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A Comparative Study between Clinical Efficacy of Rapid and Slow Bolus Dose of Ephedrine During Elective Cesarean Section under Spinal Anesthesia

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ABSTRACT

Background: A common physiological complication associated with spinal anesthesia during cesarean section is hypotension, which causes both maternal and fetal adverse effects. Therefore, Ephedrine isone of the most commonly used medications among the vasopressors in obstetric anesthesia for many yearsdue toits favorable pharmacodynamics profile and maintainuteroplacental blood flow.

Aim of the study: To evaluate and compare the clinical efficacy of slow and rapid bolus dose of ephedrine on hemodynamic status.

Patient and method: Sixty full-term pregnant women were scheduled for elective cesarean section under spinal anesthesia were randomly allocated into two groups, both of themreceived 5 mg of ephedrine to treat hypotension,

Result: Heart rate was significantly higher in Group R than the Group Sat 6, 12, 18, and 24 minfrom spinal induction. MAP at 6 and 30 minfrom spinal induction was significantly higher among the low group than that in the rapid group (75.9 versus 68.7 mmHg, P= 0.015; and 89.3 versus 84.2, P= 0.011). Nostatic difference between 2 groups regarding the incidence ofintra and postoperative nausea and vomiting and intra or postoperative shivering.

Conclusion: Slow bolus of ephedrine is as effective as rapid bolus in treatment of hypotension associated with spinal anesthesia in maintaining blood pressure and heart rate, where the heart rate was more stable in slow bolus than rapid one that needed more boluses of ephedrine for treatment of hypotension.

Keywords: Cesarean section, spinal anesthesia, hypotension, ephedrine

INTRODUCTION

This template,Spinal anesthesia also called a spinal block, subarachnoid block, intradural block, and intrathecal block, is a form of neuraxial regional anesthesia involving the injection of a local anesthetic into the cerebral spinal fluid in the subarachnoid space, generally through a fine needle, was first used in 1900 [1].

Advantage of regional anesthesia include

1. Simplicity, rapid onset, dense motor block.
2. Avoidance of potential airway complication associated with general anesthesia (as the inability to intubate, inability toventilate, aspiration pneumonitis).
3. Less neonatal exposure to potentially depressant drugs.
4. An awake mother at the birth of her child.
5. The option of using spinal opioids for post-operative pain relief.
6. Decrease morbidity and mortality[2,3]

In spinal anesthesia, the needle is placed past the dura mater in subarachnoid space and between lumbar vertebrae (in the lower back), where it acts on spinal nerve roots and part of the spinal cord. The resulting anesthesia usually extend from the legs to the abdomen or the chest. Spinal anesthesia is often selected for elective or emergency cesarean section [4[. In order to reach this space, the needle must pierce through several layers of tissue and ligaments which include the

supraspinatus ligament, interspinous ligament, and ligamentum flavum. Because the spinal cord (conus medullaris) is typically at the L1 or L2 level of the spine, the needle should be inserted below this between L3 and L4 space or L4 and L5 space in order to avoid injury to the spinal cord,(figure 1) [5].

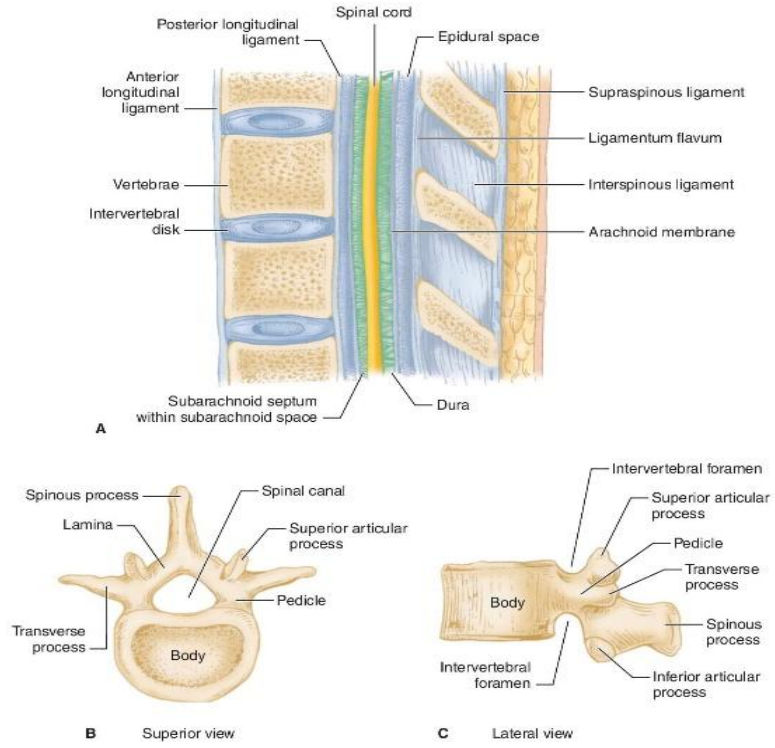

***Fig. 1*: A sagittal section through lumber vertebrae, B, C common features of vertebrae.**

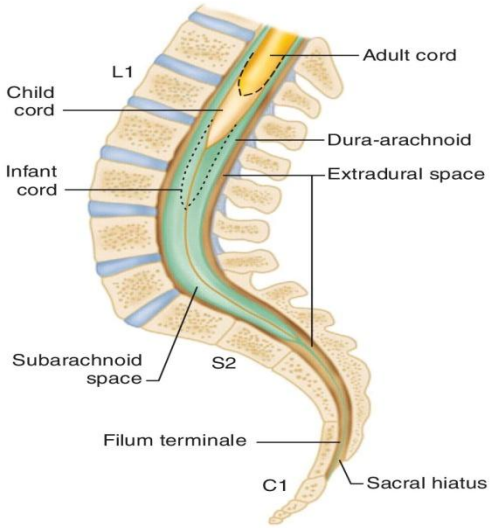

***Fig.* 2: Sagital view through the lumber vertebrae and sacrum**

Technical Considerations and Positioning :

