THE EFFECTIVENESS OF INTRAVENOUS PARECOXIB SODIUM AS AN ANALGESIC ALTERNATIVE TO MORPHINE IN SUSPECTED ACUTE RENAL COLIC IN EMERGENCY DEPARTMENT HOSPITAL UNIVERSITI SAINS MALAYSIA

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DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICINE

(EMERGENCY MEDICINE)

UNIVERSITI SAINS MALAYSIA

2016

ACKNOWLEDGEMENTS

In the name of Allah, the Most Gracious and the Most Merciful. Alhamdulillah, all praises belongs to Him for the strengths and His blessing in completing this study. It is also a great pleasure for me to extend my gratitude to the following persons who have been kind enough to extend their assistance, guidance, advice and comments right from the beginning until the completion of my dissertation. Special appreciation to my supervisor, Dr Kamarul Aryffin bin Baharuddin (Head of Department, lecturer and supervisor, Department of Emergency Medicine, Hospital Universiti Sains Malaysia), Dr Wan Nor Arifin Wan Mansor (Co-supervisor, lecturer, Unit of Biostatistics and Research Methodology, Universiti Sains Malaysia), all my lectures, specialists, my colleagues and staff of Emergency Department, Hospital Universiti Sains Malaysia.

Last but not least, I would like to express my gratitude to my beloved husband, Dr Tengku Ahmad Damitri Al-Astani bin Tengku Din for his understanding, support, assistance, encouragement, patience and love throughout my postgraduate study and during the writing of my dissertation.

My deepest gratitude goes to my beloved parents ; Haji Ismail bin Sulaiman and Hajah Saripah binti Hasan, and also special thanks to my children Tengku Nurdanisha Al-Awatiff, Tengku Nurdarina Al-Afifah, Tengku Nurdalieya Al-Aliyah, Tengku Nurdamia Al-Athirah for their understanding and patience.

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LIST OF ABBREVIATIONS

APEX	Accelerated Programme for Excellent
BUSE	Blood Urea Serum Electrolyte
CNS	Central Nervous System
CT	Computerized Tomography
COX-1/2	Cyclooxygenase 1/2
C&S	Culture and Sensitivity
ED	Emergency Department
FBC	Full Blood Count
FDA	Food and Drug Administration
HUSM	Hospital Universiti Sains Malaysia
KUB	Kidney Ureter Bladder
MOH	Ministry of Health
MAP	Magnesium Ammonium Phosphate
NCCT	Non-contrast Computerized Tomography
NRS	Numeric Rating Scale
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs

IASP	International Association for Study of Pain
IM	Intramuscular
IV	Intravenous
IVU	Intravenous Urography
L1	Lumbar -1
PUJ	Pelviureteric Junction
SPSS	Statistical Packages for Social Sciences
T11	Thoracic - 11
UTI	Urinary Tract Infection
US	Ultrasound
VAS	Visual Analogue Scale
VRS	Verbal Categorical Rating Scale

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KEBERKESANAN INTRAVENUS PARECOXIB SODIUM SEBAGAI ANALGESIA ALTERNATIF KEPADA MORPHINE DALAM RAWATAN SAKIT BUAH PINGGANG AKUT DI JABATAN KECEMASAN HOSPITAL UNIVERSITI SAINS MALAYSIA

ABSTRAK

Pengenalan : Pesakit dengan kolik buah pinggang biasanya datang ke Jabatan Kecemasan dengan kesakitan yang teruk dan tidak tertanggung. Pakar Perubatan Kecemasan menggunakan pelbagai jenis ubat untuk merawat masalah ini, namun setakat ini tiada lagi ubat yang terbukti untuk melegakan kesakitan sepenuhnya. Kajian ini bertujuan untuk membandingkan keberkesanan IV parecoxib berbanding IV morphine terhadap pesakit yang disyaki mengalami kolik buah pinggang akut di Jabatan Kecemasan. **Objektif** : Objektif kajian ini adalah untuk membandingkan antara IV parecoxib dan morphine di Jabatan Kecemasan HUSM mengenai pengurangan skor kesakitan di kalangan pesakit kolik buah pinggang akut dari masa ke masa, pengurangan skor kesakitan di antara kumpulan dari masa ke masa dan untuk membandingkan keberkesanan penurunan tahap kesakitan antara kedua-dua ubat (pengurangan sebanyak 2 skor tahap kesakitan) selepas 5 minit ubat diberi. Kesan-kesan sampingan kedua-dua ubat juga dinilai. **Methodologi** : Kajian ini melalui proses randomisasi dan kajian buta tunggal untuk membandingkan IV parecoxib 40 mg dengan IV morphine 0.10mg/kg terhadap pesakit dewasa yang datang ke ED dengan simptom sakit buah pinggang akut dengan NRS 6 dan ke atas. Pemerhatian berperingkat seperti tekanan darah, denyutan nadi, tahap oksigen dan NRS dilakukan pada 0, 5, 15, 30 minit begitu juga dengan kesan sampingan dinilai selepas 30 minit ubat diberi. Hasil utama dalam kajian ini adalah penurunan NRS. Analisis data

