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CLINICAL ARTICLE

A randomized controlled trial on the value of misoprostol for the treatment of retained placenta in a low-resource setting

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ABSTRACT

Objective: To evaluate the efficacy and safety of misoprostol among patients with retained placenta in a low-resource setting. *Methods:* A prospective, multicenter, randomized, double-blind, placebo-controlled trial was carried out in Tanzania between April 2008 and November 2011. It included patients who delivered at a gestational age of 28 weeks or more and had blood loss of 750 mL or less at 30 minutes after delivery. Sublingual misoprostol (800 μg) was compared with placebo as the primary treatment. Power analysis showed that 117 patients would be required to observe a reduction of 40% in the incidence of manual removal of the placenta (MRP; $P = 0.05$, 80% power), the primary outcome. The secondary outcomes were blood loss and number of blood transfusions. *Results:* Interim analysis after recruitment of 95 patients showed that incidence of MRP, total blood loss, and incidence of blood transfusions were similar in the misoprostol (MRP, 40%; blood loss, 803 mL; blood transfusion, 15%) and placebo (MRP, 33%, blood loss 787 mL, blood transfusion, 23%) groups. The trial was stopped because continuation would not alter the interim conclusion that misoprostol was ineffective. *Conclusion:* Treatment with misoprostol was found to have no clinically significant beneficial effect among women with retained placenta.

Clinical Trial Registration: Current Controlled Trials ISRCTN16104753

1. Introduction

Retained placenta is diagnosed when the placenta is not expelled within a certain time interval after the delivery of a neonate [1,2]. The interval after which a prolonged third stage is diagnosed as retained placenta varies among countries [2]. At the study site in Tanzania—as in most English-speaking settings—retained placenta is defined as lack of expulsion of the placenta within 30 minutes of the neonate being delivered [3]. Retained placenta can be complicated by postpartum hemorrhage and infection, which may cause maternal morbidity and mortality [2,4]. The need to reduce maternal mortality has been recognized worldwide by the Millennium Development Goals [5].

Tanzania is an under-resourced country. The maternal mortality rate is 454 women per 100 000 live births [6]. In a retrospective study on causes of maternal mortality in Tanzania, retained placenta was responsible for 13% of the maternal deaths [4]. The incidence of retained placenta is estimated to be 1%–2% worldwide, but the exact figure for Tanzania is not known; however, it has been reported that the incidence is lower in low-resource settings than in high-resource settings [7].

The blood loss that accompanies retained placenta can be very severe and often requires emergency medical treatment such as administration of injectable uterotonics, intravenous replacement of fluid loss, manual removal of the placenta (MRP) under analgesia, and blood transfusions [8]. These interventions are done by skilled personnel and require equipment. In many under-resourced countries, women have home deliveries and transport to health facilities is costly. Many basic health facilities are not equipped to perform MRP or to give a blood transfusion. Transport to higher care facilities requires time and funds—commodities that are often lacking in emergency circumstances [4,5]. Non-surgical treatment of retained placenta with an effective and cheap drug might be lifesaving in such conditions.

Prostaglandin administration might reduce the need for MRP. A randomized controlled trial (RCT) on intravenously administered prostaglandin versus placebo showed that 250 μg of prostaglandin E2 (sulprostone) administered intravenously 60 minutes postpartum effectively reduced the need for MRP from 82% in the placebo group to 51% in the sulprostone group within 30 minutes of administration [9]. Blood loss was 388 mL less in the sulprostone group than in the placebo group (average blood loss: 1062 mL for sulprostone versus 1450 mL for placebo, respectively). Regrettably, sulprostone is

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relatively expensive and needs a cold chain; as a result, it is not affordable in an under-resourced setting.

Misoprostol is an inexpensive E1 analog that is pharmaceutically stable at room temperature. Misoprostol has strong uterotonic properties and has many routes of administration, including oral, sublingual, vaginal, and rectal [10]. Sublingual administration is preferred because the highest serum peak concentration is reached in the shortest time compared with the other routes of administration [11]. It therefore seemed appropriate to test whether misoprostol can lower the need for MRP among patients in under-resourced settings.

