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Randomized Double Masked Trial of *Zhi Byed 11*, a Tibetan Traditional Medicine, Versus Misoprostol to Prevent Postpartum Hemorrhage in Lhasa, Tibet

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Abstract

The objective of this study was to compare a Tibetan traditional medicine (the uterotonic *Zhi Byed 11* [*ZB11*]) to oral misoprostol for prophylaxis of postpartum hemorrhage (PPH). We conducted a double-blind randomized controlled trial at three hospitals in Lhasa, Tibet, People's Republic of China. Women (N = 967) were randomized to either *ZB11* or misoprostol groups. Postpartum blood loss was measured in a calibrated blood collection drape. The primary combined outcome was incidence of PPH, defined as measured blood loss (MBL) ≥ 500 mL, administration of open label uterotonics, or maternal death. We found that the rate of the combined outcome was lower among the misoprostol group (16.1% versus 21.8% for *ZB11; P* = .02). Frequency of PPH was lower with misoprostol (12.4% versus 17.4%; *P* = .02). There were no significant differences in MBL > 1000 mL or mean or median MBL. Fever was significantly more common in the misoprostol group (*P* = .03). The rate of combined outcome was significantly lower among women receiving misoprostol. However, other indices of obstetric hemorrhage were not significantly different.

Keywords

postpartum hemorrhage; obstetric hemorrhage; complementary medicine; randomized controlled trial

INTRODUCTION

Obstetric hemorrhage is the leading cause of maternal death worldwide and causes at least 150,000 deaths annually in developing countries.[1] In the Tibetan Autonomous Region (TAR) of the People's Republic of China (PRC), postpartum hemorrhage (PPH) is a leading cause of maternal morbidity and mortality.[2]

Tibet has a centuries long, well developed system of traditional medicine. Present day health facilities and practitioners carry on this traditional system that has been formulated in compendiums and formalized in training. One traditional Tibetan formula, *Zhi Byed 11 (ZB11)*, is comprised of 11 ingredients (herbal, mineral, and animal) that are commonly found in Tibetan medical practice and has been used for more than 700 years to prevent and treat obstetric hemorrhage.[3] Although it has never been subjected to rigorous prospective evaluation nor has its effectiveness been compared to a placebo, traditional Tibetan medicine practitioners recommend prophylactic administration of *ZB11* at the time of complete dilation for PPH.[3]

The following animal, vegetable, and mineral ingredients comprise *ZB11*. The first term, shown in italics, is the Tibetan name; the second term, in parentheses, is the Latin name; and when possible, the common name for the same substance is also given. Vegetable ingredients include *Ma Nu* (Inula racemosa, Inule henelium L; elecampane), *Ol Mo Se* (Sinopodophyllum hexandrum royle; mayapple), *Lcum Rtsa* (Rheum palmatum l; rhubarb), *A Ru Ra* (Terminalia chehula Retz, Chebulic myrobalan), *Star Bu* (Hippophae rhamnoides L; sea buckhorn), and *Sga Skya* (Zingiber officinale rose; ginger). Mineral ingredients include *Rgya Tsha* (Sal ammoniacum; salt of sulfur/tar), *Bul Tog* (Trona; bicarbonate carbonate), and *Cong Zhi*

(Calcitum; calcium). The animal ingredients include *Sbrul Sha* (Zaocys dhumnades cantor; black snake meat) and *Sdig Srin* (Potamon yunnanense kemp; freshwater crab shell) (M. Tshomo, unpublished data, 2004; Figure 1 available online only at www.jmwh.org).

Gas chromatography-mass spectroscopy analysis at the Center for Human Toxicology, University of Utah, found the purgative and cathartic components: rhein, chrysophanol, and alantolactone. Both rhein and chrysophanol have cathartic and purgative properties also found in the senna species, known as a laxative.[4–6] The uterotonic properties of *ZB11* may be attributable to these and other individual ingredients which have cathartic, purgative, and emmenagogic (ability to promote menstrual flow) properties and to interactions between the ingredients.

