A Pilot Study on Procedural Sedation

Among Adult Patients

at

Emergency Department HUSM, Kelantan

Comparing

Fentanyl with Midazolam versus Fentanyl with Propofol

By

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LIST OF ABBREVIATION

$EtCO_2$	=	End tidal Carbon Dioxide
ETT	=	Endotracheal tube
HUSM	=	Hospital Universiti Sains Malaysia
HR	=	Heart rate
RR	=	Respiratory rate
SPO_2	=	Oxygen saturation
iqr	=	Interquarter range
BP	=	Blood pressure
IV	=	Intravenous
ED	=	Emergency Department
PCO_2	=	Partial pressure of Carbon Dioxide
SBP	=	Systolic blood pressure
DBP	=	Diastolic blood pressure
MAP	=	Mean Arterial Pressure
sd	=	Standard deviation

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ABSTRACT

A pilot study on procedural sedation among adult patients at Department of Emergency Hospital Universiti Sains Malaysia Kelantan. A comparison between fentanyl with midazolam and fentanyl with propofol.

Introduction

This is a pilot study looking at the safety and effectiveness of procedural sedation technique carried out at the Emergency Department (ED) HUSM Kelantan over a period of one year extending from December 2004 to December 2005. In other words, there were no study has been carried out before to compare the effectiveness and efficacy of using midazolam and propofol for any brief, intense procedures in ED setting. With this study, the standard drugs used and the measures during procedural sedation can be applied in all emergency departments.

Objectives

The objectives are:

1. to compare the safety and efficacy between a combination of fentanyl and propofol with fentanyl and midazolam;
2. to observe outcomes in subjects undergoing a procedure at the ED when they are under procedural sedation. These outcomes include the blood pressure, mean arterial pressure, respiratory rate, heart rate, oxygen saturation, end tidal carbon dioxide and duration to regain full consciousness after the procedural sedation.

Methodology

Fourty patients were needed for its significant evaluation in this study. They were randomly selected using the computer generated random permuted blocks of four patients. 20 patients were grouped together as A and the remaining 20 patients as group B. Drugs used were single blinded to prevent any biasness. Drug A represents proporfol while drug B represents midazolam. The procedures involved include, orthopaedic manipulation such as reduction of fractures, reduction of dislocated joints, abcess drainage, toilet and wound debridment, laceration wounds repaired and cardioversion.

These subjects were monitored for their vital signs and end tidal carbon dioxide every ten minutes till the procedure is completed. The duration of recovery were documented when the subjects had completed the procedure until regaining a full consciousness or recovery. Patients were continued to be monitored at the observation ward before being discharged home or admitted to the respective ward. These findings were analysed using Mann-Whytney U statistical analysis.

Result

Majority of patients under study were represented by Malays and 75.6% were males. The youngest subject was 13 years old while the oldest was 78 years of age with the mean age of 37.8 years.

None of the patients developed any complication while under procedural sedation. Both propofol and mizadolam were found to be not significant (p value > 0.05) in outcomes as follow:

1) Blood pressure
2) Mean Arterial pressure
3) Heart rate
4) Respiratory Rate
5) Oxygen saturation
6) End tidal CO_2

This study also found that patients who received propofol (mean 29 ± 11.03) regained full consciousness at a much faster rate when compared to midazolam (mean 71.75 ± 60.63), p value < 0.001, better choice of drug to be used in the ED setting for procedural sedation.

The recommended dose for propofol to be used for procedural sedation at the ED setting is 1mg/kg as a bolus dose followed by 0.5mg/kg if required in a titrating dose while for midazolam the recommended dose is 0.1 mg/kg as a bolus dose followed by 0.1mg/kg if needed in a titrating dose.

Capnograph has proven to be a very sensitive instrument to detect early sign of hypoventilation and is strongly recommended to be used when procedural sedation is performed at the ED setting.

Conclusion

This pilot study has proved there were no difference between the studied drugs midazolam and propofol during procedural sedation. Instead, propofol has shown to be more efficacious and shortened the recovery time for patients to regain full consciousness.

These two drugs can be used as procedural sedation agents in ED for various short intense painful procedures.

Key words: Procedural sedation; Midazolam; Propofol; Emergency department

ABSTRAK

Kajian awal mengenai "procedural sedation" ke atas pesakit dewasa di Jabatan Kecemasan Hospital Universiti Sains Malaysia, Kelantan. Membandingkan keberkesanan di antara gabungan ubat fentanyl dan midazolam dengan fentanyl dan propofol.

