THE EFFECTS OF PROPHYLACTIC GRANISETRON ON MATERNAL HAEMODYNAMICS DURING ELECTIVE CAESAREAN SECTION UNDER SPINAL ANAESTHESIA: A RANDOMISED CONTROL STUDY

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ABSTRACT

Background:

Neuraxial anaesthesia for caesarean delivery is preferred to general anaesthesia because it minimizes the risk of failed intubation, ventilation and aspiration. Maternal hypotension, a recognized complication of post spinal anaesthesia due to sympathetic blockage may be detrimental to the outcome due to pressure dependant uteroplacental flow. Granisetron, a selective 5-HT3 receptor antagonist potentially improves hypotension despite it usage as anti-emetic for post operative nausea and vomiting. The study conducted to determine the effects of prophylactic intravenous Granisetron on haemodynamics of parturients undergoing LSCS under SA as well as the usage of vasopressors intra-operatively. The Apgar score and post operative nausea and vomiting will be observed.

Methods:

This was a stratified balanced randomisation (1:1), single blinded, parallel group study conducted in Hospital Universiti Sains Malaysia. Eligible participants were screened preoperatively to meet the inclusion and exclusion criteria. Consented parturient scheduled for elective caesarean section under spinal anaesthesia were randomized into 2 arms, the group that received intravenous Granisetron pre spinal anaesthesia versus the group that received intravenous Granisetron 30 minutes post spinal anaesthesia using computerized software randomization. A slow bolus of intravenous Granisetron 1 mg was given. All patients were subjected to standard spinal anaesthesia using intrathecal heavy Marcaine 1.9mls (9.5mg) in combination with intrathecal morphine 0.1mg and intrathecal fentanyl 25mcg.

Spinal anaesthesia is given at the level L3/L4 or L4/L5 using Pencan or Spinocan size 27G or 25G. All participants were placed on the operating table in the supine position, 15° of left lateral tilt with supplemental oxygen nasal prong 3 litres/min and standard haemodynamic monitoring, non-invasive blood pressure, SPO2, ECG and end tidal CO2. Haemodynamics and vasopressors requirement were recorded every 3 minutes for 30 minutes from the start of spinal anaesthesia. We used an analysis of variance (ANOVA) for the primary end point which studied mean arterial pressure and heart rate. The requirement of vasopressors was analysed using Chi-square test. The Apgar score and post operative vomiting were observed.

Results:

The results show that the mean MAP of parturients given intravenous granisetron pre spinal anaesthesia results was higher compare to the post spinal anaesthesia results for each time of measurements (p value < 0.05). There was no significant different between the two groups as for heart rate variation. The comparison between the 2 groups vasopressors ussage show significant difference ($p<0.05$), whereby the group that receives intravenous Granisetron prior of SA had stable hemodynamic and require less vasopressor compare to the other group. Both groups have no different in term of Apgar score and post operative nausea and vomiting.

Conclusion:

Intravenous Granisetron administration prior to spinal anaesthesia stabilize haemodynamic of parturients LSCS.

ABSTRAK

Latar belakang:

Anestesia neuraxial untuk pembedahan caesarean menjadi pilihan berbanding anestesia am kerana ia mengurangkan risiko intubasi, ventilasi dan aspirasi. Penurunan tekanan darah ibu adalah salah satu komplikasi anestesia neuraxial, ia mengurangkan fungsi simpatatik yang membawa kepada penurunan dalam vaskular sistemik dan tekanan vena pusat. Granisetron adalah antagonis reseptor 5-HT3 selektif berpotensi meningkatkan tekanan darah walaupun penggunaannya sebagai ubat mencegah loya dan muntah selepas pembedahan. Kajian ini dijalankan untuk menentukan kesan Granisetron terhadap haemodinamik pesakit yang menjalani pembedahan caesarean elektif di bawah anestesia neuraxial serta penggunaan vassopressors secara intra-operatif. Skor Apgar dan kebarangkalian loya dan muntah selepas pembedahan akan diperhatikan.

Kaedah:

Ini adalah penggabungan seimbang berstrata (1: 1), satu kajian kumpulan selari yang dilakukan di HUSM. Peserta yang layak dan memenuhi kriteria kemasukan dan pengecualian untuk kajian akan disaring sebelum pembedahan. Pesakit yang dipilih untuk pembedahan caesarean di bawah anestesia neuraxial dibahagi secara rawak kepada 2 lengan, iaitu kumpulan yang menerima intravena Granisetron sebelum anestesia dan kumpulan yang menerima intravena Granisetron selepas anestesia menggunakan perisian komputer. Intravena Granisetron diberikan bolus 1mg secara perlahan. Semua pesakit diberi anestesia neuraxial menggunakan Marcaine 1.9mls (9.5mg) berat intrathecal dengan kombinasi 0.1mg intrathecal morphine dan 25mcg intrathecal fentanyl.