The gas chromatography-mass spectroscopy also identified long-chain fatty acids, alcohols and methyl esters, eudesma (5,11 (13)-diene-8,12-olide), physcion, and chrysophanol (9,10-anthracenedione, 1,8-dihydroxy-3-methyl).[5] Fatty acid esters, such as the linoleic acid methyl ester and oleic acid methyl ester, are prostaglandin precursors and are involved in prostaglandin synthesis, another plausible mechanism of action for *ZB11*.[7–10] Linoleic acid has been shown to cause significant increases in prostaglandin synthesis.[11] Some of the ingredients of *ZB11* known to Western herbal practitioners as cathartics, purgatives, and emmenagogics include *ma nu* (Inula helenium); *lcum rtsa* (Rheum palmatum or rhubarb); *ol mo ' se* (Podophyllum peltatum or mayapple), which is an uterine stimulant, emmenogogue, and abortifacient; *sga skya* (Zingiber officinale), an abortifacient; and *star bu* (sea buckthorn), which is not only a cathartic, but also has diuretic properties (M. Tshomo, unpublished data, 2004).[12,13]

ZB11 costs only USD $0.04 per dose, is culturally acceptable, widely available in Tibet, and can be administered orally by the woman herself, a relative, or an unskilled attendant. If proven efficacious and safe, *ZB11* could decrease the incidence of PPH among the 85% of women in the TAR who deliver at home with an unskilled attendant or alone with no attendant. Tibet does not have a history of traditional birth attendants.[14] In the TAR, PPH is a leading cause of maternal morbidity and mortality,[15] but because of the large number of births that occur outside of health facilities or at home, exact numbers of maternal deaths are unknown and estimates may be underreported.[2,15]

The internationally recognized best practice prevention of PPH includes active management of the third stage of labor (AMTSL), with the administration of a uterotonic at the time of delivery of the baby or within 5 minutes.[16] While oxytocin remains the preferred drug of choice for the prevention and treatment of PPH in hospital settings,[16] it requires safe injection capacity and refrigeration, and therefore it cannot be self-administered or administered by unskilled attendants. There has been recent interest in the use of misoprostol to prevent PPH in developing countries because of its low cost, oral administration, and long shelf-life. Several recent studies in developing countries have tested the efficacy of misoprostol, an E_1 analogue prostaglandin, against oxytocin,[17,18] other uterotonics, or placebo[19–22] for the prevention of PPH. In these studies, the mean difference in measured blood loss (MBL) in the first hour following delivery in the misoprostol group ranged from 45 to 85 mL less than the placebo group.[18,19,21] A recent study in India by Derman et al.,[19] which included 1620 women (812 women in the misoprostol group and 808 in the placebo group) documented that the prophylactic use of misoprostol at the community level reduced PPH by 50% compared to placebo. Since 2006, the International Confederation of Midwives (ICM) and the International Federation of Gynecology and Obstetrics (FIGO) have recommended misoprostol for prophylaxis of PPH in the absence of oxytocin or when safe injection is not feasible.[23]

Oral prophylaxis with misoprostol, self-administered by the woman, an unskilled attendant, or by a relative, was not recommended at the time this study was implemented and has not been

approved in Tibet. There were concerns that misoprostol's well known side effects (particularly shivering and fever[17,18,24–26]) might decrease acceptability and use among attendants and women. Furthermore, misoprostol can cause uterine hyperstimulation in the third trimester, leading to concern about inadvertent administration during labor (before the baby is born), with resultant fetal and/or maternal compromise. Finally, the price of misoprostol (USD $1 per 600 mcg dose at the time of the study) is beyond the means of many families; the annual income of a family in the TAR is USD $362 rural to $1445 urban.[27,28] Therefore, a lower cost, locally available, and culturally acceptable prophylactic uterotonic that does not have some of the potential risks of shivering or fever could be of substantial value for reducing the incidence of PPH in the TAR.

