Misoprostol as an adjunct to standard uterotonics for treatment of post-partum haemorrhage: a multicentre, double-blind randomised trial

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Summary

Background Post-partum haemorrhage is a leading cause of global maternal morbidity and mortality. Misoprostol, a prostaglandin analogue with uterotonic activity, is an attractive option for treatment because it is stable, active orally, and inexpensive. We aimed to assess the effectiveness of misoprostol as an adjunct to standard uterotonics compared with standard uterotonics alone for treatment of post-partum haemorrhage.

Methods Women delivering vaginally who had clinically diagnosed post-partum haemorrhage due to uterine atony were enrolled from participating hospitals in Argentina, Egypt, South Africa, Thailand, and Vietnam between July, 2005, and August, 2008. Computer-generated randomisation was used to assign women to receive 600 µg misoprostol or matching placebo sublingually; both groups were also given routine injectable uterotonics. Allocation was concealed by distribution of sealed and sequentially numbered treatment packs in the order that women were enrolled. Providers and women were masked to treatment assignment. The primary outcome was blood loss of 500 mL or more within 60 min after randomisation. Analysis was by intention to treat. This study is registered, number ISRCTN34455240.

Findings 1422 women were assigned to receive misoprostol (n=705) or placebo (n=717). The proportion of women with blood loss of 500 mL or more within 60 min was similar between the misoprostol group (100 [14%]) and the placebo group (100 [14%]; relative risk 1·02, 95% CI 0·79–1·32). In the first 60 min, an increased proportion of women on misoprostol versus placebo, had shivering (455/704 [65%] *vs* 230/717 [32%]; 2·01, 1·79–2·27) and body temperature of 38°C or higher (303/704 [43%] *vs* 107/717 [15%]; 2·88, 2·37–2·50).

Interpretation Findings from this study do not support clinical use of 600 µg sublingual misoprostol in addition to standard injectable uterotonics for treatment of post-partum haemorrhage.

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Introduction

Haemorrhage is the leading cause of maternal mortality in low-resource settings:[1] an estimated 125 000 deaths are due to post-partum haemorrhage every year.[2] Maternal death from haemorrhage is rare in high-resource settings, suggesting that medical interventions for haemorrhage contribute substantially to survival. Conventional treatment of post-partum haemorrhage relies heavily on hospital-based interventions. However, post-partum haemorrhage is largely unpredictable,[3] and can lead to death within hours. Simple treatment methods are needed for implementation at all levels of care.

Misoprostol is a prostaglandin E1 analogue that is widely marketed in tablet form, and is registered for use in the prevention and treatment of peptic ulcer disease. It is thermostable, can be taken orally, and is fairly inexpensive. Although misoprostol is less effective than oxytocin for prevention of post-partum haemorrhage,[4] it has been promoted widely for the ease with which the drug can be taken,[5] and the positive results from a trial of misoprostol administration by rural birth attendants in India.[6] Concerns about misuse[7] and side-effects[8] have emerged, and misoprostol use for labour induction seems to increase post-partum blood loss.[9]

Clinical use of misoprostol for post-partum haemorrhage is based on weak evidence.[10,11] At the start of our study, three randomised trials of misoprostol for treatment of post-partum haemorrhage had been published.[12–14] Lokugamage and colleagues[12] reported that 800 µg rectal misoprostol stopped post-partum haemorrhage significantly more effectively than did combined intramuscular syntometrine and intravenous syntocinon. However, in that trial treatment allocation was unblinded and the outcome was subjective assessment of clinical response, so investigator bias could have favoured the misoprostol group. Hofmeyr[13] and Walraven[14] and their colleagues did double-blind trials and showed reduced blood loss with misoprostol compared with placebo, both in combination with standard uterotonics, but the differences were not significant. In a meta-analysis of the results of these trials, misoprostol significantly reduced the primary outcome of additional blood loss of 500 mL or more (relative risk 0·57, 95% CI 0·34–0·96).[15] However, in a systematic review, Mousa and Alfirevic[16] concluded that evidence for any advantage from

addition of misoprostol to standard uterotonic treatment was insufficient, and called for more safety data on misoprostol as adjunctive treatment for post-partum haemorrhage.[16] The main side-effects of misoprostol are shivering and pyrexia, which are dose-dependent.[11,17]

We aimed to establish whether further blood loss could be reduced with the addition of 600 µg misoprostol sublingually to standard uterotonic treatment (mostly oxytocin) in women with post-partum haemorrhage that was suspected to be caused by uterine atony in vaginal delivery. Findings from pharmacokinetic data show that sublingual administration results in the most rapid absorption, and the highest serum concentrations and bioavailability.[18,19] Reduced blood loss with this simple, inexpensive adjunctive treatment for post-partum haemorrhage could have major public health implications. Conversely, demonstration of lack of efficacy would provide evidence to help avoid further use of an ineffective and potentially harmful drug.