Anestesia diberikan pada kawasan L3 / L4 atau L4 / L5 menggunakan pencan atau saiz spinocan 27G atau 25G. Semua pesakit yang diletakkan di atas meja operasi di kedudukan condong ke kiri 15 °, dengan tambahan oksigen 3 liter / min dan pemantauan hemodinamik standard, tekanan darah tidak invasif, SPO2, ECG dan CO2. Kami menggunakan analisis varians (ANOVA) untuk titik akhir utama. Model ini termasuk tekanan darah dan denyut nadi. Keperluan vasopressor dianalisis menggunakan ujian Chi-square. Skor Apgar dan muntah selepas pembedahan diperhatikan.

Keputusan:

Hasil kajian menunjukkan terdapat perbezaan yang signifikan antara perbezaan masa pengukuran MAP untuk kumpulan yang menerima Granisetron intravena sebelum anestesia dan kumpulan yang menerima granisetron intravena selepas anestesia ($p < 0.05$). Tiada perbezaan yang ketara antara kedua-dua kumpulan untuk variasi kadar denyutan jantung. Perbandingan antara 2 kumpulan tentang penggunaan vasopressor menunjukkan perbezaan yang signifikan ($p < 0.05$), di mana kumpulan yang menerima Granisetron intravena sebelum anestesia mempunyai hemodinamik yang stabil dan memerlukan jumlah vasopressor yang kurang berbanding dengan kumpulan yang lain. Kedua-dua kumpulan ini tidak berbeza dari segi skor Apgar dan loya dan muntah selepas pembedahan.

Kesimpulan:

Intravena Granisetron yang diberikan sebelum anestesia boleh menstabilkan haemodinamik pesakit yang menjalani LSCS.

LIST OF ABBREVIATION

ANOVA – Analysis of variance

ASA – American Society Anaesthesiologist

BP – Blood pressure

CO2 – Carbon dioxide

ECG – Electrocardiography

FDA – Federal Drug Association

HR – Heart rate

L3/L4 – Level between 3^{rd} and 4^{th} lumbar

LSCS – Lower section caesarean section

MAP – Mean arterial pressure

p-value – Probability

SPO2 – Oxygen saturation

SA – Spinal anaesthesia

5HT3 – 5 Hydroxytryptamine

CHAPTER 1: INTRODUCTION

1.1 **Introduction**

Spinal anaesthesia (SA) is the usual anaesthetic technique used for caesarean section unless contraindicated. Increased use of neuraxial techniques instead of general anaesthesia for lower section caesarean delivery (LSCS) has improved maternal safety(1). Neuraxial anaesthesia for LSCS is preferred to general anaesthesia because it minimizes the risk of failed intubation, ventilation and aspiration(1). Hypotension is one of the side effects of SA beside nausea, vomiting and bradycardia. Incidence of hypotension in obstetric patient has been estimated as 50% to 60%. SA is more rapid in onset and more reliable in providing surgical anaesthesia from the mid-thoracic level to the sacrum with a failure rate of only 1% but the risk of profound hypotension is higher with SA than with epidural anaesthesia, because the onset of the sympathectomy is more rapid and dosing is not titrated(1).

Maternal hypotension is a recognized complication of post SA, there will be sympathetic blockage leading to decrease in systemic vascular resistance and central venous pressure. A study on detection of hypotension during LSCS with continuous non-invasive arterial pressure device or intermittent oscillometric arterial pressure measurement showed that 91% of patient were detected of hypotension post SA using continuous non-invasive arterial pressure monitoring(2). Hypotension in parturients compromises uteroplacental circulation and without autoregulation mechanism, leading to further fetal hypoperfusion. Even with a healthy uteroplacental unit, prolonged maternal hypotension can significantly decrease uterine blood flow and lead to progressive fetal acidosis(1). Maternal hypotension and fetal outcome are improved with avoidance of aortocaval compression (left uterine displacement), hydration and appropriate use of vasopressors(1).

