COMPARING TWO DIFFERENT DOSES OF INTRAVENOUS GRANISETRON VERSUS INTRAVENOUS PETHIDINE FOR PREVENTION OF SHIVERING IN PATIENTS UNDERGOING SPINAL ANAESTHESIA

BY

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ABSTRAK

Tajuk: Membandingkan dua jenis dos intravena granisetron yang berbeza dengan intravena pethidine untuk mengelakkan mengigil selepas pembiusan spinal.

Later Belakang: Mengigil selepas pembiusan adalah keadaan yang stress kepada fisologi dan psikologi. Walaupun pethidine merupakan pilihan pertama terapi, ia membawa kesan sampingan seperti mengantuk, loya dan muntah. Intravena (IV) granisetron dengan dos 40 mcg/kg telah dibuktikan dalam kajian sebelum ini dapat mengelakkan komplikasi mengigil selepas pembiusan. Sekarang, tiada kajian menunjukkan dos minimal granisetron dapat mengelakkan mengigil selepas pembiusan spinal. Kajian ini adalah untuk membandingkan dua dos granisetron yang berbeza dengan pethidine yang dapat mengelakkan mengigil selepas pembiusan.

Metodologi: Ini merupakan kajian prospektif rawak plasebo rabun dua pihak. Seramai 96 pesakit dalam kumpulan ASA I dan II, berumur dalam lingkungan 18 hingga 65 tahun menjalani pembedahan ortopedik anggota kaki melalui pembiusan spinal telah dikaji. Pesakit secara rawak dipilih untuk menerima samada suntikan intravena (IV) granisetron 10 mcg/kg (Kumpulan 1), IV granisetron 40 mcg/kg (Kumpulan 2) atau IV pethidine 0.4 mg/kg (Kumpulan 3) sebelum suntikan “intrathecal” dengan menggunakan 15mg hyperbaric bupivacaine 0.5%. Insiden dan tahap mengigil telah direkodkan.

Keputusan: Secara keseluruhan, kejadian menggigil semasa pembiusan spinal dalam kajian kami adalah tidak signifikan antara 3 kumpulan ($p = 0.404$). Manakala, IV pethidine adalah lebih cenderung mengakibatkan kesan mengantuk berbanding dengan granisetron ($p < 0.001$).

Kesimpulan: IV granisetron 10 mcg/kg mempunyai efikasi yang sama apabila dibandingkan dengan IV granisetron 40 mcg/kg dan IV pethidine 0.4 mg/kg dalam mencegah kejadian gigilan ketika pembiusan spina untuk pembedahan ortopedik anggota kaki.

ABSTRACT

Title: Comparing two different doses of intravenous granisetron versus intravenous pethidine for prevention of shivering in patients undergoing spinal anaesthesia

Background: Post-anaesthesia shivering is physiologically and psychologically stressful event. Pethidine, which is commonly recognised as first-line therapy, can have several side effects such as sedative effects, nausea and vomiting. Granisetron has been proven in various studies for prevention of post-anaesthesia shivering at 40mcg/kg intravenously. To date, no study has demonstrated the minimum dose of granisetron to prevent post-anaesthesia shivering. This study compared two different dosages of intravenous granisetron versus pethidine for prevention of post-anaesthesia shivering.

Methods: This was a prospective, randomized, double-blinded study. A total of 96 patients with ASA classification I and II, aged between 18 and 65 years old scheduled for orthopaedic lower limb surgery under spinal anaesthesia were recruited. Patients were randomly allocated to receive either intravenous (IV) granisetron 10mcg/kg (Group 1), IV granisetron 40mcg/kg (Group 2) or IV pethidine 0.4mg/kg (Group 3) before an intrathecal injection of 15 mg 0.5% hyperbaric bupivacaine. The incidence and severity of shivering with side effects of tested drugs were recorded.

Results: The incidence of shivering associated with spinal anaesthesia in our study was not significant different amongst the 3 groups ($p = 0.404$). However, pethidine was associated with sedative effects when compared with granisetron ($p < 0.001$).

Conclusions: IV granisetron at 10mcg/kg had similar efficacy when compared to both IV granisetron 40mcg/kg and IV pethidine 0.4mg/kg in preventing shivering during spinal anaesthesia for orthopaedic lower limb surgery.

