Treatment of post-partum haemorrhage with sublingual misoprostol versus oxytocin in women not exposed to oxytocin during labour: a double-blind, randomised, non-inferiority trial

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Summary

Background **Oxytocin, the standard of care for treatment of post-partum haemorrhage, is not available in all settings because of refrigeration requirements and the need for intravenous administration. Misoprostol, an effective uterotonic agent with several advantages for resource-poor settings, has been investigated as an alternative. This trial established whether sublingual misoprostol was similarly efficacious to intravenous oxytocin for treatment of post-partum haemorrhage in women not exposed to oxytocin during labour.**

Methods **In this double-blind, non-inferiority trial, 9348 women not exposed to prophylactic oxytocin had blood loss measured after vaginal delivery at four hospitals in Ecuador, Egypt, and Vietnam (one secondary-level and three tertiary-level facilities). 978 (10%) women were diagnosed with primary post-partum haemorrhage and were randomly assigned to receive 800 µg misoprostol (n=488) or 40 IU intravenous oxytocin (n=490). Providers and women were masked to treatment assignment. Primary endpoints were cessation of active bleeding within 20 min and additional blood loss of 300 mL or more after treatment. Clinical equivalence of misoprostol would be accepted if the upper bound of the 97·5% CI fell below the predefined non-inferiority margin of 6%. All outcomes were assessed from the time of initial treatment. This study is registered with ClinicalTrials.gov, number NCT00116350.**

Findings **All randomly assigned participants were analysed. Active bleeding was controlled within 20 min with study treatment alone for 440 (90%) women given misoprostol and 468 (96%) given oxytocin (relative risk [RR] 0·94, 95% CI 0·91–0·98; crude difference 5·3%, 95% CI 2·6–8·6). Additional blood loss of 300 mL or greater after treatment occurred for 147 (30%) of women receiving misoprostol and 83 (17%) receiving oxytocin (RR 1·78, 95% CI 1·40–2·26). Shivering (229 [47%] *vs* 82 [17%]; RR 2·80, 95% CI 2·25–3·49) and fever (217 [44%] *vs* 27 [6%]; 8·07, 5·52–11·8) were significantly more common with misoprostol than with oxytocin. No women had hysterectomies or died.**

Interpretation **In settings in which use of oxytocin is not feasible, misoprostol might be a suitable first-line treatment alternative for post-partum haemorrhage.**

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Introduction

Post-partum haemorrhage remains a major threat to women.[1] Since uterine atony is an important cause of this condition, uterotonic agents to control bleeding are the standard of care worldwide. Yet the risk of dying from post-partum haemorrhage remains 100 times higher in developing countries than in developed countries.[2,3] This disparity is largely attributable to the greater likelihood of deliveries unattended by trained personnel, restricted access to uterotonic drugs, and geographic isolation in developing countries. Although oxytocin remains the drug of choice to treat excessive post-partum bleeding,[4] it is not always feasible to provide, especially in resource-poor settings, because of its requirements for storage, skilled personnel, and parenteral administration.

Misoprostol, a prostaglandin E1 analogue with proven uterotonic potency, offers several advantages, including simple oral administration and stability at ambient temperatures.[5] Studies have shown misoprostol prophylaxis to be more effective than placebo in prevention of post-partum haemorrhage in community-based settings but less effective than injectable oxytocin.[6–9] Some work has shown misoprostol's potential for treatment of post-partum haemorrhage,[10–21] but the evidence is insufficient to recommend its use.[22,23]

The present study was undertaken because of the need for alternative treatment options for use in settings in which oxytocin is not available or its use is not feasible. We did a multicentre, randomised, double-blind trial to establish the non-inferiority of misoprostol (800 µg sublingual) compared with intravenous oxytocin (40 IU) when administered as treatment for post-partum haemorrhage in women who were not exposed to oxytocin in the second or third stages of labour. In view of misoprostol's logistical advantages, evidence of its clinical equivalency to oxytocin would enable widespread use in resource-poor settings.

