ETOMIDATE VERSUS KETAMINE FOR PROCEDURAL SEDATION IN PAEDIATRIC PATIENTS IN THE EMERGENCY DEPARTMENT

By

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Dissertation Submitted in

Partial Fulfilment of the Requirements

for the degree of Master Of Medicine

(Emergency Medicine)

UNIVERSITI SAINS MALAYSIA

2012

ACKNOWLEDGEMENT

There are a lot of efforts, sweats and tears in completing this dissertation. This dissertation would not be reality without the guidance and help from many individuals and organizations. Here, I would like to express the highest appreciation to them.

My deepest appreciation to my supervisor for this study, Dr. Abu Yazid Bin Md Noh, Emergency Physician in the Department of Emergency Medicine, Hospital Universiti Sains Malaysia (HUSM) and my co-supervisor, Associate Professor Dr. Nik Hisamuddin Bin Nik Abdul Rahman, Emergency Physician and Head of Department, Department of Emergency Medicine HUSM. Without their help and guidance, this study and dissertation will never be conducted successfully.

Similar appreciation goes to the patients and parents that willing to participate in this study, and to all my lecturers, medical officers, sisters, staff nurses, medical assistants and hospital staffs that willing to help me in conducting the study. I was definitely indebted to your kindness and assistant.

My sincere thanks to Dr Wan Mohd Zahiruddin Bin Wan Mohammad, lecturer in Department of Community Medicine, Universiti Sains Malaysia (USM) who willing to guide me in the statistical part of this dissertation.

I also wanted to extend my gratitude and thank the Pharmacy Department HUSM who willing to spend their time in helping me for this study.

Special thanks also to Dr. Md Saed Bin Mian, Dr. Mohd Amin Bin Mohidin and Dr. Muhammad Ramdhan Bin Abd Aziz, Emergency Physician in Hospital Sultanah

Aminah Johor Bahru for their wisdoms, guidance and support which help me in completion of this study.

My love and special gratitude to my beloved wife, daughter and families. Thank you for your undivided support and sacrifices.

Last but not least, thank you to all that help me in this dissertation, I am truly indebted to you all.

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LIST OF ABBREVIATION

AAP	=	American Academy of Paediatrics
AHA	=	American Heart Association
ASA	=	American Society of Anesthesiologists
CMR	=	Closed manipulative reduction
$CMRO_2$	=	Cerebral metabolic rate of oxygen
CNS	=	Central nervous system
DBP	=	Diastolic blood pressure
ED	=	Emergency department
GABA	=	Gamma Aminobutyric acid
GCS	=	Glasgow coma scale
HUSM	=	Hospital Universiti Sains Malaysia
ICP	=	Intracranial pressure
IqR	=	Interquartile range
IV	=	Intravenous
n	=	Number of subject
NMDA	=	N-Methyl-D-aspartate
O_2	=	Oxygen
PALS	=	Paediatric Advance Life Support
PSA	=	Procedural sedation and analgesia
SBP	=	Systolic blood pressure
SD	=	Standard deviation
T&S	=	Toilet and suturing
URTI	=	Upper respiratory tract infection

ABSTRAK

Perbandingan antara Etomidate dan Ketamine di dalam prosedur sedatif di kalangan pesakit paediatrik di jabatan kecemasan

Objektif Kajian

Objektif kajian ini adalah untuk membuat perbandingan masa sedatif (T_1) antara Etomidate dengan Ketamine dan tahap keselamatan kedua-dua ubat semasa prosedur sedatif dan pelalian (PSA) di kalangan kanak-kanak di dalam Jabatan Kecemasan.

Tatacara Kajian

Kajian rawak terkawal dan separuh terbuka ini telah di jalankan di Jabatan Kecemasan Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan daripada 1 Jun 2010 sehingga 31 Mei 2011. 29 kanak-kanak berumur daripada 2 tahun hingga ke 12 tahun telah dimasukkan untuk menyertai kajian ini dengan keizinan ibu bapa mereka.

Mereka diagihkan secara rawak kepada 2 kumpulan iaitu kumpulan Etomidate yang mana mereka menerima IV Fentanyl 1µg/kg dengan IV Etomidate, 0.2 mg/kg dan kumpulan Ketamine yang menerima IV Ketamine 1.5 mg/kg. 13 pesakit telah dimasukkan ke kumpulan Etomidate dan 16 pesakit ke kumpulan Ketamine. Masa sedatif (T_1) dikira bermula dari masa mula-mula ubat sedatif

diberikan hinggalah pesakit tidur iaitu pada skor Ramsay yang ke-4. Tanda-tanda vital akan dicatitkan dan komplikasi semasa prosedur didokumenkan sehingga pesakit-pesakit dikeluarkan dari Jabatan Kecemasan.