dilakukan menggunakan ukuran berulang ANOVA. **Keputusan** : Keputusan kajian ini tidak menunjukkan perbezaan yang ketara terhadap penurunan NRS di antara pesakit yang menerima IV parecoxib atau morphine ($F(3,126)=0.229$, $P=0.876$). Perbandingan antara kesan efektif pada 5 minit di antara kumpulan adalah tidak signifikan ($P=0.498$). Pesakit yang menerima IV morphine mengalami pening, muntah dan loya masing-masing sebanyak 22.7 %, 13.6 % dan 4.5% berbanding 4.5% mengalami loya sahaja dalam kumpulan parecoxib. **Kesimpulan** : Kajian ini menunjukkan tidak ada perbezaan penurunan tahap kesakitan bagi pesakit yang menerima IV morphine atau parecoxib , begitu juga dengan kesan efektif pada masa selepas 5 minit ubat diberi. Berdasarkan kesan yang efektif dan juga kurangnya kesan sampingan, IV parecoxib mampu untuk dijadikan sebagai ubat penahan sakit alternatif kepada morphine dalam merawat sakit buah pinggang akut seterusnya diperluaskan dalam pelbagai kes di ED HUSM.

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ABSTRACT

Background : Patients with renal colic usually presented to Emergency Department with severe and excruciating pain. Emergency Physicians using numerous medications to treat the problem, however none of them had been proven to relieve the pain completely. This study aimed to compare the effectiveness of IV parecoxib versus IV morphine in suspected acute renal colic in Emergency Department . **Objectives** : The objectives of this study were comparison between IV parecoxib sodium and morphine in Emergenency Department HUSM regarding pain score reduction among acute renal colic patient over time, mean pain score reduction by group over time and to compare the effectiveness of both analgesics (reduction by 2 pain scores) after 5 minutes of drug administration. The side effects of both drugs will be evaluated too. **Methods** : A randomized, single-blinded study comparing IV parecoxib 40 mg versus IV morphine at 0.10 mg/kg was conducted in adult patients who presented with features suggestive of acute renal colic and NRS of 6 or more. Periodic assessment of vital signs and NRS were taken at 0, 5, 15 and 30 minutes as well as evaluation of side effects within 30 minutes after the administration of the study drugs. The primary outcome was the reduction of NRS. The data was analyzed by repeated measures ANOVA analysis.

Results : There was no significant difference in the mean NRS between patients in IV parecoxib group and morphine group over time ($F(3,126)=0.229$, $P=0.876$). Comparison of the effectiveness at 5 minutes between the groups was not significant ($P=0.498$). Dizziness, vomiting and nausea were experienced in 22.7%, 13.6% and

4.5% of patients respectively in IV morphine group as compared to parecoxib group 4.5% experienced of nausea only. **Conclusions :** There was no significant difference in NRS between the groups over time, as well as in term of the effectiveness at 5 minutes. Due to lack of IV parecoxib side effect compared to morphine, IV parecoxib seemed to be valuable in the future and can be used as analgesic alternative to morphine in acute renal colic as well as extended further to treat a variety of cases presented in ED HUSM.

CHAPTER 1

INTRODUCTION

1.1 Literature Review

1.1.1 Background

The commonest reason make patients seek care in Emergency Department (ED) is pain and emergency physicians treat many patients who have severe pain, ranging from shingles to long bone fractures to myocardial infarction. The volume and severity of pain-related problems make pain management a core skill in emergency medicine (Todd, et al. 2002).

According to International Association for the Study of Pain (IASP), pain is described as 'unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage'. Therefore, although the word pain usually refers to physical pain, it may well involve mental pain as well.