The sublingual route was identified as having the greatest potential for treatment of post-partum haemorrhage because of its rapid uptake, long-lasting duration of effect, and greatest bioavailability compared with other routes of misoprostol administration.[24] Because there was no consensus about the optimum misoprostol dose for PPH treatment,[22,23,25,26] a dose high enough to show efficacy when compared with intravenous oxytocin was selected on the basis of published work and expert opinion. This dose had previously been tested in a randomised controlled trial investigating misoprostol use for first-line treatment of post-partum haemorrhage and did not result in excessive side-effects.[17] Nonetheless, cases of temperatures of 40·0°C or higher after misoprostol for treatment of this condition at doses ranging from 600 µg to 1000 µg have been reported,[18–20] and the trade-offs between efficacy and safety were thus carefully considered. For comparison, and to be sure that we achieved the maximum efficacy of oxytocin, we selected the highest oxytocin dose recommended.

Methods

Study setting and patients

This double-blind, randomised trial, undertaken between August, 2005, and January, 2008, was implemented in one secondary and three tertiary hospitals in Ecuador (one), Egypt (one), and Vietnam (two), where the administration of oxytocic drugs during the second (eg, induction or augmentation) and third stages of labour (active management) was not routine practice. This clinical context was chosen to generate results applicable to several situations and delivery settings in which oxytocin might not be available or feasible to use. A concurrent trial following a similar study protocol was also undertaken elsewhere, enrolling women who were given oxytocin prophylactically during the third stage of labour.[27] These study contexts were chosen to imitate the two most common clinical circumstances of childbirth.

At hospital admission, women were screened for eligibility and informed about the study in their own languages. Women who had a known allergy to prostaglandin, had received any uterotonic drug in labour, had a caesarean section, delivered outside the study site, or whose post-partum bleeding was not suspected to be due to atonic uterus were excluded from the study. Informed consent was obtained for all women and documented via signature or thumb print. Study staff measured haemoglobin with a handheld device (Hemocue, Ängelholm, Sweden) and post-partum blood loss by use of a polyurethane receptacle with a calibrated funnel (Brasss-V Drapes, Excellent Fixable Drapes, Madurai, Tamil Nadu, India). Sociodemographic and delivery characteristics, haemoglobin concentration before delivery, and blood loss at 1 h post partum were documented for all consenting women, irrespective of whether they later received treatment for post-partum haemorrhage.

Immediately after delivery, the blood collection drape was placed beneath the woman's buttocks. Diagnosis of post-partum haemorrhage could occur at any time and at any amount of blood loss; however, the protocol instructed providers to begin treatment immediately if blood loss exceeded 700 mL on the drape. Since many women can tolerate blood loss of 500 mL or greater with no serious consequence,[28] a 700 mL marker was selected to avoid enrolling women with lower amounts of blood loss who might not need or benefit from uterotonic treatment.

The protocol was approved by all relevant ethics committees in participating countries and is reported in accordance with the revised CONSORT statement.[29,30] Monitoring continued throughout the trial to ensure protocol adherence, and an independent Data Safety and Monitoring Board (DSMB) undertook one interim review when two-thirds of enrolment was available for analysis, and one final review when enrolment was complete.

Randomisation and masking

Women were observed for 1 h after delivery, and if post-partum haemorrhage was due to suspected uterine atony, study staff immediately administered the next sequentially numbered allocated treatment packet. Every packet contained one active treatment (either one ampoule of 40 IU oxytocin or four tablets of 200 µg misoprostol) and matching placebo (either one ampoule of saline solution or four placebo tablets resembling misoprostol),

