COMPARISON OF EFFECTIVENESS AND SAFETY OF KETAMINE WITH MIDAZOLAM AGAINST HIGHER DOSE OF KETAMINE AS PROCEDURAL SEDATION FOR LUMBAR PUNCTURE IN PAEDIATRIC LEUKAEMIC PATIENTS

by

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LIST OF SYMBOLS, ABBREVIATIONS OR NOMENCLATURE

ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
ASA	American Society of Anaesthesiologists
BMA	Bone marrow aspiration
CSF	Cerebrospinal fluid
HUSM	Hospital Universiti Sains Malaysia
K2	Ketamine at a dose of 2mg/kg
kg	Kilogram
KM	Ketamine at a dose of 1mg/kg with midazolam at a dose of 0.1mg/kg
LP	Lumbar puncture
mg	Milligram
PSA	Procedural Sedation and anaesthesia
SPSS	Statistical Package for the Social Sciences
UKALL	United Kingdoms acute lymphoblastic leukemia protocol

ABSTRACT

MALAY VERSION

ENGLISH VERSION

ABSTRAK

OBJEKTIF: Untuk membandingkan keberkesanan dan keselamatan ketamine pada dos tinggi berbanding gabungan ketamine dan midazolam untuk prosedur tusukan lumbar pada kanak-kanak berpenyakit leukemia.

METODOLOGI: Sebanyak 29 orang pesakit leukemia telah menjalani pengambilan air tulang belakang di dalam “double blinded cross-over clinical trial”. Terdapat 2 kumpulan iaitu kumpulan yang menerima dos tunggal ketamine (2mg/kg berat badan) dan kumpulan yang menerima dos gabungan ketamine (1mg/kg berat badan) dengan midazolam (0.1mg/kg berat badan) . Kesemua ubat diberi secara intravena. Hasil utama yang dinilai ialah masa untuk mencapai pelalian yang dikehendaki (aras 6 pelalian Ramsay), jangka masa menyempurnakan tusukan lumbar, masa untuk pesakit sedar sepenuhnya (skor pemulihan Aldrete sekurang-kurangnya 8) dan kesan buruk ubat.

KEPUTUSAN: Dua puluh tujuh pesakit (93 peratus) telah berjaya telah mencapai pelalian dengan kedua-dua kumpulan dos. Purata masa untuk mencapai pelalian dan kembali sedar adalah lebih cepat dengan penggunaan dos tunggal ketamine (nilai $p < 0.05$). Purata masa untuk mencapai pelalian ialah 7.56 minit dengan dos tunggal ketamine berbanding 8.74 minit menggunakan dos gabungan KM. Purata masa untuk kembali sedar adalah 132 minit untuk rawatan K2 dan 173 minit untuk dos gabungan KM. Tidak terdapat perbezaan yang signifikan dengan masa yang diambil untuk menyempurnakan tusukan lumbar (nilai $p = 0.06$). Kesan buruk lebih kerap berlaku dengan dos tunggal K2 tetapi ianya tidak signifikan secara statistik (ujian McNemer

0.250). Lapan pesakit (30 peratus) yang menerima dos tunggal K2 dan tujuh pesakit KM (26 peratus) memerlukan dos tambahan ketamine.

KESIMPULAN: Dos tunggal ketamine 2mg per kg berat badan adalah selamat dan berkesan untuk prosedur tusukan lumbar pada kanak-kanak berpenyakit leukemia, walaubagaimana pun penambahan dos diperlukan. Pesakit perlu pemerhatian rapi semasa prosedur dijalankan.

ABSTRACT

TITLE: Comparison of effectiveness and safety of ketamine with midazolam against higher dose of ketamine as procedural sedation for lumbar puncture in paediatric leukemic patients

INTRODUCTION: Children with leukaemia undergo several invasive procedures. Sedation is used to make these procedures more comforting to the patient as it is necessary for successful outcome. However sedatives can have devastating effects. In our centre as well as others, combination of ketamine with midazolam has been used for years without specific protocol.

OBJECTIVE: To compare the effectiveness and safety of combination ketamine and midazolam against higher dose of ketamine as procedural sedation for lumbar puncture in paediatric leukemic patients.

METHOD: A total of 29 paediatric leukaemia patients underwent 58 lumbar punctures in a double blinded crossover clinical trial. The 2 regimes compared were KM regime who received combined intravenous midazolam 0.1mg per kg with ketamine 1mg per kg against K2 regime who received higher dose of intravenous ketamine i.e. 2mg per kg. The main outcomes measured were time to achieve the desired sedation (Ramsay level of sedation at 6), time to complete lumbar puncture, time to regain consciousness (Aldrete recovery score of at least 8) and adverse effects.