Methods

Participants

All women delivering vaginally were eligible to participate in the study if they had clinically diagnosed post-partum haemorrhage that was suspected to be due to uterine atony, and they needed additional uterotonics. Participants were enrolled from hospitals in Argentina, Egypt, South Africa, Thailand, and Vietnam between July, 2005, and August, 2008. Women were not eligible for the trial if: delivery was by caesarean section; misoprostol could not be given sublingually; any severe allergic or bleeding disorders (eg, haemophilia) were recorded; temperature was higher than 38·5°C; the delivery was defined as a miscarriage according to local gestational age limits; or the placenta was not delivered.

Women were provided with information about the trial during antenatal care. At admission for delivery, women were approached to participate in the trial and invited to give informed consent; all women provided written consent. The trial was approved by the ethics committees of the participating centres and by the Scientific and Ethical Review Group for the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction. The findings are reported in accordance with the revised CONSORT guidelines.[20]

Randomisation and masking

A computer-generated randomisation sequence was derived centrally by Gynuity Health Projects (New York, NY, USA), and was stratified by country. Within the strata women were individually allocated by block randomisation (varying blocks of six and eight) to receive 600 µg misoprostol sublingually (three tablets of 200 µg; GyMiso, HRA Pharma, Paris, France) or matching placebo; both groups received standard uterotonics. The standard utertonic was in most cases 10 IU oxytocin given intramuscularly or by slow intravenous injection. The use of uterine massage was not consistent. The randomisation code was not shown to any participating trial centre or member of the study team until the trial was closed.

Treatment boxes were identical in appearance for both groups, and placebo tablets were identical in shape, colour, weight, feel, and taste to misoprostol tablets. To conceal allocation, treatment boxes were sealed and numbered sequentially according to the randomisation sequence, and distributed in the order that women were judged to be eligible and were enrolled in the study. After diagnosis of post-partum haemorrhage, standard uterotonics were given immediately as per standard practice at participating hospitals. Participants were then randomly allocated to treatment by the health provider, and received the study drug as soon as possible after standard uterotonics. Both providers and participants were masked to treatment allocation.

Procedures

The primary outcome was measured blood loss of 500 mL or more within 60 min after randomisation. Secondary outcomes were: need for blood transfusion; haemoglobin concentration of less than 80 g/L within 24 h post partum

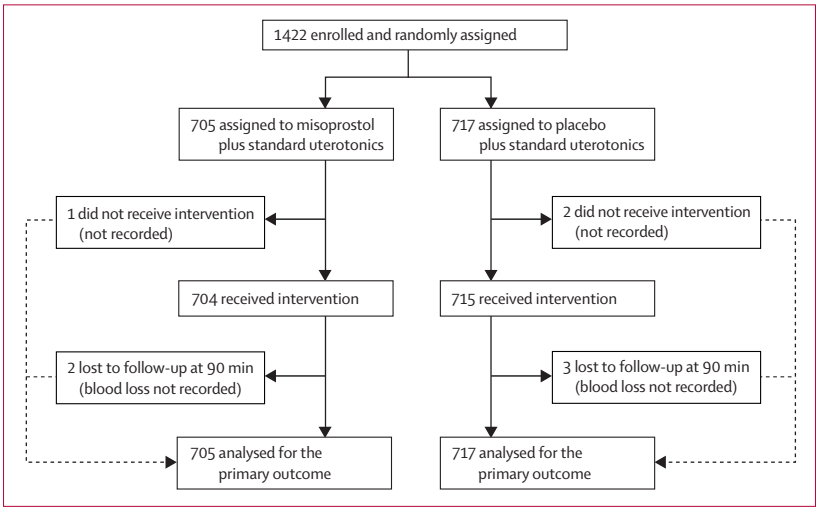

Figure 1: **Trial profile**

	Misoprostol (n=705)	Placebo (n=717)
Age (years)	26 (5·6)	26 (6·0)
Nulliparous	287 (41%)	290 (40%)
Type of uterotonic given during active management of third stage of labour		
Oxytocin	688 (98%)	701 (98%)
Ergometrine	44 (6%)	49 (7%)
Prostaglandins	8 (1%)	6 (1%)
Any uterotonic taken before study drug	645 (91%)	647 (90%)
Birthweight of neonate (g)	3148 (589)	3164 (557)

Data are mean (SD) or number (%).

