GRANISETRON VS. GRANISETRON AND DEXAMETHASONE ON THE REDUCTION OF POSTOPERATIVE NAUSEA AND VOMITING (PONV) AFTER CAESAREAN SECTION WITH INTRATHECAL MORPHINE: A RANDOMISED CONTROLLED TRIAL

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LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS

ASA	American Society of Anaesthesiologist
BMI	body mass index
BP	blood pressure
CONSORT	Consolidated Standards of Reporting Trials
CTZ	chemoreceptor trigger zone
DM	diabetes mellitus
g	gram
HR	heart rate
hr	hour
HUSM	Hospital Universiti Sains Malaysia
HREC	Human Research Ethics Committee
ICU	Intensive Care Unit
ICD-10	International Classification of Disease-10
ITM	Intrathecal Morphine
IV	intravenous
kg	kilogram
LSCS	Lower Segment Caeserean Section
m	metre
mcg	microgram
mg	miligram
min	minute
ml	mililitre
NIBP	non-invasive blood pressure

NTS	nucleus tractus solitarius
PONV	postoperative nausea and vomiting
RCT	Randomised Controlled Trial
RR	respiratory rate
SD	standard deviation
Sp02	saturation of peripheral oxygen
t.	tablet

ABSTRAK

Latar Belakang

Penggunaan intratekal morfin (ITM) terbukti berkesan dalam mengurangkan kadar kesakitan selepas pembedahan. Walau bagaimanapun, penggunaan ITM dikaitkan dengan kesan sampingan seperti mual dan muntah. Dalam kajian ini, kami ingin membandingkan keberkesanan antara terapi kombinasi granisetron dan dexamethasone atau granisetron sahaja dalam kejadian loya dan muntah selepas pembedahan (PONV) dalam kalangan pesakit yang menjalani pembedahan Caeserean elektif bawah pembiusan separa badan dan ITM.

Kaedah

Kajian prospektif ini adalah satu kajian rawak terkawal melibatkan 126 ibu mengandung kumpulan American Society of Anesthesiologist (ASA) I-II yang menjalani pembedahan elektif Caesarean. Pesakit-pesakit ini dibahagikan kepada dua kumpulan, iaitu kumpulan A (n=63) dan kumpulan B (n=63). Pesakit kumpulan A menerima 1mg intravena (IV) granisetron dan 4mg IV dexamethasone manakala pesakit kumpulan B menerima 1mg IV granisetron sahaja. Pesakit seterusnya dipantau selama 24 jam selepas pembedahan. Episode loya, muntah dan keperluan penggunaan ubat tahan muntah direkodkan pada jam pertama, ke- 4, ke-8, ke-12, dan ke-24 selepas pembedahan.

Keputusan

Tiada perbezaan signifikan secara statistik dalam kejadian loya dah muntah di antara kedua-dua kumpulan pada jam pertama, ke-4, ke-8, ke-12 dan jam ke-24 selepas pembedahan, p=0.999. Episod loya dan muntah pada jam pertama selepas pembedahan adalah sama di antara kedua-dua kumpulan. Pada jam ke-4 selepas pembedahan, didapati pesakit kumpulan A mengalami episod loya lebih daripada pesakit kumpulan B (8.8% *vs* 7%), tetapi episod muntah didapati sama di antara kedua-dua kumpulan tersebut, p=0.999. Tiada episod loya dan muntah direkodkan pada jam ke-24 selepas pembedahan. Penggunaan ubat tahan muntah (*rescue antiemetic*) antara kedua-dua kumpulan juga tidak menunjukkan perbezaan yang signifikan, p=0.999.

Kesimpulan

Penggunaan kombinasi granisetron dan dexamethasone adalah setanding dengan penggunaan granisteron dalam pencegahan loya dan muntah selepas pembedahan Caesarean elektif menggunakan spinal and morfin intratekal.