RESULTS: Twenty seven patients (93%) were successfully sedated with each of the regimens. Mean time taken for sedation and mean time to be fully conscious after sedation were significantly less (p value <0.05) in K2 regime. Mean time taken for sedation in K2 regime was 7.56 minutes (SD 4.4) and in KM regime it was 8.74 minutes (SD 3.6). Mean time to be fully conscious was 132 minutes (SD 93.5) for K2 regime while it took 173 minutes (SD 88.8) for patients in KM regime. There is no statistically significant difference in mean time taken to complete LP between the 2 regimes (P=0.06). Two patients in K2 regime developed tachycardia and one patient had pain after procedure while no patient in KM regimen had either of these. Five patients from either of the groups had desaturation. This was not statistically significant (McNemer Test 0.250) but it could be clinically relevant. Eight patients (30%) in KM regime required top-up doses of ketamine and 7 patients (26%) required top-up doses of ketamine in K2 regime.

CONCLUSION: Ketamine as a sole agent is as effective and safe as combination of midazolam and ketamine. It should be considered in procedural sedation for lumbar puncture in paediatric leukemic patients. It has faster induction and reversibility but it cause more adverse reactions and do not reduce time taken for lumbar puncture. An initial dose of 2mg per kg is safe to be used with another top up dose of 0.5mg per kg. Top up doses are frequently required.

INTRODUCTION

1. INTRODUCTION

1.1 Procedural sedation

Procedural sedation differs in its definition. American College of Emergency Physicians (2004) defined procedural sedation and analgesia (PSA) as a technique of administering sedatives or dissociative agents with or without analgesics to induce a state that allows the subject to tolerate unpleasant procedures while maintaining cardio respiratory function (Brown *et al*. 2005). Level of sedation and anaesthesia is categorized to mild, moderate, deep sedation and general anaesthesia. The level depends on type and degree of stimulation required by the subject to respond. Levels of sedation have been well defined and approved by the American Society of Anaesthesiologists (ASA) and House of Delegates in 1999 (Table 1). The airway, breathing and cardiac function are increasingly affected as the level of sedation and anaesthesia increases. The old term “conscious sedation” which is used in relation to moderate sedation has been discouraged but is still being used in classification of level of sedation and analgesia by ASA (1996). The degree at which a subject is sedated is a continuum. This continuum from mild to moderate, deep and finally into general anaesthesia widely varies. As the time after administration increases it can change from mild sedation to deeper levels without even adding further drugs or doses. Practitioners involved in sedating children should be aware of this continuum. They should be well prepared for any adverse reactions that might arise in the deeper levels of sedation. PSA is meant for moderate and deep sedation and not to extend into general anaesthesias (Innes *et al*. 1999).

Dissociative sedation is a term used to describe a trans-like cataleptic stage which provides sedation, analgesia and amnesia while airway protective reflexes are maintained including stable ventilation and cardiovascular status. Ketamine is an example of a drug that provides dissociative sedation where by in ketamine the continuum of sedation is not observed.

The ideal sedation end point would be one at which the procedure can be done with as little distress to the patient as possible. Here patient must have the protective airway reflexes and stable cardiopulmonary status.

Table 1. Continuum of depth of Sedation: Definition of General Anaesthesia and Levels of Sedation/Analgesia

	Minimal Sedation (Anxiolysis)	Moderate Sedation/Analgesia (Conscious Sedation)	Deep Sedation/Analgesia	General Anaesthesia
Responsiveness	Normal response to verbal stimulation	Purposeful response to verbal or tactile stimulation	Purposeful response after repeated or painful stimulation	Unarousable, even with painful stimulus
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Spontaneous ventilation	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained	May be impaired

Adopted from Anesthesiology 2002;96(4):1004-17

Paediatric oncology patients especially leukaemia patients must undergo several invasive procedures which can be quite painful. Procedural sedation and anaesthesia makes these procedures more comfortable to the patients. Procedural sedation is commonly performed outside operation theatre settings by non anaesthetists. The number of drugs that can be ideally used for sedation by non anaesthetists is limited and should be used with caution. However new drugs are being introduced and used by non anaesthetists and many are shown to be safe. In spite of common use of sedatives, still there is lack of specific guidelines for sedation to be followed in emergency departments as well as elective settings (Bhatt *et al.* 2010). Choice of sedatives is mostly used according to the experience of centres and those performing the procedures. The drug to be used and the depth of sedation required varies according to individual needs. Some patients need minimal anxiolytics while others require high sedation to control motor system as well. The reason for the lack of guidelines may be due to wide variability of patient conditions and pharmacokinetic and pharmacodynamic properties of the used drugs. There are conflicting evidence in terms of optimal route, dosage and drugs to be used for sedation. This has lead to wide variation in recommendations during PSA (Deasy and Babl 2010).