Keputusan Kajian

Daripada 29 subjek, Cuma 23 subjek sahaja yang mencapai tahap sedatif yang mencukupi menggunakan ubat kajian untuk menjalankan prosedur. Semua pesakit yang tidak mencapai tahap sedatif yang mencukupi adalah daripada kumpulan Etomidate. Daripada 23 subjek itu, median T_1 untuk kumpulan Etomidate adalah 5.0 minit (IqR = 9.0) dan Kumpulan Ketamine, median T_1 adalah 1.5 minit (IqR = 4.0) Tiada perbezaan statistic antara T_1 Etomidate dan Ketamine (P value = 0.17)

Dalam kajian ini, komplikasi yang dapat dilihat ialah jeluak dan muntah, dan insiden didalam kedua-dua kumpulan adalah sama dan tiada perbezaan yang ketara (P value = 0.53). Tiada komplikasi serius berlaku semasa kajian ini.

Rumusan

Kajian ini menunjukkan bahawa masa sedatif antara Etomidate dan Ketamine tidak mempunyai perbezaan ketara dikalangan kanak-kanak. Kajian ini juga membuktikan Etomidate tidak se efektif Ketamine untuk PSA dikalangan kanak-kanak. Bagaimanapun, kedua-dua ubat sedatif ini terbukti selamat untuk kanak-kanak Malaysia tanpa mendatangkan kesan komplikasi yang serius.

ABSTRACT

Etomidate versus ketamine for procedural sedation in paediatric patients in the Emergency Department

Objective

The objectives of the study was to compare the sedation time (T_1) between Etomidate versus Ketamine and the safety of both drugs in the procedural sedation and analgesia among paediatric patients in Emergency department.

Method

A single blinded, randomized control study was conducted in Emergency Department Hospital Universiti Sains Malaysia, Kubang Kerian Kelantan, from 1st Jun 2010 untill 31st May 2011. 29 paediatric patients aged from 2 years old until 12 years old were recruited with the permission of their parents. They were randomized to two group, Etomidate group which received IV Fentanyl 1µg/kg plus IV Etomidate 0.2mg/kg and Ketamine group which received IV ketamine 1.5mg/kg. 13 patients randomized to Etomidate group and 16 patients to Ketamine group. Sedation time (T_1) was measured from the start of administrating the sedation drug until patients achieved adequate sedation which is characterized by Ramsay sedation score of 4. Vital sign was monitored and any adverse events documented until patients safely discharged/ admitted.

Results

From 29 subjects, only 23 subjects able to achieved adequate sedation level with the study drugs. All subjects who did not achieved adequate sedation level were from Etomidate group. From those 23 subjects, median T_1 for Etomidate group was 5.0 minutes (IqR 9.0). In the Ketamine group, the median T_1 was 1.5 minutes (IqR 4.0). There was no statistical difference in the T_1 between the Etomidate group and Ketamine group (*P* value = 0.17).

In this study, the adverse event that has been documented was retching and vomiting and the incidence between the two groups of study drug was similar and no significant difference. (*P* value = 0.53). There was no serious adverse effect documented during this study.

Conclusion

This study proved that sedation time between Etomidate and Ketamine for the PSA were not significantly differ and Etomidate was less effective for PSA compared to the Ketamine in the paediatric age group. Nevertheless, both groups of sedative agents were relatively safe to be used without any serious adverse effect in the paediatric population in Malaysia.

1. INTRODUCTION

Procedural sedation and analgesia (PSA) which was previously known as conscious sedation was one of the commonly performed procedure in the emergency department (ED) (Pitetti *et al.*, 2003; Mace et al., 2008).

PSA was defined as a procedure where patients are given sedative or dissociative drugs, with or without an analgesic agent to put the patients into a state of depressed level of consciousness which allow them to undergo and tolerate painful or unpleasant procedures without impairing their cardiorespiratory function and protective reflexes (Jagoda *et al.*, 1998; Godwin *et al.*, 2005).

Even though it is relatively safe and efficacious in ED (Pitetti *et al.*, 2003), PSA is not without complications (Pena and Krauss, 1999; Bhatt *et al.*, 2009). In 1999, Pena et al, did a study about the adverse events associated with PSA among paediatric patients in the ED. They found that 2.7% of the patients in the study experienced side effects. The common adverse events were oxygen desaturation, paradoxical reaction, emesis, bradycardia, apnea and laryngospasm (Pena and Krauss, 1999).

In order to make PSA safer, several guidelines had been published and multiple studies had been done and are still on going in order to look for the ideal sedative agent and advancement in patients monitoring (Committee on Drugs and Section on Anesthesiology, 1985; Committee on Drugs, 1992; Jagoda *et al.*, 1998; Godwin *et al.*, 2005).

Until today, no study had been done in comparing Etomidate with other sedative agents in Malaysian paediatric population. Even though Etomidate is "unpopular" sedative agent in paediatric procedural sedation, its pharmacodynamics which maintain cardiovascular stability is important in becoming an alternative to other sedative agents, especially in patients where ketamine is contraindicated due to severe hypertension or hypersensitive to the Ketamine.

The aim of this study was to compare the efficacy and safety between two sedative agents which were Etomidate and Ketamine in procedural sedation among the paediatric population in ED. This study hopefully can help the emergency doctor in selecting a better and safer agent for PSA especially in local Malaysian population.

