Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomised controlled trial

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Summary

Background **Postpartum haemorrhage is a major cause of maternal mortality in the developing world. Although effective methods for prevention and treatment of such haemorrhage exist—such as the uterotonic drug oxytocin—most are not feasible in resource-poor settings where many births occur at home. We aimed to investigate whether oral misoprostol, a potential alternative to oxytocin, could prevent postpartum haemorrhage in a community home-birth setting.**

Methods **In a placebo-controlled trial undertaken between September, 2002, and December, 2005, 1620 women in rural India were randomised to receive oral misoprostol (n=812) or placebo (n=808) after delivery. 25 auxiliary nurse midwives undertook the deliveries, administered the study drug, and measured blood loss. The primary outcome was the incidence of acute postpartum haemorrhage (defined as ≥500 mL bleeding) within 2 h of delivery. Analysis was by intention-to-treat. The trial was registered with the US clinical trials database (http://www. clinicaltrials.gov) as number NCT00097123.**

Findings **Oral misoprostol was associated with a significant reduction in the rate of acute postpartum haemorrhage (12·0% to 6·4%, p<0·0001; relative risk 0·53 [95% CI 0·39–0·74]) and acute severe postpartum haemorrhage (1·2% to 0·2%, p<0·0001; 0·20 [0·04–0·91]. One case of postpartum haemorrhage was prevented for every 18 women treated. Misoprostol was also associated with a decrease in mean postpartum blood loss (262·3 mL to 214·3 mL, p<0·0001). Postpartum haemorrhage rates fell over time in both groups but remained significantly higher in the placebo group. Women taking misoprostol had a higher rate of transitory symptoms of chills and fever than the control.**

Interpretation **Oral misoprostol was associated with significant decreases in the rate of acute postpartum haemorrhage and mean blood loss. The drug's low cost, ease of administration, stability, and a positive safety profile make it a good option in resource-poor settings.**

Introduction

Globally, about 500 000 women die annually from complications during pregnancy or childbirth.[1] The most common cause of maternal mortality is postpartum haemorrhage, accounting for one-third of maternal deaths. 99% of these deaths occur in developing countries in women who rarely receive prophylaxis because they give birth outside of a hospital setting.[2]

India is representative of the scope and magnitude of the problem. In rural India, 50% of births are at home or in rudimentary facilities without a physician in attendance. The maternal mortality rate in India is estimated at 407 per 100 000 livebirths and postpartum haemorrhage accounts for 30% of these deaths.[3] Given the high prevalence of anaemia—80% of women are anaemic—blood loss can be fatal in the absence of prompt and appropriate life-saving care.[4,5]

The leading cause of postpartum haemorrhage is uterine atony, most often preventable by conventional uterotonics, among which oxytocin is usually preferred.[6–8] However, the use of oxytocin is not yet feasible in much of the developing world where deliveries still take place in rural areas with untrained birth attendants.[7,9–11] Injectable uterotonics, such as oxytocin are unstable in high temperatures, and require cold-chain storage and skills that birth attendants who do not practice active management of the third stage of labour might not possess.[10,12]

Misoprostol, an E_1 prostaglandin analogue, has been suggested as an alternative to oxytocin since it could act as an effective uterotonic agent, is inexpensive ($1 per dose), can be taken orally, does not need refrigeration, and has a long shelf-life.[13–16]

Hospital-based trials and those done at primary-health centres have proven the safety and efficacy of both misoprostol and oxytocin for the prevention of postpartum haemorrhage. Researchers have identified that where active management of the third stage of labour is practised, oxytocin is usually the preferred drug.[6,7,17–22] However, no large, randomised, placebo-controlled trial has shown the efficacy, safety, and feasibility of misoprostol (oral, rectal, or sublingual) for the prevention of postpartum haemorrhage in a community setting where a physician is not in attendance.[7]

Our hypothesis was that 600 µg oral misoprostol would reduce the rate of acute postpartum haemorrhage by 50%, compared with women given a placebo. We aimed to test this hypothesis in rural women in India, to see whether the drug, administered by auxiliary nurse midwives (ANMs), would be safe and efficacious enough to make feasible its large-scale implementation.

