Articles

WHO multicentre randomised trial of misoprostol in the management of the third stage of labour

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Summary

Background Postpartum haemorrhage is a leading cause of maternal morbidity and mortality. Active management of the third stage of labour, including use of a uterotonic agent, has been shown to reduce blood loss. Misoprostol (a prostaglandin E1 analogue) has been suggested for this purpose because it has strong uterotonic effects, can be given orally, is inexpensive, and does not need refrigeration for storage. We did a multicentre, double-blind, randomised controlled trial to determine whether oral misoprostol is as effective as oxytocin during the third stage of labour.

Methods In hospitals in Argentina, China, Egypt, Ireland, Nigeria, South Africa, Switzerland, Thailand, and Vietnam, we randomly assigned women about to deliver vaginally to receive 600 μg misoprostol orally or 10 IU oxytocin intravenously or intramuscularly, according to routine practice, plus corresponding identical placebos. The medications were administered immediately after delivery as part of the active management of the third stage of labour. The primary outcomes were measured postpartum blood loss of 1000 mL or more, and the use of additional uterotonics without an unacceptable level of side-effects. We chose an upper limit of a 35% increase in the risk of blood loss of 1000 mL or more as the margin of clinical equivalence, which was assessed by the confidence interval of the relative risk. Analysis was by intention to treat.

Findings 9264 women were assigned misoprostol and 9266 oxytocin. 37 women in the misoprostol group and 34 in the oxytocin group had emergency caesarean sections and were excluded. 366 (4%) of women on misoprostol had a measured blood loss of 1000 mL or more, compared with 263 (3%) of those on oxytocin (relative risk 1·39 [95% CI 1·19–1·63], p<0·0001). 1398 (15%) women in the misoprostol group and 1002 (11%) in the oxytocin group required additional uterotonics (1·40 [1·29–1·51], p<0·0001). Misoprostol use was also associated with a significantly higher incidence of shivering (3·48 [3·15–3·84]) and raised body temperature (7·17 [5·67–9·07]) in the first hour after delivery.

Interpretation 10 IU oxytocin (intravenous or intramuscular) is preferable to 600 μg oral misoprostol in the active management of the third stage of labour in hospital settings where active management is the norm.

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Introduction

Postpartum haemorrhage is a leading cause of severe maternal morbidity and death, in more developed and less developed countries. In Zimbabwe, one study found that obstetric haemorrhage was responsible for 25% of maternal deaths, with a cause-specific maternal mortality rate of 40 per 100 000 livebirths.[1] Similarly, in Nigeria, postpartum haemorrhage was found to have a case-fatality rate of 2·2% at a teaching hospital.[2] The use of uterotonic agents in the management of the third stage of labour reduces the amount of bleeding and the need for blood transfusion, but is associated with side-effects, especially when ergot alkaloids are used.[3] Furthermore, these agents are given by injection, and ergot preparations require refrigeration and protection against light to preserve their effectiveness. Some prostaglandins such as prostaglandin F2α and synthetic prostaglandin E2 derivatives have been found to prevent postpartum haemorrhage in the third stage of labour,[4] but these agents are expensive, and also have to be given by injection and are associated with side-effects.

Misoprostol—a prostaglandin E1 analogue registered for the prevention and treatment of peptic-ulcer disease—has attracted widespread attention because of its strong uterotonic effects and ease of administration. These

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effects have been studied in early pregnancy, orally and vaginally after mifepristone for medical abortion,[5,6] for cervical ripening before surgical termination of pregnancy,[7] and at term for induction of labour.[8] El-Refaey and colleagues reported the first use of oral misoprostol for the management of the third stage of labour in an observational study.[9,10] 600 μg misoprostol were given orally to 237 women after vaginal delivery. Estimated blood loss of 500 mL or more occurred in 6% of women, and a further 5% needed therapeutic uterotonics. Shivering was noted in 62%, and there was a mean increase of 0·5°C in body temperature after misoprostol administration. In a randomised controlled trial from South Africa,[11] shivering was reported in 41% of women receiving 600 μg misoprostol, 37% of those who received 400 μg, and 15% of those who received placebo. We confirmed these side-effects in a dose-finding trial.[12]

We present here the results of a trial to test the hypothesis that misoprostol use in the active management of the third stage of labour is equivalent to that of oxytocin in terms of measured blood loss of 1000 mL or more and the use of additional uterotonics without an unacceptable level of side-effects.