2. LITERATURE REVIEW

2.1 History of sedation and anaesthesia

For centuries, human had utilised different remedies in rendering patients unconscious and alleviating their pain in order to perform painful and noxious surgical procedures. The history dated back from the ancient Chinese, Rome, Greek and Egypt who used variety of plants and herbs such as cannabis, poppy seed (opium) and mandrake for their surgery (Chu, 2004; Al-Mazrooa and Abdel-Halim, 2009; Krishnan, 2011). Later the knowledge on sedation and anaesthesia was expanded to Muslim countries and Europe, and it was refined and studied until now which benefited the modern medicine.

Realizing the importance and the widely used of sedative agent in patient care, in 1985, American Academy of Paediatrics (AAP) published a guidelines on sedation and anaesthesia in paediatric patients. AAP defined conscious sedation as slightly depressed of conscious level in patients but they still can maintain and respond to some extend of physical and or verbal stimulation (Committee on Drugs and Section on Anesthesiology, 1985). In 1992, AAP again published another article about the sedation among paediatric patients who undergoes diagnostic and therapeutic procedures. It comprised the guidelines for monitoring and managing the children during and after the procedure (Committee on Drugs, 1992).

American College of Emergency Physician later on introduced the term of procedural sedation and analgesia (PSA) and conscious sedation was changed to moderate sedation. This term was introduced because it was more accurate in

defining the procedure that being done and more practical to be used especially in defining the continuum of sedation in patients (Jagoda *et al.*, 1998; Innes *et al.*, 1999; Krauss and Green, 2000).

2.2 Procedural Sedation and analgesia

Trauma cases among children are one of the common cases seen in emergency department. This is due to playing related injury, motorvehicle accident and others (Lam LT *et al.*, 1999). Most of them need some kind of interventions either wound debridement, toilet and suturing and closed manual reduction. These procedures are certainly unpleasant experiences to the children. To alleviate the pain, anxiety and stress during such procedure, PSA was introduced in the ED

The main aim of PSA is to allow patients to tolerate painful and unpleasant procedures by alleviating the pain, stress, anxiety and discomfort. It is also being used to decrease and prevent movements in uncooperative patients especially children, during specific procedures (e.g imaging, toilet and suturing etc.) (American Society of Anesthesiologists Task Force on Sedation Analgesia by Non-Anesthesiologists, 2002).

There were several levels of sedation that had been described by the American Society of Anaesthesiology (ASA):

Minimal sedation (anxiolysis)

It is the state during which patients respond normally to verbal commands after induced by sedative agents. Cognitive function and coordination may be

impaired but the body is still maintaining ventilatory and cardiovascular function and reflexes.

Moderate sedation/analgesia (conscious sedation)

It is defined as drugs induced depression of consciousness. Patients still respond purposefully to verbal commands alone or accompanied by light physical stimulation. No interventions are needed to maintain an adequate cardiorespiratory function.

Deep sedation/analgesia

It is a state of depression of consciousness, in which patients are difficult to be aroused but still respond purposefully with repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Airway and respiratory function maybe impaired. Cardiovascular stability is usually preserved.

General anesthesia

It is a state where patients develops loss of consciousness after induced by the anaesthetic drugs. Patients do not respond to any stimuli. Cardiorespiratory function is usually impaired, and assisted ventilation is commonly needed.

(American Society of Anesthesiologists Task Force on Sedation Analgesia by Non-Anesthesiologists, 2002; Krauss and Green, 2006)

PSA is important in the ED especially in children because failure to alleviate the pain and handling of uncooperative children will affect the success of the procedure, patients and family satisfaction and impair the patients care (Mace et al., 2008).

The ideal agents for procedural sedation and analgesia in ED are still an Utopia for the Emergency Physician. It must have all the sedative, anxiolytic, amnestic and analgesic properties which can be achieved in a rapid onset and also had a fast recovery time without any adverse reaction (Blackburn and Vissers, 2000; Di Liddo *et al.*, 2006).

Many studies and publication had proved the efficacy and safety of procedural sedation and analgesia to be performed in the ED setting (Glickman, 1995; Pena and Krauss, 1999; Mace et al., 2008; McQueen *et al.*, 2009) and multiple agents had been introduced and used for the procedures. Generally sedative drug commonly used in PSA were divided into Barbiturates and Non-Barbiturates like benzodiazepines and Etomidate (American Society of Anesthesiologists Task Force on Sedation Analgesia by Non-Anesthesiologists, 2002; Godwin *et al.*, 2005; Kost and Roy, 2010).

Barbiturates such as thiopental exert their sedative effect mainly by potentiating the effect of Gamma Aminobutyric acid (GABA) neurotransmitter which was the main inhibitory neurotransmitter in the CNS. Barbiturates will directly stimulate $GABA_A$ receptor and enhanced the effect of GABA neurotransmitter toward these receptors and lead to suppression of reticular activating system (Stoelting and Hiller, 2006).

Meanwhile, non-barbiturate sedative agents like benzodiazepine had been used widely over the decades in children, but due to its cardiorespiratory side effect and longer recovery time, other agents have gradually been introduced. Examples were Ketamine, Propofol and Etomidate (Di Liddo *et al.*, 2006; Kost and Roy, 2010). These agents had gained a significant popularity among emergency setting in view of their rapid onset and short duration of sedative effect without marked hangover period.

