EVALUATING THE EFFECTIVENESS OF KETAMINE PLUS ATROPIN AS ANESTHESIA FOR INTRATHECAL CHEMOTHERAPY AND BONE MARROW PROCEDURE AT HUE CENTRAL HOSPITAL, VIETNAM

Pham Nhu Hiep[1], Tran Kiem Hao[1], Nguyen Thi Kim Hoa[2], Chau Van Ha[2], Phan Canh Duy[1], Nguyen Huu Son[2], Kazuyo Watanabe[1], Bui Ngoc Lan[3]

ABSTRACT

Background: *Ketamine is a phencyclidine and cyclohexamine derivative. Ketamine and atropine have been increasingly used in recent years as an effective form of deep sedation/anaesthesia in children in developed countries, but not in developing countries like Vietnam.*

Objective: *This pioneer trial aimed to evaluate the effectiveness of using ketamine plus atropine as anaesthetic agents for paediatric oncology procedures. From this study, we establish a protocol for anaesthesia in paediatric oncology procedures.*

Methods: *A descriptive and prospective study on 223 paediatric patients of both sexes (129 males and 94 females) aged 7.2 months to 15 years (mean age: 4.0 ± 3.4 years) and with body weight between 6.5 to 55 kg (mean weight: 15.3 ± 6.2 kg) was carried out from January 2015 to June 2019. The patients had been diagnosed with acute leukaemia, lymphoma or solid tumor. They underwent intrathecal chemotherapy and bone marrow aspirations or bone marrow biopsy for diagnostic as well as therapeutic purposes. After obtaining informed consent from their parents, the research was performed. Datas were analysed by Medcalc software.*

Results: *The total number of procedures was 810. Bone marrow aspiration was performed 402 times, bone marrow biopsy was done 30 times and intrathecal chemotherapy given 378 times. All procedures were successfully completed. The mean dose of ketamine and atropine used 1.55 ± 0.31 mg/kg and 0.100 ± 0.029 mg respectively. The recovery time was 9.2 ± 7.3 minutes. Only 0.12% experienced apnoea; 1.2% muscular hypertonicity; 4.3% nystagmus, and hyperactivity; 3.7% hypersalivation, 2.5% hallucination and 5.5% vomiting; none of the patients had laryngospasm or transient rash. All of the patients' parents were satisfied with the use of anaesthetics.*

Conclusions: *This is a pioneer trial for children in Vietnam. The dose of 1.5mg/kg intravenous ketamine and 0.1mg atropine were found to be effective and suitable dose in children requiring deep sedation for painful procedures and produce only minimal side effects. We established a protocol with the above doses and continue to apply this in order to reduce pain, trauma, and complications during the procedures.*

Keywords: *ketamine, atropin, anesthesia, children*

I. INTRODUCTION

Ketamine is a phencyclidine and cyclohexamine derivative. It is unique among the sedative analgesics in producing disociative state between the thalamus and the limbic system which is characterized by four features: sedation, analgesia, amnesia and catalepsy. Ketamine does not lead to loss of protective reflexes. In developed countries,

1. Adult Oncology Center, Hue Central Hospital
2. Pediatric Center, Hue Central Hospital
3. Asian Children's Care League, Tokyo, Japan
4. National Children Hospital

- Received: 25/7/2019; Revised: 31/7/2019;
- Accepted: 26/8/2019
- Corresponding author: Nguyen Thi Kim Hoa
Email: kimhoa.fmi@gmail.com

Ketamine and atropine has been increasingly used in recent years as an effective form of deep sedation, anesthesia in children.

In Vietnam, children with blood diseases, especially children with cancer are often carried out painful procedures with out anesthesia such as bone marrow aspiration/biopsy, intrathecal chemotherapy for diagnosis and treatment. Therefore, using sedative analgesics relieving the pain and fear, minimizing the trauma for the children is necessary. However, to our knowledge there is no established anesthetic protocol yet for children experiencing the above procedures.

So, we conducted this study using the combination of ketamine and atropine at Pediatric Hematology-oncology Department - Hue Central Hospital with purposes: (1) To evaluate the effectiveness and safety of using ketamine combined with atropine as sedative analgesics in painful procedures in children. (2) To recommend the pediatric anesthetic protocol.

