"A COMPARATIVE STUDY OF RINGER LACTATE SOLUTION AND 6% HYDROXYETHYL STARCH SOLUTION AS PRELOADING FLUID FOR PREVENTION OF HYPOTENSION IN PATIENTS UNDERGOING ELECTIVE CAESAREAN SECTION UNDER SPINAL ANAESTHESIA – A RANDOMISED CLINICAL TRIAL"

By

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Dissertation submitted to

B. L. D. E. UNIVERSITY, VIJAYAPUR, KARNATAKA

In partial fulfillment of the requirements for the degree of

DOCTOR OF MEDICINE

IN

ANAESTHESIOLOGY

Under the guidance of

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Place: VIJAYAPUR **Dr. YASASWANI TEJA B.**

LIST OF ABBREVIATION

ASA	-	American society of anaesthesiologists
Cms	-	Centimeters
DBP	-	Diastolic blood pressure
FHS	-	Fetal heart sounds
FRC	-	Functional Residual Capacity
HES	-	Hydroxyethyl starch
HR	-	Heart rate
IV	-	Intravenous
Inj	-	Injection
Kg	-	Kilograms
L	-	Litre
LSCS	-	Lower segment caesarean section
MAP	-	Mean arterial pressure
Min	-	Minutes
RL	-	Ringer's lactate
SAB	-	Sub arachnoid block
SA	-	Spinal anesthesia
SBP	-	Systolic blood pressure

ABSTRACT

BACKGROUND:

Regional anesthesia has been the choice of preference for elective cesarean sections. Hypotension remains a common and potentially serious complication during spinal anesthesia for cesarean delivery. Fluid preloading attenuates the hypotensive response to spinal anesthesia. Preloading of patients with either crystalloid or colloid solutions reduces the incidence and severity of hypotension.

AIMS:

Our aim was to compare the preloading efficacy of Ringer's lactate solution at 20 ml/ Kg body weight and 6% Hydroxyethyl starch at 10 ml/ Kg body weight in prevention of hypotension following spinal anesthesia in parturients undergoing elective caesarean section.

MATERIALS AND METHODS:

This study was conducted at Shri B.M.Patil Medical College & Hospital,Vijayapur. 72 non labouring ASA class 1 women undergoing elective caesarean section were randomly divided into two groups of 36 patients each. Each subject was preloaded over a period of 20 minutes before spinal anesthesia with either of the fluids.

Group RL - Preloaded with Ringer lactate 20ml/kg.

Group HES - Preloaded with 6%Hydroxyethyl starch 10ml/kg.

RESULTS:

Demographic characters of both groups were comparable. There was significant difference in both the groups comparing mean systolic blood pressure, mean diastolic blood pressure and mean arterial pressure. Insignificant change in mean heart rate was noted between the Ringer's lactate group and Hydroxy

ethylstarch group. No allergic reactions to hydroxy ethyl starch in the studied subjects were noted. Vasopressor requirement was also less in the Hydroxy ethyl starch group as compared to the Ringer's lactate group

CONCLUSION:

We conclude that preloading subjects with 6% Hydroxy ethyl starch is beneficial than preloading with Ringer's lactate solution as it produces better hemodynamic stability to subjects.However the incidence of hypotension was only reduced but not completely eliminated with 6% HES in this study.

KEYWORDS:

Spinal anesthesia; Hypotension; Ringer's lactate; 6% Hydroxy ethyl starch.

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INTRODUCTION

Spinal anesthesia has emerged as the preferred technique of anaesthesia in pregnant patients posted for caesarean section. This technique has several advantages, including a decreased risk of failed intubation and aspiration of gastric contents, avoidance of neonatal depressant agents[1].

Spinal anaesthesia is however not without disadvantages. The most significant one being hypotension which may decrease uterine blood flow causing fetal hypoxia, acidosis and neonatal depression[2]. The neurobehavioural assessment of neonates born following spinal anaesthesia is better than general anaesthesia[3].

Various attempts have been made prophylactically to decrease the incidence and severity of hypotension. Traditionally fluid preloading with intravenous crystalloids or colloids have been the most commonest and standard practice to compensate this relative hypovolemic state which occurs during spinal anaesthesia for caesarean section.

Crystalloids may reduce the risk of hypotension but do not completely eliminate it. These solutions are not effective expanders of plasma volume since 75% of infused crystalloid solution rapidly diffuses into interstitial space; its effect is only transient[4]. In view of the above, colloids can be useful alternative to combat these relative hypovolemic states. Colloids remain in circulation for longer time than crystalloids and do not readily diffuse into the interstitial space. These fluids have a volume expanding effect; hence a lesser volume is required. But it has been found by many workers that colloids are not effective in preventing spinal hypotension[5].

This study has been studied by various people in their institutions. No such study has been conducted in our institution till date. Hence an attempt has been made in this direction.

AIMS AND OBJECTIVES

Aim

To compare the preloading efficacy of Ringer's lactate solution at 20ml/kg body weight and 6% Hydroxyethyl starch at 10ml/kg body weight for prevention of hypotension following spinal anaesthesia.

Objectives

1. To observe the incidence of hypotension in both the groups.
2. Number of rescue doses of vasopressor, inj.Mephentermine required for correction of hypotension in both the groups.
3. To study allergic reactions of 6% HES if any.

PHYSIOLOGY OF PREGNANCY

Maternal physiologic changes in pregnancy occur as a result of hormonal alterations, mechanical effects of gravid uterus, increased metabolic and oxygen requirements, metabolic demands of fetoplacental unit and haemodynamic alterations associated with the placental circulation. Such changes become more significant as pregnancy progresses and they have major implications for anaesthetic management[6].

Cardiovascular system

Approximately 50% of the increase in cardiac output occurs by 8th week of pregnancy. Although this increase in cardiac output is due to an increase in both stroke volume and heart rate, the most important factor is stroke volume which increases by 20% to 50% at term from non pregnant state.

Because of the decrease in peripheral vascular resistance, arterial blood pressure does not change in a normal pregnant woman. Cardiac output decreases during the third trimester due to effects of the supine position in the pregnant patient at term. Ueland and colleagues found that the decrease in cardiac output was due to obstruction of the IVC by the gravid uterus, which did not occur when women were placed in the lateral position.

Despite the increase in blood volume and cardiac output, parturients at term are susceptible to hypotension especially when in the supine position. Upto 10% of pregnant patients at term show signs of severe hypotension when assuming supine position. This phenomenon has been termed Supine Hypotension Syndrome. To compensate, collateral routes of venous return develop, including the paravertebral veins to the azygous vein. Unlike compression of the venacava, compression of the aorta is generally not associated with maternal symptoms in a healthy parturient, but it may be associated with decreased uteroplacental perfusion[7].

Anaesthetics and drugs that cause vasodilation or anaesthetic techniques that cause sympathectomy(eg: neuraxial techniques) may exacerbate the symptoms of aortocaval compression. In the operating room a small pillow or a wedge should be used to provide left uterine displacement of 15-20 degrees.

Respiratory system

Functional residual capacity(FRC) begins to decrease in the second trimester of the pregnancy and is decreased to 80% of the nonpregnant value at full term. This decrease in FRC causes maternal hypoxemia to develop very quickly after apnea associated with the induction of general anaesthesia.

Capillary engorgement of the mucosa and oedema of the oropharynx, larynx and trachea may result in a difficult intubation.

Haematological system

Maternal blood volume begins to increase early in pregnancy as a result of changes in osmoregulation and the renin angiotensin system, causing sodium retention and increasing total body water to 8.5L.By term, blood volume increases by upto 45% whereas red cell volume increases by only 30%.This differential increase leads to the " physiologic anemia" of pregnancy with an average haemoglobin and haematocrit of 11.6g/dl and 35.5% respectively.

A state of hypercoagulability exists in pregnancy, with increased levels of most coagulation factors. Fibrinogen and factor VII are markedly increased[8].

Gastrointestinal system

GIT undergoes significant anatomic and physiologic changes that increase the risk of aspiration associated with general anaesthesia. Progesterone relaxes smooth muscle consequently it impairs esophageal and intestinal motility during pregnancy.

Renal system

The increase in GFR by 50% generally precedes the expansion of blood volume and is considered to be a marker of pregnancy induced vasodilation.

Central nervous system

Pregnant women demonstrate increased sensitivity to both regional and general anaesthetics. Pregnant women require less local anaesthetics than non pregnant women do, to reach a given dermatomal sensory level.

Uterine blood flow

Uterine blood flow lacks autoregulation(vessels are maximally dilated during pregnancy) and uterine artery flow is therefore dependanton maternal blood pressure and cardiac output. Consequently, factors that alter blood flow through the uterus will adversely affect the fetal blood supply.

Uterine blood flow decreases during periods of maternal hypotension, which can occur as a result of hypovolemia, haemorrhage, aortocaval compression and sympathetic blockade. Anaesthetics may dramatically influence uterine blood either by alterations in perfusion pressure or by changes in uterine vascular resistance[9].

Sympathetic blockade after neuraxial techniques may reduce maternal blood pressure and the decrease in pressure will affect uterine blood flow[10]. This response may be exaggerated in patients who are not adequately prehydrated.Giving fluids intravenously (preloading) before neuraxial anesthesia does not completely prevent maternal hypotension but it does increase maternal cardiac output. Thus it may help to preserve uteroplacental blood flow[11].Aortocaval compression may further compound these effects.

SPINAL ANAESTHESIA

Anatomy of vertebral column

Proficiency in spinal anaesthesia requires a thorough understanding of the anatomy of the spine and the spinal cord. The anaesthesiologist must be familiar with the surface anatomy of the spine.

Vertebral Column

The vertebral column forms a canal and functions to protect the spinal cord. It consists of

Cervical vertebra	-	7
Thoracic vertebra	-	12
Lumbar vertebra	-	5
Sacral vertebra	-	5
Coccygeal vertebrae	-	5

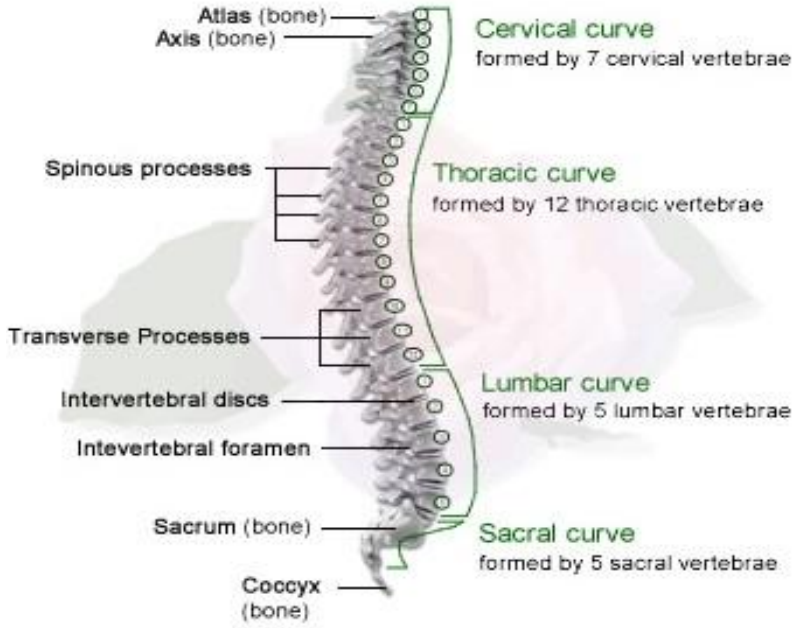


FIGURE -1:VERTEBRAL COLUMN

The sacral and coccygeal vertebrae are fused in adult life.

Adult vertebral column has got 4 curvatures – cervical, thoracic, lumbar and sacral curvatures. Curvatures of cervical and lumbar zones are convex forwards andwhereas thoracic and sacral vertebrae are concave forwards.

In supine position, the 3rd lumbar vertebra marks the highest point of lumbar curve and the 5th thoracic vertebra is the lowest point of dorsal curve.

Typical vertebra

It is represented by mid thoracic vertebra and consists of the following parts.

a) The Body
b) The vertebral arch
c) The transverse process and spinous process
d) The articular process: 2 superior articularprocesses and 2 inferior articular processes.

Spinous processes of all cervical, first 2 thoracic vertebrae and last 4 lumbar vertebrae are practically horizontal and are therefore located opposite to the bodies of their respective vertebra. The other spinous processes are inclined downwards, their tips being opposite to the bodies of the vertebrae of the next corresponding vertebra except for L1.The direction of the spinous process determines the direction in which spinal needle used must be inserted.

Topographic Line of Tuffier:

For practical purposes, a line across the back between the crests of the ilia passes over the spine of the fourth lumbar vertebra in sitting position. It may also pass over the interspace between the 4th and 5th lumbar vertebra, while a patient is lying in lateral position.This line serves as a surface landmark on the back for proper identification of interspaces between the spinous processes of the vertebrae.

The structures pierced at the back when punctured with spinal needle in the midline are skin, subcutaneous tissue, supraspinousligament,interspinous ligament, ligamentumflavum, areolar tissue, epidural space, dura mater spinalis, arachnoid mater, subarachnoid space. The spinal needle punctures dura mater and once in subarachnoid space, CSF flows freely.

Vertebral Canal

The vertebral column forms a canal and protects the spinal cord. The canal is bounded infront by bodies of the vertebrae and intervertebral discs and posteriorly by the laminae,ligamentumflavum and the arch which bears spinous processes and by the interspinousligaments, laterally it is bounded by pedicles and laminae.

Contents:

a) Roots of spinal nerves.

b) Meninges with spinal cord and CSF.

c) Vessels fat and areolar tissues of extradural space.

Spinal cord

In the first trimester foetus, the spinal cord extends from the foramen magnum to the end of the spinal column. Thereafter, the vertebral column lengthens more than the spinal cord so that at birth the spinal cord ends at approximately the level of the third lumbar vertebra. In adults, the caudad tip of the spinal cord typically lies at the level of the first lumbar vertebra. However, in 30% of people the spinal cord may end at T12, whereas in 10% it may extend to L3. It is 45cms in length in adults[12].