ABSTRACT

Background

Intrathecal morphine (ITM) has proven to be excellent in reducing postoperative pain. However, its use is associated with the occurrence of postoperative nausea and vomiting (PONV). In this study, we wish to compare the efficacy between the combination therapy of granisetron and dexamethasone versus granisetron alone on the occurrence of postoperative nausea and vomiting (PONV) in parturients undergoing elective Caesarean delivery.

Method

This is a prospective double-blinded, randomised controlled trial (RCT) involving 126 parturients of American Society of Anesthesiologist (ASA) physical status I and II undergoing elective Caesarean deliveries. Subjects were randomly allocated into 2 groups (n=63), to either receive a combination of 1mg intravenous (IV) granisetron plus 4mg iv dexamethasone (Group A) or to receive 1mg IV granisetron (Group B). They were assessed at 1, 4, 8, 12 and 24-hour postoperatively. Episodes of nausea, retching, vomiting and the requirement of rescue antiemetics at these time intervals were recorded.

Results

There are no statistically significant differences in the occurrence of nausea, retching and vomiting between both groups at 1, 4, 8, 12 and 24 hours postoperatively, p=0.999.

It was observed that the occurrence of PONV at 1-hour postoperatively was similar between both groups. At 4-hour postoperatively the occurrence of nausea and retching in group A was slightly more than in group B (8.8% vs 7%) but the incidence of vomiting

was similar between both groups (p=0.999). At 8-hour postoperatively, group A recorded a slightly higher occurrence of retching than group B (3.5% vs 1.8%) but then again, this is also statistically insignificant (p=0.999). There was an incident of retching in group B, but there was no episode of PONV seen in patients in group A (1.8% vs 0, p=0.999) at 12-hour post surgery. No episode of PONV were recorded thereafter. It was also found that the usage of rescue antiemetics were similar in both groups of subjects, p=0.999.

Conclusion

The use of granisetron is comparable with the use of granisetron and dexamethasone in the prevention of PONV in parturients receiving intrathecal morphine for elective Caesarean section.

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND

Low-dose intrathecal morphine has been proven efficient as a mode to reduce postoperative pain in many surgical areas including Caesarean delivery. Its use however is associated with side effects which invariably include postoperative nausea and vomiting (PONV).

PONV has always been an issue of great interest in anaesthesiology as the occurrence of PONV is regarded as unpleasant, disturbing and causes patients' discontent. Major complications such as pulmonary aspiration and scar dehiscence maybe uncommon, but intractable nausea and vomiting will lead to delayed postoperative anaesthesia care discharge and prolonged hospital admissions.

Many efforts were undertaken to reduce the incidences of PONV. Pharmacological agents from various classes and their combinations which include serotonin receptor-3 (5HT-3) antagonists, neurokinin inhibitors (NKI), corticosteroids, antihistamines and butyrophenones are known to be beneficial in combating PONV. One common combination therapy being used is a 5HT-3 antagonist and a corticosteroid.

Various studies highlighted the benefit of a serotonin receptor-3 antagonist plus a corticosteroid in combating PONV, but the evidences of these drug usage in Caesarean delivery are conflicting and lacking.

1.2 STUDY RATIONALE

In recent years, hospitals in Malaysia adapt to the administration of intrathecal morphine (ITM) routinely during Caesarean deliveries. With the addition of a single low-dose morphine, patients would experience improved postoperative analgesia. However, the supplementation of morphine would raise the incidences of PONV.

To tackle this problem, we concur to the combination therapy of antiemetics for the prevention of PONV in parturients undergoing Caesarean section supplemented by ITM. It is a standard practice in Malaysian hospitals whereby a serotonin receptor antagonist of either ondansetron or granisetron with the addition of Dexamethasone is administered after the delivery of intrathecal morphine.

Despite being routinely used, the evidence on the efficacy of a serotonin antagonist and corticosteroid combination in parturients are conflicting and lacking. In this study, we would like to compare the occurrences of PONV in patients undergoing Cesarean sections with ITM in those given a combination of granisetron - dexamethasone versus that of granisetron alone. In addition, the requirements of rescue antiemetics between both study groups will also be evaluated.

