The Clinical Effect of Fentanyl in Comparison with Ketamine in Analgesic Effect for Oncology Procedures in Children: A Randomized, Double-Blinded, Crossover Trial

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Background: *Children often require relief of pain and anxiety when undergoing painful procedures.*
Objective: *To determine the differences by comparing fentanyl and ketamine used in cancer-diagnosed children undergoing painful procedures.*
Material and Method: *A randomized, double-blinded, crossover trial was conducted with 55 children undergoing painful procedures (intrathecal chemotherapy and/or bone marrow aspiration/biopsy). Patients were randomly assigned in a double-blinded fashion to receive either intravenous fentanyl or ketamine at 1 mcg/kg/dose and 1 mg/kg/dose, respectively. The result in effectiveness of the drug was measured using three parameters, 1) satisfaction score ranging from 0 to 10, 2) perception of procedural pain using FLACC scale, Wong-Baker FACES Pain Rating Scale and Visual Analog Scale, and 3) the frequency of vomiting nausea score.*
Results: *The satisfaction among patients receiving fentanyl was significantly greater than ketamine ($p = 0.007$). In addition, both painful and nausea/vomiting were significantly decreased in the patients receiving fentanyl ($p = 0.002$ and $p<0.001$, respectively). No serious complications were observed.*
Conclusion: *This study demonstrated that intravenous fentanyl generated a superior clinical effect in satisfaction, decreased pain and nausea/vomiting, and showed no significant side-effects over ketamine. Fentanyl may also be recommended as a reasonable option before undergoing oncology procedures in children with cancer.*

Keywords: *Children with cancer, Satisfaction, Nausea and vomiting, Painful*

J Med Assoc Thai 2015; 98 (4): 358-64
Full text. e-Journal: *http://www.jmatonline.com*

Lumbar puncture and bone marrow procedure are the main key investigations for pediatric hemato-oncologic malignancy. The treatments consist of intravenous, especially intrathecal chemotherapy for both treatments and CNS prophylaxis[1]. The schedule of intrathecal chemotherapy administration depends on individual protocols, varying from weekly during the induction phase to every three months during the maintenance phase[2]. Pain is the most common complication associated with these procedures.

Ketamine is a dissociative anesthetic drug that is used as a premedication before undergoing these procedures. Sedation helps reduce the child's movements during the procedure and decreases anxiety and pain. Despite its excellent anxiolytic effect[3], ketamine-associated side effects including nausea, vomiting, hypersalivation, respiratory compromise, emergence phenomenon, nightmare, and hallucination[4] are well documented, and could be the cause of prolonged recovery and hospitalization[5]. For these reasons, fentanyl might be considered as a drug of choice with regards to its less nausea and vomiting resulting in better cooperation and more rapid recovery than ketamine. Even though, fentanyl has less sedative effect and nausea/vomiting compared to ketamine but hypotension, bradycardia, and hypoventilation could occur requiring close observation. However, the standard guideline on using those drugs to prevent pain has not been well established. Therefore, the objective of the present study was to study the clinical effect of fentanyl compared with ketamine as a premedication before undergoing the painful procedure in pediatric oncology.

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Material and Method

Study design and setting

The children were enrolled in a randomized, double-blind, crossover controlled trial conducted between May and November 2012 at Phramongkutklao

Hospital in Bangkok, Thailand. Parental-informed consent was obtained before enrolling in the study. The study was performed according to the Declaration of Helsinki, and the protocols were approved by the Ethics Committee of the Phramongkutklao Hospital.

Eligibility and exclusion criteria

All children between 1 and 18 years with cancers who required intravenous sedative medication and invasive procedure (bone marrow procedure and/or lumbar puncture) were eligible to enroll in the study. Patients were excluded if they received anti-emetic drugs or had nausea/vomiting or pain within 24 hours of the treatment. The exclusion criteria included patients with a known allergy to ketamine or fentanyl, contraindications for ketamine or fentanyl such as increased intracranial pressure, respiratory compromise, vascular aneurysm, or major psychiatric problem.