ABBREVIATIONS

5-HT	Serotonin or 5-Hydroxytrptamine
5-HT3	**5**-Hydroxytryptamine type 3
ANOVA	Analysis of Variance
BMI	Body Mass Index
BP	Blood Pressure
ECG	Electrocardiogram
PGH	Penang General Hospital
HUSM	Hospital Universiti Sains Malaysia
HR	Heart Rate
ISMP	Institute for Safe Medication Practices
IV	Intravenous or Intravena (Malay language)
NIBP	Non-invasive Blood Pressure
SBP	Systolic Blood Pressure
SpO2	Oxygen Saturation
SPSS	Statistical Package for the Social Science

1.1 INTRODUCTION

Perioperative shivering is one of the common distressing events encountered during our daily anaesthesia practice. Its incidence is estimated ranging from 6 – 60% after spinal anaesthesia(1). Shivering is physiologically and psychologically stressful to both patients and attending anaesthetist. Apart from interfering vital signs monitoring secondary to motion artefacts, it can increase risk of myocardium ischaemia in those with limited reserve, increase carbon dioxide production, increase metabolic oxygen consumption and thus hypoxia, increase respiratory workload with raise minute ventilation and cause unpleasant experiences in operation theatre.

Thus, various pharmacological and non-pharmacological methods have been attempted for preventing and treating post-anaesthesia shivering. One of the most common physical methods is surface warming. However, it is considered not to be as useful as drugs for this purpose because the skin surface contributes to only 20% of shivering control. Moreover, it can be useful only during slight hypothermia with core temperature > 35°C (2). On the other hand, various drugs have been studied and used to prevent post-anaesthesia shivering, but none of these drugs have received universal acceptance (3). Different problems and side effects are associated with these drugs. For example, tramadol is known to cause nausea and vomiting. Pethidine is associated with bradycardia, nausea and vomiting, sedative effects, respiratory depression and haemodynamic changes. Sedative effects of ketamine (4) can be dangerous to elderly populations.

Recently, granisetron, a specific 5-HT3 receptor antagonist, at a dose of 40mcg/kg, has been found to be effective in reducing the incidence of post- anaesthesia shivering in some studies. The mechanism of action of granisetron anti-shivering effect could be

related to the inhibition of serotonin reuptake on the pre-optic anterior hypothalamic region (4). Serotonin (5-hydroxytryptamine [5-HT]) is a biological amine that acts as a neurotransmitter in the brain and the spinal cord. Studies suggest that the serotoninergic system has a role in the control of post-anaesthesia shivering. The 5-HT3 receptor antagonist inhibits the uptake of serotonin in the pre-optic anterior hypothalamic region, which influences both heat production and heat loss (4). In animal models, direct intraventricular injection of serotonin influences body temperature and shivering (2). Granisetron is currently registered in the Ministry of Health Drug Formulary, 2013, at a dose of 10-40mcg/kg in children over 2 years old or at a dose of 1 – 3 mg in an adult as intravenous (IV) bolus for prevention of nausea and vomiting associated with chemotherapy and radiotherapy. It is easily available in Malaysia government hospital and routinely used for prevention of post-operative nausea and vomiting in anaesthesia service. It gains its popularity with relative safer profile as compared to other anti-emetic medications. For the purpose of prevention post-anaesthesia shivering, IV granisetron 40 mcg/kg is recommended in most studies. Iqbal et al. (5) showed that the IV granisetron (at dose of 40mcg/kg) is equally effective with IV pethidine (25mg) in preventing post-operative shivering compared to negative control group (saline group). The incidences of shivering among 3 groups of subjects in their study were reported as below: Group Pethidine (7%) and Group Granisetron (17%) and Group Saline (60%), with $p<0.05$. Another study by Sajedi et al. (6) in year 2008 found that the prophylactic used of granisetron at 40mcg/kg was as effective as pethidine 0.4mg/kg or tramadol 0.1mg/kg in preventing post-anaesthesia shivering in a group of patients undergoing elective orthopaedic lower limb surgery under general anaesthesia. Teoh et al.(7) showed that at this 40mcg/kg, granisetron had a similar efficacy with IV Ketamine 0.25mg/kg in prevention of shivering during spinal anaesthesia for elective orthopaedic lower limb

surgery in a group of 90 subjects in Malaysia. They showed that the incidence of shivering was significantly higher in control group (i.e. normal saline), which is 43.3% compared to granisetron group with incidence of 10%. A.A. Eldaba and Y.M. Amr in 2012 (8) compared IV granisetron 10mcg/kg versus IV normal saline in a group of 80 children age 2 – 5 year old who underwent spinal anaesthesia for lower limb surgery. They found that IV granisetron 10mcg/kg was effective in preventing post-spinal shivering.