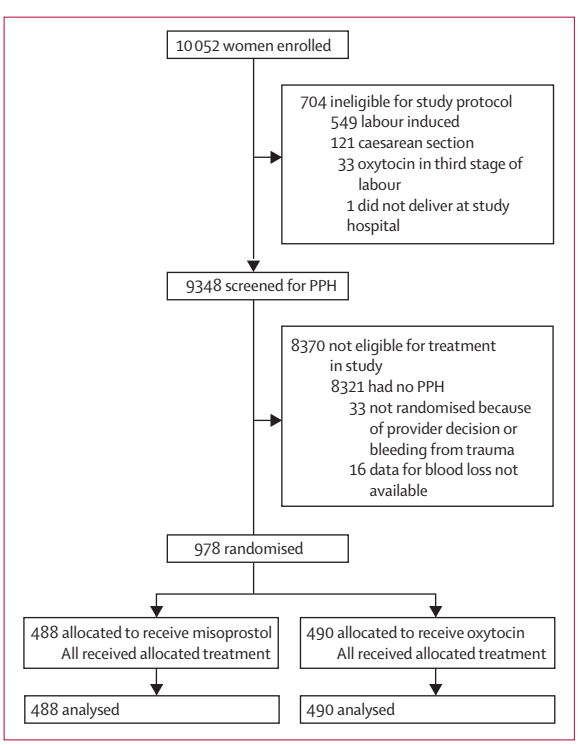

Figure 1: **Trial profile**
PPH=post-partum haemorrhage.

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which were administered simultaneously. Oxytocin or saline solution (Boulevard Pharmaceutical Compounding Center, Worcester, MA, USA) was administered in a litre of intravenous solution over 15 min, and misoprostol or placebo tablets (GyMiso, HRA Pharma, Paris, France) were placed under the tongue for 20 min. Sealed and opaque packets were administered to patients in the order that they were diagnosed, and providers and women were masked to treatment assignment. A computer-generated random allocation sequence in blocks of ten was maintained by Gynuity Health Projects in New York, USA, and was concealed from study staff who enrolled and allocated treatments.

Procedures

Cumulative blood loss measures were recorded with the same drape at time of diagnosis of post-partum haemorrhage, treatment administration, 20 min after treatment, and when active bleeding stopped. Active bleeding cessation was assessed by the provider on the basis of a noticeable reduction in the rate of bleeding, and the time was recorded. For women whose active bleeding did not stop with first-line treatment or whose condition deteriorated within the first 20 min, providers were instructed to give care in accordance with hospital protocol. Providers were asked to restrict additional use of misoprostol to 200 μg. Side-effects after treatment and provision of any additional intervention were recorded. Before discharge, women were asked a series of questions to assess the acceptability of treatment and side-effects. Haemoglobin was measured before discharge, when possible at least 12 h after removal of any intravenous line.

Data were collected and recorded by trained staff and reviewed by a designated nurse midwife or physician at every hospital. All forms were translated into local languages and data were entered locally onto a centralised online database developed by Gynuity Health Projects and the Geneva Foundation for Medical Education and Research (Switzerland). Data were reviewed and cleaned by study monitors throughout the trial and transferred for analysis into SPSS (version 15.0).

Statistical analysis

This study was designed as a non-inferiority trial to establish whether misoprostol was as efficacious as was oxytocin, the internationally recognised standard first-line treatment for post-partum haemorrhage.[4] Oxytocin has never been tested against placebo, and there have been no published trials establishing the efficacy of oxytocin.[31] On the basis of available information and expert opinion, we postulated that oxytocin alone would stop bleeding within 20 min for 88% of women. Misoprostol was expected to have a similar efficacy rate, and a 6% margin of non-inferiority was deemed acceptable. With an assumption of an 82% efficacy rate for misoprostol, we calculated that a sample size of 870 women was needed to establish clinical equivalency with a power of 80% at an α error of 0·05 (one-sided test). The sample was increased by 10% to account for any deviations in protocol resulting in un-analysable outcomes, thus 958 women (479 per group) were to be enrolled.

