COMPARISON OF INTRAVENOUS TRANEXAMIC ACID VERSUS SUBLINGUAL MISOPROSTOL IN REDUCING BLOOD LOSS IN PATIENTS UNDERGOING CAESAREAN SECTION.

By

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Under the Guidance of

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Dr. DEEKSHA RAO.M

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

GLOSSARY	ABBREVIATIONS
AUC	Area under the curve
APGAR	Appearance, Pulse, Grimace, Activity, and Respiration
BMI	Body mass index
CNS	Central nervous system
CS	Caesarean section
Ep2/Ep3	E-series prostanoid receptors
FDA	Food and Drug Administration
HB	Hemoglobin
IQR	Interquartile range
LSCS	Lower segment Caesarean section
NSAIDs	Nonsteroidal anti-inflammatory drugs
PG E1	Prostaglandin E1
PPH	Postpartum hemorrhage
SPO_2	Oxygen saturation
TXA	Tranexamic acid
WHO	World health organization

COMPARISON OF INTRAVENOUS TRANEXAMIC ACID VERSUS SUBLINGUAL MISOPROSTOL IN REDUCING BLOOD LOSS IN PATIENTS UNDERGOING CAESAREAN SECTION.

ABSTRACT

BACKGROUND: Caesarean section is the most often performed major surgeries on women all over the world. The most common caesarean section consequences are primary or secondary postpartum haemorrhage. It has the potential to raise maternal mortality and morbidity rates.

AIM: To compare the effectiveness of intravenous tranexamic acid (TXA) and sublingual misoprostol in reducing blood loss in patients undergoing caesarean section.

MATERIALS & METHODS: Conducted a randomized prospective control trial from January 2020 to June 2021. A total of 118 participants were enrolled in the study.

RESULTS: The mean age identified in the TXA and misoprostol group were 24.12 ± 3.3 and 23.81 ± 3.64 respectively. The mean of mops count in the misoprostol and TXA group were noted as 4.73 ± 1.27 and 3.2 ± 1.45 respectively. Around 8.47% of the participants in the misoprostol group required uterotonics, whereas, 15.25% in the TXA group required uterotonics. The pre-operative and post-operative haemoglobin in the misoprostol group were identified as 11.67 ± 1.37 and 10.78 ± 1.12 whereas, it was identified as 11.76 ± 1.43 and 11.17 ± 1.4 in the TXA group. The common side effects identified in the misoprostol group was chills, vomiting and fever with 47.46%, 13.56% and 11.86% while, it was 11.86%, 5.08% and 3.39% in the TXA group.

CONCLUSION: The present study concluded that the use of tranexamic acid significantly reduced the intraoperative and perioperative blood loss much better than misoprostol during caesarean section. Also tranexamic acid is better agent and can be administered routinely in patients undergoing caesarean section, as side effects of tranexamic acid were lesser than that of misoprostol. Hence tranexamic acid can be administered routinely in patients undergoing caesarean section.

INTRODUCTION

INTRODUCTION:

Cesarean section can be defined "as a fetal delivery through an open abdominal incision (laparotomy) and an incision in the uterus (hysterotomy) after the period of viability".[1] In comparison to vaginal delivery, the rising rate of caesarean section is a source of fear for health of the general public and obstetricians around the world, as it increases financial burden and puts the maternal health at danger.

Fetal distress, previous history of cesarean section, non-progress of labor, oligohydramnios, malpresentation, cephalo pelvic disorders and pre-eclampsia are the common indications of cesarean section.[2] It causes approximately 35.9 deaths per 100,000 live births, whereas vaginal delivery is responsible for only 9.2 deaths per 100,000 live births.[3]

The use of continuous electronic fetal monitoring for early detection of fetal distress and malpresentation is the leading reason of rising caesarean rates in developed countries. At the same, the cause is unclear in developing countries.[4,5] Caesarean section is linked to serious maternal complications such obstetric hemorrhage, hysterectomy, anemia, blood transfusion, and infection. Obstetric hemorrhage is the main reason for maternal mortality and morbidities.[6,7] Newborn sepsis, neonatal death, stillbirth, perinatal hypoxia, poor APGAR score, and preterm are the neonatal outcomes identified in caesarean section.[3]

Hemorrhages reported 13.4% of maternal deaths in developed countries.[8] The incidence of PPH is 4.84 percent for elective Caesarean section and 6.75 percent for emergency Caesarean section. Postpartum hemorrhage is recorded in 1-5 percent of deliveries in both industrialized and underdeveloped countries.[9]

Following birth, less than 500 mL of blood loss is regarded physiologically acceptable, and anything more than that is referred to as postpartum hemorrhage (PPH).[10] Primary PPH is

defined as blood loss of more than 500 mL in vaginal delivery and 1500 mL during Caesarean section within the first 24 hours of delivery. Excessive vaginal blood loss or copious local discharge that occurs at least 24 hours after the end of the third stage of labour is the secondary PPH.[11] Since the lower uterine segment is not well developed in elective caesarean sections, bleeding will be more than in emergency caesarean sections where the lower uterine segment is well formed.

The risk factors for postpartum hemorrhage have been identified as a third stage that lasts for a long time, multigravida, episiotomy, fetal macrosomia, and a history of postpartum hemorrhage. Postpartum hemorrhage is related with problems such as orthostatic hypotension, anemia, and tiredness. In the most severe cases, hemorrhagic shock can also cause anterior pituitary ischemia, resulting in lactation failure.[12]

The medication oxytocin is the first-line treatment for postpartum bleeding. The advantages of oxytocin identified at the vaginal birth can apply to the cesarean section also. Because oxytocin is light and heat sensitive, it must be kept in the refrigerator. Its use in poorer countries is restricted.[13,14]

Another frequent strategy is to employ anti fibrinolytic drugs like TXA, prostaglandin analogues like misoprostol, carboprost and ergot alkaloids such as methergine as a preventative measure to minimize perioperative hemorrhage.

NEED OF THE STUDY:

Cesarean delivery is becoming more common, which can lead to postpartum hemorrhage because the average blood loss during caesarean section is double that of vaginal delivery.[15] In women with pre-eclampsia, prolonged labor, or heart disease, oxytocin is not the best medication for preventing PPH. Furthermore, it has been found that 10 to 42 percent of pregnant women who receive oxytocin require additional agents such as ergot alkaloids and prostaglandins.[16] The purpose of this study was to assess the safety and efficacy of intravenous tranexamic acid against sublingual misoprostol in minimizing blood loss in caesarean section patients.

AIMS & OBJECTIVES

AIMS AND OBJECTIVES:

1. To assess the effectiveness of intravenous tranexamic acid in reducing blood loss in patients undergoing caesarean section.
2. To evaluate the effectiveness of sublingual misoprostol in reducing blood loss in patients undergoing caesarean section.
3. To compare the effectiveness of the above drugs by assessing intraoperative and postoperative blood loss.

REVIEW OF LITERATURE

REVIEW OF LITERATURE:

1.Caesarean section:

Definition and classification:

Cesarean section is a "surgical operation used to deliver a fetus through the abdominal route after the viability phase". [2]

Table 1: Robson's classification of cesarean section.[17,18]

Groups	Clinical characteristics
1	Nulliparous, singleton, cephalic, ≥37 weeks, spontaneous labor
2	Nulliparous, singleton, cephalic, ≥37 weeks, induced labor or cesarean section before labor 2a – Nulliparous, singleton, cephalic, ≥37 weeks gestation, induced labour 2b - Nulliparous, singleton, cephalic, ≥37 weeks gestation, caesarean section before labour
3	Multiparous (excluding previous cesarean section), singleton, cephalic, ≥37 weeks, spontaneous labor
4	Multiparous without previous cesarean section, singleton, cephalic, ≥37 weeks, induced labor or cesarean section before labor 4a – Multiparous without a previous uterine scar, with singleton, cephalic pregnancy, ≥ 37 weeks gestation, induced labour 4b - Multiparous without a previous uterine scar, with singleton, cephalic pregnancy, ≥ 37 weeks gestation, caesarean section before labour
5	Multiparous with prior cesarean section, singleton, cephalic, ≥37 weeks
6	All nulliparous breeches
7	All multiparous breeches (including previous cesarean section)
8	All multiple pregnancies (including previous cesarean section)
9	All pregnancies with abnormal lie (including those previous cesarean sections)
10	All Singleton, cephalic, ≤36 weeks (including previous cesarean section)

Table 2: "Lucas classification based on the urgency of cesarean section"[18]

Category	Definitions
Emergency	Immediate threat to life of women or fetus
Urgent	Maternal or fetal compromise which is not immediately life-threatening
Scheduled	Needing early delivery but no maternal or fetal compromise
Elective	At a time to suit the women and maternity team

Types of Caesarean Section:

According to site of incision

a. Classical caesarean section
b. Lower Segment caesarean section
    i. Low transverse
    ii. Low vertical
    iii. Cutting of constriction ring

According to number of sections

a. Primary caesarean section
b. Repeat caesarean section

According to opening of the peritoneal cavity

a. Transperitoneal – peritoneal cavity is opened before incising the uterus
b. Extraperitoneal – lower uterine segment is reached either inferiorly or laterally by reflecting the Utero-vesical fold of peritoneum, indicated in case of uterine infection or chorioamnionitis

Epidemiology

Cesarean section births accounted for 21.1 percent of all births worldwide in 2015.[19] Every year, 20 million caesarean sections are performed around the world. From 2003 to 2011, the

rate of caesarean section per live delivery jumped from 21.2 percent to 48 percent.[20] The cesarean rate is identified as 21% in developed countries.[21]

Increased incidence could be because of:

1. High forceps and challenging mid forceps procedures are replaced with caesarean sections.
2. Increased breech presentation caesarean section deliveries
3. Destructive operations are replaced by caesarean sections.
4. Caesarean section has a lower morbidity and mortality rate, which supports its use.
5. More repeat caesarean sections because of more primary caesarean sections

Indications

Maternal indications:

a. Contracted pelvis
b. Cephalo Pelvic Disproportion
c. Failed progress of labour
d. Antepartum haemorrhage
e. Infection
f. Pelvic tumour, especially if impacted in the Pelvis
g. Carcinoma Cervix
h. Abnormal uterine action
i. Previous uterine scar – hysterotomy or metroplasty
j. Previous successful repair of Vesico Vaginal Fistula
k. Maternal request
l. Repeated caesarean section
m. Classical section

n. History of puerperal infection after previous section

o. Suspected weak scar

p. HSG or Hysteroscopy revealed defective scar

q. Vaginal bleeding

r. Associated conditions as Ante Partum Haemorrhage or Malpresentation

s. Marked tenderness over the scar during current labour

Foetal indications:

a. Malpresentation or Malposition of the foetus

b. Bad Obstetric history

c. Cord Prolapse

d. Foetal Macrosomia

e. Higher order multiple pregnancies

f. Preterm births

g. Foetal distress

h. Precious baby

Contraindications:

Dead foetus except in

a. Extreme degree of pelvic contraction

b. Neglected shoulder

c. Severe accidental haemorrhage

d. DIC

e. Extensive scar or pyogenic infection

Complications:

Maternal complications

a. Complications of anesthesia
b. Hemorrhage
c. Injury to the nearby structure
d. Infections
e. Deep venous thrombosis
f. Abnormal placentation
g. Infertility issues

Fetal complications:

a. Preterm delivery
b. Respiratory distress syndrome
c. Delayed initiation of breastfeeding
d. Childhood allergy
e. Childhood obesity

a. Blood loss in Cesarean section:

Following birth, loss of 500 mL blood is regarded physiologically acceptable, and more than that is referred to as postpartum haemorrhage.[10] During vaginal delivery, if there is a blood loss of more than 500 mL and more than 1500 mL with caesarean section is taken as the cut off value. The two types of postpartum bleeding are primary and secondary.[22] The prevalence of primary type is 5% of all deliveries.[10] The secondary PPH is defined as excessive vaginal blood loss that occurs at least 24 hours after the completion of the third stage of labour.[11]

Epidemiology

The most common reason for maternal morbidity and mortality is obstetric hemorrhage. “In the year 2000, 529,000 maternal fatalities were reported around the world. The majority of the deaths happened in countries with minimal resources. In developed regions, a woman's lifetime chance of maternal death is 1 in 2800, whereas in developing regions, it is 1 in 61. In Africa and Asia, hemorrhage is the greatest cause of maternal death, accounting for 33.9 percent and 30.8 percent, respectively”.[23] In affluent countries, hemorrhage was responsible for 13.4% of maternal fatalities.[8] Postpartum hemorrhage is recorded in 1-5 percent of deliveries in both industrialized and underdeveloped countries.[9]

Etiology, risk factors, focus on postpartum hemorrhage

The most common reasons for postpartum hemorrhage include uterine atony, vaginal hematoma, cervical or vaginal tear, adherent placenta, uterine angle extension, and retained placenta. Antepartum hemorrhage, accelerated labor, chorioamnionitis, fetal macrosomia, maternal anemia, maternal obesity, multifetal gestation, prolonged labor, preeclampsia, and primiparity have all been found as risk factors for postpartum hemorrhage.[24]

Pathophysiology

Uterine atony is caused by high maternal parity, chorioamnionitis, prolonged oxytocin administration, general anaesthesia, and other circumstances. Multiple gestation, polyhydramnios, foetal macrosomia, and uterine fibroids are among conditions that can cause uterine distention. Excessive umbilical cord traction, a short umbilical cord, and placental fundal attachment are all risk factors for uterine inversion. Genital tract injuries can be caused by surgical vaginal delivery or a hasty birth.

A retained placenta and improper placentation can occur if the placenta is partial at delivery,

the placenta has a succenturiate lobe, or previous uterine surgery. Coagulation problems are typically found in patients with foetal death in utero, placental abruption, sepsis, disseminated intravascular coagulopathy, and a history of a hereditary coagulation deficiency.

Patients who are bleeding on presentation to labor and delivery, history of PPH, hematocrit < 30%, history of bleeding diathesis or coagulation deficit, morbidly adherent placenta or with hypotension or tachycardia on presentation to labor and delivery are under the high risk for PPH.[25]

Atonic postpartum hemorrhage

Atonic postpartum hemorrhage is associated with multiple pregnancies, placenta previa, previous PPH history, BMI >30, protracted labor, fetal macrosomia>4kg, and primipara> 40 years. The factors related with atonic postpartum hemorrhage include known protective factors (e.g., caesarean delivery) and risk factors (e.g., nulliparity, vaginal birth following caesarean delivery).[26]

Women having vaginal and caesarean deliveries, regardless of whether they had a previous caesarean delivery, experienced an increase in atonic postpartum hemorrhage in Azar Mehrabadi et al. study. Atonic postpartum hemorrhage was the most common among caesarean deliveries in all caesarean sub-categories (cesareans without labor, those with spontaneous labor, those who had labor induction). Those who had an instrumental vaginal delivery had a higher rate of atonic postpartum hemorrhage than those who had a vaginal delivery.[27]

Blood Loss Calculation:

Methods used:

- Clinical methods
- Direct methods
- Laboratory based measurement
- Others

Clinical Methods:

Subjective characters are used to determine the blood loss Shock Index (SI) = Heart rate/ Systolic blood pressure Normal range of SI ranges between 0.5 – 0.7.

The value between 0.9 – 1.1 indicates significant Hemorrhage

Rule of 30:

The patients have lost 30% of the volume of the blood in case the below parameters are identified:

If the SBP declined by 30mmHg Heart rate increased by 30bpm. Respiratory rate increased by 30 breaths per minute Hematocrit decreased by 30% Urine output less than 30ml per hour.

Assessment based on severity of hemorrhage: Gutierrez et al.[28] classified hemorrhage into four classes:

- Class I
- Class II
- Class III
- Class IV

Table 3: Classification of hemorrhage [28]

Parameters	Class I	Class II	Class III	Class IV
Blood loss (ml)	<750	750–1500	1500–2000	>2000
Blood loss (%)	<15%	15–30%	30–40%	>40%
Pulse rate (beats/min)	<100	>100	>120	>140
Blood pressure	Normal	Decreased	Decreased	Decreased
Respiratory rate (breaths/min)	14–20	20-30	30-40	>35
Urine output (ml/hour)	>30	20-30	5-15	Negligible
CNS symptoms	Normal	Anxious	Lethargic	Confused

Visual estimation:

It is considered the commonly practiced method. Visual estimate has two primary advantages: real-time evaluation and correlation of results. In several studies, there were considerable disparities between clinical estimations and actual measurements. In Prasertcharoenusk, et al [29] study the prevalence of PPH was underestimated in the visual estimation.

According to a study by Duthie et al.,[30] blood loss during caesarean section is significantly underestimated.

The tendency to underestimate the quantity of blood loss was higher in Stafford et al.[31], study when the calculated blood loss was >1000ml.

10 x 10 cm swab =60 ml

30 x 30 cm swab = 140ml 45 x 45 cm swab = 350 ml

1 kg of soaked swab = 1000ml 50 cm floor spill = 500 ml

7 5 cm floor spill = 1000 ml

100 cm floor spill = 1500 ml

Direct methods:

It is the oldest method used for assessing the blood loss. Bed pan and standard measuring jar, Rubberized blood mat, Kelly's pad and Calibrated drape method are used to determine the blood loss after normal vaginal delivery.

Gravimetric method:

It's a simple approach to figure out how much blood was lost during a caesarean section.

It consists of two methods: patient weighing and swab weighing.

Patient weighing method:

The patient's weight is measured before and after surgery using this procedure. Allowance should be made for infusion, drain, insensible water loss and tissue removal.

Swab weighing method:

It is the gold standard method.[29]

The difference between swabs taken before and after operation and blood absorbed by the swabs would be determined.

1 gm of weight gain = 1 ml of blood loss.

Estimation errors due to evaporation can be eliminated by weighing the soaked pads immediately after surgery. It also aids in reducing measurement inconsistency or inter-observer variation. It denotes a practically real value hence it is considered as a standard method for comparability.[32]

Laboratory based Measurements

Calorimetric method:[33]

A known volume of tap water is used to wash the contaminated blood swaps. Then, ammonium hydroxide as a deforming agent is added to provide a 1 in 1000 dilution. The concentration of the resultant solution must be assessed after blood is collected in the suction container and added to the water.

Blood loss in ml = Hb % of washing fluid & volume of washing fluid

Hb% of patients blood x dilution factor of patients Hb%

Alkalinhematin (or) acid hematin method: In this method the blood collected is mixed with the standardized solution. It converts hemoglobin into an acid hematin or cyanomethemoglobin and can be measured by using a spectrophotometer or calorimeter.

Electrolyte conductivity method: In this method an automated blood loss meter is used based on the electrolyte conductivity.

Radioactivity method: In this method an intravenous injection of known amount of radioisotope is injected preoperatively and is followed by measuring the radioactivity of the blood-soaked swabs whichis collected during the surgery.

Blood volume Measurements:

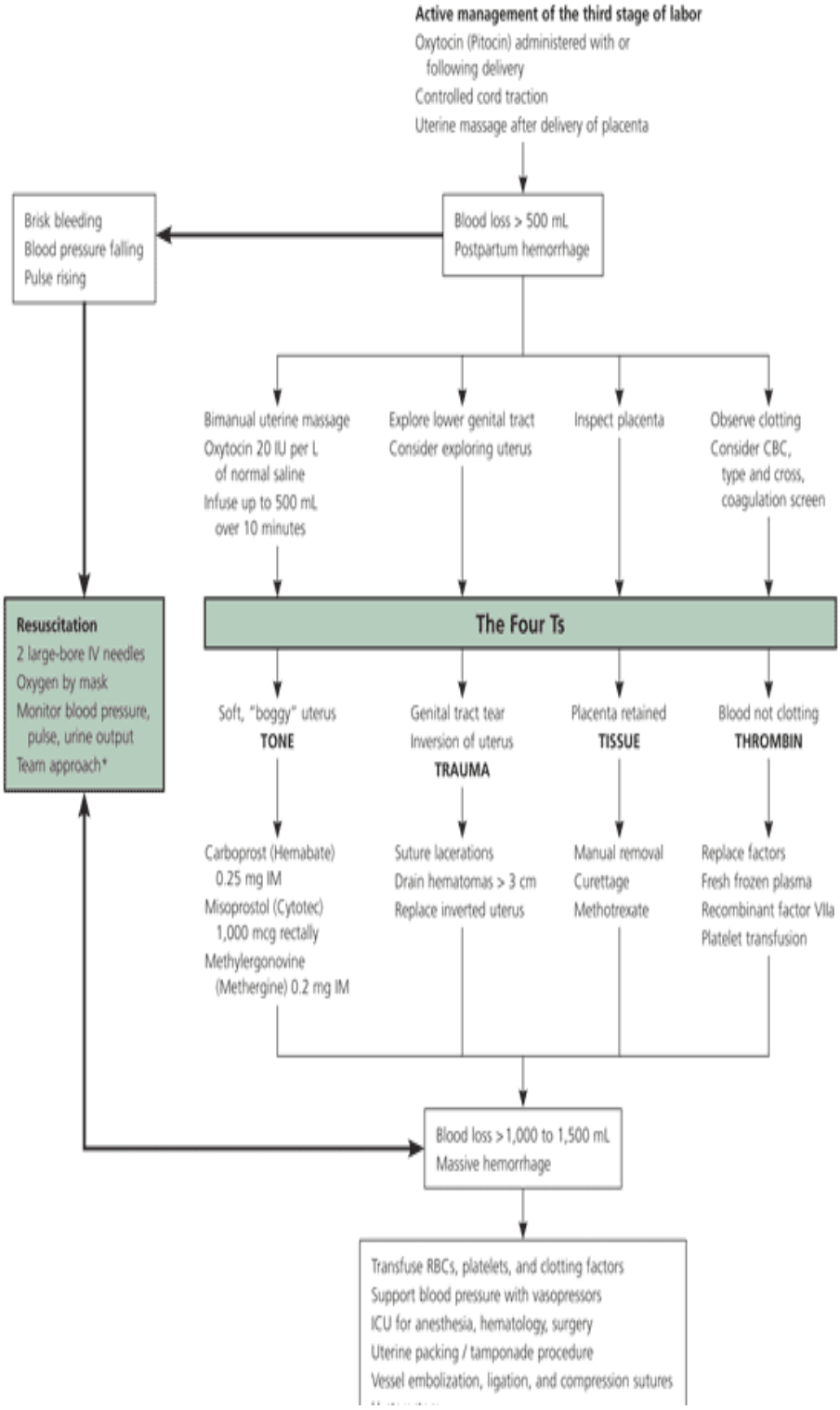
Dye method: The dye used in this method should neither be catabolised nor rapidly removed from the Circulation. In order to measure the volume of blood, a dye called evans blue dye can be used.

Radio Isotope Method: Before surgery a radio isotope like I^{131} labelled albumin or Cr^{51} labled RBC can be used and the post-operative radioactivity can be measured by Geiger muller counter.

