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COMPARISON OF PREOPERATIVE MISOPROSTOL VERSUS STANDARD ACTIVE MANAGEMENT IN MINIMIZING BLOOD LOSS DURING ELECTIVE CAESAREAN SECTION

Dr Javeria Mumtaz[1*], Dr Rizwana Gull[2], Dr Sajida Asghar[3], Dr Saniya Naheed[4], Dr Ammarah Nadeem[5], Dr Anisa Saleem[6]

[1*,2,5,6]Assistant Professor, Department of Obstetrics and Gynaecology, HBS Medical and Dental College, Islamabad, Pakistan
[3,4]Associate Professor, Department of Obstetrics and Gynaecology, HBS Medical and Dental College, Islamabad, Pakistan

***Corresponding Author:** Dr. Javeria Mumtaz,
*Assistant Professor, Department of Obstetrics and Gynaecology, HBS Medical and Dental College, Islamabad, Pakistan, Email: javeria.tiwana@yahoo.com

ABSTRACT

Background: Blood loss in the third stage of labour can be fatal if massive postpartum hemorrhage occurs during or after a delivery. In practice most of the patients have been found to develop hemorrhage immediately after delivery till the discharge of placenta, a period known as third stage of labour. Preventive measures are routinely practiced to minify the chances of post-partum hemorrhage.

Objective: A study was conducted to analyse the effect of pre-operative rectal misoprostol in addition to active management of third stage of labour in minimizing blood loss within 24 hours after elective caesarean delivery.

Material and Methods: This randomized control trial was conducted in MCH center, PIMS, Islamabad after taking clearance from ethical committee from January 2019 to june 2019. A total of 126 patients were randomly allocated to either of two groups. Group A, who received a combination of rectal misoprostol + active management of third stage of labour (n=63) or Group B, who received active management of third stage of labour alone (n=63). Women with uncomplicated singleton pregnancy, having gestational age of >37 completed weeks who were undergoing elective cesarean section including fetal malpresentation, repeat cesarean delivery (previous 1 or 2 scar) were included in the study. The primary outcome measure was blood loss estimation and need of blood transfusions. Statistical analysis was done in SPSS version 21.0.

Results: The average age of women was 30.1 years in combination and 30.2 years in AMTSL alone group. The gestational age was 38.7 weeks in the combination group and 39.0 weeks in the AMTSL alone group. In the combination group, the average blood loss was 441.1 ml whereas in the AMTSL alone group it was 461.2 ml. The number of blood transfusions were remarkebly greater in-the AMTSL alone group compared to combination group (15.4% versus 1.6%, p-value, 0.008). Frequency of postpartum hemorrhage was 0 (0.0%) in-the combination compared to 2 (3.17%) in AMTSL alone group.

Conclusion: The reduction of blood loss was not significant with the addition of misoprostol with AMTSL in elective LSCS. However, blood transfusions and additional uterotonics were significantly reduced with additional misoprostol compared to AMTSL alone.

Key words: Misoprostol, oxytocin, AMTSL, hemorrhage

INTRODUCTION

Postpartum hemorrhage is the leading reason of maternal morbidity and mortality, responsible for more than quarter of all maternal deaths worldwide that can be prevented.[1] The large W.H.O multi country survey in middle and low income countries had shown the results that out of 274,985 births, 1.2 % of women had reported post-partum hemorrhage and those with a post-partum hemorrhage, 14.4% had a worse maternal out-come and 3.1% mortality.[2]

The risk of primary PPH is increased with Cesarean section (4.3% / 1000).[3] In Pakistan demographic health survey (PDHS) 2012-13, there were 14 % of deliveries conducted by a Cesarean section.[4]

Primary postpartum hemorrhage is defined as blood loss within 24 hours of delivery from genital tract, loss of more than 500 ml after SVD and more than 1000 ml after caesarean.[5] Potential effects of postpartum hemorrhage include anemia, fatigue, disseminated intravascular coagulation, renal failure, hemorrhagic shock and even death.[6]

Evidence suggests huge risks to women with local data also supporting this finding. In this regard a study conducted at AKUH Pakistan showed that 14/26 about 54% occurrence of postpartum hemorrhage were due to uterine atony making it the most common cause of primary PPH[7] followed by laceration tears and haematoma.