Therefore, a team of US-based midwives, obstetricians, and anthropologists joined a team of Tibetan midwives and obstetricians to conduct a randomized controlled trial (RCT) of *ZB11* versus misoprostol for the prevention of PPH.

METHODS

This double-blind, double placebo, randomized two-arm trial was conducted between August 2005 and March 2007 at three obstetric units in Lhasa, TAR, PRC: Mentzikhang Traditional Tibetan Medicine and Astrology Hospital, which provides both Tibetan and Western allopathic care; the Lhasa Municipal Hospital; and the Lhasa Maternal and Child Health Hospital. The latter two are public hospitals, administered and staffed by providers trained in Western-style medicine.

Before initiation of the study, there had been limited experience with Western-style biomedical research in the study hospitals. Two years of ethnographic research and relationship building between the United States and Tibetan investigators and the community[14,29,30] preceded a subsequent 2-year observational study.[14,29–32] US and Tibetan investigators conducted training workshops with the Tibetan physician, nurse, and nurse-midwife data collectors, which covered evidence-based obstetric care, clinical research, research ethics, data collection, and the use of a closed-end, plastic blood collection drape. A Tibetan Research Committee, comprised of the directors and assistant directors of the three participating hospitals' obstetric services, was established. US researchers also assisted the Mentzikhang Hospital in establishing the first internationally recognized institutional review board (IRB) in Tibet (US Office of Human Relations Programs no. IRB00004589).

The study was approved by the IRBs of the University of Utah, University of California, San Francisco, Research Triangle Initiative International (the data coordinating center) and the Mentzikhang Hospital. This trial (NCT00147420) was registered with the US clinical trials database (www.clinicaltrials.gov). Pregnant women 18 years of age or older with a viable intrauterine singleton pregnancy ≥ 28 weeks gestation were considered eligible for study participation. Women were screened for eligibility on admission to the hospital labor ward by trained clinician-data collectors. Exclusion criteria for this study included: previous or planned caesarean section, no fetal heart rate, preeclampsia, severe anemia (hemoglobin < 7), history of bleeding disorders, mental disability, body temperature >38°C, serious medical illness, or active hemorrhage at the time of screening. Women with a history of glaucoma or asthma were excluded because they are known contraindications for misoprostol administration.[33] Women who were in too much pain from active labor to provide informed consent were also considered ineligible.[34,35]

Trained study personnel read the informed consent document in either Tibetan or Mandarin Chinese to eligible women. To be eligible to consent to the study, women were required to answer correctly 12 of 16 comprehension questions to demonstrate their understanding of the

informed consent information. No woman was excluded for this reason. Consent was documented by the woman's signature or with a thumb print and a witness' signature if the woman was illiterate.[30]

Based on the published literature on misoprostol[19] and a lack of published literature on *ZB11*, we hypothesized that 600 mcg misoprostol would be more effective than the traditional dose of *ZB11* in reducing the frequency of a combined outcome, defined as either PPH (MBL ≥ 500 mL), administration of open label uterotonics within the 1 hour observation period after delivery, or maternal death. Secondary outcomes included: MBL ≥ 500 to 999 mL, MBL ≥1000 mL, mean and median MBL during the first hour postpartum, and side effects.

A single oral dose of *ZB11* (or its identical placebo) was comprised of three green gel capsules. *ZB11* study drug gel capsules were manufactured in a single lot using a traditional formulation by the Mentzikhang Traditional Tibetan Medicine Factory (Lhasa, TAR, PRC) expressly for this study. *ZB11*'s production, standardization, and stability up to 6 months were analyzed by the Mentzikhang manufacturer before the study. The study lot of *ZB11* and its placebo were examined by gas chromatography-mass spectroscopy at the Center for Human Toxicology at the University of Utah at three consecutive 6-month intervals. The sample was tested for heavy metals and none were documented.[36]

Misoprostol tablets (GyMiso) and identical placebo tablets were manufactured by U-Liang Pharmaceutical Ltd specifically for this study. The dose of misoprostol was 600 mcg (three 200-mcg tablets).