Figure 1: The suction apparatus used:

Figure 2: The mop used here measured 10x 10 cm:

Figure 3: Management of PPH:[34]



Medical management - types of drugs used

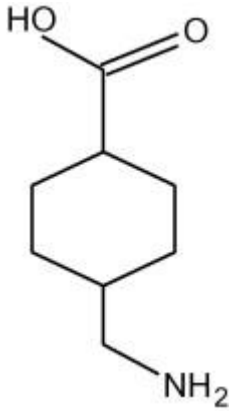
Table 4: Preventative and therapeutic drugs for postpartum haemorrhage[24]

Drugs	Dosage	Contraindications	MOA	Adverse effects
First-line Medications				
Oxytocin (Pitocin)	Prevention 10 IU intramuscularly or 5–10 IU IV bolus Treatment: Infuse 500 mL of 20 to 40 IU in 1 L normal saline for 10 minutes, then 250 mL for 10 minutes.	Water intoxication can occur due to an overdose or extended consumption. Following a caesarean delivery, IV usage may cause hypotension.	Constricts spiral arteries, reduces blood flow to the uterus by stimulating the upper section of the myometrium to contract rhythmically.	Rare
Second-line Medications				
Carboprost (Hemabate), a prostaglandin $F_{2\text{-alpha}}$ analog	Treatment 250micrograms intramuscularly or into the myometrium, For a total of 2 milligrams, repeat every 15 to 90 minutes.	Avoid in patients with asthma or significant renal, hepatic, or cardiac disease	Improves uterine contractility increasing the number of oxytocin receptors and causes vasoconstriction	Nausea, vomiting, and diarrhea
Methylergonovine (Methergine)	Treatment Repeat every two to four hours with 0.2 mg intramuscularly.	Avoid in Pregnancy hypertensive diseases, including chronic hypertension	Causes vasoconstriction and contracts smooth muscles, the upper and lower uterine segments.	Nausea, vomiting, and high blood pressure
Misoprostol (Cytotec),† a prostaglandin E_1 analog	Prevention 600 mcg orally Treatment: 800 - 1,000 mcg rectally or 600 - 800 mcg sublingually or orally	Use with caution in patients with cardiovascular disease	Causes generalized smoot muscle contraction	Nausea, vomiting, diarrhea, pyrexia, and shivering
Tranexamic	Treatment: - 1g IV over 10 minutes, can be repeated after 30 minutes	Use within three hours of the onset of bleeding	Inhibits the breakdown of fibrin and fibrinogen by plasmin	May increase risk of thrombosis and cause visual defects

a. Tranexamic acid

Tranexamic acid is a potent antifibrinolytic drug idenified in two isomeric forms; the antifibrinolytic potency resides in the trans-isomeric form. [35] It is a synthetic reversible competitive inhibitor to the lysine receptor on plasminogen. Binding of lysine receptor prevents plasmin from binding to and eventually stabilizing the fibrin matrix.[36] It enters tissues and fluids in different concentrations and crosses the placenta. It is excreted into the urine. [35]

Figure 4: Chemical structure of tranexamic acid [37]



Adverse effects: [36]

- Seizures
- Headaches
- Backache
- Abdominal Pain
- Nausea
- Vomiting
- Diarrhea
- Fatigue
- Pulmonary Embolism
- Deep Vein Thrombosis

- Anaphylaxis
- Impaired Color Vision
- Visual Disturbances.

Contraindications [36]

- Known Allergy To Tranexamic Acid
- Intracranial Bleeding
- Known Defective Color Vision,
- Previous history of venous, arterial thromboembolism or active thromboembolic disease.

b. Misoprostol

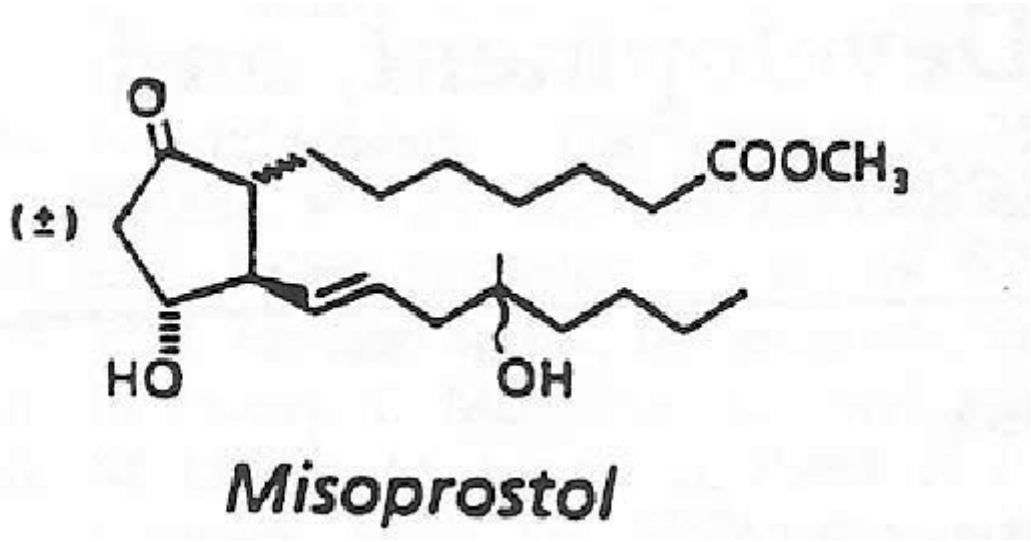
For avoiding PPH following caesarean delivery, misoprostol can be used instead of injectable uterotonic drugs. A PG E1 analogue is misoprostol. It has a strong uterotonic effect via binding to E-series prostanoid receptors (Ep2/Ep3) preferentially. It is relatively affordable and has a longer shelf life when stored at room temperature. According to the WHO, it is an important medicine for primary PPH, particularly in countries with limited resources.[38] Misoprostol is easily absorbed by the mouth, buccal, sublingual, vaginal and rectal routes of administration .[39]

Oral, vaginal, sublingual, buccal or rectal are the various routes of misoprostol administration. When compared to oral misoprostol, vaginal misoprostol has a slower absorption, lower peak plasma levels, and slower elimination. Also, overall exposure to the drug and effects on the cervix and uterus are greater with the vaginal administration. [28]

Rectal administration followed the same pattern as vaginal administration, but with a lower AUC. While the AUC of sublingual administration is comparable to that of vaginal administration, absorption and peak levels are higher than those of vaginal or oral

administration. This may result in a greater number of gastrointestinal side effects. Sublingual administration can also elicit uterine contractions at the same rate as vaginal administration and has a modest variation in absorption.[28] When compared to sublingual delivery, the buccal route showed a lower AUC, lower peak concentration, and fewer adverse effects. The absorption patterns of the buccal and vaginal routes are similar, although the overall serum level is lower. They also have similar effects on the tone and activity of the uterus. Misoprostol's efficacy is unaffected by the use of nonsteroidal anti-inflammatory drugs (NSAIDs) for pain treatment. [28]

Figure 5: Chemical structure of Misoprostol [29]



Adverse effects [40]

- Shivering/Chills
- Diarrhoea
- Abdominal Pain
- Hyperthermia
- Nausea
- Vomiting

- Flatulence
- Constipation
- Dyspepsia
- Headache

Contraindications [40]

- Previous allergic reaction or hypersensitivity to prostaglandin.
- Patients at risk for gastric ulcers secondary to NSAID use.

Blood loss can be reduced using IV tranexamic acid in patients undergoing Caesarean section:

TXA is a synthetic derivative of the amino acid lysine that inhibits fibrinolysis by reversibly inhibiting the lysine binding sites on plasminogen molecules.[41] 1 gram intravenous TXA administered over 5 minutes for 10 minutes before to skin incision for elective caesarean delivery is tried in many centres. Tranexamic acid is licensed by the FDA for severe menstrual bleeding and short-term prophylaxis in hemophilia. Elective cesarean sections, Total knee arthroplasty, Orthognathic surgery, Cardiac surgery, Spinal surgeries, Transurethral retrograde prostatectomy, Non-traumatic subarachnoid hemorrhage, Postpartum hemorrhage and Gastrointestinal bleeding are the intravenous uses of TXA.

Seizures, headaches, backache, abdominal pain, nausea, vomiting, diarrhea, fatigue, pulmonary embolism, deep vein thrombosis, anaphylaxis, impaired color vision, and other visual disturbances are the possible adverse effects associated with tranexamic acid.

Contraindications for tranexamic acid include known allergy to TXA, intracranial bleeding, known defective color vision, history of venous or arterial thromboembolism or active thromboembolic disease. TXA is a plasminogen-specific synthetic reversible competitive

inhibitor of the Lysine receptor. The binding of this receptor can prevent plasmin from binding to and ultimately stabilizing the fibrin matrix.[42]

Tranexamic acid reduced blood loss from the time of placental delivery to 2 hours postpartum and from the completion of LSCS to 2 hours postpartum when compared to the placebo group. in the Bhatia, et al. research.[43] In a meta-analysis study[44] , the TXA group showed a reduction in intraoperative and postpartum blood loss. With the TXA group, the fall in hemoglobin and hematocrit values was reduced, reducing the need for blood transfusions. According to the findings of the Ifunanya NJ, et al. study, the placebo group required more uterotonic than the tranexamic group.[45]

Sublingual misoprostol to lowering the amount of blood lost after Caesarean section:

Misoprostol is a PG E1 analogue that is synthesised. Misoprostol is used for medical management of miscarriage, induction of labour, cervical ripening before surgical procedures, and the treatment of postpartum haemorrhage. Misoprostol has been recognised as having low cost, a long shelf life, no requirement for refrigeration, and global availability. Cervical softening and dilatation, uterine contractions, nausea, vomiting, diarrhoea, fever, and chills are all side effects of misoprostol.

Misoprostol is administered via oral, vaginal, sublingual, buccal, and rectal methods. Vaginal misoprostol is associated with slower absorption, lower peak plasma levels and slower clearance as compared to oral misoprostol.[46,47,31] Overall exposure to the drug and effects on the cervix and uterus are more with the vaginal misoprostol.[47] Misoprostol delivery via the rectal route shows a similar pattern to vaginal administration, but with a lower area under the curve.[12]

When compared to vaginal or oral administration, the AUC for sublingual administration is similar to vaginal administration, but it exhibits faster absorption and greater peak levels.[48]

This leads to an increase in gastrointestinal side effects. It also generates uterine contractions at the same rate as vaginal administration and has less absorption variance.