The effectiveness of sedation depends on many factors such as types of drugs, dosage, subject route of administration and others. Effective sedation is mandatory for these procedures to get the best outcome. PSA is intended to result in a depressed level of consciousness that allows the subject to maintain oxygenation and airway control independently. It minimizes the unnecessary adverse effects during sedation for various procedures such as lumbar puncture and bone marrow aspiration. Minimizing pain

allows patient to be less distress and more compliant to procedures. This allows treating doctors to perform the procedures more competently.

Despite the known advantages of the procedural sedation, children remain deprived of adequate sedation in fear of adverse side effects and myths related to it (O'Brien *et al.* 2003). In many circumstances pain is considered a normal response. Many practitioners assume that children do not feel pain and do not develop memories of these painful procedures. In the past because of these assumptions pain in children during procedures has been largely ignored. Pain as a subject has not got the attention in research until recently (McGrath and Hillier 1992) (Zeltzer *et al.* 1992). Some fear the continuum of sedation causing deeper level of sedation while others avoid prescribing drugs like opioids in fear that children may become addicted to it (Elliot *et al.* 1987). Inadequate analgesics make the child to suffer from pain. Every effort should be made to administer adequate sedation to comfort the child (Zempsky and Cravero 2004).

1.2 Leukaemia

Leukaemia is the most common malignancy in children accounting for one third of all malignancies in this age group. Incidence of leukaemia in United States and in United Kingdom is 12 to 15 per 100000 (Office for National Statistics of United Kingdom, National Institute of Health, United States). This has been quite static during the last decade. According to statistics of 2003-2005 from National Cancer Council of Malaysia, malignancies including leukaemia in paediatrics are increasing. Prevalence of leukaemia in Malaysia is not far different from Western countries (Sinnah *et al.* 1978). It is a major cause of morbidity and mortality in paediatric age group. Seventy six

percent of leukaemia in paediatric age group is acute lymphoblastic leukaemia and most of remaining is acute myeloblastic leukaemia (Xie, Davies 2003). Chronic myeloid leukaemia is rare in children. In Peninsular, Malaysia the incidence of acute lymphoblastic leukaemia is 433 per 100,000 population in age group between 0 to 19 years and that of acute myeloid leukaemia is 179 (National cancer registry, Malaysia 2003). Acute lymphoblastic leukaemia can be classified immunophenotypically into B and T cell type depending on cell surface cluster of differentiation. This classification is important in risk stratification. ALL B cell type are more common and have a better prognosis (O'Brien and Lacayo 2008).

Cancer has been on the rise in Malaysia. It is the fourth most common cause of death from medically certified deaths in general population of Malaysia (Lim 2002) after ischemic heart disease, road traffic accidents and strokes. Treatment of cancer in the country still has obstacles that hinder the treatment. These include poor insight of its severity, seriousness of the disease and its extensive management. Lots of taboos exist regarding cancer among the people including well educated individuals. Several websites are easily accessible advertising alternative methods of so called “natural medicine”. They do claim that health care system are been polluted with chemicals that are killing. These sites also claim that health insurance companies are biased in sponsoring only medical treatments and should be called prescribed medicine insurance rather than health insurance. Many believe cancer is not curable and treatments are not available. Lots of people fear the treatment and think that cancer treatments do more harm than benefit. Commonly patients default during the initial investigations and therapy. Some take the alternative treatment like traditional healers, “bomoh”, homeotherapy, food supplements and others. Many of them presents at late stage of the

disease following failure of alternative treatment. These customs and practices are common among people with different types of cancer (Leong *et al.* 2009).

Advances in cancer treatment leads to better prognosis. The five year survival rate has sharply increased over the last few decades (Gatta *et al.* 2005). One of the reasons is the availability of more effective drugs and new methods to deliver them (Hasle *et al.* 1995). Protocols of chemotherapy in HUSM for ALL patients have been adopted from United States Children's cancer group and AML from BFM study group. Lately both ALL and AML protocols were revised based on United Kingdom's ALL (UKALL) and AML protocol. Some studies show that prognosis in Malaysia for leukaemia is also quite similar to Western figures (Bosco and Teh 1995). A study done by Nasiruddin from HUSM in 2007, on 5 year survival in ALL treated in HUSM showed that it is comparable to developing countries like China (study done for dissertation and not yet published).

