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Effectiveness Of Ondansetron Prior To Spinal Anesthesia In Obese Parturients Undergoing Caesarean Delivery

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Abstract

Spinal anesthesia is the preferred route of anesthesia for parturients undergoing casesarean section (Hawkins et al., 2011). Parturients with obesity undergo caesarean delivery and have higher rates of initial intrathecal failure comparatively to non-obese (Hood, et al, 2015). Obesity is on the rise leading to a reconsideration as to the dosing of spinal anesthetic type (Dennis, 2017). Historically, the utilization of ondansetron, as a selective 5-HT3 antagonist, has been utilized prior to spinal administration to prevent the sympathectomy that can occur (Sahoo et al., 2012). This has decreased the utilization of vasopressors which can be detrimental to the fetus during cesarean (Kinsella et al., 2017).

A literature search was performed using major databases. 30 articles experimental studies, randomized control trials (RCT) and systematic reviews of RCTs with or without meta-analysis published within the last ten years were selected for initial review. 17 articles were identified as related to obesity and pregnancy undergoing spinal anesthesia for cesarean section.

Ondansetron's utilization as an effective attenuator of a subarachnoid block sympathectomy has been accepted through various studies. However, through the literature review, a gap in obesity with dosing of prophylactic 5-HT3 antagonists and intrathecal local anesthetics, as well as, objective non-invasive data collecting to facilitate spinal anesthetic hypotension from occurring.

Effectiveness of Ondansetron prior to Spinal Anesthesia

in Obese Parturients Undergoing Cesarean Delivery

Spinal anesthesia is the premier choice for parturients undergoing cesarean delivery due to its rapid onset of action, superior postoperative pain control and lower mortality rates, comparatively to general anesthesia (Hawkins et al., 2011). The awake post-operative state for mother-baby bonding, faster recovery of gastrointestinal function, better postoperative analgesia, and lower placental drug transfer, are additional benefits of spinal anesthesia comparative to general anesthesia (Ganeshanavar et al., 2011). Cesarean sections require a sensory block to T4-T6, which causes an extended sympathetic block in 55% to 90% of patients (Trabelsi, 2015). Sensory block of T4 is associated with an and extended sympathetic block leading to sympathectomy. Sympathectomy is the reduction in vascular resistance from sympathetic blockade after spinal anesthesia which can be detrimental to hemodynamic stability and perfusion in conjunction with hypotension mediated aortocaval compression from the gravid uterus (Nivatpumin & Thamvittayakul, 2016). Hypotension may also present as maternal nausea and vomiting, and result in fetal complications such as hypoxia and acidosis (Nivatpumin & Thamvittayakul, 2016).

Sympathectomy causes a decrease in cardiac output through relative parasympathetic dominance, as evident by bradycardia (Sahoo et al., 2012). It also causes a decrease in systemic vascular resistance primarily due to inhibition of the Bezold-Jarisch reflex (BJR) and reverse Bainbridge reflexes (Ortiz-Gomez et al., 2014). According to Ortiz-Gomez (2014), the BJR is mediated through the vagal afferents. When the vagal afferents are activated, this causes hypotension and bradycardia to occur (Nivatpumin & Thamvittayakul, 2016). The Bezold-Jarisch reflex facilitates reduction in hypotension, however but with a spinal mediated

sympathetic blockade it is unable to mitigate. Furthermore, reduction in blood volume in the intracardiac wall leads to increase vagal activity by triggering of serotonin sensitive chemoreceptors (Nivatpumin & Thamvittayakul, 2016). This increase in vagal activity potentiates the severity of bradycardia and vasodilation.

The Bainbridge Reflex, also known as the atrial receptor reflex, occurs on both an afferent sensor and efferent response (Barash, 2017). The afferent sensors have stretch receptors located in the right atrium and sense central venous pressure (CVP) via cranial nerve ten. Along the efferent response high central venous pressure increases sympathetic nervous system tone and decreases parasympathetic tone per cranial nerve ten resulting in an increase heart rate (Barash, 2017). Thus, a sympathetic blockade coupled with the parasympathetic dominance results in a reverse Bainbridge Reflex (Ortiz-Gomez et al., 2014).