Above, the spinal cord is continuous with medulla oblongata, below it tapers of rapidly into a cervical extremity termed the conusmedullaris, from the apex of which a delicate non nervous filament named the filumterminale descends to the back of the first segment of the coccyx.

Lumbar and sacral nerves descend almost vertically to meet their corresponding lateral foramina and are known as caudaequina.

The Meninges

The spinal cord is ensheathed by three memebranes from outside to inside:

1. **Dura Mater**: It is a thick, dense, inelastic membrane and outermost of the three membranes covering the spinal cord.

   Inner meningeal layer

   Outer endosteal layer

Dural sac extends usually to the level of lower border of L2 vertebra.Dural sheath then continues as the covering of the FilumTerminale. Main fibres of the dura mater are longitudinal. So,lumbar puncture needle should be introduced with its bevel parallel to the direction of the fibres so that it separates rather than dividing these fibres.

2. **Arachnoid Mater**: It is a thin delicate membrane enveloping the brain and spinal cord and lying between piamater internally and dura mater externally.It is separated from dura mater by subdural space and from piamater by subarachnoid space, which is filled with cerebrospinal fluid.
3. **Pia Mater**: It is a vascular membrane consisting of a plexus of minute blood vessels held together by an extremely fine areolar tissue.From each lateral surface of the pia mater or fibrous band, the ligamentumdiverticulatum projects into subarachnoid space and it is attached by series of pointed processes to the dura asfar down as the 1st lumbar nerve.

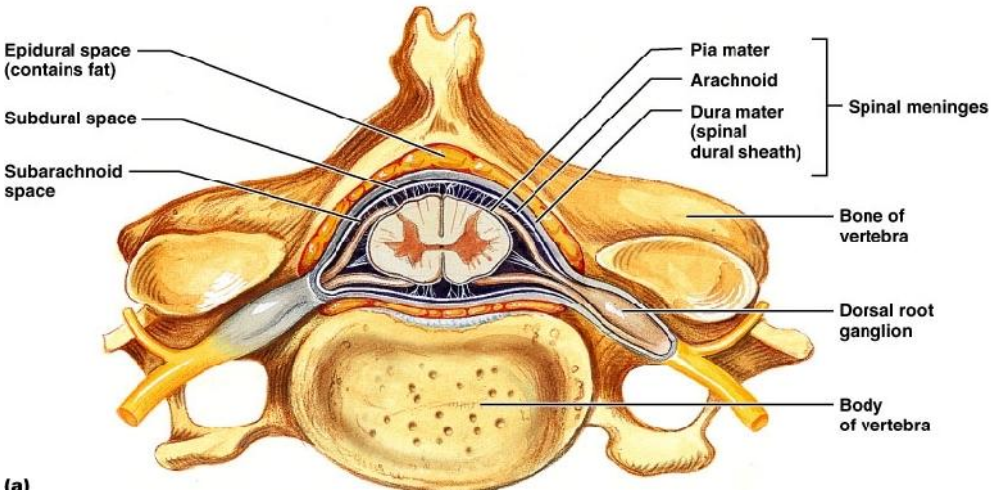


FIGURE -2:VERTEBRAL COLUMN AND SPINAL CORD

Spinal nerves:

The spinal cord is divided into segments by the pair of spinal nerves, which arise from it. These pairs are 31 in number and are as follows:

a) Cervical - 8

b) Thoracic - 12

c) Lumbar - 5

d) Sacral - 5

e) Coccygeal - 1

The nerve roots in the dura mater have no epineural sheaths and are therefore easily affected by doses of analgesic drugs brought into contact with them.

Spinal Nerves:

Each spinal nerve has got anterior and posterior root.

Anterior root/ ventral:

It is efferent and motor. Sympathetic preganglionic axons arise from the cell in the intermediolateral horn of spinal cord from T1 toL2.

Posterior root:

The posterior root is larger than the anterior root. All afferent impulses from whole body including viscera, pass into the posterior roots (largelysensory).

Each posterior root has a ganglion and conveys fibres of

1. Pain
2. Touch
3. Temperature
4. Deep or muscle sensation from bones, joints, tendons, etc.
5. Afferents from the viscera (accompanying sympathetic)
6. Vasodilator fibres.

The anterior and posterior roots of spinal nerves, each with its covering of pia-arachnoid and dura mater cross the extradural space and unite in the intervertebral foramina to form the spinal nerve trunks, which soon divide into anterior and posterior primary divisions – mixed nerves.

Anesthetic drugs affect autonomic, sensory and motor fibres in that order and fibres which block easily will hold the drug longer. Thus sensory block lasts longer than motor and usually ascends two segments higher than motor blockade.

The skin area innervated by given spinal nerve and its corresponding cord segment is called a dermatome.

Dermatomal levels of spinal anaesthesia for common surgical procedures.

Procedure	Dermatomal level
Upper abdominal surgery	T4
Intestinal, gynecologic and urologic surgery	T6
Trans urethral resection of the prostate	T10
Vaginal delivery and hip surgery	T10
Thigh surgery and lower leg amputations	L1
Foot and ankle surgery	L2
Perineal and anal surgery	S2- S5(Saddle block)

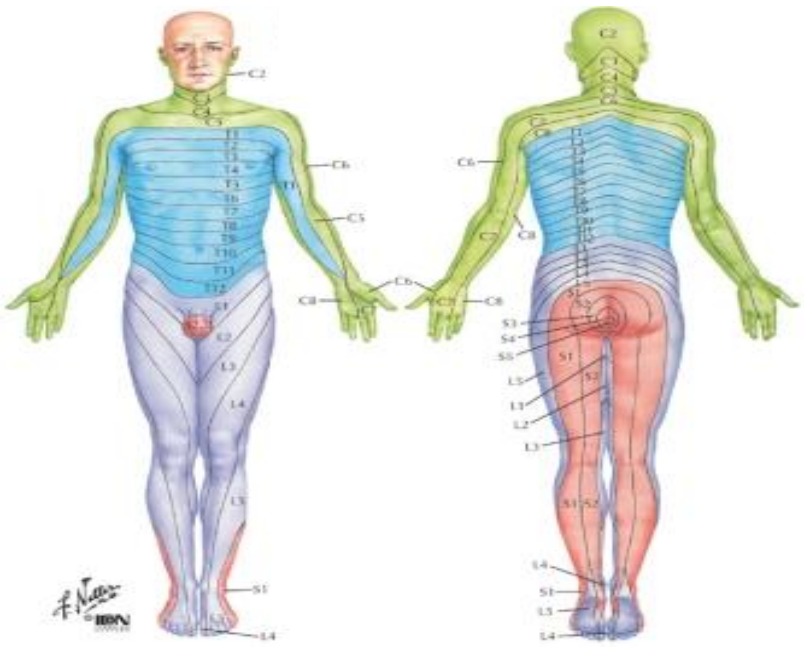


FIGURE-3: DERMATOMES OF HUMAN BODY

PHYSIOLOGY

Subarachnoid block

Spinal nerve rootlets are the principal sites of neural blockade.

Differential nerve block

It refers to a clinically important phenomenon in which nerve fibers sub serving different functions display varying sensitivity to local anaesthetic blockade.

Differential block occurs with both peripheral nerve blocks and central neuraxial blocks. In the peripheral nervous system, differential block is a temporary phenomenon, with sympathetic block occurring first, followed in time by sensory and motor block. In contrast, with spinal and epidural anaesthesia differential block is manifested as a spatial separation in the modalities blocked. This is seen most clearly with spinal anaesthesia, where the level of sympathetic block may extend to as many as two to six dermatomes higher than the level at which pin prick sensation is absent, which in turn extends two to three dermatomes higher than the level of the motor block. This spatial separation is believed to result from a gradual decrease in local anaesthetic concentration within the CSF as a function of distance from the site of injection[13].

The order of blockade of nerve fibres:

1. Autonomic preganglion 'B' fibres.
2. Temperature fibres – cold first, then warm.
3. Pin prick fibres
4. Fibres conveying pain of greater than pin-prick.
5. Touch fibres
6. Deep pressure fibres
7. Somatic motor fibres
8. Fibres conveying vibration sense and proprioceptive impulse.

During recovery, return of sensibility in the reverse order was assumed.But it has been suggested that sympathetic activity returns before sensation.Local analgesics act mainly on the nerve roots leaving the cord, although some drug molecules reach its substance. It depends on:

1. Accessibility, diffusion across the pia mater, the spaces of Virchow-Robin, thearachnoid villi
2. Lipid solubility and
3. Tissue blood flow.

Drug molecules are removed from intradural space by absorption intoblood vessels in the pia mater and by movements into the cord substance. Theextent of spinal anesthesia depends mainly on factors such as:

1. Dose of drug injected
2. Specific gravity of local anesthetic solution
3. Volume of the drug
4. Concentration of drug in subarachnoid space
5. Position of the patient during injection
6. Posture of the patient after injection
7. Choice of intervertebral space
8. Patient factors – pregnancy, old age,height,weight.

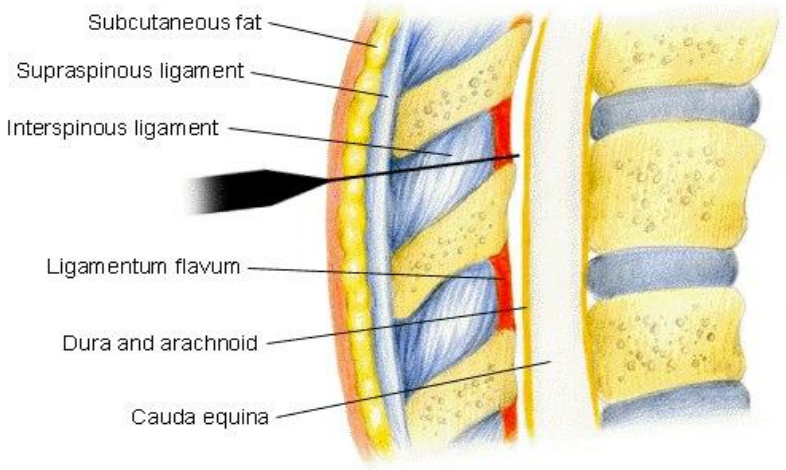


FIGURE-4:STRUCTURES PIERCED DURING SPINAL ANESTHESIA

HYPOTENSION

Hypotension is the most common immediate complication of spinal anaesthesia[14]. Sympathetic blockade causes arterial and physiologically more significant arteriolar vasodilation of vascular smooth muscles. As a result, total peripheral resistance decreases by 15 to 18%[15].

Veins and venules with only few smooth muscles on their walls retain no significant residual tone following spinal anesthesia. They can vasodilate maximally[16]. Hypotension is secondary to a decrease in cardiac output as a result of peripheral pooling of blood and diminished venous return to the heart[17].

Management of Hypotension

As a general dictum, if a patient's normal systolic blood pressuredecreases by more than 25% of the preanesthetic level, steps should be taken to correct it[18].Severe decrease inarterial pressure during anesthesia is usually a result of decreased cardiac output,which is inturn caused by decrease in venous return by faulty patient positioning.So, patient positioning is very important in the correction of hypotension, whichincorporates maintaining head down position and which leads to adequate venousreturn[19,20].

Prophylactically, left uterine displacement using a wedge to avoid aortocaval compression is recommended[21].

Vasopressors have a definite role in the treatment of arterialhypotension when use of head-down position alone has proven inadequate torestore blood pressure to acceptable levels[22,23].Ephedrine andmephentermine are commonly used vasopressors associated with an increase inthe mean arterial pressure and a decrease in venous capacitance thereby restoringblood pressure and heart rate during spinal anesthesia[24].

Prehydration of patients with fluids would expand the vascular space and

hence compensate for the reduction in systemic vascular resistance following induction of spinal anesthesia[25].

Preloading can be done using either crystalloids or colloid solutions[26].As approximately 75% of any crystalloid diffuses into interstitial space, its efficacy in expansion of plasma volume is only transient[27].

Administration of colloids is a more logical choice in prevention of hypotension during spinal anesthesia since it remains in the intravascular compartment for prolonged periods than crystalloids[28].

RINGER'S LACTATE

Lactated ringer's solution is a solution that is isotonic with blood and intended for intravenous administration.Its grouped under crystalloids.

It's very similar, though not identical to Hartmann's solution which has slightly different ionic concentrations.

One litre of lactated ringer's solution contains

130 meq of sodium ion	=	130mmol/l
109meq of chloride ion	=	109mmol/l
28meq of lactate	=	28mmol/l
4meq of potassium ion	=	4mmol/l
3meq of calcium ion	=	1.5mmol/l
Osmolarity	=	273mosm/l

Lactate is metabolized into bicarbonate in liver which can help correct metabolic acidosis. Sodium, lactate, chloride and potassium are derived from sodium Chloride (Nacl), sodium lactate, calcium chloride and potassium chloride respectively.

Although its pH is 6.5, its an alkalizing solution.

Development of Ringer Lactate solution:

Ringer lactate solution was invented in the early 1880 by Sydney Ringer by British physician and physiologist.Ringerwas studying the beating of an isolated frog heartoutside of the body. He hoped to identify the substances in blood that would allow the isolated heart to beat normally for atime. The original solution of anorganic salts was further modified by Alexis Hartmann for the purpose of treating acidosis in children. Hartmann added lactate, which mitigates changes in pH by acting as a buffer

for acid. Thus the solution came to be known as Lactated ringer's solution or Hartmann's solution.

THERAPY:

Lactated ringer's solution is often used for fluid resuscitation after a blood loss due to trauma, surgery or aburn injury. The IV dose of lactated ringer's solution is usually calculated by estimated fluid loss and presumed fluid deficit. For fluid resuscitation the usual rate of administration is 10-20ml/kg/hr. Lactated ringer solution is not suitable for maintenance theraphy. Because the sodium content (130meq/l) is considered too high, particularly for children and the potassium content (4meq/l) is too low, in view of electrolyte daily requirement.