Since pain has become a common presentation in Emergency Department (ED), Malaysia Ministry of Health (MOH) has been implementing pain as the 5^{th} vital sign together with blood pressure, heart rate, respiratory rate and temperature to all hospitals under MOH since 2011. All staff from all health facilities especially those in Emergency Department (ED) currently are being trained to make sure this implementation is running smoothly and accordingly since in triage area before patient being transferred to the treatment area.

1.1.2 Pain Assessment

Valid and reliable assessment of pain is essential for both clinical trials and effective pain management. Assessment of acute pain from trauma or disease can be a simple and straightforward task (H Breivik, et al. 2008) .

There are multiple pain assessment tools available in assessing acute pain such as visual analogue scale (VAS), numeric rating scale (NRS) and verbal categorical rating scale (VRS).

The well-known visual analogue scale (VAS) and numeric rating scale (NRS) for assessment of pain intensity agree well and both are equally sensitive in assessing acute pain after surgery, and they are both superior to a four-point verbal categorical rating scale (VRS). They function best for the patient's subjective feeling of the intensity of pain right now—present pain intensity. They may be used for worst, least, or average pain over the last 24 h, or during the last week. However, there are some limitations with this, as memory of pain is not accurate and often coloured by changing context factors. They are also used to assess ‘unpleasantness’ of pain and to grade impact of pain on function. The indicated ranges of the categories of the VRS scale on the numeric rating scale (NRS) are approximate, with significant variation both between patients and in individuals at different time points. A study using simultaneous recordings of pain intensity on VAS, NRS, and VRS scales in a large number of patients demonstrated the superiority of the VAS and NRS over VRS. A computerized simulation study, randomly sampling 10000 times, repeatedly from simultaneous observations of VAS, NRS, and VRS, documented that the power to detect a difference in pain intensity was higher with the NRS and the VAS data compared with the VRS data (H Breivik, et al. 2008).

However, to date there is still no specific test that can measure the severity of patients' pain. Vital signs such as blood pressure and heart rate have been showed to be inconsistent with the severity of pain. To infer severity, the verbal or visual analogue scale has become widely accepted now (Boswell M & B. Elliot Cole 2006).

1.1.3 Renal colic

Renal colic is a common problem presented to the ED and pain can be quite significant, requires a rapid and effective medical response. Emergency physicians use a multitude of medications for analgesia in renal colic (Safdar, et al. 2008).

Renal colic affects 5%-12% of individuals at least once in their lifetime (Safdar, et al. 2006). The condition is accompanied by excruciating pain that requires prompt and effective pain control. The preferred route of medication administration for this acute pain is intravenous. Both NSAIDs and opioids are considered appropriate analgesics. However the most effective analgesic regimen has not been determinated (Safdar, et al. 2006).

Renal colic caused by acute partial or complete ureteric obstruction due to a calculus in the vast majority of the cases. However, in approximately 5% of the patients, renal colic may be caused by conditons unrelated to a stone disease such as pyelonephritis and pelviureteric junction (PUJ) obstruction (Shokeir, A. A.2001).

The traditional explanation for renal colic has been that the ureteric obstruction causes a direct increase in intraluminal pressure of the collecting system, physically stretching it, and stimulating nerve endings in the lamina propria. In response to this distension, the smooth muscle in the wall of the ureter contracts as it trials to move the stone. If the stone becomes lodges and unable to moves, these muscles develop spasm.

A prolonged isotonic contraction leads to increase production of lactic acid which irritates both slow-type A and fast-type C fibers. Afferent impulses are generated that travel to the spinal cord, adjoining it at the T11 to L1 levels with subsequent projections to higher levels of central nervous system. This pain can also be perceived in any organ sharing in the urinary tract innervation such as the gastrointestinal organs and other components of the genitourinary system (Shokeir, A. A. 2001).

Stones in the urinary tract or bladder stones are often called; urinary stone is the presence of stones in the urinary tract, from the kidneys, ureters, urinary bladder into the urethra. Many factors that unfavorable formations of stones, yet the exact cause of urinary tract stones is not yet known. On the nucleation process of hydrogen, sodium, uric acid and uric crystals of hydroxyapatite forms the core of calcium ions and oxalate is then glue (adhesion) in the nucleus to form a mixture of stones. This process is called heterogeneous nucleation. Urinary tract stones in general contain elements of calcium oxalate or calcium phosphate, uric acid, magnesium ammonium phosphate (MAP), xanthin, and cystine. Urinary tract stones have a basic component of calcium about 75% in the form of calcium oxalate or calcium phosphate, oxalate and phosphate mixture. Identification of urinary tract stones can be done with the analysis of stone, so that the type and composition of the stones can be known. Many found the jar of a stone while in the developed countries more plentiful upper urinary stones (kidney and ureter), this difference affected the nutritional status and mobility of daily activities. The average prevalence worldwide is 1-12% of the population suffer from urinary tract stones (Pako R.P , et al 2015).

