The Factors of Ketamine that Affect Sedation in Children with Oncology Procedures: Parent Satisfaction Perspective

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Background: *The pain and its complication during sedation with ketamine remain a significant problem for children with hematologic malignancy.*

Objective: *The purpose of the present study was to evaluate further the parental satisfaction for procedural sedation and analgesia during pediatric hematology/oncology procedures performed by pediatrician in the Department of Pediatrics, Phramongkutklao Hospital.*

Material and Method: *The authors prospectively evaluated our experience using intravenous ketamine 1 mg/kg for oncology patients undergoing procedures at Department of Pediatrics, Phramongkutklao Hospital. The procedure was assessed by way of a physician-completed form and by evaluation of questionnaires given to parents to estimate levels of pain by using a 0 to 10 mm visual analog scale (VAS) at 2 hours after procedures and results in any adverse events with respect to age, gender, procedures performed, ketamine dosage and recovery time.*

Results: *Total of 46 children aged 6 months to 15 years with 46 procedures were observed at pediatric unit post-procedure. The indications for procedural sedation and analgesia included lumbar puncture and intrathecal chemotherapy (50%), bone marrow aspiration or biopsy (21.7%), and both procedures (28.3%). The median VAS scale during oncology procedures was 3, which were expressed by all the parents/guardians of the children treated. Adverse effects were observed in all children including nausea (30.4%), hypersalivation (26.1%), vomiting (21.7%), hallucination (4.2%). No child required admission to hospital and there were no serious complications.*

Conclusion: *Intravenous ketamine 1 mg/kg is effective for invasive procedures in children with malignancy. The use of intravenous ketamine may produce psychedelic effects in children. These adverse effects may alter the child's comfort and parental satisfaction especially in the young children.*

Keywords: *Ketamine sedation, Parent satisfaction, Hematology/oncology procedure*

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The hematology/oncology procedures including intrathecal chemotherapy, bone marrow aspiration/biopsy are painful. Children often require relief of pain and anxiety while undergoing therapeutic procedures. Sedation helps to reduces the children's movements during procedures and decrease their anxiety and pain. It has been the policy that the sedation for children who require these procedures be provided by non-anesthesiologist[1]. Effective and safe procedural sedation require the selection of appropriate drugs and appropriate doses. There are a variety of drugs available including ketamine, midazolam that provide effective and safe procedural sedation in children. In our hospital, the authors use ketamine for procedural sedation at present. Ketamine[2] is a dissociative drug which was first developed in 1962 and introduced to use as an intravenous anesthetic in a hospital setting started in 1970s. The term of dissociative anesthesia was to interrupt selectively association pathways of the brain before producing sensory blockade. It may selectively depress the thalamoneocortical system. Ketamine is the non-competitive NMDA receptor antagonism and is associated with the analgesic effect; it also blocks

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dopamine uptake and therefore elevates synaptic dopamine levels, which contribute to the induction of the anesthetic state and hallucinations. The drug remains popular in the developing world. Ketamine is given as an intravenous dose at 1 mg/kg/dose (the maximum dose of 50 mg). The onset of action is rapid at 30 minutes. Ketamine provides well-documented amnesia and analgesia, with minimal effect on the airway and vital reflexes, hypersalivation and hallucinations, commonly in children. At the present, there is little knowledge about parent perspective on ketamine sedative for pediatric oncology procedures. The purpose of the study was to evaluate further the parental satisfaction including the analgesic effect by using pain scores and to describe the potential side-effects on parent satisfaction during pediatric oncology procedures by using intravenous ketamine as a single agent performed by pediatricians in the Department of Pediatrics, Phramongkutklao Hospital.

Material and Method

The authors prospectively surveyed our experience using intravenous ketamine for children undergoing oncology procedures at the Department of Pediatrics, Phramongkutklao Hospital from March 2012 to October 2012. Pediatric patients between the age of 6 months and 15 years who underwent painful procedures during this period were enrolled. The exclusion criteria included patients who were allergic to ketamine; those who had contraindications for ketamine. All procedures were performed by a trained pediatric specialist. The procedure was assessed by having parents estimating the levels of pain which implies that the higher the scale number, the more painful by using a 0 to 10 mm visual analog scale (VAS) at 2 hours after procedures. Then, parents were provided with data collection forms to take home with them. Questionnaires and any symptoms were recorded for the 24 hr (4-6 hr in the hospital and 18-20 hr at home) following the procedure. Parents were contacted by a research coordinator/nurse on the following day to assess outcomes. Parental-informed consent was obtained before participation into the study. The present study was performed in accordance with the declaration of Helsinki, and the protocol was approved by the local ethics committee at Pharmongkutklao Hospital.