Both study medications were produced using documented good manufacturing practices. In addition, a random sample of 20 packed study envelopes were tested by the data coordinating center (RTI International); they found the packing assignment to be correct. Bioequivalence to US-manufactured misoprostol was analyzed and identified as 99% (range, 96.5–101.8%) of the label claim.

To ensure balanced randomization and to conceal treatment assignment, a computer-generated randomization list with a random block size for each hospital was used. The data coordinating center generated a randomization list stratified by hospital, which was drawn with a 1:1 ratio (one *ZB11* assignment to every misoprostol assignment).

The senior US member of the research team (M.W.V.), who was not involved in patient care in the TAR, prepared all of the study envelopes. *ZB11* is traditionally given at full dilation (M. Tshomo, unpublished data, 2004), and misoprostol used prophylactically is given immediately after delivery,[16] so the study medications were administered at different times. Thus, each study envelope contained two smaller envelopes: one envelope contained either *ZB11* or *ZB11* placebo, and the other envelope contained either misoprostol or misoprostol placebo. The smaller envelopes were marked so that the envelope that was to be used at full dilation was marked as "*ZB11*" (*ZB11* or its placebo) and the envelope to be used after the delivery of the baby was marked "misoprostol" (misoprostol or its placebo). All patients received only one active drug and one placebo drug. No patient received two placebos or two active drugs. Sealed opaque study medication envelopes were distributed to the hospitals by research study staff. Envelopes were kept in locked cabinets in the hospital delivery rooms and in the research study office.

Trained clinician-data collectors interviewed women on admission to collect demographic information and medical and obstetric history; they subsequently abstracted data from patient medical records. Labor and delivery progress, complications, medications, and maternal and neonatal outcomes were recorded concurrently with patient care. Side effects were monitored for 1 hour following administration of each study medication. All women were observed and

queried about possible medication side effects at 1 hour after each study drug administration. All data were recorded on standardized data collection forms using numbered patient identifiers. Original data forms with patient identifiers were kept in locked storage units.

As was the norm in all of the institutions, patients were moved to the delivery room when they were dilated to 7 to 8 cm. Once fully dilated, the study participants were randomized to either the *ZB11* or misoprostol arm (one of two study arms) by the study clinician who took the next sequentially numbered sealed opaque envelope out of a locked cabinet in the delivery room. Study participants were randomized to receive either active *ZB11* at full dilation and placebo misoprostol immediately after delivery (within 5 min) or placebo *ZB11* at full dilation and active misoprostol immediately after delivery (within 5 min). Neither study providers nor research staff was aware of the treatment assignments.

Postpartum blood loss was measured using a closed-end blood collection drape (BRASSS-V drape blood collection receptacle[37]) for 1 hour after delivery of the baby. The blood drape was placed under the woman's buttocks before delivery and the collection pouch was opened after delivery of the baby. At the end of the 1-hour blood collection period, blood and clots that pooled under the mother were swept into the drape; the bottom of the drape was cut open, and the contents emptied into a solid graduated cylinder, measured, and the amount recorded in mL.

Data collection forms were reviewed for accuracy by hospital-based study staff before being submitted to the research office for data entry into Epi Info software (version 3.3; Centers for Disease Control and Prevention, Atlanta, GA) by office-based study staff and transmitted electronically using BLAST software (version 9.0; Hologram Publishing, Pittsboro, NC) to the data coordinating center.

An independent Data Safety and Monitoring Board (DSMB) appointed by the National Institute of Child Health and Human Development (NICHD) undertook one review of interim data at the point of the sample size reestimation (29%; n = 280). The DSMB also undertook an interim review for safety and efficacy when patient enrollment was at 72% (n = 696) and conducted a final review when the study was complete (n = 967 randomized and n = 960 completed the trial).