The hormonal changes of pregnancy affect the per vertebral ligament us structures, including the ligamentum flavum. The ligamentum flavum may feel less dense and "softer" in pregnant women than in non-pregnant Patients; thus, sensing the passage of the spinal needle through the ligamentum flavum may be more difficult [6].

It may also be more difficult for a pregnant woman to achieve flexion of the lumbar spine due to Increased lumbar lordosis during pregnancy may reduce the vertebral interspinous gap, thus creating technical difficulty in administering neuraxial anesthesia. Widening of the pelvis results in a head-down tilt when a pregnant woman is in the lateral position. This may increase the rostral spread of hyperbaric local anesthetics when injected intrathecally with patients in the lateral position. (Figure 3).

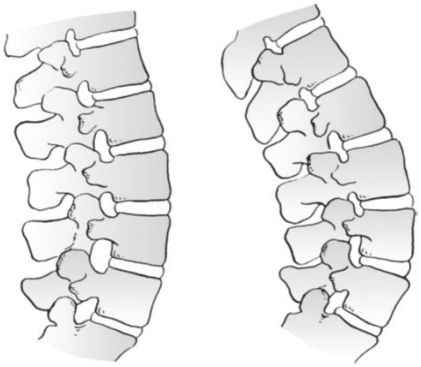

***Fig. 3*: Effects of pregnancy on the lumbar spine. Lt, non-pregnant RT, pregnant. There isa marked increase in lumbar lordosis & narrowing of the interspinous spaces during pregnancy**

Sitting position makes insertion easier in obese women because it helps visualization of the midline and increases the rate of efflux of cerebrospinal fluid (CSF) from a small gauge spinal needle & improves ventilation, in the lateral patient position, the onset of sensory block to (T 10) is more rapid and there may be a slightly lower incidence of hypotension [7].

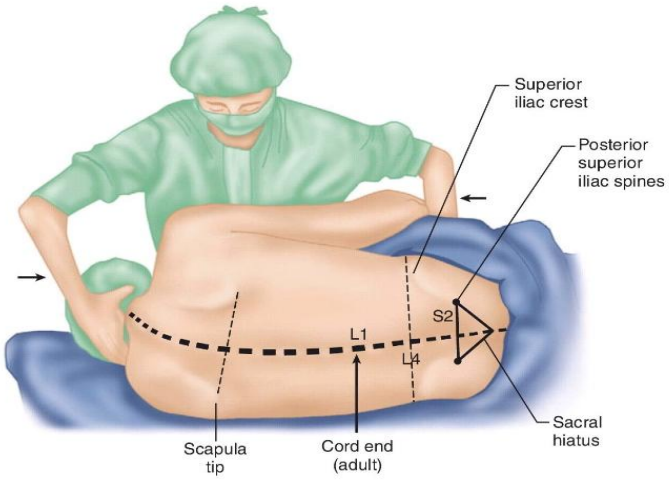

***Fig. 4*: Lateral decubitus position for neuraxial blockade**

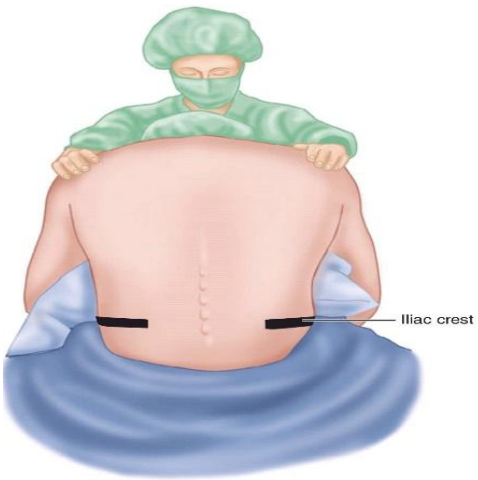

***Fig. 5*: Sitting position of neuraxial blockade**

Physiological changes during pregnancy:

Cardiac output and blood volume increase to meet accelerated maternal and fetal metabolic demands. An increase in plasma volume over an increase in red cell mass produces dilutional anemia and reduces blood viscosity. [8] At term, blood volume has increased by 1000–1500 mL in most women, allowing them to easily tolerate the blood loss associated with delivery; total blood volume reaches 90 mL/kg. Average blood loss during vaginal delivery is 400–500 mL, compared with 800–1000 mL for a cesarean section. Blood volume does not return to normal until 1–2 weeks after delivery.

The increase in cardiac output is due to increases in both heart rate and stroke volume. Decreases in cardiac output can occur in the supine position after week 20 of pregnancy. Such decreases are secondary to impeded venous return to the heart as the enlarging uterus compresses the inferior vena cava. Approximately 5% of women at term develop supine hypotension syndrome (aortocaval compression) [5].

A decrease in systemic vascular resistance by the second trimester decreases both diastolic and, to a lesser degree, systolic blood pressure. The response to adrenergic agents and vasoconstrictors is blunted.