Randomization and study protocol

After enrolled and gave inform consent to the investigators, patients were randomized with a computer generated randomized type of treatment table in a downward direction, supplied by a statistician, to receive one of two interventions during the first period in a double-blinded fashion. Patients received one of two options during the first period: intravenous fentanyl 1 mcg/kg/dose (maximum single dose 50 mcg, total amount 5 ml with NSS, drugs 1), or intravenous ketamine 1 mg/kg/dose (maximum single dose 50 mg, total amount 5 ml with NSS, drugs 2). The same amount defined as the amount of Normal saline solution (NSS) plus the drug, (ketamine or fentanyl to equal the total volume of 5 ml in order to be sure that the drug solution was perfectly blinded to both physicians and patients). Given the crossover design, the treatment was reversely assigned during the second period (1 to 2, 2 to 1). The interval between the two treatment periods was between a week and three months. For allocation concealment, the type of treatment was stored in sequentially numbered, sealed, opaque envelopes. The envelopes were opened by nurse (third party) who prepared the medications at the sedation room just before the beginning of the procedure. The study drugs, either fentanyl or ketamine, were administered immediately before inducing sedation and before lumbar puncture and administrating intrathecal chemotherapy or bone marrow procedure. The care provider and the participants were blinded for intervention. Parents were provided with data collection forms including satisfactory score, vomiting, and severity of nausea. These were given in the recovery room and patients took them home. Parents were telephoned at home by the research coordinator to ensure that they were not having any significant difficulty and to assess the satisfactory outcomes.

Outcome measurements

The collected data included patient demographics, procedures, satisfaction, painfulness, nausea, and vomiting.

Primary outcome

To study the satisfaction of fentanyl compared with ketamine in pediatric oncology patients undergoing painful procedures.

For patients aged less than eight years old, the parents would observe and record scores.

For patients aged equal or more than eight years old, the parents asked patients how they felt and recorded the scores.

The scores were measured at 24 hours after procedures by using scores ranging from 0 to 10.

Secondary outcome

To study the pain score, using FLACC (Face, Legs, Activity, Cry, Consolability) scale that used to assess pain for children who are unable to communicate their pain, Wong-Baker FACES Pain Rating Scale and Visual Analog Scale used in patients aged three months to four years, more than four to eight years and more than eight years old, respectively. The score ranging from 0 to 10 were measured two hours after procedures in the hospital when the patients were full recovery from sedation.

For patients aged less than eight years old, the parents would observe and record scores.

For patients aged equal or more than eight years old, the parents asked patients how they felt and recorded the scores.

The side effects such as nausea and vomiting of fentanyl compared with ketamine in pediatric oncology patients undergoing painful procedures. The side effects were observed during 24 hours for a minimum of two to four hours in the recovery room and 18 hours at home (total 24 hours).

Statistical analysis

The STATA/MP 12 was used for the statistical analysis, consisted of T test for degree of satisfaction and painfulness, Chi-square test for severity of nausea

and vomiting. A sample size calculation for crossover design (type I error of 5% and 80% power) showed that total 60 children would permit to detect a significant difference between the two treatments with a two-sided test. A *p*-value of less than 0.05 was considered statistically significant unless otherwise stated.

Results

Patient characteristics

Sixty-four children diagnosed with childhood malignancy were scheduled for invasive procedures and required sedation before procedures. We excluded nine patients due the use of only one drug (three for only ketamine and six for only fentanyl). Admissible patient completed the cross-over included 27 boys and 28 girls (55 total) ranging in age from 1 to 16 years (median 6 years) as shown in Table 1. Washout period was one week to 22 weeks (median 4 weeks). Most patients were exhibited acute lymphoblastic leukemia (ALL). They were randomly and equally allocated in sequence in two groups. All were considered valid and included in the study analysis. Characteristics of the enrolled patients were listed in Table 1.

Table 1. Patient demographic data (n = 55)

Patient characteristic	n (%)
Gender	
Male	27 (49.1)
Female	28 (50.9)
Age (years)	
1-4	9 (16.4)
>4 -8	24 (43.6)
>8	22 (40.0)
Wash out period (weeks)	
Mean	5.8
Median (range)	4 (1-22)
Diagnosis	
ALL	38 (69.1)
AML	5 (9.1)
CML	1 (1.8)
LL	4 (7.3)
BL	5 (9.1)
ALCL	2 (3.6)

ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CML = chronic myeloid leukemia; LL = lymphoblastic lymphoma; BL = Burkitt's lymphoma; ALCL = anaplastic large cell lymphoma

In all, 110 procedures were performed, 80 intrathecal chemotherapy (72.7%), 11 bone marrow aspiration (10%), and 19 combined intrathecal chemotherapy and bone marrow aspiration (17.3%).

Analysis of primary outcome

Satisfaction was evaluated in patients receiving fentanyl and ketamine. The satisfaction in the group given fentanyl was 10 (8-10) superior to the group with ketamine 9 (5-10) ($p = 0.007$). If we divided the patients by age group, patients older than eight receiving fentanyl were more satisfied than the group with ketamine for 10 (8-10) and 9 (5-10), respectively ($p = 0.005$) as shown in Table 2.