Sample-size calculations for this randomized trial assumed a 25% incidence of the combined outcome with no treatment. There were no available data reporting PPH rates amongst women given *ZB11* for active management of the third stage of labor. Therefore, we assumed a marginal effect of a 10% decrease in this endpoint in the *ZB11* group (i.e., *ZB11* rate = p_2 = 22.5%). Misoprostol has reduced PPH by 30% to 40% compared to placebo in previous studies.[38–41] We therefore assumed a 40% decrease in PPH in the misoprostol group (i.e., misoprostol rate = p_2 =15%).[42] Assuming a two-sided test with 5% type I error rate, a sample of 424 women per treatment group would provide 80% power to detect the difference in the combined outcome between the two groups.[43] Because of the uncertainty of these estimates, we employed a method that allowed an interim sample size reestimation.[44] Upon evaluation of the sample size reestimation with interim data in May 2006 at 29% enrollment, the DSMB recommended continuation of the trial as originally planned. In January 2007, the DSMB recommended continuing the trial to the final sample size of 967 randomized patients.

The primary analysis compared the proportion of women with the combined outcome in the *ZB11* group with the misoprostol group in intent to treat analysis. The null hypothesis was that there was no difference in this proportion between the two groups. Significance tests were two-tailed with a final significance level adjusted for the interim look (α = .0492).[45] Prospectively identified secondary outcomes, including incidence of MBL ≥ 500 to 999 mL, MBL ≥ 1000 mL, mean and median blood loss, and the administration of open label uterotonics within the

1-hour observation period after delivery, were also compared between the two groups. Relationships between categorical variables and treatment group were tested using a Cochran-Mantel-Haenszel chi-square test. The relationship between mean log blood loss (mL) and treatment group was tested using linear regression. Differences in median blood loss were compared using a non-parametric Wilcoxin-Mann-Whitney test for a location difference between the two groups. The primary and secondary analyses were adjusted for the hospital of delivery.

RESULTS

Two thousand three hundred and three women were screened for eligibility, 1352 were initially eligible for enrollment, and 967 were randomized to receive either *ZB11* (n = 480) or misoprostol (n = 487; Figure 2). Nine hundred and sixty patients completed the study.

Maternal demographic and clinical characteristics by treatment group are shown in Table 1. The two groups did not differ significantly in any characteristic. Maternal outcomes and complications not related to the primary study outcomes were not different between the two groups except that more women in the *ZB11* group experienced at least one maternal complication compared to the misoprostol group ($P = .0395$; Table 2). Complete data were available on more than 99% of patients.

The rate of the combined outcome was significantly lower among women receiving misoprostol (16.1%) than *ZB11* (21.8%; $P = .019$), and the frequency of PPH was also lower with misoprostol (12.4% versus 17.4%; $P = .022$) at $\alpha = .0492$ based on an O'Brien-Fleming significance level (Table 3). The relative risk of the combined outcome was 0.82 (0.68, 0.98) in women receiving misoprostol compared with *ZB11*. There were no significant differences in blood loss ≥ 1000 mL (misoprostol 2.1% versus *ZB11* 3.1%; $P = .29$). There were no significant differences in either the mean (misoprostol = 304.3 mL versus *ZB11* = 331.7 mL; $P = .15$) or median (misoprostol = 250 mL, *ZB11* = 265 mL; $P = .09$) blood loss between the groups. There were no maternal deaths.

The blood loss distribution was not normally distributed, with a range from 40 to 1600 mL for misoprostol and 30 to 1450 mL for *ZB11*; however, the median blood loss was similar between the groups. Rates of PPH fell over the course of the study in both groups. Several women who had not met the criteria for PPH were administered additional uterotonics, all within 60 minutes following delivery, primarily at the beginning of the trial. In total, 39 women (21 in *ZB11*, 18 in misoprostol groups) received additional uterotonics with blood loss ranging from 80 to 480 mL. Among side effects, diarrhea, shivering, and fever were more common in the misoprostol group compared to *ZB11*; however, only fever reached statistical significance ($P = .03$; Table 4).