Table 1: cardiovascular adaptation at term gestation

Figure 2. Parameter	**Figure 1.** Change
Figure 4. Cardiac output	**Figure 3.** ↑ 20 % – 50 %
Figure 6. Stroke volume	**Figure 5.** ↑ 30 %
Figure 8. Heart rate	**Figure 7.** ↑ 20 %
Figure 10. Systemic vascular resistance	**Figure 9.** ↓ 30 %
Figure 12. Mean arterial pressure	**Figure 11.** ↓ 20 %
Figure 14. Plasma volume	**Figure 13.** ↑ 10 – 50 %
Figure 16. Oxygen consumption	**Figure 15.** ↑ 50 %

Aortocaval compression (Supine hypotension syndrome):
Asymptomatic reduction in cardiac output in the supine position occurs in up to 15 % of parturients and is referred to as the supine hypotensive syndrome. Although supine hypotension is classically described beyond 20 weeks gestation, partial or complete compression can occur before this time.Manifestations of the supine hypotensive syndrome include:

- Dizziness
- Nausea
- Maternal hypotension
- Shortness of breath
- Tachycardia
- Fetal distress

Compression of the inferior vena cava by the enlarged uterus reduces venous return and can result in profound hypotension.[7].Vena caval compression reduces venous return and cardiac output with a compensatory increase in SVR; this may be symptomless (‘concealed’), or associated with hypotension, bradycardia, or syncope (‘revealed’). Reduced placental blood flow may result from the reduced cardiac output, vasoconstriction, and compression of the aorta, Neuraxial or general anesthesia will exaggerate these hemodynamic effects.[1].

Treatment consists of:
- Ensuring left uterine displacement
- Elevation of the legs (not Trendelenburg positioning)
- Fluid administration
- Vasopressor administration [7].

Hypotension:

Hypotension is abnormally low blood pressure, especially in the arteries of the systemic circulation that is low enough that the flow of blood to the organs of the body is inadequate and symptoms and/or signs of low blood flow develop. Blood pressure is the force of blood pushing against the walls of the arteries as the heart pumps out blood. Hypotension is generally considered to be systolic blood pressure less than 100 millimeters of mercury (mm Hg) or diastolic less than 60 mm Hg or 20% drop below the base-line [9,10], Blood pressure is continuously regulated by the autonomic nervous system, using an elaborate network of receptors, nerves, and hormones to balance the effects of the sympathetic nervous system, which tends to raise blood pressure.

The vast and rapid compensation abilities of the autonomic nervous system allow normal individuals to maintain an acceptable blood pressure over a wide range of activities and in many disease states[11]. However, in practice blood pressure is considered too low only if noticeable symptoms are present. For some people who exercise and are in top physical condition, low blood pressure is a sign of good health and fitness [4].For many people, excessively low blood pressure can cause dizziness and fainting or indicate serious heart, endocrine, or neurological disorders.

Severely low blood pressure can deprive the brain and other vital organs of oxygen and nutrients, leading to a life-threatening condition called shock. The symptoms of low blood pressure include lightheadedness, dizziness, and fainting [12].

These symptoms are most prominent when individuals go from the ding or sitting position to the standing position (orthostatic hypotension).It is usually transient and represents a delay in the normal compensatory ability of the autonomic nervous system [13].

Pregnancy increases dependence on the sympathetic nervous system for the maintenance of venous return and systemic vascular resistance[14].

This together with the effects of aortocaval compression, a dose of local anesthetic, patient positioning, fluid preloading and co-loading, and the use of prophylactic or therapeutic vasopressors [4]. means that pregnant patients are particularly prone to hypotension and hemodynamic instability from sympathetic block induced by neuraxial anesthesia (6).it is estimated that around 80% of patients who undergo LSCS under spinal anesthesia will develop hypotension during the procedure[12].

Patients with higher baseline sympathetic activation have been shown to have more marked hypotension after spinal anesthesia.

The degree of hypotension was greater at higher levels of spinal anesthesia. More than 50% of the patients with T5 or higher levels of anesthesia had a significant decrease in blood pressure. Excessive vasodilatation, or insufficient constriction of the resistance blood vessels (mostly arterioles), causes hypotension.

This can be due to decreased sympathetic nervous system output or to increased parasympathetic activity occurring as a consequence of injury to the brain or spinal cord or of dysautonomia. An intrinsic abnormality in the autonomic system functioning [4]. Many strategies have been described to prevent and treat hypotension in obstetric patients. No pharmacological techniques include the use of lateral uterine displacement, intravenous rehydration (preload), and lower limb wrapping. Unfortunately, these are not very effective and it is usually necessary to use a vasopressor [4].

Spinal anesthesia in obstetrics differs from spinal anesthesia in non-pregnant patients in several ways. Smaller doses of local anesthetic are needed for spinal anesthesia in pregnancy, and the spread in cerebrospinal fluid (CSF) is less predictable[16]. Pregnant women exhibit a more rapid onset and a longer duration of spinal anesthesia than non-pregnant women who receive the same dose of local anesthetic. These results are consistent with enhanced neural sensitivity to local anesthetics; pregnancy-associated elevation in CSF pH may contribute to these effects [6]. The dose of hyperbaric local anesthetic required in term pregnant women is 25% lower than that in non-pregnant women[17,18].

