An Open Label Randomized Controlled Trial On The Efficacy Of Adding Intranasal Fentanyl To Intravenous Tramadol In Patients With Moderate To Severe Pain Following Acute Musculoskeletal Injuries

By

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LIST OF ABBREVIATIONS

CI	Confidence interval
HUSM	Hospital Universiti Sains Malaysia
MAD	Mucosal atomizer device
MAP	Mean arterial pressure
MAP_Diff	Mean arterial pressure difference
SD	Standard deviation
VAS	Visual analogue scale
VAS_Diff	Visual analogue scale difference

ABSTRACT

An open label randomized controlled trial on the efficacy of adding intranasal fentanyl to intravenous tramadol in patients with moderate to severe pain following acute musculoskeletal injuries

Introduction: Intra-nasal fentanyl, as an alternative route of analgesic administration, has been shown to be effective particularly in pediatric population and in prehospital setting. Studies on such use among adult patients in emergency department are limited. **Methods:** An open-label study was conducted to evaluate the effectiveness of adding 1.5 mcg/kg intranasal fentanyl on top of 2 mg/kg intravenous tramadol (FENTANYL_TRAMADOL, n = 10) as compared to 2 mg/kg intravenous tramadol alone (TRAMADOL, n = 10) in adult patients with acute musculoskeletal injuries in moderate to severe pain. **Results:** When analyzed using independent t-test, the mean visual analog scale (VAS) difference between pre- and 10-minute post-intervention was found to be 29.8 mm (SD +/- 8.4 mm) in the FENTANYL_TRAMADOL arm and 19.6 mm (SD +/- 9.7 mm) in the TRAMADOL arm [t(8) = 2.515, p = 0.022, 95% confidence interval (CI) 1.68 to 18.72 mm]. A significantly greater albeit transient reduction in mean arterial pressure 10 minutes post-intervention was noted in the FENTANYL_TRAMADOL arm as compared to those in the TRAMADOL arm (13.35 mmHg vs 7.65 mmHg, using Mann-Whitney U test with U-value = 21.5; p = 0.029; r = 0.48). Patients in the FENTANYL_TRAMADOL arm also experienced a higher incidence of transient dizziness 10 minutes post-intervention. **Conclusion:** Although effective, intra-nasal fentanyl in adult patients may not be ready for primetime as it may result in significant reduction in blood pressure.

ABSTRAK

Kajian rawak label terbuka efikasi penggunaan intranasal fentanyl bersama intravena tramadol pada pesakit tahap kesakitan sedang dan teruk disebabkan kecederaan otot dan tulang akut

Pengenalan : Intra-nasal fentanyl sebagai laluan administrasi analgesic alternative telah terbukti efektif lebih-lebih lagi pada populasi pediatrik dan untuk kegunaan prehospital. Kajian pada populasi dewasa masih terhad. **Metodologi :** Kajian label terbuka dibuat untuk menilai tahap efektif penambahan 1.5 mcg/kg intranasal fentanyl ke atas 2 mg/kg intravena tramadol (FENTANYL_TRAMADOL, n = 10) berbanding penggunaan 2 mg/kg intravena tramadol secara bersendirina (TRAMADOL, n = 10) pada pesakit dewasa yang mempunyai kecederaan tulang dan otot akut dengan tahap kesakitan sedang sehingga teruk. **Keputusan :** Analisis di buat menggunakan 'independent t-test ', perbezaan min 'visual analogue scale (VAS)' sebelum dan 10 minit selepas intervensi adalah 29.8 mm (SD +/- 8.4 mm) untuk kumpulan FENTANYL_TRAMADOL dan 19.6 mm (SD +/- 9.7 mm) untuk kumpulan TRAMADOL [t(8) = 2.515, p = 0.022, 95% confidence interval (CI) 1.68 to 18.72 mm]. Penurunan signifikan 'mean arterial pressure (MAP)' yang berlaku sementara terjadi pada minit ke 10 selepas intervensi dapat dilihat pada kumpulan FENTANYL_TRAMADOL berbanding kumpulan TRAMADOL (13.35 mmHg vs 7.65 mmHg, Mann-Whitney U test with U-value = 21.5; p = 0.029; r = 0.48). Pesakit kumpulan FENTANYL_TRAMADOL juga mengalami simptom pening yang lebih tinggi berbanding kumpulan TRAMADOL tetapi ia berlaku hanya untuk waktu sementara 10 minit selepas intervensi. **Konklusi :** Walaupun efektif, fentanyl intranasal untuk pesakit dewasa masih belum bersedia untuk digunakan secara meluas disebabkan ia dapat menyebabkan penurunan tekanan darah yang signifikan.