Methods

Setting and patients

The study was undertaken between September, 2002, and December, 2005, in four primary-health centre areas of Belgaum District, Karnataka State, India, covering 19 sub-centres serving 43 villages with a total population of 100 000. Within these villages, more than half the deliveries are at homes or sub-centres (village facilities with no doctor present) Most of these deliveries are undertaken by ANMs who practise "expectant management" of the third stage of labour without a physician in attendance. The midwives participating in the study were responsible for screening and recruiting study participants during the antepartum period, obtaining informed consent, providing the intervention, measuring blood loss, following-up the participants and their newborns for 6 weeks' postpartum, and collecting study data. The midwives were initially trained over 5 days in the conduct of research and implementation of the study protocol. They were tested before and after training, and certified. After 1 year, they were retrained for 2 days, and attended monthly meetings for ongoing skill reinforcement. There were changes in auxiliary nurse midwife personnel during the 3-year study, primarily in the first year, with six of the original 18 midwives having left and being replaced by seven new midwives. In total, 25 midwives participated over the course of the study.

Pregnant women residing in the study villages and anticipating an uncomplicated spontaneous vaginal delivery were eligible for inclusion and were screened at or beyond 28 weeks of gestation. Participants deemed to be at high risk and inapropriate for home or sub-centre births according to India's ministry of health guidelines were excluded from the trial on the basis of the following criteria: previous or planned caesarean section; haemoglobin levels below 80 g/L; antepartum bleeding; hypertension in the current pregnancy; multiple pregnancy; history of previous pregnancy complications including antepartum or postpartum haemorrhage, retained placenta, and acute inversion of the uterus. Women with a history of other high risk conditions such as diabetes, heart disease, seizures, placenta praevia, or breech delivery were similarly excluded, as were women with a history of bronchial asthma because of a known contraindication to misoprostol.

Informed consent was obtained by the midwife in the local language, and a signature or left hand thumb impression was obtained. For illiterate or semi-literate participants, an oral consent was obtained with a written confirmation by the woman's relative. Study eligibility was re-assessed before randomisation.[23]

Study drug

A single oral dose of 600 µg of misoprostol (three tablets) or placebo (three tablets that were identical in appearance) was administered after delivery of the baby and within 5 min of clamping and cutting of the umbilical cord. After being given the drug, the women were monitored by the midwife for a minimum of 2 h according to the usual standard of care procedure to determine the need for transfer to a higher level facility. Blood loss, uterine tone, changes in blood pressure, pulse, and pallor, as well as possible maternal and neonatal side effects from the misoprostol were documented in the data collection form designed for the study.[23]

Oral misoprostol (as 200 µg tablets) was obtained from a Taiwanese pharmaceutical company (U-Liang Ltd) where international Good Manufacturing Practices (GMP) were documented. The identical placebo was specifically manufactured for the study. Two lots of study drug and placebo were used during the trial, with 510 women randomised with the first lot and 1110 women with the second. There was a 4-month interruption in the randomisation process until the second lot of study drug became available. Bioequivalence to the US-manufactured misoprostol was ascertained by two independent laboratories for each of the two lots of drugs. Drug activity in the two lots was identified as 97·5% (range 85·7–103·8) and 95·5% (86·4–99·1) of the label claim, respectively. A subset of the first lot that had been in the field for 2–3 months, under varying temperature and humidity conditions, was also tested and the activity was found to be 98·8% (94·8–101·6) of the label claim.