Renal colic can be diagnosed by clinical, biochemical and also radiological. Patients with renal colic usually presented with characteristic loin pain may or not radiated to the groin, may have vomiting and fever. They usually but not always have

haematuria (macroscopic or microscopic). However, 15% of patients with proven stone on imaging will not have haematuria. They may have a previous history of renal calculus (IAEM CG3 Emergency Department Management of Renal Colic & suspected Renal Calculus 2014).

Biochemical Investigations also important such as urine dipstick for red cells, white cells and nitrites and a urine pH. Urine should be sent for culture if dipstick urinalysis is abnormal. Serum urea, creatinine, sodium and potassium should be analysed as a measure of renal function. Serum uric acid and calcium should also be performed if the patient has not had a previous normal result (within 1 year). This might be the only occasion when a patient with hypercalcaemia may be identified. Patients with fever should also have blood samples for CRP and FBC sent to the laboratory. If intervention is likely or planned a coagulation test should be considered (IAEM CG3 Emergency Department Management of Renal Colic & suspected Renal Calculus 2014).

Stone analysis should be performed in certain high risk stone formers. This would include first presentation at a young age, bilateral stones or large stones at presentation. NCCT has become the standard method for diagnosing acute flank pain. It can identify the presence of the stone, its diameter and density. NCCT should be used to confirm a diagnosis in patients presenting with acute flank pain because it is superior to IVU. The radiation risk can be reduced by using low-dose CT (IAEM CG3 Emergency Department Management of Renal Colic & suspected Renal Calculus 2014).

However, given that ureterolithiasis is a benign and recurrent disease, emergency physicians should consider diagnostic strategies that limit radiation

exposure. Ultrasonography (US) is an imaging modality that may be used to investigate renal colic that does not expose the patient to radiation or contrast material. Although reported estimates of the sensitivity of ultrasonography (US) to visualize ureteral calculi vary widely and are lower than that of computerized tomography (CT) (12%–93%), ultrasound (US) is highly accurate in detecting hydronephrosis, perinephric fluid and abnormal urinary jets, which often indicate the presence of calculi with sensitivity nearing 100. The specificity of US for direct or indirect findings compatible with ureterolithiasis is greater than 90% in some studies. Additionally, US has been recognized as a useful imaging tool for patients in whom radiation exposure should be avoided (Edmonds M. L., et al 2010). Since US machine mostly available in emergency setting worldwide, so it is not possible to diagnose renal colic in ED level.

1.1.4 Treatment of renal colic

A variety of drugs is used for renal colic, including antispasmodics, NSAIDs and opioids (O'Connor, et al.2000).

Parecoxib is the first selective COX-2 inhibitors for parenteral administration. It is prodrug of Valdecoxib which is more than 28,000 fold more selective for COX-2 versus COX-1 in vitro. It is use for acute pain management post operation. Onset of pain relief in 7-13 min, with a single dose of IV/IM Parecoxib Sodium 40mg. Analgesic lasting from 6 to more than 12 hours. Parecoxib is intravenous pro-drug that is metabolized to valdecoxib, is the first COX-2 agent available in North America that can be given by the IV and IM routes. In dental, gynaecologic and orthopaedic pain, parecoxib (20 mg IV or IM) provided a similar degree and duration of analgesia to intravenous ketorolac (30–60 mg), and more prolonged analgesia than IV morphine (4 mg) (Daniels, et al. 2001) .

Another multicenter study in Latin America looked at the use of parecoxib in acute renal colic and it showed that parecoxib is effective as ketoprofen in the treatment of renal colic (Glina S, et al. 2011).