Pengenalan

Kajian ini merupakan satu kajian awal untuk melihat tahap selamat dan keberkesanan teknik "procedural sedation" yang dijalankan di Jabatan Kecemasan (ED) HUSM Kelantan selama setahun bermula dari bulan Disember 2004 hingga Disember 2005. Dengan lain perkataan, tiada kajian telah dibuat sebelum ini tentang perbandingan keberkesanan antara ubat midazolam dengan propofol untuk digunakan di jabatan kecemasan. Dengan penemuan kajian ini, suatu ketetapan ubat-ubatan dan tatakerja di dalam teknik procedural sedation boleh dimulakan di semua jabatan kecemasan.

Objektif

Kajian awal berbentuk ini bermatlamat untuk :

1) membandingkan tahap selamat dan keberkesanan di antara fentanyl dan propofol dengan fentanyl dan midazolam;
2) mengkaji kesudahan kesan seperti tekanan darah, kadar pernafasan, kadar denyutan jantung, purata tekanan arteri (MAP), ketepuan oksigen, nilai

akhiran karbon dioksida dan jangka masa yang diambil untuk pesakit kembali sedar sepenuhnya selepas "procedural sedation" tamat.

Tatacara kajian

Seramai 40 orang pesakit telah menyertai kajian ini di mana mereka di pilih secara rawak berkomputer dengan blok empat pesakit. Mereka kemudiannya dibahagi kepada dua kumpulan iaitu 20 orang di dalam kumpulan A dan 20 orang lagi di dalam kumpulan B. Ubat-ubatan yang dipilih disesuaikan secara tutupan satu (single blinded) bagi menghindari kecenderungan atau bias. Ubat A mewakili propofol manakala ubat B adalah midazolam.

Rawatan yang memerlukan "procedural sedation" ini termasuklah manipulasi ortopedik seperti pembetulan tulang patah, pembetulan sendi yang teralih, kardioversi, perawatan luka yang parah, menjahit luka dan merawat bengkak yang mengadungi nanah.

Tekanan darah, kadar pernafasan, kadar denyutan jantung, purata tekanan arteri (MAP), ketepuan oksigen dan nilai akhiran karbon dioksida didalam pernafasan setiap pesakit diawasi, setiap sepuluh minit sehingga tamat tatakerja. Jangka masa pesakit kembali sedar sepenuhnya juga telah direkodkan.

Setiap pesakit yang telah selesai menjalani rawatan semasa procedural sedation akan terus diawasi di wad pemerhatian sebelum dibenarkan pulang ke rumah atau dimasukkan ke wad-wad tertentu.

Data-data yang telah diperolehi telah dianalisa menggunakan "Mann-Whitney U analysis".

Keputusan

Kajian ini telah didominasi oleh pesakit Melayu dan 75.6% daripada subjek adalah lelaki. Pesakit termuda di dalam kajian ini berusia 13 tahun manakala subjek tertua pula berumur 78 tahun dengan purata umur adalah 37.8 tahun.

Tiada subjek pesakit di dalam kajian ini telah mengalami sebarang komplikasi semasa di bawah teknik "procedural sedation". Perbandingan antara propofol dan midazolam didapati tiada signifikasi (p value > 0.05) di dalam penemuan berikut:

1) Tekanan darah
2) Purata tekanan arteri
3) Kadar denyutan jantung
4) Ketepuan Oksigen didalam darah
5) Kadar pernafasan
6) Nilai akhiran karbon dioksida didalam pernafasan

Kajian ini juga menunjukkan pesakit yang menerima propofol (purata 29 ± 11.03) pulih dari kesan "procedural sedation" lebih cepat berbanding dengan pesakit yang menerima midazolam (71.75 ± 60.63), yang mana menjadikan propofol lebih sesuai digunakan di jabatan kecemasan.

Dos propofol yang disyorkan berkesan dalam teknik "procedural sedation" di jabatan kecemasan adalah sebanyak 1mg/kg sebagai dos "bolus" diikuti oleh 0.5mg/kg bila diperlukan manakala bagi midazolam dos yang disyorkan adalah sebanyak 0.1 mg/kg dos "bolus" dan 0.1mg/kg bila diperlukan.