ABSTRACT

AN OPEN LABEL RANDOMIZED CONTROLLED TRIAL ON THE EFFICACY OF ADDING INTRANASAL FENTANYL TO INTRAVENOUS TRAMADOL IN PATIENTS WITH MODERATE TO SEVERE PAIN FOLLOWING ACUTE MUSCULOSKELETAL INJURIES

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Introduction: Intra-nasal fentanyl, as an alternative route of analgesic administration, has been shown to be effective particularly in pediatric population and in prehospital setting. Studies on such use among adult patients in emergency department are limited.

Objectives: The aim of this study was To compare intranasal fentanyl with intravenous tramadol as analgesia with intravenous tramadol

Methods: An open-label study was conducted to evaluate the effectiveness of adding 1.5 mcg/kg intranasal fentanyl on top of 2 mg/kg intravenous tramadol (FENTANYL_TRAMADOL, n = 10) as compared to 2 mg/kg intravenous tramadol alone (TRAMADOL, n = 10) in adult patients with acute musculoskeletal injuries in moderate to severe pain.

Results: When analyzed using independent t-test, the mean visual analog scale (VAS) difference between pre- and 10-minute post-intervention was found to be 29.8 mm (SD +/- 8.4 mm) in the FENTANYL_TRAMADOL arm and 19.6 mm (SD +/- 9.7 mm) in the TRAMADOL arm [t(8) = 2.515, p = 0.022, 95% confidence interval (CI) 1.68 to 18.72 mm]. A significantly greater albeit transient reduction in mean arterial pressure 10 minutes post-intervention was noted in the FENTANYL_TRAMADOL arm as compared to those in the TRAMADOL arm (13.35 mmHg vs 7.65 mmHg, using Mann-Whitney U test with U-value = 21.5; p = 0.029; r = 0.48). Patients in the FENTANYL_TRAMADOL arm also experienced a higher incidence of transient dizziness 10 minutes post-intervention.

Conclusion: Although effective, intra-nasal fentanyl in adult patients may not be ready for primetime as it may result in significant reduction in blood pressure.

Dr Nik Arif Nik Mohamed : Supervisor

1. INTRODUCTION

1.1 Overview

Pain is the most common reason for patients come attending the emergency department (ED) (Tanabe and Buschmann, 1999a). Adequate analgesia in EDs is an important goal of treatment. In emergency department pain intensity is high, and most of the time analgesics are underutilized at the same time delays to treatment are common. Most patients whom presented to ED with complain of pain expected rapid delivery of pain medication after arrival in ED (Fosnocht *et al.*, 2001). According to Grant (2006), there was a significant delay in patients with acute pain receiving any form of analgesia.

In United States and Canada, the median time interval from triage to analgesic administration was 90 minutes and it was stated in a study that only 29% of patients who were given analgesics received them within 1 hour of arrival. The most common analgesics administered were opiods and morphine being the most commonly used followed by ibuprofen (Todd *et al.*, 2007).

In certain cases, physician working in ED need to consider certain pertinent issues such as ease of intravenous (IV) access and patient preference for analgesia route of administration and most of the time for patient with severe pain, intravenous analgesia is usually preferable (Thomas, 2013). However there are few other available routes that promise

good analgesia delivery which provide adequate pain control such intranasal and oral transmucosal (Lotsch *et al.*, 2013).

The intranasal route is a convenient form of delivery that is applicable to several opioids and has the potential for self-administration, combined with a rapid onset of action. It has been increasingly viewed as a new alternative route for drug administration and it has been proven to be useful in-hospital and out-of-hospital pain management (Prommer and Thompson, 2011)

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It is important for a clinican in ED to know how to manage pain properly and decide which drug is better including the route of administration which may affect the onset and the ease of administration of the drug. Different route of drug administration will have different time of onset and less invasive route is much more preferred as it may avoid unnecessary difficulties. As in ED, it is best to treat pain in a fast and effective way. This might improve outcome of patient as pain may cause patient to be anxious and they may feel loss of control.

1.2 *Objective*

1.2.1 General Objective :

To compare intranasal fentanyl with intravenous tramadol as analgesia with intravenous tramadol

1.2.2 Specific Objective :

To compare mean of pain score between intranasal fentanyl with intravenous tramadol and intravenous tramadol alone.

To compare mean arterial pressure and incidence of side effects in between both group.

1.2.3 Research Question :

1. Does intranasal fentanyl together with intravenous tramadol reduce pain score better than intravenous tramadol alone?
2. Does intranasal fentanyl together with intravenous tramadol reduce mean arterial pressure more than intravenous tramadol alone?
3. Does intranasal fentanyl together with intravenous tramadol cause more side effects than intravenous tramadol alone?