The objective of the study was to determine whether sublingually administered misoprostol can reduce the incidence of manually removed placenta (MRP) and/or the quantity of blood loss among patients with retained placenta in an under-resourced setting. We note, however, that an RCT in a high-resource setting was published toward the end of the present study in which misoprostol and placebo orally administered 60 minutes postpartum among women with retained placenta showed similar expulsion rates of approximately 50% in both groups [12].

2. Materials and methods

The present placebo-controlled multicenter, randomized, double-blind trial was carried out between April 1, 2008, and November 1, 2011, among women with retained placenta at 7 hospitals in Tanzania: 2 regional hospitals (Lindi and Mtwara), 2 mission hospitals (Ndanda and Nyangao), 2 urban regional hospitals (Amana and Temeke), and 1 university teaching hospital (Muhimbili). The National Institute of Medical Research (NIMR) and the Senate Research and Publication Committee of Muhimbili University of Health and Allied Sciences and the Muhimbili National Hospital in Tanzania gave permission for the study. Women received oral and written information in Kiswahili about enrollment in the study and provided written informed consent.

The trial protocol has been published [13]. All doctors and midwives in each labor ward received verbal and written training before the start of the study. In all hospitals, a leading staff member was appointed as principal investigator.

All laboring women received active management of the third stage of labor (AMTSL): namely, injection with 5 IU of oxytocin within 1 minute of delivering the infant, delayed early cord clamping, controlled cord traction (CCT) with 1 the first uterine contractions, and massage of the uterus after delivery of the placenta. Women were eligible for the study if the placenta had not been expelled 30 minutes after delivery of a neonate of 1 kg or heavier, or a gestational age of 28 weeks or more. The exclusion criteria were a hemoglobin concentration of less than 100 g/L (6.2 mmol/L), a blood loss of more than 750 mL, a pulse rate of more than 120 beats per minute, or a reduction in diastolic blood pressure of more than 20 mm Hg after delivery.

Potential participants were identified in the delivery rooms 20 minutes postpartum. The urine bladder was catheterized, a cannula was inserted, and normal saline solution was administered. CCT was performed again and a blood sample was taken for cross-matching and hemoglobin.

The randomization scheme used balanced variable blocks: in the labor ward were closed envelopes containing the registration papers in addition to the blinded study medication. A technique of over-encapsulation was used for both the 800-μg misoprostol tablets and the placebo tablets. All tablets were the same size, and the placebo had a bitter taste and dissolved sublingually similar to misoprostol. The study medication was packed in airtight dispensing bags. Small batches of study medication were manufactured during the trial such that new study medication was available 4 times during the trial. Allocation was in accordance with the sequence of enrolment in each of the 7 hospitals. Patients, staff, and researchers were blind to the allocation.

Women provided consent and were enrolled in the study 30 minutes after delivery of their newborn. The envelope was opened and the study medication was administered sublingually. From then on, CCT was performed every 10 minutes to check whether placental separation from the uterine wall had taken place. Blood loss was calculated by weighing self-absorbable mattresses. When blood loss exceeded 1500 mL, an emergency MRP was performed. If the placenta was still retained 30 minutes after receiving the study medication, the patient underwent MRP. Partially expelled placentas, which needed MRP or curettage to remove the remaining products of conception, were classified as MRP.

The patients enrolled in the trial were observed for 12–24 hours postpartum. Vital signs, fundal height, and blood loss were monitored, and a hemoglobin sample was obtained before discharge. If required, patients received blood transfusions in accordance with the hospitals' guidelines. All patients received combined ferrous sulfate and folic acid tablets in accordance with the national policy on postpartum care.

The primary endpoint of the trial was MRP and the secondary outcome variable was the quantity of blood loss. Because measurement of blood loss during delivery is unreliable, the secondary "surrogate" outcome variable was the amount of units of packed cells administered.