Capnograph adalah alat yang sensitif di dalam mengesan tanda awal "hypoventilation" dan ditekankan penggunaannya di jabatan kecemasan apabila "procedural sedation" dijalankan.

Rumusan

Kajian ini telah menunjukkan tiada perbezaan di antara ubat midazolam dengan propofol ke atas procedural sedation. Malah kajian ini menunjukkan propofol lebih baik kerana pesakit mengambil masa yang begitu singkat untuk kembali sedar sepenuhnya

Secara am kedua-dua ubat ini, midazolam dan propofol adalah selamat untuk digunakan di jabatan kecemasan.

Kata kunci: Procedural sedation; Midazolam; Propofol; Jabatan kecemasan

1. INTRODUCTION

Patients attended the emergency department for any forms of trauma and critically ill conditions frequently presented with physical or mental pain and agitation. These stresses may be associated with tremendous neuro-humoral elevation of plasma catecholamine, cortisol, glucose, antidiuretic hormone and acute phase protein levels. These elevations can cause significant tachycardia, hypertension, vasoconstriction, increase oxygen consumption, blunting of immune response, salt and water retention. In addition to that these patients are extremely anxious.

During these critical situations, a procedure may be indicated and such patient would be subjected to some forms of chemical induction to facilitate the procedure planned to either save their lives or salvage the remaining functioning organs or limbs. A collective decisions need to be made to choose the most appropriate form of chemical induction for the purpose of analgesia or sedation which most of the time patients would receive the latter.

The superiority of one of these drugs and the lack of potentially dangerous adverse reactions would determine the appropriate choice of such drug to be recommended at the emergency department setting.

In addition to that this study was also intended to evaluate the importance of using a capnograph routinely at the emergency department when procedural sedation is delivered. It is also hope that with the findings derived from this pilot study it would generate further interest to expand such study into a larger scale thus enable the relevant data to be used in making appropriate and relevant recommendations for procedural

sedation to be made as one of the techniques to be practiced widely in all emergency departments in hospitals throughout Malaysia.

A standard protocol could then be developed while the existing clinical guidelines practice may need to be reviewed to broaden the scope of procedural sedation in emergency and outpatient settings.

2. LITERATURE REVIEW

There are various levels of sedation that could be induced during a procedure as classified by the Joint Commission on the Accreditation of Healthcare Organization (JCAHCO, 2001). These include the followings:

a) Minimal sedation or anxiolytic.

Patient who received minimal sedation responds normally to verbal commands. The cognitive function may be clinically impaired but ventilatory and cardiovascular functions are unaffected.

b) Moderate sedation or analgesia

This level is also known as conscious sedation which is characterized by patient being purposefully responsive to verbal command regardless whether there is tactile stimulation. Spontaneous ventilation is adequate and cardiovascular function is maintained.

c) Deep sedation or analgesia

Patient is not easily aroused but responds purposefully to painful stimulation. At this level, the patient may not be able to maintain a patent airway but spontaneous ventilation may be adequate. Cardiovascular function is usually maintained.

d) Anesthesia

Comprises of general anesthesia and spinal or major regional anesthesia. It does not however include local anesthesia. At this level patient may not be aroused even by a painful stimulation. The patients often require some

assistance in maintaining a patent airway and positive pressure ventilation. Cardiovascular function may be impaired.

The level of sedation achieved by a patient could not be adequately assessed especially when the assessment is being carried out by inexperienced doctors. The subjective clinical assessment is also regarded unreliable (Bell at al. 2004). This could lead to some challenge particularly when an urgent procedure is required to be carried out. One way to resolve this problem is to rely on an accurate assessment using a specific tool. Modified Ramsay Scale (Table 1.1) for example, has been used widely to assess the level of sedation in a patient.

Table 1.1: Modified Ramsay Scale

State of patient	Score
Anxious, agitated, restless	1
Awake, cooperative, orientated, tranquil	2
Semi-asleep but responds to commands	3
Asleep but responds briskly to glabellar tap or loud auditory stimulus	4
Asleep with sluggish or decreased response to glabellar tap or loud auditory stimulus	5
No response can be elicited	6

Ref: Modified Ramsay Scale: 1974

One of the approaches that are getting more popular of late is using a technique known as procedural sedation. It is a moderate level of sedation and is the preliminary stage before a patient goes into a stage of deep sedation and eventually achieved a state of general anaesthesia (Lazear, 1999). The Joint Commission on the Accreditation of Healthcare Organization (JCAHO, 1998) has defined procedural sedation as "a state of minimally depressed level of consciousness in which the patient retains the ability to independently and continuously maintain a patent airway and responds appropriately to physical and verbal stimuli". This simply means that a patient who has been given procedural sedation should experienced drowsiness but arousable and is able to follow commands.