Table 1: **Baseline characteristics of participants**

	Misoprostol (n=705)	Placebo (n=717)	Relative risk (95% CI)
Primary outcome			
Blood loss of ≥500 mL within 60 min after randomisation	100 (14%)	100 (14%)	1·02 (0·79 to 1·32)
Secondary outcomes			
Blood transfusion after randomisation	103 (15%)	117 (16%)	0·89 (0·70 to 1·14)
Haemoglobin concentration of <80 g/L within 24 h post partum or need for blood transfusion*	121 (18%)	139 (20%)	0·89 (0·72 to 1·11)
Blood loss after randomisation			
Within 60 min (mL)	200 (100–306)	200 (100–340)	0 (0 to 0)†
≥1000 mL	9 (1%)	9 (1%)	1·02 (0·41 to 2·55)
Within 90 min (mL)‡	250 (120–440)	250 (120–450)	0 (–40 to 20)†
≥500 mL	149 (21%)	162 (23%)	0·93 (0·77 to 1·14)
≥1000 mL	17 (2%)	22 (3%)	0·78 (0·42 to 1·47)
Any uterotonic after randomisation	188 (27%)	203 (28%)	0·94 (0·79 to 1·11)
Maternal death	2 (<1%)	0	NA
Severe morbidity§	8 (1%)	10 (1%)	0·81 (0·32 to 2·00)

Data are number (%) or median (IQR), unless otherwise indicated. NA=not applicable. *Data were recorded for 691 patients receiving misoprostol and 710 patients receiving placebo; outcomes could not be measured in remaining patients. †These data are median difference (95% CI). ‡Data were recorded for 703 patients receiving misoprostol and 714 patients receiving placebo; outcomes could not be measured in remaining patients. §Defined as hysterectomy or admission to a maternal intensive care unit.

Table 2: **Primary and secondary outcomes**

or need for blood transfusion; median blood loss at 60 min and 90 min after randomisation; blood loss of 500 mL or more within 90 min after randomisation; blood loss of 1000 mL or more within 60 min and 90 min after randomisation; need for any additional uterotonic; maternal death; severe morbidity (hysterectomy or admission to a maternal intensive care unit); side-effects (shivering, pyrexia, diarrhoea, vomiting, or nausea) within 60 min and 90 min after randomisation; and need for any other interventions. Unless otherwise specified, all secondary outcomes were recorded from randomisation up until discharge. Providers assessed side-effects by direct observation or questioning of participants, and every woman with a side-effect was asked to classify the side-effect as mild, moderate, or severe. Any side-effect needing treatment was recorded as severe. Body temperature was assessed with standard thermometers that were routinely used in every hospital.

The trial adhered to the methods used for blood loss measurement in the WHO trial of misoprostol for the prevention of post-partum haemorrhage.[4] Blood collection started immediately after the study drug was given. A fresh, non-absorbent sheet was placed under the buttocks of the woman. A low-profile plastic fracture bedpan was positioned below the woman's perineum to collect all subsequent blood lost for 90 min. The blood in the bedpan plus any spilled blood from the non-absorbent sheet or blood-soaked gauze swabs, or both, was transferred to a jar and the volume was measured. At the centre in Egypt, blood was collected into a calibrated plastic sheet that was placed below the woman immediately after she took the study drug, and the volume was measured accordingly. Measures of blood loss were recorded at 60 min and 90 min after randomisation. If bleeding did not stop, providers continued to provide standard care for post-partum haemorrhage according to local protocol. Thus the only addition to routine care was use of the study drug.

Baseline characteristics, blood loss at 60 min and 90 min after randomisation, side-effects and all other interventions were obtained and recorded on paper forms by trained study staff at the time of the delivery; data were reviewed by the principal investigator at each hospital. All data entry forms were stored at the participating hospital. Data were entered locally into a centralised online database developed by the Geneva Foundation for Medical Education and Research, Switzerland. All data were available for viewing by designated study monitors throughout the trial. Regular monitoring continued throughout the trial period to ensure protocol adherence and reliable data recording and data entry.