This is attributed to the following factors:

- Reduction of spinal CSF volume

Uterine enlargement and vena caval compression result in engorgement of the epidural veins. The enlarged epidural veins also may displace CSF from the thoracolumbar region of the subarachnoid space, as does the greater intra-abdominal pressure of pregnancy [16].

- Enhanced neural sensitivity to local anesthetics
- Increased rostral spread when injections are made with the patient in the lateral position
- Inward displacement of intervertebral foramina soft tissue, resulting from increased abdominal pressure (19).
- A higher level of the apex of the thoracic kyphosis (the lowest point of the thoracic spinal canal in the supine position) during late pregnancy[20].
- The lower specific gravity of CSF[21].

Bupivacaine:

Bupivacaine is a local anesthetic drug belonging to the amino amide group. It is commonly marketed under various trade names, including Marcain, Marcaine I Carestream Dental), Sensorcaine (Astra Zeneca), and Vivacaine (Septodont).With a half-life of 3.5hr in adult and 8.1hr in pediatrics' Chemical formula CI8H28N20 and molecular weight of 288.43 g/mol. Bupivacaine was the first long-acting amide local anesthetic. The chemical structure makes bupivacaine significantly more hydrophobic than mepivacaine and lidocaine, slower in onset but of longer duration. Bupivacaine is highly protein-bound, which is consistent with long duration and potential for cardiotoxicity. Bupivacaine is popular for use in a wide array of applications, including infiltration (0.25%), %), peripheral nerve blocks (0.25%-0.5%), spinal (0.5% and 0.75%) and epidural (0.0626%) anesthesia. Because of systemic toxicity, it is not used for IV regional anesthesia[22].

Bupivacaine has a lower therapeutic index, concerning cardiovascular toxicity compared to lidocaine. Bupivacaine is more slowly absorbed into plasma than lidocaine and produces plasma peak concentrations that are approximately 40% lowerClinically used concentrations of bupivacaine vary from 0.05% (epidural continuous infusions for labor analgesia and acute pain management) to0.5% ~(spinal anesthesia and peripheral nerve blocks). The 0.75% concentration is specificallycontraindicated for obstetric epidural anesthesia due to concerns about cardiac toxicity[22].

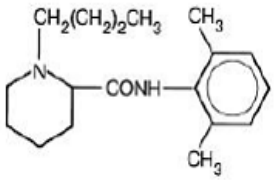

***Fig.* 6 : Chemical structure of BUPIVACAINE**

Ephedrine:
Ephedrine, a sympathomimetic amine, acts on part of the sympathetic nervous system (SNS). The principal mechanism of action relies on its indirect stimulation of the adrenergic receptor system by increasing the activity of noradrenaline at the postsynaptic α- and β-receptors. The presence of direct interactions with α-receptors is unlikely, but still controversial [23, 24].

Intravenous administration causes rapid increases in heart rate, cardiac output, and blood pressure that last 10–15 minutes;repeat doses have a decreasing effect on tachyphylaxis), Intramuscular injection has a slower rate of onset (5–10 minutes)but a longer duration of effect (35–45 minutes). Ephedrine has a half-life of 3–6 hours and is eliminated largely unchanged in the urine[25].

Ephedrine has a stimulatory effect on the CNS, relaxes bronchial smooth muscle, and increases trigon and sphincter muscle tone in the urinary bladder. Uterine and placental artery blood flow is not adversely affected when ephedrine is used to sustain blood pressure during spinal anesthesia for C/S[26]. Besides, umbilical artery vascular resistance remains unchanged [27, 28].Although ephedrine is effective in maintaining or restoring blood pressure during spinal anesthesia when administered intravenously[29].preemptive intramuscular administration of the drug is not a reliable preventive measure [30].

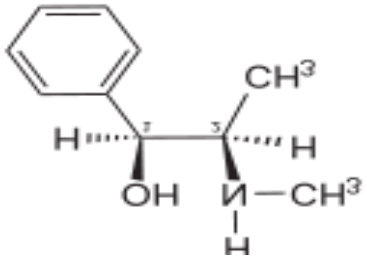

***Fig. 7*:Chemical structure of EPHEDRINE**

PATIENT AND METHODS

This study is a rospective, randomized, double-blind clinical trial. The study was conducted in the elective operation theatres in Madenat Al-Imamen Al-Khadumain (Al Khadumia previously) and Baghdad medical city in Baghdad, Iraq, from June to December 2018. Ethical approval of the study was obtained from the scientific Council, written informed consent from each participant in the study, and permission from the hospital was obtained.

A total of 60 patients that were scheduled for elective cesarean section by spinal anesthesia.
Patients were randomly allocated to 2 groups (each of which consisted of 30 patients) prepared by an anesthesiologist in charge not part of the study, Both groups received 5 mg of ephedrine to treat hypotension

1. Group (R) Rapid (n=30)received it as a rapid intravenous bolus (5mg)
2. Group (S) Slow (n=30)received it slowly over 20 s (20 ml syringe contained saline, and 5 mg ephedrine (5mg/20ml)

The inclusion criteria for patients included:
1- Elective C/S.
2- ASA of Class II.
3- Patient age from 18 to 40 years old.
4- Height between (150-175) cm
5- Weight between (65-95) kg.

The exclusion criteria for the patients included:
1. Patient refusal.
2. Pregnant with twin baby.
3. Fetal abnormality.

4. History of allergy to drugs used.
5. Patient with cardiac disease.
6. Patient with placenta preivea or accrete.
7. Contraindications to spinal anesthesia (bleeding tendencies, valvular heart disease, lower backache, sepsis).