The main goals of procedural sedation and analgesia are to give patients some relief from both pain and anxiety. In addition to that this technique has clinically shown to be effective in reducing the stress response and improves patient's compliance to undergo a procedure.

In general, procedural sedation should be accompanied by analgesia simply because analgesia is able to potentiate the effect of sedatives. This could result in the low requirement to use sedatives.

The use of procedural sedation has generated much interest and debate despite this technique has been widely practiced in many settings which previously regarded to be of anaesthesiology domains (Lazear, 1999).

Procedural sedation offers many advantages. Firstly patients are able to maintain the consciousness while undergoing an unpleasant procedure. Their tolerance to such painful procedure made them able to cooperate with the care providers thereby increase

the compliance further. Beside that, this technique did not disrupt much of the patient's daily activity. Upon discharged from the hospital such patients could resume their job and daily activity within a relatively short period of time with minimal discomfort (Lazear, 1999). Furthermore, children who have subjected to procedural sedation were found to require minimal physical restraint when undergoing a procedure making it a very child friendly technique.

Interestingly, most patients receiving procedural sedation would not recall the procedure carried out and wake up in a comfortable and composed state without significant physical and psychological insults thus making such approach an appropriate choice to be used in other settings such as the Emergency Department and outpatient setting. Moreover procedural sedation allows patient to return to their pre sedation state without much risk of going into re-sedation.

Finally, as more nurses and care providers are currently being trained in administering sedatives, procedural sedation could be safely carried out by them which could eventually minimize the inpatient hospital charges. Smith in his study with cardiac patients undergoing a six hour procedure has found a significant reduction in cost as compared to sedation administered by an anaesthesiologist (Smith, 1997). A shorter recovery times and rapid return to the pre sedation state would require a much less expensive nursing care and short duration of hospitalization (Lazear, 1999). This makes it a very suitable technique to use in developed and developing countries.

Among the settings found to be of benefit to patients undergoing procedural sedation include procedures done in dentistry (dental and oral surgery), radiology, medical (bronchoscopy, endoscopy, cardiac studies, pacemaker placement), and

gynaecology (in vitro fertilization). This approach has also being utilized in the outpatient setting (Lazear, 1999). In the emergency departments procedural sedation has been widely indicated to overtly anxious patient who is undergoing a procedure such as repair of complicated lacerations, reduction of fractures, application of plaster casts, incision and drainage of abscesses and wound care(Lazear, 1999) thus making it an appropriate technique of choice.

Despite its promising outcome and benefit, some precautions are still required. Patients undergoing procedural sedation must be closely and continuously monitored to avoid any progression into a deeper state of sedation. Should this occur the actual purpose of procedural sedation would be nullified. Monitoring could be achieved effectively through visual observation coupled with the use of pulse oxymeter and a capnograph.

One of the 'tools' that can be relied on assessing the patient for the procedural sedation is to score the patient according to the Mallampati Score (Table 1.2). This score system is used to evaluate the ease of intubation should any complications arise during the procedure and it is done by assessing both tonsil and tonsillar fossa visibility. During the examination, the pharynx is visualized with the mouth opened at rest and phonation is listened to while any tongue protrusion abnormality is assessed. Higher Mallampati score (ie. a score of 4) indicated a higher risk and is associated with difficult intubation and sleep apnea.(Mallampati 1985 CASJ 32(4): 429-34).

In this study, the score that include in the inclusion criteria are class 1 and class 2.

Table 1.2: Mallampati Scoring

Class	Description
Class 1	Entire tonsil clearly visible
Class 2	Upper half of tonsil fossa visible
Class 3	Soft and hard palate clearly visible
Class 4	Only hard palate visible

Unfortunately, there have been a rather limited number of studies to justify the role of procedural sedation in the emergency department settings worldwide and Malaysia is of no exception. Among the reasons assumed by the main researcher to contribute to such limited usage of procedural sedation particularly in Malaysia include:

(i) the reluctance of anaesthetists to allow such technique to be carried by a non anaesthesiology trained personnel for reasons better known to them;

(ii) emergency medicine is a very new sub-specialized discipline in Malaysia and procedural sedation has not been widely delivered in the emergency department setting;

(iii) the apprehension to allow trained nurses and care providers to deliver sedating agents because of the existing strict policy and

(iv) patients presented at the emergency department were assumed to have foods in their stomach that made the attending doctors disregard any procedure requiring sedation to be carried out without prior consultation with the anaesthetist.