When compared to sublingual administration, the buccal route is associated with lower AUC, peak concentration, and fewer adverse effects.[49] The buccal route has a similar absorption pattern to the vaginal route, but results in lower serum levels. The buccal and vaginal modes of administration have similar effects on uterine tone and activity. Misoprostol's efficacy is unaffected by the use of nonsteroidal anti-inflammatory drugs (NSAIDs) for pain treatment. [50,51] In a prospective study by Youssef AEA et. al, similar results was noted. [52]

Comparison of both drugs in reducing Caesarean section blood loss

The hemoglobin level reduction, number of used gauze, and blood suction were higher in the TXA group than in the misoprostol group, according to Pakniat H, et al[53] Bose D, et al. conducted a study in which TXA was found to reduce blood loss when compared to misoprostol in a group of 163 women. The misoprostol group experienced little side effects, while the TXA group experienced a shorter surgery time.[54]

Pakniat H, et al., conducted a study in 158 women. The goal of the trial was to see if intravenous tranexamic acid plus sublingual misoprostol may help reduce bleeding following a caesarean surgery. Hemoglobin level reduction, gauze use, and blood suction were all higher in the TXA group with 2.45 0.84, 4.67 1.34, and 260.25 79.06 cc, respectively, than in the misoprostol group with 2.14 1.38 g/dL, 3.25 1.31, and 193.94 104.79 cc. The TXA group's mean blood pressure was discovered to be lower than the misoprostol group's for the entire length of surgery. The overall bleeding was shown to be lower in the sublingual misoprostol group in this study.[53]

Bose D, et al.,performed a study on 163 women. The study's goal was to see how effective misoprostol when given sublingually and intravenous TXA injections were at decreasing blood loss during LSCS. According to the findings, TXA reduced blood loss by 416ml compared to 505ml in the misoprostol group. The misoprostol group had few side effects, and the TXA group's surgery duration was cut in half. TXA can be utilized together with oxytocin following cord clamping in elective/emergency LSCS to minimize perioperative blood loss, according to the findings.[54]

Sahhaf, et al conducted a double-blinded randomized control clinical trial on 200 women. The study compared the anti-hemorrhagic effects of TXA and Misoprostol in the treatment of postpartum haemorrhage. The average age of the patients was found to be 26.7± 6.5 years in the study. The TXA and misoprostol groups had sonographic gestational ages of 37.7± 3.4 weeks and 37.4± 3.3 weeks, respectively. The TXA group had a haemorrhage of 1.2 ± 0.33 litres, while the misoprostol group had 1.18 ±0.47 litres. The TXA group had higher haemoglobin levels than the misoprostol group after 6-12 hours of labour. According to this research, misoprostol has no preference for TXA.[55]

Ifunanya NJ, et al., conducted a double-blind randomized controlled trial in 168 women. The study's goal was to see if tranexamic acid may help prevent postpartum hemorrhage in women who underwent caesarean section. The placebo group required 7.4% more uterotonic than the tranexamic group (33.3%). The TXA group had a decreased incidence of main postpartum hemorrhage (11.9% vs. 50% in the placebo group). This study found that IV tranexamic acid can be given before the caesarean section skin incision. It can help to minimize the requirement for uterotonics and the occurrence of primary postpartum depression.[56]

Tabatabaie S, et al performed a randomized trial in 300 pregnant women. The researchers wanted to see how TXA and Misoprostol changed blood loss during and after a caesarean surgery. The mean haemoglobin scores before the operation in the Tranexamic acid group, Misoprostol group, and placebo group were 11.96±1, 11.62±1.21, and 12.28±1.26 mg/dl, respectively. The postoperative Hb levels were 10.9 ±0.99 mg/dl, 10.46±1.04 mg/dl, and 10.93±1.34 mg/dl. Between the three groups, there was a substantial difference in blood loss throughout the procedure and the first two hours afterward.[57]

Sanad, et al. conducted a study in 74 full-term pregnant primigravidas. The goal of the research was to see if tranexamic acid may decrease blood loss during and after an elective caesarean delivery. The control (group II) had lower hemoglobin and hematocrit levels than those who received a bolus injection of 1-gram IV tranexamic acid diluted in 20 ml of 5% dextrose solution slowly over 5 minutes at 10 minutes before incision (group I). In comparison to the other groups, group I experienced less blood loss. During the postoperative phase, the group II patients required additional ecbolic treatment. According to the findings, TXA is efficient in minimizing blood loss during lower segment CS.[58]

Kalpana S. et al performed a randomized case-controlled prospective study in 300 women. The goal of the trial was to see if preoperative intravenous tranexamic acid was effective and safe in minimizing blood loss during and after caesarean section. Blood loss was shown to be reduced in the tranexamic acid group, with 74.28ml compared to 114.48ml in the control group. Administration of TXA reduced blood loss in this study.[59]

Novikova N, et al conducted a meta-analysis study. The goal of the trial was to see if Tranexamic acid was safe and helpful at preventing postpartum haemorrhage. When

compared to vaginal birth, TXA was helpful in minimizing the occurrence of blood loss higher than 1000 mL in women who had undergone CS. In comparison to CS, the effect of TXA on blood loss larger than 400 mL or 500 mL was stronger in vaginal birth. When comparing the TXA group to the placebo or no intervention group, the mean blood loss was reduced in the TXA group. In the TXA group, additional medical interventions and blood transfusions were less common. Minor adverse effects in the TXA group included nausea, vomiting, and dizziness. According to the findings, using TXA can reduce postpartum blood loss and hence prevent PPH.[60]

Gungorduk K, et al., conducted a randomized, placebo-controlled study on 660 women. The goal of the trial was to see how effective and safe tranexamic acid (TXA) was at reducing blood loss after elective caesarean sections. The average estimated blood loss for the TXA and placebo groups was 499.9± 206.4 mL and 600.7± 215.7 mL, respectively. The TXA group included 2.1 percent of women with an estimated blood loss >1000 mL, compared to 5.8 percent in the placebo group. 8.5 percent of women in the TXA group required additional uterotonic medicines, compared to 14.5 percent in the placebo group. The TXA was found to reduce bleeding during CS in this study.[61]

Acharya S, et al. conducted a comparative study on 100 women The goal of the study was to see how effective tranexamic acid is at reducing blood loss after caesarean sections and what negative effects it has. The mean intraoperative blood loss in the TXA group and the control group was 443.62± 86.73ml and 667.40± 131.01ml, respectively. In the TXA group, the mean postoperative decline in hemoglobin was 0.82 ±0.27, while the mean postoperative drop in hematocrit was 2.60±0.91. In the control group, the mean postoperative decline in hemoglobin was 1.86 ±0.64, while the mean postoperative reduction in hematocrit was 5.49

±1.97. According to the findings, tranexamic acid is a safe and effective medication for reducing blood loss during caesarean delivery. [62]

Movafegh A, et al conducted a study on 100 women. The aim of the study was to see how intravenous tranexamic acid affected bleeding during and post caesarean birth. For intraoperative bleeding, the TXA group had a mean blood loss of 262.5± 39.6 mL, while the control group had a mean blood loss of 404.7± 94.4 mL. For postoperative hemorrhage, the mean blood loss was 262.5 ±39.6 and 404.7 ±94.4 mL in the TXA and control groups, respectively. The TXA group had less oxytocin administration, with 39.8 units compared to 43.54 units in the control group. Intravenous tranexamic acid, helps reduce intraoperative and postoperative blood loss. [63]

Bhatia SK, et al. conducted a study on 100 women. The goal of the trial was to see if tranexamic acid may reduce blood loss after a placental delivery following a lower segment caesarean operation. In both the research and control groups, the haemoglobin level was somewhat lower. According to the findings, tranexamic acid is useful in lowering blood loss during CS. [43]

Shahid A, et al performed a randomized double-blind placebo-controlled study. The goal of the trial was to see how effective and safe tranexamic acid was during caesarean section. The quantity of blood lost in the tranexamic acid group, with 356.44± 143.2 ml. The quantity of blood lost in the TXA group was 35.68 ±23.29 ml, while the placebo group lost 43.63 ±28.04 ml. The TXA can be utilized safely and successfully in LSCS to minimize intraoperative blood loss, according to the findings. [64]

Ali SAA, et al performed a randomized, controlled study in 200 pregnant women. The study's goal was to see how effective and safe tranexamic acid was at reducing blood loss

after elective caesarean sections. In comparison to the control group, the study group experienced less acute post-partum vaginal bleeding in the first two hours. In the study group, hemoglobin decrease was found to be lower. TXA is useful in reducing bleeding after elective caesarean sections, according to this study.[65]

J X, et al conducted a randomized, double-blind, case-controlled study on 174 pregnant women. The goal was to see how effective tranexamic acid is at controlling bleeding in women who have had a caesarean section. Blood loss was lower in the TXA group (46.6± 42.7 vs. 84.7 ±80.2 in the control group) between the end of CS and 2 h postpartum. Total blood loss from placental birth to 2 hours postpartum was found to be 379.2 ±160.1 and 441.7± 189.5 in the TXA and control groups, respectively. PPH was stopped in 75.6 percent of the control women and 92.0 percent of the TXA women. TXA therapy is useful in lowering blood loss in patients receiving CS, according to this study. [64]

Abdel Aleem et al conducted a trial in 740 women. The goal was to see how tranexamic acid affected bleeding during and after an elective caesarean operation. The study found that the tranexamic acid group had an average blood loss of 241.6 ±6.77 ml, while the control group had an average blood loss of 510±7.72 ml. The TXA group had a reduced mean reduction in hematocrit and hemoglobin levels. According to the findings, pre-operative tranexamic acid administration is linked to less bleeding during and after an elective caesarean section.[67]

Gungorduk, et al conducted a study on 660 women. The study's goal was to see how effective and safe tranexamic acid was at reducing bleeding after elective caesarean sections. In the TXA and placebo groups, the mean estimated blood loss was 499.9± 206.4 mL and 600.7± 215.7 mL, respectively. 14.5 percent of participants in the control group required additional uterotonic medications, compared to 8.5 percent in the TXA group. This study

concluded that the TXA can be utilized to minimize CS hemorrhage in a safe and effective manner. [61]

Nayak L, et al conducted a prospective study on 200 women. The study's goal was to see how effective sublingual misoprostol was at reducing caesarean blood loss. The overall blood loss was lower than in the control group, according to the findings. The study group had lower postoperative drops in Hb and hematocrit. Misoprostol can minimize caesarean blood loss, according to one study. [68]

Sood AK, et al. performed a prospective randomized controlled study in 174 women. The goal of the trial was to see how effective sublingual misoprostol was at reducing intraoperative blood loss. In the misoprostol and placebo groups, the mean intraoperative blood loss was 595± 108 ml and 651 ±118 ml, respectively. In the misoprostol group, 22.25 percent of women required additional uterotonic medicines, compared to 42.8 percent in the placebo group. The misoprostol group had a lower perioperative Hb fall of 0.87± 0.29 g than the placebo group, which had a higher fall of 1.01± 0.26 g. The study found that using sublingual misoprostol during caesarean birth can reduce intraoperative bleeding and the requirement for extra uterotonic medications. [69]

LACUNAE OF LITERATURE

PPH is one of the occasions when an obstetrician faces so much stress as the time for management is limited and the stakes are high. Though there are various management options available for post-partum haemorrhage, there are very few studies which compare the efficacy of these drugs. Hence, there is a paucity of information available to surgeons regarding this topic.

MATERIALS & METHODS

MATERIALS & METHODS

Study site: This study was conducted in the Department of Obstetrics and Gynaecology at Sri Devaraj Urs Medical College, Tamaka , Kolar- 563101

Study population: All the eligible patients admitted for elective or emergency caesarean section in the Department of Obstetrics and Gynaecology at Sri Devaraj Urs Medical College were considered as study population.

Study design: The current study was a Randomized prospective control trial.

Sample size: The sample size was calculated from the formula.

$$n = \frac{2Sp^2[Z_{1-\alpha/2} + Z_{1-\beta}]^2}{\mu^2_d}$$

$$Sp^2 = \frac{s_1^2 + s_2^2}{2}$$

The sample size was calculated based on the mean suction blood loss in both tranexamic acid and misoprostol groups in previous study by Pakhniat et al[53] Thus considering a 90% power and an alpha error of 1% , a sample size of 59 was taken in each group

Sampling method: All the eligible subjects were recruited into the study consecutively by convenient sampling till the sample size is reached.

Study duration: The data collection for the study was done between January 2020 to June 2021.

Inclusion Criteria:

- Pregnant woman with age between completed 18 and 40 years with gestational age between 37 weeks and 42 weeks.
- Singleton pregnancy

- Patients undergoing lower segment caesarean section under spinal anaesthesia

Exclusion criteria:

- Antepartum haemorrhage.
- Pre-eclampsia and Eclampsia.
- Having underlying disease (heart, liver, kidney, pulmonanry)
- Allergy to tranexamic acid (allergy, thromboembolic events during pregnancy) and misoprostol.
- Coagulation disorders, intra uterine fetal demise, polyhydramnios, fibroid, DIC, anti-coagulant therapy.
- Previous history of uterine rupture

Ethical considerations: Study was approved by institutional human ethics committee. Informed written consent was obtained from all the study participants and only those participants willing to sign the informed consent were included in the study. The risks and benefits involved in the study and voluntary nature of participation were explained to the participants before obtaining consent. Confidentiality of the study participants was maintained.