1.2.4 Hypothesis :

Intranasal fentanyl together with intravenous tramadol has significant difference of mean than intravenous tramadol alone as an analgesia.

1.2.5 Term Definition :

Pain : An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (Merskey *et al.,* 1986)

Intranasal : Occurring within or administration through nose.

Intravenous : Within or administered through venous.

Visual Analog Scale : pain measurement instrument.

Musculoskeletal injury : related to muscles or bones damage.

2. LITERATURE REVIEW

Pharmacologic agent administration for analgesia is still the main modality to treat pain. It is important to select appropriate pharmacologic agent for analgesia to effectively manage pain as in acute pain usually accompanied by anxiety. There are various type of analgesic available in emergency department and tramadol and fentanyl is part of it.

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (Merskey *et al.*, 1986). It is an unpleasant sensation that brain interprets after a peripheral lesion of nociceptive intensity (MOTOC *et al.*, 2010). There are 3 types of fibers that carry pain signals to the brain which are A-beta, A-delta and the unmyelinated C fibers (Ard and Haines, 2002).

Physiological pain model focus on underlying causative mechanism which can be due to either nociceptive pain which is a normal functioning nociceptive system alerting the brain to bodily injury such as pain due to acute musculoskeletal injury or neuropathic and central pain which is a manifestation of nociceptive system dysfunction (Woessner, 2002).

As for management of pain in general, WHO ladder for pain management can be used as a guide for choosing the proper analgesia which suggest the use of opioids in pain management (Vargas-Schaffer, 2010). Tramadol a synthetic opioid of the aminocyclohexanol group and is widely being used in management of moderate to severe pain in emergency department (Ahmad *et al.*, 2010). It is usually administered via oral, intramuscular and intravenous route and it has analgesic potency equivalent to pethidine (Smith *et al.*, 2011). As

for fentanyl, it is a synthetic phenylpiperidine derivative which is 50 to 80 times more potent analgesic than morphine (Smith *et al.*, 2011).

Opiod is the main analgesia used in moderate to severe pain but its use is usually affected by concern that it can cause adverse event such as hypotension and sometime we are concerned of drug seeking behavior (Ducharme, 2015) . At the same time opioids also may cause vomiting and nausea. Due to this reason we need to consider few factors to make proper use of opiod as analgesia. Example of this include route of administration and desired time of onset, initial dose, frequency of administration which is titrated against analgesic response, concurrent use of nonopioid analgesics and adjunctive agent, incidence and severity of side effects and lastly whether the analgesic will be continued in an inpatient or ambulatory setting (Ducharme, 2015).

Despite of all documented adverse event related with opioid use, there are differences between clinical pharmacology and laboratory pharmacology for opioids. There will be differences when opioids is given to a person who suffer from pain and a person who is not in pain. As an example, respiratory depression was seen in studies of volunteers who are not in pain but respiratory depression was kept to a minimum when appropriate regular doses of opioids are given to patients with pain (McQuay, 1999).

According to McQuay (1999), to attain differences of time of onset of an opiod is achieved by changing the route of administration or formulation. Fast onset of effect is not a critical factor if the patient is receiving continuous analgesic for chronic pain. However, it is relevant in patients taking the drug on as-needed basis for acute pain (McQuay, 1999).

Opioids act at the relay station of nociceptive-propagating pathways. It has the property to bind at specific receptor site at pre- and post terminal nerve endings resulting in an inhibition of a release of the excitatory neurotransmitter of the nociceptive-propagating pathways. Due to the inhibition, impulse is interrupted and nociceptive signal is no longer transmitted. It is different if compared to analgesic which has peripheral site of action (Freye, 2008).

Anesthetic delivery has been the same for the past 150 years. The new routes and delivery systems promise improved convenience, improved safety, increased effectiveness, increased bioavailability, continuous delivery with fewer peaks and valleys, decreased side effects, decreased dosage and frequency of administration, and decreased cost. One of the important delivery systems in the near future is transmucosal drug delivery which include nasal, buccal, ocular, rectal, and mucosa (Stanley, 2000). Mucosal membranes are thinner and more highly vascularized, there is the potential of giving large molecules, like peptides and proteins. Because their drug delivery is much faster, the transmucosal systems also allow the possibility of titrating drugs and thus provide enhanced flexibility (Stanley, 2000).