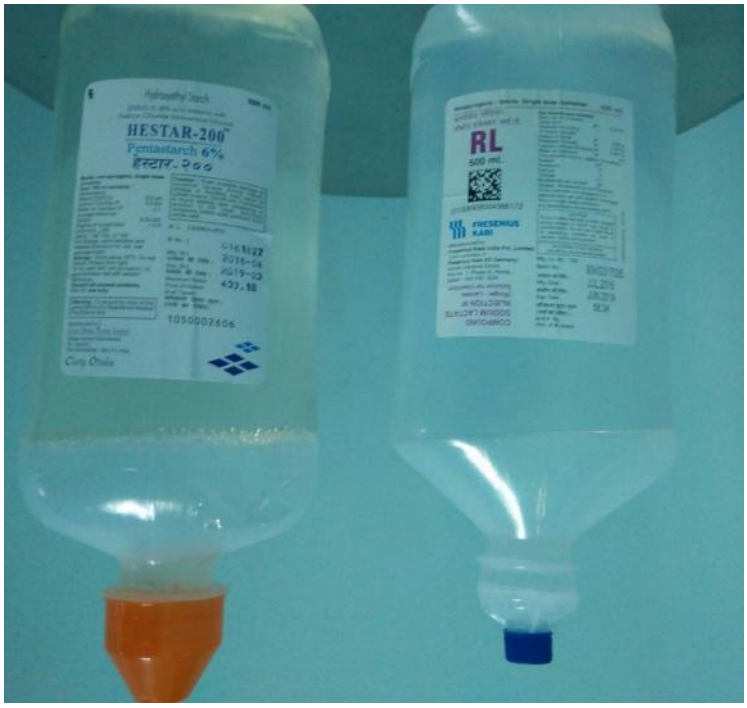


Fig-5 Picture showing RL & 6% HES

HYDROXYETHYL STARCH

Early discoveries of Ziese W triggered the first step in development of volaemic colloidhydroxyethyl starch. His work included the amylase mediated catabolism of starch. First step in the development of hydroxyethyl starch lay dormant for over 20 years. In 1957, Wiedersheim saw the practicability of using a less rapidly degradable form of starch as a means of restoring diminished plasma volume in cases subjected to hemorrhagic shock. For the first time, thestudies of Wiedersheim amalgamated the ideas of hydroxyethylation of starch and its logical extension, its use as a volaemiccolloid.Investigations of uses of hydroxyethyl starch was started in the year 1960 by Walton and his colleagues. The first specimen of hydroxyethyl starch to beused in man was the hydroxyethyl starch 450/0.7. Since these early studies,numerousinvestigations have reviewed the effectiveness of several species of hydroxyethyl starch in volume resuscitation.

Structure:

Hydroxyethyl starch is a complex polysaccharide (average molecularweight 450,000 daltons) that is available in a 6% aqueous solution forintravascular volume expansion during the perioperative period. It has gotpredominantly 1,4-α-glycosidic linkage with 1,6-α-glycosidic branch pointevery 16 to 25 glucose linkage.Hydroxyethyl starch is derived from amylopectin, a branchedpolysaccharide polymer. Three types of hydroxyethyl starch are availabledepending upon the molecular weight and degree of substitution. The degree ofsubstitution varies between 0.5-0.7. Average molecular weight of this 6%solution is 450000 daltons in vitro and the degree of substitution is 0.7, whichindicates 7 out of 10 glucose molecules are substituted by hydroxyethyl groups.

The higher the degree of substitution, the slower the hydrolysis and elimination.

The high molecular weight preparations are stored in the reticuloendothelial cellsfor a prolonged period. To overcome this problem, starch preparations with lowmolecular weight and faster elimination has been used.

Hydroxyethyl starch Preparations:

1. High molecular weight hydroxyethyl starch (HES 450/0.7).
2. Medium molecular weight hydroxy ethyl starch (HES 200/0.5)
3. Low molecular weight hydroxy ethyl starch (HES 40/0.5)

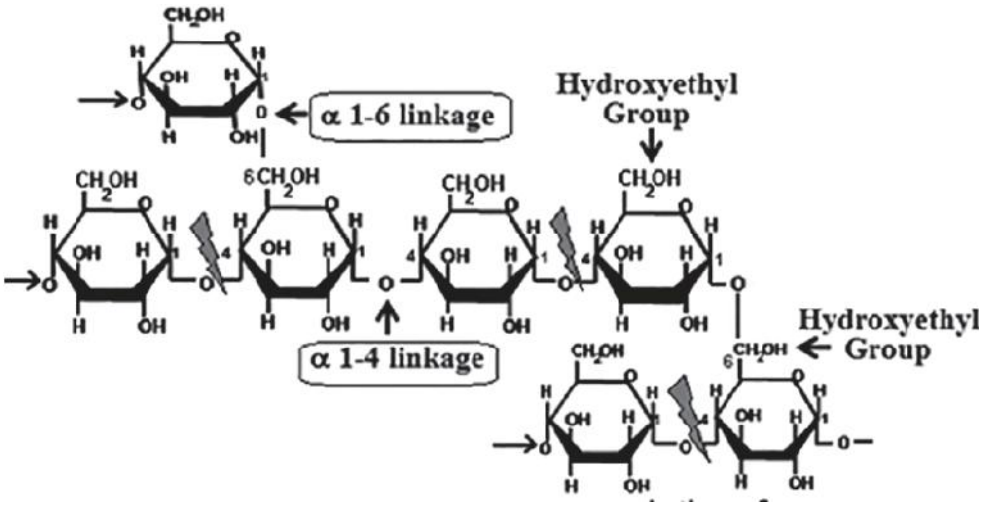
Composition:

1. Each 100 ml contains:
2. Hydroxyethyl starch (450/ 0.7) 6.0 gm
3. Sodium chloride (450/ 0.7) 0.9 gm
4. Water for injection (450/0.7) q.s.
5. Average molecular weight 450000
6. Degree of substitution 0.70
7. mosmol/ L 308
8. Sodium 154meq/L
9. Cl 154meq/L

The molecular weight distribution is defined as the sum of the number of molecules of eachmolecular weight times their mass divided by total weight of the molecules.The number of average molecular weight (Mw) is the number of molecules of a particular molecular weight divided by the total number of molecules. Molar substitution (ms) and degree of substitution are used to describe the extent of

hydroxyethylation of glucose units. Hetastarch has beendesignated as 450/0.7, indicating average weight of 450,000 daltons and a molarsubstitution of 0.7.

Molar substitution (ms) and weight average (Mw) plays an important role in plasma volume expansion and duration of plasma expansion of hydroxyethyl starch.



CHEMICAL STRUCTURE OF 6%HES

Pharmacological Properties:

Hydroxyethyl starch maintains adequate oncotic pressure. It maintains:

a) Plasma volumes and

b) Blood flow

Plasma Volume:

The colloid oncotic pressure of the plasma proteins which is about 25 mm Hg is the main factor for the retention of intravascular volume and the prevention of interstitial edema. Hydroxyethyl starch provides high colloid oncotic pressure,and hence fluid is retained in intravascular space.

Blood Flow:

If the plasma volume is lost from the vascular bed, the body responds by peripheralvasoconstriction. Replacement of lost plasma volume by water and

electrolytes alone causes areduction in the capillary hydrostatic pressure. The plasma oncotic pressure is also reduced.This results in an equilibrium between the hydrostatic and the oncotic pressure at a sub-normalcapillary pressure which gives a reduced capillary flow.

Plasma Volume Expansion of Hydroxyethyl Starch:

Normally, it is mainly albumin, which is responsible for the maintenanceof oncotic pressure in blood. If albumin is to be replaced by artificial colloid, thiscolloid must exert sufficient colloid oncotic pressure. The molecular weight ofadministered colloid should be sufficiently high to prevent its excretion rapidlyout of the body, hydroxyethyl starch replaces lost albumin and plays its role asplasma volume expander.

Hydroxyethyl starch has a molecular weight of 450000 daltons with adegree of substitution of 0.5. It exerts a colloid oncotic pressure of 58.5 cm H2Oand one litre of Hydroxyethyl starch increase the plasma oncotic pressure ofpatients in hypovolaemic shock by 36%. In order to achieve a prolongedintravascular existence of hydroxyethyl starch for effective plasma volumeexpansion, it is necessary that hydroxyethyl starch molecules should be aboverenal threshold.

Metabolism:

Hydroxyethyl starch molecules below 70,000 daltons are primarily eliminated via the kidneys as is evidenced by the rapid decline in the serum levels of it, as early as 3.6 hours post infusion and early urinary recovery of large amounts of hydroxyethylstarch.Fraction of hydroxyethyl starch that is subjected to slower renal elimination is at first cleaved by intracellular alpha-amylases at 1,4-glycosidic linkage and then by intravascular glomerular filtration. Rate of degradation torenallyexcretable fraction of hydroxyethyl starch depends on the degree of molar

substitution and the pattern of substitution. Acute or chronic administration of hydroxyethyl starch leads to transient storage in liver, spleen and other organs till it breaks down and eliminated by tissue glucosidases. Patients with normal renal fucntion rapidly eliminate hydroxyethyl starch. The residual hydroxyethyl starch dose is metabolized in tissues by tissue glucosidases and excreted renally and also extra-renally via the bile and the stool. Patients with chronic renal failure tend to store extensively hydroxyethyl starch in tissues due to non-dialyzability. So, hydroxyethyl starch is strictly contraindicated in these patients. About 46% of administered hydroxyethyl starch is excreted in urine by 2 days and 64% in 8 days.

Indication of Hydroxyethyl Starch:

1. Used in volume replacement therapy in routine surgery.
2. Used for hemodilution
3. Used for resuscitation of hypovolaemia due to:
    a) Hemorrhage
    b) Acute trauma
    c) Burns
    d) Sepsis
    e) Water and electrolyte loss in acute gastrointestinal disturbances
    f) Surgery
4. In cardiopulmonary bypass surgery.

Contraindication for Hydroxyethyl Starch:

1. Starch Allergy
2. Severe congestive cardiac failure[38]
3. Renal failure[39,40]
4. Severe coagulation disturbances

5. Excessive fluid overload
6. Cerebral hemorrhage

Adverse Reactions:

1. Anaphylactic reactions in less than 0.08% cases manifested as rash, pruritus,angioedema leading to cardiovascular collapse and respiratory arrest.
2. Hematological: Transient decrease in platelet count, prolonged thrombin,partial thromboplastin time and decrease in tensile clot strength was noted[41.42].
3. Gastrointestinal: Nausea and vomiting occurs rarely. Hyperamylasaemia cancomplicate the diagnosis of pancreatitis. The serum amylase levels reach twotimes the normal value after infusion of hydroxyethyl starch. This is due toformation of hydroxyethyl starch-amylase complex and undergoes slowerrenal excretion. Use of amylase in diagnosis of pancreatitis should be avoidedfor up to 3-5 days if the patient has received HES.
4. Miscellaneous: Rigor, fever, headache.

Advantages of Hydroxyethyl Starch over the other available plasma expanders:

1. Greater stability
2. Less antigenic
3. Less interference with blood cross-matching
4. Possible less coagulation toxicity.

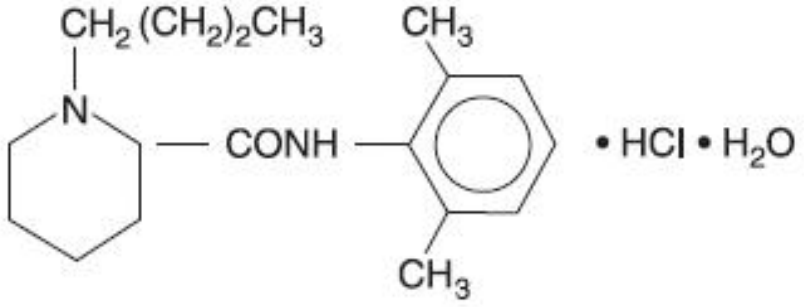
BUPIVACAINE

Bupivacaine is an amide local anesthetic commonly used for spinal and epidural anesthesia and analgesia [29].Its long duration of action, differential sensory to motor block [30] and relative lack of tachyphylaxis makes it a popular choice.

It ischemically known as 1-butyl-2piperidy formo-2'6'-xylidide hydrochloride.

Bupivacaine was synthetized by Swedish investigator BoafEkenstam et al.

It is a white crystalline powder soluble in water.



Chemical structure of bupivacaine

Physiochemical Properties:

a) Chemically amide (2,6-methyl amide)

b) Molecular weight – 325

c) Solubility: The base is sparingly soluble, but the hydrochloride form isreadily soluble in water.

d) Melting point: 247-258ºC

e) Stability and sterilization: Highly stable, can withstand repeatedautoclaving

f) pH of saturated solution – 5.2

g) Specific gravity – 1.021 at 37ºC.

Mechanism of Action:

Bupivacaine has got some mechanism of action similar to that of any otherlocal anesthetic [31]. Primary action of local anesthetics is on the cell membrane ofthe axon, on which it produces electrical stabilization. The large transientincrease in permeability of sodium ions necessary for propagation of the impulseis prevented. Thus, resting membrane potential is maintained and depolarizationin response to stimulation is inhibited. Initially, the threshold for electrical excitation is raised, the rate of rise of action potential reduced and conductionslowed. Eventually, propagation of impulse fails.

Sodium conductance [32] is blocked as follows:

a) Local anesthetics in the cationic form act on the receptors within the sodium channels on the cell membrane and block it. The localanesthetic reaches sodium channel either via the lipophilic pathwaydirectly across the membrane, or via the axoplasmic opening. Thismechanism accounts for 90% of the nerve blocking effects of amidelocal anesthetics.
b) The second mechanism of action is by membrane expansion. This is a non-specific action in contrast to the more specific drug-receptor interaction.

Dosage:

As with all local anesthetics, the dosage of bupivacaine varies and depends upon[33,34]

a) Area to be anesthetized
b) Vascularity of the tissue to be blocked
c) The number of neuronal segments to be blocked
d) Individual tolerance
e) Technique of local anesthesia.

Hyperbaric bupivacaine is the most commonly used agent for spinal anesthesia.Its duration of action is 1.5-2 hrs.Hyperbaric solutions have the advantage of greater predictability of block height than plain solutions do and they allow the anesthesiologist to adjust block height by adjusting table position [35].