The data safety and monitoring board convened twice to review the data. After 400 women had been recruited, the first meeting took place to review the rate of side-effects with 600 µg misoprostol, and to confirm that the trial had an adequate sample size. After 700 women had been recruited, the second meeting took place to assess treatment effectiveness. The trial investigators were advised to continue with recruitment after both interim analyses.

Statistical analysis

On the basis of a systematic review of previous trials,[11] we estimated that additional blood loss of 500 mL or more would occur in about 16% of women on placebo. Therefore, 691 women per group would be needed to detect a reduction to 10% in women receiving misoprostol (relative risk reduction of 37%) at a 5% significance level (two-sided test) with 90% power, so the trial size was set at 1400 women.

All analyses were by intention to treat. Comparisons between treatment groups for baseline characteristics were done to ensure comparability between study groups and to identify any possible confounding factors. Categorical outcomes are presented as percentages and were compared between treatment groups with relative risks (95% CI). Continuous outcomes were not distributed normally, so these data are presented as median (IQR) values; treatment groups were compared from the difference in median values, and 95% CIs were derived with a bootstrap procedure. Stratified analyses were done with the Cochran-Mantel-Haenszel statistic. Homogeneity tests (Breslow-Day) were done to assess the association between outcomes and treatment across participating countries. The number needed to harm (95% CI) was calculated for side-effects if a significant difference was recorded. All statistical analyses were done with SAS (version 9.2), and we judged p values of less than 0·05 to be significant.

This study is registered, number ISRCTN34455240.

Role of the funding source
The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all of the trial data and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. 1422 women were enrolled and randomly assigned to receive 600 µg misoprostol sublingually plus standard uterotonics (n=705 participants), or placebo plus standard uterotonics (n=717). Baseline characteristics were similar for participants allocated to each study group (table 1).

Analysis of the primary outcome showed no significant difference in the proportion of women with measured blood loss of 500 mL or more within 60 min after randomisation between the misoprostol and placebo groups (table 2). This result was consistent across the five trial centres (data not shown). Stratified analysis to account for any potential differences between nuliparous and multiparous women did not detect any differences between the treatment groups (data not shown). Stratification by labour induction with and without misoprostol was not done because no participants were induced with misoprostol. Stratified analyses by country did not differ from the previously presented results.

We recorded no significant difference between treatment groups in secondary effectiveness outcomes of: blood loss of 1000 mL or more within 60 min and 90 min after randomisation; blood loss of 500 mL or more within 90 min after randomisation; median blood loss at 60 min; and haemoglobin concentration of less than 80 g/L within 24 h post partum or need for blood transfusion before discharge as requested on the basis of the health provider's clinical judgment (table 2). Additional uterotonics to stop bleeding and avoid the need for blood transfusion after randomisation were given with similar frequency to women allocated to misoprostol and placebo (table 2).

Within 60 min and 90 min after randomisation, shivering was the most common side-effect and was strongly associated with misoprostol (table 3). Furthermore, severe shivering occurred in more women on misoprostol than on placebo. Misoprostol use was also associated with an increased proportion of women who had a temperature of 38°C or higher within 60 min and 90 min after randomisation, a temperature of 40°C or higher within 60 min and 90 min after randomisation, or vomited within 60 min or 90 min after randomisation. Reports of diarrhoea and nausea were infrequent, and differences between the treatment groups were not clinically or statistically significant. Numbers needed to harm suggested that for every three women treated with misoprostol plus standard uterotonics, one additional episode of shivering would be recorded compared with use of standard uterotonics alone. Similarly, for every 35 women treated with misoprostol plus standard uterotonics, one additional episode of vomiting would be expected compared with use of standard uterotonics alone (table 3).

