Original Article

Iran J Ped Hematol Oncol. 2018, Vol 8. No 2, 87-96

Sedative and Analgesic efficacy of Propofol-Ketamine and Propofol-Remifentanil During Painful Procedures in Children with Acute Lymphoblastic Leukemia

Hamidreza Shetabi MD[1], Mohammad Golparvar MD[2], Sahar Ghanbardezfoli MD[3,*], Mohammad Torfenejad MD[4]

1. Assistant Professor of Anesthesia, Anesthesiology and Critical Care Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.
2. Professor of Anesthesia, Anesthesiology and Critical Care Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.
3. MD, Anesthesiology and Critical Care Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.
4. Pediatrician, Isfahan University of Medical Sciences, Isfahan, Iran.
*Corresponding author: Sahar Ghanbardezfoli, MD, Anesthesiology and Critical Care Research Center, Isfahan University of Medical Sciences, Isfahan, Iran. Email: Sghd2010@gmail.com.

Received: 24 September 2017 **Accepted:** 22 February 2018

Abstract

Background: Lumbar puncture (LP) and bone marrow aspiration or biopsy in pediatric patients with hematological diseases is often repeated at regular intervals. These procedures are painful and unpleasant and bring a lot of stress for the children and their families. This study aimed to compare the effectiveness of two drug combinations of propofol-ketamine and propofol-remifentanil in children with acute lymphoblastic leukemia under bone marrow aspiration or biopsy and lumbar puncture (LP).

Materials and Methods: In this clinical trial, 81 children aged 6 months to 14 years old with acute lymphoblastic leukemia who were candidates for lumbar puncture, bone marrow aspiration or biopsy were randomly divided into two groups of receiving Propofol-Ketamine and receiving Propofol-Remifentanil. In each group, hemodynamic indices, sedation, side effects, the onset of effectiveness and duration of remaining in the recovery room were measured and recorded. Data were analyzed using Chi square test, Mann-Whitney, independent t-test, and Fisher's exact test with a significant level of $p<0.05$.

Results: The need for repeating drug's dosage was significantly lower in the group received Propofol-Ketamine than the other group ($p=0.009$). The mean of systolic blood pressure and arterial oxygen saturation at the end of the procedure was significantly lower in the Propofol-Remifentanil receiving group (respectively $p=0.040$ and $p=0.001$). During the procedure, the frequency of hypotension was significantly higher in the Propofol-Remifentanil receiving group ($p=0.048$). The recovery duration was reported significantly longer for the Propofol-Ketamine receiving group ($p=0.004$). Sedation indices, other hemodynamic indices, and the onset of effectiveness caused no significant difference between two groups ($p>0.05$).

Conclusion: It seems that the combination of Propofol-Ketamine could be a more appropriate combination in children especially in patients with unstable hemodynamics due to lower need for repetition of the drug dose and more hemodynamic stability.

Keywords: Acute Lymphoblastic Leukemia, Children, Ketamine, Propofol, Remifentanil, Sedation

Introduction

Lumbar Puncture (LP) and bone marrow aspiration or biopsy in pediatric patients with hematological diseases is often repeated at regular intervals. These procedures are painful and unpleasant and bring a lot of stress for the children and their families (1). Performing these procedures with minimum pain and mental sequel is an ideal target for pediatric oncologists (2). An ideal sedation agent should not only have a rapid onset and a smooth recovery period, but also provide sufficient analgesia, sedation with adequate cardiovascular and respiratory function, amnesia, and motor control immobile throughout the procedures (1).

A combination of analgesia and sedative drugs during painful procedures in pediatric oncology is recommended by the

World Health Organization and the American Academy of Pediatrics (3).

It is common to combine opioids and anesthetics to attain adequate anesthesia with lower dose requirements than those needs for individual drugs because of the synergistic interactions which can reduce unwanted side effects and improve recovery (3, 4).

Propofol is an anesthetic drug with rapid induction and recovery time which has low side effects and easy titration (5).

Administration of Propofol, due to its favorable pharmacokinetic properties, has been increased during the recent years, especially at outpatient centers. This drug, with fast start and end of action, is an appropriate drug for inducing sedation in diagnostic and therapeutic procedures for children with blood malignancies (6). Propofol is a sedative/anesthetic agent but for painful procedure it must be administered along with an analgesic drug such as opiates (7).

Ketamine is one of the derivatives of phencyclidine and is a drug with sedative and analgesic properties that can be administered alone or with other drugs to induce painlessness during diagnostic and therapeutic procedures in children (8).