Pharmacological Action of Bupivacaine:

Central Nervous System:

Overdose of Bupivacaine [36] produces light headedness and dizzinessfollowed by visual and auditory disturbances such as difficulty to focus andtinnitus. Disorientation and drowsiness can also occur. Shivering and tremors offacial muscles and distal part of extremities can occur. Ultimately generalizedtonic-clonic seizures occur. Further increase in dose cause respiratory arrest.

Since, bupivacaine is a potent drug, smaller doses can cause rapid onset of toxicsymptoms when compared to other drugs.

Autonomic Nervous System:

Bupivacaine does not inhibit the nor-adrenaline uptake and has nosympathetic potentiation effect. Preganglionic beta-fibres have a fasterconduction time and are more sensitive to the action of local anesthetics includingbupivacaine. Involvement of preganglionic sympathetic fibres is the cause ofwidespread vasodilatation and consequent hypotension that occurs in epidural andparavertebral block. When used for conduction blockade, all local anestheticsparticularly bupivacaine produce higher incidence of sensory blockade than motorfibres.

Neuromuscular Junction:

Bupivacaine, like other local anesthetics can block motor nerves, if presentin sufficient concentrations. But has no effect on neuromuscular junction as such.

Cardiovascular System:

The primary cardiac electrophysiologic effect of local anesthetic is adecrease in the maximum rate of depolarization in Purkinje fibres and ventricularmuscles. This is due to a decrease in availability of sodium channels. Actionpotential duration and the effective refractory period is also decreased. Thedepression of rapid phase of depolarization in Purkinje fibres and ventricularmuscle by bupivacaine is far greater compared to lignocaine. Also, the rate ofrecovery of the block is slower with bupivcaine. Therefore, bupivacaine is highlyarrhythmogenic. The cardiac contractility is reduced by bupivacaine. This is byblocking the calcium transport. Low concentration of bupivacaine producesvasoconstriction, while high doses cause vasodilatation.

Respiratory System:

Respiratory depression may be caused if excessive plasma level isreached, which in turn results in depression of medullary respiratory centre andalso due to paralysis of respiratory muscles as may occur in high spinal or totalspinal anesthesia.

Pharmacokinetics of Bupivacaine:

Absorption: Absorption of local anesthetics is determined by site of injection,dosage and addition of a vasoconstriction. Absorption is faster in regions ofhigher vascularity and also in some regions e.g., absorption of drug afterintercostal block is faster than after brachial plexus block. Higher dosage leads tofaster absorption. Addition of vasoconstrictor does not prolong the duration ofaction of bupivacaine significantly but decreases its absorption.

Distribution: Distributed throughout all body tissues. Volume of distribution is72 litres. Clearance is 0.47 litres/ minute. The more highly perfused organs showhigher concentration of the drug. Blood concentration of the drug decreasesmarkedly as it

passes through the pulmonary vasculature. Because of the mass,skeletal tissue forms the largest reservoir of bupivacvaine.

The placental transfer of bupivacaine as with other amide local anesthetics is governed by two factors,the degree of ionization at physiologic pH and the extent of protein binding.Bupivacaine has a p^{ka} of 8.05(highly ionized at physiologic pH) and is 95% protein bound,thus,it has limited transfer to the placenta when compared to other local anesthetics.

The UV/M ratio(the ratio at delivery of the concentration of local anesthetic in blood or plasma from the umbilical vein to the concentration of local anesthetic in maternal blood) for bupivacaine ranges from 0.31% to 0.44% and is much lower than that for lidocaine[37].

Biotransformation and Excretion: Metabolized in liver. Undergoes dealkylationand hydroxylation and then conjugated to form a water solublecompound. The drug is excreted by the kidneys.

Toxicity: In human beings, bupivacaine is four to five times more toxic thanlignocaine.

Adverse Reactions: Due to overdosage, inadvertent IV injections or slow metabolicdegradation.

CNS Effects: First manifestation may be nervousness, dizziness, blurred vision,tremors followed by drowsiness, convulsions, unconsciousness and respiratoryarrest.

CVS Effects: Myocardial depression, hypotension and cardiac arrest. Inobstetrics, fetal bradycardia may occur.

Other Effects: Nausea, vomiting, chills, constriction of pupils and tinnitus.Allergic reactions include urticaria, bronchospasm, hypotension.

REVIEW OF LITERATURE

1. **Riley ET, Cohen SE, Rubenstein AJ, Flanagan B(1995)** [43] conducted a study on prevention of hypotension after spinal anesthesia for cesarean section by comparing six percent hetastarch versus lactated Ringer's solution . Forty nonlaboring ASA class I and II women having nonurgent cesarean sections were randomized to receive either 500 mL of 6% hetastarch plus 1 L lactated Ringer's solution (LR) (n = 20), or 2 L of LR (n = 20) prior to induction. Hypotension occurred in 45% of patients who received hetastarchvs 85% of those who received only LR minimum systolic blood pressure was lower in the LR group than in the hetastarchgroup .In addition, the LR group had a higher maximum heart rate a shorter mean time to hypotension , and required more 5-mg doses of ephedrine for treatment of hypotension than the hetastarch group. It was concluded that 6% hetastarch plus LR is more effective than LR alone and that its routine use before spinal anesthesia for cesarean section.

2. **Ueyama H,He YL, Tanigami H, MashimoT,YoshiyaI (1999)** [44] studied the effects of crystalloid and colloid preload on blood volume in the parturient undergoing spinal anesthesia for elective cesarean section. Thirty-six healthy parturientsscheduled for elective cesarean section during spinal anesthesia were allocated randomly to one of three groups receiving 1.5 L lactated Ringer's solution (LR; n = 12), 0.5 Lhydroxyethylstarch solution, 6% (0.5 L HES; n = 12), and 1.0 Lhydroxyethylstarch solution, 6% (1.0 L HES; n = 12), respectively.

   Significant increases in cardiac output were observed in the 0.5-L and 1.0-L HES groups ($P < 0.01$). The incidence of hypotension was 75% for the

LR group, 58% for the 0.5-LHES group, and 17% for the 1.0-L HES group, respectively.It was concluded that the incidence of hypotension developed in the 1.0-L HES group was significantly lower than that in the LR and 0.5-L HES groups, showing that greater volume expansion results in less hypotension.

3. **Tamilselvan P, Fernando R, Bray J, Sodhi M, Columb M (2009)** [45] conducted a study on the effects of crystalloid and colloid preload on cardiac output in the parturient undergoing planned cesarean delivery under spinal anesthesia a suprasternal Doppler flow technique to measure maternal cardiac output (CO) and corrected flow time (FTc, a measure of intravascular volume) before and after spinal anesthesia after 3 fluid preload regimens was used. Sixty healthy term women were randomized to receive 1 of 3 fluid preload regimens given over 15 min: 1.5 L crystalloid (Hartman's solution), 0.5 L of 6% w/v hydroxyethyl starch (HES) solution (HES 0.5), or 1 L of 6% w/v HES solution (HES 1.0). Although CO and FTc increased after preload in all groups this was only maintained with HES 1.0 after spinal anesthesia .

   Despite CO and FTc increases after fluid preload, particularly with HES 1.0 L, hypotension still occurred. The data suggest that CO increases after these preload regimens cannot compensate for reductions in arterial blood pressure after spinal anesthesia.

4. **Siddik SM, Aouad MT, Kai GE, Sfeir MM, Baraka AS (2000)**[46] conducted a study comparing Hydroxyethylstarch 10% and Ringer's solution for preloading before spinal anesthesia for cesarean section.

   40 healthy women undergoing elective Cesarean section HES, 500 ml (n = 20), or LR, IL (n = 20), was administered during 10 min before spinal

anesthesia. The incidence of hypotension, (systolic blood pressure < 80% of baseline and < 100 mm Hg), and the amount of ephedrine used to treat it were compared. The incidence of hypotension was higher in the LR than in HES group (80% vs 40%). Mean minimum systolic blood pressure was lower in the LR than in the HES group. More doses of ephedrine were required to treat hypotension in the LR than in the HES group. The incidence of nausea and/or vomiting was lower in the HES than in the crystalloid group. It was concluded that preloading patients undergoing elective cesarean section with 500 ml HES 10%, decreases the incidence and severity of spinal-induced hypotension more than preloading with 1 L of LR solution.

5. **Yokoyama N, Nishikawa K, Saito Y, Saito S, Goto F (2004)** [47] studied comparison of the effects of colloid and crystalloid solution for volume preloading on maternal hemodynamics and neonatal outcome in spinal anesthesia for cesarean section.32 healthy parturients undergoing cesarean section were randomized to receive either acetated Ringer's solution (1,000 ml, n=8, AR group), 6% hydroxyethylstarch(1,000 ml, n=9, HES group), or no preload (n=10) before spinal anesthesia. . In addition, emergency cases (n=5) such as prolonged labor without any maternal complication were also included for analysis.

   The incidence of hypotension, systolic blood pressure <80% of baseline or <100 mmHg, and the amount of ephedrine used to treat hypotension were compared.It was concluded that in healthy patients with full-term pregnancy, volume preloading has little effect on maternal hemodynamics and neonatal outcomes, suggesting that stable perioperative management is possible with or without volume preload before spinal

anesthesia. However, preloading may be needed for prevention of hypotension in emergency cases.

6. **Dahlgren G, Granath F, Wessel H, Irestedt L (2007)** [48] studied prediction of hypotension during spinal anesthesia for Cesarean section and its relation to the effect of crystalloid or colloid preload. 55 healthy parturients scheduled for elective cesarean section under spinal anesthesia were preoperatively investigated with a supine stress test with measurement of maternal heart rate, blood pressure, right uterine artery pulsatility index and symptoms in the left lateral and supine positions. They were then randomized to receive a colloid or crystalloid preload before anesthesia.

   The stress test was positive, indicating a reduced tolerance to the supine position, in 36%. The sensitivity and specificity of the stress test for clinically significant hypotension (symptomatic hypotension) for patients randomized to the crystalloid group (n=25) were 69% and 92% respectively. Patients with a positive stress test receiving a crystalloid preload showed a higher frequency of hypotension compared to all other groups and also a greater need for ephedrine.

   Pregnant women with a positive preoperative supine stress test constitute a subset at increased risk for clinically significant hypotension during cesarean delivery under spinal anesthesia. These women seem more likely to benefit from prophylactic colloid solution.

7. **Ko JS, Kim CS, Cho HS, Choi DH(2007)**[49] conducted a study on crystalloid versus colloid solution for prevention of hypotension during spinal or low-dose combined spinal-epidural anesthesia for elective cesarean delivery. Women undergoing elective cesarean delivery were randomly allocated to one

of four groups (50 in each) to receive crystalloid preload before spinal anesthesia, colloid preload before spinal anesthesia, crystalloid preload before combined spinal-epidural anesthesia, and colloid preload before combined spinal-epidural anesthesia. It was concluded that colloid preload and low-dose spinal anesthesia alone or in combination lowered the incidences of hypotension and nausea.

8. **Madi-Jebara S et al,(2008)** [50] studied prevention of hypotension after spinal anesthesia for cesarean section using 6% hydroxyethyl starch 130/0.4 (Voluven) versus lactated Ringer's solution. One hundred and twenty nonlaboring ASA I and II women having non urgent LSCS were enrolled in this prospective and randomized study. Subjects were randomly assigned to receive prior to anesthesia either 1 liter of LR (Gr I: n = 59) or 500 ml of HES 130/0.4 (Gr II : n = 61).39 patients in Gr II while 48 pts in Gr I experienced hypotension . It was concluded that HES 130/0.4 is more effective than LR to prevent hypotension following spinal anesthesia for CS.
9. **Teoh WH,Sia AT(2009)** [51],conducted a study on colloid preload versus coload for spinal anesthesia for cesarean delivery: the effects on maternal cardiac output. 40 ASA I and II patients scheduled for elective cesarean delivery were recruited. Patients were randomized to Group P (preload of 15 mL/kg HES) or Group C (coload, given when cerebrospinal fluid identified. Intravascular volume expansion with 15 mL/kg HES 130/0.4 given as a preload, but not coload, significantly increased maternal CO for the first 5 min after spinal anesthesia for cesarean delivery.
10. **Zorko N, Kamenik M, Starc V (2009**) [52] studied the effect of Trendelenburg position, lactated Ringer's solution and 6% hydroxyethyl starch solution

on cardiac output after spinal anesthesia.Seventy patients scheduled for lower extremity orthopedic surgery under spinal anesthesia were allocated randomly to one of the three treatment groups. In the Trendelenburg group, the patients were placed in the Trendelenburg position immediately after the spinal block for 10 min. In the hydroxyethyl starch group and the lactated Ringer's group, the patients received an infusion of 500 mL of 6% hydroxyethyl starch solution or 1000 mL of lactated Ringer's solution over 20 min after the spinal block**.** In the Trendelenburg group, CO did not change while the patient was in the Trendelenburg position. In the hydroxyethyl starch group, CO increased significantly after the block and remained significantly increased until the end of measurements. In the lactated Ringer's group, CO increased significantly 10 and 20 min after the block but, after stopping the infusion, CO started to decrease.

It was concluded that the decrease in CO after spinal anesthesia is prevented by placing the patient in the Trendelenburg position, or infusion of either lactated Ringer's solution or 6% hydroxyetyl starch solution. Although the effects of the infusion of the lactated Ringer's solution are transient, the effects of the infusion of 6% hydroxyethyl starch solution are extended beyond the time of infusion.

11. **Hasan AB et al (2012)** [53] conducted a study oncomparison of three fluid regimens for preloading in elective caesarean section under spinal anaesthesia**.** 90 non-labouring ASA grade 1 and 2 patients were divided randomly into three groups. Group-RL received Ringer's Lactate 20ml/kg as preloading fluid. Group-H received Hydroxyethylstarch-6% 8ml/kg and Group-RLH

received preloading fluid with combination of Ringer's Lactate 10ml/kg and Hydroxyethylstarch-6% 4ml/kg.