Serotonin released during hypotensive event will lead to Bezold-Jarisch reflex by the activation of left ventricular mechanoreceptors and chemoreceptors causing parasympathetic system activity hence cause bradycardia(3). Serotonin antagonist drugs potentially improved hypotension and prevent the Bezold-Jarisch reflex(4). Hence may reduce the consumption of vasopressors, intravenous ephedrine or intravenous phenylephrine in parturients post SA(5).

Granisetron is a selective 5-HT3 receptor antagonist with low side effect and multiple therapeutic benefits. The study of evaluating the potential effect on fetal tissue after exposure to granisetron during pregnancy. Primary cells were isolated from human fetal organs of 16-19 weeks gestational age and treated with 3 ng/mL or 30 ng/mL of granisetron. At granisetron 3 ng/mL there was no detectable toxicity or on any fetal tissue(6). Granisetron is categorized as drug category B for usage in pregnancy by FDA, proven no teratogenic effect to fetus.

In standard practice, selective 5-HT3 receptor antagonist such as granisetron is given in LSCS patient as an anti-emetic for prevention of post operative nausea vomiting. It is listed in the National Drug Formulary of Malaysia for post-operative nausea and vomiting (Pharmacy Services Division Malaysia, 2011). However it is also known to reduce the post SA hypotension and bradycardia effect. Granisetron also has action in reducing shivering in patients under SA and as anti-pruritic post intrathecal opioids' usage.

Study have shown that the usage of intravenous ondansetron 4mg 5 minutes before SA reduced hypotension and vasopressor usage in parturients undergoing LSCS(3). Comparison of the effects of intravenous ondansetron, granisetron and placebo on haemodynamic changes and motor and sensory blockade induced by SA in parturients undergoing LSCS concluded that both group that received intravenous granisetron and ondansetron significantly decreased in developing hypotension and decreased in usage of

vasopressors(7). Intravenous granisetron was also used in a double blind randomised control study to determine the drug effectiveness in prevention of hypotension and bradycardia during SA in LSCS involving 200 parturients, divided into 2 groups and were given intravenous Granisetron and normal saline as placebo respectively(5). Mean arterial blood pressure, heart rate, vasopressors consumption and Apgar scores were monitored. The conclusion showed that 1mg of intravenous Granisetron before anaesthesia in an LSCS significantly reduces hypotension, bradycardia and vasopressors usage(5). Parturients undergoing LSCS have reduced event of hypotension and vasopressor usage when intravenous serotonin antagonist given before SA in parturients (11). Administration of 1mg of intravenous Granisetron before SA in LSCS patients significantly reduces hypotension, bradycardia and vasopressors usage(12). Another study done showed that type 3 serotonin blockade by intravenous granisetron pre-treatment does not reduce spinal induced hypotension in parturient undergoing elective caesarean section; however there is reduction in need of rescue vasopressor(13).

Intravenous granisetron control nausea and vomiting during LSCS under SA(8). As standard practice, intravenous granisetron is given towards the end of operation for post-operative nausea vomiting. This study is conducted is to determine the effect of granisetron that may prevent further hypotension if this anti-emetic drug is given 5 minutes prior to SA comparing to the standard current practice which is given towards the end of operation for post operative nausea and vomiting. The study conducted by administer intravenous granisetron 5 minutes before SA as for the interventional group comparing to the control group, which the granisetron is given towards the end of LSCS which is approximately 30 minutes based on standard operation time in our hospital. In order to determine the effects of

prophylactic intravenous Granisetron on haemodynamics of parturients undergoing elective LSCS under SA, the blood pressure, heart rate and mean arterial pressure will be monitored. The usage of vasopressors, ephedrine and phenylephrine will be calculated. There is evidence suggest that ephedrine causes a reduction in fetal pH and base excess, although without affecting the Apgar index, when compared to other vasopressors such as phenylephrine (14). The outcome of delivered fetus will be observed through Apgar score and as for parturients, post operative nausea and vomiting will also be observed and second dose of anti-emetic will be given accordingly.

CHAPTER 2: OBJECTIVES OF THE STUDY

2.1 GENERAL OBJECTIVES

To compare haemodynamics in parturients undergoing LSCS receiving intravenous Granisetron pre spinal anaesthesia and post SA.