The primary outcomes, which were individually calculated, were the proportion of women who ceased active bleeding within 20 min after study treatment alone and those who lost 300 mL or more of blood after treatment. The crude risk difference and 97·5% CI with a one-sided probability were calculated for the primary outcome of active bleeding cessation within 20 min. Non-inferiority of misoprostol would be established if the upper bound of the 97·5% CI for the arithmetic difference in the proportion of women whose active bleeding was not controlled with initial treatment alone was less than 6%. The primary outcome of additional

	Misoprostol (n=488)	Oxytocin (n=490)
Age (years)		
Mean (SD)	25 (6)	25 (5)
Range	14–42	15–45
Currently married	464 (95%)	462 (94%)
Educational attainment*		
No education	68 (14%)	48 (10%)
Primary	142 (29%)	148 (30%)
Secondary and higher	278 (57%)	293 (60%)
Number of livebirths†		
0	222 (46%)	227 (46%)
1–3	247 (51%)	250 (51%)
≥4	18 (4%)	13 (3%)
Duration of gestation at delivery (weeks)		
Mean (SD)	39·3 (1·2)	39·2 (1·3)
Range	33·5–43·1	32·0–43·0
Known previous PPH	9 (2%)	19 (4%)
Haemoglobin before delivery (g/L)		
Mean (SD)	121 (16)	120 (17)
Range	82–169	79–163
Suturing after delivery	360 (74%)	366 (75%)
Labour induction or augmentation	0	0
Oxytocin prophylaxis	0	0
Early cord clamping	362 (74%)	367 (75%)
Controlled cord traction	316 (65%)	298 (61%)
Uterine massage	277 (57%)	264 (54%)
Mean time to placental delivery (min [SD])‡	9·4 (9·1)	9·2 (8·4)
Blood loss at time of PPH treatment (mL)		
Median (IQR)	700 (670–800)	700 (680–800)
Mean (SD)	765 (185)	744 (150)
Range	400–1800	450–1500

Data are number (%), unless otherwise indicated. PPH=post-partum haemorrhage. *Data were not available for one woman in the oxytocin group. †Data were not available for one woman in the misoprostol group. ‡Data were not available for four women in the misoprostol group and for two in the oxytocin group.

Table 1: **Women's baseline characteristics**

	Misoprostol (n=488)	Oxytocin (n=490)	RR (95% CI)	p value
Primary outcomes				
Active bleeding controlled within 20 min with initial uterotonic treatment	440 (90%)	468 (96%)	0·94 (0·91–0·98)	0·001
Additional blood loss ≥300 mL	147 (30%)	83 (17%)	1·78 (1·40–2·26)	<0·0001
Secondary outcomes				
Time to active bleeding controlled (min)				
Median (IQR)	13 (10–16)	11 (8–15)	..	0·001
Mean (SD)	13·4 (8·2)	11·8 (6·6)	..	0·001
Range	0–84	0–77	..	..
Additional blood loss after treatment given (mL)				
Median (IQR)	200 (110–300)	150 (100–225)	..	<0·0001
Mean (SD)	244 (186)	190 (174)	..	<0·0001
Range	0–1100	0–2250	..	..
Additional blood loss ≥500 mL after treatment	53 (11%)	20 (4%)	2·84 (1·63–5·01)	<0·0001
Additional blood loss ≥1000 mL after treatment	5 (1%)	3 (1%)	1·67 (0·40–6·96)	0·360
Total blood loss when active bleeding stopped (mL)				
Median (IQR)	900 (810–1100)	850 (800–1000)	..	..
Mean (SD)	1009 (297)	935 (244)	..	<0·0001
Range	450–2500	450–3500	..	..
Hb after treatment (g/L)*				
Median (IQR)	98 (88–108)	100 (91–109)	..	0·052
Mean (SD)	98 (14)	101 (14)	..	0·025
Range	58–145	59–144	..	..
Drop in Hb ≥20 g/L or blood transfusion	250 (51%)	230 (47%)	1·09 (0·96–1·24)	0·101
Drop in Hb ≥30 g/L or blood transfusion	199 (41%)	148 (30%)	1·35 (1·14–1·60)	<0·0001
Additional interventions				
Additional uterotonic drugs	61 (13%)	31 (6%)	1·98 (1·31–2·99)	0·001
Blood transfusion	41 (8%)	26 (5%)	1·58 (0·98–2·55)	0·036
Hysterectomy/other surgery	0	0	..	..
Exploration under anaesthesia	99 (20%)	90 (18%)	1·10 (0·85–1·43)	0·249
Fluids and/or plasma expanders	89 (18%)	47 (10%)	1·90 (1·37–2·65)	<0·0001
Bimanual compression	294 (60%)	283 (58%)	1·04 (0·94–1·16)	0·234
Maternal death	0	0	..	..