Ketamine can protect airway reflexes and spontaneous respiration due to its analgesic,sedative and amnestic properties. The use of ketamine alone is associated with complications such as postoperative dysphoria, emergence phenomenon, vomiting, and laryngospasm. However, it's administration combined with Propofol leads to less respiratory and hemodynamic effects (5). A number of studies demonstrated that the combination of Ketamine and Propofol (ketofol) for sedation is safe and effective. The combination of the two drugs can reduce side effects induced by each drug administration and leads to a rapid recovery time (9). Remifentanil is a relatively new, ultra short-acting (8-10 min duration of action) opioid without active metabolites (10).

Remifentanil has been used in conscious sedation and analgesia for almost 2 decades. It is often used in combination with Propofol. It's pharmacogenetics allows for quicker post operative recovery. Furthermore, it allows patients to be relatively conscious while maintaining appropriate analgesic sedation (11). However, it produces consistent hypotension as a side effect (12).

Infusion combinations of Propofol and Remifentanil for induction and maintenance of deep sedation or non-intubated general anesthesia have been shown to be safe and effective in providing analgesia, stable sedation/hypnosis and satisfactory operating conditions along with a shorter recovery period in comparison with other conventional balanced anesthetic techniques (13).

Considering that no studies have so far compared the effects of two drug combinations of Propofol-Ketamine and Propofol-Remifentanil in children with blood malignancies undergoing bone marrow aspiration or biopsy and LP, the present study was conducted to compare the effect of these two combinations on sedation and analgesia and also hemodynamic changes, respiratory indices, side effects, onset of effectiveness, and duration of recovery.

Materials and Methods

The present study was a randomized double-blind clinical trial which was conducted in Seyed-Al-Shohada educational hospital of Isfahan in 2016 after gaining approval from the faculty of medicine (ethnic code IR.mui. Rec.1395.3.462)

Eighty one children aged from 6 months to 14 years old with acute lymphoblastic leukemia (ALL) who were candidates for LP, bone marrow aspiration or biopsy and referred to Seyed-Al-Shohada hospital were enrolled in this study. Before the initiation of the study, informed consent was obtained from each parent. The children had no history of allergic reaction

to any of the administered drugs in the study, had not used any other analgesic or pre-anesthetic drugs, and also had no cardiovascular diseases, respiratory diseases, liver diseases, nervous system disorders, epilepsy or history of seizures, tumor or brain metastases, chronic pain syndromes, high intraocular or intracranial pressure and head damage. Fasting time for children aged 6 to 36 months was 6 hours and for older children was 8 hours. Patients were allowed to drink water until 2 hours prior to the surgery. In the operating room, patients were divided into two groups of receiving Propofol-Ketamine (PK group) and receiving Propofol-Remifentanil (PR group), using the table of random numbers. Then for each group, heart rate, systolic and diastolic blood pressures, mean arterial blood pressure, and arterial oxygen saturation were measured before the injection of anesthetics and recorded by the assistant nurse. These measurements were repeated at the end of the procedure and at the time of transferring the patient from the recovery room to the ward. The administered drugs were prepared by one of the research assistants and after coding were given to the administrator:

Syringes No. 1, 2, and 3 contaied Propofol with density of 1mg/cc, Ketamine with density of 0.3 mg/cc, and normal saline (as placebo) respectively for the first group, and syringes No. 4, 5 and 6 contained propofol with density of 1mg/cc, normal saline (as placebo) and remifentanil with density of 1micg/cc, respectively, for the second group. In addition, syringes No. 7 and 8 containing 0.5mg/cc of Propofol and 0.5 micg/cc of Remifentanil that were prepared and covered in black.

The administrator prescribed 1cc/kg from the syringes No. 1 and 2 at the start of the sedation, and syringe No. 3 before prepping for the first group, 1 cc/kg from syringes No. 4 and 5 at the start of the sedation, and from syringe No. 6 before prepping for the second group. In case of needing more drug during the procedure, 1cc/kg of syringe No. 7 was administered for the first group and 1cc/kg of the syringe No. 8 was administered for the second group. The codes were provided to the administrator after statistical analysis. Then, the children were laid on their side and auxiliary oxygen was applied for them using a mask (4-6 lit/min). Next, the procedure was performed by a pediatric oncologist. At the beginning of the procedure, the depth of patients' sedation and patients' pain severity were measured and recorded using University of Michigan Sedation Scale (UMSS) and Universal Pain Assessment Tool (UPAT), respectively (Table I and Figure 1).