The data were entered into a SPSS database (version 15.0). Each procedure was considered as an independent event. The data were then analyzed using descriptive statistics to identify the visual analog scale (VAS) and compare the VAS among the age groups. The resulted in any adverse events were reported with respect to age, gender, procedures performed, ketamine dosage and recovery time. A binary logistic regression model was built to explain the independent association of the parental satisfaction. A *p*-value of less than 0.05 was considered statistically significant unless otherwise stated.

Results

During the study period, a total of 46 patients including 21 male (46%) and 25 female (54%) were performed under sedation with intravenous ketamine. These involved the underlying primary diagnoses of the patients as shown in Table 1. The number of various procedures was included lumbar puncture (LP) in 50%, bone marrow aspiration (BMA)/biopsy in 21.7%, and combined two procedures in 28.3%. All procedures were done successfully under the ketamine sedation at 1 mg/kg/dose (maximum 50 mg). Ten patients were required to repeat the dose of ketamine as these patients awoke before procedures were completed. No other sedative agents were given during procedures. The mean recovery time and dose given in various procedures were shown in Table 2. The median VAS scale during oncology procedures was 3; range (0-8) which was expressed by all the parents/guardians of the children treated. The median VAS pain score observed in the age between 6 months-6.9 years was 4;

Table 1. Patient characteristics

	Number (%)
Gender	
Boy	21 (46)
Girl	25 (54)
Age distribution	
6 months-5 years	24 (52)
5 years-10 years	13 (28)
10 years-15 years	9 (20)
Diagnosis	
Acute lymphoblastic leukemia	28 (60.8)
Acute myeloid leukemia	7 (15.2)
Non-Hodgkin's lymphoma	6 (13.1)
Chromic myeloid leukemia	3 (6.6)
Neuroblastoma	2 (4.3)
Procedures	
Lumbar puncture (LP) $\pm$ intrathecal	23 (50)
Bone marrow aspiration (BMA) $\pm$ biopsy	10 (21.7)
Combination of two procedures	13 (28.3)

Table 2. Procedure, ketamine dose and recovery times

	LP (n = 23)	BMA (n = 10)	Combined (n = 13)
Ketamine dose (mg/kg)	1.2 (1-1.4)	1.4 (1-1.6)	1.5 (1.2-1.7)
Mean recovery time (min)	8.13	9.8	9.5

Table 3. Adverse effects of sedation during 24 hr

Adverse effects	Number (%)
Nausea	14 (30.4)
Vomiting	10 (21.7)
Increased salivation and secretion	12 (26.1)
Hallucination	2 (4.3)

range (0-8), and between 7 years-15 years was 2; range (0-6). There was a statistical difference of significance between visual analog scale (VAS) between 2 groups of age ($p = 0.001$).

The side-effects within 24 hours after the procedures were observed in all children including nausea (30.4%), hypersalivation (26.1%), vomiting (21.7%) and hallucination (4.3%), as shown in Table 3. All vomiting events occurred in the patients who received double doses of intravenous ketamine and eight of those were less than seven years of age.

The hallucination in two patients was observed only in those aged more than ten years. No patient developed airway obstruction or required admission to hospital and there were no serious complications.

Only twenty-one patients (46%) preferred to use ketamine sedation with the next episode (satisfied). Twenty-five patients (54%) declined to use ketamine sedation (unsatisfied). Unsatisfactory was detected the most in the age group less than 7 years. In addition, unsatisfactory was found more frequently in seventeen girl participants (68%) than in eight boys (38%). The vomiting and the age group less than 7 years were shown to be the independent risk factors of unsatisfactory (OR 18.57 (girls) (95% CI 1.52-226.47)), (OR 5.7 (boys) (95% CI 1.21-26.87)), respectively.

Discussion

The present study is a perspective evaluation of satisfaction of caregiver regarding the use of ketamine sedation in 46 pediatric patients undergoing oncology procedures at outpatient pediatric department. The sedative agents such as midazolam, ketamine, fentanyl[3] are commonly used for oncology procedures in other areas of the hospital without guidelines. There is no evidence that ketamine is less safe than other commonly used sedatives, in fact the risks of airway compromise or cardiorespiratory instability may be less with ketamine[4]. The combination of midazolam and ketamine to reduce some side-effects has been investigated although the outcome is still unclear[5]. The results of the current study show that using intravenous ketamine at 1 mg/kg/dose for our procedures had some analgesic effect and important side-effects, which affected parents satisfaction.