The chance of spontaneous expulsion of the placenta between 30 and 60 minutes after delivery of the newborn in the case of strict AMTSL was found to be 36% in the Bristol study on active management of labor (incidence of retained placenta: 3.0% at 30 minutes; 1.9% at 60 minutes) [14], and 56% in preliminary observations among a group with partly active and partly expectative management (incidence of retained placenta: 9% at 30 minutes; 5% at 60 minutes; data not shown). The power analysis was based on the assumption that not all women will receive active management of labor (this happens regularly in Tanzania despite thorough instruction); as a result, the best estimate for a reduction in MRP rate for retained placenta at 30 minutes postpartum was 44% at 60 minutes postpartum. For reasons of patient safety, a 2:1 randomization was used so that the number of women who received placebo was as small as possible. On the basis of a 2:1 randomization of misoprostol to placebo, it was calculated that a sample size of 117 women would be needed to show a 40% reduction in MRP (5% level of significance, 2-tailed α, 80% power). Consequently, 39 patients were required for the placebo group and 78 for the misoprostol group.

Baseline characteristics of the women enrolled in the trial were recorded and analyzed to confirm the absence of confounding variables between the 2 groups. Outcome variables were analyzed according to the "intention to treat" principle. The data management safety board installed to monitor the safety and efficacy of the study checked the data after the enrollment of every 10 patients. As part of the study protocol, it was planned that an interim analysis would be performed after 75% of patients were recruited, again to monitor safety and efficacy.

Excel version 14.4, 2011 (Microsoft, Redmond, WA, USA) and SPSS version 20 (IBM, Armonk, NY, USA) were used for statistical analysis. Student t test and χ^2 test were used to compare variables as appropriate, and a P value of less than 0.05 was considered to be significant. The relative risk (RR) and 95% confidence intervals (CIs) were calculated for the primary and secondary outcome variables.

3. Results

The study was stopped prematurely before the predefined sample size of 117 patients with retained placenta had been reached. As a result, 104 women were assessed for eligibility, 97 received study medication, and 95 were included in the data analysis. Fig. 1 shows the flow of women through the study.

There were 65 women in the misoprostol group and 30 in the placebo group (Table 1). There was a small difference in baseline characteristics