During the entire time of sedation and performing the procedure, patients' heart rate and arterial oxygen saturation were constantly monitored and their blood pressures were intermittently and non-invasively measured. The minimum UMSS score of 2 was meeded to start the procedure.

In case of any drop in arterial oxygen saturation< 90% or apnea (stop breathing for more than 10 seconds), respiratory support was performed using face mask and bag. The following items were recorded for each patient: the onset of effectiveness, the duration of procedure, the time interval between the end of the procedure and patients' wakening, duration of staying in the recovery room (the time interval between entering the recovery room and transferring to the ward), probable complications during the procedure and in the recovery room (including tachycardia, hypotension, hypertension, apnea, nausea, vomiting, agitation, coughing, dizziness, diplopia, shivering, hallucination,…), and also patient's need for auxiliary ventilation during the operation.

After the operation, patients were transferred to the ward and after reaching an Aldrete score of 9 or 10, they were discharged from the hospital. Patients were monitored for at least 2 hours after the end of the operation.

Data were analyzed using Mann-Whitney, independent t-test, Chi square test, and Fisher's exact test.
SPSS (version 22) was used for data analysis and 0.05 was considered as the significant level for all the statistical tests.

Results

None of the patients were excluded or withdrew from the study.

Demographic characteristics

No significant difference was found between two groups regarding their age, gender, and weight. The mean age in the PK group was 5.3 years and in the PR group was 5.8 years. (Table II and III).

Type of the procedure

There was no significant difference between two groups in terms of frequency distribution of the type of the procedure (p=0.72).

Sedation index score

Concerning the level of sedation, no significant difference was found between the two groups at the beginning of the procedure (Table IV).

Pain severity

With respect to the mean score of pain severity, no significant difference was observed between the two groups at the beginning of the procedure (Table V).

Hemodynamic indices

There was no significant difference between the two groups regarding their systolic, diastolic, and mean arterial pressure before injecting the anesthetics and before transferring the patients from the recovery room to the ward (p>0.05).
However at the end of the procedure, the mean of systolic blood pressure was significantly lower in the PR group compared to the PK group (p= 0.04). The mean of arterial oxygen saturation showed no significant difference between the two groups before injecting the anesthetics and before transferring from the recovery room to the ward (p>0.05); however, it was significantly lower in the PR group compared to the PK group at the end of the procedure (p=0.04). The mean of heart rate caused no significant difference between the two groups at any of the measured times (p>0.05).

Side effects

During the procedure, the frequency of hypotension was significantly higher in PR group, compared to PK group (p=0.048); however, no significant difference was observed between two groups during the procedure and recovery considering the frequency of other complications (p>0.05).
In PR group (n=40), 3 patients had apnea who received respiratory support using face mask and bag, while in PK group (n=41), no patient had apnea. However, this difference was not significant (Table VI).
The side effects were defined as below:
Hypertension: an increase in the mean arterial blood pressure (mmHg) for at least 20% more than the baseline (before injecting the anesthetics).
Hypotension: a decrease in the mean arterial blood pressure (mmHg) for at least 20% from the baseline (before injecting the anesthetics).
Tachycardia: an increase in the number of heart rate for at least 20% more than the baseline (before injecting the anesthetics).
Bradycardia: the number of heart rate < 60 beats per minute.

Time

The mean of the effectiveness onset and the duration of the procedure exerted no significant difference between the two groups; however, the mean time from the end of the procedure to patient's awakening, the duration of staying in the recovery room, and the total duration of the mentioned times were significantly higher in PK group compared to the PR group (TableVII).

Motion during the procedure and the need for repeating drug's dosage

Chi square test showed that the frequency distribution of motion during the procedure had no significant difference between the two groups, but the frequency of the need for repeating the drug's dosage was significantly lower in PK group compared to the PR group (Table VIII).