Hypotension was less in Group-RLH (6.7%) whereas in Group-H and Group-RL hypotension was 20% and 47.7% respectively. Systolic blood pressure decreased significantly in all three groups. But the decreasing was less in Group-RLH than other two groups.It was concluded that preloading with low volume colloid (4ml/kg) plus crystalloid (10ml/kg) is superior to crystalloid or colloid alone.

12. **Mitra T, Das A, Majumdar S, Bhattacharyya T, Mandal RD, Hajra BK (2014)** [54]conducted a study on prevention of altered hemodynamics after spinal anesthesia by comparing volume preloading with tetrastarch, succinylated gelatin and ringer lactate solution for the patients undergoing lower segment caesarean section.

    96 ASA-I healthy, nonlaboringparturients were randomly divided in 3 groups HES, SG, RL (n = 32 each) and received 10 ml/kg HES 130/0.4; 10 ml/kg SG (4% modified fluid gelatin) and 20 ml/kg RL respectively prior to SA scheduled for cesarean section. The fall in systolic blood pressure (SBP) (<100 mm Hg) noted among 5 (15.63%), 12 (37.5%) and 14 (43.75%) parturients in groups HES, SG, RL respectively . Lower preloading volume and less intra-operative vasopressor requirement was noted in HES group for maintaining BP.

13. **Tawfik MM et al,(2014**) [55]conducted a study on comparison between colloid preload and crystalloid co-load in cesarean section under spinal anesthesia . 210 patients scheduled for elective cesarean section under spinal anesthesia were randomly allocated to receive either 6% hydroxyethyl starch 130/0.4 500

mL before spinal anesthesia (colloid preload) or Ringer's acetate solution 1000 mL administered rapidly starting with intrathecal injection (crystalloid co-load).

There were no significant differences in the incidence of hypotension or severe hypotension between colloid preload and crystalloid co-load groups, respectively.It was concluded that the use of 1000 mL crystalloid co-load has similar effect to 500 mL colloid preload in reducing the incidence of hypotension after spinal anesthesia for elective cesarean delivery. Neithertechnique can totally prevent hypotension and should be combined with vasopressor use.

14. **Alimian M, Mohseni M, Safaeian R, Faiz SH, Majedi MA(2014)**[56]conducted a study on comparison of hydroxyethyl starch 6% and crystalloids for preloading in elective caesarean section under spinal anesthesia.90 healthyparturients posted for elective caesarean section were randomly allocated to receive lactated ringer's solution (1000 ml), sodium chloride 0.9% (1000 ml) or HES (7.5 mL/Kg) as preloading before spinal anesthesia.

    The incidence of hypotension and required dose of ephedrine was lower in HES group.It was concluded that Preloading with HES is more effective than crystalloids in prevention hypotension after spinal anesthesia without significant difference in Apgar score and umblical cord blood pH.

15. **Mercier FJet al, (2014**) [57] conducted a study on 6% Hydroxyethyl starch (130/0.4) vs Ringer's lactate preloading before spinal anaesthesia for caesarean delivery. 167 healthy parturients undergoing elective caesarean delivery under SA were included in this multicentre, randomized, double-blind study. Patients

received 500 ml of 6% HES (130/0.4)+500 ml of RL (HES group) or 1000 ml of RL (RL group) i.v before SA.

The incidence of both hypotension and symptomatic hypotension (i.e. with dizziness, nausea/vomiting, or both) was significantly lower in the HES group vs the RL group. There was no significant difference in total phenylephrine requirements. It was concluded that compared with a pure RL preloading, a mixed HES-RL preloading significantly improved prevention of both hypotension and symptomatic hypotension based on early phenylephrine bolus administration and did not induce adverse effects.

16. **Arora P, Singh RM, Kundra S, GautamPL(2015)** [58] studied the effects of fluid administration before caesarean delivery. 90 ASA I/II term parturients posted for elective caesarean section. Patients were randomly allocated to three Groups. Group A (n=30) was given 10 ml/kg of 6% hydroxyethyl starch (HES) 20 minutes prior to spinal anaesthesia, GroupB (n=30) was given 10 ml/kg of 6% HES by rapid infusion in 10 minutes immediately after spinal anaesthesia and Group C (n=30) was given 10 ml/kg of Ringer's Lactate 20 minutes prior to spinal anaesthesia. Incidence of hypotension was 66.66% in Group C as compared to 36.66% in Groups A and 40% in Group B respectively

The incidence of hypotension and ephedrine consumption was significantly higher in Group C as compared to Groups A and B .It was concluded that colloid preloading and co-loading are equally effective and both are superior to crystalloid preloading for prevention of maternal hypotension in caesarean section patients.

17. **MatsotaP, KarakostaA, PandaziA, NiokouD, ChristodoulakiK, Kostopan agiotou G (2015**) [59] conducted a study on the effect of 0.5 L 6% hydroxyethyl starch 130/0.42 versus 1 L Ringer's lactate preload on the hemodynamic status of parturients undergoing spinal anesthesia for elective cesarean delivery using arterial pulse contour analysis.

    Thirty-two ASA I/II parturients scheduled for elective LSCS were preloaded with either 1 L R/L (Group R/L, n = 16) or 0.5 L HES 6% 130/0.42 (Group T, n = 16) approximately 25 min before SA. The incidence of hypotension was 73.3% in Group R/L and 46.7% in Group T. HES compared to R/L preload was associated with a shorter overall duration of hypotensive episodes a significantly less usage of ephedrine and phenylephrine and a greater impact, although not statistically significant, on cardiac index (CI) and stroke volume index (SVI). It was concluded that preloading with 0.5 L HES 130/0.42 produced more stable hemodynamics compared to 1 L R/L solution in obstetric patients.

18. **Madhusudan Upadya, Sonal Bhat, and Seema Paul(2016)** [60] conducted a study on six percent hetastarch versus lactated Ringer's solution – for preloading before spinal anesthesia for cesarean section on 50 nonlaboring ASA class I and II women undergoing elective cesarean section. Patients were randomly divided into two groups and were preloaded either with 1000 ml Ringer's lactate (RL) or 500 ml of 6% hetastarch 30 min prior to the surgery.

    Results of the study showed the incidence of hypotension to be 28% in the hetastarch group and 80% in the RL group. Rescue ephedrine

requirements for the treatment of hypotension were significantly less in patients who were preloaded with 6% hetastarch prior to cesarean section.

MATERIALS AND METHODS

Source of data

This study was carried out in the department of anaesthesiology, BLDEU'S ShriB.M.Patil Medical College,Hospital and research centre,Vijayapur.

Study was conducted after institutional approval and ethical clearance from college ethical committee.

Informed consent was taken from all patients.

Period of collection of data **:** December 2014 to August 2016.

Study design **:** Randomized Clinical trial

Study period **:** 21 months from Dec 2014 to Aug 2016

Sample size: 72 Non laboring ASA class 1 women of age in between 20-35 yrs undergoing elective caesarean section were randomly divided into **two groups** of **36** patients each by using a computer generated randomization table.

Group RL - Preloaded with Ringer lactate solution.

Group HES - Preloaded with 6%Hydroxyethyl starch solution.

Sample size calculation:

With reference to the below article sample size has been calculated.

Madi-Jebara S *et al*, Prevention of hypotension after spinal anesthesia for cesarean section; 6% hydroxyethyl starch versus lactated Ringer's solution. Br J Anaesth. 2008 Oct-Dec;56(4):203-7.

Considering the average incidence of these two groups 34%, at 95% confidence level with 90% power the sample size is 36.

$$n = \frac{(Z_{\alpha} + Z_{\beta})^2 \times 2 \times P \times (1-P)}{d^2}$$

Z_α – Z value at α level = 95%

Z_β – Z value at β level = 90%

P = common incidence value

d = difference between two proportions

Inclusion criteria

- Patients belonging to ASA grade 1.
- Age 20 to 35 years.
- Non labouring patients.

Exclusion criteria

- Parturient with fetal distress,pre-eclampsia,placentaprevia, abruption placenta.
- Any parturient in whom spinal anesthesia is contraindicated.

Statistical analysis:

All characteristics were summarized descriptively. For continuous variables, the summary statistics of N, mean, standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries. Data were represented using Mean ±SD, and analyzed by Chi square test for association, the differences of the analysis variables was tested with the t-test. If the p-value was < 0.05, then the results will be considered to be significant. Data were analyzed using SPSS software v.24.0.

METHODOLOGY

Pre anesthetic evaluation

All standard investigations for all cases like complete hemogram, urine analysis, blood grouping and Rh typing and random blood sugar were done.

PAE was done on the previous day of surgery. The procedure was explained to each patient. Informed written consent and cooperation was sought from the patient.

Basal parameters like heart rate, BP, FHS were recorded using conventional methods.

A peripheral intravenous line with 18G cannula was secured in one of the upper limbs. Volume infusion was determined according to body weight. Patients in group RL received Ringer's lactate 20ml/kg and patients in group HES received 6%Hydroxy ethyl starch at 10ml/kg. Both these solutions were infused over a period of 20 minutes before performance of subarachnoid block. After preloading, all patients were given Ringer lactate solution for fluid maintenance.

Under aseptic precautions subarachnoid block was performed using 2ml of 0.5% hyperbaric bupivacaine.

Immediately after the injection of bupivacaine blood pressure and heart rate were recorded at an interval of every minute up to 5 min, every 5 min upto 30 min, every 15 min upto 90 min duration. Also basal parameters were noted 2hrs after the procedure. Level of block was checked after 5 min and 10 min.

Hypotension in this context is defined as a decrease in the systolic blood pressure by more than 20% from the initial baseline level. Hypotension was managed by increasing fluid infusion rate and trendelenberg position(only after the local anesthetic was fixed).

If hypotension persisted inspite of above measures injection Mephentermine was administered intravenously 3mg bolus at 1 minute interval until blood pressure increased to acceptable level.

Bradycardia was treated with inj. Atropine 0.6mgIV.

OBSERVATIONS AND RESULTS

72non labouring ASA class 1 women undergoing elective caesarean section were randomly divided into two groups of **36** patients eachby using a computer generated randomization table.

Group RL - Preloaded with Ringer lactate solution.

Group HES - Preloaded with 6%Hydroxyethyl starch solution

Table 1: Distribution of cases among study groups

Groups	**N**	**%**
Group A	36	50.0%
Group B	36	50.0%
Total	72	100%

Graph1: Distribution of cases among study groups

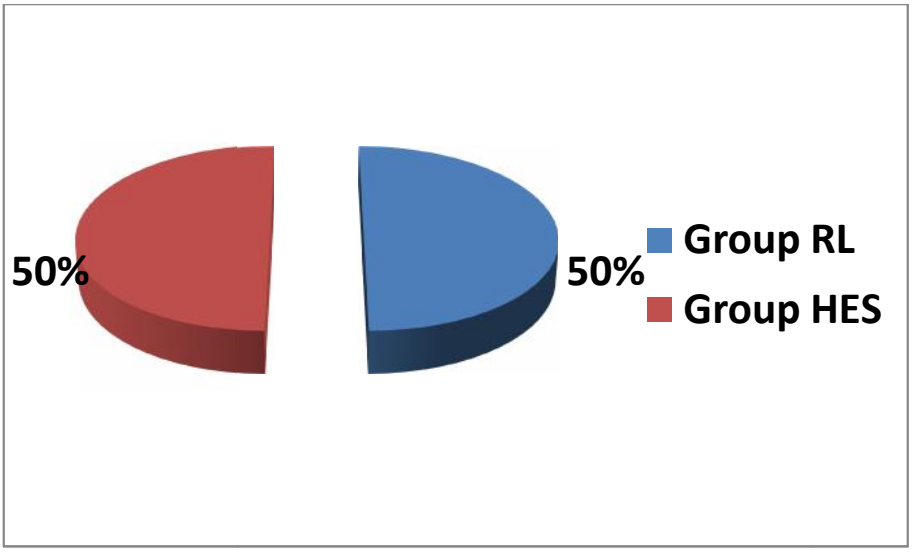
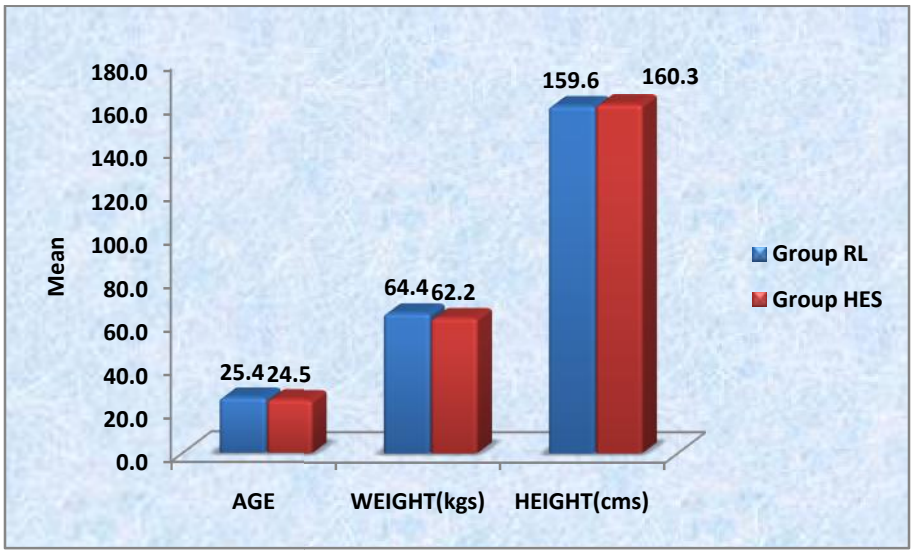


Table 2: Comparison of mean values of selected parameters between study groups

Parameters	Group RL		Group HES		p value	Significance
	Mean	SD	Mean	SD		
AGE (yrs)	25.4	4.4	24.5	3.9	0.367	Not Sig
WEIGHT(kgs)	64.4	8.0	62.2	6.0	0.191	Not Sig
HEIGHT(cms)	159.6	4.0	160.3	4.0	0.414	Not Sig

Graph 2: Comparison of mean values of selected parameters between study groups

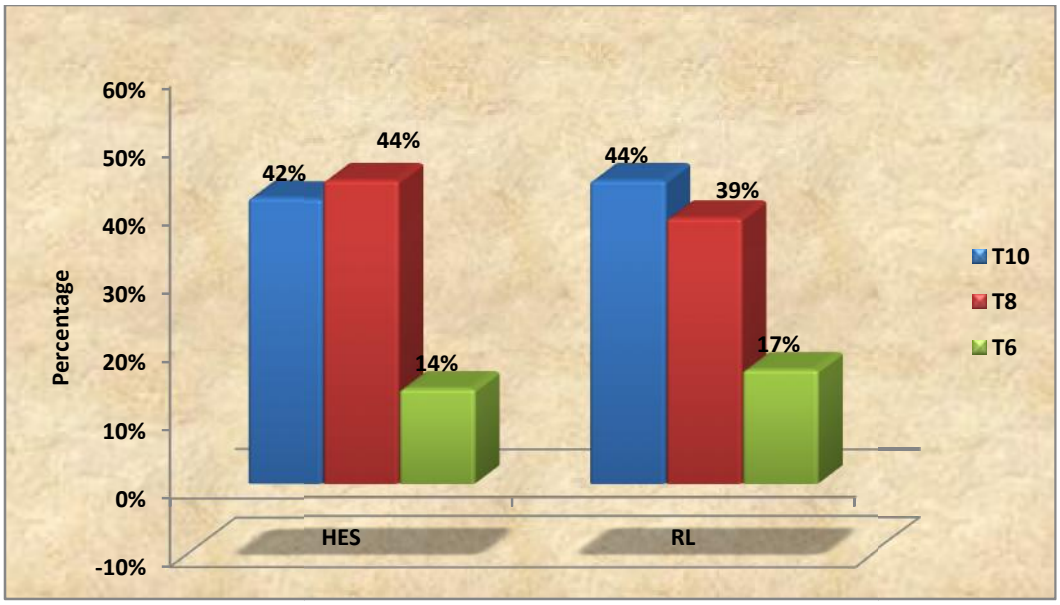


Mean age,height and weight of both the groups showed no significant difference.P value >0.05.

