STUDY ON THE EFFECTIVENSS OF NEBULIZED FENTANYL CITRATE AS MODALITY OF ANALGESIA IN CHILDREN WITH ACUTE PAIN

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To my family especially my mother, Puan Maimunah Saidin, thank you for the never ending support and encouragement since then till now in all the hardships and obstacles that I have been through.

Last but not least, my son, Raden Muhammad Syaqil Rizqin. Through you, I am a better person today.

Alhamdulillah. Thank you.

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ABSTRAK

Pengenalan: Kajian ini adalah bertujuan untuk meneliti keberkesanan sedutan fentanyl citrate di dalam merawat kesakitan akut di kalangan kanak-kanak.

Metodologi: Kanak-kanak berusia diantara 5 hingga 15 tahun yang mengalami kesakitan akut pelbagai punca telah dimasukkan ke dalam kajian melalui kaedah persampelan mudah dan diberikan rawatan sedutan fentanyl citrate pada dos 4 mcg/kg melalui pemanduan oksigen. Kadar kesakitan diperiksa dengan menggunakan *Wong and Baker faces pain scale* sebelum rawatan dan seterusnya setiap 5 minit sehingga satu jam selepas pemberian sedutan fentanyl. Tanda-tanda vital direkod dan kesan sampingan rawatan turut dipantau.

Keputusan: Seramai 42 pesakit yang mengalami kesakitan akut dari pelbagai punca telah menyertai kajian ini. Kesemua pesakit menerima rawatan sedutan fentanyl citrate tanpa sebarang masalah. 2 pesakit telah dikeluarkan dari kajian berikutan kegagalan rawatan dalam mengurangkan kadar kesakitan. Punca-punca kesakitan dikategorikan kepada kepatahan (n= 14), kecederaan otot dan tisu (n=15) dan sakit perut akut (n= 11). Min markah kesakitan pada 10 minit pemberian rawatan telah menurun sebanyak 2.65 (95% CI 2.62 hingga 2.73). Markah kesakitan terus berkurangan pada minit ke 15 (perbezaan min markah kesakitan 4.20; 95% CI 4.01 hingga 4.09) diikuti dengan min markah kesakitan yang mendatar dari minit ke 20 sehingga satu jam setelah rawatan. Pengurangan markah kesakitan pada setiap waktu setelah pemberian rawatan sedutan fentanyl adalah sangat signifikan ($P < 0.001$). Tiada sebarang kesan sampingan atau kemerosotan tanda vital diperhatikan berikutan rawatan ini.

Konklusi: Kaedah rawatan sedutan fentanyl citrate pada dos 4 mcg/kg adalah efektif dalam merawat kesakitan akut di kalangan kanak-kanak tanpa menyebabkan sebarang kesan sampingan. Kaedah ini adalah disarankan sebagai salah satu cara rawatan dalam perawatan kesakitan akut melibatkan kanak-kanak.

ABSTRACT

Introduction: To assess the effectiveness of nebulized fentanyl citrate in treating children presenting with acute severe pain of various aetiologies.

Methods: Patients aged 5 to 15 years old presented with acute severe pain of any causes were enrolled into the study through convenient sampling and received intravenous preparation of fentanyl citrate at dose of 4 mcg/kg administered through oxygen driven nebulizer circuit. Pain scores were assessed at pre-treatment and subsequently at 5 minutes interval until 60 minutes post-treatment using Wong and Baker faces pain scale. Vital signs and potential adverse events were also monitored.

Results: 42 children with acute pain of various causes participated in this study and tolerated the nebulized fentanyl citrate well. 2 patients were withdrawn due to insufficient pain control post treatment. The pain aetiologies were categorized into fractures (n=14), soft tissue injuries (n=15) and abdominal pain (n=11). The mean pain score at 10 minutes on nebulized fentanyl administration decreased by 2.65 (95% CI 2.62 to 2.73) from the baseline. Pain score continued to decrease at 15 minutes (mean pain score difference 4.20; 95% CI 4.01 to 4.39) followed by a sustained plateau pain score at 20 minutes until 60 minutes. The pain score reduction at all-time intervals measured post-treatment were highly significant ($P < 0.001$). No adverse events or vital signs deterioration observed following nebulized fentanyl.

Conclusion: Nebulized fentanyl citrate at dose of 4 mcg/kg given through oxygen drive nebulizer circuit was effective in treating children with acute severe pain without causing adverse events and should be considered as a modality of acute pain treatment in children population.

1.0 INTRODUCTION

1.1 Introduction

Acute pain management in children population can be challenging. Children presenting to emergency department with acute severe pain require fast and effective pain relieve, yet evidence showed on the contrary. One study demonstrated that majority of children with painful conditions were less likely to receive adequate analgesia as compared to adult patients with similar conditions (Brown *et al.*, 1990). This was supported by subsequent studies demonstrating on inadequacy of pain relieve in children with burns and fractures and over one third of children with severe fractures did not receive adequate analgesia (Friedland and Kulick, 1994) (Cimpello *et al.*, 2004).