The analgesic effect of ketamine is also significant when choosing appropriate sedation. A recent study[6] found ketamine being a safe and effective alternative to morphine in the immediate postoperative period. In contrast, our study demonstrated that the group less than 7 years still had higher pain score than the older ages. The reasons maybe the toleration for painful procedure in young children is lower which implies giving adding another sedative agent for them. The pediatric oncology sedation trial (POST)[3] showed that during the first twelve hours following intrathecal chemotherapy and sedation with midazolam and propofol, twenty-five children who were randomized to placebo or fentanyl 1 mg/kg/dose as an analgesic experienced significant, lower pain scores after receiving fentanyl. This finding implied that the other analgesic agents such as fentanyl might benefit the combination of ketamine for young children who undergo procedures which are painful. Further study should be undertaken to determine the clinical significance.

In our series, the majority of adverse effects from ketamine were minor and self-limited. All children were discharged on home the same day. However, half of their caregiver denied the use of ketamine in the following sedation especially in the age group of less than 7 years. This could be from side-effects of ketamine especially in nausea/vomiting and hallucination. Nausea/Vomiting events after the procedure were accounted for the majority of the present adverse events in the study. In previous studies[7-9], the prevalence of vomiting was significantly higher with

ketamine (10% to 26% with ketamine alone versus 5.4% with ketamine/midazolam and 1.8% with fentanyl/midazolam). Using intravenous ketamine in our study, 21.7% of patients experienced vomiting and 30.4% experienced nausea.

The symptoms usually occurred during the recovery phase when the patient was alert. Parker et al[10] also revealed that increased vomiting was more common in younger children. Our data also support that younger patients have a higher incidence of vomiting especially with those dissatisfied with the care given by caregiver. The clinical significance of this finding remains to be determined. Vomiting increases frequently a delayed in discharging, length of stay and patient satisfaction. This could explain why our results revealed more than 50% decline in the use of ketamine sedation at the next episode. In addition, poor control of nausea and vomiting can lead to dehydration, electrolyte imbalance and the need for hospital admission to correct these problems. Langston et al[11] investigated two hundred sixty-eight patients who were randomized to placebo or ondansetron 0.15 mg/kg/dose to prevent vomiting after giving intravenous ketamine 1 mg/kg/dose for procedural sedation at emergency department. The result revealed intravenous ondansetron significantly reduced the incidence of vomiting to 7.8% in the ondansetron group compared to 18.9% in the placebo group. However, even intravenous ondansetron improves vomiting in this situation, the high cost of this medication is limits its clinical use. Traivaree et al[12] demonstrated that thirty-three children who received intravenous dexamethasone 0.25 mg/kg had a significant reduction of vomiting and nausea after sedation with intravenous ketamine compared to placebo with no significance side-effects. The present study concluded that the combination of low cost and high efficacy makes dexamethasone a reasonable option for prophylaxis against nausea and vomiting in this population, especially in low income countries. The hallucination reactions with ketamine, seen often in adults, occur less frequently in children[13]. The authors observed these reactions in only 2 (4.2%) of our patients. Most of the previous studies reported less than 10% incidence of hallucinatory reactions with ketamine-midazolam although some reported higher incidences[14,15]. Interestingly, the authors also found that younger children often required a second dose of ketamine for adequate sedation; this finding also reported by Cheuk DK et al[16]. It may be explained by renal clearance leading to a shorter half-life and faster drug metabolism of ketamine in children[17]. This reason could also explain the total accumulative dose of ketamine related to adverse side-effects.

The present study might have several limitations. This observational study was in a case series of children in whom our physicians selected ketamine for sedative agents. Because of our enrollment for patients represent a non-probability sampling of patients, failure to enroll all eligible patients would make this study susceptible to selection bias. The external validity of the present study might be limited as it could be applied to patients who received ketamine sedation alone in oncology procedures only.

Conclusion

The authors performed the perspective study of parent perspective satisfaction on procedural sedation and analgesia for intravenous ketamine regimens and found a high prevalence of nausea and vomiting. These adverse effects might alter the child's comfort and parental satisfaction. Our method of managing during procedures with ketamine sedation in children seemed to work well but was not at the high levels of satisfaction with parents. Caregivers should be counseled about potential side-effects after procedural sedation and analgesia, particularly for young children. Analgesic and antiemetic drugs may be increased measurable to benefit the satisfaction in children who undergo procedures that are painful and risk the consequence of nausea and vomiting.