Methods

Participants

We assessed women on admission to labour wards in Argentina, China, Egypt, Ireland, Nigeria, South Africa, Switzerland, Thailand, and Vietnam. Women were not eligible if they had asthma or other severe chronic allergic conditions, if the delivery was regarded as an abortion, if caesarean section was already planned, if they had a body temperature of greater than 38°C, or if they were not willing or able to give informed consent. We excluded from the analysis of outcomes the women who had an emergency caesarean section after randomisation because these women were not eligible to receive the interventions and did not have the outcomes measured.

The trial was approved by the ethics committees of the participating hospitals and by the Scientific and Ethical Review Group of the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, Geneva, Switzerland.

Procedures

The random allocation schedule was generated centrally at WHO, Geneva, Switzerland, by computer-generated random numbers and was stratified by country. Within the strata, women were individually randomised into one of two intervention groups with randomly varying block sizes of 4–6 women.

Specially designed, treatment-pack dispensers holding 25 treatment packs were placed in a central location close to delivery beds in the labour wards. The treatment packs were sealed, numbered sequentially, and could only be taken from the dispenser consecutively. Randomisation took place during the second stage of labour, when there was reasonable certainty that vaginal delivery would occur. The researcher took the next treatment pack from the dispenser and immediately wrote the woman's name on the pack and in the trial participants' list. At this point, the woman was considered to have entered the trial. If, for any reason, the contents of the pack were not used, the pack was returned to the WHO coordination centre in Geneva.

Each treatment pack contained three tablets, one ampoule, one syringe, and needle and swabs for injection. The treatment packs and their contents were identical in shape, colour, weight, and feel. Each woman received an injection and three tablets. The injection was given intramuscularly or intravenously according to the routine practice of the trial centres.

Misoprostol was provided in 200 μg tablets (Searle, Skokie, IL, USA) and oxytocin in 10 IU ampoules (Novartis Pharma, Basel, Switzerland). 18 975 treatment packs were prepared and distributed to the centres; 445 of these were not used by the closure of recruitment. Three random checks were made on the treatment packs to see whether the packing was error-free and all contents included. Additional quality control was done by the manufacturers to check whether we included correct active or placebos in the packs.

Each woman received either misoprostol 600 μg (3×200 μg tablets), or 10 IU oxytocin plus the corresponding placebo immediately after the baby was delivered and the cord was clamped and cut. If the women already had an intravenous line in place (eg, for epidural analgesia or augmentation of labour) or if the hospital's routine practice was to give oxytocin intravenously, the oxytocin (or placebo) was given via this route as a bolus injection. The routine management of the third stage of labour was ascertained before the trial through a survey of all centres. During the trial the third stage of labour was managed actively, as routinely practised in the participating hospitals. The active management consisted of the use of a uterotonic, clamping and cutting of the umbilical cord immediately after delivery of the infant, and either fundal or suprapubic pressure with cord traction after signs of placental separation. All centres followed their standard procedures in cases for which haemorrhage was regarded as abnormal.

The two prespecified primary outcomes were: measured postpartum blood loss of 1000 mL or more and the use of additional uterotonics. Secondary outcomes were: measured blood loss of 500 mL or more, blood transfusion, manual removal of placenta, any clinically diagnosed postpartum haemorrhage beyond the first hour after delivery, and additional measures required to treat clinically diagnosed haemorrhage (examination under general anaesthesia, bimanual compression, hysterectomy, suturing of cervical tears, and maternal admission to intensive-care unit).

