A COMPARATIVE STUDY OF OXYTOCIN/MISOPROSTOL/METHYLERGOMETRINE FOR ACTIVE MANAGEMENT OF THE THIRD STAGE OF LABOUR
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ABSTRACT

BACKGROUND
The third stage of labour is indeed the unforgiving stage of the labour and in it lurks more unheralded treachery than in both the other stages of labour combined. Many lifesaving drugs have been discovered and used for the management of this stage of labour. According to the WHO multicentric randomised trial using oral misoprostol with oxytocic, they concluded that oral misoprostol was associated with significantly high incidence of side effects like shivering and rise in body temperature and hence oxytocin is preferred to 600 mg of oral misoprostol in management of 3rd stage of labour in hospital settings, but still misoprostol has been suggested for the management of third stage of labour in developing countries, because it has strong uterotonic effects, can be given orally, inexpensive and does not need refrigeration.

The aim of the study is to compare oxytocin, misoprostol, methylergometrine for active management of the third stage of labour.

MATERIALS AND METHODS
A total of 300 women of 37 weeks to 42 weeks of gestation delivering vaginally in Konaseema Institute of Medical Sciences, Amalapuram, Andhra Pradesh. 300 women allocated into 3 groups of 100 each to receive 10 IU I.M. oxytocin, 600 mcg sublingual misoprostol or 200 mcg I.M. methylergometrine, respectively. Primary outcome measure was blood loss in the third stage of labor; secondary measures were duration of the third stage, side effects and complications.

RESULTS
Subjects who received 600 mcg of misoprostol had the least blood loss (113 mL), followed by oxytocin and methylergometrine. The shortest mean duration of the third stage was with misoprostol (4.34 mins.). Shivering and pyrexia were observed in misoprostol group and raised blood pressure in methylergometrine group.

CONCLUSION
Misoprostol is as effective as oxytocin and both are more effective than methylergometrine in active management of the third stage of labour. Misoprostol therefore can be used in places where facilities of storage and parenteral administration of oxytocin is limited.

KEYWORDS
Postpartum Haemorrhage, Misoprostol, Oxytocin, Methergine.

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BACKGROUND
PPH has been a nightmare for obstetricians since centuries. In developing countries, PPH continues to be a leading cause accounting for 25-43% of maternal deaths.¹ Atonic PPH is the most common of PPH and the leading cause of maternal death.² One intervention that has been promoted as an effective method in preventing atonic PPH is the active management of the third stage of labour.² By various studies conducted, it has been proved the prevention of PPH can be achieved by active management of the third stage in almost 40% of cases. Several drugs reduce PPH by stimulating the uterus to contract. Ergot derivatives have been used for decades, although oxytocin is the drug of choice; in some centers, methylergometrine is still being used. Several prostaglandins are used as the second or third line agents. These drugs, however, must be refrigerated to remain effective. Moreover, most uterotonics must be
administered by injection, which requires sterile equipment and training in safe administration, prerequisites, which are unavailable for most women delivering in poor underdeveloped countries. Misoprostol, a prostaglandin E1 analog, is heat stable and can be administered orally, rectally or sublingually. Most of the randomised studies of prophylactic misoprostol have used oral and rectal administration, though a recent pharmacokinetic study showed that sublingual administration achieves the highest peak concentration and the best bioavailability. The purpose of this study is to compare these most frequently used uterotonics agents in terms of their efficacy and side effects.

Aims and Objectives
A comparative study of oxytocin, misoprostol, methylergometrine for active management of the third stage of labour with regards to their influence on:
1. Duration of the third stage of labour.
2. Amount of blood loss.
3. Adverse effects.
4. Need for additional uterotonics in each group.

MATERIALS AND METHODS
Source of data- Source- 300 patients admitted to labour ward of OBG Department of Konaseema Institute of Medical College and Hospital, Amalapuram.

300 pregnant women undergoing spontaneous or induced labour with intended vaginal delivery were included. Sampling method is systematic random sampling. Study type is prospective randomised controlled trial. The women were selected according to the following criteria.

Inclusion Criteria
Women between 37-42 weeks of gestation, deliveries through vaginal route were scheduled, singleton foetus, cephalic presentation. Consent of the patient and relatives will be taken after explaining the procedure.

Exclusion Criteria
Pregnant women with any high-risk pregnancy, previous cesarean section or any previous surgery of the uterus, instrumental delivery, history of manual removal of placenta in previous pregnancy, anaemia, twins, polyhydramnios, malpresentation, intrapartum death, foetal anomaly and contraindications for induction of labour.