Data are number (%), unless otherwise indicated. RR=relative risk. Hb=haemoglobin. *Post-partum haemoglobin measure excludes women receiving blood transfusion.

Table 2: **Primary and secondary outcomes**

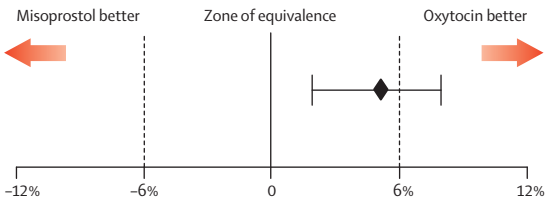

Figure 2: **Non-inferiority of misoprostol relative to oxytocin based on 95% CI analysis of primary outcome**
The diamond represents the point estimate of the difference in the event rates, and the horizontal bars represent the associated two-sided 95% CIs. The upper bound is identical to those of the one-sided 97·5% CI used in this study for establishing non-inferiority. Clinical equivalence of misoprostol would be accepted if the upper bound of the 97·5% CI fell below the predefined non-inferiority margin (Δ=6%).

blood loss of 300 mL or more after treatment was analysed to confirm consistency in main study outcomes. Secondary outcomes were total blood loss after treatment, change in haemoglobin concentration after treatment, time to active bleeding cessation, and any other additional interventions. All outcomes were assessed from the time of initial treatment per protocol.

Characteristics of the two treatment groups were compared by use of χ^2 or Fisher's exact test for categorical variables and *t* tests or Mann-Whitney *U* test for continuous variables. Relative risks (RR) with 95% CI were calculated to measure treatment effects for main study outcomes. Stratified analyses by site were done as needed to explore statistical heterogeneity of effect between study sites. Crude relative risks were adjusted for sites by calculation of Mantel-Haenszel weighted relative risks, with Greenland and Robbins 95% CIs. The Breslow and Day χ^2 test was also used to assess homogeneity of outcomes by site.

This trial is registered with ClinicalTrials.gov, number NCT00116350.

Role of the funding source

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

Results

Figure 1 shows the trial profile. Blood loss was measured for 9348 women having vaginal deliveries, of whom 978 (10%) women were diagnosed with primary post-partum haemorrhage and were randomly assigned to receive 800 µg sublingual misoprostol (n=488) or 40 IU oxytocin given intravenously (n=490). Baseline characteristics did not differ between the two treatment groups (table 1). Median blood loss at time of treatment was 700 mL for both groups (table 1). All women were treated according to protocol, and no women were excluded after randomisation. Difficulties in administration of treatments (eg, holding tablets under the tongue or administering intravenous line) were uncommon (data not shown).

Active bleeding was controlled within 20 min for 440 (90%) of women given misoprostol and 468 (96%) given oxytocin (RR 0·94, 95% CI 0·91–0·98). 147 (30%) women bled 300 mL or more after misoprostol treatment versus 83 (17%) after oxytocin treatment (1·78, 1·40–2·26). Results for additional blood loss of 500 mL or more followed a similar pattern (2·84, 1·63–5·01; table 2).

Severe blood loss of 1000 mL after treatment occurred in 1% or less of women in both treatment groups (1·67, 0·40–6·96; table 2).