Based on the assumption listed above procedural sedation has never been regarded safe to be administered at the emergency department setting and any attempts to perform such technique may only create controversies and debates among the care providers. This is the main reason for this pilot project to be carried out to determine the safety as well as efficacy of procedural sedation to be delivered in the emergency department setting.

The use of an effective short acting drug in procedural sedation relieves patients from numerous unpleasant side effects that commonly seen with the use of conventional long acting Diazepam. For this reason, midazolam has been widely used as an effective sedating agent with clinically proven minimal adverse effects. Another sedating agent which has been used is propofol.

Midazolam

Is a short acting benzodiazepine which has significant sedative- hypnotic effects. It has been widely used in many surgical procedures performed under local anaesthesia. This includes endoscopy (Waring et al. 2003). The use of midazolam has been well documented to enhance patient's comfort, improve operating conditions and most importantly due to its amnesic properties it prevents patient from recalling of unpleasant events during a procedure (Ghoneim et al. 1996).

In addition to that midazolam which act indirectly as a Gamma Amino Butyric Acid agonist is relatively cardio-respiratory safe. Once administered, it is rapid in onset and has short duration of action which makes midazolam a very popular drug of choice to

be used in procedural sedation. The recommended dose is 0.1mg/kg which is delivered intravenously.

Propofol

It is a short acting hypnotic agent which has been approved by the Food and Drug Administration (FDA) to be also useful in procedural sedation. Propofol is capable of reducing cerebral metabolism as well as cerebral blood flow that reduce the oxygen demand while maintain the normal intracranial pressure. This drug is regarded very suitable for non head injury cases undergoing procedures that require sedation. When given via intravenous route the effect is almost immediate. With a short half life patient on propofol made rapid recovery. Its analgesic effect is markedly even and benefit patient who is undergoing any painful procedure.

Propofol has bronchodilating effect which makes it an appropriate drug of choice for patient with bronchial asthma. Its antiemetic properties gave an added advantage to minimize post sedation nausea.

Propofol is however seen to reduce the mean arterial pressure (MAP) which makes it a rather poor choice in patient who develops hypotension and those with head injury. Apnea and injection pain are other disadvantages for using this drug.

Propofol alone may cause deep sedation and analgesia. Deep sedation is said to take place when purposeful response triggered with repeated stimuli while moderate sedation (conscious sedation) is purposeful respond to light stimuli such as verbal and tactile. The respiratory depression occurs mainly during the deep sedation and not in

moderate sedation. In deep sedation, the protection airway reflex is intact, thus reduces the risk of aspiration.

Minor et al (2002) have shown that respiratory depression occurred in 19 % of cases receiving propofol alone as compared to those who received fentanyl alone (20 %) while a combined midazolam with fentanyl cause respiratory depression in 23 % of cases.

Due to deep or over sedation produced by proporfol within the normal range, its use in emergency and other departments has been objected by anesthetists.

Cull Vincent et al (2000) reported in their studies on cardioversion performed at the Emergency Department, have found that propofol is superior with a short recovery period and least side effect. A dose of 1.5 mg/kg administered intravenously has been used for such procedure.

One of the main side effects of propofol is apnea which if not anticipated could lead to hypoxia. This usually occurs when propofol is given at a higher dose. Basset et al (2002) and Guenther et al (2000) have showed that with a bolus dose of 1mg/kg followed by 0.5 mg/kg (when it is necessary) may reduce both the hypoxia and apnea instead of 1.5 mg/kg dosage. In addition to that assisted ventilation and oxygenation may improve hypoxia and apnea further.

When comparing propofol with midazolam and fentanyl, Basset et al (2002) concluded that the respiratory depression is more frequent in those patients receiving propofol than those who were receiving midazolam and fentanyl.