Ondansetron has been extensively researched for its selective inhibition of the 5-HT3 receptors (Ortiz-Gomez et al., 2014). 5-HT3 receptor sites are located in the peripheral afferent terminals of the vagus nerve, and blockade of 5-HT3 receptor inhibits the Bezold-Jarisch reflex (Ortiz-Gomez et al., 2014). The suppression of the BJR attenuates a decrease in the sympathectomy that occurs through spinal anesthesia. Specifically, ondansetron may attenuate arterial hypotension by blocking serotonin-induced bradycardia (Ortiz-Gomez et al., 2014). Weight based dosing of ondansetron has been shown to increase the mean arterial pressure of patients undergoing cesarean section when given 0.15 mg/kg compared to a control group (Fattahi et al., 2015).

Background

Obstetric Anatomical Changes

The Parturient's physiological changes facilitate blood flow and oxygen delivery to the fetus. Hyperemia results due to blood volume increase by 40% whereas plasma volume increases by 30% to 50% and red blood cell volume by up to 30% (Barash, 2017). This change in circulating volume results in a physiologic anemia of pregnancy decreasing in blood viscosity improving blood flow to the fetus. A prothrombotic state exists in Parturient's due to all clotting factors, with exception to factors XI and XIII, increasing (Barash, 2017). This results in an increased risk of deep vein thromboembolism (Barash, 2017). Secondarily, fibronlysis occurs later in pregnancy resulting in a form of compensated disseminated intravascular coagulopathy (DIC). Likewise, dilutional thrombocytopenia is common and occurs in 8% of pregnancies, but this thrombocytopenia does not cause an increased in neuraxial hematomas (Barash, 2017).

With regards to cardiovascular changes, an increase in blood volume, stroke volume and heart rate, result in a 45% increase in cardiac output by the end of the first trimester (Barash, 2017). However, a lack of sensitivity to vasopressors and an accentuated sensitivity to decreases in preload, leave the parturient, during anesthesia, needing more close regulation of blood pressure (Barash, 2017). Venous return, especially starting after 20 weeks gestation, can be severely compromised due to the gravid uterus compressing the inferior vena cava, resulting in supine hypotension syndrome (Barash, 2017). While in labor, cardiac output increases another 50% and these changes take several days postpartum to resolve (Barash,2017). Due to systemic vascular resistance decreasing, a mild drop in blood pressure over pre-labor recordings is normal (Barash, 2017).

Pregnant women are more sensitive to neuraxial local anesthetics and require lower doses than nonpregnant patients (Barash, 2017). This can be correlated to a decrease in serum cholinesterase activity by nearly 20% to 30%, resulting in a longer duration of ester-type anesthetics (Barash, 2017). Increased progesterone levels in CSF are directly proportionate to the increased segmental spread and sensitivity of nerves to local anesthetics (Nagelhout, 2018). The pregnant patient has a decreased epidural space volume due to epidural vein engorgement, leading to narrowing of the epidural and subarachnoid space (Barash, 2017). Spread of neuraxial anesthesia also increases in pregnancy due to thoracolumbar cerebrospinal fluid volume (Nagelhout, 2018). Hormonal changes, increase in progesterone, relaxin and estrogen, also play a role during the first trimester when little mechanical compression is evident (Nagelhout, 2108). Relaxation of the ligamentous results in accentuation of lumbar lordosis, causing the intercristal line to occur at L3-4 in pregnant patients (Barash, 2017).

Obesity and Pregnancy

Obesity affects over 20% of pregnancies. (Nagelhout, 2018). Extra fat deposits require their share of cardiac output. For every 100 g of fat, cardiac output increases by 30-50 mL/min which may lead to cardiomyopathy (Soens et al., 2007). While afterload in non-obese parturientst is reduced, afterload reduction in obese pregnant patients may be impaired due to increased peripheral vascular resistance and arterial stiffness (Cho et al., 2020). As such, obesity is associated with increased incidence of hypertension, hyperlipidemia, poor cardiac function, coronary artery disease, diabetes mellitus and cerebrovascular accidents (Soens et al., 2007). Furthermore, higher BMI is associated with increased intra-abdominal pressure, causing CSF to decrease in volume-exaggerated hypotension (Wang et al., 2018).

During pregnancy, exacerbation of obesity associated comorbidities due to increases in secretion of human placental lactogen, human chorionic gonadotropin and steroid hormones. Moreover, the increase in these hormones affects the resistance of target tissues to insulin (Soens et al., 2007). Other hormones, such as estrogen, accelerate insulin secretion from pancreatic Beta cells (Nagelhout, 2018). Collectively, these hormonal changes cause hyperinsulinemia and fat deposition, further compounding the already obese patient. Finally, increased fat panniculus may further compress the aortocaval in the supine position during the second trimester leading to hypoplacental perfusion to the fetus (Soens et al., 2007).