Opioids have been traditional first-line therapy for patients suffering from acute renal colic. The 2 most common opioids study are morphine and meperidine. A randomized controlled trial (RCT) comparing 10 mg of IV morphine with 100 mg of IV meperidine found they were equally effective. However, because of meperidine's greater abuse potential and increased side-effect profile, the authors of the study recommended morphine over meperidine (O'Connor, et al. 2000)

According to meta-analysis of 20 trials (2009), NSAIDs and strong opioid analgesics have comparable efficacy. Morphine 5-10 mg IM in an alternative treatment to NSAIDs for acute pain management in patients with renal colic and preferred over NSAIDs in women who are pregnant. The concomitant administration of an antiemetic may be considered for the prevention or control of nausea and vomiting (National Institute for Health and Care Excellence (NICE) Renal colic - acute 2009). A recent Cochrane Review on Randomized Clinical Trials comparing opioids and NSAIDs in acute renal colic found that both drugs reduced patient-reported pain scores (Safdar, et al. 2008).

1.2 Rationale for the study

The cornerstone of ureteral colic management is analgesia, which can be achieved most expediently with parenteral narcotics or nonsteroidal anti-inflammatory drugs (NSAIDs). Parenteral narcotics are the mainstay of analgesia for patients with acute renal colic. They work primarily on the central nervous system (CNS) to reduce the perception of pain.

Of the NSAIDs, the only one approved by the US Food and Drug Administration (FDA) for parenteral use is ketorolac. Ketorolac works at the peripheral site of pain production rather than on the CNS. Ketorolac has fewer adverse effects compared to opioids and has been proven in multiple studies to be as effective as opioid analgesics (J Stuart Wolf, Jr et al. 2015).

However because parenteral Ketorolac currently not available in ED HUSM and and the only parenteral NSAIDs available is Parecoxib Sodium (COX -2). There were no studies yet regarding parecoxib sodium in managing renal colic patient. Apart from that, in this study we try to find an other solution despite of giving opioids in managing renal colic in view of adverse effects of morphine include respiratory depression, drowsiness, mood changes, nausea, vomiting, increases in the cerebrospinal fluid pressure and cough reflex depression.

The findings from this study will provide better treatment for the future patients presented with acute renal colic in Emergency Department HUSM.

1.3 Objectives

The general objective of this study was to determine the usage of parecoxib sodium (Dynastat) as an analgesic alternative to Morphine in suspected acute renal colic in ED HUSM. The specific objectives were:

1. To compare mean pain score (NRS) between IV Parecoxib and IV Morphine groups among acute renal colic patients over time in ED HUSM ,
2. To compare mean pain score (NRS) within the groups over time,
3. To compare effectiveness of both analgesics (reduction by 2 pain score [NRS]) after 5 minutes of drug administration
4. To decribe the side effects of both drugs clinically.

1.4 Methods

1.4.1 Study design and participants

This was a randomized, single-blinded study comparing IV parecoxib sodium 40 mg versus IV morphine at 0.10 mg/kg in adult patients presented to ED HUSM who met the inclusion and exclusion criteria of acute renal colic with NRS of 6 or more. This study were conducted from October 2015 until March 2016.

1.4.2 Inclusion/exclusion/withdrawal criteria

Inclusion criteria in this study including :

1. Adult 18 years old and above
2. First episode of renal colic based on clinical assessment
3. Recurrent episode of renal colic.

Exclusion criteria were :

1. Pregnant patients or breastfeeding mother
2. Patient who had received analgesic within 6 hours of presentation
3. Patients at high risk of cardiovascular disease
4. Patient who are undergoing any major surgery (cardiac or major vascular surgery),
5. Patients who have previously had a myocardial infarction or stroke
6. Patients with known hypersensitivity to parecoxib sodium, valdecoxib, morphine or to any other ingredient of the product
7. Patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin, NSAIDs or other COX-2 specific inhibitors or after taking morphine
8. Patients who have demonstrated allergic-type reactions to sulfonamides, patients with severe hepatic impairment (Child-Pugh score $\geq$10)
9. Patient who had a history of drug dependence or were currently using methadone

Patient automatically withdrawn from this study when he or she who initially agreed verbally, however after treatment given, refuse to sign the consent form and patient who end-up with other diagnosis after 30 days of follow up.

1.4.3 Interventional therapy methods

The two drugs used in this study for comparisons were IV parecoxib sodium and IV morphine sulphate. The parecoxib used in this study was manufactured by Pharmacia & Upjohn Kalamazoo, Michigan, USA; it was produced for Pfizer using the

trade name of Dynastat. Each vial of Dynastat contains 40 mg of parecoxib sodium for reconstruction. After reconstitution, the final concentration of parecoxib is 20mg/mL.