Data were collected using pre-constructed form sheet including name, age, height, weight & body mass index (BMI). A detailed history was obtained, a general examination was done and investigations were evaluated, BBaselineblood pressure and the pulse rate were recorded initially before the intervention., pulse rate and spo2 were continuously monitored throughout the operation by electrocardiogram and oxymetry, blood pressure readings wweretaken every 3 min untilthe end of the operation, using an automated noninvasive blood pressure monitoring apparatus for measurement of blood pressure.

All patients were premeditated with 10mg IV metoclopramide, 50mg IV ranitidine.

All patients in both groups were prepared with 2 wide bore cannula 18G & preloaded with a ringer's lactate 1000-1500 ml, spinal anesthesia was conducting in a sitting position. Under full aseptic technique and after a skin infiltration with 2% plain lidocaine, a 25G needle (sprotte) was inserted into the L3-L4 orL4-L5 intervertebral space with the patient in sitting position.

After confirming free flow of cerebrospinal fluid (CSF), 0.5% hyperbaric bupivacaine (2 -2.5 ml), (10-12mg) was injected intrathecally. Once the procedure was over.

Allpatients were placed in the supine position with a left pelvic tilt to avoid aortocaval compression, Oxygen 4-5 L/min was given using a facemask.
The onset of spinal anesthesia was confirmed by asking the patient about the numbness of the legs & the surgery was started when the sensory level of the block reached T5 determined by the loss of cold stimulus sensation.

For the study purposes data collected {Maternal blood pressure (BP), peripheral oxygen saturation(SPO2)& Pulse rate } were recorded in(3,6,12,18,24,30 & 45 min).

Vasopressor (ephedrine) 1st dose was used to treat maternal hypotension when developed after giving spinal anesthesia (if MAP less than 20% from baseline or systolic BP less than 100mmHg), both groups continued to received their maintaince fluids 10L/kg/hr during operation.

In Group R (Rapid): ephedrine was given as a rapid intravenous bolus1ml=5mggiven followed by 19ml N/S, while in Group S (Slow): it was given slowly over 20 s (20 ml syringe contained N/S, and 5 mg ephedrine) (5mg/20ml) all 20 ml given. (Both groups received equal volume)

If needed another 2nd or 3rd bolus dose of ephedrine was given (there's no improvement in MAP or systolic BP),if after 3rd bolus dose of ephedrine, BP targets were not met, the hypotension was treated by the anesthiologiest in charge & his advice for any extra action, these cases were considered a drop of from the study & it was only 1 case.

Total number of ephedrine boluses used, total amount of IV fluids infused, associated nausea, vomiting & shivering (intra or post op) if present, were all observed & recorded.

After delivery of the baby, patients were also received (2mg midazolam & 20mg ketamine) as sedative drug & 50mg tramadol for shivering.

Only 5 patients did not develop hypotension following spinal anesthesia were dropped off from the study.

Statistical analysis
The data analyzed using Statistical Package for Social Sciences (SPSS) version 25. The data presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages. Independent t-test (two tailed) was used to compare the continuous variables among study groups accordingly. Z-test was used to compare the categorical variables among study groups accordingly. A level of P – value less than 0.05 was considered significant.

RESULTS

The total number of study patients in this study was 60, All of them were undergone C/S under spinal anesthesia. They were divided into two groups, Group (Rapid) included 30 patients received rapid bolus doses of ephedrine and Group (Slow) included the other 30 patients who received slow bolus doses of ephedrine for management of spinal-induced hypotension.

General Characteristics

The distribution of study patients by general characteristics is shown in figure (8) and table (2). The study patient's age was ranging from 18 to 40 years with a mean of 26.35 years and a standard deviation (SD) of ± 5.4 years. The highest proportion of study patients was aged < 30 years (65%).

According to BMI level, the highest proportion of study patients was obese (55%).

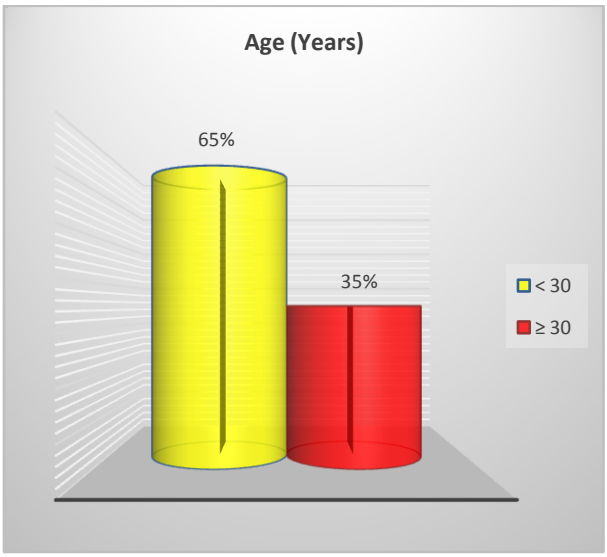

***Fig*.8: Distribution of study patients by age**

Table 2: Distribution of study patients by BMI level

BMILevel	No. (n= 60)	Percentage (%)
Normal	3	5.0
Overweight	24	40.0
Obese	33	55.0

In comparison between study group by age and BMI, we noticed that there were no significant differences (P ≥ 0.05) in age and BMI between study groups as shown in table (3).