Additionally, the incident of cesarean delivery increases by two-fold when compared to non-obese parturients. Likewise, complication rates increase in obese parturients undergoing c-section due to higher infectious and thromboembolic events, leading to increased rate of hospital admissions and overall healthcare costs (Gunatilake, 2013).

Caesarean Section under General Anesthesia

Due to mortality being 17 times greater when compared to general anesthesia, SAB, or Neuraxial anesthesia, is the preferred technique for cesarean delivery (Chestnut, 2020). However, general anesthesia is more appropriate when there is maternal hemorrhage, fetal distress, patient refusal of regional anesthesia, contraindications to regional anesthesia and coagulopathy (Chestnut, 2020). Benefits of general anesthesia include speed of onset, greater hemodynamic stability, and secured airway (Chestnut, 2020). Drawbacks of general anesthesia include difficult laryngoscopy, mask ventilation and intubation (Chestnut, 2020). Additional risk of aspiration and neonatal respiratory and CNS depression. Failure to successfully manage the airway in the operating room is the most common cause of maternal death (Chestnut, 2020).

Planning for a difficult intubation is paramount. The HELP position (head elevated laryngoscopy position) facilitates visualization of the glottic opening by aligning the sternal notch and external auditory meatus (Chestnut, 2020). Prophylaxis against aspiration, and aspiration pneumonitis, are the utilization of sodium citrate, H2 receptor antagonist and gastrokinetic agents to neutralize and, increase pH of gastric acid, hasten gastric emptying and increase lower esophageal sphincter tone (Chestnut, 2020). Extubating the patient awake is preferable, as full stomach considerations need to be considered (Chestnut, 2020).

Spinal Anesthesia for Cesarean Section

Single injection spinal anesthesia is the most commonly used anesthetic technique for cesarean delivery (Nagelhout, 2018). Advantages of this method include rapid onset and more reliable block with smaller less toxic doses of local anesthetic compared to epidural anesthesia (Nagelhout, 2018). With its rapid onset and decrease overall operating room times, makes it an economical anesthetic (Nagelhout, 2018)

Bupivacaine, in the isobaric or hyperbaric form, is the standard local anesthetic of choice of cesarean delivery via spinal anesthesia (Sia et al., 2013). Hyperbaric bupivacaine is the more commonly utilized due to the predictability of a denser T4 level segmental block and quicker onset of action given its increased baricity (Sia et al., 2013). The migration of the local anesthetic cephalad in cerebral spinal fluid (CSF) depends on its density relative to CSF (Miller, 2015). A hyperbaric solution is denser, or heavier, than CSF, thus causing more cephalad a spread in a head-down patient (Miller, 2015). In contrast, an isobaric solution tends to remain at the level of injection. However, the compound curvature of the spine in the supine fashion limits the upward spread of hyperbaric anesthetics (Nagelhout, 2018). Baricity, level of injection, patient's height

and vertebral column anatomy and dose amount all affect the level of neural blockade following

spinal anesthesia (Miller, 2015).

Neuraxial Local Anesthetics

Although, ropivacaine, levobupivacaine, lidocaine and 2-Chloroprocaine have been

documented for usage in neuraxial anesthesia, bupivacaine is the local anesthetic of choice for c-

section (Sia et al., 2013). Utilization of bupivacaine benefits through minimal tachyphylaxis and

low placental transfer because of increase protein binding and increase ionization. In addition, it

provides greater sensory block, more rapid onset, and long duration relative to other local

anesthetics (Chestnut, 2020).

For example, 13 mg of 0.75% Bupivacaine, is effective in 95% of patients providing up to 120

minutes of surgical anesthesia, isobaric bupivacaine in the 0.5% concentration may lasts up to

three hours, when 15 mg is given (Nagelhout, 2018). With that said, reduction in bupivacaine

dose results in less hypotension but it also associated with increased risk of intraoperative pain, a

shorter duration of anesthesia and slower onset (Nagelhout, 2018). Hypotension occurs in about

90% of parturients, expressed as nausea and vomiting, and if left untreated can result in altered

level of consciousness, uteroplacental hypoperfusion and cardiovascular collapse (Trabelsi,

2015) (Nagelhout, 2018).