Table 3: Distribution of sensory level at 5 min among study groups

SENSORY LEVEL 5 min	HES		RL		Total		p value
	N	%	N	%	N	%	
T10	15	41.7%	16	44.4%	31	43.1%	0.880 (Not Significant)
T8	16	44.4%	14	38.9%	30	41.7%	
T6	5	13.9%	6	16.7%	11	15.3%	
Total	36	100.0%	36	100.0%	72	100.0%	

Graph 3: Distribution of sensory level at 5 min among study groups

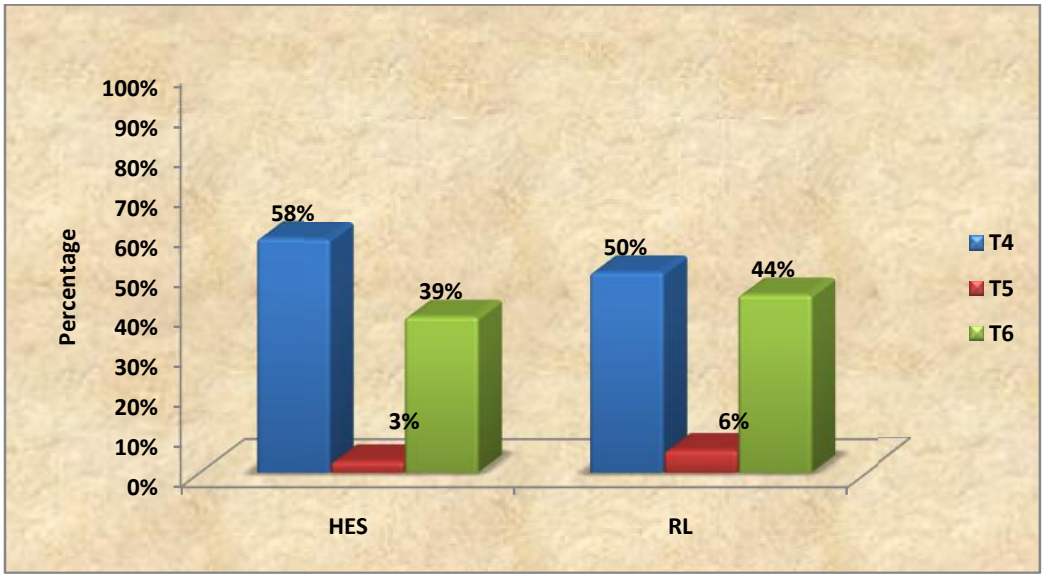


Level of sensory blockade at the end of 5 mins showed no significant difference among both groups.

Table 4: Distribution of Sensory Level at 10 min among study groups

Sensory Level 10 min	HES		RL		Total		p value
	N	%	N	%	N	%	
T4	21	58.3%	18	50.0%	39	54.2%	0.706 (Not Significant)
T5	1	2.8%	2	5.6%	3	4.2%	
T6	14	38.9%	16	44.4%	30	41.7%	
Total	36	100.0%	36	100.0%	72	100.0%	

Graph 4: Distribution of sensory level at 10 min among study groups



Level of sensory blockade after 10 mins showed no significant difference among both the groups.

Table 5:Baseline hemodynamic parameters in both groups

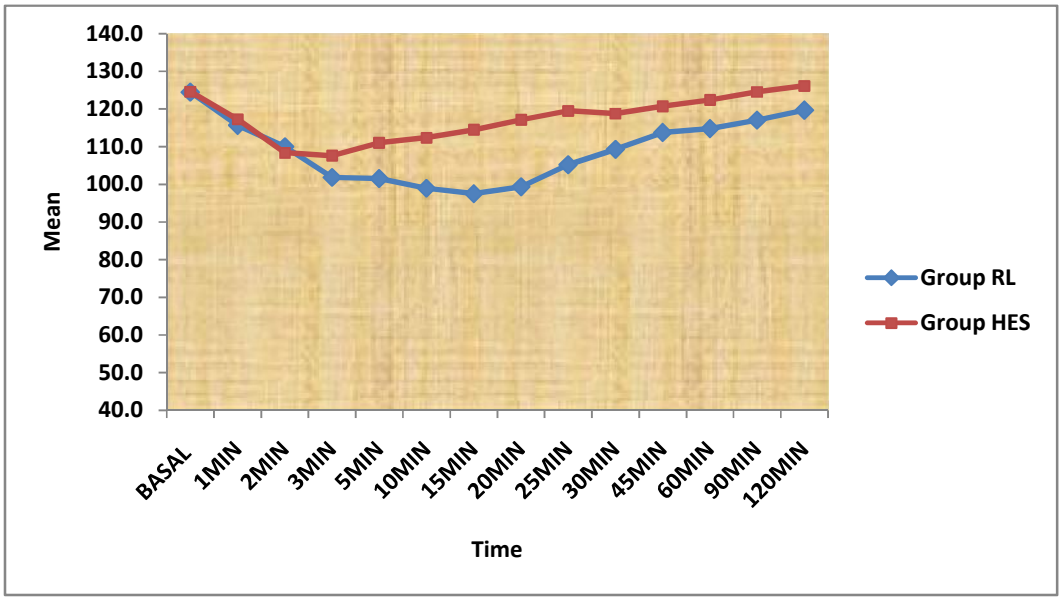
Parameters	Group RL		Group HES		p value	Significance
	Mean	SD	Mean	SD		
BASAL SBP	124.4	8.4	122.8	5.1	0.319	Not Sig
BASAL DBP	82.7	6.3	80.2	9.4	0.190	Not Sig
BASAL MAP	96.4	4.9	94.1	4.1	0.072	Not sig
BASAL HR	93.9	11.2	92.0	8.5	0.416	Not Sig

There is no significant difference in baseline hemodyamic parameters among both groups.

Table 6: Comparison of mean values of SBP between study groups at different time intervals

Parameters	Group RL		Group HES		p value	Significance
	Mean	SD	Mean	SD		
BASAL	124.4	8.4	122.8	5.1	0.319	Not Sig
1MIN	115.6	11.0	117.3	5.2	0.413	Not Sig
2MIN	110.0	11.3	108.4	6.6	0.463	Not Sig
3MIN	101.8	9.9	107.5	5.0	0.003	Significant
5MIN	101.5	10.5	111.0	4.5	<0.001	Significant
10MIN	98.9	8.5	112.4	5.2	<0.001	Significant
15MIN	97.5	7.8	114.4	4.4	<0.001	Significant
20MIN	99.4	8.6	117.1	5.2	<0.001	Significant
25MIN	105.2	7.4	119.5	6.0	<0.001	Significant
30MIN	109.3	8.7	118.8	7.5	<0.001	Significant
45MIN	113.7	7.9	120.7	6.7	<0.001	Significant
60MIN	114.8	7.3	122.3	5.8	<0.001	Significant
90MIN	117.0	7.5	124.6	5.9	<0.001	Significant
120MIN	119.6	7.0	126.1	6.0	<0.001	Significant

Graph 5: Comparison of mean values of SBP between study groups at different time interval



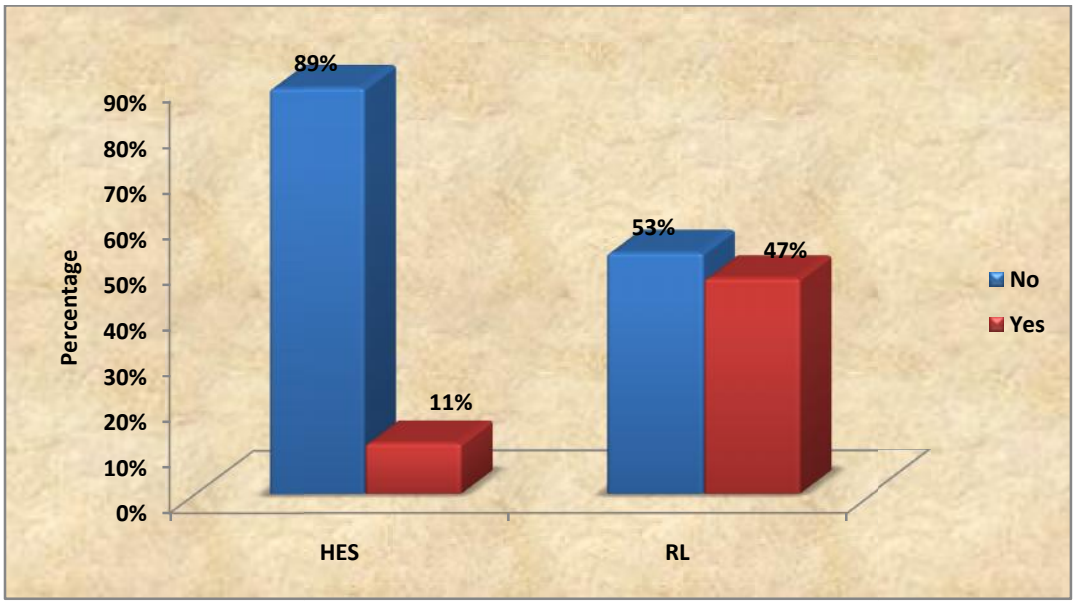
In our study in patients who received RL as preloading fluid the mean systolic blood pressure was 124.4± 8.4 before spinal anesthesia following sub arachnoid block SBP dropped to 101.5±10.5 at 5 mins, 98.9±8.5 after 10 mins, 97.5±7.8 after 15 mins(maximum fall).Then there was a gradual rise in SBP and at the end of 60 mins , mean SBP was 114.8±7.3.

In patients who received HES as preloading fluid the mean SBP was 122.8±5.1 before spinal anesthesia. Following SAB, the mean SBP was 111.0±4.5 at the end of 5 mins,112.4±5.2 at the end of 10 mins,114.4±4.4 at the end of 15 mins. Thereafter, mean SBP steadily increased and was 122.3±5.8 at the end of 60 mins.

Table 7: Distribution of Rescue doses among study groups

Rescue dose	HES		RL		Total		p value
	N	%	N	%	N	%	
No	32	88.9%	19	52.8%	51	70.8%	0.001 (Significant)
Yes	4	11.1%	17	47.2%	21	29.2%	
Total	36	100.0%	36	100.0%	72	100.0%	

Graph 6: Distribution of Rescue dose among study groups



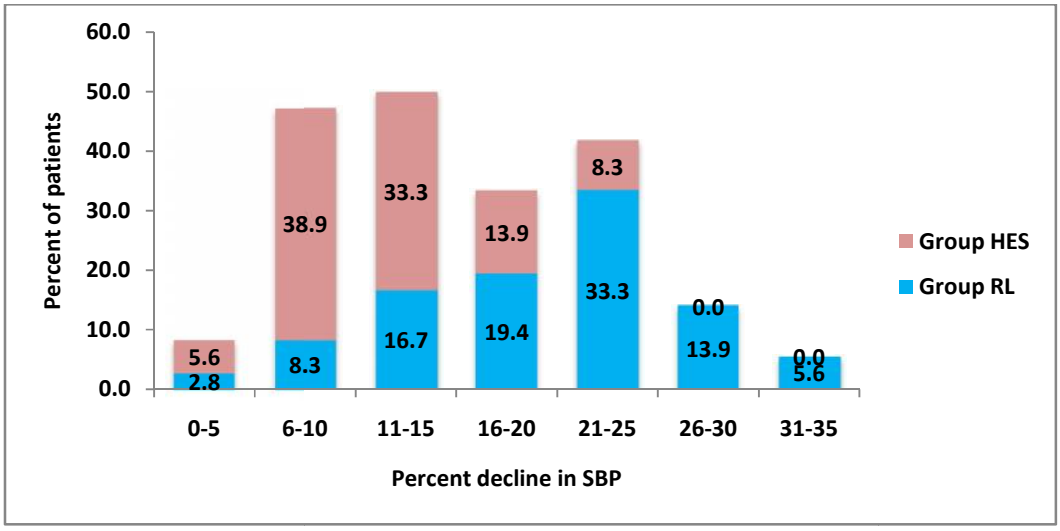
Number of rescue doses required in both the groups was compared and was found to have significant difference(P<0.05).