Several barriers have been identified in providing adequate pain management in children. These include different pain behaviours expressed by children, inadequate assessment due to unfamiliarity in scoring pain as well as analgesic dosage among children population, different type of paediatric pain scale assessment and reluctance of medical doctors in using more invasive techniques such as intramuscular or intravenous routes (Drendel A, 2005).

Standard approach in providing pain relieve in children with acute pain involve either administration of oral or rectal analgesia for mild to moderate painful conditions. More significant pain would be treated with parenteral opioid analgesia either by intramuscular or intravenous route. Invasive route of analgesia delivery may lead to significant distress and pain to the children while application of topical anaesthetic agents prior to IV cannulation may cause unacceptable delay in treating acute pain. In addition, peripheral venous cannulation in children is associated with a significant higher failure rate compared to adult (Armin Sabri, 2013). Therefore, availability of other alternative methods of analgesia delivery for instance

nebulization or inhalational route may be able to provide rapid and effective pain relieve without causing additional pain and distress among children with acute pain.

1.2 Literature review

Opioids analgesia remain the mainstay for treatment in acute severe pain regardless whether the patient belongs to paediatric or adult group. Briefly, opioids analgesia are broadly divided into three main classes with fentanyl being in different class; phenylperidine compared to morphine; phenanthrene derivative (MP Sasada, 2011). Opioids are probably used too infrequently with inadequate doses in treating children especially due to unfounded fear of potential side effects (Verghese and Hannallah, 2010). Most of opioids can be given orally, intravenously, rectally or intramuscularly in children population. Adverse effects with opioids use include respiratory depression, nausea, vomiting, pruritus, urticarial or hypotension. Adverse cardiorespiratory complications with opioid use depends on the child age, weight and underlying medical conditions (Verghese and Hannallah, 2010). Infants of less than 3 months of age, premature infants, history of apnoea following opioid use, heart, liver or renal diseases and head injury have increased risk of cardiorespiratory complications secondary to opioid administration. Even though so, the presence of these medical conditions do not preclude the use of opioid analgesics. Children with risk factors may safely be treated with opioid by titrating the doses and use of lower dosage with continuous monitoring of child's haemodynamic status (ACPeds, 2002; Verghese and Hannallah, 2010).

Fentanyl is a short acting synthetic opioid approximately one hundred times more potent than morphine. Fentanyl has rapid onset of action within one minute when given intravenously due to its high lipid solubility and rapid distribution (MP Sasada, 2011). The usual intravenous dose in children is 1-2 mcg/kg (Verghese and Hannallah, 2010). Due to difference of opioid classes compared to morphine, fentanyl does not cause significant histamine release thus account to

minimal risk of cardiorespiratory depressive effects (MP Sasada, 2011). However, in rare occasion fentanyl may potentially cause skeletal and thoracic muscle wall rigidity following rapid intravenous 'push'. This effect is more likely to occur in smaller infants less than six months old given with high dose at 5 mcg/kg but may also manifest at lower dosage; 1-2 mcg/kg especially when given with iv push. Fentanyl induced chest wall rigidity can be managed with iv naloxone; opioid antagonist at dose of 0.01 mg/kg, muscle relaxants such as suxamethonium or rocuronium and mechanical ventilation (ACPeds, 2002; Verghese and Hannallah, 2010).

Pharmacokinetic studies demonstrated that therapeutic plasma concentration of opioids can be achieved through inhalational administration. One of the early pharmacokinetic study on inhalational morphine demonstrated that the absolute bioavailability of inhaled opioids were approximately 20% of the equivalent intravenous dose though this may vary (Chrubasik *et al.*, 1988). Consequently, in light of this early pharmacokinetic evidence of inhaled opioid, it is highly possible that fentanyl being a potent synthetic opioid with high lipophilic property is rapidly absorbed through trans pulmonary mucosa. Further pharmacokinetic study demonstrated on the equipotency of intra venous fentanyl to intra venous morphine was at 1 mcg/kg (Galinski *et al.*, 2005; Gordon, 2007). In view of this, taking into account of 20 % absolute bioavailability of inhaled opioid, therefore the suggested nebulized or inhalational fentanyl dosage is approximately five times higher than the intravenous route i.e. 5 mcg/kg (Farahmand *et al.*, 2014).

Subsequent pharmacokinetic studies on fentanyl citrate demonstrated variably low absolute bioavailability and peak serum concentrations following inhalational route of delivery using standard nebulizer circuit (Paut O, 2003; Worsley *et al.*, 1990). There were several factors affecting the pharmacokinetic properties of inhalational opioids namely design and advancement of nebulization apparatus as well as respiratory physiology of the subjects

(Alexander and Rowbotham, 1998). Studies on nebulization apparatus using radiolabelling technique demonstrated that only 10% of inhaled dose reached the lungs for trans mucosal membrane absorption while the remaining of the drug particles may be deposited in the oropharynx and central airways, adhered to the tubing apparatus or loss during exhalation (McCallion *et al.*, 1996; Newman *et al.*, 1981)