2.2 PRIMARY OBJECTIVES

2.2.1 To compare the Mean Arterial Pressure every 3 minutes in patients receiving intravenous Granisetron pre SA versus 30 minutes post SA

2.2.2 To compare the heart rate every 3 minutes in patients receiving intravenous Granisetron pre SA versus 30 minutes post SA

2.2.3 To assess the requirement of vasopressors consumption in patients receiving intravenous Granisetron pre SA versus 30 minutes post SA

2. 3 SECONDARY OBJECTIVES

2.3.1 To assess for post operative nausea and vomiting

2.3.2 To assess the Apgar scores at 1 and 5 minutes after delivery for each group of patients

CHAPTER 3: MANUSCRIPT

3.1. Title page

Title:

The effects of prophylactic Granisetron on maternal haemodynamics during elective caesarean section under spinal anaesthesia: A randomised control study

Running head:

To compare haemodynamics in parturients undergoing caesarean section receiving intravenous Granisetron pre SA and post SA.

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3.2 Abstract

Background:

Neuraxial anaesthesia for caesarean delivery is preferred to general anaesthesia because it minimizes the risk of failed intubation, ventilation and aspiration. Maternal hypotension is a recognized complication of post spinal anaesthesia, there will be sympathetic blockage leading to decrease in systemic vascular resistance and central venous pressure. Granisetron is a selective 5-HT3 receptor antagonist potentially improved hypotension despite it usage as anti-emetic for post operative nausea and vomiting. The study conducted to determine the effects of prophylactic intravenous Granisetron on haemodynamics of parturients undergoing LSCS under SA as well as the usage of vassopressors intra-operatively. The Apgar score and post operative nausea and vomiting will be observed.

Methods:

This was a stratified balanced randomisation (1:1), single blinded, parallel group study conducted in HUSM. Eligible participants screened preoperatively meet the inclusion and exclusion criteria. Consented parturient scheduled for LSCS under SA randomized into 2 arms, the group that received pre SA intravenous Granisetron and the group that received intravenous Granisetron post SA using computerized software randomization. Intravenous Granisetron given 1mg slow bolus. All patients were given standard SA using intrathecal heavy Marcaine 1.9mls (9.5mg) in combination with intrathecal morphine 0.1mg and intrathecal fentanyl 25mcg. SA is given at the level L3/L4 or L4/L5 using pencan or spinocan size 27G or 25G. All parturients placed on the operating table in the supine position, 15° of left lateral tilt with supplemental oxygen nasal prong 3 litres/min and standard haemodynamic monitoring, non-invasive blood pressure, SPO2, ECG and end tidal CO2. We

used an analysis of variance (ANOVA) for the primary end point. The model included MAP and HR. The requirement of vasopressors was analysed using Chi-square test. The Apgar score and post operative vomiting was observed.

Results:

The results showed that there were highly significant mean differences between different time of measurements of MAP for intravenous Granisetron pre SA and intravenous granisetron post SA group ($p<0.05$). There was no significant different between the two groups as for HR variation. The comparison between the 2 groups vasopressors usage showed significant difference ($p<0.05$), whereby the group that received intravenous Granisetron prior of SA had stable hemodynamic and require less vasopressors compare to the other group. Both groups have no different in term of Apgar score and post operative nausea and vomiting.

Conclusion:

Intravenous Granisetron administered prior to SA stabilized haemodynamic of parturients underwent LSCS.

3.3 Introduction

SA is the usual anaesthetic technique used for caesarean section unless contraindicated as it improves maternal safety compare to general anaesthesia(9). Neuraxial anaesthesia for caesarean delivery is preferred to general anaesthesia because it minimizes the risk of failed intubation, ventilation and aspiration(1). Hypotension is one of the side effect of SA beside nausea, vomiting and bradycardia. Incidence of hypotension in obstetric patient has been estimated as 50% to 60%. SA is more rapid in onset and more reliable in providing surgical anaesthesia from the mid-thoracic level to the sacrum with a failure rate of only 1% but the risk of profound hypotension is higher with SA than with epidural anaesthesia, because the onset of the sympathectomy is more rapid and dosing is not titrated(1).

During hypotension, serotonin released will lead to Bezold-Jarisch reflex. (4). The Bezold-Jarich reflex cause an increase in parasympathetic activity, resulting in hypotension, vasodilation, and bradycardia(10). Intravenous granisetron showed the efficacy in supressing the bradycardia and hypotension. Granisetron is a selective 5-HT3 receptor antagonist with low side effect and multiple therapeutic benefits. Granisetron is categorized as drug category B for usage in pregnancy by FDA, proven has no side effects to fetus.(6). Parturients undergoing LSCS have reduced event of hypotension and vasopressor usage when intravenous serotonin antagonist given before SA in parturients (11). Administration of 1mg of intravenous Granisetron before SA in LSCS patients significantly reduces hypotension, bradycardia and vasopressors usage(12).