Table 3: Comparison between study groups by age and BMI

Variable	Study Group		P - Value
	Rapid Mean ± SD	Slow Mean ± SD	
Age (Years)	26.9 ± 5.6	25.8 ± 5.3	**0.435**
BMI (kg/m^2)	30.0 ± 2.9	35.1 ± 14.21	**0.063**

Clinical parameters

Mean Arterial Pressure (MAP)

The comparison between study groups by mean of MAP is shown in figure (9) and table (4). In this study, mean of MAP at 6 and 30 min from spinal induction was significantly higher among slow group than that in rapid group (75.9 versus 68.7 mmHg, P= 0.015; and 89.3 versus 84.2, P= 0.011).

There were no significant differences (P ≥ 0.05) between study groups in means of MAP in all other times.

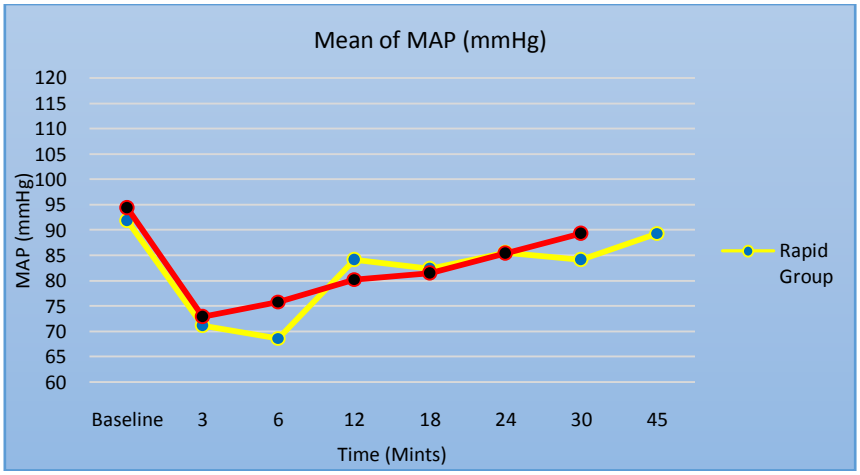

***Fig. 9*: Mean of MAP in study groups**

Table 4: Comparison between study groups by mean of MAP

Time	MAP (mmHg)		P - Value
	Rapid Group Mean ± SD	Slow Group Mean ± SD	
Baseline	91.9 ± 10.5	94.4 ± 9.3	**0.327**
After 3 Mints	71.2 ± 9.6	72.9 ± 12.6	**0.552**
After 6 Mints	68.7 ± 6.4	75.9 ± 14.0	**0.015**
After 12 Mints	84.2 ± 8.7	80.3 ± 8.1	**0.081**
After 18 Mints	82.4 ± 12.6	81.5 ± 4.9	**0.717**
After 24 Mints	85.5 ± 10.0	85.4 ± 8.5	**0.967**
After 30 Mints	84.2 ± 4.6	89.3 ± 9.6	**0.011**
After 45 Mints	89.4 ± 4.7	91.2 ± 6.4	**0.203**

Heart Rate

The comparison between study groups by mean of heart rate is shown in figure (10) and table (5). Mean of heart rate at 6, 12, 18, and 24 min from spinal induction was significantly higher among rapid group than that in slow group (110.8 versus 102.7 bpm, P= 0.033; 116.4 versus 103.1 bpm, P= 0.011; 112.7 versus 101.6 bpm, P= 0.001; and 107.6 versus 101.8 bpm, P= 0.004 respectively).

Table 5: Comparison between study groups by mean heart rate

Time	Heart Rate (Beats/mint)		P - Value
	Rapid GroupMean ± SD	Slow GroupMean ± SD	
Baseline	109.7 ± 11.0	113.1 ± 10.6	**0.227**
After 3 Mints	101.5 ± 17.9	97.6 ± 18.6	**0.411**
After 6 Mints	110.8 ± 18.0	102.7 ± 9.0	**0.033**
After 12 Mints	116.4 ± 21.9	103.1 ± 16.6	**0.011**
After 18 Mints	112.7 ± 6.4	101.6 ± 14.4	**0.001**
After 24 Mints	107.6 ± 8.7	101.8 ± 5.6	**0.004**
After 30 Mints	105.0 ± 7.0	101.8 ± 7.6	**0.09**
After 45 Mints	99.4 ± 5.7	97.6 ± 6.1	**0.242**

There were no significant differences (P ≥ 0.05) between study group in means of heart rate at baseline and at three, 30, and 45 min from spinal induction.

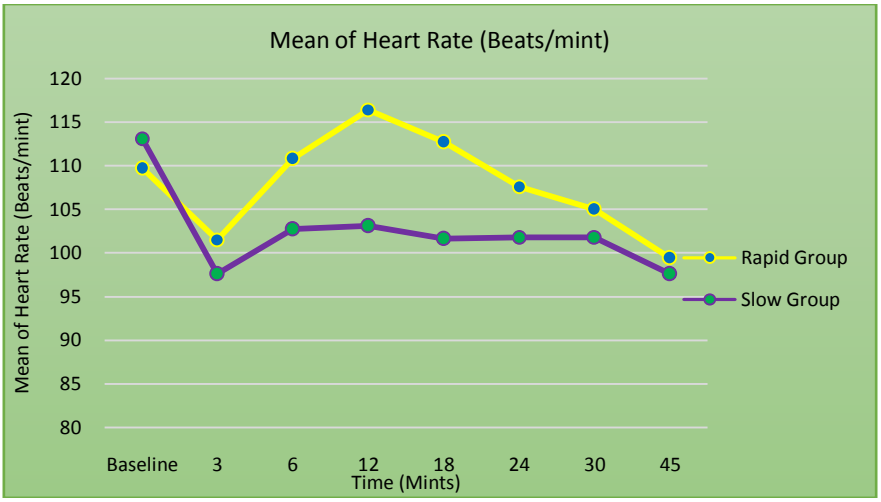

***Fig.10*: Mean of heart rate in study groups**

Ephedrine and amount of fluid:

Figure (10) and table 6 show the comparison between study groups by ephedrine and fluid dose needed during operation. In rapid group, 21 patients (70%) were needed one dose of ephedrine (5 mg) compared to 24 patients (80%) in slow group; while three patients (10%) in rapid group were needed two doses (10 mg) compared to six patients (20%) in slow group. No patients in slow group needed three doses (15 mg) compared to six patients (20%) in a rapid group.

No statistically significant difference ($P \geq 0.05$) between study groups in mean of ephedrine and amount of fluid (both groups received the same amount of fluid) needed during operation.

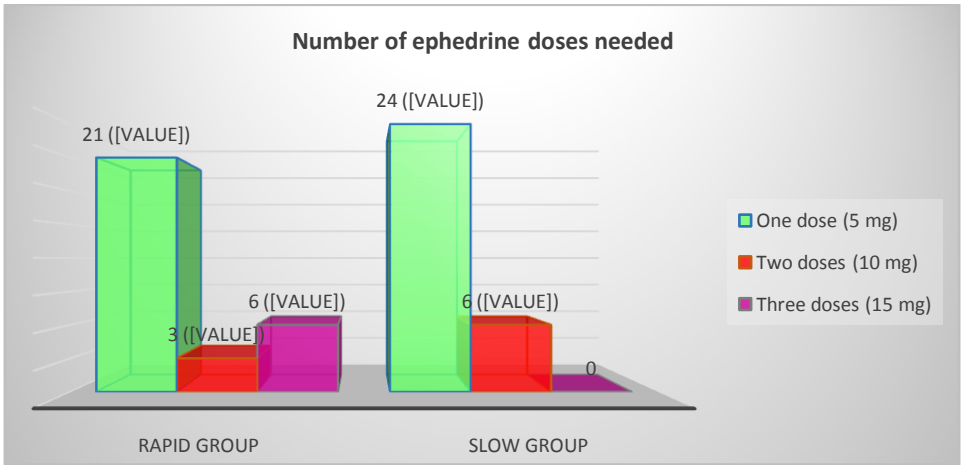

***Fig.*10: Number of ephedrine doses needed in study groups**

Table 6: Comparison between study groups by ephedrine and fluid dose needed during operation

Variable	Study Group		P – Value
	Rapid Mean ± SD	Slow Mean ± SD	
Ephedrine (mg)	7.5 ± 4.1	6.0 ± 2.0	**0.08**
Fluid (Pint)	5.8 ± 0.6	5.7 ± 0.5	**0.479**

Side effect associated with ephedrine

The comparison between study groups by side effect associated with ephedrine is shown in table (7). We noticed that there was no statistical significant difference (P= 0.417) between study groups by intra or postoperative nausea and vomiting (70% in rapid group and 60% in slow group).

Regarding intra or postoperative shivering, it was seen in equal frequency in both groups (60% of patients in each group developed either intra or postoperative shivering).

Table 7: Comparison between study groups by side effect associated with ephedrine

Side effect	Rapid Group (%) n= 30	Slow Group (%) n= 30	P - Value
Intra or postoperative nausea and vomiting			
Yes	21 (70.0)	18 (60.0)	**0.417**
No	9 (30.0)	12 (40.0)	
Intra or postoperative shivering			
Yes	18 (60.0)	18 (60.0)	1.0
No	12 (40.0)	12 (40.0)	

DISCUSSION

Hypotension inducing a neuraxial blockade during cesarean section is the foremost concern for an anesthesiologist. Severe and sustained hypotension can impair the uterine and intervillous blood flow and in due course result in fetal acidosis and neonatal depression [31]. Despite preventive measures, as fluid preload and left lateral tilt, a pharmacological agent is still needed for hypotension treatment [32]. A recent survey found that it was used as the sole vasopressor by 95% of consultant obstetric anesthetists in the United Kingdom [33]. Ephedrine is commonly used in the treatment of hypotension during spinal anesthesia. It causes pronounced stimulation of beta receptors and stimulation of alpha receptors, increasing systolic and diastolic arterial pressure and heart rate, while not leading to significant uterine vasoconstriction because it has minimal alpha-adrenergic activity in the uterine vasculature [34][35]but its overall efficacy is poor [36].

There is a limited works of literature compared the rate of infusion of ephedrine in anesthesia. In the current study, sixty patients undergone cesarean section under spinal anesthesia participated. They were divided into two groups, Group (Rapid) included 30 patients received rapid bolus doses of ephedrine and Group (Slow) included the other 30 patients who received slow bolus doses of ephedrine for management of spinal-induced hypotension.

In our study and at six and 30 mints from spinal induction, mean of MAP was significantly higher among slow group than that in rapid group (75.9 68.7 versus 68.7 mmHg, P= 0.015; and 89.3 versus 89.3, P= 0.011), while no significant differences ($P \geq 0.05$) between study groups in means.