Method of Collection of Data
The cases were divided into three groups of 100 each. Group I, 100 subjects were given oxytocin 10 IU I.M.; group II, 100 subjects were given 600 mcg misoprostol sublingually; group III, 100 subjects were given 0.2 mg of methylergometrine I.M. after the delivery of the baby, but before separation of the placenta. Placenta was delivered by controlled cord traction (Brandt Andrew's method). After the delivery of the placenta, duration of the third stage was noted in minutes. The placenta was inspected for its completeness and the total amount of bleeding measured after breaking the clots and cleansing the whole vagina and cervix of the clots. The amount of blood loss was measured with number of equal-sized pads soaked. One full-soaked pad = 20 mL of blood loss. Comparison will be made in terms of quantitative assessment of blood loss, duration of third stage, incidence of PPH, additional requirements of drugs, side effects and efficacy. The results observed were subjected to statistical analysis by Student's t-test, odds ratio, Chi-square test and a 'p' value of <0.05 was considered as significant.

Patients were monitored for 6 hours postpartum to see for developmental side effects like abdominal pain, nausea, vomiting, shivering and pyrexia. Vitals like blood pressure and pulse rate are monitored. In case of excessive blood loss, other uterotonics were given immediately. Hb% was measured before and 24 hours after delivery to quantify the blood loss.

Statistics- SAS Software was used. ANOVA was applied for the comparisons.

RESULTS
This study was done in KIMS Hospital, 300 women undergoing full-term vaginal delivery with or without episiotomy were enrolled to compare the efficacy and side effects of oxytocin, misoprostol with IM methylergometrine for management of III stage of labor. Study was done over a period 2 years and source of data being 300 women enrolled and randomly distributed to three groups. 100 women in group I received oxytocin and 100 women in group II received misoprostol, group III received methylergometrine.

Table 1- Age Comparison- The majority of patients were in age group of 20-24 years. The average age of patients in group I (oxytocin) 24.94±4.25 yrs.; group II (misoprostol) 24.07±4.01 yrs. and group III (methylergometrine) 23.71±3.51 yrs. The majority of the patients are nulliparous.

Table 2- In group I (oxytocin) 52% are nulliparous, in group II (misoprostol) 55% nulliparous and in group III methylergometrine 62% are nulliparous. The results were not statistically significant. Table 3- Mean duration of third stage of labour- The mean duration in group I (oxytocin) is 4.50±95 minutes; group II (misoprostol) is 4.34±1.08 minutes and group III (methylergometrine) is 5.13±1.41 minutes. Table 4- Mean blood loss during third stage of labour- The mean blood loss in group I (oxytocin) is 119.45±40.4 mL; in group II (misoprostol) is 113.33±27.28 mL and in group III (methylergometrine) 173.35±90.17 mL. Table 5- Requirement for Additional Uterotonics- The need for additional requirements in group I (oxytocin) is 3%; in group II (misoprostol) is 1% and in group III (methylergometrine) is 7%. Table 6- Side Effects- The side effects observed in group I (oxytocin) were nil; in group II (misoprostol) are shivering (in 23% of cases) and fever (in 11% of cases) and in group III are nausea (in 22% of cases) and vomiting (in 10% of cases). Table 7- The complications observed in group I (oxytocin) were nil; in group II (misoprostol) are PPH 1% and in group III (methylergometrine) are PPH 1%, retained placenta 2%.
tol offers one of administration of good 8±45.7 mL) and methylergometrine intravenous oxytocin and -J. Evid. Based Med. Healthc., developing countries including India. Misopros of third stage of labour, blood loss and adverse effects of three oxytocic regimes. The sublingual route of administration of misoprostol was chosen in the present study because of better pharmacokinetics compared with oral or vaginal routes. Sublingual tablets were easy to administer and well accepted by women. Oral misoprostol has been found to have comparable results to standard parenteral oxytocics in reducing PPH. However, conflicting results showing that misoprostol is less effective than traditional uterotonics have also been published. A recent Cochrane meta-analysis concluded that misoprostol is better than a placebo, but less effective than conventional parenteral oxytocics during active management of third stage of labor.

In this present study, the mean age in group I (oxytocin) is 24.58±3.46 years; in group II (misoprostol) 23.92±3.19 years and in group III (methylergometrine) is 25.89±2.79. The difference between the age groups is not statistically significant. By comparing the parity, the nulliparous cases in group I (oxytocin) are 52%; in group II (misoprostol) 55% and in group III (methylergometrine) 62%. The multiparous cases in group I (oxytocin) are 48%; in group II (misoprostol) are 45% and group III (methylergometrine) are 38%. There was no significant difference regarding parity. In the present study, mean duration of third stage was 4.5±0.95 minutes in oxytocin group, 4.34±1.08 minutes, 5.13±1.41 minutes in methylergometrine group. The difference between the mean of three groups is significant (p=0.00004).