The fentanyl serum concentrations following inhalational delivery were found to be much lower than the suggested therapeutic threshold; 2 ng/ml in spontaneously breathing subjects. The pilot pharmacokinetic study on inhalational fentanyl through standard nebulizer machine at 300 mcg produced a low peak serum concentration; 0.4 ng/ml which later plateaued off at 0.2 ng/ml (Worsely *et al.*, 1990). The lower inhaled fentanyl dosage at 100 mcg only demonstrated a plateau serum concentration at 0.1 ng/ml. These findings were supported by subsequent pharmacokinetic study which demonstrated on variability of peak serum concentration of nebulized fentanyl; 0.63 ng/ml and 1.37 ng/ml with initial concentration of 250 mcg and 500 mcg respectively; significantly lower compared to control group i.e. 4.36 ng/ml that received iv fentanyl 100 mcg (Paut *et al.*, 2003). Interestingly, the time taken to reach peak serum concentration was within five minute whether fentanyl was given via inhalational or IV route. The bioavailability of inhaled fentanyl was found to be less than 30% (25% and 29% for concentration of 250 mcg and 500 mcg respectively). Albeit the notably low absolute bioavailability and lower peak serum concentration compared to suggested therapeutic threshold at 2 ng/ml demonstrated in these studies, fentanyl citrate, being very potent and highly lipophilic delivered via inhalational route was sufficient to cause significant pain score reduction in studied subjects (Paut O, 2003; Worsley *et al.*, 1990) .

Alternative methods of opioid delivery are still new in modern medicine world. Studies had been done in recent years in assessing evidence to support the efficacy and effectiveness of intranasal, inhalational or nebulized fentanyl citrate in delivering rapid pain relieve in various

painful conditions among adult and children population (Deaton *et al.*, 2015; Farahmand *et al.*, 2014; Furyk *et al.*, 2009). However the evidence of inhalational fentanyl in paediatric population has not been strong. Till date there were only 2 randomized control trial (RCT) involving children population (Furyk *et al.*, 2009; JR Miner, 2007). Furyk *et al* in 2009 conducted a RCT comparing the efficacy of nebulized fentanyl to IV morphine in treating children with acute severe limb fractures. In the study, a standard nebulizer circuit was used to administer the nebulized fentanyl at concentration of 4 mcg/kg lower than the suggested nebulized fentanyl dosage at 5 mg/kg. The study demonstrated that nebulized fentanyl was as effective as IV morphine in alleviating pain in children with limb fractures. The evidence derived from this study was consistent with another RCT conducted in adult population with similar inhalational fentanyl dosage i.e. 4 mcg/kg given through standard nebulizer circuit (Farahmand *et al.*, 2014).

The evidence on safety issue of inhaled opioid including fentanyl in treating acute pain is limited partly due to the fact that the utilization of pulmonary route for systemic drug delivery in pain management is relatively recent approach. The potential side effects of inhalational or nebulized fentanyl would be similar to the known side effects associated with its intravenous administration. These include drowsiness, vertigo, nausea, vomiting, hypotension, bradycardia respiratory depression, cough, bronchospasm, muscular rigidity and allergic reactions. The potential direct respiratory side effects of nebulized opioid especially cough or bronchospasm would not be of a major concern with regard to fentanyl citrate as it is associated with minimal allergic risk due to insignificant fentanyl induced histamine release as opposed to morphine (MP Sasada, 2011). While inhalational opioid is still a new approach in pain management, nebulized opioids including fentanyl citrate have already been widely used in treating patient with respiratory symptoms in terminal cancer and other respiratory disease. Nebulized fentanyl citrate and morphine have been found to be effective in reducing dyspnoea and improve oxygen

saturation in terminally ill cancer patient without causing any direct adverse effects to the airway including bronchospasm (Chandler, 1999; Coyne *et al.*, 2002; Graff *et al.*, 2004). With regard to inhalational fentanyl in acute pain management, there was no significant adverse events demonstrated since previous pharmacokinetic studies (Paut O, 2003; Worsley *et al.*, 1990). The RCTs in children did not encounter any adverse events related to administration of fentanyl citrate by inhalational method (Furyk *et al.*, 2009; Miner, 2010). There was no significant change in term of Glasgow Coma Score, Ramsay Sedation Score, blood pressure, respiratory rate or oxygen saturation. The RCT involving adult population also demonstrated on efficacy of nebulized fentanyl citrate without any significant adverse events. (Bartfield *et al.*, 2003; Deaton *et al.*, 2015; Farahmand *et al.*, 2014). No instances of antidote naloxone administration or resuscitative measures such as intubation or ventilation were necessary in all RCTs involving adult and paediatric populations. Even though more work is required to address on the safety concern of inhalational fentanyl, the available evidence so far demonstrated that nebulization fentanyl is both effective and safe.