The nasal mucosa is highly vascularized. The blood-vascular system is only separated of the nasal lumen by two cell layers (Marttin *et al.*, 1998), which offers the possibility of a rapid drug absorption. Nasal drug delivery can be an attractive alternative to intravenous and intramuscular injections. This is one good reason to promote intranasal route for drug administration. Intravenous and intramuscular administration is invasive and sometime may cause discomfort to patient (Hartstein and Barry, 2008). At the same time it will take some time for clinician to establish an intravenous line for drug administration. The human nasal

mucosa contains drug-metabolising enzymes but the extent and clinical significance of human nasal first-pass metabolism is unknown (Dale *et al.*, 2002).

The widespread interest in intranasal route for therapeutic purposes other than the topically nasal drug delivery arises from the particular anatomical, physiological and histological characteristics of the nasal cavity, which provides potential for rapid systemic drug absorption and quick onset of action (Mygind and Dahl, 1998). In addition, intranasal absorption avoids the gastrointestinal and hepatic presystemic metabolism, enhancing drug bioavailability in comparison with that obtained after gastrointestinal absorption (Leonard *et al.*, 2007).

A study of patient-controlled intranasal analgesia (PCINA) in acute postoperative pain which used intravenous fentanyl solution for intranasal route showed that patient satisfaction is comparable to patient-controlled intravenous analgesia and intranasal route for analgesia represents an interesting alternative non-invasive method (Striebel *et al.*, 1996). Intranasal fentanyl at the standard intravenous concentration of 50 mcg/mL appeared to be an effective analgesic for children in the emergency setting presenting with acute injuries (Crellin *et al.*, 2010). As compare to other intranasal analgesic agent, fentanyl in concentration of 50 mcg/mL is easily available without need to further concentrate the drug preparation which may be costly.

Previously intranasal diamorphine shown to be as efficacious as intramuscular morphine sulphate with a plus point that it was better tolerated and accepted especially in children. Intranasal diamorphine is effective, safe, and acceptable method of analgesia for children requiring opiates in the A & E department (Wilson *et al.*, 1997). However because of

its limited availability cause limitation of its use. As for fentanyl, it is widely available in our emergency department which make it easily accessible in daily practice.

Intranasal fentanyl has been shown to have therapeutic serum levels in 2 minutes, reflecting the good venous outflow of nasal mucosa and the bypassing of the liver, avoiding hepatic first-pass metabolism (Borland *et al.,* 2005). Intranasal fentanyl has a bioavailability of 89%, with a short onset of action approximately 7 min and duration times approximately 1 hour (Panagiotou and Mystakidou, 2010). In the clinical setting, intranasal fentanyl can be administered promptly into the nasal cavity without the delays resulting in effective analgesia. As per previous study for intravenous tramadol, onset of the effect of intravenous tramadol already can be seen at 10 minutes post drug administration which resulted in a significant pain reduction (Ahmad *et al.*, 2010). Hence this study used 10 minutes as the time to measure pain score to compare which group provide pain relief faster than the other group.

According to Hansen and Dahl (2013), there were only limited quality evidence exists for the efficacy of intranasal fentanyl in ED. More double-blinded, randomized controlled trials are needed to validate the use of intranasal fentanyl in ED. It must be highlighted that only three studies involving use of intranasal fentanyl which involved adults related to presentation to emergency department and all of them were done in prehospital setting (Hansen and Dahl, 2013).

Previous study done in emergency department which involved children showed that there were no significant adverse effects of intranasal fentanyl noted (Borland *et al.*, 2007). In another study done in emergency department, there were no significant desaturations, reductions in respiratory rate or bradycardias observed (Younge *et al.,* 1999). There was also

no significant differences in pulse rate, respiratory rate, blood pressure or oxygen saturations even when improvement in pain scores had been achieved (Borland *et al.*, 2002). This is very important in choosing pharmacologic agent for analgesia as clinician would prefer analgesia with less adverse effects and ease of administration.

Prehospital use intranasal fentanyl in adult population was also promising as previous study done in prehospital setting showed that intranasal fentanyl was an effective analgesic agent and it may be offset to some degree than intravenous morphine as it requires no intravenous access to administer even if IV morphine appear more effective than intranasal fentanyl (Middleton *et al.*, 2010).

As per survey done by Paediatric Research in Emergency Departments International Collaborative (PREDICT) done in Australia and New Zealand which include all pediatric emergency department and several large mixed emergency department, it is recommended that intranasal fentanyl dose to be use is 1.5 mcg/mL and certain emergency department reported use of intranasal fentanyl dose from 1-2 mcg/mL. Eleven emergency department use standard intravenous formulation 50mcg/mL solution and two other emergency department use a specially produced concentrated fentanyl solution at 150 mcg/mL (Herd and Borland, 2009). This showed that the easily available fentanyl citrate is effective and can be used as analgesia in emergency department. However there were limited evidence regarding its use in adults.