II. PATIENTS AND METHOD

2.1. Patients

223 patients admitted at Hue Pediatric Center, Hue Central Hospital, Vietnam from 1/2015 to 6/2019, in which there were 129 boys and 94 girls. The exclusive criteria: Age less than 3 months; Active pulmonary infection; History of airway instability, tracheal surgery or tracheal stenosis; Cardiovascular disease in which raised blood pressure or heart rate may be deleterious (eg. angina, heart failure, aneurysm or uncontrolled hypertension); Adverse reactions to ketamine; Raised intracranial pressure; Glaucoma; Psychiatric illness; Full meal within 3 hours of administration.

2.2. Method

A prospective and descriptive study. Figure 1 is the anesthesia protocol for children. The present study was approved by the Hue Central Hospital Review Board and conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Statistical analysis: Data were analyzed by using Medcalc program.

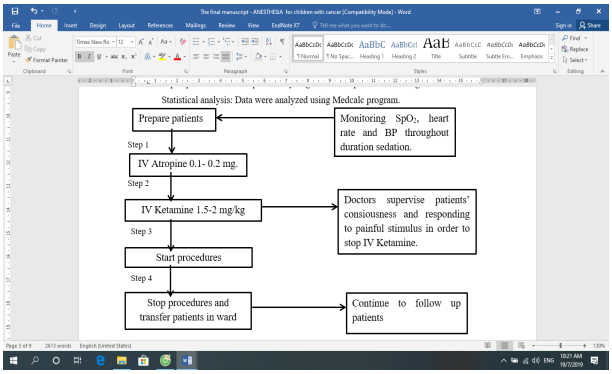

Figure 1. Protocol for using anethesia

III. RESULTS

Two hundred and twenty-three patients were enrolled to the study, in which there were 129 boys and 94 girls, the ratio of male/female = 1.38/1. The age ranged between 7.2 months to 15 years, mean age was 4.0 ± 3.4 years, and body weight ranged 6.5 to 55 kg (mean weight: 15.3 ± 6.2 kg).

The total number of procedures performed were 810, in which there were 402 times of bone marrow aspirations, 30 times of bone marrow biopsy 378 times of intrathecal chemotherapy (302 times: 1 drug and 75 times: 3 drugs). The mean dose of ketamin was 1.55 ± 0.31mg (range 1.0 – 2.2 mg) and the mean dose of atropine was 0.100 ± 0.029mg (range 0.10 - 0.32 mg).

The recovery time was 9.2 ± 7.3 minutes (range 1-40 mins) and mean duration of the procedure was 8.0 ± 1.5 minutes (range 6-15 mins).

There wasn't any difference in SpO_2 saturation before and after using anethesia (p=0.12). Heart rate and blood pressure before and after using anesthesia were not different (table 1). Side effects after using drug occurred in one patient including apnea (0.12%), hypersalivation 3.7% and vomitting 5.5%. There were 10 times (1.2%) that patients experienced muscular hypertonicity. Hallucination happened in 2.5% patients (table 2). There was 4.3% nystagmus and hyperactivity. 99.88% procedures successfully finished, except one patient appeared apnea, so we had to cancel the procedure. 100% parents were satisfied when their childrens expericenced the procedures with sedation/anesthesia.

Table 1. Comparison of SpO_2 , pulse and blood pressure value

	The average value before IV administration	The average value after IV administration	P
The mean SpO_2 (%)	97.5 ± 1.8	97.0 ± 3.6	0.12
The mean heart rate (beats/min)	121.1 ± 22.6	121.7 ± 24.1	0.56
The mean systolic blood pressure (mmHg)	89.7 ± 6.7	90.3 ± 8.3	0.10
The mean diastolic blood pressure (mmHg)	58.5 ± 10.7	57.6 ± 11.2	0.83

Table 2. Side effects after using anesthesia drug

Variables	Quantity	%
Apnea	1	0.12
Hypersalivation	30	3.7
Vomiting	45	5.5
Muscular hypertonicity	10	1.2
Hallucination	20	2.5

IV. DISCUSSION

In our study, the ratio of male/female was 1.38/1. According to Kidd, Ng KC and Heinz, this ratio were higher: 1.75/1, 1.9/1 and 1/9/1 respectively [1] [2] [3]. The mean age was 4.0 ± 3.4 years, and body weight ranged 6.5 to 55 kg (mean weight: 15.3 ± 6.2kg). Similarly, Traivaree enrolled 46 children aged 6 months to 15 years [4]. According to Kidd and Heinz, they gavesed anethesia in older children with age ranged between 14 months to 15 years, 13 months to 14.5 years respectively [1], [3].