There are numerous measures and scales for assessing children's pain which can be classified as physiological, behavioural or self-report, depending on the nature of the response that is measured. The physiological parameters of pain may include tachycardia, crying, sweating, blood pressure elevation, flushing and muscle tension. However none of these physiological changes are neither sensitive nor correlate directly with a child experiencing pain. These parameters can be confounded especially by fear, anxiety or fever (Liebelt, 2000). The observation of child's behaviour during acute pain is another method of pain measurement. Presence of brow bulge, eye squeeze, nasolabial furrow, open lips, horizontal stretch mouth and chin quiver may provide an assessment of infant pain expression (Liebelt, 2000). The Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) is reliable in children under age of five years old, which assess pain by examining six pain behaviours- crying, facial

expression, verbal expression, torso position, touch behaviour and leg position – on a 13 point scale ranging from 4 (no pain) to 13 (worst pain) (McGrath *et al.*, 1998). On the other hand, the faces pain scales are more popular pain measures compared to other pain assessment tools as they are simple to use and most children can readily identify with facial expression of actual children or cartoon drawing. The faces pain scales self-report measures on pain intensity in acute, procedural and recurrent pain that can be used reliably for developmentally normal children over four years of age (Chambers *et al.*, 1998). One of the most widely used and best validated faces pain scales is Wong and Baker Faces Pain Scale (WBFPS) (Figure 1). The WBFPS is a well validated, self-reported pain scale commonly used to assess pain in children above four years of age (Bosenberg *et al.*, 2003; Tomlinson *et al.*, 2010) The pain scale consists of six cartoon-like faces, with different pain expression. Each face scale reflects the number of pain score (0-10). 'NO HURT' reflects pain score of 0/10 whereas 'HURT WORST' signifies very severe pain; pain score 10/10. The strength of this scale is its acceptability, given the consistency finding that it is preferred by children, parents and practitioners when compared to other faces pain scales (Chambers *et al.*, 1998; Tomlinson *et al.*, 2010).

Figure 1. Wong and Baker Faces Pain Scale (Wong DL, 1997)

1.3 Justification of study

The ideal pain management in children population should be efficacious, providing rapid pain relieve, easy to administer and most importantly does not cause additional pain or discomfort. Undoubtedly, intramuscular and intravenous route of analgesia delivery would cause more pain and distress to children who is already in pain. Although intravenous analgesia provides advantageous of quick relief and easily titrated, peripheral cannulation can be challenging in any circumstances while intramuscular administration has delayed onset of action, difficult titration and is more painful. Therefore availability of alternative methods of providing fast and rapid analgesia such as inhalational or nebulize route may improve patients care by reducing analgesia time without causing further discomfort and pain. As fentanyl pharmacokinetic properties being highly potent and lipid soluble make it well suited opioid analgesia to be delivered via trans pulmonary delivery.

The evidence on effectiveness of trans pulmonary delivery of fentanyl is limited as inhalational method of opioid delivery is still naive in medical practice. Of particular, there was only one RCT in children in looking into the efficacy of nebulized fentanyl delivered using standard nebulizer circuit in treating children with suspected limb fracture (Furyk *et al.*, 2009). Although the RCT demonstrated favourable outcome but with number of limitations namely small sample size and short duration of study period, new evidence derive from this study will strengthen the available evidence hence forth may serve as preliminary data for further research in the future.

1.4 Objectives of study

General Objective

To assess the effectiveness of nebulized fentanyl citrate in treating children with acute severe pain.

Specific Objectives

I. To determine the effectiveness of nebulized fentanyl citrate in reducing pain score in children with acute severe pain of various aetiologies.

II. The primary end point is to analyze whether administration of nebulized fentanyl citrate using a standard nebulizer circuit will result in significant decrease on pain score among children with acute pain.

III. To assess side effects following treatment with nebulized fentanyl citrate in acute pain among children.

CHAPTER 2: STUDY PROTOCOL

2.1 Study protocol submitted for ethical approval

Study design

This is a single arm prospective interventional clinical study. The study does not include randomization or placebo control. The primary end point is to evaluate the effectiveness of nebulized fentanyl in causing clinically significant pain score reduction in children presented to our emergency department with acute severe pain of various aetiologies. The main purpose of this study is to advocate fast and effective analgesia delivery in children without causing other unnecessary pain and discomfort. As peripheral venous cannulation in children is associated with high failure rate, this may potentially cause increase in dropout rate which may negatively affect the study protocol. Furthermore, administration of nebulized placebo is not ethically or humanly acceptable in treating acute severe pain. In addition, this is also to avoid protocol violation which had occurred in one previous RCT in which the parents requested for their children to be in nebulized fentanyl group as to avoid intravenous cannulation if possible (Miner *et al.*, 2007).

Study duration

Study duration is planned from January 2017 until Mac 2017.

Study location

Emergency Department, Hospital Universiti Sains Malaysia (HUSM), Kubang Kerian, Kelantan, Malaysia.

Reference population

Children presenting to Emergency Department Hospital Universiti Sains Malaysia with acute pain of various cause.

Study population

Children aged five to fifteen years old presenting to Emergency Department Hospital Universiti Sains Malaysia with acute pain of various causes in the period from January 2017 till Mac 2017.

Study participants

Children aged five to fifteen years old presenting to Emergency Department Hospital Universiti Sains Malaysia with acute pain of various cause in the period from January 2017 till Mac 2017 and fulfill inclusion and exclusion criteria.

INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria

i. Children aged five to fifteen years old with acute pain of various aetiologies presented to Emergency Department Hospital Sains Malaysia.
ii. Pain score > 6 /10 assessed by Wong & Baker Faces Pain Scale (WBFPS)
iii. American Society of Anaesthesiologist (ASA) classification I or II.
iv. Consented parents or legal guardians.