DISCUSSION

This is the first RCT conducted in the TAR, the first RCT of *ZB11* as an uterotonic agent to prevent PPH, and one of the few RCTs of an herbal preparation to induce uterine contractions. We predicted a 10% effect reduction in the combined outcome for *ZB11* (22.5% incidence) and that misoprostol would have a 40% decrease (15% incidence). The results of this study support our hypothesis that misoprostol would significantly reduce the combined outcome, 16.1% with misoprostol versus 21.8% with *ZB11* ($P = .02$).

The strengths of our trial are a sample size of nearly 970 deliveries, a rigorous preparation period, including extensive training in research and research ethics, stringent testing of the study medication, and supportive supervision of data collection and trial management. Limitations included the on-site inexperience in conducting research studies, diverse practices

among delivery attendants within and between hospitals, a lack of biomedical efficacy evidence for *ZB11*, and the lack of a preexisting system to monitor standard of care in the criteria and timing for other uterotonic administration.

As in many other trials, including the recent Derman et al.,[19] where researchers demonstrated that oral misoprostol could effectively prevent PPH in a community setting where expectant management of the third stage of labor was practiced, rates of PPH decreased over time, until they were essentially the same at the end of the study although significantly lower in the misoprostol group.

Implications for further research include a possible comparison of *ZB11* to placebo to determine its efficacy. Other traditional medications that have been used as uterotonics might also be studied with the use of a rigorous methodology such as the one used here. Because many women deliver alone or without a skilled attendant, the search for a reliable, safe uterotonic that is culturally acceptable and inexpensive should continue.

CONCLUSIONS

The statistical results of our study indicate that if oral misoprostol is available, affordable, and accessible, it would decrease the rate of PPH ≥ 500 mL more than *ZB11*, but that there were no differences in severe PPH or mean/median blood loss. Globally, a variety of traditional preparations exist to increase uterine contractions and to prevent or treat PPH; however, few have been tested against allopathic preparations. The current study demonstrated how one traditional preparation was rigorously tested by a multidisciplinary team. Our process might set the stage for future research of traditional medications.

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Figure 1.
Zhi Byed 11 (ZB11) ingredients.