1.3 LITERATURE REVIEW

Postoperative nausea and vomiting (PONV) and Intrathecal Morphine (ITM).

Low-dose intrathecal morphine (ITM) has been implemented for more than a decade to supplement regional anaesthesia. It has been proven to provide effective postoperative analgesia in many disciplines which include general surgery, orthopaedics and in obstetrics surgery. The administration of intrathecal morphine shows reduction in postoperative pain up to 24 hours. *Abouleish et al.* [1] in their study in 1988 demonstrated that the usage of intrathecal morphine in combination to hyperbaric bupivacaine shows significant reduction in postoperative analgesia consumption. However, the side effects associated with ITM use could not be ignored. This includes sedation, respiratory depression, pruritus and urinary retention [2]. One of the most common side effects is postoperative nausea and vomiting (PONV) with incidences up to 25% [4]. *Dahl et a*l [5] published in his literature that the number needed to treat (NNT) for nausea (from 5 RCTs), was 6.3 (95% CI: 4.2, 12.5) and vomiting (from 6 RCTs) was 10.1 (95% CI: 5.7, 41.0).

PONV has always been an issue of great interest in anaesthesiology. It is defined as nausea, retching or vomiting occurring within 24 hours of anaesthesia. Nausea is described as an unpleasant sensation related to the urge to vomit [6]. Retching is defined as an involuntary effort to vomit but without the expulsion of the gastric contents, which if present defines vomiting [6]. It does not only cause patients' dissatisfaction but more than that, it is profoundly distressing.

PONV is considered as the commonest post anaesthesia outcome patients would like to avoid [7]. Complications such as aspiration of gastric contents, and scar dehiscence maybe uncommon, but intractable nausea and vomiting will lead to delayed postoperative anaesthesia care discharge and prolonged admissions [8].

Risks factors associated with PONV has been evaluated by various researches including randomised controlled trials (RCTs). A study by Apfel et al [9] demonstrated that the female gender was the strongest patient-related predictor of PONV. This is subsequently followed by history of PONV or motion sickness, non-smoking status and age. With the presence of these factors the incidences of PONV may raise as high as 80%. The administration of inhalational agents was found to be the most significant anaesthesia-related factor, followed by duration of anaesthesia, postoperative opioid use as well as the delivery of nitrous oxide. Other factors such as type of surgery and menstrual were proved insignificant to the development of PONV.

Risks scoring system were then developed to predict the development of PONV. A few include the scoring system by Koivuranta and the commonly used Apfel score. *Koivuranta et al.* [10] proposed that female gender, non-smokers, history of PONV, history of motion sickness and duration of surgery exceeding 60 minutes as the important factors contributing to PONV. Apfel [11] developed a scoring system to risk-stratify patients into low, moderate and those of high risk of developing PONV. He implicates female gender, history of PONV or motion sickness, non-smoking status and postoperative opioid use as the main contributing factors of PONV and relates that the presence of either factor above increases the risk of PONV each by about 20%.

Combination of 5HT-3 Antagonist and Dexamethasone for PONV

Much effort and studies has been conducted to provide solutions in reducing the incidences of PONV [12][13]. Multimodal approach with risk reduction strategies and combination therapy of antiemetics were applied in guidelines to reduce the incidences of PONV [14]. This include the use of various classes of antiemetics and their combinations among which are serotonin receptor-3 (5HT-3) antagonists, neurokinin inhibitors (NKI), corticosteroids, antihistamines and butyrophenones [14][15].