IV morphine sulphate was manufactured by Duopharm (M) Sdn. Bhd, Selangor, Malaysia. Each milliliter of injection contained 10 mg of morphine sulphate. The dosage for IV morphine was 0.1 mg/kg. Once was calculated based on body weight, the morphine solution diluted to 2 mL of volume; this to make parecoxib and morphine appeared identical.

1.4.4 Procedures

The informations regarding this study were made in each entrance in ED HUSM. Patients who suspected presented with from acute renal colic with NRS score 6 and more were triaged to yellow zone by paramedics.

Vital signs (Blood Pressure, heart rate, respiratory rate, pulse oxymetry, temperature) were measured and recorded by staffnurse on duty. Treating doctor took prompt history as well as record patient's pain score according to NRS (Numeric Rating Scale). If the symptoms suggestive of acute renal colic and NRS score was 6 or more, the doctor discussed with the patient regarding this study. The patients were under close monitoring throughout this study for 30 minutes. Patients who agreed verbally may sign the consent form after medication given. The patient's spouse or any close family members are allowed to be with the patient throughout this study period and listened to explanation by doctor regarding this study.

Researcher prepared envelopes which labeled as Envelope A and Envelope B. Each envelope was already numbered accordingly from number 1 to number 48. The envelope selected based on patient's number. For example : First patient got the

Envelope number 1 who is already randomized to Blok B, the second patient got the envelope number 2 who is randomized to Blok A and continued the same for other patients.

After the patient agreed to involve in this study, the researcher took the envelope according to patient's number based on computer-generated randomization and the researcher prepared and administered the drug to the patient.

Periodic assessment of vital signs (blood pressure, pulse rate, oxygen saturation) and NRS taken by treating doctor at 0, 5,15 and 30 minutes intervals after the administration of the study drug.

Patient who developed side effects of the drugs within 30 minutes, prompt treatment given accordingly. If no complication, the patient either discharged with follow up appointment at clinic or warded for further investigations.

Patients who being discharged, information card will be provided to contact us to make sure patient did not get any serious side effect.

The evaluation of the patient continued at day 30 to confirm the final diagnosis of the patient either really diagnose as renal colic or end up with other diagnosis. If end up with other diagnosis, these patient automatically withdrawn from this study.

During this study, the patient undergone normal procedures such as blood tests (FBC, BUSE,CREATININE), urine test (UFEME/ C&S), radiograph if necessary (KUB x-ray/ KUB ultrasound).

Bedside ultrasound KUB performed at ED to look for evidence of stone and hydronephrosis as well as bedside ultrasound gynaecology performed to look for evidence of pregnancy for women in childbearing age.

1.4.5 Measured parameters

In this study, we use NRS for rating patients' pain score. Patients are asked to rate their pain on a scale from 0 to 10, where 0 represents "no pain" and 10 represents "the worst pain possible," using whole numbers (11 integers including zero). Patients may then be questioned as to their goals and expectations with respect to their pain rating as a measure of satisfaction with the degree of analgesia. Often the value of "4" is used to confirm clinical nursing judgment as to the need for further intervention or documentation that the patient's goals for analgesia have been achieved. (Hartrick, et al. 2003). In this study we use NRS ≥6 as rating for moderate to severe pain.

1.4.6 Outcomes

The primary outcome is reduction of NRS. If at 30 minutes, NRS was still 6 and more, the rescue medication given to patient (IV morphine) and continuous close monitoring of the vital signs. The side effect and drug evaluation also evaluated within this 30 minute of drug administration. The effectiveness of drugs in this study is defined as the reduction of NRS by 2 score within 5 minutes of drugs administration.

1.4.7 Sample size

Sample size calculation was done using PS software version 3.0.43 for comparison of two means (α=0.05, power=80%, SD of NRS=2.3, expected difference in NRS=2). The calculated sample size was 22 per group of the drugs (n=44 overall). After considering 10% of dropout rate, the total patient needed were 24 patients per group (n=48 overall).

1.4.8 Randomization

Patients were randomized into two groups using a computer-generated randomization https://www.sealedenvelope.com/randomisation/simulation/ (random block size) (Kernan, et al 1999).