Exclusion criteria

i. Underlying medical conditions which include heart, liver, renal diseases and malignancy.

ii. Underlying bronchial asthma on preventer or having acute exacerbation on presentation.

iii. Concurrent upper respiratory tract infection.

iv. Concurrent lower respiratory tract infection.

v. Concurrent head injury including cerebral concussion.

vi. ASA classification > II.

vii. received iv narcotics (opioids) or any other oral, parenteral and suppository analgesia four hours prior to presentation

viii. Known allergy to opiod analgesia.

ix. Pain score < 6/10 assessed by Wong & Baker Faces Pain Scale (WBFPS)

Sampling Method

Convenience sampling will be used for sampling method. All children aged five to fifteen years old with acute severe pain of various aetiologies (pain score > 6/10 on WBFPS), fulfill inclusion and exclusion criteria and consented by parents or legal guardians will be included in the study.

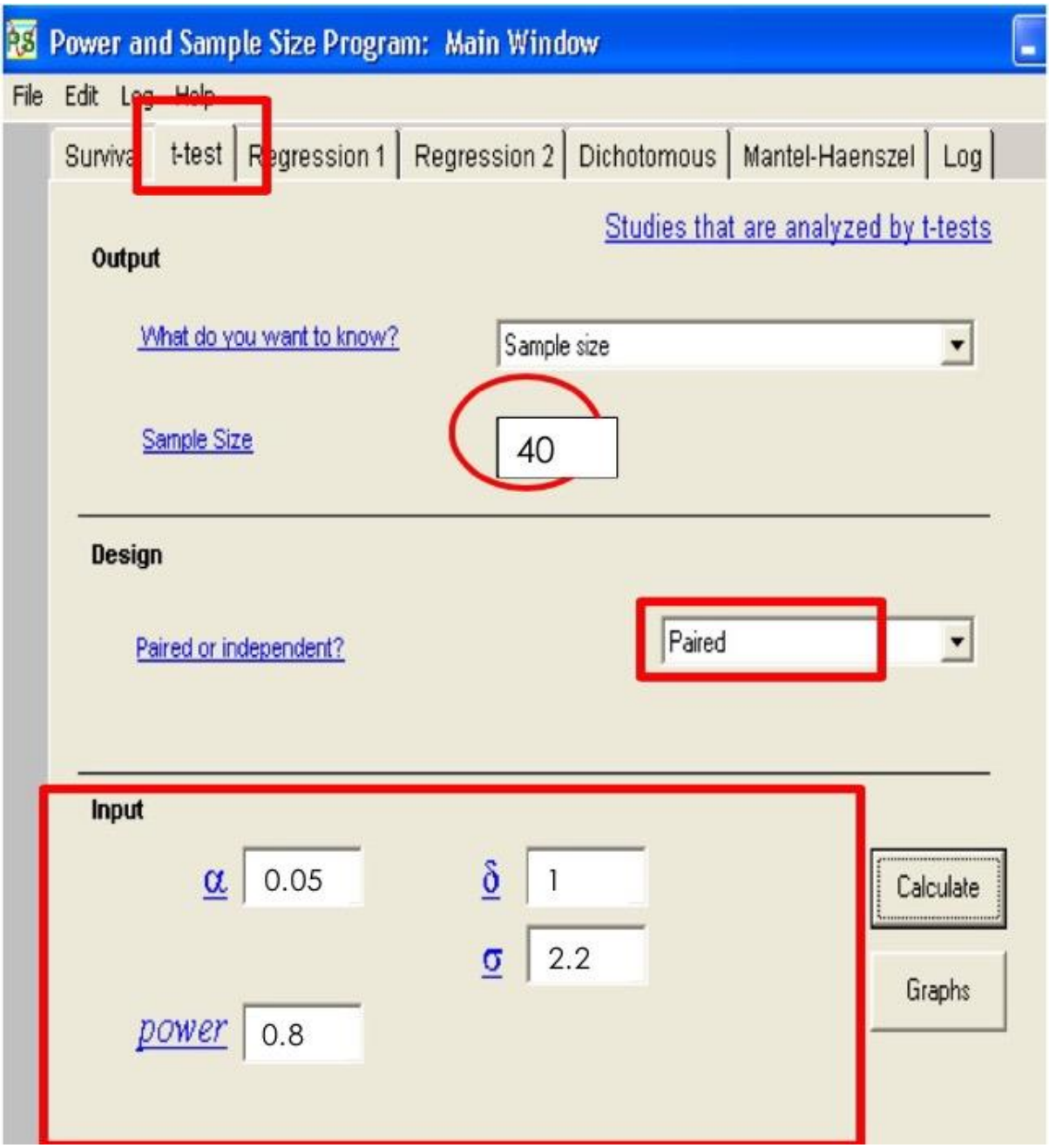
Sample Size Calculation

Sample size calculation is determined using **software PS: Power & Sample Size Calculation Version 3.1.2. 2014** developed by William D. Dupont and Walter D. Plummer Jr.