Local Anesthetics

Local anesthetics are a group of drugs which reversibly block initiation of an action

potential (Nagelhout, 2018). The main action of local anesthetics is by reversibly binding to

voltage-gated sodium channels (Na^+), which play the most significant role to initiation and

propagation of the action potential (Nagelhout, 2018). The guarded receptor or modulate receptor

hypothesis of local anesthetics to how local anesthetics preferentially bind to both open and/or

inactivated sodium channels (Nagelhout, 2018). When the sodium channel is repetitively depolarized, local anesthetics work faster, this is known as the use-dependent or phasic block, and further explains the mechanism of action (Nagelhout, 2018). Thus, the more the channel is depolarized the more time it is available for the sodium channel to be open and inactive allowing more availability for a local anesthetic blockade (Nagelhout, 2018). Local anesthetics effectively block the excitability and propagation of the action potential by preventing the initiation of an action potential (Nagelhout, 2018). This lack of propagation results in different fibers, based on diameter and myelination, being blocked in a specific order (Nagelhout, 2018). First autonomic fibers, followed by somatic sensory and finally somatic motor nerve dysfunction occurs (Nagelhout, 2018). Clinically, this is expressed as autonomic dysfunction, decrease sensory sensation and muscle paralysis distal to the injection site, in this order (Nagelhout, 2018). Muscle paralysis, followed by sensory sensation and finally autonomic dysfunction returns, once the local anesthetic is metabolized in the liver or by hydrolysis, in the plasma (Nagelhout, 2018).

How long a local anesthetic will last depend primarily on whether the drug is more hydrophilic (water soluble) as they are ionized amines, meaning they have a hydrogen ion attached and thus can't penetrate the lipid bilayer (Nagelhout, 2018). The other facet is how lipophilic the drug is, or non-ionized, meaning no hydrogen molecule is attached, and can thus, the local anesthetic molecule can penetrate and mitigate an action potential (Nagelhout, 2018). The increased duration of onset of the local onset depends primarily on its protein binding (Nagelhout, 2018). Thus, the more protein binding the local anesthetic has the faster onset of action (Nagelhout, 2018). The protein binding of bupivacaine is 97% protein bound, one of the primary reasons for its preference as an anesthetic during cesarean section (Nagelhout, 2018).

Zofran (Ondansetron)

5-HT3 receptors are distributed extensively on neurons in the gastrointestinal tract and brain, specifically the chemoreceptor trigger zone (Flood, 2021). Serotonin is released from the enterochromaffin cells in the small intestine and central nervous system (Flood, 2021). Serotonin stimulates the vagal afferents and initiates the vomiting reflex (Flood, 2021). Ondansetron is a selective 5-HT3 antagonist, so it does not alter dopamine, histamine, adrenergic or cholinergic receptor activity (Flood, 2021).

Major side effects with ondansetron are QT prolongation (Flood, 2021). EKG monitoring is needed for patients with hypokalemia, hypomagnesemia, congestive heart failure and other medications that can lead to QT prolongation (Flood, 2021). The risk of QT prolongation increases with dosing and frequency of Zoran administration (Flood, 2021).

Literature Review

Methods

A literature search was performed using Medline, CINHAL, SCOPUS, DUNEDigitalUNE, PubMed, EMBASE, Cochrane Library, and Google Scholar. Experimental studies, randomized control trials (RCT) and systematic reviews of RCTs with or without meta-analysis published within the last ten years were selected for initial review. In addition, the search produced non-experimental studies, systematic review of a combination of RCTs, quasi-experimental and non-experimental studies, or non-experimental studies only, with or without meta-analysis. Lower level of research identified qualitative studies or systematic reviews of qualitative studies. This extensive search identified 30 articles for consideration with varied degree of relevancy based on the original PICO question such as, maternal obesity, spinal hypotension, intrathecal hypotension, cesarean and spinal anesthesia. Duplicity of studies, as well as single patient case reports were excluded. Common areas of study were examined from

author to author and from review to review. Limited high quality research in the obese

parturients undergoing spinal anesthesia for caesarean section was evident.

Ondansetron Dosing & Hypotension

Tubog et al. (2017) conducted a systematic review and meta-analysis of 13 RCTs. In all,

Tubog et al. evaluated outcomes of 1,225 participants who received prophylactic ondansetron vs

placebo or other 5-HT3 antagonist pharmacologic intervention and spinal anesthesia used as

primary anesthetic technique. Hypotension and bradycardia were summarized using a risk ratio

(RR) with 95% confidence interval (CI).