Blood loss was measured from the time of delivery of the baby until the mother was transferred to postnatal care. Immediately after the cord was clamped and cut, the blood collection was started by passing a flat bedpan under the buttocks for women delivering in beds or putting in place an unsoiled receiver for women delivering on gynaecological tables. Blood collection continued in the immediate postdelivery period until the third stage of the labour was completed; the woman was then transferred to the postnatal ward. This period usually lasted up to 1 h postpartum. The collected blood was poured into a standard measuring jar provided by WHO, and its volume measured. To simplify the procedure for measurement of blood loss, small gauze swabs soaked with blood were put into the measuring jar and included in the measurement together with the blood and clots. We did a validity study before the trial to assess the effect of gauze swabs on estimation of blood loss and found that it was likely to result in about a 10% increase in the measurements.

Shivering was assessed by direct observation or indirect questioning (ie, "Do you have any complaints?"). If shivering was detected or reported, the woman was asked whether she would regard her

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experience as mild, moderate, or severe. Any side-effect necessitating treatment was recorded as severe, and a special form with details of the event was completed. Body temperature was assessed with the standard thermometers routinely used in each centre. High body temperature was defined as an axillary temperature greater than 38°C. Shivering and pyrexia were both assessed within 1 h of delivery.

The trial data safety and monitoring committee met twice, after about 6000 and 12 000 women were recruited. The steering committee was advised to continue with recruitment after both interim analyses.

Statistical analysis

The question guiding the sample-size calculation of this equivalence trial was, "What level of (weaker) efficacy of oral 600 μg misoprostol would be clinically acceptable as equivalent to the standard regimen of 10 IU oxytocin?" The sample-size calculation was based on the occurrence of measured (not estimated) blood loss of 1000 mL of more. An increase in relative risk of up to 35% with misoprostol was regarded as acceptable. 20 246 women were needed to provide 90% power for a two-sided, 5% level test to detect a proportional change of 35% or more if the rate of blood loss of 1000 mL or more was 2% with oxytocin. Similarly, 13 338 women were needed if the rate of blood loss of 1000 mL or more was 3% with oxytocin.

Relative risks with 95% CI were used to measure the treatment effect for the main outcomes. Crude relative risks were calculated first, and these were adjusted for centres by means of the Mantel-Haenszel weighted relative risk and the Greenland and Robbins 95% CI. The Breslow and Day χ^2 test for homogeneity across centres was used. Risk differences and 95% CI were also calculated for the primary outcomes by the "traditional" method with crude proportions.[13] From these risk differences and 95% CI, the number needed to treat (and its 95% CI) with oxytocin to prevent an extra case of blood loss greater than or equal to 1000 mL was calculated.[13]

Effect modification for the primary outcomes was assessed by subgroup analyses specified a priori with the following variables: parity, use of epidural analgesia, and use of oxytocin or prostaglandin before delivery.

Results

Of the 29 295 women screened for eligibility between April, 1998, and November, 1999, 19 025 were eligible. 18 530 of these eligible women were enrolled into the trial. The most common reasons for not being eligible were no consent given or obtained (6203 [60·4%]) and planned caesarean section (5381 [52·4%]). 495 eligible women were not randomised either because the attending health worker refused or because the women delivered too quickly. 9264 women were randomly assigned misoprostol and 9266 oxytocin (figure 1). 2734 women were recruited in Argentina, 2195 in China, 3436 in Egypt, 449 in Ireland, 1570 in Nigeria, 2819 in South Africa, 356 in Switzerland, 1819 in Thailand, and 3152 in Vietnam.

Among randomised women, 37 in the misoprostol group and 34 in the oxytocin group had an emergency caesarean section. These women neither received the interventions nor had the outcomes measured, and were therefore excluded from the analysis of outcomes. A further small group of women had some missing outcome data and could not be included in the corresponding analyses (figure 1).

The two groups were similar with regard to baseline characteristics and risk factors associated with the primary outcomes (table 1). 39 (0·4%) of 9227 women in the misoprostol group and 20 (0·2%) of 9232 women in the oxytocin group did not receive the allocated treatment. These women were included in the analysis in the groups as randomised. In both groups, more than 96% of women were randomised less than 2 h before delivery. 137 (1·5%) women in the misoprostol group and 138 (1·5%) in the oxytocin group were randomised immediately after delivery because of shortage of staff or unexpectedly speedy delivery. All of these women had given consent earlier, but packs were drawn and the women's names were recorded after delivery.