Procedures

The primary outcome was the incidence of acute postpartum haemorrhage (blood loss ≥500 mL within 2 h of delivery). Acute severe postpartum haemorrhage (blood loss ≥1000 mL within 2 h of delivery) and mean

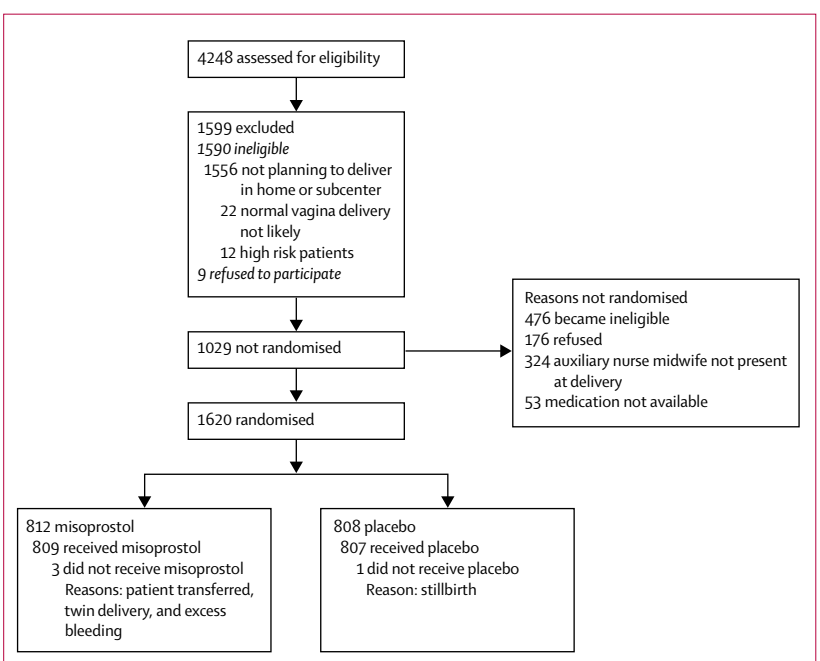

Figure 1: **Trial profile**

blood loss were predetermined secondary outcomes. We measured the need for transfer to a higher level facility, use of additional open-label uterotonic agents, blood transfusion, surgical intervention, maternal death, and drug-related maternal and neonatal side-effects.

The study was approved by institutional review boards at the University of Missouri-Kansas City, the collaborating Indian site, Jawaharlal Nehru Medical College, Belgaum, Karnataka, India, as well as the US National Institutes of Health, the Indian Council of Medical Research, and RTI International, NC, USA, the data coordinating centre.[24] This study is reported in accordance with revised CONSORT Guidelines.[25]

	Misoprostol (n=812)	Placebo (n=808)
Age in years; mean (SD)	23·3 (3·3)	23·2 (3·1)
Duration in years between previous and current pregnancy; mean (SD)	2·8 (1·3)	2·8 (1·4)
Haemoglobin in g/L; mean (SD)	96 (9)	96 (9)
Nulliparous	248 (30·5%)	225 (27·9%)
Parity 1–2	472 (58·1%)	496 (61·4%)
Parity ≥3	92 (11·3%)	87 (10·8%)
Literacy	511 (62·9%)	511 (63·2%)
<3 prenatal visits	100 (12·3%)	92 (11·4%)
≥3 prenatal visits	712 (87·7%)	716 (88·6%)
Home delivery	380 (46·9%)	365 (45·2%)
Preterm delivery	173 (21·3%)	181 (22·4%)
Perineal tear	79 (9·7%)	84 (10·4%)
Infant sex being male	433 (53·3%)	394 (48·8%)
Birthweight <1500 g	0 (0·0%)	1 (0·1%)
Birthweight 1500–1999 g	10 (1·2%)	4 (0·5%)
Birthweight 2000–2499 g	103 (12·7%)	116 (14·4%)
Birthweight 2500–3499 g	659 (81·2%)	638 (79·0%)
Birthweight ≥3500 g	40 (4·9%)	49 (6·1%)

Numbers are n (%) unless otherwise specified.