RR is the measurement of the risk of a certain event happening in one group compared to

the risk of the same event happening in another group. The figure is achieved by dividing the risk

in one group by the risk in another group. CI is a range to provide confidence with how precise

the data is. CIs are calculated at a confidence level ranging from 90% to 99.9%. CI is considered

a more useful measure of the mean to indicate how reliable the results reflect the whole

population. In Tubog et al., the RR for hypotension was 0.63 and CI was 0.45 to 0.88. The RR

for patients receiving ondansetron was 0.31, 95% CI [0.19, 0.5] (Tubog et al., 2017). This

concluded attenuation of spinal induced hypotension (SIH) and bradycardia occurred with

utilization of prophylactic ondansetron. Limitations of this systematic review and meta-analysis

included lack of dosing regiments for further validation.

Sahoo et al. (2012) conducted a prospective double-blind, placebo-controlled trial

involved 52 participants who were either given ondansetron 4 mg (Group O) or given normal

saline (Group S). Although small sample size was a limitation, decreases in mean arterial

pressure were significantly lower in the ondansetron group. At 5 minutes: the 4mg ondansetron

group (M = 88 mmHg, SD = 11.7) versus normal saline group (M = 82.2 mmHg, SD = 10.5, p =

0.038); at 6 minutes: 4 mg ondansetron group (M = 87.5, SD = 11.3) versus normal saline group (M = 80.4, SD = 10.8 mmHg, p = 0.025). (Sahoo et al., 2012). In contrast, decreases in heart were more common in normal saline group (Sahoo et al., 2012). The differences in heart rate were statistically different at 24 minutes in the 4 mg ondansetron group (M = 93.9 beats/min, SD = 16.5) versus normal saline group (M = 82.9 beats/min, SD = 14.1, p = 0.031) and at 45 minutes: 4 mg ondansetron group (M = 94.3 beats/min, SD = 16.2) versus the normal saline group (M = 83.1, SD = 7.5, p = 0.02) (Sahoo et al., 2012). Patients in the 4mg ondansetron group required significantly less (p = 0.009) vasopressors and had significantly lower incidence of nausea and vomiting, one case within Group O compared to 7 instances in Group S (p = 0.049) (Sahoo et al., 2012).

Ondansetron utilization for prevention of hypotension during spinal anesthesia was investigated by Oofuvong et al. (2018), specifically with focus on weight-based dosing variations. Oofuvong et al. utilized a prospective triple-blinded, parallel group, randomized controlled trial including 228 participants and collected data to compare for normally and non-normally distributed data. P value of <0.05% was considered statistically significant. Utilization of ondansetron 0.05 mg/kg (group O1) or ondansetron 0.1 mg/kg (group O2) five minutes prior to spinal anesthesia was compared to the third group who received 0.9% NaCl crystalloid (group O3). Oofuvong et al. (2018) defined hypotension as a decrease in MAP >30% from baseline and found the incidence in group O1 (81.9%) O2 (84.5%) and O3 (73.6%) (Oofuvong et al. (2018). Overall heart rate throughout the groups were not different among the three groups. Interestingly, incidence of hypotension between the three groups, either before or after cesarean delivery, were significantly higher in group O1, 0.05 mg/kg compared to control group O3, 0.9% NaCl (Oofuvong et al., 2018).

Ortiz-Gomez et al. (2014) conducted a prospective double-blind, randomized, placebo controlled study including 128 pregnant women undergoing cesarean delivery via spinal anesthesia. The women were separated into four groups, 32 women in each, the groups received either placebo or ondansetron in 2, 4 or 8 mg doses prior to intrathecal anesthesia (Ortiz-Gomez et al., 2014). This study found no difference in the number of patients with hypotension in the placebo (43.8%) and ondansetron 2mg (53.1%), 4mg (56.3%) and 8mg (53.1%) (Ortiz-Gomez et al., 2014). Nor, Ortiz-Gomez et al. concluded, were the percentage of time points with systolic hypotension; $M = 7.3\%$ in the placebo group, and $M = 11.1\%$, $M = 15.7\%$ and $M = 12.6\%$ in the ondansetron 2, 4 and 8 mg groups respectively ($p = 0.32$). Likewise, no difference occurred with regards to utilization of ephedrine ($P = 0.11$) or phenylephrine ($P = 0.89$) requirements and the number of patients with adverse effects (Ortiz-Gomez et al., 2014).