Ample studies were conducted to evaluate the efficacy of combination therapy between serotonin receptor antagonist and a corticosteroid to lessen the occurrence of PONV. In 2013, Ryu et al [16] concluded that the combination between ramosetron-dexamethasone was superior in reducing PONV after laparoscopic cholecystectomy compared to ramosetron alone. A study published by Cho E et al [17] recently comparing the efficacy between the combination of palonosetron-dexamethasone vs palonosetron monotherapy for the prevention of PONV in opioid-based anaesthesia revealed that the combination therapy of palonosetron-dexamethasone reduces the PONV incidence.

There were various studies comparing the efficacy of granisetron-dexamethasone to granisetron in both the adult and paediatric population. Granisetron is the first generation serotonin receptor antagonist. In dose of 5-20mcg/kg it is known to be as effective as ondansetron in both gynaecological and laparoscopic surgery [18][19]. Its effect is best up to 24 hours of its administration [20]. Dexamethasone, a potent corticosteroid effectively reduces the incidence of PONV [21][22]. Given after induction rather than at

the end of surgery with a dose of 4mg-8mg, administration of dexamethasone too has proved effective in preventing PONV [22][23].

Comparative studies demonstrating the superiority of granisetron and dexamethasone to granisetron alone include those undergoing modified radical mastectomy [24] and thyroidectomy [25]. The combination of these drugs also showed promising results in the paediatric population. These include those undergoing middle ear surgery [26] and paediatric strabismus surgery [27].

Combination of 5HT-3 Antagonist and Dexamethasone in Parturients

While numerous studies assessing the combination of 5HT-3 antagonist and dexamethasone in different surgical areas, studies pertaining parturients are lacking and the results were confounding.

A study issued by the African Health Sciences concur with the previous' studies results. The incidence of PONV in 108 parturients was significantly reduced in those receiving the combination of ondansetron and dexamethasone compared to those receiving ondansetron alone with a p-value of 0.003 [28]. On the contrary, a study published in 2013 involving 86 parturients conducted by A Demirhan et al [29] revealed that the combination of ondansetron - dexamethasone was no superior than either drug alone.

Also, a study published by T. Suryayee et al in 2015 in the Journal of Dental and Medical Sciences found out that the differences in the incidence of PONV in those undergoing elective Caeserean deliveries were not significant in parturients receiving granisetron and

dexamethasone to granisetron alone [30]. A more recent study in 2018 by Swastika Saro et al also attest the superiority of the combination therapy in preventing PONV. He revealed that the combination of palonosetron-dexamethasone proved no better than palonosetron alone [31].

CHAPTER 2: STUDY OBJECTIVES

2.1 GENERAL OBJECTIVES

To compare the efficacy between combination therapy of granisetron plus dexamethasone versus granisetron alone on postoperative nausea and vomiting (PONV) in patients undergoing elective Caesarean section with intrathecal morphine.

2.2 SPECIFIC OBJECTIVES

a) To compare the incidence of nausea, retching and vomiting at 1 hour, 4 hours, 8 hours, 12 hours and at 24 hours postoperatively between the group of patients receiving the combination therapy of granisetron plus dexamethasone versus that of granisetron alone.

b) To compare the requirements of rescue antiemetics between both groups of patients at 1 hour, 4 hours, 8 hours, 12 hours and at 24 hours postoperatively between the group of patients receiving the combination therapy of granisetron plus dexamethasone versus that of granisetron alone.

2.3 RESEARCH HYPOTHESIS

NULL HYPOTHESES

There is no significant difference on the incidence of postoperative nausea and vomiting after intrathecal morphine for Cesarean section between patients receiving the combination therapy of granisetron and dexamethasone versus patients receiving granisetron alone.

There is no significant difference in the requirements of rescue antiemetics between both groups of patients.

ALTERNATIVE HYPOTHESES

Patients receiving the combination therapy of Granisetron and Dexamethasone has a lower incidence of PONV after Cesarean section using intrathecal morphine compared to patients receiving Granisetron alone.

Patients receiving both Granisetron and Dexamethasone require less rescue antiemetics than that of patients receiving Granisetron monoterapy.