Pethidine is one of the common drug used to treat post anaesthesia shivering. It has been extensively evaluated and is widely recognized as the first line therapy for peri-operative shivering (9). The mechanism of action of pethidine in the treatment of post-anaesthesia shivering is not completely understood. The site of action is most probably either the thermoregulatory center or the opioid receptor. It is suggested that pethidine acts via k- rather than μ-opioid receptors to prevent shivering. The anti-shivering action of pethidine can be inhibited by high dose naloxone, which blocks both μ and k receptors, but not by low dose of naloxone which only block μ receptors (5). In a meta-analysis over 20 trials by Peter Kranke et al. (10) in year 2002, it is reported that the side effects of pethidine could be nausea and vomiting (7.3%), respiratory depression (4.2%). Therefore, the use of pethidine can be limited by its side effects profile, which also include delayed gastric emptying and prolong length of recovery stay. These can increase the overall cost of treatment.

At the sametime, Sajedi et al. (6) suggested limitations use of opoids in their study were risk of respiratory depression, sedation, nausea and vomiting. On the other hand, Parvin Sajedi et al. (6) concluded in their study that granisetron able to provide the benefits without further increasing the risk of respiratory and cardiovascular side effects. In this study, they suggested that their limitation was lack of previous studies in determining the dose of granisetron in control post anaesthesia shivering.

In this study, we examine the minimum dose of intravenous granisetron that can prevent post-spinal anaesthesia shivering. If at dose of 10mcg/kg of intravenous granisetron can prevent post-spinal anaesthesia shivering, it will mean that there may be less side effects, lower treatment cost and at the same time reduction in the incidence post-operative nausea and vomiting.

In conclusion, primary prevention of post-anaesthesia shivering with a cost-effective drug with minimal side effects should be sought as the current first line therapy with IV pethidine is limited by its unfavourable side effects profile. To the best of our knowledge, there is no study in Malaysia that compares two different dosages of granisetron versus pethidine in the prevention of post –spinal anaesthesia shivering.

2.1 General Objectives

To determine the effectiveness of IV granisetron 10mcg/kg versus IV granisetron 40 mcg/kg in the prevention of shivering during spinal anaesthesia for elective orthopaedic lower limb surgery with IV pethidine 0.4mg/kg as positive control.

2.2 Specific Objectives

To compare the incidence of side effects of IV granisetron at two different dosage versus pethidine.

3.1 TITLE:

Article Title : Comparing Two Different Doses of Intravenous Granisetron versus Intravenous Pethidine for Prevention of Shivering in Patients Undergoing Spinal Anaesthesia

Running Head : Effects of Two Different Doses of Intravenous Granisetron versus Intravenous Pethidine on Shivering Post Spinal Anaesthesia

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3.2 ABSTRACT

Background: Post-anaesthesia shivering is physiologically and psychologically stressful event. Pethidine, which is commonly recognised as first-line therapy, can have several side effects such as sedative effects, nausea and vomiting. Granisetron has been proven in various studies for prevention of post-anaesthesia shivering at 40mcg/kg intravenously. To date, no study has demonstrated the minimum dose of granisetron to prevent post-anaesthesia shivering. This study compared two different dosages of intravenous granisetron versus pethidine for prevention of post-anaesthesia shivering.

Methods: This was a prospective, randomized, double-blinded study. A total of 96 patients with ASA classification I and II, aged between 18 and 65 years old scheduled for orthopaedic lower limb surgery under spinal anaesthesia were recruited. Patients were randomly allocated to receive either intravenous (IV) granisetron 10mcg/kg (Group 1), IV granisetron 40mcg/kg (Group 2) or IV pethidine 0.4mg/kg (Group 3) before an intrathecal injection of 15 mg 0.5% hyperbaric bupivacaine. The incidence and severity of shivering with side effects of tested drugs were recorded.

Results: The incidence of shivering associated with spinal anaesthesia in our study was not significant different amongst the 3 groups ($p = 0.404$). However, pethidine was associated with sedative effects when compared with granisetron ($p < 0.001$).