Data collection tools: All the relevant parameters were documented in a structured study proforma.

Methodology:

SAMPLING PROCEDURE:

Prospective randomized study was planned in patients aged between completed 18 to 40

years with gestational age between 37 to 42 weeks, undergoing emergency or elective surgery under spinal anesthesia in the department of obstetrics and gynecology department of RLJH, Kolar after getting ethical clearance from the college ethical committee.

Pre-operatively procedure was explained, written and informed consent was obtained. All the routine investigations required for pre-operative evaluation was done for the proposed surgery. They were randomly allocated into 2 groups by lottery method.

In the operating room I.V line was secured and the patient was shifted to the OT room, under aspectic precaution patient was painted and draped, spinal anaesthesia was given, and caesarean section done.

Group A – intravenous tranexamic acid will be given. (A dose of 1 gram slowly over 2 minutes, at least 10 minutes before the start of the procedure).

Group B – sublingual misoprostol of 400mcg as soon as the baby was extracted. In both the group, 20 units of oxytocin was administered in 1 L of RL with the rate of 1000 CC/h.

PARAMETERS OBSERVED:

1. Number of mops, pads soaked, suction volume excluding the amniotic fluid.
2. Preoperative and post-operative haemoglobin.
3. $SPO_{2,}$ Heart rate, BP and Respiratory Rate were recorded. Intraoperatively, the vitals were recorded after every 5 minutes for 30 minutes after injection, thereafter every 10 minutes throughout surgery
4. The presence of any complication in the pre-operative and post-operative periods was noted, particularly in relation to respiratory or cardiovascular problems, nausea or vomiting and headache.

STATISTICAL METHODS:

Mops, Suction volume, Pre-Operative HB, Post-Operative HB were considered as primary outcome variables. Misoprostol and Tranexamic acid were considered as primary explanatory variables.

Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency, and proportion for categorical variables. Non normally distributed quantitative variables were summarized by median and interquartile range (IQR). Data was also represented using appropriate diagrams like bar diagrams and pie chart. All Quantitative variables were checked for normal distribution within each category of explanatory variable by using visual inspection of histograms and normality Q-Q plots. Shapiro- wilk test was also conducted to assess normal distribution. Shapiro wilk test p value of >0.05 was considered as normal distribution. Categorical outcomes were compared between study groups using Chi square test /Fisher's Exact test. For normally distributed Quantitative parameters the mean values were compared between study groups using independent sample t-test. The change in the quantitative parameters, before and after the intervention was assessed by paired t-test. P value < 0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis.[70]

RESULTS

RESULTS:

A total of 118 subjects were included in the final analysis.

TABLE 5: Comparison of mean of age between study groups (N=118)

Parameter	Study groups (Mean± SD)		P value
	Tranexamic acid (N=59)	Misoprostol (N=59)	
Age (Years)	24.12 ± 3.3	23.81 ± 3.64	0.634

The mean age was 24.12 ± 3.3 in tranexamic acid group, and 23.81 ± 3.64 in misoprostol group. The difference between two groups was not statistically significant (P value 0.634). (Table 5)

TABLE 6: Comparison of gestational age between study groups (N=118)

Gestational Age (weeks)	Study groups				Chi square	P value
	Tranexamic Acid (N=59)		Misoprostol (N=59)			
	N	Percentage %	N	Percentage %		
37- 40	43	72.88%	42	71.19%	0.042	0.837
40+1- 42	16	27.1%	17	28.81%		

Out of 59 participants in tranexamic acid group, 43 (72.88%) participants belonged to gestational age (37 to 40) and 16 (27.12%) participants belonged to gestational age (40^{+1} to 42). Out of 59 participants in misoprostol group 42 (71.19%) participants belonged to gestational age (37 to 40) and 17 (28.81%) participants belonged to gestational age (40^{+1} to 42). The difference in proportions in both the groups was statistically not significant (p value 0.837). (Table 6 & Figure 6)

GRAPH 6: Staked bar chart of gestational age between study groups (N=118)

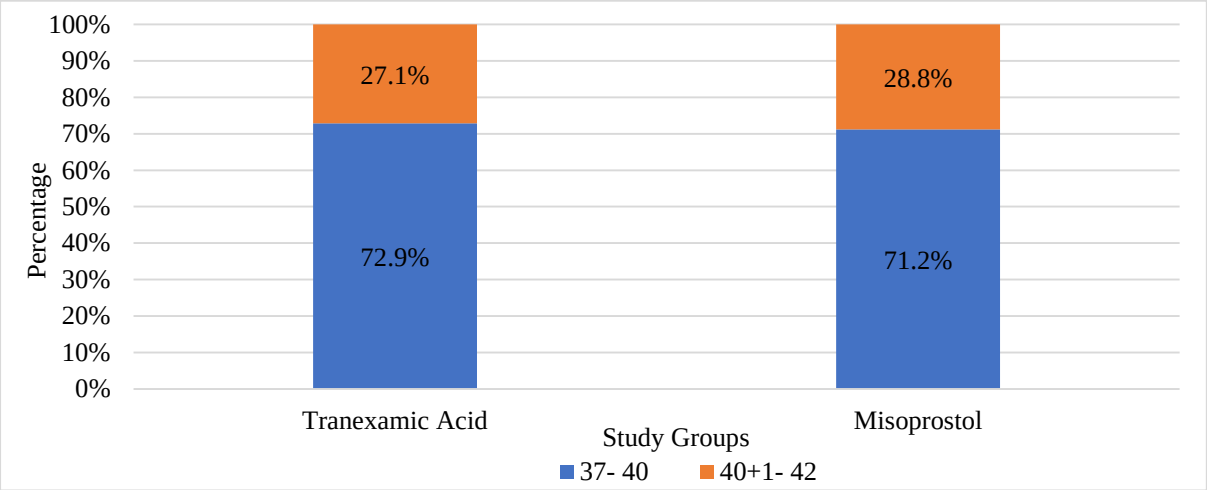


Table 7: Comparison of elective/ emergency caesarean section between study groups (N=118)

Type of caesarean section	Study groups				Chi square	P Value
	Tranexamic Acid (N=59)		Misoprostol (N=59)			
	N	Percentage %	N	Percentage %		
Elective	21	35.59	24	40.68	0.323	0.570
Emergency	38	64.41	35	59.32		

Out of 59 participants in tranexamic acid group, 21(35.59%) participants belonged to elective group and 38 (64.41%) participants belonged to emergency group. Out of 59 in misoprostol group 24 (40.68%) participants belonged to elective group and 35 (59.32%) participants belonged to emergency group. The difference in proportions in both the groups was statistically not significant (p value 0.57). (Table 7 & Figure 7)

Graph 7: Staked bar chart of comparison of elective/ emergency caesarean section between study groups (N=118)

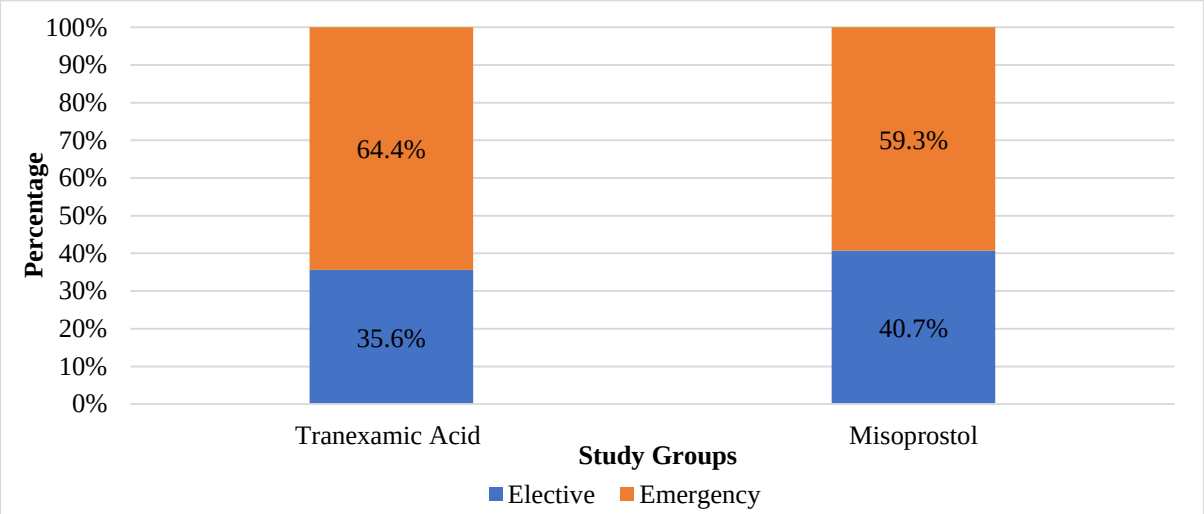


Table 8: Descriptive analysis of indication in the study groups (N=118)

Indication	Frequency	Percentages
Previous LSCS (Elective)	25	21.19%
Fetal distress	24	20.34%
CDMR	16	13.56%
Previous LSCS (Emergency)	16	13.56%
CPD	8	6.78%
Oligohydramnios	7	5.93%
Contracted pelvis	6	5.08%
Failed induction	5	4.24%
Malpresentation	4	3.39%
Deep transverse arrest	4	3.39%
Malpresentation	3	2.54%

Out of 118 participants in total, 25 patients underwent elective caesarean section, 24 patients underwent caesarean section in view of fetal distress, 16 underwent emergency caesarean section in view of previous caesarean section and 16 underwent in view of maternal desire. (Table 8 & Figure 8)

Graph 8: Bar chart of indication in the study population (N=118)

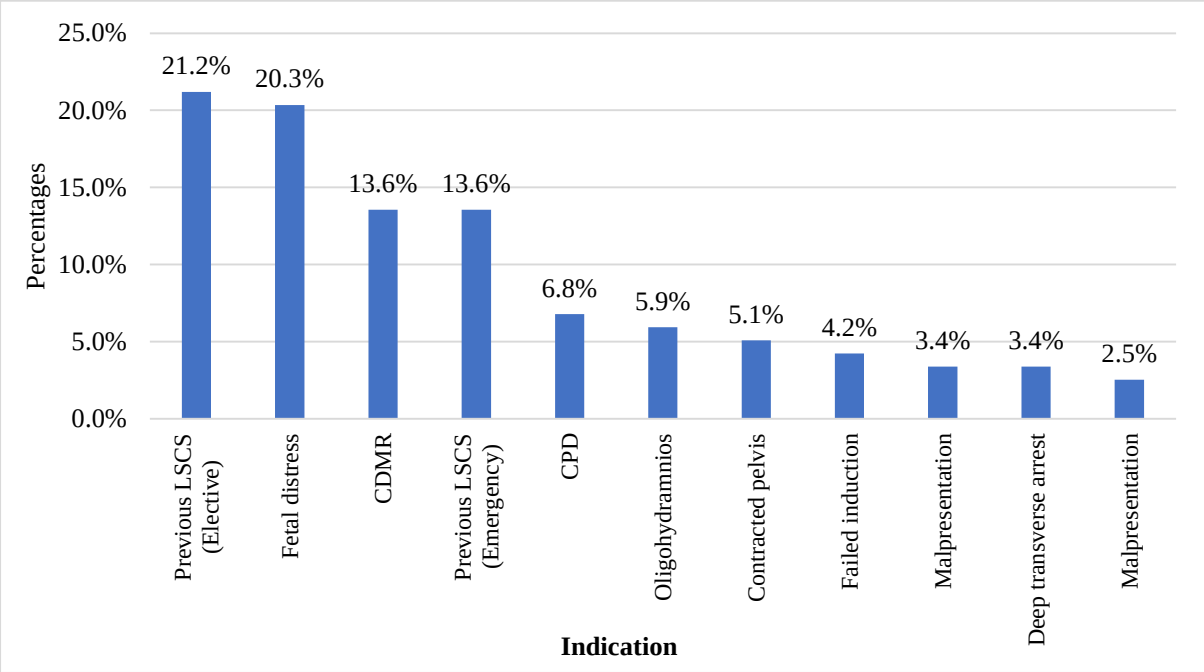


Table 9: Comparison of mean of mops count between study groups (N=118)