CHAPTER 3: STUDY PROTOCOL & ETHICAL APPROVAL

3.1 STUDY PROTOCOL

Study Design

Prospective, randomised, double-blinded clinical trial (RCT).

Study Site

Operation Theatre, Hospital Universiti Sains Malaysia (HUSM) Kubang Kerian, Kelantan.

Study Population

Reference Population

Patients undergoing elective Cesarean delivery in Malaysia.

Source Population

Patients undergoing elective Cesarean delivery in Kelantan.

Source Population

Patients undergoing elective Cesarean delivery in HUSM, Kubang Kerian.

Sampling Frame

Patients undergoing Cesarean delivery in HUSM Kubang Kerian, from the 1st of June 2019 until the of 30th January 2020.

Research Criteria

Inclusion Criteria:

a) Pregnant women

b)18-45 years old

c) American Society of Anaesthesiologists (ASA) I-II

d)2 risks factors or more for PONV according to Apfel.

Exclusion Criteria:

a) Unfit for spinal anaesthesia.

- Coagulopathy
- Uncorrected hypovolemia
- Indeterminate neurologic disease
- Infection at site of injection
- Raised intracranial pressure(ICP)

b) Morbidly obese patients, BMI> 40 kg/m2 according to ICD-10.

c) Patients allergic towards morphine.

d) Contraindicated for antiemetics use

- Granisetron: allergy towards Granisetron, prolonged QT interval
- Ondansetron: allergy towards ondansetron, prolonged QT interval
- Dexamethasone: allergy towards Dexamethasone, uncontrolled DM.

Withdrawal Criteria

a) Admission to ICU post surgery.

b) Conversion to general anaesthesia for any reason.

Operational Terms

Nausea is described as an unpleasant sensation related to the urge to vomit.

Retching is defined as an involuntary effort to vomit but without the expulsion of the gastric contents.

Vomiting is an involuntary effort to vomit but with the expulsion of the gastric contents.

Postoperative period is the period from the time of completion of skin suturing.

Sample size estimation

Significance level, $\alpha = 0.05$

Power, 80% = 0.8

We based our assumption that the combination of a serotonin receptor antagonist with a corticosteroid would be superior than its monotherapy and thus, the addition of Dexamethasone to Granisetron would reduce the incidence of PONV from 20% to 3.3% [26][27]. From the calculation using PS software, we would need to study 57 experimental subjects and 57 subjects to be able to reject the null hypothesis.

The sample required for each group is 57, and with the additional 10% for dropout rate, this study required 63 patients in each group, giving a total of 126 patients.

Sampling method and subject recruitment

Sampling was by convenience sampling based on time frame and target number of subjects. Subjects were enrolled during our preoperative assessment in ward. They were explained thoroughly on the study including the risks and benefits. An informed and written consent were obtained during the acquaintance. Subjects were given a copy of the consent for their keepsake. Concealment of the allocation sequence will be adhered to minimise bias to treatment.

Research Tool

None.

Study Protocol & Method

126 subjects were enrolled in this study. Informed and written consent from each patient were collected from the selected 126 parturients aged between 18 and 45 years old who were American Society of Anaesthesiologists (ASA) I and II category undergoing Caesarean deliveries from the 1st of June 2019 till the 30th of January 2020. Subjects who had coagulopathy, uncorrected hypovolemia, infection at site of injection and raised intracranial pressure (ICP) were excluded from the study. Others, who were contraindicated for either morphine, granisetron or dexamethasone administration, morbidly obese patients with BMI of 40 kg/m2 or more were also excluded from this study. Patients' information including gravity and parity, age, weight, height, smoking status, history of PONV or motion sickness were obtained.

Patients were then subjected to fasting 6 hours prior to surgery. Clear fluids were allowed up to 2 hours prior surgery. Intravenous (IV) metaclopromide 10mg, IV ranitidine 50mg and mist sodium citrate 30mls were administered as part of acid aspiration prophylaxis. All antacids were given in ward prior to surgery.