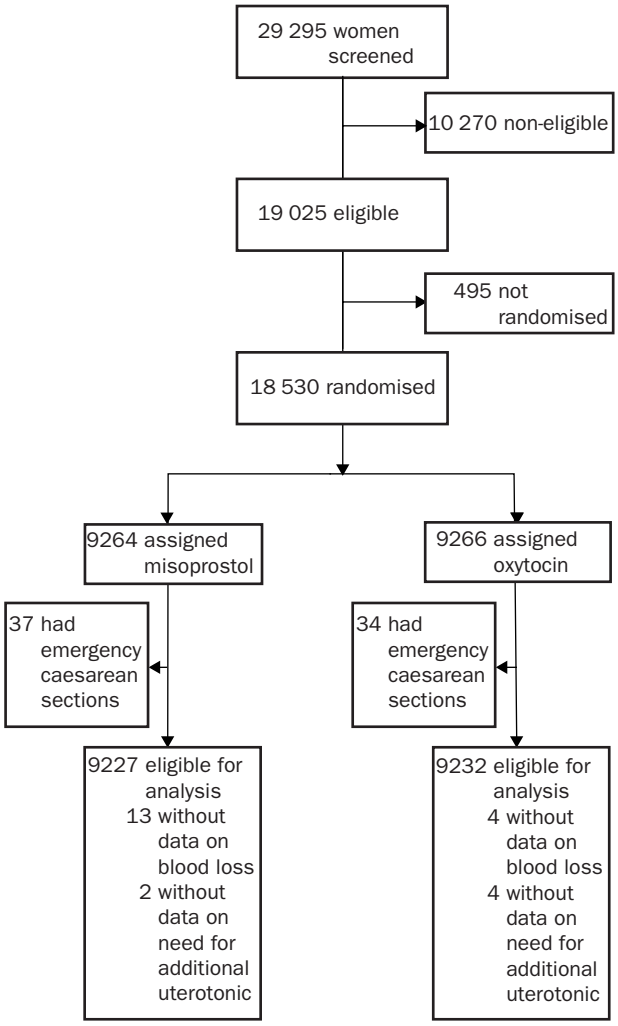

Figure 1: **Trial profile**

	Misoprostol (n=9264)	Oxytocin (n=9266)
Mean (SD) maternal age (years)	26·5 (5·5)*	26·3 (5·4)†
Parity=0	4153 (45%)	4245 (46%)
Parity ⩾5	482 (5%)	482 (5%)
Mean (SD) gestational age (weeks)	38·7 (2·3)‡	38·7 (2·2)§
Gestational age <37 weeks	1126 (12%)	1082 (11%)
Low birthweight (<2500 g)	684 (7%)	709 (8%)
Oxytocin or prostaglandin before birth of baby	3517 (38%)	3503 (38%)
Epidural analgesia	572 (6%)	557 (6%)
Assisted vaginal delivery	843 (9%)	764 (8%)
Perineal suturing	6152 (66%)	6129 (66%)

*Data available for 9248 women only. †Data available for 9238 women only. ‡Data available for 9261 women only. §Data available for 9262 women only.