Paediatric oncology patients require several invasive procedures for diagnosis, staging, monitoring and treatment. These procedures include repeated venipunctures, administrations of fluids and medications, lumbar punctures and bone marrow aspirations. Many of them are invasive, painful and cause anxiety in children and caretakers who are already in stress from disease and its complications. With current protocols of chemotherapy for leukaemia, patients undergo an average of at least one lumbar puncture in each month depending on the phase of chemotherapy. Even though LP is a short procedure, it is invasive, painful and definitely causes anxiety. The stress related to LP is much higher compared to its invasiveness and pain. General acceptance of LP is very low in Kelantan (Malaysia) population especially among Malays (Ling

and Boey 2000). However it is better accepted by parents in cases of leukaemia. This could be because of severity of disease and importance of treatment. Patients, their families and treating paramedics are also stressed during LP (Santacroce 2002). The goal of procedural sedation is to sedate the subject to minimal effective duration so that the procedure can be done without causing pain while minimizing adverse events. Administering more drugs can prolong the sedation period and increase adverse events including time to keep subjects nil by mouth.

1.3 Lumbar Puncture

Lumbar puncture is a widely used medical procedure as a diagnostic as well as a therapeutic tool. Indication for LP varies according to clinical presentation. In the emergency department LP is mostly used as a diagnostic tool for meningoencephalitis. It is also useful in diagnosis of other conditions such as neurosyphillis and Guillain Barre' syndrome. Lumbar puncture is contra indicated when there is increased intracranial pressure, infection of the skin over the LP site, severe thrombocytopenia of platelet less than 50000 per microlitre and coagulopathy. Headache is common after LP. Vomiting and vertigo are other complications observed. It can also be complicated with diplopia, brain herniation, epidural, subdural and subarachnoid haemorrhage and meningitis.

Early central nervous system (CNS) involvement is often subclinical in leukaemia. Lumbar puncture (LP) is a diagnostic, preventive and therapeutic intervention for leukemic CNS involvement and relapse. Lumbar puncture is done to obtain cerebrospinal fluid and to administer intrathecal drugs. Cerebrospinal fluids are

evaluated for blast cells to look for CNS infiltration. Chemotherapy protocols for CNS infiltrated leukaemia are more extensive whereby more frequent intrathecal administrations of drugs are adopted. The other option in CNS infiltration is cranial irradiation which is markedly neurotoxic. Since intrathecal chemotherapy is as effective as irradiation in prevention of CNS relapse and much safer (Goldsby, Liu et al 2010), it is preferred over irradiation (Hasle *et al*. 1995), (Schrappe *et al*. 1998).

Cerebrospinal fluid is obtained with a needle inserted between lumbar vertebra L3 and L4. Spinal cord ends between L1 and L2. This space lies where an imaginary line connecting bilateral posterior iliac crests cross the spine. This space is very small in children. The procedure is even more difficult in obese children. Patient lies at lateral position with the back at the edge of bed. Plane of the back is perpendicular to the bed. Patient is held with supine flexed by tucking both knees to abdomen and slight neck flexion. This allows intervertebral space to be wider and more accessible. In bigger children LP can also be done in the sitting position. Unless children are not well sedated, they are difficult to position properly. Introduction into this small space must be precise to avoid hitting vessels and bone that gives a traumatic tap. Traumatic taps can introduce blast cells and organisms from blood into cerebrospinal fluid. Inadequate sedation is not acceptable because the procedure is painful. Operator may fail to perform the procedure because patient is uncooperative keeps moving due to inadequate sedation.

1.4 Statement of the problem

Ineffective sedation not only fails these procedures but also end in traumatic LPs. Multiple attempts during the procedure creates more anxiety to patient and parents. Failed attempts create a vicious circle making subsequent trials even more difficult. Patients will be punctured multiple times with many puncture sites and more pain. Management of leukaemia in each individual is a long course. It requires practitioners, patient and relatives to have a long and close relation between them. Failure of multiple attempts might badly affect the relationship between patient, parents and doctors. Our experience in the oncology ward where many medical officers are working chronic patients and relatives mark practitioners either 'good' or bad in terms of performing procedures. They look forward for the 'good' practitioners to perform procedures on them. Provider's skills and knowledge and how they communicate plays a major role in effecting relationship between patients, relatives and paramedics (Liu *et al.* 2008).

Traumatic LPs are a main concern in treating patients with leukaemia. Leukemic patients are immunocompromised. Even though rare it can introduce leukemic cells as well as pathogens from blood to a previously normal CSF (Rech *et al*. 2005). This can lead to meningitis and CNS infiltration requiring prolonged antibiotics or intensive chemotherapy which could have been prevented with proper sedation. Properly planned procedures and effective sedation helps in decreasing the adverse effects of these procedures (Keidan *et al*. 2005).