Conclusions: IV granisetron at 10mcg/kg had similar efficacy when compared to both IV granisetron 40mcg/kg and IV pethidine 0.4mg/kg in preventing shivering during spinal anaesthesia for orthopaedic lower limb surgery.

Keywords: *Spinal Anaesthesia, Shivering, Granisetron, Pethidine, Subarachnoid block, 5-HT3*

3.3 INTRODUCTION

Perioperative shivering is commonly encountered in our daily anaesthesia practice with estimated incidence varied from 6 -60% after spinal anaesthesia (1). Shivering is physiologically and psychologically stressful to both patients and anaesthetist. Various methods are available for prevention post-anaesthesia shivering. Although surface warming is a common physical method used for prevention of shivering, it is not considered to be as effective as pharmacological methods for this purpose. It is because of skin surfaces contributes to only 20% of shivering control (2). Although pethidine is one of the drugs used for prevention post-anaesthesia shivering, it is associated with bradycardia, nausea and vomiting (10), respiratory depression (10), sedative effects and hemodynamic changes. This can be dangerous to elderly patients and those at risk patients. Avoidance of one post-anaesthesia complications should not raise up another side effects secondary from adding another one medication. Thus, granisetron, a specific 5-HT3 receptor antagonist, at a dose of 40mcg/kg, has been introduced and found to be effective in reducing the incidence of post-anaesthesia shivering in some studies. The mechanism of action of granisetron anti-shivering effect could be related to the inhibition of serotonin reuptake on the pre-optic anterior hypothalamic region (4). Serotonin (5-hydroxytryptamine [5-HT]) is a biological amine that has neurotransmitter function in the brain and the spinal cord. Studies suggest that the serotoninergic system has a role in the control of post-anaesthesia shivering. The 5-HT3 receptor antagonist inhibits the uptake of serotonin in the pre-optic anterior hypothalamic region, which influences both heat production and heat loss (4). In animal models, direct intraventricular injection of serotonin influences body temperature and shivering (2). Granisetron is currently registered in the Ministry of Health Drug Formulary, 2013, at a dose of 10-40mcg/kg in

children over 2 years old or at a dose of 1 – 3 mg in an adult as intravenous (IV) bolus for prevention of nausea and vomiting associated with chemotherapy and radiotherapy. For prevention post-anaesthesia shivering, IV granisetron 40 mcg/kg is recommended in most studies. A.A. Eldaba and Y.M. Amr in 2012 (8) compared IV granisetron 10mcg/kg versus IV normal saline in a group of 80 children age 2 – 5 year old who underwent spinal anaesthesia for lower limb surgery. They found that IV granisetron 10mcg/kg was effective in preventing post-spinal shivering.

In this study, we examine the minimum dose of intravenous granisetron that can prevent post-spinal anaesthesia shivering. If at dose of 10mcg/kg of intravenous granisetron can prevent post-spinal anaesthesia shivering, it will mean that there may be less side effects, lower treatment cost and at the same time reduction in the incidence post-operative nausea and vomiting. Hence, patients should be offered a drug that can be administered at the lowest possible dose with no additional significant side effects.

3.4 METHODOLOGY

Research Design

This was a prospective, randomized, double-blinded study to compare two different doses of IV granisetron versus IV pethidine for prevention of shivering post-spinal anaesthesia with at the same time side effects of both drugs been compared.

Study settings and period

The study was conducted on patients who were scheduled for orthopaedic lower limb surgeries in Hospital Universiti Sains Malaysia (HUSM) and General Hospital Penang (GHPP) from September 2015 to August 2016 after ethical approvals were obtained (JEPeM code: USM/JEPeM/15020061; NMRR code: NMRR-15-822-24575 (IIR)).

Patients

Patients were recruited based on the inclusion and exclusion criteria listed below.

Inclusion criteria

i. Age between 18 – 65 years old
ii. American Society of Anaesthesiology Classification I and II
iii. BMI 18 – 30 kg/m2

Exclusion criteria

i. Pregnancy
ii. Psychological disorders patient
iii. Thyroid disorder patient

iv. Patient contraindication for spinal anaesthesia

v. Baseline body temperature outside range of 36.5 – 38 ℃

vi. Patient likely to require blood transfusion

Sample size calculation

Sample size calculation for this study is based on Power and Sample Size Calculation Programme (PS version 3.0.43). Previous data showed that median incidence of shivering related to neuraxial anaesthesia in the control group was 57.6%. The sample size is then calculated using the assumption that the incidence of shivering among the patients receiving effective medication pethidine will be 18.2%, in keeping with the previous study(6). The power of the study will be 0.8 and type 1 error of 0.05. With additional dropout rate of 15%, a total of 96 patients with 32 patients in each group will be needed.