In practice, granisetron is given at the end of operation as anti-emetic. It is an effective drug for prevention of nausea and vomiting during and after SA for LSCS. (8). This study conducted to determine the effect of granisetron that may prevent further hypotension if

given prior to SA comparing to the current practice. This study is conducted is to determine the effect of granisetron that may prevent further hypotension if this anti-emetic drug is given 5 minutes prior to SA comparing to the standard current practice which is given towards the end of operation for post operative nausea and vomiting. The study conducted by administer intravenous granisetron 5 minutes before SA as for the interventional group comparing to the control group, which the granisetron is given towards the end of LSCS which is approximately 30 minutes based on standard operation time in our hospital. In order to determine the effects of prophylactic intravenous Granisetron on haemodynamics of parturients undergoing LSCS under SA, the BP, HR and MAP will be monitored. The usage of vasopressors, ephedrine and phenylephrine will be calculated. The outcome of delivered fetus will be observed through Apgar score and as for parturients, post operative nausea and vomiting will also be observed and second dose of anti-emetic will be given accordingly.

3.4 Methodology

Study design

This was a stratified balanced randomisation (1:1), single blinded, parallel group study conducted in HUSM.

Participants

Eligibility of the patients was screened during pre-operative assessment. Eligible participants screened preoperatively were parturient undergoing LSCS under SA classified as ASA I and II, aging from 18 until 45 years old and termed pregnancy. Exclusion criteria were parturient undergoing emergency LSCS, anaesthetized under general anaesthesia, combined spinal epidural anaesthesia or epidural anaesthesia, premature pregnancy, parturient diagnosed with pregnancy induced hypertension or essential hypertension, liver disease, heart disease, electrolytes imbalance and on serotonin antagonist or agonist treatment.

Study settings

The study took place at Hospital Universiti Sains Malaysia from June 2017 until August 2018 with estimated elective LSCS about 30 cases per month.

Intervention

Consented parturient scheduled for LSCS under SA randomized into 2 arms. Group E (pre-SA) and group O (post-SA) using computerized software randomization. All patients were given standard SA using intrathecal heavy Marcaine 1.9mls (9.5mg) in

combination with intrathecal morphine 0.1mg and intrathecal fentanyl 25mcg. SA was given at the level L3/L4 or L4/L5 using pencan or spinocan size 27G or 25G.

Intravenous Granisetron 1mg was diluted in 5cc syringe and another 5cc syringe of normal saline pre-prepared at induction room and given by the anaesthetist. The study was single-blinded where the data collector and the patients who involve during the operation are blinded to the assigned group. The syringes prepared were labelled as drug I and II. Each group received drug I, 5minutes pre spinal anaesthesia and drug II 30 minutes post spinal anaesthesia.

The Group E received drug I, which was Intravenous Granisetron 1mg slow bolus 5 minutes prior to SA and drug II which was 5ml of normal saline 30 minutes post SA. Group O received drug I which was intravenous 5ml of normal saline 5 minutes pre-SA and drug II which was intravenous Granisetron 1mg slow bolus 30 minutes post SA. All drugs labelled and administered by anaesthetist to patient according to the randomization list.

All parturients placed on the operating table in the supine position, 15° of left lateral tilt with supplemental oxygen nasal prong 3 litres/min and standard haemodynamic monitoring, non-invasive BP, SPO2, ECG and end tidal CO2. The BP, MAP and HR were recorded every 3 minutes for 30 minutes from the starting of SA. Requirement of vasopressors either ephedrine or phenylephrine consumption were recorded from starting of SA up to 30 minutes post SA. Vasopressors administered if MAP less than 70mmHg or a drop of BP 20% from patient initial BP before SA. Intravenous Ephedrine bolus of 6mmHg was given if HR less than 90 beats/min or intravenous Phenylephrine 50mcg was given if HR more than 90 beats/min. The data collection ended after 30 minutes post

SA. Apgar scores at 1 and 5 minutes were charted once baby delivered. Vomiting and requirement of anti-vomiting drugs were recorded.

Outcome

The primary endpoint was to compare the haemodynamics of parturients undergoing LSCS receiving intravenous Granisetron pre SA with parturients that received intravenous Granisetron post SA based on the monitoring of MAP, HR and requirement of vassopressors. Additional observation on requirement of anti-emetics post operative and Apgar score of newborn in both groups.