First-line treatment with oxytocin stopped post-partum bleeding, on average, 2 min faster than did treatment with misoprostol (p=0·001; table 2). Additional median blood loss was 200 mL (IQR 110–300) for women given misoprostol and 150 mL (100–225) for those given oxytocin (p<0·0001). The crude overall difference in the proportion of women in the two treatment groups, whose active bleeding was not controlled with first-line treatment, was 5·3% (95% CI 2·6–8·6), which ranged from –2·6% to 25·8% between study sites (figure 2).

Despite measured differences in blood loss, median haemoglobin measures after treatment were similar between the groups, and the proportions of women who had a drop in haemoglobin of 20 g/L or more were similar (table 2). Haemoglobin decreases differed significantly between treatment groups only for post-partum haemoglobin concentrations with a drop of 30 g/L or more (table 2).

Provision of additional uterotonic drugs, blood transfusion, and fluids or plasma expanders was more frequent for women given misoprostol than for those given oxytocin (table 2). Twice as many women were given additional uterotonic drugs in the misoprostol group than in the oxytocin group (RR 1·98, 95% CI 1·31–2·99; table 2). More women receiving misoprostol were provided with a blood transfusion than were those receiving oxytocin (1·58, 0·98–2·55; table 2). Higher rates of fluids or plasma administration in women given misoprostol were mainly caused by the larger number of fevers in one site (Ecuador).

Women in the misoprostol group had a significantly higher incidence of transient shivering and fever than did those in the oxytocin group (table 3). Treatment with misoprostol was associated with an increased risk of raised body temperature of 40·0°C or more (high fever). 66 women reported high fever in the misoprostol group versus none in the oxytocin group. All these cases resolved with antipyretic treatment and cool compresses within several hours and without complication. Most cases (58 of 66) of high fever were documented at the site in Ecuador. The rate of temperature of 40·0°C or higher in Ecuador was 36% (58/163), compared with reported rates of 0% (none of 198) in Alexandria (Egypt), 2% (one of 53) in Binh Duong (Vietnam), and 9% (seven of 74) in Tudu (Vietnam). Indeed, rates of shivering and any fever were substantially lower in sites outside Ecuador (misoprostol group: shivering 26% [83/325]; fever 20% [66/325]; oxytocin group: shivering 9% [30/328]; fever 6% [21/328]), compared with overall rates (table 3). Except for one woman in Alexandria (Egypt) who reported fever as not tolerable, all reports of intolerable shivering and fever occurred in Ecuador.

Few women vomited, but more did in the misoprostol group than in the oxytocin group (table 3). Nausea, fainting, diarrhoea, and other reported side-effects were very infrequent, and rates did not vary by study group (table 3). Women reported that both treatment administrations (sublingual tablets and intravenous treatment) were acceptable (data not shown).

	Misoprostol (n=488)	Oxytocin (n=490)	RR (95% CI)	p value
Shivering	229 (47%)	82 (17%)	2·80 (2·25–3·49)	<0·0001
Participants reporting shivering as intolerable	55 (11%)	1 (<1%)	55·2 (7·70–397)	<0·0001
Fever (any)	217 (44%)	27 (6%)	8·07 (5·52–11·8)	<0·0001
Participants reporting fever as intolerable	45 (9%)	0	..	<0·0001
Temperature ≥40·0°C	66 (14%)	0	..	<0·0001
Participants reporting high fever as intolerable	22 (5%)	0	..	<0·0001
Nausea	49 (10%)	41 (8%)	1·20 (0·81–1·78)	0·213
Participants reporting nausea as intolerable	0	0	..	..
Vomiting	24 (5%)	7 (1%)	3·44 (1·50–7·92)	0·001
Participants reporting vomiting as intolerable	1 (<1%)	0	..	0·499
Fainting	4 (1%)	4 (1%)	1·00 (0·25–3·99)	0·635
Participants reporting fainting as intolerable	0	0	..	..
Diarrhoea	2 (<1%)	2 (<1%)	1·00 (0·14–7·10)	0·686
Participants reporting diarrhoea as intolerable	0	0	..	..
Other	21 (4%)	20 (4%)	1·05 (0·58–1·92)	0·495
Participants reporting other side-effect as intolerable	2 (<1%)	1 (<1%)	2·01 (0·18–22·1)	0·498

Data are number (%), unless otherwise indicated. RR=relative risk.