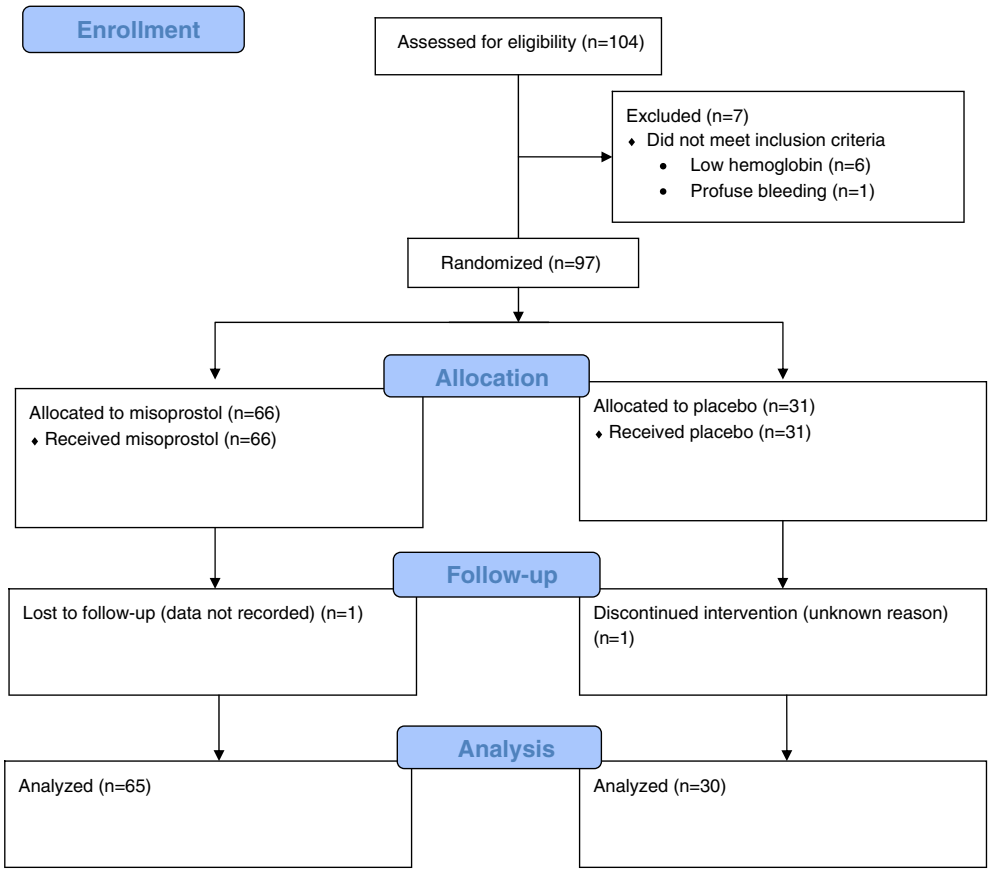

Fig. 1. Flow of patients through the study.

between the groups: namely, the placebo group had earlier administration of oxytocin. This intervention is regarded as beneficial for spontaneous expulsion of the placenta. The difference in the administration time of oxytocin was caused by delayed administration (>30 minutes) for 3 patients in the misoprostol group compared with no delayed administration in the placebo group. The research protocol was correctly followed for 83 women; however, 14 women received the trial medication too early (within 30 minutes of delivery of the newborn).

An interim analysis was planned after 75% of participants were recruited. At that time, however, multiple enrollments took place in a short time at the 7 participating hospitals; thus, interim analysis was done after inclusion of 80% of the patients (n = 95). The incidence of MRP did not significantly differ between the groups (misoprostol, 40%; placebo, 33%; RR, 1.20; 95% CI, 0.67–2.16) (Table 2). The mean blood loss was also similar in both groups (803 ± 495 mL and 787 ± 404 mL, respectively), as was the number of blood transfusions (RR, 0.66; 95% CI, 0.28–1.56).

Because only 22 more patients were needed to reach the number defined in the power analysis, a "best-case situation" was calculated for the primary outcome of MRP. In this situation, all remaining patients given misoprostol (n = 13) would expel the placenta and all remaining patients given placebo (n = 9) would have MRP. Even in such a situation, misoprostol would not be shown to be effective in reducing the need for MRP (misoprostol, 26 MRP, 33%; placebo, 19 MRP, 48%; $P = 0.10$; RR, 0.68; 95% CI, 0.43–1.06). On the basis of these projections, the data management safety board decided to stop the study for reasons of futility.

Table 1
Demographic and obstetric characteristics of the participant.[a]

	Misoprostol (n = 65)	Placebo (n = 30)	*P* value
Age, y	27.0 ± 6.7	28.5 ± 6.7	0.30
Parity	2.3 ± 1.5	2.6 ± 1.8	0.40
Hemoglobin third trimester, g/dL	10.7 ± 1.3	10.3 ± 1.5	0.35
Mode of delivery			
Spontaneous vertex	61 (94)	30 (100)	0.59
Spontaneous breech	2 (3)	0	
Vacuum extraction	1 (1.5)	0	
Not recorded	1 (1.5)	0	
Perineum			
Episiotomy	5 (8)	3 (10)	0.95
Rupture	8 (12)	4(13)	
Intact	47 (72)	20 (67)	
Not recorded	5 (8)	3 (10)	
Time oxytocin administered, min			
Mean	5.7 ± 9.6	2.9 ± 2.0	0.03
Median (range)	3 (0–60)	2 (0–10)	
CCT performed before inclusion	61 (94)	26 (87)	0.24
Bladder emptied before inclusion	62 (95)	25 (83)	0.11
Blood loss before inclusion, mL	262 ± 149	270 ± 146	0.81
Time study medication administered, min	33.7 ± 14.1[b]	32.3 ± 14.2[c]	0.54
Study medication administered <30 min	9 (14)	5 (17)	0.71

Abbreviation: CCT, controlled cord traction.
[a] Values are given as mean ± SD or number (percentage) unless stated otherwise.
[b] Not recorded in 5 women.
[c] Not recorded in 3 women.