The subjects were randomised using a computer-generated randomisation software using block size 3 into 2 groups. The order of interventions within each block was random as determined by computer random number generator. This technique was chosen to ensure similar numbers of patients in each group at any point during the study. In this study, blinding was applied to the patients and the assessors of PONV, which comprise of the Acute Pain Service (APS) team members.

Each group consisted of 63 subjects each. Patients in group A received the combination of IV granistron 1mg [32] plus IV dexamethasone 4mg and those in group B received 1mg IV granisetron and 1ml of normal saline instead of dexamethasone. Standard monitoring with continuous noninvasive blood pressure monitoring (NIBP), electrocardiogram (ECG) and respiratory rate and pulse oximetry (SPO_2) was undertaken for all subjects throughout anaesthesia.

Ringer's lactate solution 10ml/kg was infused for co-loading [33-35]. Spinal anaesthesia was administered in the upright position. We implement a height-based dosing of local anaesthetic for spinal anaesthesia in parturients. Intrathecal fentanyl 15-20 micrograms (mcg) plus morphine 0.1 miligram (mg) were added to supplement the spinal anaesthesia.

Height-based dose for spinal anaesthesia

Patient's height (cm)	Dose of heavy marcaine 0.5%	Dose of fentanyl	Dose of morphine
<150cm	1.5ml	15-20mcg	0.1mg 0.1ml
151-154cm	1.7ml	15-20mcg	0.1mg 0.1ml
155cm>	1.9ml	15-20mcg	0.1mg 0.1ml

IV dexamethasone 4 mg was administered after the completion of spinal anaesthesia while IV granisetron 1mg was administered after cord clamping. These drugs were given by the anaesthetist who performed the anaethesia. The anaesthetist in charge was not blinded as this was important to ensure safety of patients should any complication arises during the delivery of anaesthesia.