Table 1: **Baseline characteristics**

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	Misoprostol	Oxytocin	Relative risk (95% CI)	p
Primary outcomes				
Blood loss ⩾1000 mL*	366/9214 (4%)	263/9228 (3%)	1·39 (1·19–1·63)	<0·0001
Use of additional uterotonics*	1398/9225 (15%)	1002/9228 (11%)	1·40 (1·29–1·51)	<0·0001
Secondary outcomes				
Blood loss ⩾500 mL	1793/9213 (20%)	1248/9227 (14%)	1·44 (1·35–1·54)	<0·0001
Need for blood transfusion	72/9221 (0·8%)	97/9226 (1%)	0·74 (0·55–1·01)	0·06
Manual removal of placenta	219/9225 (2%)	215/9228 (2%)	1·02 (0·85–1·23)	0·88
Delayed postpartum haemorrhage	37/9226 (0·4%)	31/9229 (0·3%)	1·19 (0·74–1·92)	0·54
Bimanual compression	84/9224 (0·9%)	80/9231 (0·9%)	1·05 (0·77–1·43)	0·81
Exploration under general anaesthesia	70/9224 (0·8%)	61/9231 (0·7%)	1·15 (0·82–1·62)	0·48
Hysterectomy	4/9224 (0·04%)	8/9231 (0·09%)	0·50 (0·15–1·66)	0·39
Admission to intensive care	4/9224 (0·04%)	5/9231 (0·05%)	0·80 (0·22–2·98)	1·00†
Maternal death	2/9225 (0·02%)	2/9230 (0·02%)	1·00 (0·14–7·10)	1·00†

*Excluding 37 and 34 women with emergency caesarean section and 13 and 4 women lost to follow-up in misoprostol and oxytocin groups, respectively, for blood loss ⩾1000 mL, and two and four women without information on the need for additional uterotonics. †Fisher's exact test used.

Table 2: **Primary and secondary outcomes according to treatment group**

Centre	Misoprostol	Oxytocin
Argentina	96/1358 (7%)	49/1361 (4%)
China	18/1093 (2%)	10/1098 (0·9%)
Egypt	3/1708 (0·2%)	6/1703 (0·4%)
Ireland	15/221 (7%)	9/225 (4%)
Nigeria	36/785 (5%)	40/783 (5%)
South Africa	56/1405 (4%)	51/1409 (4%)
Switzerland	17/173 (10%)	16/177 (9%)
Thailand	57/900 (6%)	24/899 (3%)
Vietnam	67/1570 (4%)	57/1572 (4%)

Table 3: **Rate of blood loss of 1000 mL or more by centre**

A higher proportion of women in the misoprostol group than the oxytocin group had measured blood loss of at least 1000 mL and use of additional uterotonics (table 2). The additional uterotonic was oxytocin in most cases in the misoprostol group (77%) and in the oxytocin (80%) group. The crude overall difference in the rate of blood loss of 1000 mL or more between misoprostol and oxytocin was 1·1% (95% CI 0·6–1·6), which ranged from −0·2 to 3·7% between centres. After adjusting for centre characteristics, we obtained the same relative risks and almost identical 95% CIs (1·20–1·63 and 1·30–1·51 for blood loss and additional uterotonics, respectively). The number of women who needed to receive oxytocin rather than misoprostol to prevent one extra case of blood loss of at least 1000 mL was 89 (61–167), and the number who needed to receive oxytocin rather than misoprostol to prevent one extra case of the use of additional uterotonics was 23 (19–30).

There was statistical heterogeneity between centres for measured blood loss of 1000 mL or more (p=0·02) and for the use of additional uterotonics (p<0·0001). The relative risk of having measured blood loss of 1000 mL for a woman receiving misoprostol ranged from 0·50 to 2·37 across centres (table 3). We did not collect individual data on route of administration of oxytocin, but used the presence of an intravenous line as a proxy for intravenous oxytocin administration. Regarding this variable as a possible effect modifier did not influence the pattern of the results.

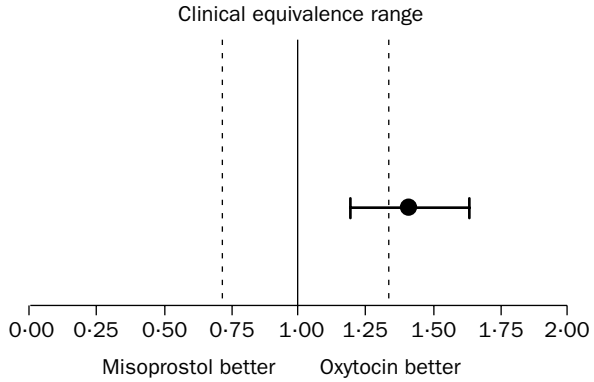

Figure 2: **Relative risk of blood loss of 1000 mL or more with misoprostol compared with oxytocin**
Vertical dotted lines represent margins of clinical equivalence determined a priori. Solid line represents null effect.