Table I: The university of Michigan sedation scale for children

Responsiveness	score
Awake and alert	0
Minimally sedated;tired/sleepy,appropriate response to verbal conversion or sound	1
Moderately sedated;somnolent/sleeping,easily aroused with light tactile stimulation or a simple verbal command	2
Deeply sedated; deep sleep, arousable only with significant physical stimulation	3
unarousable	4

Table II: Distribution of patients according to age and weight

variable	PK		PR		P values
	Mean	SD	Mean	SD	
Age(year)	5.3	2.7	5.8	3.3	**0.44**
Weight(kg)	18	7.8	19.01	9.3	**0.60**

Table III:Distribution of patients according to gender

gender	PK		PR		P value
	number	percent	number	percent	
Male	24	58.5	23	57.5	
Female	17	41.5	17	42.5	**0.92**
Total	**41**	**100**	**40**	**100**	

Table IV: Sedation index score

Level of sedation(UMSS)	PK		PR		P value
	Mean	SD	Mean	SD	
2	0	0	1	2.5	
3	14	34.1	15	37.5	**0.54**
4	27	65.9	24	60	
Total	**41**	**100**	**40**	**100**	

TableV: Pain severity

variable	PK		PR		P value
	Mean	SD	Mean	SD	
Pain severity score (UPAT)	2.3	1.6	1.7	1.4	**0.12**

TableVI: Side effects of the two drug combinations

	Side effect	PK		PR		P values
		N	%	N	%	
During the procedure	tachycardia	0	0	1	2.5	**0.50**
	hypotension	9	22	15	37.5	**0.048**
	hypertension	1	2.4	3	7.5	**0.30**
	apnea	0	0	3	7.5	**0.12**
At the recovery	tachycardia	3	7.3	2	5	**0.50**
	hypotension	11	26.8	13	32.5	**0.58**
	hypertension	3	7.3	2	5	**0.50**

TableVII: Timing in the procedure (minute)

variable	PK		PR		P values
	Mean	SD	Mean	SD	
onset of effectiveness	3.7	0.7	3.6	1.2	**0.78**
duration of the procedure	5.1	1.6	4.8	0.10	**0.35**
Duration from the end of the procedure until patient's wakening	5.9	3.8	1.5	2.4	**<0.001**
Recovery duration	27.02	3.6	24.7	3.6	**0.004**
Total	**41.7**	**6.4**	**34.6**	**5.9**	**<0.001**

Table VIII: Motion during the procedure and the need for repeating drugs' dosage

variable	PK		PR		P values
	number	percent	number	percent	
Motion during the procedure	15	36.6	15	37.5	**0.93**
need for repeating drug's dosage	3	7.3	12	30	**0.009**

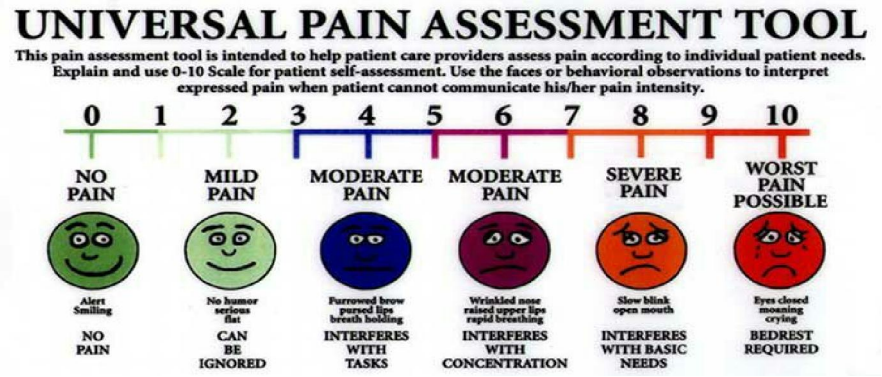

Figure 1. UPAT Journal of Pain & Relief March 18, 2014(22).

Discussion

Short hemato-oncologic procedures are often painful in children. Children with cancer may remember the bad memory due to the painful procedure, especially the frequent order at which these trouble experiences occur (2).

The goals of procedural sedation are to provide an adequate level of sedation while minimizing pain and anxiety, maximizing amnesia, minimizing the potential for adverse drug-related events, controlling behavior, and maintaining a stable cardiovascular and respiratory status(9).

So far, few studies have been conducted about using sedative and analgesic drugs during painful oncology operations. In addition, no study have evaluated yet the sedative and analgesic effects of Propofol-Ketamine and Propofol-Remifentanil combination in children with ALL undergoing, Lumbar Puncture and bone marrow aspiration/biopsy.

In the present study, the effectiveness of these two drug combinations were compared regarding their sedation, hemodynamic and respiratory indices, side effects, the onset of effectiveness, and duration of staying at the recovery room.

In this study, placebo-controlled group was not used because the procedures are very painful without the administration of analgesia.

Various studies have shown that infusion combinations of Propofol andRemifentanil for induction and maintenance of deep sedation or non-intubated general anesthesia are safe and effective in providing analgesia, stable sedation /hypnosis, satisfactory operating conditions, and a shorter recovery period compared to other conventional balanced anesthetic techniques (13).