The details on sample size calculations are as follow:

- Standard Deviation SD: 2.2 (Furyk *et al.*, 2009)
- Minimum clinically significant difference (MCSD) of pain score (σ): 1 (Deborah Tomlinson, 2010)

- Power of study: 80%
- Type 1 error (α): 0.05 → Zα: 1.96 (normal deviation reflecting Type 1 error / 95% CI)
- Consider 10% drop out rate
- Total number of patient (n): 42



Research protocols and data collection

Eligibility of patients to be included in the study will be determined by age group, inclusion and exclusion criteria as was listed above. Suitable candidate will be sampled into the study only after written consent has been obtained from the parents and legal guardians. Assent will also be obtained from children above twelve years old. Details of the study protocols which include the aim and the objectives, flow and study procedures as well as complication monitoring will be addressed in written consent.

Study procedures will be carried out in yellow zone with availability of emergency trolley. The procedures will neither interrupt nor changed patients' definitive management. Intravenous cannulation and blood taking procedure would still be done after patient have achieved satisfactory control over severe pain. Topical anaesthetic agent will be applied shortly after enrolment to facilitate peripheral venous cannulation.

Demographic information and initial vital signs with pain score assessment will be recorded prior to treatment with nebulized fentanyl citrate. The pre- treatment parameters are as following:

Demographic parameters:

1. Age (years)
2. Gender (Male, Female)
3. Weight (kg)
4. Underlying medical conditions
    a. Heart disease
    b. Liver disease
    c. Renal disease
    d. Malignancy

e. Bronchial asthma

f. Known allergy to opioid analgesia

5. ASA classification
6. Diagnosis on presentation

Vital signs parameters:

1. Glasgow Coma Scale (GCS)
2. Ramsay Sedation score (RSS)
3. Blood pressure (BP)
4. Heart rate (HR)
5. Respiratory rate (RR)
6. Oxygen saturation (SPO 2)
7. Pain score

Pain score assessment will be done using the **Wong and Baker Faces Pain Scale (WBFPS)** (Wong DL, 1997) (Figure 1). The pain scale consists of six cartoon-like faces, with different pain expression. Each face scale reflects the number of pain score (0-10). 'NO HURT' reflects pain score of 0/10 whereas 'HURT WORST' signifies very severe pain; pain score 10/10. Patients will be shown the pain scale and they chose the most appropriate cartoon-like face that reflect their pain. In this study, the pain score assessment will be done by different doctors and they will be blinded from each previous pain score assessment. Children that is not able to score the pain will be excluded from the study.

Figure 1. Wong and Baker Faces Pain Scale (Wong DL, 1997)

Nebulized fentanyl is prepared by mixing the intravenous preparation of fentanyl citrate, calculated at 4 mcg/kg with 0.9% normal saline to a five cc solution. Of note, previous works had also used intravenous preparation of fentanyl citrate in their studies (Farahmand *et al.*, 2014; Furyk *et al.*, 2009; Miner *et al.*, 2007). The maximum dosage of fentanyl citrate is 200 mcg regardless whether the calculated dosage exceeded body weight. The medication will be administered to patients as oxygen driven nebulization at 5 L/ min using a standard nebulizer circuit available in our emergency department. The nebulization time is approximately ten minutes of administration. Continuous vital signs monitoring will be done throughout study period. Subsequently, vital signs recording including GCS, RSS, BP, HR, RR, SPO2 and pain score will be done serially at five minutes interval until sixty minutes post nebulized fentanyl administration.

Treatment failure is determined by unsatisfactory pain control ten minutes on administration of nebulized fentanyl or increasing pain during observation period. Treatment would be reverted to standard care which include immediate placement of peripheral venous cannulation and administration of iv morphine at 0.5 mg every five minute until satisfactory pain control achieved or to a total of 0.1 mg/kg. This is determined at the discretion of attending physician and will be considered as treatment failure. Patients would also be withdrawn from the study if they develop any adverse effects related to fentanyl citrate administration. Any adverse events would be recorded and addressed immediately with appropriate managements according to standard operation procedure (SOP) incorporated in study protocol.

Adverse effects monitoring and interventions

Continuous vital signs monitoring will be done throughout the procedures. Potential side effects of the treatment will be monitored, recorded and treated accordingly. Iv Naloxone, an opioid antagonist will be made available by bed side along with emergency trolley equipped with advanced airway intervention devices. The potential side effects are as following:

1. Hypotension
2. Bradycardia
3. Apnoea
4. Bronchospasm
5. Oxygen desaturation
6. Nausea & vomiting
7. Drop in GCS
8. Anaphylactic reaction
9. Muscular rigidity

The potential risk of direct respiratory side effects of nebulized opioid for instance cough or bronchospasm is minimal as previous works have demonstrated on efficacy of nebulized fentanyl citrate and morphine from intravenous preparation as treatment of dyspnoea in terminal cancer and respiratory disease without causing any undesired aforementioned side effects (Chandler, 1999; Coyne *et al.*, 2002; Graff *et al.*, 2004). Moreover, unlike morphine fentanyl cause insignificant histamine release thus has minimal risk of anaphylactic reactions such as airway obstruction, cough, bronchospasm or hypotension (MP Sasada, 2011; Tintinalli JE, 2004).