Hypercapnea is another common side effect of propofol. 49% of cases receiving propofol developed hypercapnea as compared to other agents (19%). Despite being a serious adverse effect hypercapnea can be anticipated if it has been detected early. An

effective means of monitoring is crucial. Minor et al (2002) in their study however have found that hypercapnea can be monitored effectively using a capnograph. Relevant interventions could be carried out once capnograph has detected the emergence of hypercapnea.

None of the study was able to show whether propofol produces deep sedation or general anesthesia during a procedure. In order to differentiate this, a criterion of "purposeful responsive following repeated or painful stimulation" is used. In addition to that Modified Ramsay score can be applied with a score of 6 to indicate "where there are no response to pain and a sluggish respond is scored 5.

Aspiration is the most feared complication of deep sedation and this is partly due to a full stomach contents. This complication can however be prevented as recommended by Guenther et al (2002) that patient to be fasted for 4 hours before a procedure is being carried out.

Recent study has also concluded that despite causing impaired airway reflex with the use of propofol, it is not of clinical importance. This is supported by the fact that procedures done in emergency department are relatively short duration. Its antiemetic effect has also provided added advantage.

Among the indications proposed for the use of propofol in procedural sedation include the following (Blanchard et al. 2002):

- A brief procedure
- Intense painful procedure (eg: cardioversion , orthopaedic manipulation)
- Overly anxious patient

- Patient requiring immobilization
- Procedure which provides brief recovery and patient can be discharged early upon completion of such procedure

Godambe et al have concluded that a regime combining propofol and fentanyl provide a shorter time of recovery that is 23 minutes as compared to midazolam with ketamine which took about 33 minutes.

Fentanyl

Fentanyl is the most commonly used opioids in procedural sedation. It has both analgesia as well as sedation effects. When bound to stereospecific receptors it increases the pain threshold, alters pain reception and inhibits ascending pain pathways (Waring et al. 2003). Being rapid in the mode of action fentanyl is 75 -125 times more potent than morphine. Its rapid clearance with half life between 2 – 4 hours and cause minimal nausea making fentanyl a better drug of choice over morphine to be used in procedural sedation.

Procedures that require longer time however may benefit a combination of a benzodiazepine and an opioid agents (Waring et al. 2003). Extra precautions should be seriously considered when benzodiazepines and opioid agent are used as such combination could potentially increase the risk of oxygen desaturation and cardiorespiratory consequences.

The recommended dose to use fentanyl in conscious sedation is 3 to 5 mg/kg and is given intravenously.

In higher doses exceeding more than 5mg/kg, fentanyl may cause wooden chest syndrome a condition characterized by the presence of apnea, chest and muscle rigidity. Wooden chest syndrome makes ventilation become very difficult.

Procedural sedation can be carried out safely and non-invasively with the advent of new monitoring strategies. The use of pulse oxymeter, for example, coupled with a non invasive monitoring of blood pressure maximized the comfort and care in patients receiving procedural sedation.

Pulse oxymeter has been used to monitor the level of oxygenation. Since sedation could result in the emergence of apnea plus hypoventilation and failure to detect these conditions may eventually lead to oxygen desaturation. The use of pulse oxymeter has been shown clinically to be a relevant tool to monitor the existence of oxygen desaturation.

Capnograph is another very useful instrument in recognizing any ventilatory and circulatory insults that could take place during sedation. Capnograph has the capacity to provide early warning of apnea and detecting the occurrence of respiratory depression, obstruction or laryngspasm through the monitoring of end tidal expiratory carbon dioxide (EtCO2) which could be accurately measured. Respiratory depression is said to take place when O2 saturation is < 90mmHg, EtCO2 is > 50mmHg or when there is absence of EtCO2 waveform

This pilot project is initiated in an attempt to determine the effectiveness of procedural sedation while carrying a procedure at the emergency department and to make a comparison between two different sedative drugs used in combination with fentanyl.

All subjects that have agreed to participate in this study would be monitored closely using pulse oxymeter, capnograph, cardiac monitor in addition to the relevant vital signs monitoring.

3. RESEARCH OBJECTIVES

3.1 Aim of the Study

3.1.1 To initiate in the creation of a standard or comparable protocol for procedural sedation delivered at the Emergency Department setting in Malaysia.

3.1.2 To evaluate the importance of using capnography routinely when procedural sedation is given at the Emergency Department setting.

3.2 Objectives

3.2.1 General Objective

To compare the safety and efficacy between combination of fentanyl and propofol with combination of fentanyl and midazolam in procedural sedation.

