Intramuscular ketamine for prevention of postanesthesia shivering in children

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ABSTRACT

الأهداف: مقارنة تأثير حقن الكيتامين أو البثيدين عضلياً على ارتجاف ما بعد عملية استئصال اللوزتين في الأطفال.

الطريقة: تم أجراء هذا البحث على 120 طفل في مستشفى القوات المسلحة – قاعدة الملك عبد العزيز البحرية – الجبيل – المملكة العربية السعودية، خلال الفترة مابين نوفمبر 2006م وحتى أكتوبر 2007م. تراوحت أعمار المرضى مابين 5–12 عاماً، قسموا عشوائيا إلى ثلاث مجموعات احتوت كل مجموعة على 40 طفلاً. (المجموعة K) (أربعون مريض) أعطيت 1mg/kg كيتامين عضليا، (المجموعة P) (أربعون مريض) أعطيت 0.5mg/kg بثيدين عضليا، (المجموعة S) (أربعون مريض) أعطيت محلول ملح وذلك قبل بدء التخدير. تم قياس ديناميكية الدم، ومستوى الأكسجين في الدم، ودرجة الحرارة من الأذن قبل بدء التخدير ثم على فترات متتابعة بعد ذلك، كما تم تقييم درجة الارتجاف بواسطة أشخاص لا يعرفون نوع الدواء المستخدم وذلك على مقياس خماسي.

النتائج: أسفرت الدراسة عن قلة عدد المرضى المصابين بالارتجاف في (مجموعة K) عنه في (المجموعة S) (1.1.1) مقابل (19.12.17) على التوالي. لم يصاب مرضى المجموعة P بارتجاف ما بعد العملية، كما احتاج المرضى في المجموعة S إلى مسكن بعد وقت اقصر من المجموعتين K و P (p<0.005).

الخاتمة: نستنتج من هذا البحث أن جرعة وقائية من عقار الكيتامين العضلي لها تأثير ايجابي على منع ارتجاف ما بعد العملية في الأطفال. نظرياً قد يكون للكيتامين فوائد بالمقارنة مع البيثيدين من ناحية تثبيط التنفس، الغثيان، والقيئ.

Objectives: To compare the effects of intramuscular ketamine with pethidine and placebo on post operative shivering in children undergoing tonsillectomy.

Methods: A prospective randomized double-blind study was conducted at King Abdulaziz Naval Base Hospital, Jubail, Kingdom of Saudi Arabia, from November 2006 to October 2007. One hundred and twenty children (American Society of Anesthesiologists Grade 1, aged 5-12 years) were enrolled. Children were randomly allocated to receive ketamine 1 mg/kg (group K, n=40), or pethidine 0.5 mg/kg (group P, n=40), or normal saline (group S, n=40) intramuscularly just after induction of general anesthesia. Hemodynamic parameters, oxygen saturation and tympanic temperature were measured and recorded before induction of anesthesia and at regular intervals thereafter. An investigator blinded to the treatment group, graded postoperative shivering using a 5 point scale.

Results: The number of patients shivering on arrival to the recovery room and at 10 and 20 minutes after operation were significantly less in groups K (1,1,1) than in group S (19,12,17). No patient that received pethidine shivered. The time to first analgesic requirement in group S was shorter than groups K and P (p=0.001).

Conclusion: The study indicates that the use of a prophylactic low dose ketamine was found to be effective in preventing post anesthesia shivering in children undergoing tonsillectomy. Ketamine may have at least theoretical advantages over pethidine as regard respiratory depression, nausea, and vomiting.

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Postanesthetic shivering (PAS) is a common problem in the recovery room, occurring in 5-65% of patients recovering from general anesthesia.[1] It is very unpleasant and associated with an increase in oxygen consumption, cardiac output, carbon dioxide production, and circulating catecholamines together with a significant decrease in mixed venous

oxygen saturation, which could be distressing for the patients.[2] There is general agreement that PAS is a thermoregulatory phenomenon (a physiological response to anesthesia induced core hypothermia), or it may result from the release of cytokines by the surgical procedure.[3] However, non-thermoregulatory shivering may also occur in normothermic patients in response to certain anesthetics or postoperative pain. Several agents have been investigated for the prevention or treatment of PAS. Intravenous administration of opioids: pethidine, alfentanil, and nalbuphine[4,5] the non opioid analgesic tramadol,[6] the adrenergic agonist clonidine,[7] the respiratory stimulant doxapram,[8] the cholinomimetic physiostigmine, and the 5-HT3 antagonist ondansetron have all reduced the incidence of shivering, or suppressed established shivering. Pethidine has been shown to be one of the most effective treatments for PAS, however, it may cause respiratory depression, sedation, nausea and vomiting.[4] Ketamine is a non competitive antagonist at the N-methyl D-aspartate (NMDA) receptor and has analgesic properties at sub-anesthetic doses.[9] It is likely that NMDA receptor antagonist also modulate thermoregulation at multiple levels[10] and intravenous ketamine has been shown to prevent PAS in adult. Therefore, undertook a double blind, randomized study to compare the effect of intramuscular ketamine with pethidine and placebo for prevention of PAS in children undergoing tonsillectomy.