In RL group, out of 36 patients 17(47%) patients required rescue doses of inj. Mephentermine whereas in HES group out of 36 patients,4(11%) patients required rescue doses.

Table 8: Showing incidence and severity of hypotension in Group RL and Group HES following spinal anaesthesia

Percent decline in SBP	Group RL		Group HES	
	N	%	N	%
0-5	1	2.8	2	5.6
6-10	3	8.3	14	38.9
11-15	6	16.7	12	33.3
16-20	7	19.4	5	13.9
21-25	12	33.3	3	8.3
26-30	5	13.9	0	0.0
31-35	2	5.6	0	0.0
36-40	0	0.0	0	0.0

Graph 7: Showing incidence and severity of hypotension in Group RL and Group HES following spinal anaesthesia

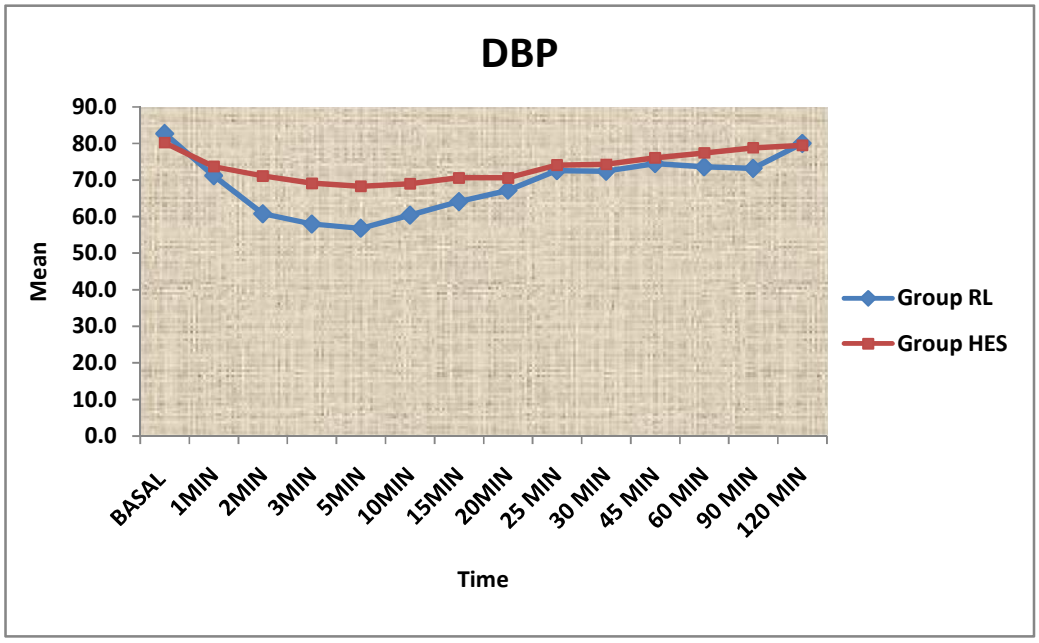


Hypotension (fall in SBP>20%) occurred in 33.3% patients in RL group whereas in HES group only8.3% of patients experienced hypotension.

Table 9: Comparison of mean values of DBP between study groups at different time interval

Parameters	Group RL		Group HES		p value	Significance
	Mean	SD	Mean	SD		
BASAL	82.7	6.3	80.2	9.4	0.190	Not Sig
1MIN	71.2	10.1	73.7	8.4	0.253	Not Sig
2MIN	60.8	11.1	71.1	8.5	<0.001	Significant
3MIN	58.0	8.8	69.1	9.6	<0.001	Significant
5MIN	56.8	7.3	68.3	7.2	<0.001	Significant
10MIN	60.4	5.4	69.0	6.6	<0.001	Significant
15MIN	64.1	7.3	70.6	8.3	0.001	Significant
20MIN	67.2	5.1	70.6	6.9	0.103	Significant
25 MIN	72.6	7.0	74.1	4.6	0.031	Significant
30 MIN	72.4	4.8	74.3	6.4	0.043	Significant
45 MIN	74.5	2.0	76.1	4.7	0.038	Significant
60 MIN	73.6	7.9	77.4	5.6	0.023	Significant
90 MIN	73.2	6.0	78.8	3.9	<0.001	Significant
120 MIN	80.0	8.0	79.5	4.1	0.711	Not Sig

Graph 8: Comparison of mean values of DBP between study groups at different time interval



In patients who received RL as preloading fluid, the baseline mean DBP was 82.7±6.3. Following SAB it was 58.0±8.8 at the end of 3 mins then it steadily increased to 73.6±7.6 at the end of 60 mins.

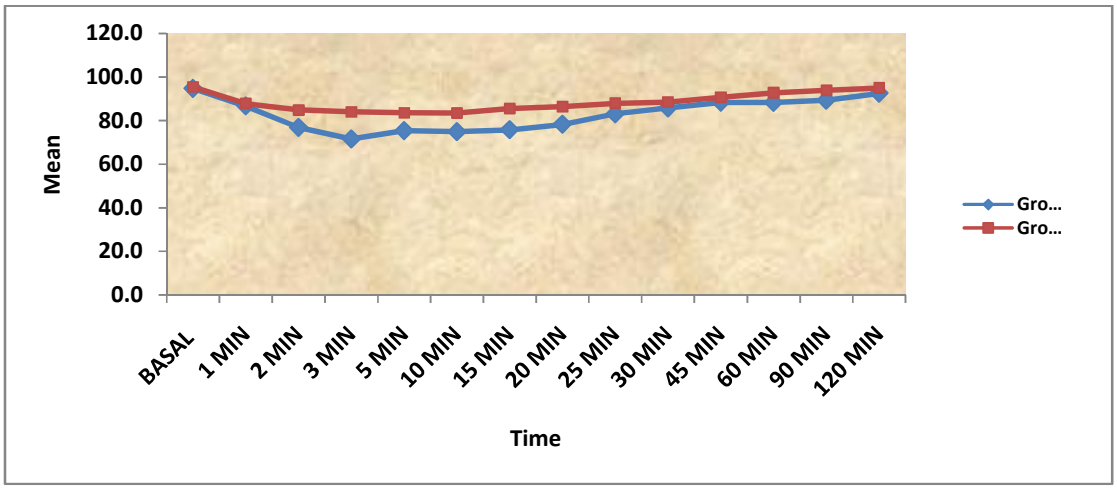
In patients of HES group baseline DBP was 80.2±9.4.Following SAB, DBP was 69.1±9.6 at the end of 3 mins and 69.0±6.6 at the end of 10 mins. Thereafter there was a steady increase in DBP to 77.4±5.6 at the end of 60 mins.

There was significant decrease in mean DBP among both the groups.

Table 10: Comparison of mean values of MAP between study groups at different time interval

Parameters	Group RL		Group HES		p value	Significance
	Mean	SD	Mean	SD		
BASAL	96.4	4.9	94.1	4.1	0.072	Not Sign
1 MIN	86.7	10.1	87.8	3.9	0.539	Not Sign
2 MIN	76.8	8.8	84.8	5.4	<0.001	Significant
3 MIN	71.5	5.6	84.0	6.2	<0.001	Significant
5 MIN	75.3	7.0	83.5	5.6	<0.001	Significant
10 MIN	74.8	6.1	83.4	5.8	<0.001	Significant
15 MIN	75.8	5.7	85.5	4.0	<0.001	Significant
20 MIN	78.3	5.6	86.4	3.2	<0.001	Significant
25 MIN	83.0	4.9	87.9	3.0	<0.001	Significant
30 MIN	85.8	5.0	88.5	2.9	0.007	Significant
45 MIN	88.4	5.2	90.6	3.1	0.031	Significant
60 MIN	88.3	5.3	92.7	2.3	<0.001	Significant
90 MIN	89.3	4.9	93.9	2.5	<0.001	Significant

Graph 9: Comparison of mean values of MAP between study groups at different time interval



In patients who received RL as preloading fluid baseline mean MAP was 96.4±4.9.Following SAB it was 71.5±5.6 at the end of 3 mins (maximum fall) and steadily increased thereafter.It was 88.3±5.3 at the end of 60 mins.

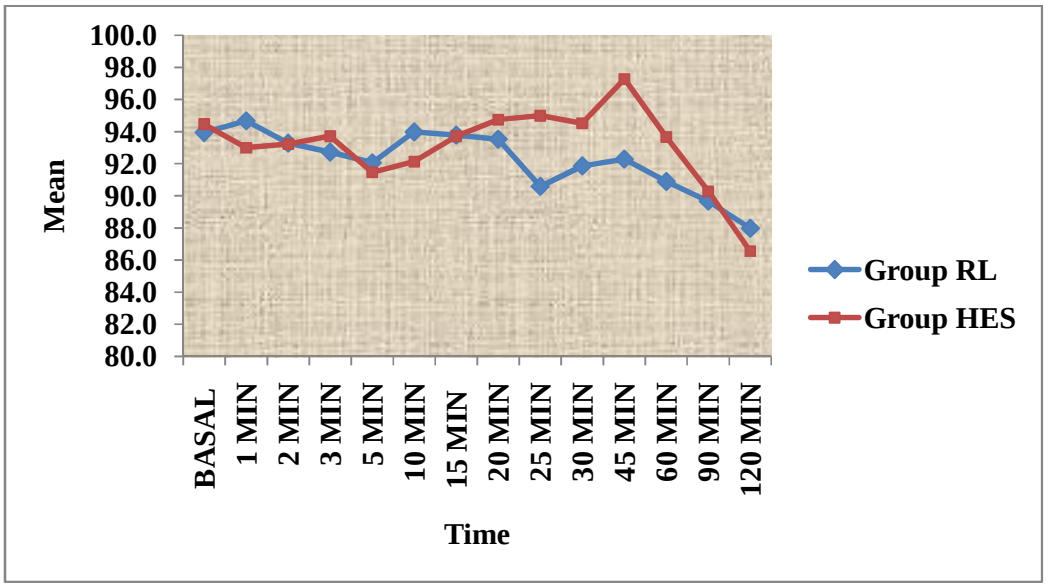
In patients of HES group baseline mean MAP was 94.1±4.1.Following SAB it was 84.0±6.2 at the end of 3 mins and then steadily increased to 92.7±2.3 at the end of 60 mins.

There was significant difference in decrease in MAP among both the groups($P<0.05$).

Table 11: Comparison of mean values of HR between study groups at different time interval

Parameters	Group RL		Group HES		p value	Significance
	Mean	SD	Mean	SD		
BASAL	93.9	11.2	92.0	8.5	0.416	Not Sig
1 MIN	94.7	11.7	93.0	8.7	0.495	Not Sig
2 MIN	93.3	11.1	93.2	9.5	0.982	Not Sig
3 MIN	92.7	13.1	93.7	8.0	0.698	Not Sig
5 MIN	92.1	14.0	91.5	6.7	0.822	Not Sig
10 MIN	94.0	13.2	92.1	7.3	0.466	Not Sig
15 MIN	93.8	12.4	93.7	6.3	0.981	Not Sig
20 MIN	93.5	12.6	94.8	7.0	0.613	Not Sig
25 MIN	90.6	11.9	95.0	7.0	0.059	Not Sig
30 MIN	91.9	12.7	94.5	7.2	0.276	Not Sig
45 MIN	92.3	11.4	97.3	8.0	0.034	Significant
60 MIN	90.9	9.5	93.7	6.6	0.154	Not Sig
90 MIN	89.7	8.5	90.3	2.6	0.681	Not Sig
120 MIN	88.0	7.5	86.6	3.5	0.306	Not Sig

Graph 10: Comparison of mean values of HR between study groups at different time interval



In RL group, baseline mean heart rate was 93.9±11.2.Following SAB it was 92.1±14 at the end of 5 mins, 90.9±9.5 at the end of 60 mins.

In HES group baseline mean heart rate was92.0±8.5.Following SAB it was 91.5±6.7 at the end of 5 mins,93.7±6.6 at the end of 60 mins.

There was no significant heart rate changes in both the groups.HR in both the groups was maintained close to baseline value.

DISCUSSION

For caesarean section, spinal anesthesia is the preferred regional anesthesia. Till date arterial hypotension has remained the most dreaded complication of spinal anesthesia, which needs special attention[61]. Prior to spinal anesthesia preloading is recommended to reduce the incidence of hypotension.

Hypotension develops as the result of various factors such as;

- The level at which the block was performed
- The level of anesthesia
- Condition of the patient and hemodynamic status.

Since BP can be described as product of cardiac output and total peripheral vascular resistance, the usual management has been directed towards one or the other of these two factors.

The use of peripheral vasoconstrictors to increase the total peripheral resistance or the use of drugs with inotropic or chronotropic cardiac action to augment the output of the heart. Another method of increasing cardiac output is to augment the venous return by the temporary expansion of blood volume[62].

Many authorities suggest that crystalloid preloading is not effective in reducing the incidence of hypotension after spinal anesthesia[63].As much as 75% of the infused volume diffuses into the interstitial spaces, and its efficacy in expanding plasma volume is only transient. Large volumes of crystalloid can also decrease the oxygen-carrying capacity and is associated with the increased risk of pulmonary and peripheral edema. It has been demonstrated that colloid may be superior for volume preloadingby sustaining an increased blood volume and thus cardiac output due to a longer intravascular half-life.

Our study was done on 72 parturients for caesarean section under spinal anesthesia, divided randomly into two groups of 36 patients each. Group RL preloaded with 20ml/kg of ringer lactate solution and group HES preloaded with 10ml/kg of 6%HES 20 min prior to SAB.

Our study has shown that preloading with 6%HES is more effective for maintenance of maternal blood pressure close to the baseline level than crystalloid preloading. Also, the incidence of hypotension has been found to be low with hestar group.

In our study there was no significant difference between the two groups with respect to maternal demographics. Table 2 shows distribution of 72 patients with respect to their age, body weight and height. Also ,there was no significant difference in baseline hemodynamic parameters and the level of sensory blockade after SA in both the groups.