	Misoprostol (n=704)*	Placebo (n=717)	Relative risk (95% CI)	Number needed to harm (95% CI)†
Within 60 min after randomisation				
Shivering				
Any	455 (65%)	230 (32%)	2·01 (1·79–2·27)	3·1 (2·7–3·6)
Severe	80 (11%)	7 (1%)	11·64 (5·41–25·03)	9·6 (7·8–12·6)
Temperature				
≥38°C	303 (43%)	107 (15%)	2·88 (2·37–2·50)	3·6 (3·1–4·2)
≥40°C	18 (3%)	3 (<1%)	6·11 (1·81–20·65)	46·7 (29·4–113·6)
Diarrhoea				
Any	2 (<1%)	3 (<1%)	0·68 (0·11–4·05)	..
Severe	0	0	NA	NA
Vomiting				
Any	36 (5%)	16 (2%)	2·30 (1·28–4·09)	34·7 (20·7–107·5)
Severe	2 (<1%)	2 (<1%)	1·02 (0·14–7·21)	..
Nausea				
Any	45 (6%)	35 (5%)	1·31 (0·85–2·01)	..
Severe	2 (<1%)	1 (<1%)	2·04 (0·18–22·41)	..
Within 90 min after randomisation				
Shivering				
Any	514 (73%)	252 (35%)	2·08 (1·86–2·32)	2·6 (2·3–3·0)
Severe	95 (13%)	13 (2%)	7·44 (4·21–13·16)	8·6 (6·9–1·1)
Temperature‡				
≥38°C	406 (58%)	137 (19%)	3·00 (2·55–3·53)	2·6 (2·3–3·0)
≥40°C	48 (7%)	3 (<1%)	16·21 (5·07–51·78)	15·6 (11·6–22·3)
Diarrhoea				
Any	6 (1%)	5 (1%)	1·22 (0·37–3·99)	..
Severe	0	0	NA	NA
Vomiting				
Any	45 (6%)	25 (3%)	1·83 (1·14–2·96)	34·4 (19·6–153·8)
Severe	2 (<1%)	2 (<1%)	1·02 (0·14–7·21)	..
Nausea				
Any	60 (9%)	49 (7%)	1·25 (0·87–1·79)	..
Severe	2 (<1%)	1 (<1%)	2·04 (0·18–22·41)	..

Data are number (%), unless otherwise indicated. ..=data unavailable because of uncertainty between benefit and harm. NA=not applicable. *Blood loss alone was recorded for one patient randomly allocated to misoprostol, and so data are supplied for 704 patients. †Misoprostol plus standard uterotonics versus placebo plus standard uterotonics. ‡Data were recorded for 702 patients receiving misoprostol and 711 patients receiving placebo; outcomes could not be measured in remaining patients.

Table 3: **Side-effects**

18 women had severe maternal morbidity, which was defined as hysterectomy or admission to a maternal intensive care unit (table 2). Two women died, both in the misoprostol group (table 2). One woman was diagnosed with severe post-partum haemorrhage that was unresponsive to treatment, and she died of disseminated intravascular coagulopathy on the day of delivery. The other woman was diagnosed with post-partum haemorrhage that was suspected to be due to uterine atony. She received a blood transfusion and a laparotomy was done under general anaesthesia, at which time a spiral tear of the left lateral wall of the uterus was

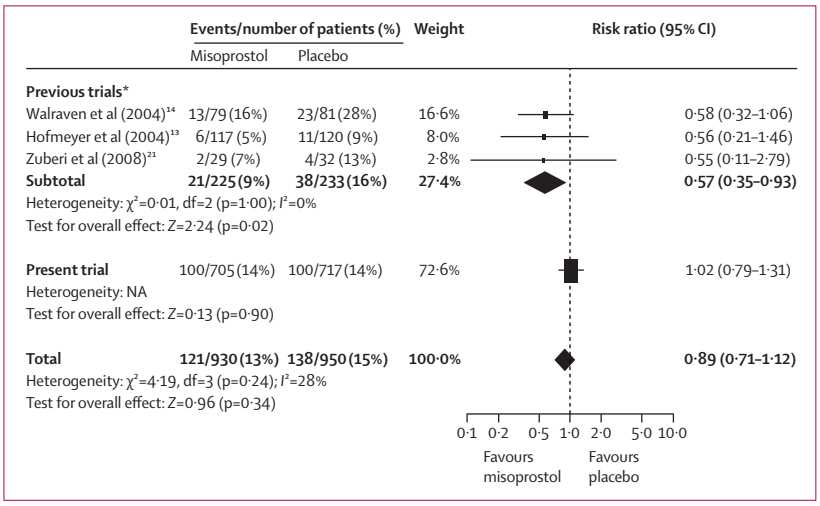

Figure 2: **Meta-analysis of blood loss of 500 mL or more within 60 min after randomisation in trials of misoprostol as an adjunct to standard uterotonics for treatment of post-partum haemorrhage**
NA=not applicable. *Misoprostol doses were: 400 µg sublingually and 200 µg orally;[14] 400 µg sublingually, 200 µg orally, and 400 µg rectally;[13] and 600 µg sublingually.[21]

identified and repaired, and the uterine artery was ligated. She was admitted to the intensive care unit for postoperative ventilation, circulatory support, and further blood transfusions, but died the next day from multiorgan failure. The final diagnosis was ruptured uterus and not uterine atony.