Potential conflicts of interest

None.

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การศึกษาเพื่อหาปัจจัยที่มีผลต่อความพึงพอใจของการวางยาสลบโดยใช้ยาเคตามีนในการทำหัตถการกับผู้ป่วยโรคทางโลหิตวิทยาและมะเร็งในเด็ก

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ภูมิหลัง: ความเจ็บปวดและภาวะแทรกซ้อนระหว่างวางยาสลบด้วยยาเคตามีน ยังคงเป็นปัญหาที่มีความสำคัญในผู้ป่วยโรคทางโลหิตวิทยาและมะเร็งในเด็ก

วัตถุประสงค์: เพื่อศึกษาถึงปัจจัยที่มีผลต่อความพึงพอใจของผู้ปกครองที่มีต่อยาสลบและยาลดปวด ที่ใช้ในการทำหัตถการทางโลหิตวิทยาและมะเร็งในเด็กของกองกุมารเวชกรรม โรงพยาบาลพระมงกุฎเกล้า

วัสดุและวิธีการ: เป็นการศึกษาโดยการสำรวจแบบไปข้างหน้าของการใช้ยาเคตามีนทางหลอดเลือดดำ โดยจะได้รับยาเคตามีนขนาด 1 มก./กก. ในการทำหัตถการทางโลหิตวิทยาและมะเร็งในเด็กของกองกุมารเวชกรรม โรงพยาบาลพระมงกุฎเกล้าโดยจะมีการกรอกแบบฟอร์มโดยแพทย์โดยใช้แบบสอบถามการประเมินความพึงพอใจที่ทำโดยผู้ปกครอง โดยดูจากการประเมินความเจ็บปวดที่มีคะแนนตั้งแต่ 0-10 ที่ 2 ชม. หลังจากการทำหัตถการและผลข้างเคียงที่เกิดขึ้นหลังจากได้รับยาเคตามีนโดยแบ่งตามช่วงอายุ เพศ หัตถการ ที่ทำขนาดยาของเคตามีนและระยะเวลาฟื้นตัว

ผลการศึกษา: ผู้ป่วยเข้าร่วมการศึกษานี้ทั้งสิ้น 46 ราย โดยอยู่ในช่วงอายุ 6 เดือน-15 ปี โดยรวมทั้งสิ้น 46 หัตถการ โดยหัตถการที่ต้องได้รับยาสลบและยาลดปวดนั้น ในการศึกษานี้คือการเจาะน้ำไขสันหลังและการให้ยาเคมีบำบัดทางน้ำไขสันหลังโดยคิดเป็นร้อยละ 50, การเจาะดูดไขกระดูกและหรือการตัดชิ้นไขกระดูกโดยคิดเป็นร้อยละ 21.7 และทำทั้งเจาะน้ำไขสันหลังและเจาะไขกระดูกโดยคิดเป็นร้อยละ 28.3 ค่าเฉลี่ยของความเจ็บปวดในการใช้ยาเคตามีนเท่ากับ 3 ซึ่งถูกประเมินโดยผู้ปกครองของผู้ป่วยเด็กทุกรายที่ทำหัตถการและในการศึกษานี้ ได้พบผลข้างเคียงจากยาที่ใช้โดยพบคลื่นไส้ร้อยละ 30.4, น้ำลายมากกว่าปกติ ร้อยละ 26.1, อาเจียน ร้อยละ 21.7 มีประสาทหลอน ร้อยละ 4.2 โดยไม่พบผลข้างเคียงที่มีความรุนแรงหรือผลข้างเคียงที่ทำให้ผู้ป่วยต้องเข้ารับการรักษาในโรงพยาบาล

สรุป: การใช้ยาเคตามีนในขนาด 1 มก./กก. นั้นมีประสิทธิภาพดีในเรื่องของความพึงพอใจของการวางยาสลบเคตามีนในการทำหัตถการที่มีความเจ็บปวดกับผู้ป่วยเด็กโรคมะเร็ง อย่างไรก็ตามยาเคตามีนเองก็มีผลข้างเคียงทำให้ประสาทหลอนได้ ซึ่งอาจมีผลต่อความสุขสบายของเด็กและความพึงพอใจของผู้ปกครองลดลงได้ โดยเฉพาะอย่างยิ่งในเด็กเล็ก