Parameter	Study groups (Mean± SD)		P value
	Tranexamic acid (N=59)	Misoprostol (N=59)	
Mops count	3.2 ± 1.45	4.73 ± 1.27	<0.001

The mean of mops count was 3.2 ± 1.45 in tranexamic acid group, and 4.73 ± 1.27 in misoprostol group. The difference in mops count between study groups was statistically significant (P value <0.001). (Table 9)

Table 10: Comparison of suction volume between study groups (N=118)

Study groups					Chi square	P Value
Suction Volume (ml)	Tranexamic Acid (N=59)		Misoprostol (N=59)			
	N	Percentage %	N	Percentage %		
<200	6	10.17	8	13.56	0.96	0.619
200- 400	26	44.07	29	49.15		
400- 600	27	45.76	22	37.29		

Out of 59 participants in tranexamic acid group, 6 (10.17%) participants suction volume was less than 200 ml, 26 (44.07%) participants suction volume was between 200 to 400 ml and 27 (45.76%) participants suction volume was between 400 to 600 ml. Out of 59 participants in misoprostol group, 8 (13.56%) participants suction volume was less than 200 ml, 29 (49.15%) participants suction volume was between 200 to 400 ml and 22 (37.29%) participants suction volume was between 400 to 600 ml. The difference in proportions in both the groups was statistically not significant (p value 0.619). (Table 10 & Figure 9)

Graph 9: Cluster bar chart of comparison of suction volume between study groups (N=118)

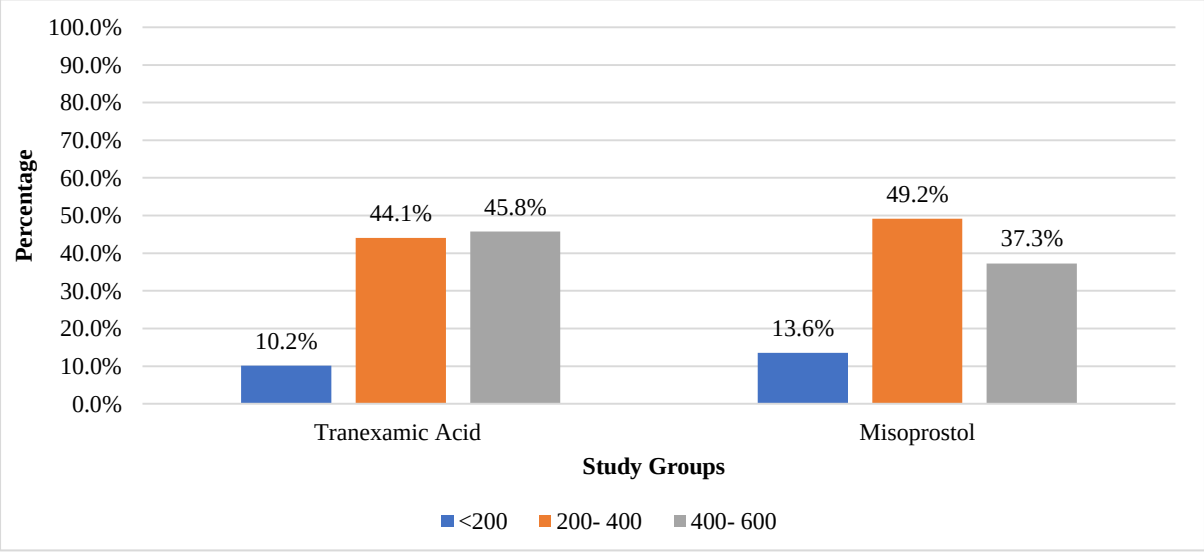


Table 11: Comparison of need for uterotonics between study groups (N=118)

Need for uterotonics	Study Groups				Chi square	P Value
	Tranexamic Acid (N=59)		Misoprostol (N=59)			
	N	Percentage %	N	Percentage %		
Yes	9	15.25	5	8.47	1.297	0.255
No	50	84.75	54	91.53		

Out of 59 participants in tranexamic acid group, 9 (15.25%) participants needed uterotonics. Out of 59 participants in misoprostol group, 5 (8.47%) participants needed uterotonics. The difference in proportions in both the groups was statistically not significant (p value 0.255). (Table 11 & Figure 10)

Graph 10: Staked bar chart of comparison of need for uterotonics between study groups (N=118)

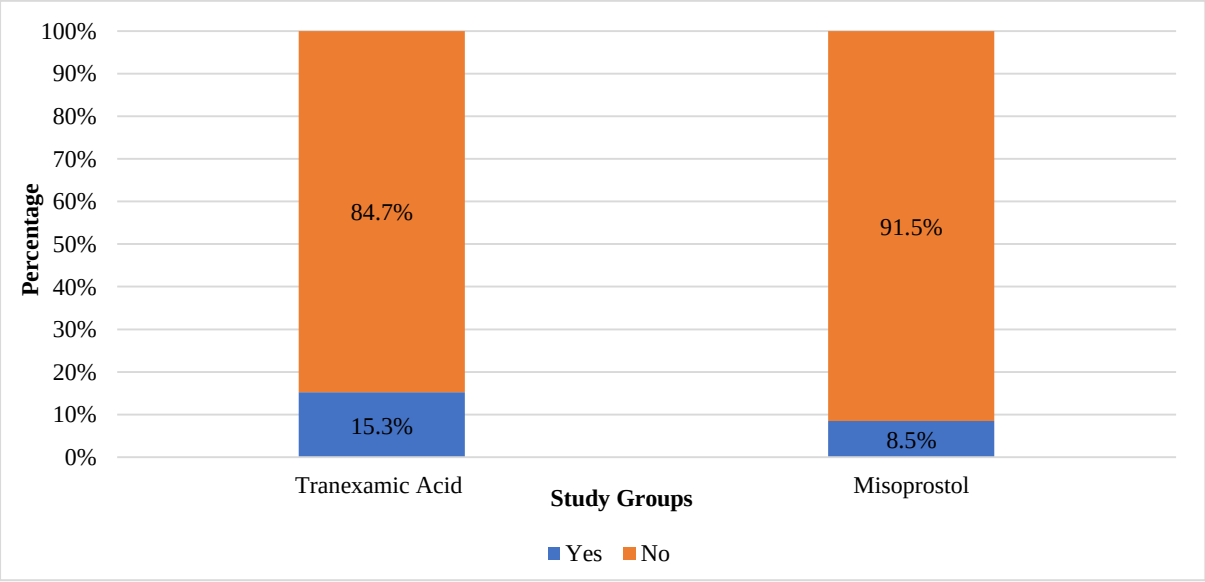


TABLE 12: Comparison of mean between pre-operative and post- operative hemoglobin in study population (Tranexamic acid) (N= 59)

Study groups					
Tranexamic acid					
HB (g/dl)	**(Mean± STD)**	**Mean Difference**	**95% CI of mean difference**		**P-Value**
			Lower	Upper	
Pre- operative	11.76 ± 1.43	0.59	0.38	0.81	<0.001
Post- operative	11.17 ± 1.4				

TABLE 13: Comparison of mean between pre-operative and post- operative hemoglobin in study population (Misoprostol) (N= 59)

Study groups					
Misoprostol					
HB (g/dl)	**(Mean± STD)**	**Mean Difference**	**95% CI of mean difference**		**P-Value**
			Lower	Upper	
Pre- operative	11.67 ± 1.37	0.89	0.66	1.12	<0.001
Post- operative	10.78 ± 1.12				

There is reduction in post-operative hemoglobin in both the groups when compared to the pre operative hemoglobin, however, the mean difference was high in Misoprostol group. (Table 13)

Table 14: Comparison of additional procedure required to control intraoperative bleeding between study groups (N=118)

Study Groups					Chi square	P value
Additional Procedure Required	Tranexamic Acid (N=59)		Misoprostol (N=59)			
	N	Percentage %	N	Percentage %		
Yes	1	1.69	0	0	*	*
No	58	98.31	59	100		

*No statistical test was applied- due to 0 subjects in the cells.

Out of 59 participants in tranexamic acid group, only 1(1.69%) participant needed additional procedure (bilateral internal iliac artery ligation) to control intraoperative bleeding. (Table 14)

Table 15: Comparison of blood transfusion between study groups (N=118)

Study Groups					Chi square	P value
Blood Transfusion	Tranexamic Acid (N=59)		Misoprostol (N=59)			
	N	Percentage %	N	Percentage %		
Yes	2	3.39	0	0	*	*
No	57	96.61	59	100		

*No statistical test was applied- due to 0 subjects in the cells.

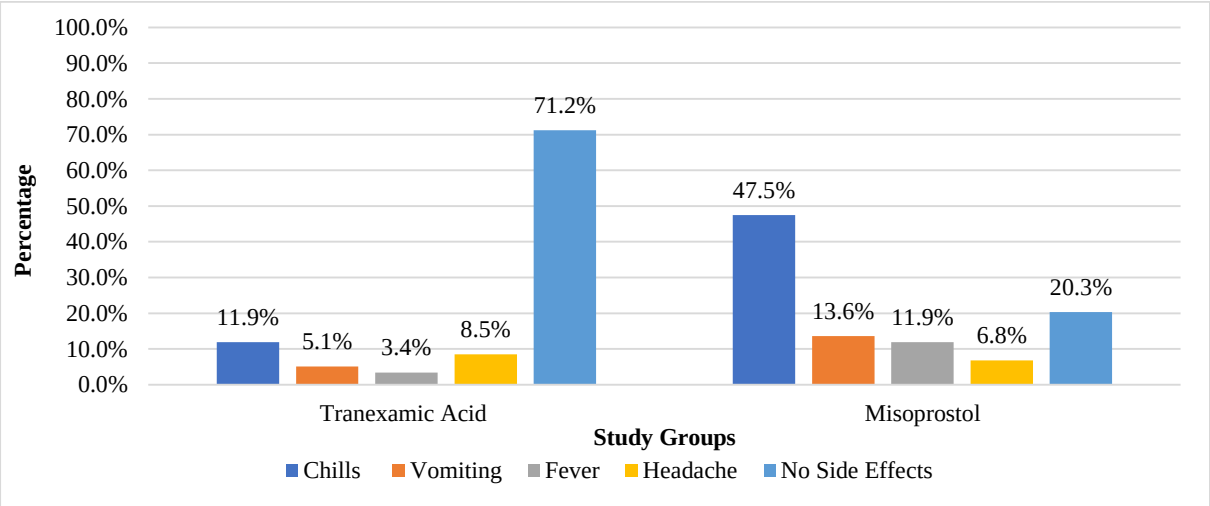
Out of 59 participants in tranexamic acid group, only 2 (3.39 %) participants needed blood transfusion, as the preoperative hemoglobin was low. (Table 15)

Table 16: Comparison of side effects between study groups (N=118)

Side Effects	Study Groups				Chi square	P Value
	Tranexamic Acid (N=59)		Misoprostol (N=59)			
	N	Percentage %	N	Percentage %		
Chills	7	11.86	28	47.46	34.428	<0.001
Vomiting	3	5.08	8	13.56		
Fever	2	3.39	7	11.86		
Headache	5	8.47	4	6.78		
No Side Effects	42	71.19	12	20.34		

Out of 59 participants in tranexamic acid group, 7 (11.86%) participants had chills, 3 (5.08%) participants had vomiting, 2 (3.39%) participants had fever and 5 (8.47%) participants had headache. Out of 59 participants in misoprostol group, 28 (47.46%) participants had chills, 8 (13.56%) participants had vomiting, 7 (11.86%) participants had fever and 4 (6.78%) participants had headache. The difference in proportions between two groups was statistically significant (p value <0.001). (Table 16 & Figure 11)

Graph 11: Cluster bar chart of comparison of side effects between study groups (N=118)



DISCUSSION

DISCUSSION:

Regardless of delivery method, obstetric hemorrhage is the top cause of maternal mortality globally. Cesarean section is the most common major surgeries performed on women around the world. When compared to a vaginal delivery, a caesarean section can result in greater difficulties. The most common complication in cesarean sections is postpartum bleeding, either primary or secondary. It has the potential to raise maternal mortality and morbidity.