Other drugs also being used for procedural sedation such as analgesic agents like opioids, inhalational agents like nitrous oxide and reversal agents like flumazenil and naloxone (Blackburn and Vissers, 2000; Kost and Roy, 2010) (Krauss and Green, 2006).

Etomidate

Etomidate is one of the ultra-short acting induction agents used in procedural sedation (Green, 2007; Buck, 2008). It is a carboxylated imidazole containing substance (Figure 2.1) that acts by enhancing the central nervous system inhibitory receptors (GABA receptors). It is relatively selective at $GABA_A$ receptor and acts by binding to these receptors and increase the affinity of GABA neurotransmitter to the receptors which lead to CNS depression (Hunt *et al.*, 2005; Stoelting and Hiller, 2006).

Etomidate is very lipid soluble and able to reach the brain rapidly and that explains why the effect of Etomidate is rapid and consciousness is lost within minute

(one arm to brain circulation time). It duration of action lasted 4-15 minutes (Buck, 2008).

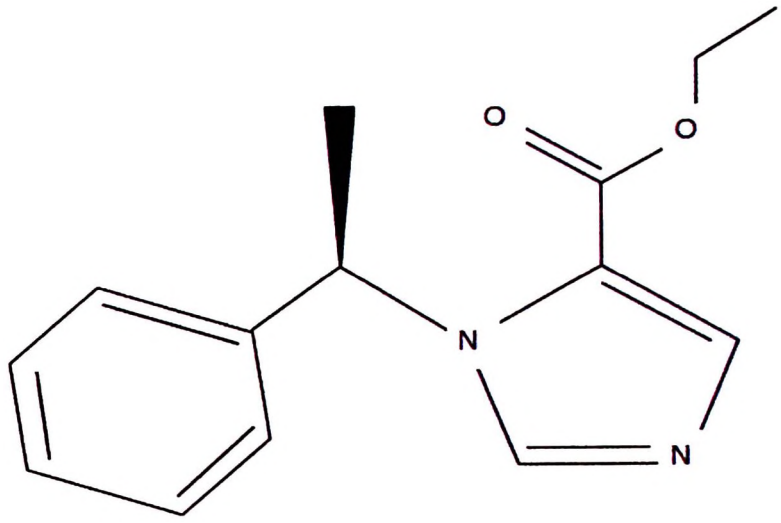

Figure 2.1: Etomidate molecular structure (National Center for Biotechnology Information; Stoelting and Hiller, 2006)

Other than its ultra-short acting properties Etomidate has less haemodynamic adverse effect compared to other induction agents, thus maintaining the cardiovascular stability and it shows a high level of efficacy when used as procedural sedation analgesia (Vinson and Bradbury, 2002; Hunt *et al.*, 2005; Krauss and Green, 2006). These properties give Etomidate an advantage to be used in patients with cardiogenic shock or patients with increase intracranial pressure (ICP) in which other agents may contraindicated. Etomidate can decrease cerebral metabolic rate of O_2 ($CMRO_2$) and cerebral blood flow and this effects are beneficial to decrease the ICP and useful for the traumatic brain injury victims (Frost, 2004; Stoelting and Hiller,

2006). It also shows a rapid recovery compared to barbiturates and has a little or no hangover effect. (Stoelting and Hiller, 2006).

Like other induction agents, Etomidate can cause a respiratory depression. In addition to that, it also can cause involuntary myoclonus (Keulen and Burton, 2003), pain at the injection site, nausea and vomiting (Frost, 2004). Some studies also showed that Etomidate can lead to temporary suppression of adrenocortical function (Schenarts *et al.*, 2001; Frost, 2004), especially if being used as continuous infusion. It is believed to be due to dose dependent inhibition of 11 beta hydroxylase in the Cortisol synthesis pathway (Frost, 2004; Stoelting and Hiller, 2006). The incidence of myoclonic movements is reduced by concomitant administration of opioid or benzodiazepines (Keulen and Burton, 2003; Buck, 2008).

Etomidate is metabolized in the liver by hydrolysis and has short elimination half-life of 2-5 hours (Stoelting and Hiller, 2006).

Etomidate has been proven to be safe for paediatric procedural sedation (Vinson and Bradbury, 2002; Mace *et al.*, 2004; Di Liddo *et al.*, 2006; Buck, 2008). Several studies had been conducted to assess the safety of Etomidate. In 1995, Mc Dowell et al in their studies involving paediatric oncology patients, newborn to 19 years of age had concluded the safety of propofol, Ketamin and Etomidate for anesthesia (McDowall *et al.*, 1995). A randomized control study also had been done in 2006 by Di Liddo and teams. In the study involving patients age 2 to 18 years old, they suggested that Etomidate may be more efficacious and appear to be equally safe as compared to the Midazolam in procedural sedation (Di Liddo *et al.*, 2006).

The standard induction dose for Etomidate is 0.2-0.4mg/kg via intravenous route (Di Liddo *et al.*, 2006; Stoelting and Hiller, 2006).