Techniques for data collection

Ethical committee approvals were obtained prior to this study. Patients who fulfilled the criteria were explained and written consent obtained during pre-anaesthesia assessment. Oral midazolam was given a night prior to the surgery and before sending patients to operation theatre. Prior to the induction of anaesthesia, non-invasive blood pressure (NIBP), heart rate (HR), oxygen saturation (SPO2), cardiac monitoring and baseline body temperature (using infrared ear thermometer) were obtained. All the patients were preloaded with 10mls/kg IV warmed crystalloid fluids over 15 minutes prior to the spinal anaesthesia. Via computer generated randomization, patients were allocated randomly into 3 groups to receive IV granisetron 10 mcg/kg (Group 1, n = 32), IV

granisetron 40 mcg/kg (Group 2, n = 32) or IV Pethidine 0.4mg/kg (Group 3, n = 32) in a total volume of 5ml over 5 minutes prior to the spinal anaesthesia. The attending anaesthesiologist was blinded to the type of drug used in the study. All the patients will be positioned for the surgery after spinal anaesthesia was performed at L3-L4 interspaces with 3mls of 0.5% hyperbaric bupivacaine. All of them were covered with forced air warmer (Bair Hugger) set at temperature 38ºC. All intravenous fluids preheated to 37˚C by fluid warming device were given as 2mls/kg/hour. The operating room temperature was maintained at 18-22ºC. Incidence and severity of shivering, and body temperature were assessed at 10 minutes interval after spinal anaesthesia till 60 minutes post-spinal anaesthesia. Blood pressure, heart rate, SPO2, respiratory rate, sedation score, incidence of nausea and vomiting were assessed every 2.5-minute interval up to 15 minutes, followed by 5-minute interval till 60 minutes post-spinal anaesthesia. At recovery area, all the above-mentioned monitoring was assessed and recorded. Shivering was noted by attending anaesthesiologist and considered once happened. Shivering was graded using a scale similar to that validated by Tsai and Chu(11):

- Grade 0: no shivering
- Grade 1: piloerection but no visible shivering
- Grade 2: muscular activity in only one muscle group
- Grade 3: muscular activity in more than one muscle group but not generalized
- Grade 4: shivering involving the whole body

Only grade 3 and 4 were considered as severe shivering, and study prophylaxis drug was considered as ineffective. IV pethidine 25mg was administered as rescue drug for severe shivering. At the same time, close monitoring vital signs were continued with

active rewarming physical methods would be reinforced further. Decrease of systolic blood pressure (SBP) less than 90 mmHg was treated with iv phenylephrine 100mcg. IV atropine 0.5mg bolus was given for heart rate less than 50 beats per minute.

Sedation score was assessed with 5-point scale(12):

i. Grade 1 : fully awake and orientated
ii. Grade 2 : drowsy
iii. Grade 3 : eyes closed but arousable to command
iv. Grade 4 : eyes closed but arousable to mild physical stimulation
v. Grade 5 : eyes closed but unarousable to mild physical stimulation

Data was analyzed using Statistical Package for the Social Science (SPSS) version 22.0 and were expressed as mean ± SD. The changes of blood pressure, HR and temperature were analyzed using analysis of variance (repeated annova) for repeated measurements between groups. Incidence of shivering as well as side effects of the study drugs were analyzed by Chi-Square test. A p-value less than 0.05 was considered statistically significant.

3.5 RESULTS

A total of 96 participants were recruited and divided into three different study groups with each group 32 patients that received different anaesthetic drug regimens i.e. IV Granisetron 10 mcg/kg (Group I), IV Granisetron 40mcg/kg (Group II), and IV Pethidine 0.4mg/kg (Group III). One of the patient from group 3 was drop out due to failed spinal anaesthesia and converted into general anaesthesia. Overall demographic data of study participants are shown in Table 1. The youngest was 18 years old and the eldest age was 65 years old. There was no statistically different with regards to age, gender, race and weight among 3 groups of patients. Significant different difference was found in height of study participants. Nevertheless, the magnitude of changes is small and negligible (Table 2). Duration of surgery among three groups of patients were similar.