Methods. This study took place in King Abdulaziz Naval Base Hospital, Jubail, Kingdom of Saudi Arabia from November 2006 to October 2007. The study was approved by the Hospital Ethics Committee. After obtaining written informed consent from a parent or a guardian for participation in the study, 120 children (American Society of Anesthesiologists grade I, aged 5-12 years) admitted as in-patients scheduled for tonsillectomy were enrolled. Patients with a history of allergy to any of the study drugs were excluded. All children had fasted 6 hours before surgery for solids and clear fluids were allowed until 3 hours before induction of anesthesia. No premedications were given, however, 1 hour before anesthetic induction the children received topical "Emila" cream to facilitate venous canulation. A standardized general anesthetic technique was used. Anesthesia was induced with thiopentone 4-6 mg/kg or 3-5% sevoflurane, and 60% nitrous oxide in oxygen if venous access could not be obtained before induction of anesthesia. A proper sized endotracheal tube was positioned, and ringer's lactate solution was infused at a rate of 10 ml/kg/hour. Anesthesia was maintained with spontaneous ventilation and manual assistance of 2-3% sevoflurane and 60% nitrous oxide in oxygen. Non invasive mean arterial pressure, heart rate, and oxygen saturation were recorded before induction of anesthesia, and every 5 minutes (min) thereafter. Tympanic membrane temperature (first temperature genius thermometer) was measured immediately after induction of anesthesia. The patients were covered with warmed sheets and were not actively heated. Ambient temperature was maintained at 20-22°C with constant humidity. Patients were randomized, by using a sealed envelope technique, to one of 3 groups; to receive ketamine 1 mg/kg (group K, n=40), pethidine 0.5 mg/kg (group P, n=40), or saline (group S, n=40). All of the study drugs were prepared in the smallest possible equal volumes so that the investigators and observers were blind to the drug given. After induction of anesthesia, and before start of surgery, the study drug was administered intramuscularly (IM) into the anterolateral aspect of the thigh. Surgery was performed by applying the same surgical technique in all participants. At the end of surgery, volatile anesthetic agent was discontinued, and the patients were extubated. After the children were fully awake, they were brought to the recovery room, breathing room air. After arrival, mean arterial pressure, heart rate, and oxygen saturation were documented every 15 minutes until 6 hours after recovery. Post anesthetic shivering was documented visually by 2 specified members of the recovery room staff, who were carefully briefed on the definition of shivering, as used in the study. Shivering was defined as readily detectable fasciculation or tremors of the face, trunk or limbs of a minimum of 15 seconds duration. Post anesthetic shivering was graded using a 5 point scale (**Table 1**) on admission to the recovery room, 5, 10, 15, 20, and 30 minutes thereafter. Tympanic temperatures were also measured and recorded at these time intervals. Pethidine 0.3 mg/kg was given intravenously for PAS >grade 2. Time to eye opening to command was noted. Pain was assessed by an independent observer; using a 5 point scale (1=no pain, 5=highest pain score), on admission to the recovery room, at 30, 60, and 120 minutes thereafter. The time to additional analgesic requirement was also noted, and ketorolac 0.5 mg/kg intravenously was administered if the pain score was ≥3. Respiratory rate and incidence of nausea and vomiting were also recorded at these time intervals. Nausea or vomiting was treated with metoclopramide 0.15 mg/kg intravenously. Six hours after recovery, an inquiry was carried out as to the occurrence of any dreams or hallucinations. The morning following surgery, the parents were inquiring on their childrens' sleep and dreaming over night, as well as the overall postoperative pain relief.

Statistical analysis was performed using Kruskal Wallis ANOVA and Mann-Whitney U-tests for pain scores, t-tests for parametric data, or chi-square test for categorical data. Statistical calculations were carried out using computer programs Microsoft Excel version 7 (Microsoft Corporation, New York, USA) and Statistical

Package for the Social Science (SPSS Inc., Chicago, Il, USA). A $p<0.05$ was considered significant.