Figure 2 is a graphical presentation of the CI for the relative risk of having a measured blood loss of 1000 mL or more with misoprostol. The dotted vertical lines represent the margins of clinical equivalence[14] between misoprostol and oxytocin expressed as a 35% increase in the rate of blood loss of 1000 mL or more as defined before the start of the trial. The whole 95% CI for the relative risk was not fully inside the range defined by the two dotted lines and crossed the upper equivalence margin. The two drugs were therefore not shown to be clinically equivalent, although this possibility cannot be completely discarded.

The misoprostol group also had a consistently higher risk than the oxytocin group of blood loss of 500 mL or more in all centres (range of relative risks 1·0–2·6). There were no significant differences between misoprostol and oxytocin with regard to other secondary outcomes such as delayed postpartum haemorrhage or manual removal of the placenta, and consequences of severe bleeding such as exploration under general anaesthesia, bimanual compression, hysterectomy, or admission to intensive care (table 2). However, we had insufficient power to detect clinically relevant differences in effects on such rarer outcomes. Fewer women in the misoprostol group needed postpartum blood transfusion (table 2).

Misoprostol was associated with a significantly higher rate of any and severe shivering, body temperature higher than 38°C, and other prostaglandin-related side-effects such as nausea, vomiting, and diarrhoea (table 4). Few women had a body temperature of greater than 40°C during the first hour post partum. For every seven to nine women treated with misoprostol, one additional woman will have "any shivering", and for every 17–21 women, one additional woman will have a temperature greater than 38°C (table 4).

We did prespecified, stratified analyses for primary outcomes and main side-effects by oxytocin or prostaglandin use before delivery and by parity. There was no evidence of effect modification of these variables on the primary outcomes or main side-effects. In three centres (in Argentina, Ireland, and Switzerland), epidural analgesia was frequently used, so we did a

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Side-effects	Misoprostol	Oxytocin	Relative risk (95% CI)	NNH (95% CI)
Any shivering	1620/9227 (18%)	466/9232 (5%)	3·48 (3·15–3·84)	8 (7–9)
Severe shivering	120/9227 (1%)	14/9232 (0·2%)	8·58 (4·93–14·91)	87 (72–111)
Body temperature >38°C	559/9198 (6%)	78/9205 (0·8%)	7·17 (5·67–9·07)	19 (17–21)
Body temperature >40°C	5/9198 (0·1%)	0/9205	Infinity	..
Nausea	77/9227 (0·8%)	34/9232 (0·4%)	2·27 (1·52–3·39)	214 (145–411)
Vomiting	66/9227 (0·7%)	25/9232 (0·3%)	2·64 (1·67–4·18)	225 (155–412)
Diarrhoea	35/9227 (0·4%)	8/9232 (0·1%)	4·38 (2·03–9·43)	342 (232–651)

NNH=number needed to harm.

Table 4: **Shivering, body temperature greater than 38°C, and other side-effects according to treatment group**

	Epidural	No epidural	Relative risk (95% CI; epidural effect)
Any shivering			
Misoprostol	195/522 (37%)	254/1244 (20%)	1·83 (1·57–2·14)
Oxytocin	46/505 (9%)	93/1263 (7·4%)	1·24 (0·88–1·73)
Relative risk (95% CI; utero-tonic effect)*	4·10 (3·05–5·52)	2·77 (2·22–3·47)	..
Temperature >38°C			
Misoprostol	75/518 (14%)	61/1221 (5%)	2·90 (2·10–4·00)
Oxytocin	6/499 (1%)	6/1244 (0·5%)	2·49 (0·81–7·69)
Relative risk (95% CI; utero-tonic effect)†	12·04 (5·29–27·41)	10·36 (4·49–23·87)	..

*Difference in relative risks p=0·04. †Difference in relative risks p=0·80.