***Table 1*: Demographic, clinical, and perinatal characteristics**

	Misoprostol (n=812)	Placebo (n=808)	Relative risk (95% CI)	p
Primary outcome				
Acute postpartum haemorrhage	52 (6·4%)	97 (12·0%)	0·53 (0·39–0·74)	<0·0001*
Secondary outcomes				
Severe postpartum haemorrhage	2 (0·2%)	10 (1·2%)	0·20 (0·04–0·91)	0·0218*
Blood loss (mL)				
1 h; mean (SD)	214·9 (795–145·4)	259·7 (783–98·2)		<0·0001*
2 h; mean (SD)	183·1 (16–95·8)	342·8 (25–319·0)		0·0397*
Total; mean (SD)	214·3 (811–144·6)	262·3 (808–203·2)		<0·0001*
Use of open-label uterotonics	3 (0·4%)	6 (0·7%)		0·3413
Required transfer	4 (0·5%)	12 (1·5%)		0·0475*
Blood transfusion	1 (0·1%)	7 (0·9%)		0·0382*
Medical procedures undertaken†	0 (0·0%)	1 (0·1%)		0·4988
Surgical interventions‡	1 (0·1%)	8 (1·0%)		0·0209*
Admitted to ICU	2 (0·2%)	2 (0·2%)		1·0000

Numbers are n (%) unless otherwise specified. *Significant p value. †Including bimanual compression of the uterus. ‡Including repair of perineal, cervical, and high vaginal lacerations, manual removal of placenta or placental fragments under anaesthesia and uterine curettage.

***Table 2*: Primary and secondary outcomes by treatment group**

When in early active labour, women were randomly assigned to receive study medication or placebo. To ensure balanced randomisation and to conceal the treatment assignment, we used a computer-generated randomisation list with a random block size. The list, stratified by the midwife, was generated by the data coordinating centre. An independent clinical pharmacist at Jawaharlal Nehru Medical College implemented the randomisation procedure and prepared envelopes containing misoprostol or placebo. The envelopes were numbered and each envelope had a five-digit code number assigned to it. The first two digits were the auxiliary nurse midwife (ANM) number, followed by a sequence number beginning with 001 and ending with 100, assigned to the individual subject. Non-distinguishable envelopes in batches of 100 were distributed to each of the ANMs affiliated with the four selected primary-health centres.

The primary outcome measure, postpartum haemorrhage, was assessed using a polyurethane blood collection drape with a calibrated receptacle specifically developed for study use. The drape was placed under the buttocks of the woman after delivery.[26] Blood loss was assessed for 1 h after delivery of the baby. In the event of persistent bleeding, the drape was removed at 1 h, blood loss measured, and a new drape used with a second measurement made at 2 h.

Regular monitoring and training of midwives continued throughout the trial and focused on improving skills for screening high risk pregnancies, adopting optimum delivery practices, and completing data collection.

An independent data-monitoring committee from the National Institutes of Health, undertook three interim reviews when patient enrolment was at 31% (n=510), 59% (n=949), and 74% (n=1189), and concluded with a final review when the study was complete (n=1620).

Statistical analysis

Based on previous studies, we assumed a 10% postpartum haemorrhage rate without the use of a prophylactic uterotonic and a 5% rate with misoprostol.[27] We calculated that to achieve 96% power to detect a reduction of 50% in the postpartum haemorrhage rate in the experimental group at p=0·05, the sample size needed to be 1600.[28]

We analysed selected demographic, clinical, and perinatal factors to assess the similarity of the two groups. We calculated the relative risk of acute and acute severe postpartum haemorrhage in women who received misoprostol compared to placebo.

Because of the skewed distribution, the logarithm of mean blood loss in the misoprostol and placebo groups was compared with *t* tests. We created box plots of