Analysis of secondary outcome

Regarding painfulness in patients who received fentanyl before undergoing the invasive procedures 1.55±1.65 (median 2; range 0-8) was less than the group with ketamine 2.44±1.66 (median 2; range 0-8) ($p = 0.002$). Nevertheless, if we divided the patients by age group according to standard pain scores for age, patients aged more than four to eight years old had less pain in the group receiving fentanyl than the group given ketamine, 1.33±1.27 (median 2; range 0-4) and 2.83±1.86 (median 2; range 0-8), respectively ($p = 0.002$) as shown in Fig. 1.

In the same way, patients receiving fentanyl before undergoing invasive procedures had less incidence of nausea and vomiting ($p<0.001$ and $p<0.001$, respectively). However, if we divided the patients by age group, the patients older than eight

Table 2. The satisfaction of fentanyl compared with ketamine in pediatric oncology patients undergoing painful procedures

	Fentanyl		Ketamine		*p*-value
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	
1-4 years	9.22±0.67	9 (8-10)	9.22±0.97	9 (7-10)	0.733
>4-8 years	9.50±0.59	10 (8-10)	9.17±0.82	9 (7-10)	0.151
>8 years	9.45±0.74	10 (8-10)	8.45±1.34	9 (5-10)	0.005
Total	9.44±0.66	10 (8-10)	8.89±1.12	9 (5-10)	0.007

t-test

receiving fentanyl had significantly less incidence of nausea (p<0.001) as shown in Fig. 2. Similar findings were noted in the incidence of vomiting, which was reported less in the group receiving fentanyl by age more than four years (p = 0.033 and p<0.001 in ages more than four to eight and more than eight, respectively) as shown in Fig. 3.

Safety

Ketamine exhibited side effects within 24 hours after injection, and mostly included hallucination for five patients (9%), nausea for 26 patients (47.28%), vomiting for 20 patients (36.36%), and increased salivation and secretion for four patients (7.27%). On the other hand, no incidence of hallucination, bradycardia, hypotension, increased salivation, and secretion within four hours after receiving fentanyl, only nausea noted in five patients (9.09%) and vomiting in two patients (3.64%) within 24 hours.

Fentanyl and ketamine were well tolerated through successive procedures of lumbar puncture with intrathecal chemotherapy and bone marrow procedures. No patient was admitted in the hospital after the procedures for any reasons. No clinically significant side effects were observed in the present study.

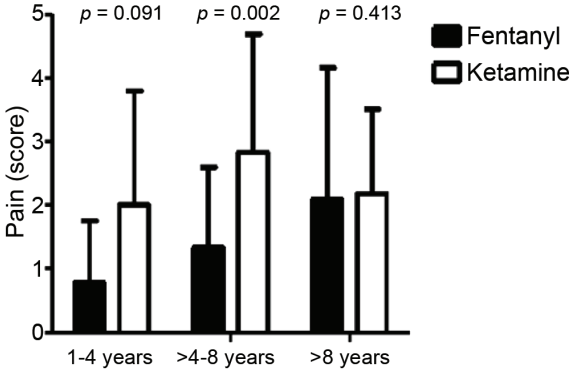

Fig. 1 Painfulness of patients receiving fentanyl compared with ketamine in pediatric oncology patients undergoing painful procedures depending on age group (n = 110), * Full score = 10.

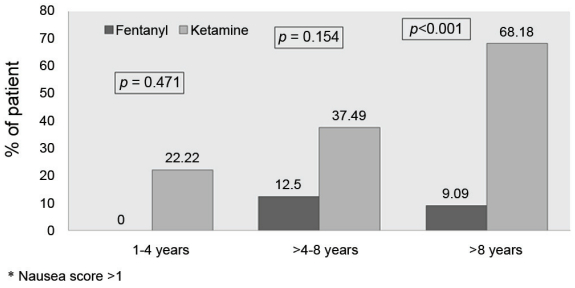

Fig. 2 Incidence of nausea depending on age group (n = 110).

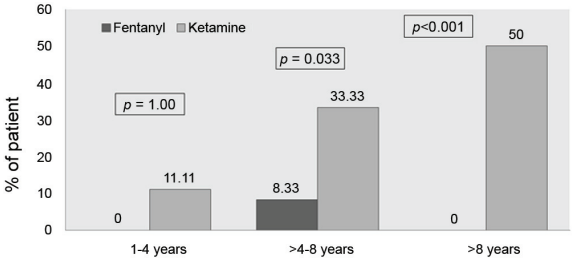

Fig. 3 Incidence of vomiting depending on age group (n = 110).