Results. One hundred and twenty children were recruited, 40 in each treatment group. The groups were similar with respect to age, weight, and duration of surgery. Hemodynamic parameters and baseline tympanic temperatures were also similar in the 3 groups (**Table 2**). Mean [standard deviation (SD)] time to eye opening to command was significantly longer in the ketamine and pethidine groups ($p=0.0001$) compared with saline group. Significantly more patients in group S had post operative shivering than those in group K on arrival to the recovery room and throughout the following 20 mins. No child given pethidine shivered. There was no difference between groups K and P ($p>0.05$). At 30 mins. after recovery, there was no difference between the 3 groups (**Table 3**). There were no significant differences in tympanic temperatures among the 3 groups throughout the observation period. However, tympanic temperatures were less than baseline values after recovery room admission in all groups. Mean (SD) respiratory rates 30 mins. after recovery were: ketamine (20.5 [4.3]/min), pethidine 19.2 [3.8]/min, and saline groups 21.4 [5.1]/min, with no significant differences between the groups over the study period. The number of children requiring further postoperative analgesia was similar in the 3 groups ($p>0.05$). The time to first analgesic requirement in group S was significantly shorter than that in group K and group P ($p<0.001$) (**Table 2**). Within the third postoperative hour, 34 patients in group S, 28 in group

Table 1 - Classification of shivering.

Classification	Points
No shivering	0
Mild fasciculations of face or neck	1
Visible tremor involving one muscle group	2
Visible tremors involving more than one muscle group	3
Gross muscular activity involving the whole body	4

Table 2 - Patient characteristics, duration of surgery, postoperative analgesic requirements, incidence of vomiting, and dreaming in the first 6 hours after surgery.

Parameter	Ketamine group	Pethidine group mean ± SD	Saline group
Age (years) (range)	9.4 (5-12)	10.1 (5-12)	9.8 (5-12)
Weight (kg)	28.3±15.2	23.8±17.2	26.4±16.2
Height (cm)	132±14.8	126±13.6	129±12.1
Baseline core temperature (°C)	36.7±0.3	36.6±0.4	36.6±0.4
Duration of surgery (min)	21.2±6.3	24.8±5.4	23.6±6.2
Time to eye opening (min)	20.1±6.6*	20.6±5.0†	7±2.4
Postoperative analgesia (n) required	33	36	38
Time to first analgesia required (min)	123.4±63.1*	119.8±59.8†	21.4±7
Incidence of vomiting (n)	5	7	5
Incidence of dreaming (n)	4	3	4

*$p<0.001$ between ketamine and saline groups,
†$p<0.001$ between pethidine and saline groups

Table 3 - Number of patients with different grades of shivering (N=40).

Time after arrival to recovery room (minutes)	Saline group	Ketamine group	Pethidine group
On arrival in recovery room			
Grade 0	23	40*	40†
Grade 1	7	0*	0†
Grade 2	2	0*	0†
Grade 3	2	0*	0†
Grade 4	6	0*	0†
5 minutes after arrival			
Grade 0	21	39*	40†
Grade 1	5	1*	0†
Grade 2	4	0*	0†
Grade 3	6	0*	0†
Grade 4	4	0*	0†
10 minutes after arrival			
Grade 0	26	39*	40†
Grade 1	8	1*	0†
Grade 2	1	0*	0†
Grade 3	2	0*	0†
Grade 4	3	0*	0†
15 minutes after arrival			
Grade 0	23	39*	40†
Grade 1	9	1*	0†
Grade 2	5	0*	0†
Grade 3	3	0*	0†
Grade 4	0	0*	0†
20 minutes after arrival			
Grade 0	23	39*	40†
Grade 1	8	1*	0†
Grade 2	6	0*	0†
Grade 3	3	0*	0†
Grade 4	0	0*	0†
30 after arrival to recovery room			
Grade 0	38	40	40
Grade 1	2	0	0
Grade 2	0	0	0
Grade 3	0	0	0
Grade 4	0	0	0

*$p<0.01$ between ketamine and saline groups,
†$p<0.01$ between pethidine and saline group.

Table 4 - Postoperative analgesia and sleep patterns during the first postoperative night (N=40).