Visual analog scale (VAS) are among the most commonly used measures of pain intensity in clinical trials (Jensen *et al.*, 2003). It is a unidimensional scale which is easy to use, requires no verbal or reading scale and is sufficiently versatile to be employed in a

variety of setting (Gallagher *et al.*, 2001). Based on previous study, findings suggested that VAS ratings of 0 to 4 milimeter (mm) can be considered as no pain; 5 to 44 mm as mild pain; 45 to 74 mm as moderate pain; 75 to 100 mm as severe pain (Jensen *et al.*, 2003). VAS is a self-completed by the respondent. The respondent is asked to place a line perpendicular to VAS line at the point that represents their pain intensity. Using a ruler, the score is determined by measuring the distance (mm) on the 10-cm line between the "no pain" anchor and the patient's mark, providing a range of scores from 0–100 (Hawker *et al.*, 2011). It takes less than one minute to complete (Downie *et al.*, 1978).

There were limited evidence regarding the use of intranasal fentanyl in adults with acute pain during their presentation at emergency department and for this reason, it is important for this study to be done. Tramadol is a common drug used in emergency department. Previous study already proves that fentanyl administered intranasally has good analgesia effect with no significant adverse effect (Hansen and Dahl, 2013). It is fast to administer compare with intravenous route which require placement of intravenous catheter for drug administration. It is important to know whether intranasal fentanyl combined with intravenous tramadol is superior in efficacy compared to intravenous tramadol which is a common analgesic drug used in acute trauma pain which require time for intravenous administration. Prolonging patient in painful state will cause more anxiety which may lead to sense of loss of control in patient with complain of pain.

3. METHODOLOGY

3.1 Study Design

A prospective, randomized, open-label single centre study was conducted for a period of 6 months from November 2014 to April 2015 to evaluate the efficacy of the use of intranasal fentanyl as an adjunct analgesia on top of intravenous tramadol in acute musculoskeletal injuries with moderate to severe pain. This study was approved by Human Ethics Committee of Universiti Sains Malaysia.

3.2 Study setting and population

This study was conducted in Emergeny Department of Hospital Universiti Sains Malaysia (HUSM) which is a 750-bedded tertiary referral centre and teaching hospital located in the east coast of Peninsular Malaysia.

3.3 Study protocol

All adult patients (above 18 years old including elderly) who presented to the emergency department of HUSM within the stipulated study period with musculoskeletal injuries which include soft tissue injury and bone fractures in moderate to severe pain were recruited consecutively after obtaining the written consent.

Patients with polytrauma or significant co-morbidities such as hypertension, diabetes mellitus and cardiovascular diseases, pregnant patients as well as those with hemodynamic instability requiring resuscitation and stabilization were excluded. As this study involves intranasal route of administration, any patient with rhinopharyngitis or any intranasal pathologies were also excluded. Similarly, patients without the mental capacity to evaluate pain severity as well as those with visual impairment and unable to mark on the line of the Visual Analog Scale (VAS) were also excluded. Inevitably, any patients who had received any form of opioid as well as those with allergic history to opioid were also excluded.

Written consent was obtained if the patients fulfilled the study criteria.. Pain score using visual analogue scale (VAS) a unidimensional pain scale that is easy to use, requires no verbal or reading scale which consist of 100 mm horizontal line was first obtained by asking the patient to place a mark 'X' to represent their pain intensity on the sheet of paper printed with VAS. A score of 45 mm to 74 mm was classified as moderate pain and score of 75 mm to 100 mm was classified as severe pain. The patients were then told that they would be allocated to either treatment package A or treatment package B. The allocation was concealed in an envelope and the patient was instructed to draw one of the envelopes in the box. The serial number of the paper in the envelope obtained was then matched with the table of block randomization that had been pre-generated using a random sequence generator online program. Patients allocated to one type of treatment did not know the type of treatment in the other arm. So, although it was an open-label study, as the patients eventually knew the type of treatment received, the patients were blinded to treatment in the other arm.

For patients who received intranasal fentanyl on top of intravenous tramadol, intranasal fentanyl was first administered at a dose of 1.5 mcg/kg with solution concentration

of 50mcg/ml using LMA MAD Nasal^{TM}. To do so, the patient was propped up to an inclination of 45 degrees before the fentanyl was delivered in increments of 0.25 mls per slow push into patients right and left nostrils alternately for the next five minutes. The intravenous access was established concurrently within 2 minutes of the intranasal fentanyl administration and intravenous metoclopramide 10 mg was then administered as an anti-emetic for all patients. This was followed by intravenous tramadol 2mg/kg administration as slow bolus over 1 minute. All treatment in both group were given within 5 minutes and at this 5 minutes, it was marked as time_0.