Wang et al., (2014) randomly assigned 155 parturients to one of five groups, equaling 30 women per group. Five minutes prior to spinal anesthesia parturients were given either 5 mL of physiological saline (Group S), 2mg (Group O2), 4 mg (Group O4), 6 mg (Group O6) or 8 mg (Group O8) of ondansetron (Wang et al., 2014). The study monitored maternal blood pressure and heart rate at 2 minute intervals for a total of 30 minutes (Wang et al., 2014). Group O4 and O6 showed significantly, $p < 0.05$, lower incidence of maternal hypotension compared to the other group (Wang et al., 2014).

A more recent study performed by Qian et al. (2020) who conducted a prospective, randomized, double-blinded dose study to evaluate dose timing whereby Ondansetron 4 mg administered 5 min (Group A) or 15 min (Group B) prior to intrathecal injection was examined. The study found that the ED_{50} of intravenous phenylephrine calculated by probit analysis was 0.33 mcg/kg/min (95% CI [0.20, 0.38]) and 0.36 mcg/kg/min (95% CI [0.32, 0.38]) in Group A

and B, respectively (Qian et al., 2020). The thought process here was that earlier administration

of ondansetron might allow peak pharmacodynamic effects to occur (Qian et al., 2020).

However, this study found earlier administration of prophylactic ondansetron caused no benefit

to lowering phenylephrine (Qian et al., 2020).

A double-blinded randomly controlled study with 63 participants was conducted by Shah

et al. (2019), allocating two groups to receive either 4 mg of ondansetron (Group O) or 10 mg of

metoclopramide (Group M). This study found comparable consumption of norepinephrine as a

vasopressor between group O and group M, 18.857 mcg (SD = 15.4865) versus 13.174 mcg (SD

= 12.685, $p = 0.1933$, respectively (Shah et al., 2019). Heart rate, systolic and diastolic blood

pressure were also comparable at all time intervals between both groups (Shah et al., 2019). This

study did have limitations, as noted by the authors, a different definition of hypotension, as well

as, ondansetron alone was not tested, thus confounding variables could occur (Shah et al., 2019).

Obesity and Spinal Anesthesia

Wang et al. (2018) conducted a double-blind study with 405 participants separated into

three groups depending on BMI: Group S <25, Group M <25, 30 and Group L >30. A minimum

of 15 patients were included in each subgroup, who were further assigned to receive 7 – 15 mg

of spinal ropivacaine (Wang et al., 2018). Group L had a significant higher incidence of

hypotension than either Groups S and M, specifically with the highest dose of ropivacaine, 15

mg, Group S 47%, Group M 53%, and Group L 93%, ($p = 0.015$), but not with other doses

(Wang et al., 2018).

Overall, Group L with BMI >30 had greater changes in MAP after spinal anesthesia

compared to the two other groups (Wang et al., 2018). Group L also required more doses of

ephedrine than the other 2 groups with 15 mg of ropivacaine only. Wang et al. (2018) also found

a decrease mean time to T6 sensory block onset to pinprick found in group L, 8.20 min (95% CI [7.75, 8.65] , p = 0.220), compared with group M, 8.73 min (95% CI [8.26, 9.19]) and group S, 8.65 min (95% CI [8.20, 9.10]) (Wang et al., 2018). Larger doses of ropivacaine were associated with earlier T6 block to pinprick, R = 0.696, p < 0.001 (Wang et al., 2018).

Major limitations to Wang et al. (2018) were the fact that there were small differences in BMIs among the 3 groups. Group S 23.4, Group M 27.1, and Group L 31.4, with only one woman >35 BMI. BMI >35 (Wang et al., 2018). The authors note, BMI >35 is uncommon in China, as opposed to the United States where this is more common (Wang et al., 2018).

Hudson et al. (2016) conducted a retrospective cohort study with 46 participants with the focus on examining the efficacy of prophylactic ondansetron in the high-risk obese parturient population. The authors found the incidence of vasopressor administration among patient receiving prophylactic ondansetron was 35.7%, whereas 46.9% in patients who did not receive prophylactic ondansetron required vasopressor administration (Hudson et al., 2016). Strikingly, 24 patients were excluded from their chart review due to the patients having a BMI <30. Of those 7, out of 24, who received prophylactic ondansetron none required vasopressors and 47% of non-obese who did not receive ondansetron prophylactically required vasopressors (Hudson et al., 2016).