Ketamine

Ketamine (Figure 2.2) is one of the sedative drugs for the procedural sedation and analgesia for variety of painfull procedure especially in the paediatric age group (Dachs and Innes, 1997; Green and Krauss, 2004). It was developed in 1962 as a rapid acting general anaesthesia and was approved for the human used in 1970 (The Center for Substance Abuse Research, 2005).

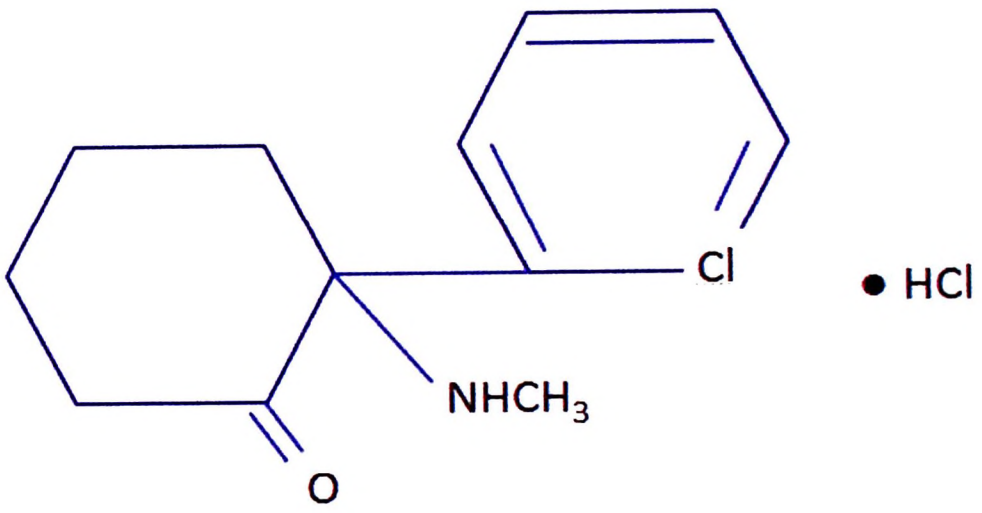

Figure 2.2: Ketamine Hydrochloride molecular structure (National Center for Biotechnology Information; Stoelting and Hiller, 2006)

As a Phencyclidine derivatives it exert its effect at the NMDA receptor (antagonist), opioid receptor (Mu antagonist while agonist in Kappa) and several other receptors site (MoA, Muscarinic and Sodium Channels) (The Center for Substance Abuse Research, 2005; Stoelting and Hiller, 2006). The effect of

Ketamine was different from the other common sedative drugs. It induced trancelike cataplectic state to the patients, which known as dissociative anaesthesia. These effects occur due to disconnection between thalamoneocortical and limbic system which lead to dissociation of these systems with the external stimuli. This dissociation generated potent analgesia, amnesia and sedation (Green and Krauss, 2004; Stoelting and Hiller, 2006). The unique about Ketamine was that, even with the dissociative state, patients still able to maintain protective airway reflexes, cardiopulmonary stability and spontaneous breathing. This property make Ketamine ideal for field anaesthesia and now is one of the agents widely used for procedural sedation and analgesia in emergency department (Glickman, 1995; Dachs and Innes, 1997; Sobel *et al.*, 1999; Green and Krauss, 2004; Krauss and Green, 2006).

Multiple studies had been performed, and Ketamine had been proven as a safe drug to be used in the paediatric age group (Glickman, 1995; Dachs and Innes, 1997; Green and Krauss, 2004; Green and Sherwin, 2005; Haley-Andrews, 2006). Nevertheless caution also must be taken in giving Ketamine because it still had its own side effect. The marked side effect encountered when using Ketamine was emergent reaction (up to 17%) especially during recovery. Other side effect that had been documented was transient laryngospasm, apnea, hypersalivation, emesis, muscular hypertonicity and random movements in the patients during the sedation period (Dachs and Innes, 1997; Sobel *et al.*, 1999; Green and Krauss, 2004; Stoelting and Hiller, 2006; Green *et al.*, 2011).

Contraindication for ketamine are psychosis disorder (e.g. schizophrenia), age less than 3 month old, any procedures which involves oropharynx that will increase risk for laryngospasm, history of disease that predispose patients to laryngospasm

(e.g. tracheal stenosis, tracheomalacia and laryngeomalacia), condition that increase intracranial and intraocular pressure (e.g. brain tumour, hydrocephalus, glaucoma). Other relative contraindications for ketamine use are patients with thyroid diseases and porphyria (Kost and Roy, 2010; Green *et al.*, 2011).

For inducing sedation, Ketamine can be administered via intravenous and intramuscular route. In Procedural sedation and analgesia, the intravenous dose is 1-1.5mg/kg and intramuscular dose is 3-4mg/kg (Dachs and Innes, 1997; Green and Krauss, 2004).

Fentanyl

Opioid is a well-known analgesic and it has been used for century for that purpose. Multiple opiate agonists had been studied and synthesized since then in order to meet the demand of the modern medicine (Brownstein, 1993).