3.2.2 Specific Objectives

To compare the outcomes between combination of fentanyl and propofol with fentanyl and midazolam on subjects during and after a procedural sedation.

The outcome measurements are:

a. Vital signs

- Systolic and Diastolic Blood pressure
- Respiratory rate

- Heart rate
- Mean Arterial Pressure (MAP)
- Oxygen saturation (SPO_2)

b. End Tidal Carbon Dioxide ($EtCO_2$)

c. Duration to regain full consciousness after the completion of a procedure.

3.3 Research Hypothesis

3.3.1 Null Hypothesis

The use of combined fentanyl and propofol has no difference over fentanyl and midazolam for procedural sedation.

3.3.2 Population

Patients who full fill the criteria for the procedural sedation

3.3.3 Intervention

Administration of either fentanyl with midazolam or fentanyl with propofol

3.3.4 Study outcomes

i. there will be no changes in hemodynamic measurement
ii. there will be no complication such as apnea
iii. there will be no hypoxia
iv. there is no difference between both drugs in the aspect of duration of regaining full consciousness.

4. METHODOLOGY

4.1 Study Design

This is a pilot project consisting of a randomized control trial study which was carried out at the Emergency Department Hospital University Sains Malaysia (HUSM), Kelantan, Malaysia over a period of 12 months commencing from December 2004 until December 2005.

HUSM is a regional tertiary referral center with an attendance rate to the emergency department exceeding 45,000 per year (Teo, 2001). It is also a teaching hospital responsible in training both the under graduate students and residency based training in many specialized fields including emergency medicine. It is situated in a state at the east coast of a peninsular called Kelantan with a population of about 1 million people dominated mainly by Malays.

This study is carried out in collaboration with an Emergency Physician at the Emergency Department, HUSM. The number of sample approved by the Ethical Committee is 160 patients but for the purpose of this pilot study, the sample approved by the Head of Department is 40 patients.

The proposal of this study was presented on October 20th 2004 to the Department Board Review and Hospital Ethical Committee and received approval to proceed. The reference for the certificate of approval is **USMKK/PPSP®/JK P&E 2004.**

All the 40 patients were selected randomly using the **computer generated random permuted blocks of four patients** and they were divided equally into two groups with twenty patients in each group. All patients recruited did not know the drug they would receive. Each group would receive either drug A or drug B.

The drugs used were **single blinded**. They were supplied by the HUSM pharmacy department and were wrapped individually and placed in an envelope. Each envelope was sealed and labeled accordingly as drug A or drug B.

The operator which consisted of emergency physician, medical officers which included the main researcher will never know the exact drug to be given until the envelope is opened in order to administer the medication to the patients in which, the dose of the drug has to be precisely calculated according to the subject's body weight.

4.2 Inclusion criteria

All adult patients who presented at the Emergency Department HUSM either for a brief or intense painful procedure; having marked anxiety or require some levels of immobilization were carefully evaluated for the suitability to be recruited in this pilot study.

The suitability of the subjects will be evaluated based on the following criteria:

4.2.1 All trauma (except head injury) and non trauma adult patients

4.2.2 All patients age 12 years old and above who gave verbal and written consent to participate in the study. Parental consent was obtained if the patient age between 12 to 18 years old.

4.2.3 All patients who were indicated for procedural sedation.

4.2.4 All patients with physical status of ASA I, II or below based upon the American Society of Anaesthesiologists Risk Classification (ASA) (Table 4.1).

4.2.5 All patients scored two and below based on Mallampati score.

Table 4.1: American Society of Anaesthesiologists Risk Classification (ASA)

Class	Description
I	Normal healthy patient with no systemic disease
II	Mild to moderate systemic disease
III	Severe systemic disease with functional limitation that is non incapacitating
IV	Severe systemic disease that is incapacitating and life threatening
V	A moribund patient not expected to survive 24 hours without surgical intervention

Source: The American Society of Anaesthesiologists Risk Classification (ASA)

4.3 Exclusion criteria

4.3.1 All subjects with positive history of allergy to the drugs being studied

4.3.2 All patients presented to the Emergency department with history of alcohol intoxication or any psychiatric conditions

4.3.3 Patient with positive history of drug abuse

4.3.4 Pregnant women

Fourty (40) patients were finally recruited for this study and were categorized equally into either one of the two groups namely Group A and Group B.