Of note, none of RCT on nebulized Fentanyl Citrate involving adult and paediatric population demonstrated any significant or life threatening adverse effects (Bartfield *et al.*, 2003; Deaton

et al., 2015; Farahmand *et al.*, 2014; Furyk *et al.*, 2009; JR Miner, 2007) No instances of antidote naloxone administration or resuscitative measures such as intubation or ventilation were necessary in all RCTs involving adult and paediatric populations. Even though more work is required to address on the safety concern of inhalational fentanyl, the available evidence so far demonstrated that nebulization fentanyl is both effective and safe. *(Please refer to literature review page 6-7).*

The specific management and interventions of above mentioned potential side effects are addressed in detailed in Appendix A

Data entry and data analysis

Statistical analysis will be done using Statistical Packages for Social Science (SPSS) version 22.0. Descriptive analysis will be expressed in frequencies and percentage for categorical variables. Means and standard deviation will be expressed in numerical variables. Difference between pain scores at pre-treatment and 10, 15, 20, 25, 30, 35, 40, 45, 50, 55 and 60 minutes post treatment will be assessed using paired t-test and repeated measure analysis of variance (ANOVA). A p value < 0.05 is considered as statistically significant for all statistical analysis in this study. A 95% confidence interval; CI will be calculated for the primary outcome of decrease in pain score in between time intervals post treatment. Decrease of one unit of faces pain scale is selected as the minimum clinically significant difference (MCSD) of pain score reduction. This is in line with previous works demonstrating that the minimum clinically significant reduction of pain score in children is either 10 mm on the 100 mm visual analogue scale (VAS) or one faces pain scale (Bulloch B, 2002; Deborah Tomlinson, 2010).

Data Privacy & Confidentiality

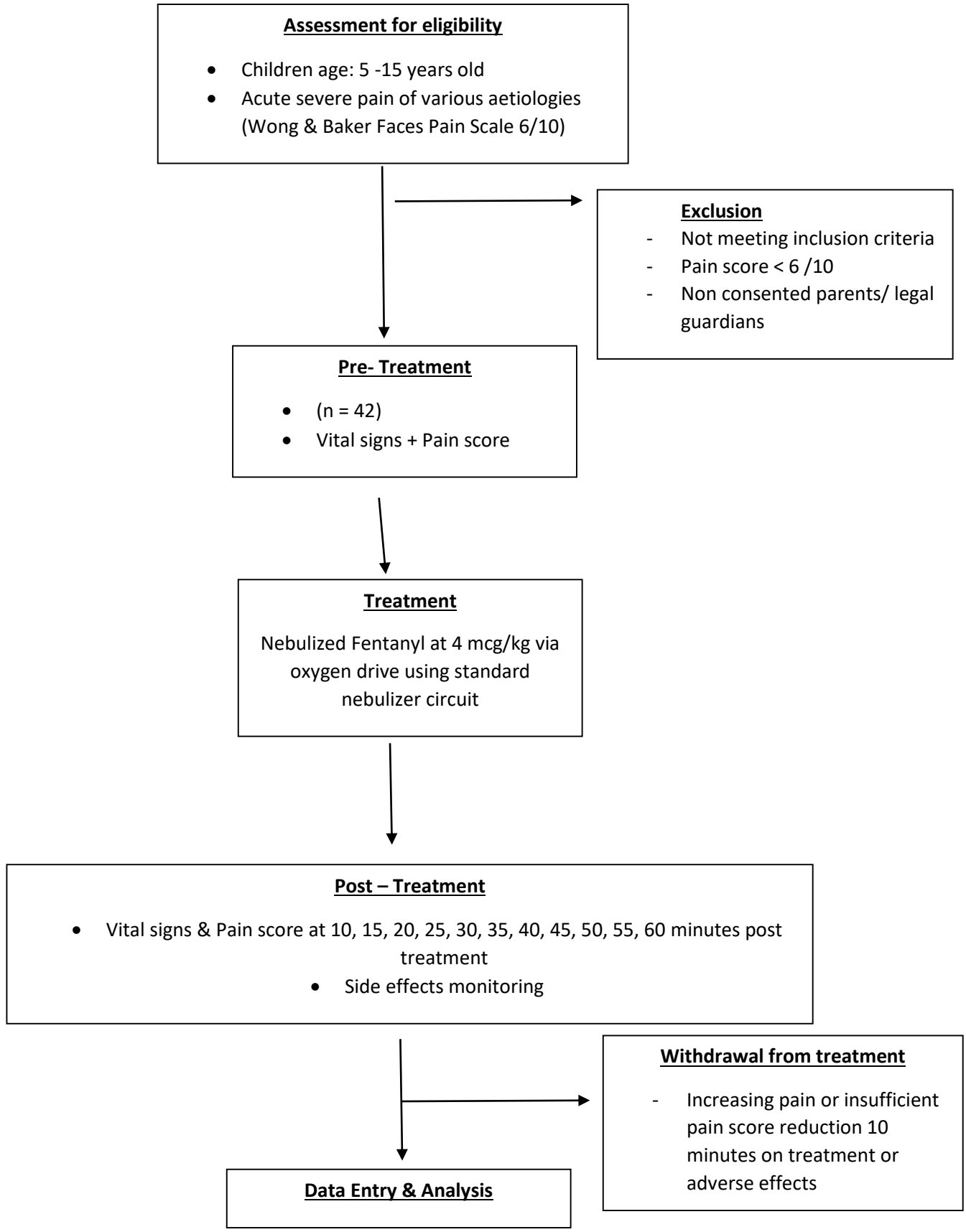
All information, copy of informed consent and data collected during the study procedure will be properly stored and locked in a locker in a designated area within Emergency Department of Hospital Universiti Sains Malaysia. All aspects concerning privacy and confidentiality will be maintained at all time and the data and information would only be accessible to primary investigator. All information will be properly stored up to two years upon completion of this study.

