovery was also a predictor of nursing satisfaction score could be explained by the fact that this was the time interval around which most of the supplemental morphine analgesia was administered. It is not surprising that PACU length of stay was also a predictor of nursing satisfaction as nurses would intuitively be pleased to observe that their patients are doing well and are discharged from PACU. Although it may be conceivable that 'awake' children are more demanding and require more attention than those who are 'asleep', the degree of patient sedation represented by Ramsay scores was not a predictor of nursing satisfaction.

One limitation of the current study is the lack of postoperative pain follow-up after discharge from PACU. This was because of the fact that 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. Another potential criticism of the study is the use of i.m. as opposed to i.v. meperidine. This was done because i.m. meperidine administration is widely used for postoperative analgesia in our institution. Moreover, this route has been demonstrated to result in peak plasma concentrations of the drug 20 min after its administration,[21] which is well below the average anaesthesia time observed in this study. Accordingly, it is unlikely that the route of meperidine administration had an impact on the outcomes of this study as the drug was likely to be available at the effect sites by the time the patients had arrived at PACU.

In conclusion, intraoperative i.v. acetaminophen administration provided adequate postoperative analgesia in paediatric patients undergoing day-care tonsillectomy, and was associated with earlier readiness for discharge from PACU when compared with intraoperative i.m. meperidine. Based on these findings, intraoperative i.v. acetaminophen appears to be a reasonable choice for postoperative analgesia in this patient population.

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