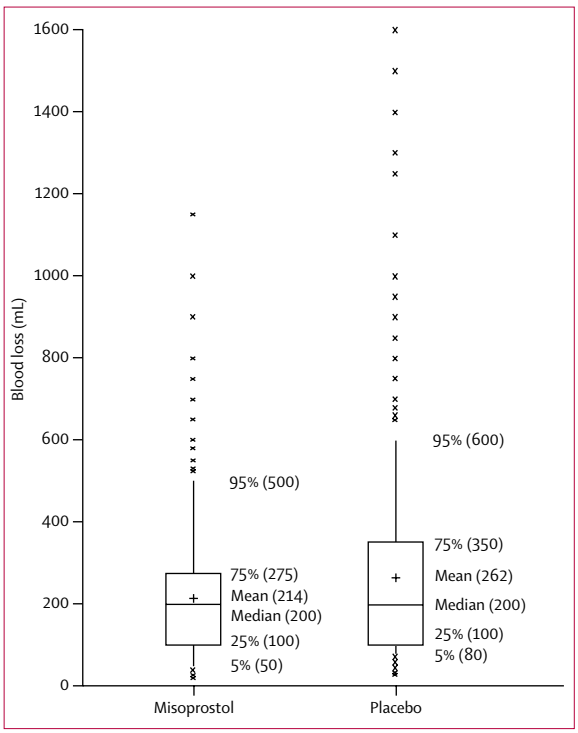

***Figure 2*: Box plot of blood loss distribution in both groups**
The bottom and top of the box represents the 25th and 75th percentiles, respectively; the upper and lower whiskers represent the 95th and 5th percentiles, respectively; the cross inside the box is the mean, and the horizontal line through the middle of the box is the median.

the blood loss distribution and computed percentage of secondary outcomes (eg, transfers) and maternal side effects (eg, shivering) by treatment group. Intention-to-treat analyses for the primary and secondary outcomes were done with SAS (version 9.1).

Role of the funding source

The US National Institute of Child Health and Human Development, under a cooperative agreement with the study team, participated in the study design, interpretation of data, and the editing and submission of the manuscript. The Bill and Melinda Gates Foundation, who also provided a grant for this research, had no direct involvement in the study.

Results

4248 women were screened for eligibility, 2649 were initially eligible for enrolment, and 1620 were randomised to receive either misoprostol (n=812) or placebo (n=808) (figure 1). Demographic, clinical, and perinatal characteristics by treatment are shown in table 1. The two groups did not differ significantly in any characteristic.

Acute postpartum haemorrhage occurred in 149 (9·2%) women in the study. The number of cases of acute postpartum haemorrhage among women receiving misoprostol was 52 (6·4%) compared with 97 (12%) in the placebo group (p<0·0001) (table 2). In women receiving misoprostol, the relative risk of acute postpartum haemorrhage was 0·53 (95% CI 0·39–0·74) compared with placebo.

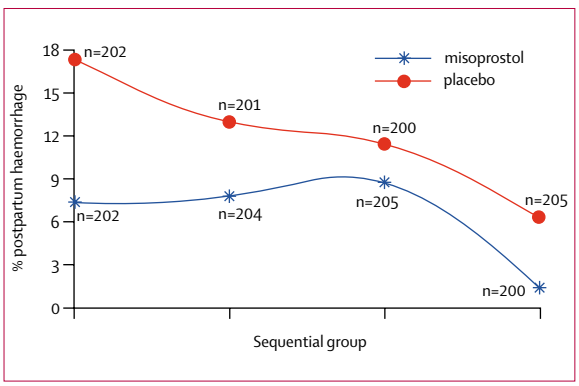

***Figure 3*: Postpartum haemorrhage rates for four sequential subgroups of randomised women, presented by treatment group**

Rates of acute severe postpartum haemorrhage were low (0·74% overall; n=12). Of the 12 women who had severe bleeding, ten were in the placebo group (relative risk 0·20; 95% CI 0·04–0·91; p 0·0218).

Use of misoprostol was responsible for a significant difference in overall mean blood loss compared with placebo (214·3 *vs* 262·3 mL; p<0·0001). There were differences in mean blood loss at 1 h (214·9 *vs* 259·7 mL; p<0·0001). Of the 41 women who continued to bleed 1–2 h postpartum (183·1 *vs* 342·8 mL; p<0·0397), a larger reduction in bleeding in the second postpartum hour was noted (table 2).

The effect of misoprostol and placebo on the distribution of blood loss is shown in figure 2. The blood loss distribution was skewed towards higher levels with more extreme values in the placebo group (range 30–1600 mL for placebo *vs* 20–1150 ml for misoprostol).