Discussion

The results of this large trial show no benefit of misoprostol in addition to standard injectable uterotonics for the treatment of post-partum haemorrhage. Moreover, misoprostol use was associated with shivering, body temperature of 38°C or higher, and vomiting.

Three randomised trials have studied use of misoprostol plus uterotonics versus uterotonics alone for treatment of post-partum haemorrhage: two were published before our study was planned,[13,14] and one was published while our trial was underway.[21] Meta-analysis of these three trials found a reduction of 40–50% in blood loss of 500 mL of more in women on misoprostol versus those on placebo (figure 2). The dose and route of administration of misoprostol differed between the three trials, but these differences are unlikely to account for variations in outcome. Variations could possibly be the result of chance since the studies have small sample sizes, and could be compounded by publication bias from other small trials with less optimistic results that have not been published.[22] In total, the three trials enrolled 458 women, whereas a major strength of our study is the large sample size (1422 women from five countries) and statistical power. Meta-analysis of the three previous trials and our trial shows a pooled risk ratio of 0·89 for blood loss with misoprostol versus placebo (figure 2). These results underscore the importance of adequately powered large trials since the pooled results of several small trials can suggest a promising beneficial effect that is not necessarily real.

This trial is limited by several factors. First, post-partum haemorrhage that was suspected to be due to uterine atony was clinically diagnosed and subject to error. Because our trial was pragmatic, misoprostol was given in clinical situations in which it would be used in routine practice had it been shown to be effective. Second, side-effects such as shivering, nausea, vomiting, and diarrhoea were recorded on the basis of women's reports or health-care providers' observations. Last, we were not able to assess the reduction in haemoglobin concentrations after delivery because haemoglobin concentration was not routinely measured before delivery at participating sites. Therefore, the haemoglobin concentration was measured 24 h after delivery only. However, randomisation produced similar study groups for all measured variables, so we do not expect that mean haemoglobin concentrations would have differed between the groups.

Misoprostol is an effective myometrial stimulant post partum, according to findings from physiological studies.[23,24] It is slightly more effective than oxytocin for induction of labour, but is accompanied by undesirable side-effects, such as uterine hyperstimulation.[25,26] The absence of effectiveness of misoprostol for treatment of post-partum haemorrhage was an unforeseen result, but is consistent with the unexpected finding that oxytocin is more effective for prevention of post-partum haemorrhage than is misoprostol.[4] However, the standard uterotonics used in the trial could have caused maximum stimulation of the myometrium such that no further uterotonic effect could be achieved. The trial does not exclude the possibility that misoprostol could be effective in the treatment of post-partum haemorrhage in settings where standard uterotonics are not available. Indeed, findings from two double-blind randomised trials of 40 IU intravenous oxytocin versus 800 µg sublingual misoprostol for primary post-partum haemorrhage have shown that misoprostol is a suitable alternative treatment for post-partum haemorrhage.[27,28]

The occurrence of two maternal deaths in the misoprostol group is probably a chance finding. As reported in previous trials,[13,14,21] shivering and pyrexia, both associated with prostaglandin use, were significantly more common in women on misoprostol than in those on placebo. One of the 18 women in the misoprostol group who had temperatures of 40°C or more had delirium. Vomiting also occurred in a significantly higher proportion of women on misoprostol than in those on placebo. In view of the dose-relation of side-effects with misoprostol, future research should use the lowest dose of misoprostol that is judged likely to be effective.

The findings of this trial do not support the use of misoprostol in addition to other conventional uterotonics for the treatment of atonic post-partum haemorrhage. Any further research on misoprostol should focus on the

possible effectiveness of misoprostol in settings where standard uterotonics are not available.

Contributors

MW, JB, GJH, GC, HA-A, PL, NTNN, and BW conceived and designed the study. All authors participated in the trial implementation. DW was responsible for data analysis, and MW, JB, GJH, GC, HA-A, PL, NTNN, DW, and BW interpreted the data. MW, JB, and GJH drafted the report with input and editing from all authors.

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Conflicts of interest

We declare that we have no conflicts of interest.

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