In the list of opioid agonist, Fentanyl (Figure 2.3) is one of the very potent opioid agonist that was produced on 1960 (Hess *et al.*, 1972; Stanley, 1992). It is a synthetic opioid that derived from the phenylpiperidine group (Chudnofsky *et al.*, 1989; Stoelting and Hiller, 2006).

Fentanyl was said to be approximately 100 times more potent than morphine as an analgesic (Drug Information Online Drugs.com; Stoelting and Hiller, 2006).

Fentanyl now is widely used in the ED, especially in PSA. This is due to its rapid onset and short duration of action. Via intravenous route, the onset is nearly intermediate (less than 30 second) and the analgesic effect can last up to 60 minutes

(Drug Information Online Drugs.com; Chudnofsky *et al.*, 1989; Krauss and Green, 2006; Lightdale *et al.*, 2008). These properties give it the advantages in ED in which the painful procedures can be done quickly and patients can recover faster and this will reduce the time of stay in ED. It also was proven to be safe for sedation and anaesthesia for adult and paediatric age group (Godambe *et al.*, 2003; Krauss and Green, 2006).

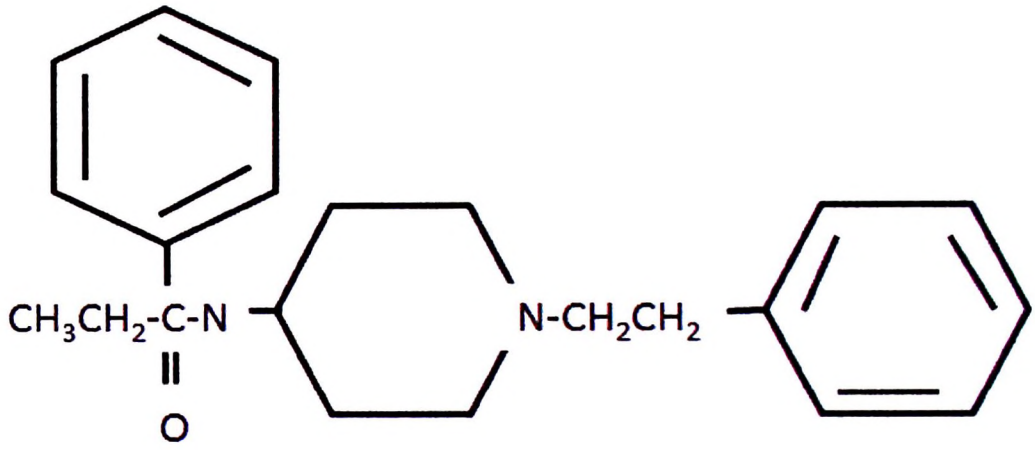

Figure 2.3: Fentanyl molecular structure (National Center for Biotechnology Information; Stoelting and Hiller, 2006)

In comparison with morphine, fentanyl does not cause the release of histamine and this made hypotension less likely with the usage of Fentanyl (Stoelting and Hiller, 2006).

Other advantage of Fentanyl is that, is readily reversible by the opioid antagonist in the circumstances of over dose and cardiorespiratory depression (Drug Information Online Drugs.com; Chudnofsky *et al.*, 1989; Stoelting and Hiller, 2006).

As like other opioid agonists, fentanyl binds to the opioid receptors (Mu, Delta and Kappa) in the central nervous system. It reacts predominantly on Mu receptor but it also has some effect toward Delta and Kappa receptors (DrugBank, 2011). These bindings will lead to inhibition of the release of nociceptor neurotransmitter and this produces a potent analgesic effect. The stimulation of the opioid receptors also gives fentanyl some sedative effect.

Fentanyl is highly protein bounded and it is metabolized in the liver and excreted in the urine as a metabolite and unchanged drugs (Stoelting and Hiller, 2006; DrugBank, 2011).

Contraindication for Fentanyl usage is patients with hypersensitive to the drug. Special precautions must be taken while administering Fentanyl to patients with increased intracranial pressure, bradyarrythmias, renal and liver impairment, mysthaenia gravis, hypothyroidism, elderly and neonates (Drug Information Online Drugs.com; MIMS USA, 2011).

As with other opioid drugs, side effects of Fentanyl includes, sedation, drowsiness, nausea and vomiting, cardiovascular adverse events (e.g: hypotension, bradycardia, cardiac arrest), respiratory depression and dependency. With high intravenous dose of Fentanyl, chest wall rigidity was reported (Vaughn and Bennett, 1981; Krauss and Green, 2006).

The usual dose of Fentanyl for an effective analgesia in the PSA is 1-2 mcg/kg and titrated to its effect (Kennedy *et al.*, 2004; Krauss and Green, 2006). With this dose, sedation effect of fentanyl is not obvious and adjunct sedative drugs have to be given (e.g Etomidate, Midazolam, propofol) (Di Liddo *et al.*, 2006; Chan and Ho, 2008).

3. RESEARCH OBJECTIVES

3.1. Research question

Are there differences in the induction time and safety between Etomidate and Ketamine in procedural sedation and analgesia (PSA) among children in Emergency Department (ED)?

3.2. Objectives

3.2.1. Primary Objective

To compare the sedation time between Etomidate versus Ketamine in the PSA among children in ED.