Sample size

Sample size calculation was based on T-test with independent sample size. Sample size calculation done for each specific objectives. The calculation revealed that the biggest sample size required is 60.5 parturients. However, to detect potential variations and avoid errors, 62 parturients are enrolled into the study with 31 candidates per arm.

Randomisation

The enrolment of participants were made one day prior to operation day during the pre-operative assessment by an anaesthetist who was not involved in the trial. For the allocation of the participants, a computer generated list of random numbers was used. Randomization sequence was created using statistical software and with 1:1 balanced allocation into 2 groups E and O. The randomization was concealed from the participants and the data collector. The anaesthetist involved opened the enveloped contained the labelled E or O, on the day of the operation and prepared and administered the

medication accordingly. The participants and data collector were kept blinded throughout the trial.

Statistical methods

We used an ANOVA for the primary end point. The model included MAP and HR. The requirement of vasopressors was analysed using Chi-square test. The secondary end point was regarding addition of anti-emetics during the conduction of study. The aimed was to assess whether the data provided evidence of superiority in term of haemodynamics stability for administrating intravenous Granisetron pre-SA.

3.5 Results

3.5.1 Introduction

The purpose of conducting this study is to determine the effect of intravenous Granisetron on maternal haemodynamic in parturients underwent elective caesarian section under spinal anaesthesia in Hospital Universiti Sains Malaysia, Kota Bharu, Kelantan. Throughout this chapter, the results of the study were presented.

3.5.2 Participants Characteristic

A total of 62 participants were recruited for this study during preoperative anaesthetic assessment, in Hospital Universiti Sains Malaysia, Kota Bharu, Kelantan. The data obtained was expressed as mean (SD=standard deviation) for numerical and n=frequency (%) for categorical variables as tabulated in Table 1. The result of the data showed that the mean age of the participants is 33.31(SD=5.21). Meanwhile, for the mean score for the total of 62 participants were 1.33, while the standard deviation is 1.17. The majority were Malay participants included in the study (n=56, 90.3%). Repeated Measure ANOVA was used to examine the differences in mean of all parameters.

3.5.3 Comparison of the Mean Arterial Pressure every 3 minutes in patients receiving intravenous Granisetron pre spinal anaesthesia versus 30 minutes post spinal anaesthesia.

The comparison of MAP within group were made based on time. There was no significant difference of mean MAP within the pre or post SA groups in repeated measure ANOVA ($F=3.13, p=0.003$). Thus, multiple analysis were performed with adjusted α based on

Bonferroni correction (Table 2) to examine whether there were significant difference between time in each group. The results showed that there were highly significant mean differences between different time of measurements for pre SA intravenous Granisetron and post SA intravenous granisetron group ($p<0.050$) . From test of between subjects effect in repeated measure ANOVA analysis, there were significant difference of mean MAP between control and interventional group ($F= 5.62$, $p=0.021$) regardless of time. The mean difference between groups was -4.58 refer to Table 3.

Comparison of calculated mean of MAP between groups based on time-treatment interaction results in repeated measure ANOVA analysis, there was a significant difference of mean PDW between groups based on time ($F= 2.12$, $p=0.017$). Then, we proceed with multiple comparisons to determine if there was a significant difference for each time. From the results, there were significant difference of mean of MAP for all measurements based on time between the two groups. The Figure 2 graph shows the mean of MAP for both groups in each measurements level. The mean MAP of parturients given intravenous granisetron pre SA reults was higher compared to the post SA results for each time of measurements.

3.5.4 Comparison of the heart rate every 3 minutes in patients receiving intravenous Granisetron pre SA versus 30 minutes post SA.

The comparison of calculated HR between the groups based on time-treatment interaction results in repeated measure ANOVA analysis. Figure 5, the graph showed comparison of HR between the group that receive intravenous granisetron pre SA compare to the group that was given intravenous granisetron post SA. There was no significant difference.

3.5.5 Assessment of the requirement of vasopressors consumption in patients receiving intravenous Granisetron pre SA versus 30 minutes post SA

Comparison of between the usage of vasopressors intraoperatively between the group that received intravenous granisetron pre spinal anaesthesia and the group that was given intravenous granisetron post spinal anesthesia. The comparison calculated using Chi-square test analysis showed significant difference (p=0.05). The results as per Figure 6, revealed that 19.35% (n=12) of the group that received intravenous Granisetron post SA required vasopressors while only 1.61% (n=1) of parturients from the group that received intravenous Granisetron pre SA required vasopressor. Further analysis showed that the group that received intravenous Granisetron post SA required more phenylephrine (27.42%) than ephedrine (3.23%).