Disagreement in the results observed in a study conducted by Gunasekaran and colleagues in 2017, as noticed that MAP was significantly higher in patients received rapid bolus doses of ephedrine (Group R) compared with patients received slow bolus (Group S) at the 5^{th} min (80.3 ± 11.5 vs. 74.7 ± 11.4 mmHg, $P = 0.04$) [37]. `

In regard to heart rate in this study and at six, 12, 18, and 24 mints from spinal induction, the mean of heart rate was significantly higher among rapid group than that in slow group (110.8 versus 102.7 beats/mint, P= 0.033; 116.4 versus 103.1 beats/mint, P= 0.011; 112.7 versus 101.6 beats/mint, P= 0.001; and 107.6 versus 101.8 beats/mint, P= 0.004 respectively), while no significant differences in means of heart rate at baseline and after three, 30, and 45 mints from spinal induction ($P \geq 0.05$).

Comparable results observed in Gunasekaran et al study in 2017, in which noticed that increase in heart rate after the first bolus was significantly more in patients received rapid bolus doses of ephedrine (Group R) when compared with patients received it slowly (Group S). Furthermore, increase in heart rate and MAP after the second bolus was comparable in the groups [37], this difference observed among the above mentioned studies may be due to many factors, as different doses of ephedrine used and different volume of infusion, the delay in onset and the relative short half-lives of the medications.

However, the decrease in HR in rapid group in our study could be probably that a second dose of ephedrine produces a less intense systemic blood pressure response than the first dose. This phenomenon, known as tachyphylaxis, occurs with many sympathomimetic. Tachyphylaxis to ephedrine appears to involve alpha receptor inhibition [38],, the repeated administration of a constant dose within a short time which leads to a rapid decline of response due to the gradual decrease in the amount of norepinephrine at the stores [38][39].

Ephedrine, an indirectly acting sympathomimetic amine, is probably the vasopressor of choice in obstetric anesthesia. Although ephedrine has mixed α and β adrenoreceptor activity, it maintains arterial pressure mainly by increases in cardiac output and heart rate as a result of its predominant activity on β1 adrenoreceptors and Ephedrine indirectly raises blood pressure by increasing the release of nor epinephrine[40].

Regardingno. ofdoses slow group used less doses than the rapid group, no patients in slow group needed three doses (15 mg) (0%) compared to six patients (20%) in rapid group, this probably could be duoto bitter distribution of the

drug. Low dose (infusion) of ephedrine caused relatively little arterial and venous constriction but increased systolic arterial pressure by increases in stroke index and heart rate [41].

The more profound vasoconstrictor effect seen accounted for by the higher doses of ephedrine used, vasoconstriction is dose related (42)

A study done by Lee at al in Dec 2015, showed no significant differences between ephedrine and phenylephrine in their efficacy for treating spinal-induced intra-operative hypotension during cesarean sections & Variable intravenous infusions of ephedrine appear to be successful [43].

Finally, in the current study, no statistical significant difference between study groups in mean of ephedrine and fluid dose needed during operation ($P \geq 0.05$).

Gunusen et al, tested the hypothesis that ephedrine infusion with crystalloid loading in spinal anesthesia could decrease hypotension compared with fluid preloading [44].

Regarding intra or postoperative nausea and vomiting in this study, a non-significant higher rate of intra or postoperative nausea and vomiting in rapid group than slow one respectively, (P= 0.417).

In comparison to other studies, disagreement observed in Gunasekaran et al study in 2017, as observed that post-operative nausea and vomiting were observed in significantly more patients received ephedrine rapidly (Group R) (35%) than those received it slowly (Group S) (0%, $P < 0.01$) [37].

Additionally, Lower results observed during determining post-operative nausea and vomiting after the use of ephedrine in spinal anesthesia in cesarean section, as observed in Cooper et al study in 2002, in which nausea and vomiting in the ephedrine group observed were (66%) [35], and in Kee et al study in 2009, in which the incidence of nausea and vomiting after ephedrine use was 35% of the patients [45].

A possible explanation to the discrepancies in the rate of post-operative nausea and vomiting and the role of ephedrine in its development might be an increase in vagal tone following reduction of preload, which is more likely to occur in the presence of beta stimulation [35].

The alternate mechanism could be a side effect of the drug or its lipid solubility, thereby exerting a central effect (46). Studies showed a high incidence of intra-operative nausea and vomiting during cesarean section under spinal anesthesia up to 80% [47].

Pregnant women are already likely to suffer from nausea and vomiting because of the pregnancy itself. This is applicable not only to the first three months of pregnancy but also to the 3rd and last trimester due to the reduced tone of the esophago-gastric junction and an increased intra-abdominal pressure [48].

Regarding intra or postoperative shivering as a complication in this study, a non-significant equal frequency in both groups developed either intra or postoperative shivering (60% for each, P=1.0).

CONCLUSION

Slow bolus of ephedrine is as effective as rapid bolus in treatment of hypotension associated with spinal anesthesia in maintaining blood pressure and heart rate, where the heart rate was more stable in slow bolus than rapid one that needed more boluses of ephedrine for treatment of hypotension.the study recommends that slowbolusdose of ephedrine can be useful in patient with cardiovascular disease (patient with ischemic heart disease &hypertensive) because theheart rate was more stable in the slow groupthan in therapid group andassociated with improvement in blood pressure.

We recommend to do a further study regarding effect of a slow and rapid bolus dose of ephedrine on the fetus.

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