In a study that was conducted by Heise et al., the effectiveness of the combination of Remifentanil and Propofol for sedation in children undergoing LP was studied and results indicated the efficiency of this combination (14). In another study conducted by Berkenbsch et al., to evaluate the sedative effect of Propofol-Remifentanil combination in children during flexible fiberoptic bronchoscopy, effective sedation and fast recovery were reported as the results of administering this combination (15). Hungerfold et al., conducted a study on 38 children hospitalized at PICU after trauma-caused brain injury and evaluated the effect of Remifentanil for creating a sufficient level of sedation in these children. Their findings showed that Remifentanil is a proper sedative drug with rapid onset of effectiveness and short recovery which allows the physician to perform multiple neurologic physical examinations (16).

However, a number of studies have demonstrated that the combination of Ketamine and Propofol (ketofol) for sedation is safe and effective. The combination of these two drugs could

reduce side effects of each medication and allows for a rapid recovery time (9).

In another study, Silva et al., evaluated the effectiveness of Propofol-Ketamine in children with blood malignancies undergoing bone marrow aspiration and reported effective sedative level, high satisfaction, and fast recovery. No serious complications were reported in their study (17).

Gray Andolfato, in a study on the effect of Propofol-Ketamine in primary orthopedic surgeries on children, also reported similar results (18). One study was conducted by Seol et al., on burnt 50 children aged 12 to 36 months old comparing two combinations of Propofol-Ketamine and Propofol-Remifentanil in terms of effective sedation and analgesia during bandaging and the duration of staying at the recovery. They reported significantly shorter recovery time in the Propofol-Remifentanil group (19).

In the present study, also, the duration of staying in the recovery was significantly shorter in the Propofol-Remifentanil group than the other group. Moreover in this group, the duration of time from the end of the procedure until patient's full consciousness was shorter than the other group. Therefore, it could be concluded that the combination of Propofol-Remifentanil can be associated with child's shorter hospitalization period and faster discharge from the hospital which is consistent with the findings of berkenbsch et al., (15).

Kramer et al., in a study conducted on 37 candidates of third molar tooth surgery, compared the effect of continuous intravenous infusion of Propofol-Ketamine and Propofol-Remifentanil. Both groups had similar sedation, respiratory parameters, and hemodynamic stability. However, the awakening time and the duration of staying in the recovery were reported longer for the Propofol-Ketamine group (20).

In the present study, the sedation level of the patients and their severity of pain were measured using UMSS and UPAT indices, respectively; and no significant difference was observed between the two groups. However, the need for repeating the drug's dose was significantly lower in the Propofol-Ketamine group compared to the other group. This difference might be due to the short half-life (8 to 10 minutes) of remifentanil and its fast clearance (21).

In the present study, nausea, vomiting, agitation, coughing, diplopia, hallucination, and shivering were not reported in any of the groups. During the procedure, 15 patients from the propofol-Remifentanil group (n=41) had hypotension which was significantly different from 9 patients in the propofol-ketamine group (n=40). Nevertheless, two groups had no significant difference during the procedure and in the recovery in terms of frequency of other side effects.

Although occurrence of three cases of apnea in the propofol-remifentanil group had no statistically significant difference with the propofol-ketamine group, this slight difference is of clinical importance due to significant importance of apnea occurrence and it's associated risks.

Considering the significant difference in the arterial oxygen saturation between two groups at the end of the procedure, it could be concluded that the combination of Propofol-Ketamine is associated with patient's higher respiratory stability condition.

Conclusion

It seems that the combination of Propofol-Ketamine is more appropriate for children with ALL undergoing bone marrow aspirasion or biopsy and LP than Propofol-remifentanil combination, especially in pations with unstable hemodynamics.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Ghadami Yazdi A, Ayatolahi V, Hashemi A, Behdad SH, Ghadami yazdi E. Effect of two Different concentration of propofol and ketamine combinations (ketofol) in pediatric patients under lumbar puncture or bone marrow aspiration. Iran J Ped Hematol Oncol 2013;3(1):187-192.

2. Abdolkarimi B, Zareifar S, Golestani Eraghi M, Saleh F. Comparison effect of intravenous ketamine with pethidine for analgesia and sedation during bone marrow procedures in onchologic children: A Randomized, double-Blind, Crossover Trial. Iran J Hematol Oncol Stem Cell Res 2016;10(4):206-211.