Sedatives can also cause unnecessary adverse effects. These are controlled drugs and their preparations are expensive. Currently in the paediatric oncology unit of

Hospital Universiti Sains Malaysia, 3 drugs are used as add on basis in procedural sedation. In order to achieve adequate sedation these three drugs are frequently required and at repeated doses. At the time of this study there is no written specific protocol for sedation to be used in paediatric haematology and oncology ward of HUSM. Safety and efficacy of used drugs are not specifically studied. In order to maintain safety of these procedures and to achieve maximum benefit from them evidence based written guideline is required. Regular and consistent training programmes of sedation should be undertaken for the operators involved (Babl *et al*. 2010).

Drugs used in PSA have sedative, analgesic and amnesic effects in reducing the state of awareness and eliminating perception of pain. The ideal drug is one that achieves sedation with lesser dose in a less time without having adverse side effects. These drugs may exert adverse side effects like hypoxemia, respiratory depression, major airway complications, hypertension, hypotension, bradycardia, poor perfusion, vomiting, prolonged sedation and death. Knowledge of these adverse events and close monitoring of the patients are the key for safety.

1.41 Current practice

Three sedative regimes are currently used in HUSM paediatric haematology and oncology ward. They are midazolam at 0.1mg/kg/dose, pethidine at 1mg/kg/dose and ketamine at 1mg/kg/dose. They are administered in additional aliquots as required. Atropine (0.01mg/kg/dose) is used in addition to antagonize the parasympathetic effects of ketamine. These preparations are made separately in different syringes and require few numbers of administrations. Multiple drugs and dosing consume more time and

human resources but also allow for more errors in drug administration, as it requires more calculations and preparations. The errors may arise regarding the drug or the dose. Time to regain consciousness would be prolonged when more number of sedatives is administered.

The choice of sedation depends on many factors. These include previous experience with specific drug to a particular patient including history of developing adverse reactions or effective sedation, condition of the patient, drug's ability to decrease patient's discomfort and induce amnesia.

In the paediatric ward of HUSM, mainly three drugs are used for procedural sedation. They are ketamine, midazolam and pethidine. Many centres outside Malaysia use other drugs for procedural sedation. These include drugs like propofol, fentanyl or mixture of ketamine with propofol (da Silva, *et al.* 2010, Haque and Fadoo Shah (2010), Erden *et al.* 2009). Others use inhaled gases like nitrous oxide (Ricard *et al.* 2009). Different routes that has been studied include per oral (Bhatnagar, *et al*. 2008) and parenteral methods. PSA can be used in elective as well as non elective procedures.

1.5 Objectives

1.51 Primary objective

Primary objective of this study was to compare the effectiveness and safety of combined intravenous midazolam with ketamine against a higher dose of intravenous

ketamine as the only drug in procedural sedation for lumbar puncture in paediatric leukemic patients.

Effectiveness of a drug is the ability of a drug to achieve the desired response from the patient. An adverse reaction is an undesired effect produced by a drug at standard doses (Goodman and Gilman, 2007).

1.52 Secondary objective

Secondary objectives were to compare the two regimens in terms of;

1. Time taken to sedate the patient; It was the time taken between administration of drug (s) (including flushing with normal saline) and time to achieve sedation level by Ramsey Score of 6
2. Time to complete procedure; It was the time taken between administrations of drug (s) (including flushing with normal saline) until completion of obtaining CSF.
3. Time to regain consciousness after sedation; It was time taken between administration of drug (s) (including flushing with normal saline) to regain consciousness by Aldrete score of at least 8.
4. Rate of adverse reactions

1.6 Research protocol

A randomized cross over clinical trial was conducted in paediatric leukemic patients. Two regimens were compared as mentioned in the chapter of subjects and methods.

1.7 Study site

This study was approved by Research Ethics Committee (Human) of Hospital Universiti Sains Malaysia (HUSM), Kelantan, Malaysia (Ref; USMKK/PPP/JEPeM ((209.3. (09)). It was conducted in paediatric haematology and oncology ward, HUSM. The study period was from 1st of June 2009 to 31st December 2010.

Universiti Sains Malaysia (USM) is one of the 4 postgraduate research universities in Malaysia. It was established in 1969 as the second university in the country and had expanded into more than 20 schools with 13 research centres where more than 20,000 students had being enrolled. The health campus of USM was established in the state of Kelantan as a distant branch in 1983. Kelantan is one of the 14 states of Malaysia situated at East Coast of Peninsular, Malaysia. Its population is multiracial but majority are Malays. HUSM is a teaching hospital in the health campus. HUSM is one of the two government hospitals in Kelantan that cater for a population of more than 1.6 million people. Ministry of Higher Education of Malaysia chose USM to implement the Accelerated Programme for Excellence (Malaysia's first APEX University) in 2008 because of its development and readiness for changes. It is the referral centre for oncology in Kelantan as well as east coast of Malaysia. HUSM

managed various types of cancers in children and adults. The services provided include diagnostic workup and management including chemotherapy, radiotherapy and surgical interventions. These services have been available for more than 20 years.