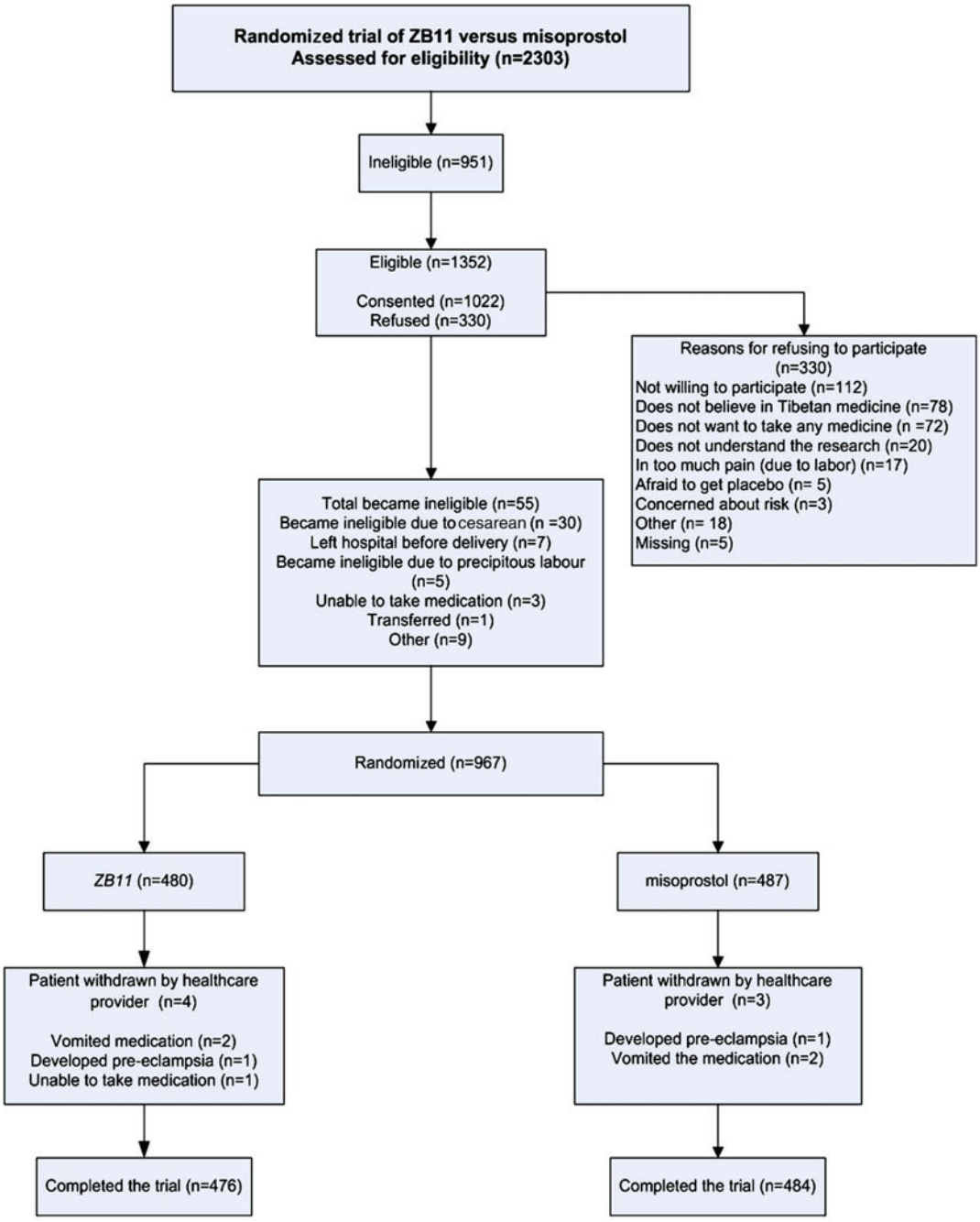

Figure 2.
Trial profile.

Table 1

Maternal Demographics by Treatment Group

Variable	Treatment Group[a]	
	Misoprostol n = 484	***ZB11* n = 476**
Age, mean (SD), y	27.0 (4.6)	26.9 (4.6)
Gravida, mean (SD)	1.7 (1.2)	1.7 (1.0)
Parity, mean (SD)	0.5 (1.0)	0.5 (0.8)
Ethnicity, n (%)		
Tibetan	449 (92.8)	427 (89.7)
Han Chinese	25 (5.2)	30 (6.3)
Other	10 (2.1)	19 (4.0)
Residence, n (%)		
Urban	291 (60.1)	299 (62.8)
Periurban	46 (9.5)	37 (7.8)
Rural	147 (30.4)	140 (29.4)
Prenatal care, n (%)	451 (93.2)	450 (94.5)
If yes, no. of visits[b]		
1	24 (5.3)	27 (6.0)
2–3	87 (19.3)	106 (23.6)
≥4	340 (75.4)	317 (70.4)
Education, mean (SD), y	5.8 (5.3)	5.4 (5.2)

[a] None of the differences in maternal demographics by treatment groups were statistically significant.

[b] Percent of visits out of the women with prenatal care.

Table 2

Maternal Clinical Characteristics by Treatment Group

Variable	Treatment Group[a]	
	Misoprostol, n = 484	***ZB11*, n = 476**
Episiotomy, n (%)	244 (50.4)	230 (48.3)
Perineal tear, n (%)	102 (21.1)	83 (17.4)
Cervical tear, n (%)	29 (6.0)	29 (6.1)
Vaginal tear, n (%)	13 (2.7)	17 (3.6)
Manual removal of the placenta, n (%)	17 (3.5)	13 (2.7)
Retained placenta (placenta not delivered intact), n (%)	8 (1.7)	13 (2.7)
Length of third stage of labor, mean (SD), min	7.2 (6.2)	6.9 (6.0)
Third stage of labor management, n (%)		
Controlled cord traction	413 (85.3)	409 (85.9)
Uterine massage	322 (66.5)	336 (70.6)
Any maternal complication,[b] n (%)	85 (17.6)	109 (22.9)
Postpartum hemorrhage	60 (12.4)	83 (17.4)
Infection	2 (0.4)	2 (0.4)
Preeclampsia	4 (0.8)	1 (0.2)
Eclampsia	1 (0.2)	0 (0.0)
Hypertension	22 (4.5)	29 (6.1)
Other	3 (0.6)	1 (0.2)