Blok A (Parecoxib) : Patient's Number : 2, 3, 6, 7, 9, 11, 12, 13, 14, 16, 22,

23, 24, 25, 26, 27, 28, 31, 32, 36, 37, 38, 42, 44

Blok B (Morphine) : Patient's Number : 1, 4, 5, 8, 10, 15, 17, 18, 19, 20, 21, 29, 30

33, 34, 35, 39, 40, 41, 43, 45, 46, 47, 48

1.4.9 Technique of blinding

This study was single blinded which means blind to the patient and blind to the treating doctor. This able to avoid bias during the assessment because the same doctor did the assessment to the patient. The drugs were prepared and administered by the researcher who was not blinded in this study

1.4.10 Ethical Approval

This study was conducted with the approval by Human Research Ethics Committee Universiti Sains Malaysia (HREC) on 13th October 2015 (Ref.USM/JEPeM/14120523).

1.4.11 Statistical methods

Data entry and statistical analyses were done using Statistical Package for Social Science (SPSS) version 22.0 software. The data was analyzed by repeated measures ANOVA.

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CHAPTER 2

STUDY PROTOCOL

2.1 Documents submitted

2.2 Ethical approval letter

2.1 Document submitted

THE EFFECTIVENESS OF IV PAREXOCIB SODIUM AS AN ANALGESIC ALTERNATIVE TO MORPHINE IN SUSPECTED ACUTE RENAL COLIC IN EMERGENCY DEPARTMENT HUSM

DEFINITION

Renal colic is clinical diagnosis. It is diagnose mainly from history and clinical examination. The classic presentation for a patient with acute renal colic is the sudden onset of severe pain originating in the flank and radiating inferiorly and anteriorly; at least 50% of patients will also have nausea and vomiting.

The diagnosis of nephrolithiasis is often made on the basis of clinical symptoms alone, although confirmatory tests are usually performed.

Examination in patients with nephrolithiasis includes the following findings:

- ✓ Dramatic costovertebral angle tenderness; pain can move to upper/lower abdominal quadrant with migration of ureteral stone
- ✓ Generally unremarkable abdominal evaluation: Possibly hypoactive bowel sounds; usually absence of peritoneal signs; possibly painful testicles but normal-appearing
- ✓ Constant body positional movements (eg, writhing, pacing)
- ✓ Tachycardia
- ✓ Hypertension
- ✓ Microscopic hematuria (J Stuart Wolf Jr, MD, FACS et.al 2014)

1. Patients suspected dependent to opioid will be identified with several indicators including:

    a) Requesting a specific drug and refusing all other suggestions (may display considerable knowledge of drugs)

    b) Presenting with inconsistents symptoms being reported (does not appear suffer significant pain)

2. Single blind in this study means :

    a) Blind to the patient

    b) Blind to the treating doctor who will further do assessment to the patient for 30 minutes after drug administration

        - This is to prevent bias during assessment because the same doctor will do the assessment to the patient.

    c) The drugs will be prepared and administered by the PI who is not blinded in this study

OBJECTIVES

a. General

- Parecoxib Sodium (Dynastat) as an analgesic alternative to Morphine in suspected Acute Renal Colic in Emergency Department (ED) HUSM.

b. Specific

1. To compare mean pain score reduction between IV Parecoxib and IV Morphine among acute renal colic patient over time in ED HUSM

2. To compare mean pain score reduction by group over time

3. To compare effectiveness of both analgesics (reduction by 2 pain score) after 5 minutes of drug administration.

4. To decribe the side effects of both drugs on clinical and PERFORMA

BACKGROUND

Pain is the most common reason patients seek care in emergency departments (ED), and emergency physicians treat many patients who have severe pain, ranging from shingles to long bone fractures to myocardial infarction. The volume and severity of pain-related problems make pain management a core skill in emergency medicine (Todd, Sloan et al. 2002).

Renal colic is a very common problem presented to the emergency department (ED). Pain can be quite significant and requires a rapid and effective medical response .Emergency physicians use a multitude of medications for analgesia in renal colic (Safdar, Degutis et al. 2008).

A variety of drugs is used for this condition, including antispasmodics, NSAIDs and opioids (O'Connor, Schug et al. 2000) .

Parecoxib is the 1st selective COX-2 inhibitors for parenteral administration. Is a prodrug of Valdecoxib which is more than 28,000 fold more selective for COX-2 versus COX-1 in vitro. It is use for acute pain management post operation. Onset of pain relief in 7- 13 min, with a single dose of IV/IM Parecoxib Sodium 40mg. Analgesic lasting from 6 to more than 12hrs. Parecoxib is intravenous prodrug that is

metabolized to valdecoxib, is the first COX-2 agent available in North America that can be given by the IV and IM routes. In dental, gynecologic, and orthopedic pain, parecoxib (20 mg IV or IM) provided a similar degree and duration of analgesia to intravenous ketorolac (30–60 mg), and more prolonged analgesia than IV morphine (4 mg) (Daniels, Grossman et al. 2001) .