Choice of rescue antiemetics

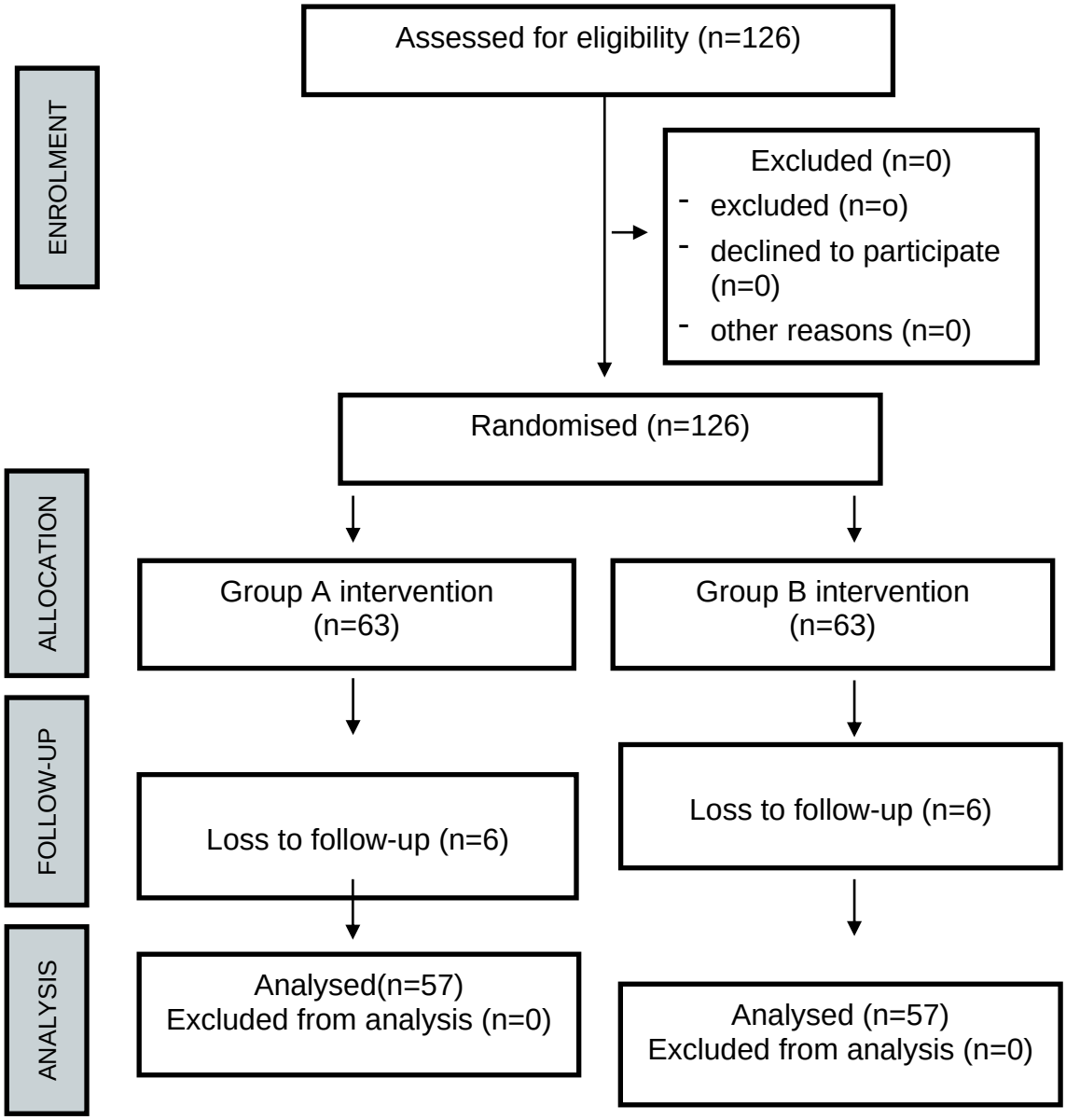
Opioids were avoided during the first 24 hours of intrathecal morphine administration. Diclofenac suppositories 1mg/kg was administered per rectal. Tablet (t.) paracetamol 1g QID and Capsule (c). voltaren were provided to patients in wards to supplement ITM as part of the postoperative analgesics.

Choice of rescue antiemetics	Group A	Group B
Less than 6 hours	4mg IV Ondansetron	4mg IV Dexamethasone
More than 6 hours	To inform anaesthesia medical officer	4mg IV Ondansetron

All patients were transferred to the recovery room and monitored for 1 hour. Patients who fulfilled the discharge criteria were sent to ward. Subjects were monitored for complications of spinal ITM for 24 hours. Assessments were carried out by the Acute Pain Services team. Episodes of nausea, retching and vomiting are recorded at each assessors' visit. The requirement of rescue antiemetics at each time interval was documented. Rescue antiemetic chosen was administered when patient developed one or more episode of vomiting.

The subjects identification ware numbered and randomisation was not disclosed to the assessors. All data collected were kept and secured for analysis. From the the 126 patients, 6 from each group were not included in the analysis. In both groups, 6 patients were loss to follow-up. Data from a total of 114 patients were analysed.

Study flow diagram *(Prepared according to CONSORT 2010 Guidelines)*



Study flow chart

Preoperative assessment and informed consent

Arrival to the operation theatre

Standard monitoring: NIBP, SPO_2, ECG, RR

Co-loading: 10mls/kg IV crystalloid

Spinal anaesthesia with intrathecal morphine (ITM).

1.9mls of heavy bupivacaine 0.5% for patients taller than 154cm in height.
1.7mls of heavy bupivacaine 0.5% for patients between 151-154cm in height.
1.5mls of heavy bupivacaine 0.5% for patients 150cm or less in height.

Start of surgery

Fetal delivery and cord clamping

Group A	**Group B**
IV Dexmethasone 4mg + IV Granisetron 1mg	IV normal saline 1 ml + IV Granisetron 1mg

Monitoring in the recovery room for 1 hour

Monitoring of study outcome

Occurrence of nausea, retching and vomiting at 1, 4, 8, 12 and 24h postoperatively

Frequency of vomiting

Rescue antiemetic requirement

Data Analysis

Analysis was performed using SPSS version 24 for MAC.