Uterotonic agents are used for prevention of atonic postpartum hemorrhage. For prophylaxis the gold standard is oxytocin so in AMTSL 10 IU oxytocin is given.[8]

Anesthesiologists consider oxy-tocin as savage drug because of its side effects on the glycemic and/or haemodynamic stability on terms of hypotension, tachycardia and myocardial ischemia so additional uterotonic may be required.[9] A study showed miso-prostol as an effective alternate for oxytocin to prevent post-partum haemorrhage.[5] Since PPH has grave consequences for both mother and the child it needs to be prevented with great focus and care.

The use of three component interventions defines the combined approach: (i) a prophylactic uterotonic agent; (ii) early clamping & division of the umbilical cord (iii) controlled cord traction. The World Health Organization has recently recommended oxytocin as the most important component of the AMTSL. Delayed cord clamping is recommended in majority of cases. Moreover, CCT is only recommended for trained health care providers.[2]

Misoprostol is synthetic prostaglandin E1 analogue used to prevent PPH by binding to smooth muscle receptors on uterus causing its contraction.[11] Oxytocin is heat labile agent, needs refrigeration while misoprostol is heat stable and kept at room temperature.[12]

Misoprostol is widely used now a days because of its low cost, affordability, fewer side effects (nausea, vomiting, diarrhea, fever, and chills) which are dose dependent and ease of administration through multiple routes (oral, buccal or rectal).[13]

The cross purpose of the study was to see if use of preoperative misoprostol in elective cesarean in addition to AMTSL allows further reduction in blood loss to avoid postpartum morbidity and mortality. We conducted a randomized controlled trial to compare misoprostol + AMTSL and AMTSL alone in terms of control of hemorrhage in women undergoing caesarean section.

MATERIAL AND METHOD

Setting

The study was conducted at the Department of Obstetrics and Gynecology, Maternal and Child Health Hospital UNIT 1, Pakistan Institute of Medical Sciences, Islamabad from January 2019 to

June 2019 after the approval of synopsis by the ethical committee. It was a randomized controlled trial with total 126 patients included in study.

Sampling Technique
Non-probability consecutive sampling

Subject Selection
Inclusion Criteria
1. Uncomplicated singleton pregnancy.
2. GA of > 37 completed weeks.
3. Elective Cesarean section including fetal malpresentation.
4. Repeat Cesarean delivery (previous 1 or 2 scar).

Exclusion Criteria
1. Multiple pregnancy
2. Uterine over distention due to polyhydramnios.
3. Macrosomic baby.
4. GA < 37 weeks.
5. In active labour.
6. Previous 3 or more scar.
7. H/O PPH due to other causes like uterine or cervical tear.

Data Collection Procedure
With the approval of the institutional ethics committee all patients presenting at mother and child health centre and fulfilling the inclusion criteria were recruited after informed verbal consent. Before procedure they were subjected to complete clinical evaluation, laboratory investigation including complete blood count and coagulation profile and sonographic evaluation especially for placental localization and fetal well-being. Those patients who agreed to be the part of study and fulfill inclusion criteria were randomly allocated into group A or B by lottery method.

Group A was given 400 mcg rectal misoprostol just before skin incision in addition to active management of third stage.
Group B was given active management of third stage only.
Following results were compared in both groups.

Primary outcome measure was blood loss estimation and need of transfusions.

Assessment of blood loss was done intraoperatively by visual assessment, gravimetric method and by change in hemoglobin, Hematocrit, RBC count estimation in blood CP report done 24 hours before and 24 hour after procedure.

Visual assessment
50 cm diameter floor spill = 500ml blood
1 fist full of clots = 500 ml blood

Gravimetric Method
Blood loss = weight of swabs preoperatively – weight of swabs postoperatively
1 gm increase in weight = 1 ml blood loss[13]

Laboratory Method

- Change in Hb = Preoperative haemoglobin – Postoperative haemoglobin
- Change in HCT = Preoperative HCT – Postoperative HCT
- Change in RBC count = preoperative RBC count -- postoperative RBC count
- 1 gm/dl drop in Hb = 3% drop in HCT = 500 ml blood loss

Secondary outcomes were additional uterotonic agents used, surgical intervention required, Neonatal outcome as APGAR score and neonatal intensive care admission and side effects of drug if noted.
All information was recorded in a self structured proforma.