Opioids have been traditional first-line therapy for patients suffering from acute renal colic. The 2 most common opioids study are morphine and meperidine. A randomized controlled trial (RCT) comparing 10 mg of IV morphine with 100 mg of IV meperidine found they were equally effective. However, because of meperidine's greater abuse potential and increased side-effect profile, the authors of the study recommended morphine over meperidine (O'Connor, Schug et al. 2000) .

Renal colic affects 5%-12% of individuals at least once in their lifetime. The condition is accompanied by excruciating pain that requires prompt and effective pain control. The preferred route of medication administration for this acute pain is intravenous. Both NSAIDs and opioids are considered appropriate analgesics. However the most effective analgesic regimen has not been determinated (Safdar, Degutis et al. 2006)

According to meta-analysis of 20 trials (2009), NSAIDs and strong opioid analgesics have comparable efficacy.

Morphine 5-10 mg IM in an alternative treatment to NSAIDs for acute pain management in patients with renal colic and preferred over NSAIDs in women who are pregnant. The concomitant administration of an antiemetic may be considered for the prevention or control of nausea and vomiting (National Institute for Health and Care Excellence (NICE). Renal colic - acute. 2009).

A recent Cochrane Review on Randomized Clinical Trials comparing opioids and NSAIDs in acute renal colic found that both drugs reduced patient-reported pain scores (Safdar, Degutis et al. 2008).

METHODOLOGY

i. Research Design

- A randomized, single-blinded study comparing IV parecoxib sodium 40 mg versus IV morphine at 0.10 mg/kg in adult patients presented to Emergency Department HUSM with acute renal colic with NRS of 6 or more.

- Patients will be randomized using a computer-generated randomization (two bock randamization). Each block consist of 24 patients.

- Researcher will prepare envelopes which labelled as Envelope A and Envelope B . Each envelope will be numberized accordingly from number 1 to number 48. The envelope will be selected based on patient's number. For example : First patient will get Envelope number 1 that will be randomized to Blok B, the second patient will get envelope number 2 that will be randomized to Blok A and continued the same for other patients.

- After the patient agree participate in this study, the researcher will take the envelope according to patient's number based on computer-generated randomization and the researcher will prepare and administer the drug to the patient.

- Periodic assessment of vital signs (blood pressure, pulse rate, oxygen saturation) and NRS will be taken by treating doctor at 0, 5,15 and 30 minutes intervals after the administration of the study drug.
- The primary outcome is reduction of NRS. If at 30 minutes, NRS is still 6 and more, the rescue medication will be given to patient (IV morphine) and close monitoring of the vital signs will be continued.
- Side effect and drug evaluation also will be evaluated within this 30 minute of drug administration.

ii. Inclusion Criteria

1 Adult 18 years old and above

2 First episode of renal colic based on clinical assessment

3 Recurrent episode of renal colic

iii. Exclusion Criteria

1. Pregnant patients or breastfeeding mother
2. Had received analgesic within 6 hours of presentation
3. Patients patients at high risk of cardiovascular disease (including patients with diabetes, ischaemic heart disease, cardiac failure, hyperlipidaemia, hypertension, or smokers) who are undergoing any major surgery (cardiac or major vascular surgery).
4. Patients who have previously had a myocardial infarction or stroke.

5. Patients with known hypersensitivity to parecoxib sodium, valdecoxib, morphine or to any other ingredient of the product.
6. Patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin, NSAIDs or other COX-2 specific inhibitors, or after taking morphine as well
7. Patients who have demonstrated allergic-type reactions to sulfonamides
8. Patients with severe hepatic impairment (Child-Pugh score ≥10)
9. Had a history of drug dependence or were currently using methadone

iv. Withdrawal Criteria

1. Patient who initially agreed verbally, however after treatment given, refuse to sign the consent form
2. Patient who end-up with other diagnosis after 30 days of follow up

v. Sampling Design and Sample Size

Low population sample size – 22 for each group of study drugs

- Total 44 patient (n = 44)
- N + 10% = 44/1-0.1

= 44/0.9

= 48

So after considering 10% dropout, each study drug consist of 24 patients

Blok A (Parecoxib sodium)