Vasopressor Utilization During C section

Kinsella et al. (2015) evaluated the management of hypotension with vasopressors during cesarean section under spinal anesthesia. Whilst ephedrine had been found to best vasopressor to preserve uterine blood flow, in sheep models, higher doses were proven to cause neonatal acidosis (Lee et al. 2002). Ephedrine crosses the placenta and possibly causes acidosis as a result of a direct fetal effect (Kinsella et al., 2015). The hypothesis is that ephedrine causes an increase

in fetal metabolic rate, seen through the umbilical arterial – venous PCO_2 difference being

greater than with phenylephrine (Kinsella et al., 2017).

Cardenas-Garcia et al. (2015) conducted an observational, single-arm, consecutive patient

study over a 20-month period monitoring the peripheral intravenous utilization of vasoactive

medications in intensive care patients. Their study concluded that norepinephrine, dopamine and

phenylephrine were approved for usage (Cardenas-Garcia et al., 2015). The authors were not

able to comment on the effectiveness, indication or influence on patient outcomes, however, safe

usage and feasibility was the major objective (Cardenas-Garcia et al., 2015).

Measuring Hemodynamic Stability in Parturients

Maternal hypotension is a common complication during cesarean section, performed by

spinal anesthesia, Sakata et al. (2017) presented the utilization of postural heart rate change with

noting heart rate variability to predict hypotension. This contrasts with nausea and vomiting

having been a previous subjective predictor before objective hypotension will develop

(Nagelhout, 2018).

Variability in heart rate reflects autonomic control and consists of high frequency (HF)

(0.20-0.40 Hz) and low frequency (LF) components (0.04 – 0.15 Hz) (Sakata et al., 2017).

Where HF represents the parasympathetic nervous system, LF represents both the

parasympathetic and the sympathetic nervous system (Sakata et al., 2017). A ratio of the power

of low and high frequency components contributing to heart variability (LF/HF) represents

activity of the sympathetic nerve system (Sakata et al., 2017).

Hypotension occurred in 35 of the 45 patients, 21 of the 35 belonged to the postural

change test (PCT)-positive group and 14 of the 35 belonged to the PCT-negative group (Sakata

et al., 2017). Hypotension incidence was higher in the PCT-positive group, who received a total

of 15 mg (SD = 11) of ephedrine, compared to 7 mg (SD = 7 mg) in the PCT negative group. In

the PCT-positive group 6 received phenylephrine as opposed to 1 in the PCT-negative group

(Sakata et al., 2017).

Sensitivity and specificity of the PCT to predict maternal hypotension during cesarean

section under spinal anesthesia was M = 60% (95% CI [52.4, 62.3]) and M = 90% (95% CI

[63.5 to 98.2]) in the PCT-positive and PCT-negative group, respectively (Sakata et al., 2017).

Sakata et al. (2017) suggested that for patients who exhibited an increase in LF/HF by greater or

equal to 2.04 times when moving to the supine position from lateral position, the risk of

hypotension during cesarean section under spinal anesthesia was increased. A high LF/HF ratio

before spinal anesthesia was determined to be an indicator of severe maternal hypotension when

spinal anesthesia was utilized for cesarean section (Sakata et al., 2017).

Prashanth et al. (2017) conducted a single blinded prospective observational study of 108

patients with usage of an ANSiscope^{TM}, which measured the level of sympatho-vagal balance

through computed value of RR interval variability. ANSindex varied from 9 to 65%, where a

higher ANSindex value was significantly associated with post spinal hypotension, p = 0.017

(Prashanth et al., 2017). A value above 24% indicated the critical level above which hypotension

appeared commonly (Prashanth et al., 2017). The ANSindex value might facilitate the

anticipation for hypotension that may ensue.