Data Analysis

Data was entered in SPSS version 21.0 for analysis
Mean and S.D was calculated for quantitative variables like age, weight, height, parity, blood loss, hemoglobin, HCT and APGAR score.
Frequencies and percentages were calculated for qualitative variables additional ureterotonic agent used, surgical intervention required and adverse reactions.
Independent sample t-test was used to compare mean blood loss in both groups.
Hemoglobin, HCT and APGAR score was also compared with independent t-test compared. Chi square test was used to compare adverse reactions. P-value < 0.05 was considered significant.

Results

In above randomized trial, a total of 126 women were enrolled. Patients were randomly equally (n=63 each) allocated to two study arms i.e. combination group (misoprostol + AMTSL) and AMTSL alone group. Majority of the women were between 25 and 35 years in both combination and AMTSL alone groups of this study (68.2% and 66.6% respectively).
In this study more than two third of the study patients were having secondary or higher qualifications whereas very few were illiterate. Majority were multigravida and multipara status (84 % in combination group and 77.7 % in alone group) in this study.
The mean height of patients was 154.8 cms in the combination group and 156.5 cms in the AMTSL alone group. The average weight of women was also comparable, with 75.1 kgs in the combination group and 73.8 kg in the AMTSL alone group. The gestational age was 38.7 weeks in the combination group and 39.0 weeks in the AMTSL alone group.
The mean blood loss was found comparable between the two study groups. In the combination group, there was an average 441.2 ml blood loss whereas in the AMTSL alone group 461.1 ml blood loss was witnessed, however, this difference in the two means was not statistically significant (p-value, 0.53), though less bleeding was observed in the combination group. Moreover, it was noted that number of blood transfusions were significantly greater in the AMTSL alone group (15.4% versus 1.6%, p-value, 0.008). (Table 1)

Table I: Comparison of PPH between the two study groups

	Misoprostol + AMTSL (n=63)	**AMTSL along (n=63)**	**p-value**
Hemorrhage (> 500 ml to < 1000 ml)			
Yes	22 (34.9%)	29 (46.0%)	0.20
No	41 (65.1%)	34 (54.0%)	
Hemorrhage (≥ 1000 ml)			
Yes	0 (0.0%)	2 (3.17%)	0.02
No	63 (100%)	61 (96.8%)	

Additional uterotonics were given to 8 (12.7%) cases in the combination group compared to 18 (28.6%) in the AMTSL alone group and this difference in the two proportion was statistically significant (p-value, 0.04). Similarly, proportionate wise more blood units were transfused in AMTSL alone group compared to combination group (17.4% versus 6.3%, respectively), however, the difference was not statistically significant (p-value, 0.35). There were 2 (3.1%) cases of adverse reactions in the combination group compared to 3 (4.7%) in the AMTSL alone group. (Table II).

Table II: Comparison of blood loss between both study groups

	Misoprostol + AMTSL (n=63)	AMTSL alone (n=63)	p-value
Additional uterotonics	8 (12.7%)	18 (28.6%)	0.04
Blood units transfused	4 (6.3%)	11 (17.4%)	0.35
Any adverse reactions	2 (3.1%)	3 (4.7%)	0.78

Baby gender was found significantly different between the two study groups (p-value, 0.01). The average birth weight was 2.9 kg in combination group and 3.1 kg in AMTSL alone group and this difference was statistically significant. There were more neonates in combination group requiring NICU admissions (47.6% versus 28.5%, p-value, 0.04). Moreover, the difference in the A.P.GAR score at 1 minute and 5 minutes was not among the two groups. (Table III) and (Figure I)