1.8 Literature review

Many studies are available regarding procedural sedation and anaesthesia in paediatric population. Majority are been done in emergency department for management of trauma and foreign bodies. Data are also available regarding sedation from paediatric oncology settings.

1.81 Ketamine

Ketamine is a derivative of phencyclidine. It was first used in 1965. Since then it has been used for anaesthesia in human as well as in animals. Ketamine has been thoroughly investigated in different clinical trials during the last two decades. There are thousands of references available in Pubmed® database. Dr John Lilly (1915-2001) was a world known American physician who experiment ketamine on himself for his migraine which he found to be relieved by regular use. Ketamine also is being largely abused as a recreational drug. Karl Jansen in his book titled as “Ketamine: dreams and realities” has described in detail about its abuse and dangerous effects.

Ketamine is a special sedative that acts as a dissociative anaesthetic. Unlike other sedatives, it does not have the continuum in its course of sedation. It separates limbic system from thalamoneocortical system so that external stimulus like pain cannot

be felt. The dissociative state does not cause respiratory depression and airway compromise. It is a non competitive N-methyl d-aspartate receptor (NMDA-R) antagonist. It alters amino acid synthesis and interferes with function of excitatory amino acids such as aspartate and glutamate (Ricci *et al.* 2010). These amino acids play a significant role in analgesia, memory and learning (Muir 2010). Ketamine also binds to opioid receptors. It produces a trancelike cataleptic state, analgesia, sedation and amnesia.

Half life of ketamine is only 10 to 15 minutes but the metabolites of ketamine lasts for another two and half hours. In humans ketamine is metabolized to norketamine and dehydronorketamine. The latter is the main metabolite. The isomer (S) of norketamine has a significant clinical activity which is comparable to ketamine that can abolish pain (Ebert *et al*. 1997). Ninety percent of metabolites are excreted br renal and the rest by fecal route. Less than 5% is excreted unchanged in urine.

Ketamine has been used widely in paediatric anaesthesia for different procedures with relatively safe history. But its use is not as common as expected (Babl, Belousoff *et al*. 2010). Ketamine is best to used for a short sedation. These include minor surgical procedures, lumbar punctures and bone marrow aspiration (Sibley, Mackenzie *et al* 2009). Ketamine also has been used in clinical settings other than sedation. This includes management of bronchial asthma (Strube and Hallam 1986) and psychiatric disorders such as majoor depression with risk for suicide in adults (Price *et al.* 2009).

When ketamine is used for sedation, it causes short term adverse effects. These include increased intracranial pressure and emergence phenomenon like vivid dreams, visual images, hallucinations and delirium. Ketamine also cause increase in intraocular pressure, tachycardia, hypertension, vomiting, slurred speech, and disorientation. Hallucinations are rare in paediatric age group. These events usually occur after peak sedation. Long term adverse effects of ketamine due to recurrent use in subsequent number of sedation are not well documented in literature. Short term adverse effects are dose related. Children undergoing ketamine should be closely monitored to prevent these adverse events (Kruger 1998).

Respiratory drive and air way protective reflexes are preserved when given intravenously at doses of 1.5 to 2mg/kg (Evans *et al.* 2005). Ketamine can be titrated in incremental doses and they are safer than large bolus doses. Some studies mention regarding cumulative risk profile especially in patients with renal and liver failure (Acworth *et al.* 2001). It also maintains blood pressure by releasing catecholamine and may act as a bronchodilator. This is beneficial in patients with low blood pressure and bronchial asthma.

Hypersecretion of saliva is commonly observed after ketamine administration. This can be decreased by anticholinergic drugs such as atropine. Ketamine also increase sympathetic activity. It should be cautiously used in patients liable to sympathetic activity such as increased intracranial and intraocular pressure which might be present in leukemic infiltration in such tissues. Emergence delirium is very rare in children but a more pleasant emergence phenomenon is more common in this age group (Treston *et al.* 2009). Other adverse reactions include nystagmus, agitation, vomiting and myoclonus. Unfortunately ketamine does not have an antidote.

Olney's lesions were described in rat's brain when ketamine were used in continuous infusion over around 6 hours (Young *et al.* 2005). These lesions were vacuoles found in the neurones of brain when NMDA receptor blockers such as ketamine were used. It is an irreversible injury which is associated with high mortality. Whether this is true in humans has not been proven as it requires highly invasive methods such as brain biopsy for its evaluation. Indirect methods looking for Olney's lesions do not show any evidence of these lesions. What is known is that ketamine do have neurological disturbances in acute phase but clinically there were no permanent changes described.