The changes of the haemodynamic profile (i.e. SBP, PR, RR and SPO2) post-spinal anaesthesia among study participants were shown in Figures 1 – 4. Although changes in the hemodynamic profile were observed among the three different study groups, the magnitude of these changes were negligible during clinical practice.

There were changes of tympanic membrane temperature in all three groups post-spinal anaesthesia when compared with on arrival temperature readings. However, the magnitude was small and is clinically irrelevant. There was no significant difference when comparison was made amongst the three groups.

Regarding incidence of shivering, no significant differences were observed amongst the three groups. The overall shivering incidence in this study group was 8.4%.

Although both granisetron group show of higher incidence of shivering when compared with pethidine, but that was statistically insignificant. Among the 8 patients who shivered post-spinal anaesthesia, none of them still had shivering when they were discharged from recovery area.

Overall recorded side effects for the three study groups of study participants are shown in Table 3. There were no significant differences in distribution of side effects for hypotension, bradycardia, nausea, headache and giddiness among the three different study groups. However, significant higher incidence of sedation score ≥2 was observed in patients received IV pethidine 0.4mg/kg, compared to the other two groups that received IV granisetron (Table 4).

3.6 DISCUSSION

This study was done to evaluate the efficacy of preventing post-anaesthesia shivering by two different doses granisetron in comparison with pethidine. In this study, we found that IV granisetron 10mcg/kg could decrease incidence of post-anaesthesia shivering and this was comparable to IV granisetron 40mcg/kg and IV pethidine 0.4mg/kg.

Shivering is one of the common and stressful problems for both patients and anaesthetist. This additional burden may cause unpleasant experience in operation theater to patients. Several undesirable effects can be a physiological stress. Thus, avoiding shivering is essential for better perioperative patient outcome.

However, the precise cause of shivering post-anaesthesia is still not yet fully understood. Multiple mechanisms have been suggested to explain its occurrence. It could be due to thermoregulatory effects secondary to core hypothermia or possible of unknown non-thermoregulatory cause. (13, 14) In our study, we try our best to standardized possible factors to avoid added risk for hypothermia by administering prewarmed intravenous fluids and by covering patients with forced air warmer. These preventive measures were also adopted in other studies. (4, 15) Although preventing hypothermia intraoperative is one of the key component in avoiding shivering intraoperative, shivering may even happen among normothermic patient. (16) Our findings in this study consistent with this theory. The mean core temperature recorded among 3 groups were still within normal human core temperature (36.5 to 37.5 C°). (17) We choose to use infrared tympanic membrane temperature for monitoring core temperature as this is one of the reliable sites which correlates well with core temperature. (4)

Regulation of post-anaesthesia shivering by 5-HT3 antagonist has not been fully understood. It is postulated the mechanism could be due to its serotonergic pathway (18) and its function on thermoregulatory effects in anterior hypothalamus. (19) A number of studies has showed granisetron can have similar prevention of post-anaesthesia shivering achievement with pethidine.(5, 6, 20, 21) Iqbal et al. (5) reported IV granisetron 40 mcg/kg was as effective as IV pethidine with no statistically different in preventing postoperative shivering. The reported incidence was 17%. When comparing granisetron with placebo, Sagir et al. (3) showed that it can significantly reduce post-anaesthesia shivering with incidence of shivering as low as 10%. In our study, the incidence of shivering in patients received IV granisetron 40 mcg/kg was 12.5%**.**

At lower dose of granisetron (10 mcg/kg), we found that it produced similar results as IV granisetron 40 mcg/kg. Eldaba & Amr (22) evaluated the efficacy of IV granisetron 10 mcg/kg in children who underwent lower limb surgeries and they concluded that granisetron was an effective agent to prevent shivering after spinal anaesthesia. There were few studies demonstrated lower dose of IV granisetron could reduce incidence of shivering post-anaesthesia. Khalifa (23) found that statistically significant lesser incidence of shivering in patient receiving 1 mg IV granisetron when compared with placebo group. Lower incidence of shivering with premedication IV granisetron 1mg was detected in study done by Kasem. (24) As compared to our study, this lower incidence could be due to the dose for spinal anaesthesia given by Kasem (24) was lower than us. At the sametime, no proper classification guidelines for shivering grading been specified in the study by Kasem. We used shivering grading scale similar to that validated by Tsai and Chu. (11)

In this study, we were unable to demonstrate the benefit of 5-HT3 antagonist on the prevention of hypotension and bradycardia post-spinal anaesthesia. Administration of IV granisetron had no effect on hemodynamic variables in our study were consistent with other studies. (21, 24, 25) Recent published meta-analysis study by Wang et al. (21) showed that 5-HT3 antagonist did not show superiority in reducing incidence of bradycardia and hypotension.