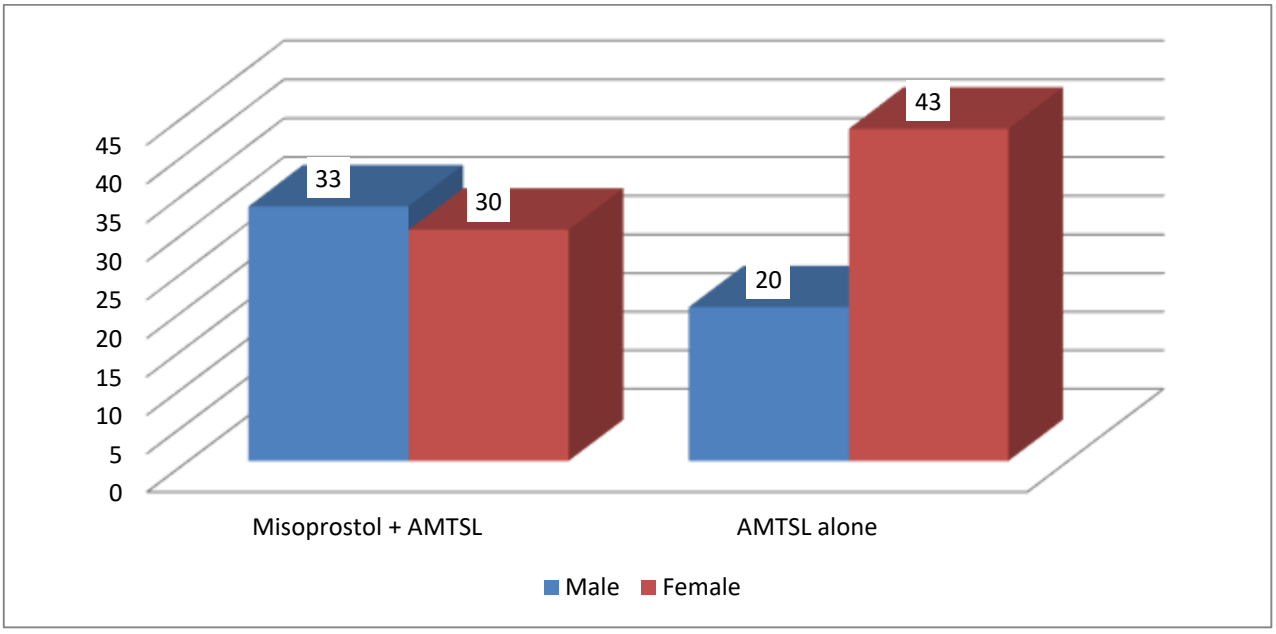

Figure I: Distribution of baby gender in the study groups

Table III: Neonatal outcome in the two study groups

	Misoprostol + AMTSL (n=63)	AMTSL alone (n=63)	p-value
Neonatal sex			
Male	33 (6.3%)	20 (17.4%)	
Female	30 (3.1%)	43 (4.7%)	0.01
Birth weight			
Mean SD	2.9 ± 0.3	3.1 ± 0.4	0.55
NICU admission	30 (47.6%)	18 (28.5%)	0.04
Apgar score			
1 minute	7.0 ± 1.9	6.8 ± 1.3	0.42
5 minute	8.4 ± 2.2	8.0 ± 1.9	0.27

DISCUSSION

Postpartum hemorrhage is one of the leading cause of morbidity and mortality during and immediately afterwards a delivery. It is a crucial complication of the third stage of labour (TSL) which is considered from delivery of fetus to up to delivery of placenta. TSL consists of 5 to 30 minutes duration of this period along with placental delivery, hemorrhage also occurs. Usually up to 250 cc to 500 cc blood loss is expected after delivery. In case hemorrhage crosses 500 ml level in vaginal delivery, and more than 1000ml in LSCS is called postpartum hemorrhage which may be life threatening for women.

Uterotonic medication normally oxytocin is used to decrease post placental blood loss by contraction of uterus. Misoprostol, a prostaglandin is also used to prevent and control postpartum hemorrhage. It can be taken by sublingual, oral, buccal, P/R routes and is found effective by many investigators. We planned and conducted a randomized controlled trial to see the effects of a combination of rectal misoprostol + AMTSL in comparison of AMTSL alone.

The age of presentation was comparable among the two groups, with overall mean age of 30.15 years with most of the cases between 25 to 35 years. Women age presentation is same as what is already witnessed by many other investigators in this region and nationally.

In this study more than two third of the study patients were having secondary or higher qualifications whereas very few were illiterate. Majority were multigravida and multipara status in this study.