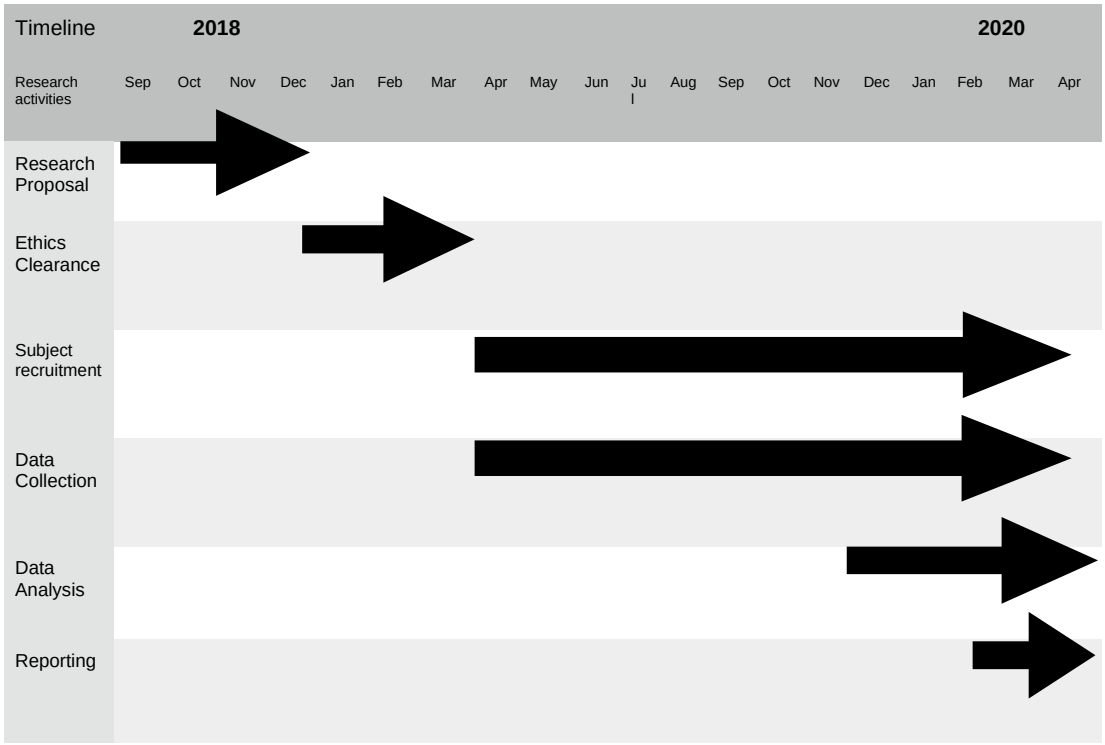
Independent T-test was used to analyse numerical datas which are age, weight, height and BMI. The frequency of vomiting at different intervals was also calculated by independent t-test. Numerical data is presented by mean (SD).

Chi-square was used to analyse categorical variables which were the incidence of nausea, retching, vomiting, and the usage of rescue antiemetics between both groups. The association between APFEL score and ASA classification between both groups was also analysed by Chi-square. Categorical data is presented as percentage.

Intended Statistical Analysis

OBJECTIVE	Parameters	Satistical analysis
Objective 1	Occurence of nausea, retching and vomiting	Chi-square
Objective 1	Frequency of vomiting	Independent T-test
Objective 2	Usage of rescue antiemetic	Chi-square

Gantt chart


Timeline
2018
2020
Research activities
Sep
Oct
Nov
Dec
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Jan
Feb
Mar
Apr
Research Proposal
Ethics Clearance
Subject recruitment
Data Collection
Data Analysis
Reporting

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