In our study the maximum fall in mean systolic blood pressure following SAB was observed in the first 20 min. Maximum fall in mean SBP in group RL was 97.5±7.8 vs 107.5±5 in HES group. There was a significant difference in the mean SBP among both the groups. In the next 30 mins there was a steady increase in the SBP in both the groups.

There was a significant difference in the incidence of hypotension among both the groups. The incidence of hypotension in RL group was 33.3%(12 out of 36) vs 8.3%(3 out of 36) in HES group. Number of rescue doses required in both the groups was compared and was found to have significant difference ($P<0.05$). In RL group, out of 36 patients 17(47%) patients required rescue doses of inj.Mephentermine whereas in HES group out of 36 patients,4(11%) patients required rescue doses.

Siddik SM et al in 2000[46], compared the preloading effect of 500 ml hydroxyethylstarch (HES) 10% with 1L Lactated Ringer's solution (LR). The incidence of hypotension was higher in the LR than in HES group (80% vs 40%). Mean minimum systolic blood pressure was lower in the LR than in the HES group (86.1 +/- 12.7 mm Hg vs 99.6 +/- 9.7 mm Hg $P < 0.05$). Systolic blood pressure < 90 mmHg occurred in two of 20 patients (10%) who received HES vs 11 of 20 patients (55%) who received LR ($P < 0.05$). More doses of ephedrine were required to treat hypotension in the LR than in the HES group (35.3 +/- 18.4 mg vs 10.6 +/- 8.6 mg; $P < 0.05$).

The results of this study are comparable to that of our study where the maximum fall in mean SBP in group RL was 97.5±7.8 vs 107.5±5 in HES.Number of rescue doses of inj.Mephentermine required in RL group,17 out of 36 patients (47%) whereas in HES group 4 out of 36 (11%) patients required rescue doses.

Mitra T et al in 2014[54], compared the hemodynamic stability after volume preloading with either Ringer's lactate (RL) or tetrastarchhydroxyethyl starch (HES) or succinylated gelatin (SG) in the patients undergoing cesarean section under spinal anesthesia. The fall in systolic blood pressure (SBP) (<100 mm Hg) noted among 5 (15.63%), 12 (37.5%) and 14 (43.75%) parturients in groups HES, SG, RL respectively. Vasopressor (phenylephrine) was used to treat hypotension when SBP <90 mm Hg. The results of our study are close to these observations where the incidence of hypotension in RL group was 33.3%(12 out of 36) vs 8.3%(3 out of 36) in HES group.

Matsota P et al in 2015[59], conducted a study on the effect of 0.5 L 6% hydroxyethyl starch 130/0.42 versus 1L Ringer's lactate preload on the hemodynamic status of parturients undergoing spinal anesthesia for elective cesarean delivery using

arterial pulse contour analysis. The incidence of hypotension was 73.3% in Group RL and 46.7% in Group HES. HES compared to RL preload was associated with a less usage of ephedrine and phenylephrine . It was concluded that preloading with 0.5L HES 130/0.42 produced more stable hemodynamics compared to 1L RL solution in obstetric patients.

Upadya M et al in 2016[60], compared six percent hetastarch versus lactated Ringer's solution for preloading before spinal anesthesia for cesarean section patients.Results of the study showed the incidence of hypotension to be 28% in the hetastarch group and 80% in the RL group. Rescue ephedrine requirements for the treatment of hypotension were significantly less in patients who were preloaded with 6% hetastarch prior to cesarean section.The results of our study were comparable with this study.

In our study we did not come across any allergic reaction to hydroxyethyl starch. Although in parturients nausea always accompanies hypotension, the incidence of nausea and vomiting in this study was very low in both the groups.

CONCLUSION

Preloading the pregnant patients who received spinal anesthesia for elective caesarean section with either Ringer lactate solution 20ml/kg or 6% hydroxyethyl starch solution 10ml/kg showed, colloid to be more effective in prevention of hypotension than crystalloid. Six percent hydroxyethyl starch offset the hypotension and hypovolemia more effectively than lactated Ringers solution in patients scheduled for the elective cesarean section under spinal anesthesia. It is also relatively free of side effects. However, we also conclude that the incidence of hypotension was only reduced but not completely eliminated in this study

Hence, we conclude that the routine use of colloids-6% hydroxyl ethyl starch as the choice for preloading prior to spinal anesthesia in order to maintain the hemodynamic stability of the parturient perioperatively.

SUMMARY

Hypotension after spinal anaesthesia for caesarean section remains a common and potentially serious complication. To reduce the incidence and severity of hypotension various maneuvers have been used. One among those is preloading the patients with iv fluids either crystalloid or colloid solutions.

Our study was designed to compare the efficacy of ringer lactate solution and 6% hydroxyethyl starch solution as preloading fluid for prevention of hypotension following spinal anaesthesia in parturients undergoing LSCS.

Our objectives in this study were to observe the incidence of hypotension in both the groups and the number of rescue doses of vasopressor required for correction of hypotension in both the groups.

In this study 72 nonlabouring ASA class 1 women undergoing elective caesarean section were randomly divided into two groups of 36 patients eachby using a computer generated randomization table.

Group RL - Preloaded with Ringer lactate solution 20ml/kg.

Group HES - Preloaded with 6%Hydroxyethyl starch solution 10ml/kg.

Both these solutions were infused over a period of 20 min before performance of subarachnoid block. After preloading all patients received ringer lactate for fluid maintenance. Under aspetic conditions spinal anesthesia given with 2ml of 0.5% bupivacaine with 25G Quincke's spinal needle in 3rd or 4th lumbar intervertebral space.

Immediately after injection, blood pressure,mean arterial pressure and heart rate were recorded at an interval of 1,2,3,5,10,15,20,25,30,45,60,90 and 120min.

Hypotension was (decrease in SBP >20%) managed with injMephentermine 3mg bolus at 1min interval until BP reached normal level. Bradycardia was treated with inj.Atropine 0.6mg.

Maximum fall in mean SBP in group RL was 97.5±7.8 vs 107.5±5 in HES group. The incidence of hypotension in RL group was 33.3%(12 out of 36) vs 8.3%(3 out of 36) in HES group. Number of rescue doses required in both the groups was compared and was found to havesignificant difference ($P<0.05$). In RL group,out of 36 patients 17(47%) patients required rescue doses of inj.Mephentermine whereas in HES group out of 36 patients,4(11%) patients required rescue doses.

In our study, we found that hydroxyethyl starch is more effective, than lactated Ringer's solution in prevention of hypotension in patients undergoing elective LSCS.

Hence, we conclude the routine use of 6% hydroxylethyl starch as preloading fluid prior to spinal anesthesia in order to maintain the hemodynamic stability of the parturient perioperatively.

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ANNEXURE-I

ETHICAL CLEARANCE CERTIFICATE

B.L.D.E. UNIVERSITY'S
SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR-586 103
INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 22-11-2014 at 3-30pm to scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected & revised version synopsis of the Thesis has been accorded Ethical Clearance.

Title comparative study of ringer's lactate & 6% hydroxyethylstarch as preloading fluid for prevention of hypotension in patients undergoing elective caesarean section under spinal anaesthesia - A randomized clinical trail.

Name of P.G. student Dr. Yasaswani Teja B.
Dept of Anaesthesiology

Name of Guide/Co-investigator Dr Vidya A. Patil.
professor of Anaesthesiology.

for

DR.TEJASWINI. VALLABHA
CHAIRMAN
INSTITUTIONAL ETHICAL COMMITTEE
BLDEU'S, SHRI.B.M.PATIL
MEDICAL COLLEGE, BIJAPUR.

Following documents were placed before E.C. for Scrutinization
1) Copy of Synopsis/Research project.
2) Copy of informed consent form
3) Any other relevant documents.

ANNEXURE-II

INFORMED CONSENT FORM

B.L.D.E.U.'s SHRI B.M. PATIL MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTRE, VIJAYAPUR – 586103, KARNATAKA

TITLE OF THE PROJECT : "A COMPARATIVE STUDY OF RINGER LACTATE SOLUTION AND 6% HYDROXYETHYL STARCH SOLUTION AS PRELOADING FLUID FOR PREVENTION OF HYPOTENSION IN PATIENTS UNDERGOING ELECTIVE CAESAREAN SECTION UNDER SPINAL ANAESTHESIA – A RANDOMISED CLINICAL TRIAL"

PRINCIPAL INVESTIGATOR: Dr YASASWANI TEJA B.
Department of Anaesthesiology
Email: yasaswani999@gmail.com

PG GUIDE : Dr. VIDYA PATIL
Prof ,Dept of Anaesthesiology
B.L.D.E. University's Shri B.M. Patil Medical College Hospital & Research Centre,

PURPOSE OF RESEARCH:

I have been informed that this study is **"**A COMPARATIVE STUDY OF RINGER LACTATE SOLUTION AND 6% HYDROXYETHYL STARCH SOLUTION AS PRELOADING FLUID FOR PREVENTION OF HYPOTENSION IN PATIENTS UNDERGOING ELECTIVE CAESAREAN SECTION UNDER SPINAL ANAESTHESIA– A RANDOMISED CLINICAL TRIAL**"**

I have been explained about the reason for doing this study and selecting me/my ward as a subject for this study. I have also been given free choice for either being included or not in the study.

PROCEDURE:

I understand that I will be doing **"**A COMPARATIVE STUDY OF RINGER LACTATE SOLUTION AND 6% HYDROXYETHYL STARCH SOLUTION AS PRELOADING FLUID FOR PREVENTION OF HYPOTENSION IN PATIENTS UNDERGOING ELECTIVE CAESAREAN SECTION UNDER SPINAL ANAESTHESIA – A RANDOMISED CLINICAL TRIAL**"**

RISKS AND DISCOMFORTS:

I understand that I/my ward may experience some pain while giving spinal anesthesia and I understand that necessary measures will be taken to reduce these complications as and when they arise.

BENEFITS:

I understand that me/my wards participation in this study will help in finding out **"** ACOMPARATIVE STUDY OF RINGER'S LACTATE SOLUTION AND 6% HETASTARCH SOLUTION ASPRELOADING FLUID FOR PREVENTION OF HYPOTENSION FOLLOWING SPINAL ANAESTHESIA**"**

CONFIDENTIALITY:

I understand that medical information produced by this study will become a part of this Hospital records and will be subjected to the confidentiality and privacy regulation of this hospital. Information of a sensitive, personal nature will not be a part of the medical records, but will be stored in the investigator's research file and identified only by a code number. The code key connecting name to numbers will be kept in a separate secure location.

If the data are used for publication in the medical literature or for teaching purpose, no names will be used and other identifiers such as photographs and audio or video tapes will be used only with my special written permission. I understand that I may see the photograph and videotapes and hear audiotapes before giving this permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time. Dr.Yasaswani is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of this study, which might influence my continued participation.

If during this study, or later, I wish to discuss my participation in or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me.

And that a copy of this consent form will be given to me for careful reading.

REFUSAL OR WITHDRAWL OF PARTICIPATION:

I understand that my participation is voluntary and I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital.

I also understand that Dr.Yasaswani will terminate my participation in this study at any time after she has explained the reasons for doing so and has helped arrange for my continued care by my own physician or therapist, if this is appropriate

INJURY STATEMENT:

I understand that in the unlikely event of injury to me/my ward, resulting directly to my participation in this study, if such injury were reported promptly, then medical treatment would be available to me, but no further compensation will be provided.

I understand that by my agreement to participate in this study, I am not waiving any of my legal rights.

I have explained to _____ the purpose of this research, the procedures required and the possible risks and benefits, to the best of my ability in patient's own language.

Date: Dr. Vidyapatil Dr.YasaswaniTeja

(Guide) (Investigator)

STUDY SUBJECT CONSENT STATEMENT

I confirm that Dr. Yasaswaniteja B. has explained to me the purpose of this research, the study procedure that I will undergo and the possible discomforts and benefits that I may experience, in my own language.

I have been explained all the above in detail in my own language and I understand the same. Therefore I agree to give my consent to participate as a subject in this research project.

_____ _____

(Participant) Date

_____ _____

(Witness to above signature) Date

ANNEXURE-III

PROFORMA

" A COMPARATIVE STUDY OF RINGER'S LACTATE SOLUTION AND 6% HYDROXYETHYL STARCH SOLUTION AS PRELOADING FLUID FOR PREVENTION OF HYPOTENSION IN PATIENTS UNDERGOING ELECTIVE CAESAREAN SECTION FOLLOWING SPINAL ANAESTHESIA -A RANDOMIZED CLINICAL TRIAL".

Name Serial no.

Age Date of admission

Sex Date of surgery

Weight IP No

Height Hospital

Occupation

Chief complaints:

Past History

Any H/o HTN/DM/IHD/CVA

Any H/O asthama/drug allergy/epilepsy/bleeding disorder

Any drug theraphy

Any H/o previous anaesthesia for any surgery

CLINICAL EXAMINATION:

General physical examination:

Pallor/icterus/clubbing/lymphadenopathy/oedema

PR

BP

RR

Temp

Teeth

Jaw movement

Airway assessment

Spine

Systemic examination:

a) **Cardiovascular system:**
b) **Respiratory system**
c) **Central nervous system:**
d) **Obstetric examination:**

ASA GRADE-

CLINICAL DIAGNOSIS:

INVESTIGATIONS:

Complete blood picture:

Bleeding time and clotting time:

Blood grouping/Rh-typing:

Random blood sugar :

Complete urine examination:

RFT: **Blood urea**

Serumcreatinin

Pre medication:

Pre loading fluid:

Drugs used during spinal anaesthesia:

Surgical time:

Supplementary drugs given:

Maintenance fluids during surgery:

Adverse effects(if any):

Time in min	Pulse rate	Systolic BP	Diastolic BP	MAP	No of rescue doses
Baseline					
After 1min					
2min					
3 min					
5min					
10 min					
15min					
20 min					
25 min					
30 min					
45 min					
60 min					
75 min					
90 min					
120 min					

KEY TO MASTER CHART

Ip no –In patient number

SBP- Systolic blood pressure

DBP- Diastolic blood pressure

MAP- Mean arterial pressure

HR-Heart rate

No –Number

M3- InjectionMephentermine 3mg