In order to decrease maternal deaths and morbidity due to bleeding, the quantity of bleeding during and post a lower segment caesarean section must be reduced. The reason of this study was to examine the efficacy of intravenous tranexamic acid and sublingual misoprostol in minimizing blood loss in caesarean section patients. The study enrolled a total of 118 participants.

AGE

In this study, the mean age identified in the TXA and misoprostol groups was 24.12 ± 3.3 and 23.81 ± 3.64 respectively. Pakniat, et al[53] conducted a study on 158 patients in which the mean of age in the in the TXA and misoprostol group were observed as 27.25 ±5.85 and 27.12 ±5.28 years. In another study by Deepak Bose, et al., study, 27.14 ± 4.59 and 27.07± 4.58 years were the mean age identified in TXA and misoprostol group respectively. [54] Hamideh Pakniat, et al.[53] Deepak Bose, et al., [54] study showed an increased mean of age as compared to the present study.

Table 17: Comparison of mean of age between various studies

Study	Population	Mean of age
Deepak Bose, et al[54]	163	Tranexamic acid (27.14 ± 4.59) Misoprostol group (27.07 ± 4.58)
Hamideh Pakniat, et al.[53]	158	Tranexamic acid (27.12 ±5.28) Misoprostol group (27.25 ±5.85)
Present study	118	Tranexamic acid (24.12 ± 3.3) Misoprostol group (23.81 ± 3.64)

GESTATIONAL AGE

In the current study, the most of the participants belonged to the gestational age (37 to 40) in the misoprostol and tranexamic acid group with 71.19% and 72.88% respectively. In Hamideh Pakniat, et al[53] study 39.25 ±1.3 and 39.05 ±2.31 weeks were identified as the mean of gestational age in the misoprostol and tranexamic acid group respectively.

Atul Kumar Sood, et al., performed a prospective randomized controlled study on 174 pregnant women in which 38.2 ± 1.6 (weeks) was identified as the mean of gestational age in the misoprostol group.[69] Similarly, Gohel Mayur, P. et al., conducted a randomized, case-controlled, prospective study on 100 women in which the mean of gestational age was observed as 38.85 ± 1.29 (weeks) in the tranexamic acid group.[59] Hamideh In Pakniat, et al[53] Atul Kumar Sood, et al[69]. Gohel Mayur, P. et al.[59], and present study showed similar results in terms of the gestational age.

Table 18: Comparison of gestational age between various studies

Study	Population	Gestational age
Hamideh Pakniat, et al.,[53]	158	Misoprostol group (39.25 ± 1.3) Tranexamic acid group (39.05 ± 2.31)
Present study	118	Misoprostol group (37 to 40) Tranexamic acid group (37 to 40)

INDICATION FOR CAESAREAN SECTION

In this study, most of the participants underwent emergency cesarean section in the misoprostol and TXA group with 59.32% and 64.41% respectively. In Kumar Sood, et al., study 63.3% of the women underwent emergency cesarean section in the misoprostol group.[69]

In the present study, the indication identified in majority of the patients were the previous LSCS (elective) with 21.19% followed by fetal distress and CDMR with 20.34% and 13.56% respectively. In Deepak Bose, et al.[54] study previous Caesarean section and fetal distress were the indications identified in most of the participants with 39.25% and 13.55% respectively. Present study and Deepak Bose, et al[54] showed similar results in terms of indications.

COMPARISON OF HEMOGLOBIN

In this study, 11.67 ± 1.37 and 10.78 ± 1.12 were identified as the pre-operative and post-operative hemoglobin estimation in the misoprostol group. In a study conducted by Atul Kumar Sood, et al.[69], pre-operative and post-operative hemoglobin estimation identified in the misoprostol group was 10.67 ± 0.90 and 9.79 ± 0.99 respectively.[69] There was a decrease identified between the mean of pre-operative and post- operative hemoglobin levels. Alaa Eldin A.[52] Youssef, et al.[52], performed a study on 420 women, in which 11.02 ± 1.4 and 10.54 ± 1.47 were observed as the pre-operative and post-operative hemoglobin in the misoprostol group.[52] Alaa Eldin A. Youssef, et al.,[52] Atul Kumar Sood, et al[69] and the present study showed similar results.

Table 19: Table Comparison of mean of Hb between various studies

Study	Population	Mean of Hb (misoprostol group)
Atul Kumar Sood, et al., [69]	174	Pre-operative (10.67 ± 0.90) Post-operative (9.79 ± 0.99)
Alaa Eldin A. Youssef, et al.[52]	420	Pre-operative (11.02 ± 1.4) Post-operative (10.54 ± 1.47)
Hamideh Pakniat, et al.,[53]	158	Pre-operative (12.84 ± 1) Post-operative (10.68 ± 1.61)
Present study	118	Pre-operative (11.67 ± 1.37) Post-operative (10.78 ± 1.12)

In the current study, the mean of pre-operative and post-operative hemoglobin estimation identified in the TXA group was 11.76 ± 1.43 and 11.17 ± 1.4 respectively. Zakaria F Sanad, et al., conducted a study on 74 pregnant women in which the pre-operative and post-operative hemoglobin identified in the TXA group was 11.78 ± 1.08 and 11.39 ± 1.08 respectively.[58] Tullika Singh, et al., performed a randomized case-controlled prospective study on 200 pregnant women in which 10.59± 0.707 and 10.03± 0.76 were identified as the pre-operative and post-operative hemoglobin in the TXA group.[71] In the present study, the mean difference of misoprostol was comparatively higher, hence tranexamic acid is considered to control blood loss better.

Zakaria F Sanad, et al.[58], Tullika Singh, et al., [71] and present study showed similar results.

Table 20: Comparison of mean of Hb between various studies

Tudy	Population	Mean of Hb (tranexamic acid group)
Hamideh Pakniat, et al.[53]	158	Pre-operative (13.15 ± 0.79) Post- operative (10.69 ± 0.99)
Zakaria F Sanad, et al.[58]	74	Pre-operative (11.78 ± 1.08) Post- operative (11.39 ± 1.08)
Tullika Singh, et al., [71]	200	Pre-operative (10.59± 0.707) Post- operative (10.03± 0.76)
Present study	118	Pre-operative (11.76 ± 1.43) Post- operative (11.17 ± 1.4)

MOPS COUNT:

In this study, 4.73 ± 1.27 and 3.2 ± 1.45 were identified as the mean of mops count in the misoprostol and tranexamic acid group respectively.

SUCTION VOLUME:

In the present study, suction volume was between 200 to 400 ml in the most of the participants in the misoprostol group with 49.15% followed by 400-600ml and <200ml with 37.29% and 13.56%%. While, in the tranexamic acid group it was between 400 to 600 ml with 45.76% followed by 200 to 400 ml and <200ml with 44.07% and 10.17% respectively. In Hamideh Pakniat, et al.[53] the mean of blood suction was 193.94 ± 104.79 cc in the misoprostol group and 260.25 ± 79.06 , in TXA group. In Hamideh Pakniat, et al[53] and present study the suction volume was more in the tranexamic acid group as compared to the misoprostol group. In Alaa Eldin A. Youssef, et al., study the mean of blood volume in suction apparatus was 227.39 ± 49.2 ml in the misoprostol group which resembles to present study results.[52]

UTEROTONICS:

In the current study, 8.47% of the participants in the misoprostol group required uterotonics. Whereas, 15.25% in the TXA group required uterotonics. In Deepak Bose, et al., study 32.1% of the participants in the TXA group required uterotonics whereas, 31.7% in the misoprostol group which was an increased rate as compared to the present study results [54].

In another study by Hamideh Pakniat, et al., 3.8% in the misoprostol group required uterotonics while, 5% in the TXA group required uterotonics.[53]

In Hamideh Pakniat, et al[53] and present study the requirement of uterotonics was lower in the misoprostol group.

Table 21: Comparison of requirement of uterotonics between various studies.

Study	Population	Uterotonics (%)
Hamideh Pakniat, et al.[53]	158	Misoprostol group (3.8%) Tranexamic acid group (5%)
Deepak Bose, et al.,[54]	163	Misoprostol group (31.7%) Tranexamic acid group (32.1%)
Present study	118	Misoprostol group (8.47%) Tranexamic acid group (15.25%)

ADDITIONAL PROCEDURES:

In this study, 1.69% of the participant in the TXA group required additional procedures. Whereas, none of the participants in misoprostol group required additional procedures. In Alaa Eldin A. Youssef, et al., study 6.10% in the misoprostol group required additional procedures.[52]

BLOOD TRANSFUSION

In the current study, 3.39% of the participants in the TXA group required blood transfusion. While, none of those in the misoprostol group required blood transfusion. In Hamideh Pakniat, et al[53] study 6.4% of the participants in the misoprostol group required blood transfusion while 1.2% in the TXA group. In another study by Alaa Eldin A. Youssef, et al.,[52] study 14.5% of participants in the misoprostol group required blood transfusion. Hamideh Pakniat, et al[53]. Alaa Eldin A. Youssef, et al[52]study showed contradictory results to the present study.

SIDE EFFECTS

In the present study, the side effects identified in the misoprostol group were chills, vomiting and fever with 47.46%, 13.56% and 11.86% while, it was 11.86%, 5.08% and 3.39% in TXA group. Hamideh Pakniat, et al., performed a study in which vomiting, nausea and fever were the side effects identified in the misoprostol group with 15.4%, 29.5% and 1.3%. Similarly, in the tranexamic acid group with 15%, 38.8% and 11.2% respectively.[53] In the present study the side effects of misoprostol was comparatively higher than TXA, especially chills, there by making TXA a better choice than misoprostol.

Table 22: Present study and Hamideh Pakniat, et al[53] study showed similar side effects.

Study	Population	Side effects
Hamideh Pakniat, et al[53]	158	**Misoprostol group** Vomiting (15.4%) Nausea (29.5%) Fever (1.3%) **Tranexamic acid group** Vomiting (15%) Nausea (38.8%) Fever (11.2%)
Present study	118	**Misoprostol group** Chills(47.46%) Vomiting (13.56%) Fever (11.86%) **Tranexamic acid group** Chills (11.86%) Vomiting (5.08%) Fever (3.39%)

SUMMARY

SUMMARY:

Cesarean birth is becoming increasingly common, which might result in postpartum haemorrhage because the average blood loss following a caesarean section is twice that of a vaginal birth. In women with preeclampsia, extended labor, or heart disease, oxytocin is not the best agent for preventing PPH. Additionally, 10 to 42 percent of pregnant women who receive oxytocin are found to require supplementary oxytocin agents such as ergot alkaloids and prostaglandins. The purpose of this study was to examine the efficacy of intravenous tranexamic acid and sublingual misoprostol in minimizing blood loss in caesarean section patients. There were a total of 118 people that participated in the study.