Table 3: **Side-effects after treatment and participants' reports of their intolerability**

Active bleeding restarted in 16 (3%) women given misoprostol compared with nine (2%) given oxytocin (RR 1·79, 95% CI 0·80–4·00). One severe adverse event was reported in the misoprostol group in Ecuador, when a patient with pre-eclampsia with high fever was referred for higher-level care and later discharged after full recovery. All side-effects after treatment were transient, and none resulted in additional complications or extended stay in hospital. There were no hysterectomies, other surgeries, or maternal deaths in study participants.

Because some sites had distinctive patterns in blood loss, recourse to additional interventions, and frequency of side-effects, stratified analyses by site were undertaken to confirm consistency in main study outcomes. We noted statistical heterogeneity in sites for both primary outcome measures: active bleeding cessation within 20 min with study treatment alone (p=0·001) and additional blood loss of 300 mL or more (p=0·003). Despite these differences, after adjusting for sites, we obtained the same relative risks and almost identical 95% CIs for active bleeding controlled within 20 min with initial study treatment (RR 0·94, 95% CI 0·91–0·98) and additional blood loss of 300 mL or more (RR 1·78, 95% CI 1·41–2·25). Stratified analyses were also undertaken for secondary outcomes by site and confirmed similar results to those presented in tables 2 and 3 (data not shown).

Discussion

This large, clinical, randomised controlled trial provides evidence that for several measures oxytocin is significantly better than is misoprostol for the treatment of post-partum haemorrhage in women not given oxytocin prophylaxis. However, the study provides evidence that, relative to oxytocin, misoprostol is also effective in controlling post-partum bleeding. Both oxytocin and misoprostol did better than the reference 88% estimated efficacy of oxytocin that was used to power the study. First-line treatment with oxytocin alone was more effective in controlling active bleeding within 20 min than was first-line treatment with misoprostol. Oxytocin stopped active bleeding on average 2 min faster than did treatment with misoprostol, resulting in about 50 mL less blood loss in women receiving oxytocin. Women given misoprostol were more likely than were those given oxytocin to have additional blood loss of 300 mL or greater, and recourse to additional interventions was more frequent in the misoprostol group than in the oxytocin group.

The crude overall difference in the proportion of women (misoprostol *vs* oxytocin) whose active bleeding was not controlled with first-line treatment was within the specified 6% margin of non-inferiority. Yet, because the upper confidence limit of this difference extends beyond the predefined margin, non-inferiority cannot be claimed, and the result must be deemed inconclusive (figure 2). Despite the large variation noted between sites in the proportion of women with uncontrolled bleeding, a stratified analysis by site confirmed consistency in study conclusions favouring oxytocin.

As recorded in other studies,[22,23,26] women given misoprostol had significantly more transient shivering and fever than did those given oxytocin. Why temperatures of 40·0°C or higher occurred with greater frequency in Ecuador than in other sites is unclear. Environmental factors such as the site's high altitude and the genetic make-up of the population have been considered. (A separate report will explore this issue further.) In view of the dose-dependent nature of misoprostol-associated side-effects, a lower dose should be investigated. Furthermore, delivery attendants should be trained to recognise and manage common side-effects after misoprostol is given for post-partum haemorrhage.