Ketamine interacts with many other drugs especially sedatives. These include sedatives such as benzodiazepines, opioids and barbiturates. When ketamine is added it enhances the sedative effects of these drugs.

Current literature revealed ketamine used intravenously at a dose of 2mg/kg/dose as a sole agent is effective and safe for sedations in lumbar puncture and bone marrow aspiration done in paediatric oncology units and emergency department (Afzal M. Sheikh 2004, Ricard *et al.* 2009). Ketamine also reduces anxiety related to these interventions because of its effectiveness (Ricard *et al.* 2009). Ketamine has been used in paediatric emergency departments safely with minimal adverse reactions such as vomiting, adverse behaviours such as anxiety and sleep disturbances (McQueen *et al.* 2009). However intravenous ketamine as a single drug for procedural sedation has not been studied as a comparison against intravenous midazolam alone or in combination with ketamine. To my understanding at the start of this study no study has been done to evaluate the effectiveness and safety of our current regimen used in HUSM and there is no similar study like this study. Likewise revision of PSA in many centres also shows

lack of proper guidelines (Borland *et al.* 2009). We need to develop an effective and safe protocol for PSA which adopt least number of drugs and doses.

Ketamine can be administered by different routes. Each route has different recommended doses. When given by intravenous route its action lasts for less than an hour. Ketamine also has been tried with oral and intramuscular route with success (McGlone *et al.* 2004, Bhatnagar *et al.* 2008). Per rectal administration of ketamine gives enough analgesia but minimal anaesthetic effect (Pedraz *et al*. 1989, Heinrich *et al.* 2004). Sublingual lozenges have also been shown to have comparable analgesic effect (Chong *et al.* 2009). Maruf and Hossain compared (n= 120 patients) giving intravenous ketamine at a dose of 1.5mg/kg with diazepam against combination of midazolam and fentanyl. The drug was given for deep sedation by anaesthetists during magnetic resonance imaging. Sedation was successful in all patients. In the 60 patients who received ketamine with diazepam there were minimal inconveniences recorded without adverse effects on vital signs including respiration (Maruf *et al*. 2010).

Trials have been done in studying the effect of ketamine and midazolam on sedation given in different procedures. Many of them were done in emergency departments. Some studies used ketamine alone intravenously. Afzal assessed degree of sedation and analgesia with needle prick. He also recorded adverse reactions (Afzal. 2004). Pruitt compared intramuscular ketamine with intramuscular midazolam during repair of facial injuries in emergency department (Pruitt *et al.* 1995). Pruitt's results show ketamine is safe and effective to be used. His study also showed midazolam decrease dysphoria associated with ketamine. Ketamine also has been studied in

epidural analgesia in post operative patients. The study showed significant decrease in pain and use of extra analgesic doses in ketamine group (Chia, Liu 1998). Low dose ketamine has been studied combined with very low dose of midazolam and additional aliquots of them in paediatric sedation in emergency department (Bleiberg *et al.* 2007). Bleiberg used midazolam intravenously at a dose of 0.05mg/kg with ketamine 0.5mg/kg as a starting dose with additional aliquots. It showed 44 percent of patients were effectively sedated with a dose of 0.75mg per kg of ketamine.

1.82 Midazolam

Midazolam is a water soluble benzodiazepine. It was produced in 1975. It has been used widely as a sedative agent in paediatrics during the last 2 decades. Midazolam has been used in many elective as well as emergency procedures by anaesthetists and non anaesthetists with quite a good safety record (Munro and Machonochie 2007).

Midazolam has sedative, hypnotic and amnesic properties without analgesic role. These effects vary with the patient's age, weight, clinical condition and route of administration. It can be given by intranasal (Chiaretti *et al.* 2011), sublingual (Kattoh *et al.* 2008), bucal, oral (Wan *et al.* 2006) rectal and intravenous routes. It is widely distributed and cross blood brain barrier. It is very safe when used alone but in combination with other sedatives it might increase the risk of respiratory depression. Midazolam can provide deep sedation. When given intravenously the peak action is reached at 5 to 10 minutes and lasts for one to five hours. Ninety seven percent of the

drug is bound to protein. Extensive hydroxylation occurs in the liver. The primary metabolite is alpha-hydroxymidazolam. It has equivalent potency as midazolam. Most of midazolam is recovered in the urine. Metabolites are conjugated by the liver with subsequent renal excretion. Amount of drug that is excreted unchanged in the urine is non-significant (Ariano RE 1994).