Table 5: **Shivering and body temperature above 38°C according to treatment group and use of epidural analgesia during labour and delivery**

stratified analysis in this subgroup for the two main side-effects of misoprostol: shivering and raised body temperature. The low prevalence of diarrhoea, nausea, and vomiting did not allow a meaningful assessment of interaction for these side-effects. The relative risk of shivering with misoprostol compared with oxytocin was higher among women with epidural analgesia than among women without epidural analgesia (p=0·04, table 5), but there was no difference in relative risk for high body temperature in women with and without epidural analgesia (p=0·80).

Discussion

We have shown that oral misoprostol (600 μg) is associated with a higher rate of measured blood loss of 1000 mL or more and the use of additional uterotonics than oxytocin 10 IU. We are 95% confident that the increased risk of blood loss with misoprostol is between 20 and 60%. This result corresponds to an absolute risk of 2·9% in the oxytocin group and 4·0% in the misoprostol group (difference 1·1% [95% CI 0·6–1·6]). Similarly, we are 95% confident that the risk of using additional uterotonics with misoprostol is between 30 and 50% higher than with oxytocin. This corresponds to an absolute risk of 10·9% in the oxytocin group and 15·2% in the misoprostol group (difference 4·3% [3·3–5·3]).

The trial had sufficient statistical power to test the a priori hypothesis for the two primary outcomes, but it did not have sufficient power for other clinically relevant outcomes such as maternal mortality. There were four maternal deaths: two in each group. Similarly, few women had severe morbidity such as exploration under anaesthesia, bimanual compression, hysterectomy, and intensive-care admission.

Blood loss was measured in a standardised way in all centres rather than by clinical estimation, as used in many previous trials of the third stage of labour. Measurement of blood loss enabled a more objective and accurate assessment than clinical estimation, since this procedure underestimates blood loss, particularly when the blood loss is more than 1000 mL.[15] All outcomes were measured in the first hour after delivery because of the organisation of postpartum care in the participating hospitals. The measurement of some secondary outcomes and side-effects might have been influenced by this factor—eg, the temperature rise and return to normal might extend beyond this period, whereas shivering is most likely to occur within the first hour (based on substudies in some centres).

Double-blinding, including double placebos, ensured that ascertainment bias in the measurement of blood loss and use of additional uterotonics was unlikely. However, unblinding could have occurred because of the higher rate of shivering associated with misoprostol. A sensitivity analysis in which women with shivering were excluded showed a similar level of comparative effectiveness for oxytocin to that in the total population (relative risk 1·32 [1·11–1·56]). Exclusion of women with diarrhoea did not change the treatment effect either.

We used the highest dose of misoprostol (600 μg) regarded as effective without an unacceptable level of side-effects.[12] Considering the observed rate of side-effects in the present trial, higher doses should probably not be tested for the prevention of postpartum haemorrhage. Oral administration of misoprostol, despite having a rapid onset of action, does not have the continuous and long-lasting effect of vaginal administration early in pregnancy. Concentrations of orally administered misoprostol in plasma peak at 30 min when used in first trimester pregnancies,[16] which might explain the lower effectiveness. With regard to the route of oxytocin administration, pharmacokinetic studies indicate that the absorption times of intramuscular and intravenous oxytocin are both 1–2 min, and their effectiveness is likely to be similar.[17]

The trial was done in an ethnically heterogeneous population, which provides external validity to the results. However, all hospitals practised active management of the third stage of labour, restricting our recommendations to settings with this routine practice. The effectiveness might be different if the two drugs were compared without other components of active management—eg, Nordstroem and colleagues[18] found that oxytocin reduced the blood loss by 22% compared with placebo when the third stage of labour was managed expectantly.

To explain the statistical heterogeneity of effect with blood loss of 1000 mL or more, we did multivariate and sensitivity analyses, but could not explain the heterogeneity. One should be very cautious in using results from individual centres, because the probability of at least one centre showing an effect reversal in a multicentre trial with nine centres like ours can be around 80%.[19] Blood loss of 500 mL or more, on the other hand, was consistently higher in the misoprostol group in all centres.