3. Coté CJ, Wilson S. American Academy of Pediatrics; American Academy of Pediatric Dentistry. Work Group on Sedation. Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures: an update. Pediatrics 2006; 118(6):2587–602.

4. Wang HY, Ting CK, Liou JY, Chen KH, Tsou MY, Chang WK. A previously published propofol-remifentanil response surface model does not predict patient response well in video-assisted thoracic surgery. Medicine (Baltimore) 2017; 96(19): 1-7.

5. Jaafarpour M, Vasigh A, Khajavikhan J, Khani A. Effect of Ketofol on Pain and Complication after Caesarean Delivery under Spinal Anaesthesia: A Randomized Double-blind Clinical Trial. J Clin Diagn Res 2017; 11(3): 4-7.

6. Scott MK, Gabrile JH, Barry DA, Aziza TS, Joseph EG, Heidi JD, et al. Comparison of intermittent versus continuous infusion of propofol for elective oncology procedures in children. Pediatri Crit Care Med 2003; 4(1): 78-82.

7. Cravero JP, Beach ML, Blike GT, Gallagher SM, Hertzog JH. The incidence and nature of adverse events during pediatric Sedation/Anesthesia with propofol for procedures outside the operating room: A Report From the Pediatric Sedation Research Consortium. Anesth Analg 2009; 108: 795–804.

8. Marx CM, Stein J, Tyler MK, Nieder ML, Shurin SB, Blumer JL. Ketamine-midazolam versus meperidine -midazolam for painful procedures in pediatric oncology patients. J Clin Oncol 1997; 15: 94-102.

9. Daabis M, Elsherbiny M, Alotibi R.Assessment of different concentration of ketofol in procedural operation. BJMP 2009; 2(1):27-31.

10. Burkle H, Dunbar S, Van Aken H. Remifentanil: a novel. Short-acting, mu-opioid. Anesth Analg 1996; 83: 646–651.

11. Sun GQ, Gao BF, Li Gj, Lei YL, Li J. Application of remifentanil for conscious sedation and analgesia in short-term ERCP and EST surgery. Medicine (Baltimore) 2017; 96(16): 1-3.

12. Bairy L, Vanderstichelen M, Jamart J,Collard E. Clonidine or remifentanil for adequate surgical conditions in patients undergoing endoscopic sinus surgery: a randomized study. Peer J 2017; 23(5): 1-11

13. Abu-Shahwan I, Propofol Mack D. and remifentanil for deep sedation in children undergoing gastrointestinal endoscopy. Paediatr Anaesth 2007;17:460–463.

14. Hayes JA, Lopez AV, Pehora CM, Robertson JM, Abla O, Crawford MW, et al. Coadministration of propofol and remifentanil for lumbar puncture in children: dose-response and an evaluation of two dose combinations. Anesthesiol 2008;109(4):613-618.

15. Berkenbosch JW, Graff GR, Stark JM, Ner Z, Tobias JD. Use of a remifentanil-propofol mixture for pediatric flexible

fiberoptic bronchoscopy sedation. Paediatr Anaesth 2004; 14(11):941-6.

16. Hungerfold JL, O`Brien N, Moore-Clingenpeel M, Srinbick EA, Sargel C, Hall M, et al. Remifentanil for sedation in children with Traumatic Brain Injury.J Intensive Care med 2017; 1:1-6.

17. Da Silva PS, de Aquiar VE, Waisberg DR, Passos RM, Park MV. Use of ketofol for procedural sedation and analgesia in children with hematological diseases. Pediatr Int 2011; 53(1):62-67.

18. Andolfatto G, Willman E. A prospective case series of pediatric procedural sedation and analgesia in the emergency department using single-syringe Ketamine-Propofol combination (Ketofol) Acad Emerg Med 2010; 17(2):194–201.

19. Seol TK, Lim JK, Yoo EK, Min SW, Kim CS, Hwang JY. Propofol-ketamine or propofol-remifentanil for deep sedation and analgesia in pediatric patients undergoing burn dressing changes: a randomized clinical trial. Paediatr Anaesth 2015; 25(6):560-566.

20. Kramer KJ, Ganzberg S, Prior S, Rashid RG. Comparison of propofol-remifentanil versus propofol-krtamine deep sedation for third molar surgery. Anesth Prog 2012; 59(3):107-117.

21. Choi EK, Seo Y, Lim DG, Park S. Post operative nausea and vomiting after thyroidectomy: a comparison between dexmedetomidine and remifentanil as part of balancedanesthesia.Korean J Anesthesiology 2017; 70(3):299-304.