- The mean age identified in the tranexamic acid and misoprostol group was 24.12 ± 3.3 and 23.81± 3.64 respectively.
- The most of the participants belonged to the gestational age (37+1 to 40 weeks) in the misoprostol and TXA group with 71.19% and 72.88% respectively.
- Most of the participants underwent emergency cesarean section in the misoprostol and tranexamic acid group with 59.32% and 64.41% respectively.
- The mean of the mops count in the misoprostol and tranexamic acid group were noted as 4.73 ± 1.27 and 3.2 ± 1.45 respectively, thereby making tranexamic acid comparatively more efficacious than misoprostol.
- Suction volume was between 200 to 400 ml in the majority of the participants in the misoprostol group with 49.15%. While it was between 400 to 600 ml in the TXA group with 45.76%.
- Around 8.47% of the participants in the misoprostol group required uterotonics. Whereas, 15.25% in the TXA group required uterotonics.
- Only 1.69% of the participant in the tranexamic acid group required additional

procedures.

- While 3.39% of the participants in the tranexamic acid group required blood transfusion.
- The pre-operative and post-operative hemoglobin in the misoprostol group were identified as 11.67 ± 1.37 and 10.78 ± 1.12 whereas, it was identified as 11.76 ± 1.43 and 11.17 ± 1.4 in TXA group. But since the mean difference of tranexamic acid was lower, it was considered better than misoprostol in reducing blood loss.
- The common side effects identified in the misoprostol group were chills, vomiting and fever with 47.46%, 13.56% and 11.86% while, it was 11.86%, 5.08% and 3.39% in the TXA group. The side effects of misoprostol was significantly higher than tranexamic acid, thereby making TXA a better choice than misoprostol .

CONCLUSION

CONCLUSION:

The present study concluded that the use of tranexamic acid significantly reduced the intraoperative and perioperative blood loss much better than misoprostol during caesarean section. Also tranexamic acid is better agent and can be administered routinely in patients undergoing caesarean section, as side effects of tranexamic acid were lesser than that of misoprostol. Hence tranexamic acid can be administered routinely in patients undergoing caesarean section.

LIMITATIONS:

A small sample size is one of the major limitations in the present study. A control group can also be considered in the study.

RECOMMENDATIONS:

Though perioperative Hemoglobin fall was also studied, better methods involving measurement of actual blood loss can be more accurate. Larger studies can be conducted with primary outcome measures like the incidence of postpartum hemorrhage, to validate the efficacy of drugs and also to identify the optimal dose and route of administration at cesarean delivery.

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ANNEXURE

ANNEXURE 1:

INFORMED CONSENT FORM

I Mrs. _____ have been explained in my own understandable language, that I will be included in a study which is **comparison of intravenous tranexamic acid versus sublingual misoprostol in reducing blood loss in patients undergoing caesarean section.**

I have been explained that my clinical findings, investigations, intraoperative findings, will be assessed and documented for study purpose.

I have been explained my participation in this study is entirely voluntary, and I can withdraw from the study any time and this will not affect my relation with my doctor or the treatment for my ailment.

I have understood that all my details found during the study are kept confidential and while publishing or sharing of the findings, my details will be masked.

I have principal investigator mobile number for enquiries.

DR. DEEKSHA RAO .M

PRINCIPAL INVESTIGATOR

PH: 8220519719

I in my sound mind give full consent to be added in the part of this study.

Signature of the patient:
Name:
Signature of the witness:
Name:
Relation to patient:
Date:
place:

ANNEXURE 2:

PROFORMA

COMPARISON OF INTRAVENOUS TRANEXAMIC ACID VERSUS SUBLINGUAL MISOPROSTOL IN REDUCING BLOOD LOSS IN PATIENTS UNDERGOING CAESAREAN SECTION.

- NAME: GENDER:
- AGE: HUSBAND NAME:
- ADDRESS: RELIGION:
- UHID NO:
- I.P NO:
- DATE &TIME OF ADMISSION:
- DATE &TIME OF DISCHARGE:

- **Complaints**
- Chief complaints:

- History of present pregnancy

- H/o amennorhea

- H/o bleeding pv/ spotting pv YES NO

- H/o pain abdomen YES NO

- Obstetrical history:

- BOOKED /UNBOOKED/REFERRED

- obstetric score

- Gravida Para Living Abortion

- Age of menarche:

- married life consanguinous marriage yes/no

- Menstrual history: regular/irregular
- Clots/ dysmenorrhea
- LMP
- EDD
- C EDD
- POG:

- **PREVIOUS HISTORY**
- Any h/o diabetes mellitus/hypertension/epilepsy/bronchial asthma
- Any h/o previous surgeries
- Any h/o drug allergies
- Any Risk Factors:

  Big baby

  Hydramnios

Multiple pregnancy

Abruption

Previous History of PPH

Prolonged labour

Grand multi

- **PERSONAL HISTORY**

  Diet

  Appetite

  Smoking

  Alcohol

  Bowel habits

- **GENERAL PHYSICAL EXAMINATION**
- Pallor/icterus/cyanosis/clubbing /lymphadenopathy/edema

- Height: weight: BMI:

- Pulse: Blood pressure:
- R/R: Temp**:**
- CVS: RS:
- Breast: spine: Thyroid:

- P/A:

- **UTERUS**
- APPROPRIATE FOR GESTATIONAL AGE
- LIE OR PRESENTATION
- CONTRACTIONS
- FHR

- **P/S:**

- **P/V:**

- **PROVISIONAL DIGNOSIS:**

- **INVESTIGATIONS:**
- HB: RBC WBC
- PCV PLT
- BLOOD SUGAR:
- BT: CT:
- BLOOD GROUPING AND TYPING:
- Antenatal hemoglobin
- Postnatal hemoglobin
- Hemoglobin difference
- Blood loss through mops and pads:
- Volume of blood in suction container:
- Mode of delivery:
- Maternal outcome:

- postpartum haemorrhage :
- Need for blood or blood components transfusion: yes/no
- Puerperal complication: yes/no
- Death: yes/no

ANNEXURE 3:

PATIENT INFORMATION SHEET

STUDY TITLE: "COMPARISON OF INTRAVENOUS TRANEXAMIC ACID VERSUS SUBLINGUAL MISOPROSTOL IN REDUCING BLOOD LOSS IN PATIENTS UNDERGOING CAESAREAN SECTION"

STUDY SITE: R.L Jalappa Hospital and Research Centre, Tamaka, Kolar.

This is to inform you that, you require administration of drugs- either tranexamic acid or misoprostol while undergoing LSCS.

We are conducting this study to assess the efficacy of the drugs.

If you are willing you will be enrolled in this study and we will do the study.

You will receive the standard care pre and post operatively

This will facilitate identifying the efficacy of the drugs. You are free to opt-out of the study at any time if you are not satisfied or apprehensive to be a part of the study. Your treatment and care will not be compromised if you refuse to be a part of the study. The study will not add any risk or financial burden to you if you are part of the study.

Your identity and clinical details will be confidential. You will not receive any financial benefit for being part of the study. You are free to contact

DR. DEEKSHA RAO. M or any other member of the above research team for any doubt or clarification you have.

Dr. DEEKSHA RAO. M

Mobile no: 8220519719

E-mail id: deekshamrao@gmail.com

ANNEXURE 4:

KEY TO MASTER CHART

Study group:

1. Tranexamic acid
2. Misoprostol

A: Age:

<20 years: 1

20-24 years: 2

25-29 years: 3

30-34 years: 4

35-39 years: 5

40 years: 6

B: Gestational age:

37- 40: 1

40+1- 41+6: 2

C: Elective/ emergency:

Elective: 1

Emergency: 2

D: Indication:

CDMR: 1

Malpresentation: 2

Previous LSCS: 3

Fetal distress: 4

CPD: 5

Contracted pelvis: 6

Malpresentation: 7

Failed induction: 8

Oligohydramnios: 9

Previous LSCS: 10

Deep transverse arrest: 11

E: Duration of the procedure:

30-45 min: 1

45-60 min: 2

F: Mops:

3: 1

4: 2

5: 3

6: 4

7: 5

8: 6

G: Suction volume:

<200ml: 1

200-400ml: 2

400-600ml: 3

H: Need for uterotonics:

yes 1

No: 2

I: Additional procedure:

yes: 1

No: 2

J: Blood transfusion:

yes 1

No: 2

K: Pre operative Hb:

8.5-9 g/dl: 1

9-9.9: 2

10- 10.9: 3

11-11.9: 4

12-12.9: 5

13-13.9: 6

L: Post operative Hb:

8.5-9 g/dl: 1

9-9.9: 2

10- 10.9: 3

11-11.9: 4

12-12.9: 5

13-13.9: 6

M: Side effects:

Fever: 1
Vomiting: 2
Chills: 3
Others: 4
No side effects: 5

MASTER CHART

MASTER SHEET

S.no	Study group	IP NUMBER:	A	B	C	D	E	F	G	H	I	J	K	L	M
1	1	847712	3	1	1	1	1	1	2	2	4	3	2	2	2
2	1	786039	3	2	2	4	1	3	3	2	6	4	2	2	5
3	1	850594	3	1	1	3	1	4	2	2	3	1	2	2	5
4	1	850988	4	1	2	9	1	2	3	2	4	3	2	2	5
5	1	803206	2	1	1	3	2	4	1	1	4	3	2	2	4
6	1	851369	4	2	2	10	1	1	2	2	4	4	2	2	3
7	1	850518	3	1	1	3	1	3	3	2	6	6	2	2	5
8	1	842922	3	1	2	9	1	4	3	2	6	5	2	2	5
9	1	827173	2	1	1	3	1	2	3	2	3	4	2	2	5
10	1	853047	2	2	2	4	1	3	2	2	6	5	2	2	2
11	1	853026	1	2	2	5	2	4	3	2	6	5	2	2	5
12	1	852126	2	2	2	10	1	1	2	2	3	1	2	2	4
13	1	853259	2	1	1	3	1	2	2	2	3	2	2	2	5
14	1	853262	4	1	2	4	1	4	3	2	3	3	2	2	5
15	1	853712	3	1	2	9	1	6	1	2	6	6	2	2	3
16	1	854419	2	1	1	3	1	2	3	1	3	4	2	2	5
17	1	850699	2	1	2	6	1	4	2	2	4	4	2	2	1
18	1	848069	2	2	2	4	2	3	3	2	5	5	2	2	5
19	1	856133	2	2	1	1	1	4	2	2	5	5	2	2	5
20	1	856353	2	2	2	5	1	1	3	2	3	2	2	2	5
21	1	862551	2	1	2	4	1	4	2	2	3	2	2	2	5
22	1	862304	2	1	1	1	1	2	3	2	2	2	2	2	5
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24	1	814494	3	2	1	6	2	5	2	2	5	5	2	2	5
25	1	852080	2	1	2	8	1	6	3	2	5	3	2	2	5
26	1	610006	3	1	2	5	1	4	2	1	6	5	1	2	4
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29	1	826708	2	1	1	3	1	1	1	2	1	1	2	2	5
30	1	867309	2	1	2	4	2	3	3	2	3	1	2	2	5
31	1	867638	2	1	2	5	1	4	2	2	5	4	2	2	5
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33	1	869937	2	1	1	3	1	5	3	1	3	2	2	2	5
34	1	864865	2	1	1	3	1	4	2	2	6	3	2	2	5
35	1	868225	2	1	2	5	1	1	3	2	5	4	2	2	5
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