The mean dose of ketamin was 1.55 ± 0.31mg which was the same dose in Heilbrunn and Evans' research [5], [6]. Heinz, Mason used a little bit higher dose of Ketamine (2mg/kg) than our dose [3], [7]. Contrast to us, Traivaree used lower dose of Ketamine (1mg/kg) and it was al so effective for invasive procedures in children with malignancy [4]. So, through many researches, the dose of intravenous ketamine up to 2 mg/kg is the effective sedative dose for invasive procedures in cancer children [6], [5], [3], [7]. The mean dose of atropine in my study was 0.100 ± 0.029mg. Similarly, Heinz, Yu Chan Kye showed the minimum dose of atropin was 0.1 mg, the usual dose of atropine was 0.01 mg/kg [3] [8].

The recovery time was 9.2 ± 7.3 minutes and the mean duration of the procedure was 8.0 ± 1.5 minutes. Similarly, Evans showed the mean duration of the procedure was 6.6 mins and the recovery time was 11 mins [6]. Heinz showed the mean time of the procedure was 10.5 minutes [3].

Table 1 showed there wasn't any difference in SpO_2 saturation before and after using anethesia (p=0.12), except one patient who appeared apnea then recovered by supportive stimulation and oxygen therapy. Similarly, in Slonim's research, one patient had oxygen desaturation < 90% [9]; in Brown'result, transient airway complication occurred in 3.2% with just one (brief desaturation) felt [10]. Table 1 also showed heart rate and blood pressure before and after anesthesia were the not different. According to Patterson, Ketamine caused modest increase in systolic pressure, diastolic blood pressure and heart rate [11].

When using Ketamine and atropine, our patients experienced some side effects. There was one patient having apnea. This was the first case we used sedation, we didn't have experience, we gave intravenously ketamine too quickly, so the patient had apnea. Contrast to us, Evans showed no major airway complications occurred [6].

3.7% of our patients experienced hypersalivation. Similarly, Yu Chan Kye showed hypersalivation occurred in 1.5% [8]. Jiaxiao Shi showed the group receiving atropine had reduced hypersalivation [12]. According to Heinz and Traivaree, the rate of hypers salivation were higher: 11.4 % and 26.1% respectively [3] [4]. Vomiting happened in 5.5% patients, which was higher in comparion with Yu ChanKye: 4.4% [8]. Contrast to us, Heinz showed higher percentage patients with vomitting 9.1% [3].

In our study, there wasn't any patient having laryngospasm or transient rash. Similarly, Sheikh didn't see any side effects of laryngospasm or transient rash. Contrast to us, the patients in Heinz study 22.7% rash and 9.1% laryngospasm [3]. There were 10 times (1.2%) that patients experienced muscular hypertonicity and recovered spontaneously. This was a reason that some protocols combined midazolam with ketamine and atropine. Hallucination happened in 2.5% patients. Similarly, Travivaree showed hallucination appeared in 4.2% [4]. Nystagmus and hyperactivity were side effects caused by ketamine, with rate 4.3%. Contrast to us, the ratio of hyperactivity due to ketamine in Heinz's study was 20.5% [3].

Ketamine causes dissociation between the thalamocortical pathways and limbic systems. After using ketamine and atropine, patients didn't cry or struggle, didn't feel painful. So, taking bone marrow sample were easier. There wasn't any case, in with the doctors didn't take enough bone marrow sample for the tests and the anesthesia helped doctors to avoid trauma for patients during the intrathecal chemotherapy procedures, and it helped to limit blast cells infiltrating to the central nervous system, reduced the patient' stress. Similarly to Mason, all procedures (solid organ biopsies) were successfully completed, and there were no major adverse events [7].