All participated patients would have their vital signs recorded. This includes:

a. Systolic and Diastolic Blood pressures using bedside monitor
b. Heart rate using bedside monitor
c. Respiratory rate using bedside monitor
d. O_2 saturation by Pulse bedside monitor
e. End Tidal Carbon Dioxide ($EtCO_2$) using bedside monitor

The bedside monitors used in this study is Datascope Spectrum with serial number as follow:

a. MM 02940 - I4
b. MM 02776 - H4
c. MM 02987 – 14
d. MM 02935 - 14

4.4 Procedures

The following procedures will be carried out uniformly during the recruitment of samples for this study.

4.4.1 Full history taking and thorough physical examination (refer Appendix 5 for the specimen of the form used) were carried out by the medical officers at the Emergency Department, HUSM and a triage was done to determine whether the patient is suitable to be included in the study.

4.4.2 Patients were numbered and matched to the drugs under study, that has been randomized using a computer generated pemutted blocks of four patients.

4.4.3 Detailed explanation regarding the study and the drugs to be used for procedural sedation were provided to all subjects before getting both the verbal and written consent. The explanations given include the effects and the side effects of the drugs under study. Patients also received explanation about the process that would take place during the procedural sedation.

4.4.4 Both verbal and written consent were obtained as required by the University Research Ethical Committee (refer Appendix 2).

4.4.5 Standard monitoring of systolic and diastolic BP, HR, RR and O_2 saturation were carried out to each patient selected into the study. One bed was allocated at the resuscitation room equipped with the following instruments throughout the study. This include: Anesthesia record from; Consent form; Pulse Oxymeter; BP set or Dynamap; modified oxygen mask with Capnograph detector; Capnograph monitor; Cardiac monitor; Oropharynx airways size 2, 3 and 4; Endotracheal tube (ETT) with stylet; Laryngoscope with Ambu bag

and magill forcep; Drugs used to reverse adverse reaction of studied drugs such as Flumazanil, Metachlopramide (Maxolon); Suction for suction (Appendix 3)

4.4.6 Patients were randomly allocated to one of the two groups:

a. Group A - Subjects received IV Fentanyl 3 mcg/kg as a bolus dose and Propofol 1mg/kg followed by Propofol 0.5mg/kg if needed.

b. Group B - Subjects received IV Fentanyl 3 mcg/kg as a bolus dose and a bolus dose of Midazolam 0.1mg/kg and 0.1mg/kg if needed.

4.4.7 Vital signs (Systolic and Diastolic blood pressures, Heart rate and Respiratory rate, O_2 saturation), $EtCO_2$ were recorded using specified instruments before giving procedural sedation. Similar monitoring was recorded during and after the planned procedure has ended. The oxygen was given to the patient via the modified nasal prone (called Microstring) directly and at the same time could detect the breathed out carbon dioxide.

4.4.8 All patients would initially received IV fentanyl and vital signs recorded. The studied drugs A or B were administered intravenously two to five minutes later. Vital signs (systolic and diastolic blood pressure, heart rate and respiratory rate); O_2 saturation; $EtCO_2$ were recorded.

4.4.9 Specific planned procedures were carried out in a usual manner.

4.4.10 Similar vital signs were monitored and recorded every 5 - 10 minutes until the procedure ended. Any adverse reactions during the procedures were closely observed, documented and managed according a standard guideline.

4.4.11 The time of regaining full consciousness in each subject was charted upon the completion of the procedure.

4.4.12 Subjects were subsequently monitored in the observation ward at the Emergency Department.

4.4.13 Vital signs were continuously recorded after 5 - 10 minutes the procedure ended.

4.4.14 Upon regaining fully consciousness subjects would be reviewed by attending medical officer before decision is made to either discharged them from the Emergency department or transferred to the specific wards for other intervention.

4.4.15 All information and findings were recorded in the official Anaesthetic Record sheet produced by HUSM (Appendix 4).

4.4.16 All staffs comprising of specialists, registrars, medical officers and paramedics were given adequate briefing about the study. This include the issues related to the subject recruitment criteria, the techniques to be carried out, vital signs monitoring and documentation and data collection through series of presentations and group discussions two months prior to the commencement of the study.

For the statistical analysis of this study, the non parametric were used due to the number of the sample being small and the distribution showed skewed to the right. The Mann – Whitney U analysis were used to compare the two groups of drugs.