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We explored the combined effect of misoprostol and epidural analgesia for shivering and body temperature greater than 38°C, and found an interaction between misoprostol and epidural analgesia on any shivering (37·4% of women who receive both will shiver; table 5). There was also an epidural-independent increase in temperature to more than 38°C with the use of misoprostol in the third stage of labour, and an independent increased risk of raised body temperature among women with epidural analgesia, in agreement with previous epidemiological studies.[20]

We identified six other trials that compared oral misoprostol with other uterotonics (oxytocin, ergometrine, or both), and one trial that compared rectal misoprostol with other uterotonics.[4] Three used 600 μg misoprostol orally (2657 women in total),[12,21,22] one used 500 μg (1000 women),[23] and three used 400 μg (1662 women).[12,24,25] One trial[12] compared 600 or 400 μg misoprostol with oxytocin. The summary relative risks of blood loss of at least 1000 mL were 0·83 (0·42–1·65), 0·90 (0·37–2·19), and 1·38 (0·78–2·42) for the 600 μg, 500 μg, and 400 μg comparisons, respectively. None of these meta-analyses had the power to test the equivalence hypothesis between the two drugs. These promising findings of the meta-analyses were not corroborated by the largest trial reported here. This apparent difference highlights the importance of doing trials of adequate sample size, since meta-analyses of small trials can often disagree with the largest trial.[26]

We did not address the introduction of misoprostol to a level of care at which there is no active management, or the use of oxytocin during the third stage of labour where it is not feasible. In other words, we did not investigate whether misoprostol is better than placebo. We identified four randomised controlled trials that compared oral misoprostol with placebo and one that compared rectal misoprostol with placebo in a systematic review.[4] There is no clear evidence from these trials, which included 1900 women in total, to indicate that misoprostol reduces the risk of blood loss of 1000 mL or more when compared with placebo.[11,27–30]

In settings in which active management of the third stage of labour with oxytocin is the norm, we do not recommend a change in practice. Oxytocin is cheap, effective, and has been shown to retain its efficacy after 12 months at 30°C even if it is exposed to light and when stored at 42°C for one year.[31,32] In health facilities considering the introduction of active management of the third stage of labour, 10 IU oxytocin should be considered as the uterotonic of choice over oral misoprostol 600 μg, perhaps through prefilled syringes for increased safety of injections.

Because of the large evidence gap for the treatment of postpartum haemorrhage, as opposed to prevention addressed in this paper, further research into treatment strategies is needed. For example, the pharmacokinetics of misoprostol might be more suitable for its use at higher doses, possibly with different routes, in the treatment of postpartum haemorrhage. Research on resolving the effective components of active management and auditing any introduction of active management in community settings is also required.

Contributors

José Villar, José Miguel Belizan, Sune Bergstroem, Olav Meirik, and Paul Van Look identified the research hypothesis and designed the study. Hazem El-Refaey and Charles Rodeck stimulated the WHO to select misoprostol as the prostaglandin to be tested for the prevention of postpartum haemorrhage. A Metin Gülmezoglu and José Villar prepared the protocol, selected the populations, and coordinated the implementation of the trial. Guillermo Carroli, Justus Hofmeyr, Gilda Piaggio, Alain Pinol, Diana Elbourne, Hazem El-Refaey, Walter Prendiville, Ken Schulz, and Paul Van Look made comments and contributed to the final trial protocol. Guillermo Carroli, Linan Cheng, Hany Abdel-Aleem, Walter Prendiville, Lekan Adetoro, Justus Hofmeyr, Christian Unger, Pisake Lumbiganon, and Nguyen Thi Nhu Ngoc implemented the trial in their respective countries and actively contributed to the overall execution of the trial. Diana Elbourne chaired the steering committee. Gilda Piaggio and Alain Pinol did the data analyses with input from José Villar, A Metin Gülmezoglu, Guillermo Carroli, and other members of the steering committee. A Metin Gülmezoglu, José Villar, Gilda Piaggio, and Guillermo Carroli wrote the paper. All the steering committee members read the report and made substantive suggestions on its content.

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