[a] Differences in maternal clinical characteristics by treatment groups were not statistically significant for all variables except maternal complication ($P = .0395$) and post-partum hemorrhage ($P = .0219$; $\alpha = .0492$), using the O'Brien-Fleming significance level.

[b] Maternal complication is a composite outcome comprised of any one or more of the following complications. Please note that these complications are not mutually exclusive.

Table 3

Outcomes by Treatment Group (Adjusted for Hospital of Delivery)

Variable	Treatment Group		Adjusted[a]	
	Misoprostol, n = 484	*ZB11*, n = 476	Relative Risk (95% CI)	*P*
Primary outcome				
Combined outcome,[b] n (%)	78 (16.1)	104 (21.8)	0.82 (0.68–0.98)	.0190[c]
Secondary outcomes				
PPH (≥500 mL), n (%)	60 (12.4)	83 (17.4)	0.80 (0.65–0.98)	.0219[c]
Use of open label uterotonics, n (%)	64 (13.2)	78 (16.4)	0.88 (0.72–1.06)	.1606
Maternal death, n (%)	0 (0.0)	0 (0.0)	—	—
Blood loss 500–999 mL, n (%)	50 (10.3)	68 (14.3)	0.81 (0.65–1.01)	.0494
Severe PPH (≥1000 mL), n (%)	10 (2.1)	15 (3.1)	—	.2908
Blood loss, mean (SD), mL	304.3 (218.1)	331.7 (244.0)	—	.1545
Blood loss, median (range), mL	250 (40–1600)	265 (30–1450)	—	.0858

PPH = postpartum hemorrhage.

[a] Relationships between categorical variables (combined outcome, PPH, use of open label uterotonics, blood loss 500–999 mL and severe PPH) and treatment (active misoprostol or active *ZB11*) were tested using a Cochran-Mantel-Haenszel chi-square test adjusting for hospital of delivery. The relationship between mean log blood loss (mL) and treatment group was adjusted for the hospital of delivery and tested using linear regression. The relationship between median blood loss (mL) and treatment group was compared using a nonparametric Wilcoxin-Mann-Whitney test for a location difference between the two treatment groups controlling for hospital. Significant *P* value at $\alpha = .0492$ (O'Brien-Fleming significance level).

[b] Combined outcome is defined as the rate of maternal death, PPH ≥ 500 mL, and/or the administration of open label uterotonic within a 1-hour observation period after delivery.

[c] Significant *P* value at $\alpha = .0492$ (O'Brien-Fleming significance level).

Table 4

Drug Side Effects by Treatment Group

Variable	Treatment Group		P^a
	Misoprostol, n = 483 n (%)	*ZB11*, n = 475 n (%)	
Nausea	14 (2.9)	14 (2.9)	.96
Vomiting	5 (1.0)	4 (0.8)	.76
Diarrhea	11 (2.3)	4 (0.8)	.07
Shivering	75 (15.5)	56 (11.8)	.09
Fever	13 (2.7)	4 (0.8)	.03[b]
Other	1 (0.2)	0 (0.0)	—

Note: Side effects were noted in the time between administration of the active study drug (*ZB11* or misoprostol) to 1 hour post delivery of the baby. Side effect is a category comprised of non–mutually exclusive variables, with some women experiencing more than one side effect. In each group, data on side effects were missing for one participant.

[a] Relationships between side effects and treatment were tested using a Cochran-Mantel-Haenszel chi-square test.

[b] Significant P value at $\alpha = 0.05$.