Midazolam has been used effectively in many procedures including in and outside hospital care. These include dental procedures (Wan *et al.* 2006) and cardioversion (Notarsetefano *et al* .2007).

Adverse effects of midazolam include respiratory depression, hypoxia, hypotension, vomiting, myoclonic jerks, excessive drooling, paradoxical excitatory reactions, allergy, nystagmus, drug interactions, withdrawal effects and tolerance (Acworth *et al.* 2001), (Deitch *et al.* 2007), (Hohl *et al.* 2008). Relative contraindications of midazolam include shock and brain injury and should not be used in hypersensitivity to midazolam.

The advantage of midazolam is that flumazenil can be used effectively as an antidote. In the early days flumazenil has been used not only in emergency reversal of midazolam effect but also after the procedure to revive the patient from sedation. This practice was not proven of use and the recommendation in the literature is not to use it as routine for revival (Lewis)

Sedation caused by midazolam is a continuum from mild sedation to general anaesthesia. Patients should be intensively observed. There should be a different

individual other than the person who is performing the procedure to monitor patient's cardiorespiratory status. Failure to recognize worsening of cardiorespiratory status can lead to severe hypoxia, hypoxic encephalopathy and death.

Midazolam has been used for procedural sedation for short procedures such as lumbar puncture and bone marrow aspiration. It is superior to diazepam because of faster sedation and early recovery. This increases compliance with patient and parent satisfaction. It has also being seen that midazolam is safer in children than adults (Rosen and Rosen 1998).

Midazolam is usually used in combination with other drugs for PSA. As mentioned above Maruf has shown that combination of midazolam with fentanyl is safe but combination of ketamine with midazolam is more economical (Maruf, Hossain *et al.* 2010). Combination of midazolam and ketamine by oral and intramuscular route has been compared during sedation for minor surgical procedures. In this study both routes has been found to be effective and safe (Bhatnagar *et al.* 2008). Intranasal midazolam has been studied against intravenous ketamine with midazolam. The combined intravenous midazolam and ketamine is more superior to intranasal midazolam as a sole agent (Acworth *et al.* 2001).

In a clinical appraisal looking at safety and effectiveness of ketamine and midazolam for sedation in emergency department, it has been shown that both were safe and effective but ketamine was preferred by physicians and parents (Munro and Machonochie 2007).

1.83 Atropine

Atropine is an anticholinergic. It antagonizes muscarinic actions of acetylcholine. In our setup atropine has been routinely used with ketamine in view that it reduces cholinergic effects of ketamine such as increased salivation and vomiting (Arnett *et al.* 1984).. Atropine is generally used in medicine for organophosphate and nerve gas poisoning.

A randomized placebo controlled double blind study (n=83) has shown a significant reduction of hypersalivation and vomiting after atropine administration following ketamine anaesthesia (Heinz *et al.* 2006). Other studies did not show enough evidence to support for atropine use in all cases of ketamine sedation (Brown *et al.* 2008). Atropine can cause increase in heart rate and augments the positive pulmonary function of ketamine (Magoon *et al.* 1998).

Glycopyrrolate which is a mucuranic anticholinergic reduce secretion from salivary glands, tracheobronchial and pharynx. It has been compared with atropine. Unlike atropine it does not cross the blood brain barrier. Glycopyrrolate cause less tachycardia compared to atropine (Toft and Romer 1987). Glycopyrrolate is never been used for this purpose in our unit as a substitute for atropine.

Adverse effects of atropine include a transient rash (Heinz *et al.* 2006) tachycardia, photophobia, fever (Garg and Sinha 2008) and dryness of mouth. Contraindications include previous hypersensitivity to the drug.

METHODOLOGY

2. SUBJECTS AND METHODS

This study was approved by Research Ethics Committee (Human) of Hospital Universiti Sains Malaysia on 08th April 2009 (Ref; USMKK/PPP/JEPeM ((209.3. (09)). It was conducted in accordance to guidelines on Good Clinical Practice. The study site was paediatric haematology and oncology ward, HUSM. The study was conducted from 1st of June 2009 to 31st December 2010. Study was supervised by paediatrician in oncology unit, paediatrician in pharmacology unit and anaesthetist.

2.1 Subjects

2.11 Inclusion criteria;

The following patients were included in the study:

1. Leukemic patients aged between 6 months to 16 years old
2. Requires 2 LPs in a 4 weeks interval in the treatment protocol
3. Consented patient / parent

2.12 Exclusion criteria

The following list of patients was excluded from the study. These conditions were selected to avoid high risk patients. They also might interfere with sedation and cause bias in the results.

1. Patients undergoing BMA in the same setting before the LP
2. Patients with relapse of leukaemia
3. Any structural obstruction to airway