Variable	Ketamine group	Pethidine group	Saline group
Good/excellent analgesia	35	32	11
Slept worse than normal	19	17	20
Bad dreams	3	2	2
Good dreams	6	6	4

Values are expressed as absolute numbers

P, and 31 in group K had pain scores ≥3, and they were treated with intravenous ketorolac, with no statistically significant difference among the treatment groups (p>0.05). The incidence of vomiting and dreaming during the first 6 hours after surgery were similar (**Table 2**). None of the children had episodes of oxygen desaturation, hallucination, tachycardia, hypotension, or hypertension. There was no significant difference in sleep patterns or dreams among the groups in the first post operative night. The numbers who felt pain relief to be good or excellent were also similar (**Table 4**).

Discussion. Prevention and treatment of PAS is an important aspect of patient care, as it may be associated with a number of deleterious sequelae, including sympathoadrenal stimulation, increased oxygen consumption, and carbon dioxide production. In our study, the incidence of PAS was 41.5% in the saline group compared to only 2.4% in the group receiving ketamine. No child given pethidine shivered. Pediatric patients have a larger surface area per kilogram than adults, together with thin skin and low fat contents that allow greater heat loss to the environment. This problem is compounded by cold operating rooms, wound exposure, intravenous fluid administration, dry anesthetic gases, and the direct effect of anesthetic agents on temperature regulation.[11] Normally, the thermoregulatory system protects body temperature against changes in ambient temperature. There is a dose-dependant decrease in the thermoregulatory threshold for shivering during general anesthesia, resulting in core hypothermia in unwarmed patients.[12] Post anesthetic shivering has been attributed to a number of factors including pain, uninhibited spinal reflexes, decreased sympathetic activity, adrenal suppression, release of pyrogenic mediators during surgery, administration of volatile anesthetic and blood loss, in addition to thermoregulatory shivering in response to hypothermia.[13]

In our study, we found no difference between the efficacy of ketamine and pethidine in preventing PAS. In contrast to other drugs used to treat PAS, we found ketamine has innocuous side effects. Clonidine may be associated with significant hypotension and sedation.[14] Doxapram, a cerebral stimulant, is also effective in suppressing PAS, however, it is associated with significant hemodynamic effects.[15] The cholinomimetic agent physiostigmine decreases heart rate and blood pressure with increased tendency for postoperative nausea and vomiting.[16] Ondansetron effectively relieves PAS, however, it is more expensive than any of the other drugs effective against PAS.[3] Pethidine has been shown to be one of the most effective treatments for PAS, however, it may potentially cause respiratory depression and postoperative nausea and vomiting, especially if it or other opioids have been given intraoperatively.[4,5,8,17] The incidence of ketamine side effects, such as bad dreams or hallucinations were low, in accordance with previous data when low dose ketamine had been used during anesthesia.[18,19] Dreaming is difficult to asses in children, and in this study, the parents were inquiring about their children's sleep and dreaming overnight. A number of factors however, may contribute to sleep disturbance or dreaming after surgery, including preoperative anxiety or sleep deprivation, the unfamiliar hospital environment, and the effects of opioids and general anesthesia. The incidence of good and bad dreams was similar in the 3 groups. This suggests that the effects of low dose ketamine are relatively unimportant in this context. Time to eye opening to command was significantly longer in the ketamine group compared to the saline group, which may be related to its pharmacokinetics. Maximum plasma concentrations occur 20-30 mins. after ketamine 0.5 mg/kg in adults, and the elimination half life is 155 mins.[20] Maximum plasma concentrations of the active metabolite, norketamine, occur more than 1 hour after intramuscular ketamine. Norketamine and ketamine have sedative effects, although marked sedation is unlikely at this dose.[9] The time to first analgesic requirement in the saline group was shorter than that in the ketamine or pethidine groups, this could be due to the analgesic properties of ketamine at subanesthetic doses, and the analgesic nature of pethidine. Within the third postoperative hour, most children in the 3 groups needed analgesia. This can be explained by the short duration of action of low dose pethidine and ketamine. Murray et al[18] showed that ketamine 0.5 mg/kg provided better analgesia than placebo after tonsillectomy in children. However, they assessed pain relief only in the first hour after surgery. One limitation of our study could be the narrow age range of our patients (5-12 years). It is difficult to assess pain in children, so we excluded children under 5 years as this is the lower age for children to have adequate cognitive and communicative skills for self reporting measures of pain.

In conclusion, we found that the incidence of PAS was significantly reduced when ketamine 1 mg/kg was given intramuscularly just after induction of general anesthesia in children without causing clinically important sedation or changes in hemodynamics. Ketamine may have at least theoretical advantages over pethidine as regard respiratory depression, nausea, and vomiting. Further studies are needed to determine the optimal dose of ketamine for this purpose.

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