As for the control group, intravenous access was established and only intravenous metoclopramide 10 mg was administered as an anti-emetic and was followed by intravenous tramadol 2mg/kg as a slow bolus over 1 minute. After 10 minutes from time_0, the same VAS were used again to assess patients pain intensity in both group. No other procedures was done on all participants in both groups until after reassessment at 10 minutes.

FLOW CHART

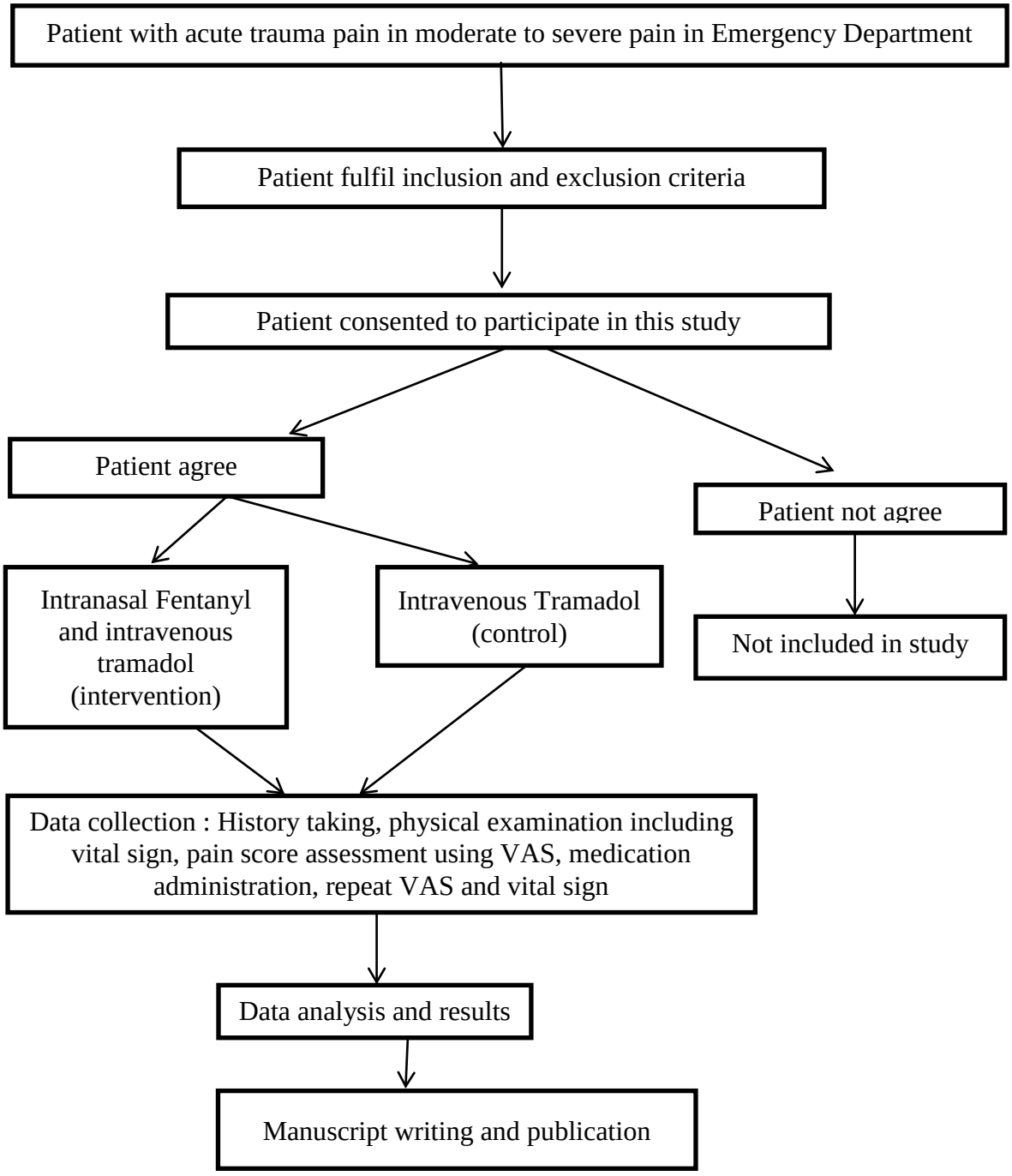

Figure 3.1 : Flow chart of the study

3.4 Measurement or key outcome

The primary outcome was the visual analogue scale reduction from pre-medication with either intranasal fentanyl with intravenous tramadol or intravenous tramadol alone and post-medication at 10 minutes. Secondary outcome was the mean arterial pressure and heart rate difference and incidence of side effects in between both group.