4. Discussion

The present study demonstrated that misoprostol administered 30 minutes after delivery of the newborn was not effective in reducing the incidence of MRP or blood transfusion among patients with retained placenta in a low-resource setting. This is in line with results from a recent RCT in a high-resource setting in which misoprostol administered orally 60 minutes postpartum was found to be ineffective [12].

Table 2
Outcome measures of the study.[a]

	Misoprostol (n = 65)	Placebo (n = 30)	*P* value
Manually removed placenta	26 (40)	10 (33)	0.53
Placenta expelled spontaneously	39 (60)	20 (67)	
Total blood loss	803 ± 495 (100–2580)	787 ± 404) (50–2080)	0.87
Postpartum hemorrhage (>1 L)	19 (29)	11 (37)	0.47
Blood loss for placenta expelled, mL	633 ± 323 (200–1560)	736 ± 439) (100–1830)	0.36
Blood loss for MRP, mL	1156 ± 533) (300–2580)	1071 ± 518 (600–2080)	0.67
Blood transfusion	10 (15)	7 (23)	0.35
Hemoglobin at discharge from hospital, g/dL	8.8 ± 1.9	10.7 ± 9.3	0.31

Abbreviation: MRP, manual removal of the placenta.
[a] Values are given as the mean ± SD (range) or number (percentage) unless stated otherwise.

The study was conducted to establish whether medical treatment with misoprostol can reduce the maternal morbidity associated with retained placenta. The study was carried out in a low-resource setting where communication is complicated and where healthcare providers are not familiar with doing research. This may have meant that 14 patients received the study medication too early (within 30 minutes of delivery). Because the trial was designed to analyze the data according the intention-to-treat principle, these 14 patients were included in the analysis. It might be argued that this would not affect the final outcome of the study because an effective drug would be expected to expel the placenta even if it were administered too early, whereas an ineffective drug would not.

The present RCT was powered to detect a 40% reduction in MRP (5% level of significance, 2-tailed alpha, 80% power). Because the study had "only" 80% power, we cannot fully rule out the possibility that a small positive effect, albeit present, was not found (type II error). The power calculation was based on a trial in which sulprostone reduced the rate of MRP by approximately 40% compared with placebo [9], with the assumption of similar efficacy between misoprostol and sulprostone. The present data suggest that the efficacy of misoprostol is lower than that of sulprostone for treatment of retained placenta.

The trial was stopped prematurely. A chief concern throughout the trial was the safety of the patients. Many women in under-resourced settings are in poor condition with a low hemoglobin level; thus, postponing MRP might be harmful. For this reason, it was considered unethical to continue a trial that would not provide definitive beneficial results.

The observed rate of spontaneous expulsion of the placenta between 30 and 60 minutes (60% in the misoprostol group and 67% in the placebo group) was close to the value of 56% used in the power calculation. These values are higher than those observed in another recent trial (the "Release Trial") in which 38% of spontaneous expulsion was reported [15]. Both the present study and the Release Trial treated patients 30 minutes after delivery of the newborn. Because intervention rates are usually higher in high-resource settings, it is not surprising that the spontaneous expulsion rates were higher in Uganda and Pakistan than in the United Kingdom (53%, 38%, and 31%, respectively) in the Release Trial. This might possibly be caused by a delay in surgical removal of the retained placenta and/or more strenuous attempts to deliver the placenta in the labor ward in the under-resourced settings. The high rate of spontaneous expulsion (two-thirds) occurring between 30 and 60 minutes postpartum in the present study suggests that careful expectative management of patients until 60 minutes after delivery is warranted.

In conclusion, the present study showed that, with or without misoprostol administration, two-thirds of placentas that were retained at 30 minutes were expelled spontaneously within 1 hour of delivery of the neonate. Misoprostol was not effective in reducing either MRP or postpartum hemorrhage.

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Conflict of interest

The authors have no conflicts of interest.

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