Outcome measured were:

1) Sedation time (T_1) – Time from the start of the administration of the research drugs (T_0) to the time when patient achieved Ramsay 4 sedation score **(APPENDIX E).**

3.2.2. Secondary objectives

1) To compare the safety between Etomidate and Ketamine used in PSA on subjects.

Outcome measurement based on adverse effect recorded **(APPENDIX A)**.

1) Respiratory (oxygen or ventilation problem)
2) Retching and vomiting
3) Cardiovascular (hypotension and bradycardia)
4) Abnormal movement (myoclonus, seizures etc)
5) Adverse event during recovery (paradoxic response) and unpleasant recovery experiences.
6) Permanent complications (neurological deficits or death)

3.3. Research hypothesis

3.3.1. Hypothesis

There were differences in sedation time and safety between Etomidate and Ketamine in PSA used in children.

3.3.2. Null hypothesis

There were no differences in sedation time and safety between Etomidate and Ketamine in PSA used in children.

3.4. Population

Paediatrics populations age from 2 years until 12 years old who need a procedural sedation.

4. METHODOLOGY

4.1. Study design

This was a prospective, single blinded, randomized controlled study, which conducted for period of 12 months from 1 June 2010 untill 31 May 2011.

The study was performed in Emergency Department Hospital Universiti Sains Malaysia (HUSM), Kubang Kerian, Kelantan. This is a teaching based Hospital and categorized as a tertiary medical center which received around 56,000 patients in year 2010 and nearly 13,500 of them was paediatric patients.

This study was approved by Research Ethics Committee (Human), Universiti Sains Malaysia. **(APPPENDIX B)**

4.2. Study Subjects

We enrolled 29 of paediatric patients age between 2-12 years old with various indication for PSA in HUSM Emergency Department, within the period of 12 months. All patients met the inclusion criteria and consented by their legal guardians and caregivers.

4.3. Study Protocol

4.3.1. Inclusion criteria

1) Children age 2-12 years old who consented by their legal guardian to participate in the study
2) Children ASA I-II **(APPENDIX C)**
3) All trauma patients with GCS 15/15.
4) All children age 2-12 years old who were indicated for PSA

4.3.2. Exclusion criteria

1) Children age 2-12 years old who did not get consent from their legal guardian to participate in the study
2) Children ASA ≥ III
3) All children with URTI and other cardiopulmonary disease.
4) All children with or suspected with renal and liver impairment.
5) All chthildren with history of allergy and contraindicated to any substance in study drugs.
6) All subject with GCS less than 15/15
7) All unstable subject.

4.4. Sample size calculation

Sample size calculation was calculated by Power and Sample Size Program version 2.1.31.

To compare the induction time and recovery time between Etomidate and Ketamine in the procedural sedation and analgesia:

Level of significant = 0.05

Study power = 0.8

Mean control = 1.6 minutes*

Standard deviation = 2.6 minutes*

We had done a study of a continuous response variable from independent control and experimental subjects with 1 control per experimental subject. In the previous study the response within each subject group was normally distributed with standard deviation 2.6. If the true difference in the experimental and control means is 1.6, we will need to study 42 experimental subjects and 42 control subjects to be able to reject the null hypothesis. Based on the study power of 0.8 and level of significant (alpha) of 0.05

*(Chan and Ho, 2008)

Estimated drop out 5% = 5 patients

Total sample size = 90 patients (45 each group)

4.5. Sampling method

This study was conducted in the Emergency department HUSM within 1 year duration from 1st June 2010 untill 31st May 2011. Paediatric patients who indicated for PSA and eligible for this study was invited to involve in the study and consent was taken.

4.6. Procedures/ Data collection

Patients who meet the criteria for the study were identified by the medical officers who work in the ED.

Full history and thorough examination were then carried out by medical officer/ investigator at the emergency department to determine whether the patients were suitable to be included in the study

For children who were suitable for the study, medical officer/investigator would asked the parents/ legal guardian for the consent (as required by ethical committee) to include the children in the study. **(APPENDIX D)**

Detailed of the study; procedures, study drugs and the aim of the study were explained to the parents/ legal guardian during the consent taking. The patients were then numbered and matched with the study drugs that had been randomized earlier.

Subsequently, patients were put in the resuscitation bed and standard vital sign monitoring (blood pressure, respiratory rate, heart rate, O_2 saturation) was carried out. (Figure 4.1)