Discussion

Ondansetron has proven effective to attenuate the Bezold-Jarish Reflex, thus decreasing

hypotension and need for pharmacological vasopressor support. Tubog et al. (2017), Oofuvong

et al. (2018) and Sahoo et al. (2012) examined the usage and dosing of ondansetron as an

effective mediator to prevent SIH. Dosing of 0.1 mg/kg in Oofuvong et al. (2018) or 4 mg in

Sahoo et al. (2012) proved to be the most effective dosing options to decrease hypotension

incidence. Ortiz-Gomez et al. (2014) found no difference from their placebo group to varied

dosing of ondansetron, 2, 4 and 8 mg, and hypotension. They also found no difference in

vasopressor requirements or systolic hypotension. This study found no difference in the number

of patients with hypotension in the placebo (43.8%) and ondansetron 2mg (53.1%), 4mg (56.3%)

and 8mg (53.1%) (Ortiz-Gomez et al., 2014)

Consideration of the amount of local anesthetic, taking into account BMI, was

emphasized in Wang et al. (2018). It took into account the speed at which a T6 level of sensory

blockade was achieved and the prevalence of hypotension. A BMI of >30, along with the

increasing dosage from 7 – 15 mg of ropivacaine, in 1 mg increments, saw a rise in the

occurrence of hypotension (Wang et al. 2018). Utilization of phenylephrine in Qian, et al. (2020)

was comparatively similar in the timing of administration at 5 and 15 min prior to intrathecal

injection. Showing that allowing more time of onset to allow the pharmacodynamics of

ondansetron to initiate are not required (Qian, et al. 2020).

Ephedrine crosses the placenta and possibly causes acidosis as a result of a direct fetal

effect (Kinsella et al, 2015). The hypothesis is that ephedrine causes an increase in fetal

metabolic rate, seen through the umbilical arterial – venous PCO2 difference was greater than

with phenylephrine (Kinsella et al., 2015). This led to a 734 patient, 20 month observational

study to determine that norepinephrine, dopamine and phenylephrine were safe and efficacious

for usage (Cardenas-Garcia et al., 2015).

Sakata et al. (2017) and Prashanth et al. (2017) presented information that can be gained

from the patient prior to spinal anesthesia which can help predict the risk of maternal

hypotension. As opposed to being reactive, analyzing threats proactive with non-invasive data facilitates more optimal maternal and placental perfusion.

Literature Gaps & Limiting Factors

Whilst comparing the above studies, limitations were noted. First and foremost, small sample sizes within study groups were major limitations. The lack of ability to define hypotension in the parturient and evaluate hemodynamic instability, while subjective signs like nausea and vomiting can be some of the earliest signs before objective changes in blood pressure are presented.

Furthermore, although this literature review found research conducted on weight-based dosing of ondansetron, no high-quality research studies, in the form or randomized controlled or meta-analysis and experimental studies, have been conducted specifically taking BMI into account. There were also not many studies in this high-quality form regarding dosing of local anesthetics and BMI.

Two studies evaluated within the literature review, one by Ortiz-Gomez et al. (2014) and another by Oofuvong et al. (2018), excluded obese patients from participating in their study, without justification.

<center>**Recommendations**</center>

The literature supports the utilization of prophylactic ondansetron to attenuate hypotension following intrathecal administration. However, lack of equivocal spinal dosing and weight-based dosing specific to obese parturients is present. There perpetual increase in frequency of obesity over the past 30 years, despite focus from Healthy People, stresses the importance of further research to be conducted (Hudson, 2016). Nearly one-fourth of the population in the United States falls into the obese category (Hudson, 2016).

Hood et al. (2015) emphasizes obese parturients undergo cesarean sections at a higher rate than their non-obese counterparts. Dennis et al. (2017) stresses the significant impact maternal obesity plays on the increase in theatre time, surgical and anesthesia time, increase in hospital admissions and theatre costs. To make the medical system more economically feasible to a growing population, research catered to this population is vital.

Equipment and data, as seen through Sakata et al. (2017) and Prashanth et al. (2017), can help predict higher risk patients prior to anesthesia being initialized. Predicting the reactivity of a patients parasympathetic and sympathetic nervous system could facilitate closer adherence to prophylactic treatment prior to anesthesia.

Conclusion

Where spinal anesthesia is the anesthetic of choice, for non-obese and obese parturients alike, there are research gaps and limitations to definitively approach clinical based changes for spinal local anesthetic dosing and prophylactic ondansetron dosing.

More research within the population of obese parturients is needed. Particularly within dosing of prophylactic 5-HT3 antagonists, intrathecal local anesthetics dosing, and objective non-invasive data collecting to facilitate spinal anesthetic hypotension from occurring. Hemodynamic instability can further compound the pathophysiological effects which obesity exerts on a parturients already compromised physiology.

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