Discussion

The present study was to evaluate the clinical effect of fentanyl in comparison with ketamine in analgesic effect during oncology procedures in children. This study showed that the patients aged over 8 years old evaluated the satisfaction score by themselves. The results showed that fentanyl was better than ketamine. This was explained by less of side effects such as nausea and vomiting in this age group allowing them to be able to tolerate with procedure without the need of sedative agents such as ketamine. For this reason, our results revealed no significant differences in the pain score between the patients who received fentanyl and those who received ketamine. In addition, Fentanyl had more potent analgesic effect than ketamine[3]. On the other hand, we observed that the side effect of ketamine (nausea/vomiting) in this age group was more severe than other groups. This was the main reasons for the patient aged more than 8 years old unsatisfied with ketamine. In the patients aged less than 8 years old, the satisfaction was evaluated by their parents. We found no statistical differences in satisfaction between the patients who received fentanyl and those who received ketamine, even though the parents evaluated their children having less pain in the fentanyl group. This could be the patients in this age range were minimally affected by the side effects of ketamine (nausea/vomiting). In addition, patient aged less than 8 years old was preoperational stage of Piaget, they have unreasonable fantasy. Therefore, their parents might interpret their fear and anxiety to be pain[6]. Further study is needed to evaluate the possibility of add-on drug regimen to increase satisfaction in this age group. Nagel et al[7] found that using propofol and midazolam with fentanyl or ondansetron for children undergoing bone marrow

aspiration and intrathecal chemotherapy could reduce pain. Moreover, using dexamethasone combined with ketamine could reduce nausea and vomiting rates as reported in the study of Traivaree et al[8]. The study showed the efficacy of dexamethasone vs. placebo in preventing nausea and vomiting from ketamine in children before undergoing intrathecal chemotherapy.

Regarding the medication safety, in the present study, none of our patients was hospitalized after the procedures for any reasons. No clinically significant side effects from ketamine and fentanyl were observed in the present study. Nevertheless, unwanted side effects from ketamine were observed but there was no evidence of such in the fentanyl group.

Lucas Da Silva et al[9] studied the difference of midazolam/fentanyl versus midazolam/ketamine administered via central venous catheter in PICU and found that the group that received midazolam/ketamine was noted to have more minor complications such as hypersecretion, desaturation, aspiration, and temporary airway obstruction. In addition, patients receiving ketamine had more incidences of nausea/vomiting and hypersalivation, which was similar to our study. However, Brown et al[10] found only 0.11% of hypersalivation comparing to 7.27% in our study. This might be due most of patients in our study had used multiple ketamine sedations for lumbar puncture procedure previously. The total accumulation dose of ketamine and the patient's underlying disease might aggravate more complications.

Hallucination was another complication in the present study. It defines as a false auditory, visual, gustatory, tactile, or olfactory perception not associated with real external stimuli[11]. According to Piaget, children aged less than seven years may have difficulty distinguishing between events occurring while dreaming and awake[12]. Therefore, we also included the sense of dizziness or nightmares or behavioral changes in children in the definition. These were the main reasons for increasing the complication in the patients aged less than 8 years old compared to other studies[9,13].

Our study had several limitations. The sample size in the present study was calculated based on repeated measurement (cross over design) given that the selected subjects were few; however, the outcome was measured two times for analysis. The application of using fentanyl and ketamine in the present study might be limit as it applied to patients who received ketamine or fentanyl for sedation before undergoing invasive procedures. Hospital variations in recording vomiting rates could potentially limit the generalizability of these results.

Conclusion

The authors found that children who received intravenous fentanyl reported significant satisfaction, reduced pain, vomiting and nausea after sedation for intrathecal chemotherapy or bone marrow procedures, comparing to the children who received ketamine. The combination of low cost, high efficacy, and apparent safety made fentanyl an attractive option to be used as premedication for the older patient undergoing bone marrow procedures and intrathecal chemotherapy.

What is already known on this topic?

Fentanyl or Ketamine is an optional first-line agent in premedication for the children undergoing bone marrow procedures and intrathecal chemotherapy especially in the setting of limitation in resource and developing countries as Thailand.

What this study adds?

The present study showed that intravenous fentanyl is superior clinical effect in satisfaction score in the age more than eight years. These make fentanyl an attractive option to be used as premedication for the older patient undergoing these procedures.

A guideline of premedication for the pre-adolescent aged patient undergoing these procedures was applied to Department of Pediatrics, Phramongkutklao Hospital and has shown the benefit of satisfaction, decreased pain, and rate of nausea/vomiting.