3.5 Sample size calculation

3.5.1 Sample size calculation

Sample size was calculated using independent t-test (Dupont and Plummer, 1990). Calculation done with **PS Power and Sample Size Calculations** Version 3.0 software.

Calculated sample size will be as below :

Table 1 : Sample size calculation

α = 0.05	SD = 15
δ = 20	m (ratio) = 1
power = 0.8	N (size) = 10 per group
	N with 10% drop out per group = 11
	Total sample size = 22

SD derived from previous study of intravenous tramadol at 10 minutes (Ahmad *et al*., 2010)

In a previous study the response at 10 minutes within each subject group was normally distributed with standard deviation 15. If the true difference in the experimental and control means is 20, we will need to study 10 experimental subjects and 10 control

subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05.

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ABSTRACT

Introduction: Intra-nasal fentanyl, as an alternative route of analgesic administration, has been shown to be effective particularly in pediatric population and in prehospital setting. Studies on such use among adult patients in emergency department are limited. **Methods:** An open-label study was conducted to evaluate the effectiveness of adding 1.5 mcg/kg intranasal fentanyl on top of 2 mg/kg intravenous tramadol (FENTANYL_TRAMADOL, n = 10) as compared to 2 mg/kg intravenous tramadol alone (TRAMADOL, n = 10) in adult patients with acute musculoskeletal injuries in moderate to severe pain. **Results:** When analyzed using independent t-test, the mean visual analog scale (VAS) difference between pre- and 10-minute post-intervention was found to be 29.8 mm (SD +/- 8.4 mm) in the FENTANYL_TRAMADOL arm and 19.6 mm (SD +/- 9.7 mm) in the TRAMADOL arm [t(8) = 2.515, p = 0.022, 95% confidence interval (CI) 1.68 to 18.72 mm]. A significantly greater albeit transient reduction in mean arterial pressure 10 minutes post intubation was noted in the FENTANYL_TRAMADOL arm as compared to those in the TRAMADOL arm (13.35 mmHg vs 7.65 mmHg, using Mann-Whitney U test with U-value = 21.5; p = 0.029; r = 0.48). Patients in the FENTANYL_TRAMADOL arm also experienced a higher incidence of transient dizziness 10 minutes post-intervention. **Conclusion:** Although effective, intra-nasal fentanyl in adult patients may not be ready for primetime as it may result in significant reduction in blood pressure.

WORD COUNT: 231 words

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INTRODUCTION

Although pain is a common presentation in emergency departments (Tanabe and Buschmann, 1999b), lack of pain control or 'oligoanalgesia' frequently occurs (Motov and Khan, 2009). In a crowded emergency department, time to analgesia is often prolonged (Hwang *et al.*, 2006) and this can be detrimental as the quality of pain management affects patients' outcomes.

One of the factors that improves the timing of pain management is the route of analgesia administration. Intra-nasal route of analgesia administration has recently been advocated as an alternative method to overcome the problem of delayed drug administration (Prommer and Thompson, 2011). In properly selected patients, intranasal route reduces time from drug administration to onset of action, reduces the burden of staff resources, eliminates needle stick exposure risk and eliminates injection pain (Wolfe and Braude, 2010). On the other hand, intravenous and intramuscular routes are relatively invasive and may cause discomfort to patients (Prommer and Thompson, 2011). Occasionally, clinicians may have the difficulty of establishing an intravenous line and thus, results in delay of drug administration.

Intranasal route enables rapid absorption because the nasal mucosa is a highly vascularised mucosa with its blood-vascular system separated from the nasal lumen by only two cell layers (Marttin *et al.*, 1998). Furthermore, the intranasal route affords a large surface area (150 – 180 m^2) (Shelley and Paech, 2008) for drug delivery and it eliminates the first pass metabolism (Leonard *et al.*, 2007); thus allows the drug to enter the cerebrospinal fluid via the olfactorial mucosa with immediate therapeutic effect (Hansen and Dahl, 2013). For example, intranasal fentanyl has been shown to achieve therapeutic serum levels within 2 minutes of administration reflecting the good venous outflow of nasal (Borland *et al.*, 2005). Additionally, there were no significant oxygen desaturations, reductions in respiratory rate nor heart rates in patients given intranasal fentanyl (Younge *et al.*, 1999).