The usefulness of pethidine for controlling shivering post-anaesthesia could be limited by its side effects, such as pruritus, nausea and vomiting, respiratory depression, sedated and bradycardia in some studies. (18, 19, 24). Our study was consistent with its sedation effects which should raise the caution when used in elderly. Elderly patient may not well tolerate pethidine and may cause delirium perioperatively. (26) In year 2004, ISMP Canada (26) recommended the limitation use of pethidine due to its adverse effects. Thus, it is important to aware that we should not cause another complication because of adding another medication for preventing of the initial anaethesia complication.

We recognize that there were confounding factors and limitation in this study. Our study involved multiple operators which can contribute bias into this study. At the same time, in term of race, Malay form the majority (80%) of study participants though the data collection were done both at Kelantan and Penang. This can be explained by Kelantan state is predominantly Malay. Although there is still insufficient data to suggest correlation between race and post-anaesthesia shivering, further work out is still required to rule out this possibility. Moreover, this was the first study comparing two different doses of IV granisetron to control post-anaesthesia shivering. Monitoring of core

temperature by using infrared tympanic membrane temperature probe may cause bias as wax in auditory canal may misleading us the true core temperature. We were unable to insert more invasive oesophageal temperature probe or thermistor in pulmonary artery as our study subjects were awake.

We hope that there will be more studies will be carried out in future to confirm our findings and the ideal agents for prevention of shivering post-anaesthesia. The ideal prevention method is still not established. In addition to adding antishivering drug, we should try the best possible method to maintain normothermia perioperatively to reduce the distressing shivering events.

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3.8 TABLES AND FIGURES

Table 1 Overall demographic data of study participants

Variable	Mean (SD)
Age, Year	37 (15)
Age Group, n (%)	
18 – 33,	48 (51)
34 – 49	21 (22)
50 – 65	26 (27)
Gender, n (%)	
Male	73 (77)
Female	22 (23)
Race, n (%)	
Malay	76 (80)
Chinese	11 (12)
Indian	7 (7)
Others	1 (1)
Treatment Group	
IV Granisetron 10 mcg/kg	32 (33.7)
IV Granisetron 40mcg/kg	32 (33.7)
IV Pethidine 0.4mg/kg	31 (32.6)
Height	166.0 (7.7)
Weight	66.5 (12.4)
Duration of surgery, minutes (SD)	110.16 (39.59)
Mean temperature, degree Celsius (SD)	36.8 (0.2)

Table 2 Demographic data of study participants according to different study groups

Variable	IV Granisetron 10 mcg/kg (n=32)	IV Granisetron 40 mcg/kg (n=32)	IV Pethidine 0.4mg/kg (n=31)	P value
Age, Year	38 (14)	34 (15)	38 (15)	0.406[a]
Age Group, n (%)				
18 – 33,	14 (44)	19 (59)	15 (48)	0.534[b]
34 – 49	10 (31)	5 (16)	6 (19)	
50 – 65	8 (25)	8 (25)	10 (33)	
Gender, n (%)				
Male	27 (84)	21 (66)	25 (81)	0.171[b]
Female	5 (16)	11 (34)	6 (19)	
Race, n (%)				
Malay	22 (69)	26 (81)	29 (91)	0.214[b]
Chinese	4 (13)	4 (13)	3 (9)	
Indian	5 (16)	2 (6)	-	
Others	1 (3)	-	-	
Height	168.6 (7.5)	164.5 (8.7)	164.8 (6.1)	<0.001[a]*
Weight	73.9 (10.9)	61.7 (12.1)	63.9 (10.8)	0.060[a]
Duration of surgery, minutes (SD)	119.84 (41.44)	108.75 (40.62)	101.61 (35.41)	0.184
Mean temperature, degree Celsius (SD)	36.9 (0.2)	36.9 (0.2)	36.9 (0.2)	0.808

Note: [a]One way ANOVA; [b]Chi-square test for homogeneity, statistically significant at $p<0.05$