Acknowledgment

The present study was approved and supported funding from Phramongkutklao College of Medicine in 2012

Potential of conflicts of interest

None.

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ประสิทธิภาพของยาเฟนตานิลเปรียบเทียบกับยาเคตามีนในการลดอาการเจ็บปวดในการเจาะน้ำไขสันหลัง และ/หรือ การเจาะไขกระดูกในผู้ป่วยเด็กโรคมะเร็ง

ชาลินี มนต์เสรีนุสรณ์, ปิยะ รุจกิจยานนท์, ชาญชัย ไตรวารี

ภูมิหลัง: *ผู้ป่วยเด็กที่ได้รับการทำหัตถการที่ก่อให้เกิดความเจ็บปวด มีความจำเป็นต้องได้รับการเตรียมผู้ป่วยเพื่อบรรเทาการเจ็บปวดและความวิตกกังวลก่อนการทำหัตถการ*

วัตถุประสงค์: *เพื่อศึกษาเปรียบเทียบประสิทธิภาพของการใช้ยาเฟนตานิลเปรียบเทียบกับยาเคตามีนในด้านของความพึงพอใจเพื่อลดอาการเจ็บปวด และการคลื่นไส้อาเจียนในผู้ป่วยเด็กโรคมะเร็งในเด็กที่ได้รับยาเฟนตานิลเทียบกับยาเคตามีนก่อนการทำหัตถการเจาะน้ำไขสันหลัง และ/หรือ การเจาะไขกระดูก*

วัสดุและวิธีการ: *ผู้ป่วยจำนวน 55 ราย ที่ให้คำยินยอมเข้าร่วมการศึกษาที่จะได้รับการทำหัตถการที่ก่อให้เกิดความเจ็บปวด (การทำหัตถการเจาะน้ำไขสันหลัง และ/หรือ การเจาะไขกระดูก) และได้รับการรักษาด้วยยา 2 ชนิด เปรียบเทียบในผู้ป่วยรายเดียวกัน โดยผู้ป่วยแต่ละรายจะได้ยาทั้ง 2 ชนิด เปรียบเทียบกัน ประกอบด้วย ยาเฟนตานิลหรือยาเคตามีน ขนาด 1 ไมโครกรัม/กิโลกรัม/ครั้ง และ 1 มิลลิกรัม/กิโลกรัม/ครั้ง ตามลำดับ โดยเปรียบเทียบผลการศึกษาในผู้ป่วยรายเดียวกันเป็นเวลา 2 ครั้ง โดยวัดจาก 3 ตัวแปร คือ ระดับความพึงพอใจ (0-10) ระดับความเจ็บปวด และผลข้างเคียง คือ ระดับการคลื่นไส้ และจำนวนครั้งของการอาเจียนหลังการได้รับยาเฟนตานิลเปรียบเทียบกับยาเคตามีน*

ผลการศึกษา: *ความพึงพอใจของผู้ป่วยที่ได้รับยาเฟนตานิลมากกว่าผู้ป่วยที่ได้รับยาเคตามีน ($p = 0.007$) ผู้ป่วยที่ได้รับยาเฟนตานิลพบว่ามีความเจ็บปวดจากการทำหัตถการน้อยกว่าที่ได้รับยาเคตามีน ($p = 0.002$) และกลุ่มที่ได้รับยาเฟนตานิลมีอาการคลื่นไส้อาเจียนต่ำกว่ากลุ่มที่ได้รับยาเคตามีน ($p<0.001$) โดยไม่พบผลข้างเคียงที่รุนแรงจากการให้ยาเฟนตานิล และ/หรือ เคตามีน*

สรุป: *การใช้ยาเฟนตานิลทางหลอดเลือดดำมีประสิทธิภาพดีกว่ายาเคตามีน ในแง่ของความพึงพอใจ การลดความเจ็บปวด และอีกทั้งยังลดผลข้างเคียงด้านการคลื่นไส้อาเจียนในผู้ป่วยเด็กโรคมะเร็งที่ได้รับการทำหัตถการการเจาะน้ำไขสันหลัง และ/หรือ การเจาะไขกระดูก โดยไม่พบผลข้างเคียงที่รุนแรง ซึ่งสามารถแนะนำให้ใช้เฟนตานิลก่อนการทำหัตถการการเจาะน้ำไขสันหลัง และ/หรือ การเจาะไขกระดูกในผู้ป่วยเด็กโรคมะเร็งได้เป็นอย่างดี*