Previous work has shown encouraging evidence of misoprostol's potential for treatment of post-partum haemorrhage in several case reports,[10–16] four small randomised controlled trials,[17–20] and one ecological community-based study.[21] However, findings are limited by the heterogeneity of the range of doses (200–1200 µg) and routes (rectal, oral, intrauterine) studied, and the small sample sizes available for analysis. Evidence lending support to its use as a stand-alone treatment for post-partum haemorrhage has been deemed insufficient.[22,23] A companion study to this Article, which enrolled women who had haemorrhages despite prophylactic treatment with 10 IU oxytocin, showed clinical equivalency of oxytocin to misoprostol with rates of efficacy of 89–90%.[27] The present trial by comparison documented a 90% rate of efficacy in the misoprostol group, which is similar to the rates achieved in the companion study; whereas oxytocin alone achieved 95%. A cross-study comparison suggests that both treatments were more effective and faster acting in women with a uterus not previously exposed to oxytocin for prophylaxis. For instance, misoprostol controlled active bleeding in the present study in 13 min versus 20 min in the companion study, and oxytocin controlled bleeding in 11 min versus 18 min in the companion study. Additionally, although there were six hysterectomies and two deaths in the companion trial, no invasive surgeries, hysterectomies, or deaths occurred in this trial. The differences in clinical outcomes in two different contexts suggest that oxytocin prophylaxis could have reduced the differences between the treatment groups by selecting a group of haemorrhaging women for treatment who were physiologically different from the wider group of women in this study. Women treated in the companion study might therefore be a specific group with poorer response to oxytocin treatment of their bleeding and a better response to an alternative uterotonic drug—in this case, misoprostol. Whether a similar effect would arise if misoprostol were used for treatment after its use for prophylaxis remains to be clarified.

The findings of this clinical study have limitations. The high efficacies achieved in this trial might not be generalisable to other delivery settings. Providers in this study were highly skilled in implementing the protocol and in providing a level of attention and timely care, which might be less likely in non-research circumstances. Several issues might affect the comparison in clinical practice: the potential for delay in administration of oxytocin via intravenous line compared with administration of misoprostol tablets, the use of a dose of oxytocin that is higher than the standard dose in some settings, and that misoprostol might take more time to act (peak serum concentrations around 20 min *vs* almost immediate for oxytocin).[24] This study could have reduced the logistical issues involved in oxytocin use and conferred some artificial advantages to oxytocin compared with misoprostol—both in ease of starting treatment and in the time to bleeding cessation. Future research will be crucial to elucidate how the clinical outcomes reported in this study might translate into programmatic effectiveness. In normal clinical practice, the two treatments could easily be similarly effective since the absolute differences recorded are quite small. Additionally, in the absence of any large randomised studies to establish the efficacy of oxytocin compared with placebo for treatment of post-partum haemorrhage, the advantage conferred by either treatment compared with placebo remains unknown and impossible to assess since a trial in which only placebo is offered to a haemorrhaging patient would not be ethical.

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This study responds to the need for data about misoprostol as a potential first-line treatment.[22] We find that intravenous oxytocin should be used when available, but 800 µg sublingual misoprostol could be an effective first-line treatment alternative when oxytocin is not available. Since many women in developing countries deliver at home or at low-level facilities, misoprostol provides a potential for immediate treatment of post-partum haemorrhage. 10% of women treated with misoprostol might need additional treatment, so referral systems would still be necessary but for fewer women than if no misoprostol were used. Although evidence exists on the feasibility and use of misoprostol for prophylaxis in such settings,[6] less is known about the feasibility of management of post-partum haemorrhage with misoprostol. Building on the efficacy and safety shown in this study, future research is needed to assess the clinical benefits and cost-effectiveness of introducing misoprostol as an alternative to universal referral for treatment in settings that do not have access to intravenous oxytocin.

Contributors

BW, JB, and RD contributed to the conception of the trial. BW, JB, RD, JD, ED, NTNN, WL, and SR participated in the study design. All authors participated in study implementation, data analysis, and interpretation of results. BW, RD, and JD drafted the report with input and editing from all authors.

Conflicts of interest

We declare that we have no conflicts of interest.

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