Ethical Issue

Inform written consent will be obtained before inclusion into this study.

Ethical approval will be obtained from the Research and Ethics Committee of the School of Medical Sciences, USM

FLOW CHART OF RESEARCH PROCEDURES



STUDY ON THE EFFECTIVENESS OF NEBULIZED FENTANYL AS MODALITY OF ANALGESIA IN CHILDREN WITH ACUTE PAIN RESEARCH PROTOCOL

PRIMARY INVESTIGATOR: DR RADEN NEZARUL BIN RADEN YAHAYA

SUPERVISOR: DR ABU YAZID BIN MD NOH

INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria

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vi. Pain score > 6 /10 assessed by Wong & Baker Faces Pain Scale (WBFPS)

vii. American Society of Anaesthesiologist (ASA) classification I or II.

viii. Consented parents or legal guardians.

Exclusion criteria

x. Underlying medical conditions which include heart, liver, renal diseases and malignancy.

xi. Underlying bronchial asthma on preventer or having acute exacerbation on presentation.

*******Patient with bronchial asthma is eligible if not on preventer inhaler and having acute exacerbation on enrollment.*

xii. Concurrent upper respiratory tract infection.

xiii. Concurrent lower respiratory tract infection.

xiv. Concurrent head injury including cerebral concussion.

xv. ASA classification > II.

xvi. Received iv narcotics (opioids) or any other oral, parenteral and suppository analgesia four hours prior to presentation

xvii. Known allergy to opiod analgesia.

xviii. Pain score < 6/10 assessed by Wong & Baker Faces Pain Scale (WBFPS)

STUDY ON EFFECTIVENESS OF NEBULIZED FENTANYL AS MODALITY OF ANALGESIA IN CHILDREN WITH ACUTE PAIN

DATA COLLECTION FORM/PROFOMA

Demographic Data

Age:_____ Date/RN:_____ Gender: M/F Weight: _____

Underlying medical conditions: **EXCLUDE IF PATIENT HAS ANY OF THESE CRITERIA**

i.	Heart disease	: Y / N
ii.	Liver disease	: Y / N
iii.	Renal disease	: Y / N
iv.	Malignancy	: Y / N
v.	Bronchial Asthma (on preventer or current exacerbation)	: Y / N
vi.	Concurrent upper or lower respiratory tract infection	: Y / N
vii.	Head injury including cerebral concussion	: Y / N
viii.	Known history of allergy to opioids analgesia	: Y / N
ix.	Receive IV narcotics 4 hours prior	: Y / N

Diagnosis: _____

ASA Classification: I / II (**EXCLUDE IF ASA > II)**

AMERICAN SOCIETY OF ANAESTHESIOLOGY RISK CLASSIFICATION (ASA)

Class	Condition
I	Normal healthy patient with no systemic illness
II	Mild to moderate systemic disease
III	Severe systemic disease with functional limitation that is otherwise incapacitating
IV	Severe systemic disease that is incapacitating and life threatening
V	Moribund patient not expected to survive 24 hours without surgical interventions

INSTRUCTION OF MEDICATION PREPARATION AND METHODS OF ADMINISTRATION

1. **Calculate 4 mcg/kg (max 200mcg) of Fentanyl Citrate & mix with 0.9% Normal Saline solution to make up to 5cc solutions.**
    a. DRUG DOSE: _____
2. Administer the medication to patient via oxygen drive nebulization at 5 L / min using standard nebulizer circuit available in emergency department.
3. Make sure SPO2 and HR is monitored throughout the procedures.
4. If patient still having severe pain 10 minutes after nebulization, rescue medication should be given.
    a. Give IV morphine at dose of 0.5 mg per minute to total dose of 0.1 mg/kg
        i. Dose of IV morphine :
5. Criteria of withdrawal from the study:
    a. Patient's request

b. Parents/legal guardian request

c. Treatment failure -require rescue medications

d. Adverse events requiring interventions

RAMSAY LEVEL OF SEDATION

Level of Sedation	Score
Awake Levels	
Patient either anxious or agitated or both	1
Patient is tranquil, cooperative & orientated	2
Patient respond only to command	3
Asleep level	
Brisk response to light glabellar tap or loud auditory stimulus	4
Sluggish response to light glabellar tap or loud auditory stimulus	5
No response to painful stimuli	6

*** Reference: M. A. E Ramsay*

WONG & BAKER FACES PAIN SCALE