In our study, 100% parents were satisfied when their childrens experienced the procedures with anesthesine, that helped the children not being afraid and not feeling painful. According to Heinz, the satisfaction rating with excellent, good, satisfactory and poor level were 74.4%, 18.6%, 2.3% and 4.7% respectively [3].

V. CONCLUSION

This is a pioneer trial for children in Vietnam. Ketamine combined with Atropine were found effective and suitable in children requiring deep sedation for painful procedures. The dose of 1.5mg/kg intravenous ketamine and minimum dose of atropine were found effective. Ketamine was tolerated well. The recovery time was rapid: 9.2 ± 7.3 minutes. Only 0.12% of our procedures experienced apnea; 1.2% muscular hypertonicity, 4.3% nystagmus, hyperactivity; 3.7% hypersalivation, 2.5% dream ; 5.5% vomiting; none of the patients had laryngospasm or transient rash. And 100% their parents were satisfied with the use of anesthetics. Thereby, we establish anesthesia protocol with the above doses and continue to apply this in order to reduce pain, trauma, and complications during the procedures.

REFERENCES

1. Kidd, L.R., Lyons, S.C., and Lloyd, G. (2016) Paediatric procedural sedation using ketamine in a UK emergency department: a 7 year review of practice. *Br J Anaesth*, 116, 518-23.
2. Ng, K.C. Ang, S.Y. (2002) Sedation with ketamine for paediatric procedures in the emergency department-a review of 500 cases. *Singapore Med J*, 43, 300-4.
3. Heinz, P., Geelhoed, G.C., Wee, C., and Pascoe, E.M. (2006) Is atropine needed with ketamine sedation? A prospective, randomised, double blind study. *Emerg Med J*, 23, 206-9.
4. Traivaree, C., Jindakam, W., Monsereenusorn, C., Rujkijyanont, P., and Lumkul, R. (2014) The factors of ketamine that affect sedation in children with oncology procedures: parent

satisfaction perspective. *J Med Assoc Thai*, 97 Suppl 2, S19-24.
5. Heilbrunn, B.R., Chang, T.P., and Liu, D.R. (2015) A retrospective comparison of ketamine dosing regimens for pediatric procedural sedation. *Eur J Emerg Med*, 22, 111-6.
6. Evans, D., Turnham, L., Barbour, K., Kobe, J., Wilson, L., Vandebeek, C. (2005) Intravenous ketamine sedation for painful oncology procedures. *Paediatr Anaesth*, 15, 131-8.
7. Mason, K.P., Padua, H., Fontaine, P.J., and Zurakowski, D. (2009) Radiologist-supervised ketamine sedation for solid organ biopsies in children and adolescents. *AJR Am J Roentgenol*, 192, 1261-5.
8. Kye, Y.C., Rhee, J.E., Kim, K., Kim, T., Jo, Y.H., Jeong, J.H. (2012) Clinical effects of adjunctive atropine during ketamine sedation in pediatric emergency patients. *Am J Emerg Med*, 30, 1981-5.
9. Slonim, A.D. Ognibene, F.P. (1998) Sedation for pediatric procedures, using ketamine and midazolam, in a primarily adult intensive care unit: a retrospective evaluation. *Crit Care Med*, 26, 1900-4.
10. Brown, L., Christian-Kopp, S., Sherwin, T.S., Khan, A., Barcega, B., Denmark, T.K. (2008) Adjunctive atropine is unnecessary during ketamine sedation in children. *Acad Emerg Med*, 15, 314-8.
11. Patterson, A.C., Wadia, S.A., Lorenz, D.J., and Stevenson, M.D. (2017) Changes in blood pressure and heart rate during sedation with ketamine in the pediatric ED. *Am J Emerg Med*, 35, 322-325.
12. Shi, J., Li, A., Wei, Z., Liu, Y., Xing, C., Shi, H. (2018) Ketamine versus ketamine pluses atropine for pediatric sedation: A meta-analysis. *Am J Emerg Med*, 36, 1280-1286.