When the primary outcome was assessed in terms of blood loss and number of transfusions, it was noted that the current study failed to reject the null hypothesis, as there was no difference between combination intervention and AMTSL alone in terms of mean blood loss in women undergoing caesarean section, however, the mean level of blood loss was insignificantly less in the combination group. Sitaula et ‘ al reported that mean blood loss was significantly associated with AMTSL alone when compared with addition of misoprostol.[14] Similarly, Sallam HF and colleagues reported that misoprostol significantly reduced blood loss during delivery and overall blood loss after delivery.[15]

Another study by Kumar SA and colleagues it was witnessed that misoprostol significantly reduced blood loss compared to placebo.[16] Borg HM et al also witnessed that pre-operative rectal misoprostol c section had significantly minimized blood loss during and after caesarean section when compared with postoperative misoprostol.[17]

Another study by Conde-Agudelo A et al concluded that the combination of misoprostol and oxytocin was significantly better in reducing blood loss during and after caesarean section than oxytocin alone.[18]

Moreover, in the present study there was a significantly greater proportion in the AMTSL alone group who required transfusions and additional uterotonics. This fact has been reported by several other investigators. Kumar SA and colleagues found that misoprostol group significantly reduced use of additional uterotonics after c-section.[16]

Borg HM et al also witnessed that no additional oxytocin and blood transfusions were required in the group of patients who were given misoprostol pre-operatively.[17]Conde-Agudelo A and colleagues witnessed that combination of misoprostol with oxytocin significantly decreased use of additional utero-tonics when compared with oxytocin alone. They concluded that misoprostol combined with oxytocin appears to be more effective than oxytocin alone in reducing intra-operative and post-operative hemorrhage during cesarean sction.[18]

The efficacy of routine administration of utero-tonic agents like oxytocin has been well established for reducing postpartum hemorrhage occurrence after vaginal birth or cesarean birth.[19] It has been assumed that the benefits of injectable utero-tonic agents detected for vaginal births also apply to caesarean deliveries.

An updated guideline of the Royal College of Obstetricians and Gynecologists on caesarean delivery suggests slow I.V bolus dose of 5 I.U of oxytocin after delivery to provide satisfactory uterine contractility, minimize delay in the delivery of the placenta, reduce intra-operative blood

loss and finally prevent post-partum hemorrhage.[20] In the present study again significantly more women in the AMTSL alone group required additional uterotonics.

In place of IV oxytocin there was a requirement of non-injectable preventer. Misoprostol, a prostaglandin E1 analogue with strong utero-tonic properties, has been suggested as an alternative to injectable utero-tonic agents for preventing post-partum hemorrhage following vaginal or caesarean deliveries. A latest Cochrane review found that oral misoprostol was associated with a higher risk of severe post-partum hemorrhage and use of additional utero-tonics after vaginal birth when compared to conventional utero-tonic agents.[21]

There are many additional benefits of misoprostol usage in pregnancy. The longer life outside the refrigerator and easy administration through oral routes of misoprostol makes it the ideal choice for the prevention of PPH and if occurred it is also useful for treating it with special benefits for low resource settings. It also has good safety profile with no consequence on blood pressure or on respiratory system, and can also be useful for women with asthama.[22]

As far as the therapy with misoprostol for the management of PPH is concerned, our study found that PPH of > 1000 ml was significantly less in the combination therapy group, thus, it appears that it reduces postpartum blood loss significantly. This fact has been proven by many investigators before as well.[20-22] But when comparing it with other drugs, there is still room of uncertainty as many studies have found oxytocin to be more effective.

This study has many advantages; firstly, very few studies have been done locally and nationally on this topic. The study methods are rigorous and RCT design has been opted. Thirdly, a reasonable sample of patients was enrolled and followed in this study.

There were few limitations of the trial as well, no long term follow-up of these patients was done so the detailed outcome of mothers and neonates is missing. Our primary focus was on the efficacy of drugs in controlling PPH and other related parameters like transfusions and additional uterotonics. The short term safety profile of the drugs in terms of hemodynamic stability, fetal distress etc. were not checked.

CONCLUSION

- Frequency of PPH in misoprostol + AMTSL group was significantly reduced. However, the combination does not reduce post cesarean mean blood loss at ELLSCS compared with AMTSL alone group.
- Blood transfusions and additional uterotonics use was significantly higher in the AMTSL alone group.

As studied women number wise limited, larger studies at national and international levels needed to compare the measurements

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