3.5.6 Assessment of the Apgar scores at 1 and 5 minutes after delivery for each group of patients

Observation of Apgar score of baby post operative revealed no difference between both groups as all showed Apgar score of 9.

3.5.7 To assess for post operative nausea and vomiting

All parturients from both groups did not have post operative nausea and vomiting or required additional intravenous Granisetron in ward post operative.

3.6 Discussion

SA used for LSCS often lead to hypotension to parturients and mainly required vassopressors to sustained haemodynamically stable intra-operatively. Intravenous Granisetron or other 5HT3 antagonist medication is given as standard practice at the end of operation for post operative nausea and vomiting especially in obstetrics cases undergoing LSCS. Administration of intravenous Granisetron prior to SA, promote in the stabilization of the BP and MAP by antagonized the effect of serotonin during hypotension.

The results of this study showed significant findings of a more stable haemodynamic in the group that received intravenous granisetron prior to SA. Comparing to other study conducted also showed the similar findings, the incidence of hypotension after spinal anesthesia was 64% in group II received normal saline and 3% in group I that received intravenous granisetron. ($P < 0.0001$). (5). Another studied done resulted, decreases MAP were significantly lower in group O (received ondansetron) than groups G (received Granisetron) and S (received normal saline) with lower vasopressor use ($P< 0.05$)(7). As for my study, using solely the intravenous Granisetron comparing prior to SA and at the end of surgery, however it would be exceptionally good in future if the study conducted the comparison between ondansetron and granisetron usage in LSCS parturients.

Another study done showed that type 3 serotonin blockade by intravenous granisetron pre-treatment does not reduce spinal induced hypotension in parturient undergoing elective caesarean section; however there is reduction in need of rescue vasopressor(13). My study showed marked reduction in the usage of vasopressor if intravenous Granisetron is given prior to SA with only 1.61%(n=1) candidate required

phenylephrine 50 mcg. Other studies also revealed that vasopressor usage was lower in the group given intravenous granisetron, with the total doses of ephedrine (4.07 ± 3.87 mg vs 10.7 ± 8.9 mg, $P < 0.0001$)(5). However in my study the requirement of vasopressor favoured more of intravenous phenylephrine compare to ephedrine as phenylephrine was superior to ephedrine in parturients, evidence suggest that ephedrine causes a reduction in fetal pH and base excess, although without affecting the Apgar index, when compared to other vasopressors such as phenylephrine (14).

As for the secondary objective, absent of post operative nausea vomiting in all cases, correlated that intravenous Granisetron is an effective drug for prevention of nausea and vomiting during and after spinal anaesthesia for caesarean section(8).

The limitation of this study was the subject taken only confined to small population in a hospital setting rather than conducting the study in a larger population involve multiple hospitals. Another limitation was all the participants were elective cases, as there might be a different outcome if the conducted studies include the emergency LSCS. The estimated blood loss and the liquor were not taken into account as this factor may contribute to haemodynamic instability intra-operatively.

Suggestion for future study is to correlate haemodynamic effect of prophylactic intravenous granisetron in emergency cases, as some cases may not have proper intravenous fluid maintenance or co-loading fluid post SA. Intravenous Granisetron prior to SA may give benefits to non obstetric patients undergoing operation that need to be explore further.

In conclusion, as an antiemetic for LSCS patients, intravenous Granisetron should be given pre-SA as it improve haemodynamic stability, resulting in less usage of vasopressors and it also has no affect on the baby Apgar score post delivery.

3.7 References

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3.8 Tables and figures

Table 1: Descriptive statistics among participants (n=323).

Variables	Mean (SD)	N(%)
Age	33.31(5.21)	
Race		
Chinese		5(8.1)
Malay		56(90.3)
Others		1(1.6)
ASA		
I		32(51.6)
II		30(48.4)
Spinal		
Post spinal anaesthesia IV granisetron		31(50.0)
Pre spinal anaesthesia IV granisetron		31(50.0)
Diagnosis		
1 previous scar with fibroid		1(1.6)
2 previous scars		16(25.8)
3 previous scars		3(4.8)
Breech presentation		16(25.8)
Failed ECV		1(1.6)
Macrosomic baby		6(9.7)
PP type II posterior		2(3.2)
Primary subfertility		1(1.6)
Refused trial of scar		9(14.5)
Severe oligohydromnios		1(1.6)
Transverse lie		2(3.2)
Twin pregnancy		1(1.6)
Unstable lie		3(4.8)