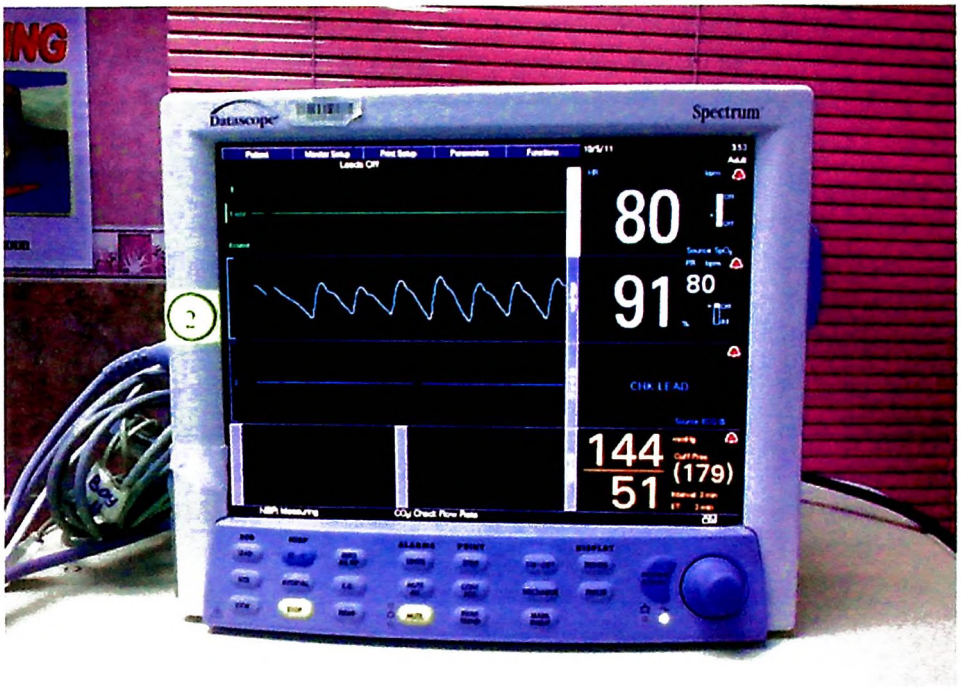

Figure 4.1: Device for vital sign monitoring (Datascope Spectrum)

The procedural sedation and analgesia was carried out in resuscitation zone (Figure 4.2) where emergency equipments recommended by the American Society of Anaesthesiology for the procedural sedation analgesia were easily available (Figure 4.3) (American Society of Anesthesiologists Task Force on Sedation Analgesia by Non-Anesthesiologists, 2002).

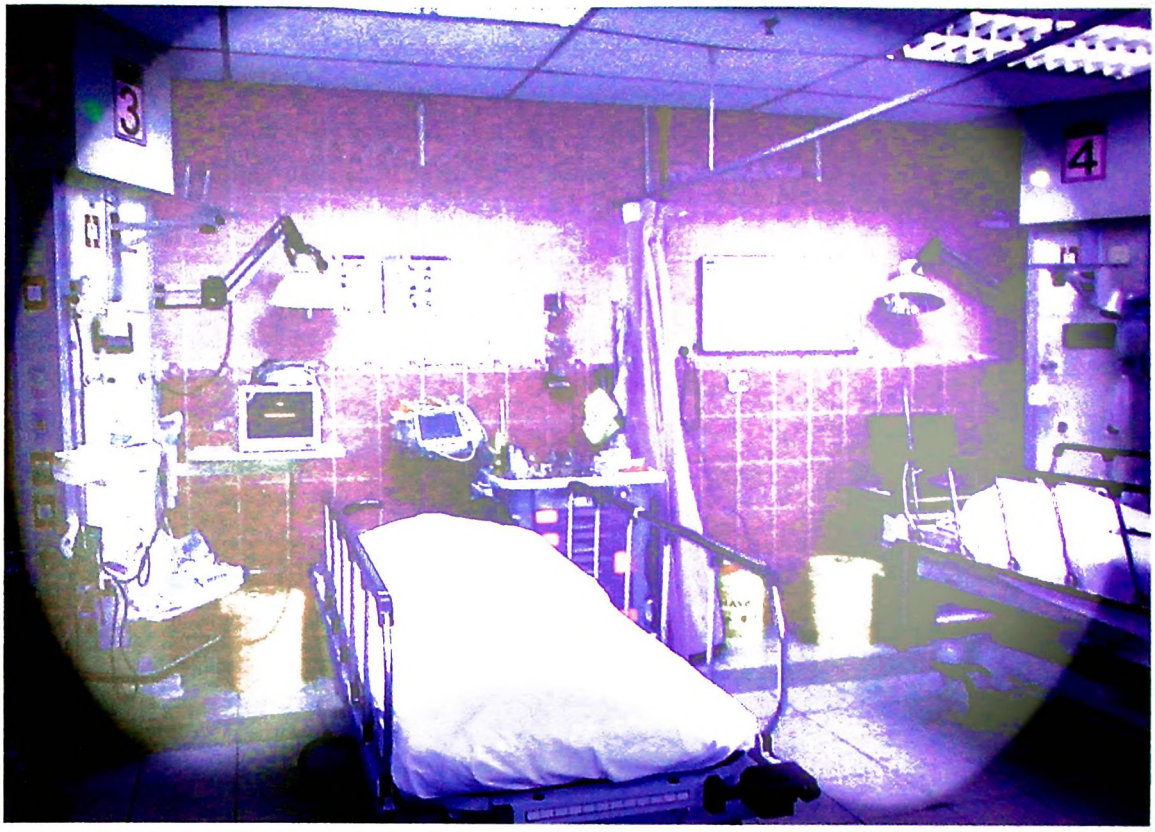

Figure 4.2: Resuscitation zone where PSA and procedures are performed

Figure 4.3: Resuscitation trolley and drugs in the resuscitation zone