Gunjan Singh et al 2009 compared the efficacy of sublingual misoprostol, intravenous oxytocin and intravenous methylergometrine in active management of the third stage of labor. Patients who received 600 mcg of misoprostol had the lowest blood loss (96.05±21 mL), followed by 400 mcg of misoprostol (126.24±49.3 mL), oxytocin (154.7±45.7 mL) and methylergometrine (223.4±73.7 mL) (P<0.01). Shortest mean duration of the third stage of labour (5.74 minutes) was with 600 mcg of misoprostol while methylergometrine had the longest (6.83 minutes) (P<0.05). In the present study, the mean blood loss in oxytocin group is 119.45±40.41 mL, in misoprostol group is 173.35±90.17 mL. The difference between the mean of three groups is significant (P<0.05).

Walraven G et al 2005 studied on misoprostol in the management of the third stage of labor in the home delivery setting in rural Gambia. The methods was using three 200 mcg misoprostol tablets and placebo or four 0.5 mg ergometrine tablets (standard treatment) and placebo. The results were misoprostol group experienced lower incidence of measured blood loss >500 mL and postpartum Hb <8 g/dl, but the difference were not statistically significant. The reduction in postpartum (compared with predelivery) Hb ≥2 g/dl was 16.4% with misoprostol and 21.2% with ergometrine (relative risk 0.77; 95% Confidence Interval (CI) 0.60-0.98; (P=0.02) shivering was more common with

**DISCUSSION**

According to who recommendations for prevention of PPH “active management of third stage of labour” should include administration of an uterotonic soon after birth of the baby, delayed cord clamping and delivery of the placenta by controlled cord traction followed by uterine massage. Adequate storage and parenteral administration of an oxytocic by a trained health worker is not feasible in many developing countries including India. Misoprostol offers distinct advantages, because it is stable at room temperature, affordable and easy to administer.

The present study compared the duration of the third stage of labour, blood loss and adverse effects of three oxytocic regimes. The sublingual route of administration of misoprostol was chosen in the present study because of better pharmacokinetics compared with oral or vaginal routes. Sublingual tablets were easy to administer and well accepted by women. Oral misoprostol has been found to have comparable results to standard parenteral oxytocics in reducing PPH. However, conflicting results showing that misoprostol is less effective than traditional uterotonics have also been published. A recent Cochrane meta-analysis concluded that misoprostol is better than a placebo, but less effective than conventional parenteral oxytocics during active management of third stage of labor.

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misoprostol, while vomiting was more common with
ergometrine. In the present study, the side effects observed
in group I (oxytocin) were nil; in group II (misoprostol) are
shivering (in 23% of cases) and fever (in 11% of cases); in
group III are nausea (in 22% of cases) and vomiting (in 10% of cases). In the present study, complications occurred in
the oxytocin group are nil, in misoprostol group are PPH in
1% cases, in methylergometrine group are PPH are 1% and
in retained placenta 2%.

CONCLUSION
Postpartum haemorrhage is a major obstetrical complication
and is one of the prime causes of maternal morbidity and
mortality. We concluded that misoprostol is as effective as
oxytocin and both of these are more effective than
methylergometrine in the active management of third stage
of labor. Methylergometrine and oxytocin have special
storage requirements with temperature between 2 and 8
degree centigrade and have to be given parentally; whereas,
misoprostol is stable at high temperature, has a shelf life of
several years and can be administered orally or sublingually.
Oxytocin is safest as far as side effects are concerned.
Whereas, with misoprostol, we observed side effects, which
settled with time without any treatment. Hence, if
misoprostol is made available to the trained birth attendants
who supervise majority of the births in India, the lives of
many women dying of atonic PPH can be saved. In low
income countries, maternal anaemia compounds the
problem of PPH; therefore, administration of sublingual
misoprostol could reduce maternal morbidity and mortality.
Avoiding the intravenous or intramuscular route allows
easier administration and this could lead to widespread
acceptance of active management of the third stage of
labour. Any attempt to keep blood loss less than 100 mL
would be a substantial intervention in low resource settings
where most women are anaemic and a blood loss of even
500 mL may have adverse effects. These advantages of
misoprostol make it a feasible drug to be used in the routine
management of the third stage of labor.

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