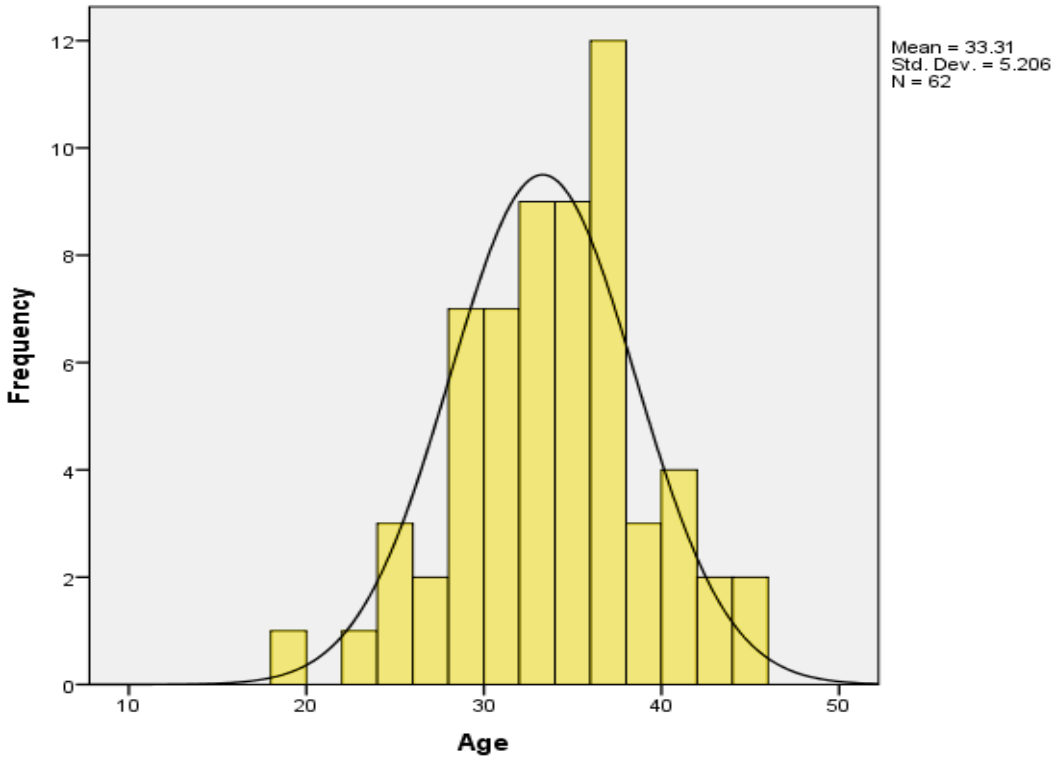

Figure 1: Distribution of age of all samples.

Table 2: Comparison of MAP within each treatment groups based on time (time effect).

Comparison	Post		Pre	
	MD[a](95%CI)	p-value[b]	MD[a](95%CI)	p-value[b]
Baseline vs 1min	11.52(2.46,20.57)	0.003	2.10(-5.13,9.33)	>0.950
Baseline vs 3 min	11.29(2.85,19.93)	0.002	3.27(-4.24,10.77)	>0.950
Baseline vs 6min	8.65(0.14,17.15)	0.042	5.07(-1.96,12.09)	0.731
Baseline vs 9 min	7.45(-1.58,16.48)	0.281	6.83(0.14,133.53)	0.041
Baseline vs 12 min	9.19(-0.69,19.08)	0.101	5.53(-1.86,12.92)	0.568
Baseline vs 15 min	8.19(-1.6318.02)	0.257	3.30(-3.85,10.45)	>0.950
Baseline vs 18 min	8.45(-1.32,18.22)	0.191	3.87(-3.85,10.45)	>0.950
Baseline vs 21 min	7.16(-2.47,16.79)	0.600	4.17(-4.48,12.81)	>0.950
Baseline vs 24 min	9.65(-0.27,19.56)	0.066	5.47(-2.65,13.59)	>0.950
Baseline vs 27 min	9.03(-0.27,19.56)	0.112	6.47(01.09,14.03)	0.209
Baseline vs 30 min	8.74(-0.97,18.46)	0.136	6.63(-0.43,13.70)	0.092

[a] Repeated measures ANOVA within group analyses were applied followed by multiple comparisons
[b]Bonferroni correction applied by correcting level of significance (α/number of pairs=0.05)
MD=mean difference