Tramadol is a synthetic opioid of the aminocyclohexanol group and it has been shown to possess analgesic potency equivalent to that of pethidine (Lee *et al.*, 1993). Fentanyl is a synthetic phenylpiperidine derivative with analgesic potency 50 to 80 times that of morphine (Smith *et al.*, 2011). Besides, fentanyl has a rapid onset of action within 6 to 8 minutes following intranasal administration due to its high lipid solubility (Clavijo *et al.*, 2012). In studies done in prehospital setting, it has been shown that intranasal fentanyl is as effective as intravenous morphine as analgesia in both adult patients (Rickard *et al.*, 2007) as well as paediatric patients (Bendall *et al.*, 2011).

Although the evidence regarding intranasal fentanyl use in emergency department is limited, the results were promising with some studies showing that intranasal fentanyl is as effective as intramuscular morphine (Younge *et al.*, 1999). In another study done in emergency department setting, intranasal fentanyl has been shown to be comparable to intravenous morphine in reducing pain following acute long bone fractures among pediatric

population (Borland *et al.*, 2007). Similarly, another study showed that intranasal fentanyl provides effective analgesia for pediatric patient with painful orthopaedic trauma (Saunders *et al.*, 2010).

Nonetheless, although intranasal fentanyl has been shown to be effective, most of the studies on intranasal fentanyl use in emergency department were done on paediatric population (Hansen and Dahl, 2013). There were limited studies of intranasal fentanyl use in adult patients in emergency department with musculoskeletal injury. Most of the study which related to emergency department were the one which involved prehospital care.

MATERIALS AND METHODS

Therefore, a prospective, randomized, open-label study was conducted to evaluate the effectiveness of adding intranasal fentanyl on top of intravenous tramadol in acute musculoskeletal injuries with moderate to severe pain. This study was approved by the Human Ethics Research Committee of Universiti Sains Malaysia.

The primary outcome of this study was the subjective improvement of pain severity as measured using the degree of visual analog scale (VAS) reduction at 10 minutes post-medication across both arms. Secondary outcomes were the changes of mean arterial pressures and heart rates before and 10-minute after interventions as well as the incidences of other side effects.

Subjects

This study was conducted in the emergency department of Hospital Universiti Sains Malaysia (HUSM), a 750-bed tertiary referral centre and teaching hospital located in the east coast of Peninsular Malaysia. All adult patients (above 18 years old) who presented within the stipulated study period with musculoskeletal injuries in moderate to severe pain were recruited consecutively after obtaining written consent.

Patients with polytrauma or significant co-morbidities such as hypertension, diabetes mellitus and cardiovascular diseases, pregnant patients as well as those with hemodynamic instability requiring resuscitation and stabilization were excluded. As this study involves the intranasal route of administration, any patient with rhinopharyngitis or any intranasal pathology were excluded. Similarly, patients without the mental capacity to evaluate pain severity as well as those with visual impairment and unable to mark on the line of the Visual Analog Scale (VAS) were also excluded. Inevitably, any patients who had received any form of opioid as well as those with allergic history to opioid were excluded.

The sample size was estimated based on the two-means formula using independent t-test with $\alpha = 0.05$ and power = 0.8. Based on a previous study done on the same population using intravenous tramadol (Ahmad *et al.*, 2010), the standard deviation of VAS change was taken as 15 mm and the estimated VAS difference was targeted at 20 mm. Accounting for a 10% drop-out rate, the sample size estimation was 11 patients per arm.

Materials

Pain severity was assessed using the Visual Analog Scale (VAS). Moderate pain is defined as 45 mm to 74 mm and severe pain is defined as 75 mm to 100 mm on VAS (Jensen *et al.*, 2003). The intranasal delivery of fentanyl was performed using a mucosal atomisation device (LMA MAD Nasal^{TM}). Due to ethical consideration and the unconventionality of intranasal route, a comparative intranasal placebo administration in the tramadol arm was not approved by our institutional human ethics research committee.

Procedure

Pain score using VAS was first obtained by asking the patient to place a mark 'X' to represent their pain intensity. Written consent was then obtained if the patients fulfilled the study criteria. The allocation was concealed and the patient was instructed to draw the allocation paper from an opaque envelope. Patients allocated to one type of treatment did not know the type of treatment in the other arm.

For patients who received intranasal fentanyl on top of intravenous tramadol (FENTANYL_TRAMADOL), intranasal fentanyl was first administered at a dose of 1.5 mcg/kg with the solution concentration of 50 mcg/ml using the LMA MAD Nasal^{TM}. To do so, the patient was propped up to an inclination of 45 degrees before the fentanyl was delivered in increments of 0.25 ml via slow push into the patient's right and left nostrils alternately for the next five minutes until the calculated dose had been achieved. The intravenous access was then concurrently established within 2 minutes after the intranasal fentanyl administration. Intravenous metoclopramide 10 mg was administered as an anti-