Women who received misoprostol were less likely to need emergency transfer to a higher level facility (4 [0·5%] *vs* 12 [1·5%], respectively), need a blood transfusion (1 [0·1%] *vs* 7 [0·9%]), or surgical interventions (1 [0·1] *vs* 8 [1·0%]). There were no differences in delayed postpartum haemorrhage (36 [4·4%] *vs* 35 [4·3%]) or infection (126 [15·5%] *vs* 150 [18·6%]) between the groups. There was one non-haemorrhage related maternal death in the placebo group. Women receiving misoprostol had a transient increase in shivering (419 [52·2%] *vs* 140 [17·3%]) and fever (34 [4·2%] *vs* 9 [1·1%]), but there were no differences in the rates of nausea, vomiting, or diarrhoea.

Figure 3 shows postpartum haemorrhage rates over the course of the study. The rates of postpartum haemorrhage fell over time, particularly in the placebo group, however the rate of haemorrhage for the treatment group remained significantly lower than the placebo group.

Although misoprostol taken orally has a reported half-life of less than 1 h, we nonetheless examined potential adverse effects of maternally-ingested misoprostol on the breastfed newborn. No differences in symptoms of

fever, vomiting, or diarrhoea were noted between newborns whose mothers were given misoprostol rather than placebo (data available from authors on request).

Discussion

We showed that misoprostol reduced acute postpartum haemorrhage in women in rural India by nearly 50% compared with placebo. Additionally, the drug was associated with a significant reduction in acute severe postpartum haemorrhage of 80%. In the misoprostol group, mean blood loss was reduced by about 20% and blood loss in the second hour postpartum was reduced by almost 50%.

Side-effects from misoprostol on the mothers were transient—being primarily shivering and fever—and there was no evidence of adverse effects on the neonates. Although more women in the misoprostol group had shivering, in a low-resource setting, this may be acceptable and clearly preferable to excessive haemorrhage.[29,30]

Several trials have shown that misoprostol is effective in preventing postpartum haemorrhage in community and hospital settings, albeit with a response often less robust than that of oxytocin.[7,19,21,22,31–33] This is the first study, to our knowledge, to show the efficacy and feasibility of misoprostol administered by midwives undertaking home and sub-centre deliveries. Evidence from studies in other community-based settings is mixed. A randomised controlled trial (no placebo) comparing misoprostol with oral methergine in rural areas of the Gambia showed a non-significant trend in reduction of postpartum haemorrhage.[11] The non-significance of the results could be due to the potential for oral methergine to have a modulating effect on blood loss. A trial in physician-based primary-health centres in rural India, where providers used active management, reported a significant reduction in median blood loss after delivery in the misoprostol group.[34] Two community-based randomised clinical trials underway in Pakistan and Tibet might offer further evidence.

The mean overall blood loss of 214 mL in the treatment group and 262 mL in controls is substantially lower than other published reports of average postpartum bleeding, suggesting a need to re-evaluate guidelines for determining normal blood loss.[35] Despite a low blood loss, the mean haemoglobin level of 96 g/L in study participants suggests that excessive acute blood loss could result in increased need for transfusion and greater morbidity.[36]

Although women who received misoprostol had an overall lower rate of postpartum haemorrhage and mean blood loss, a temporal trend of declining postpartum haemorrhage is also noted in the placebo group. This suggests that other factors might have affected results independently of the study drug. Possible explanations include the fact that midwives recruited later in the study could have been more experienced than those active in the first year, and patients at the end of the study could have benefited from the accrued effects of quality assurance activities such as ongoing midwife training and monitoring efforts. These issues will be explored in future analyses by our research team.

An unanticipated benefit of this study was the development of a new method for objective estimation of blood loss. Before this trial, the midwives were estimating blood loss visually. The calibrated drape, which provided a method of blood collection that was accurate, easy to use, and inexpensive ($1·00 per sterilised drape), might have meant earlier detection of postpartum haemorrhage.[26]

The Indian ministry of health has endorsed the use of misoprostol for deliveries in rural settings, although programme implementation has yet to occur.[37] The Nigerian health agency has also recently (January 2006) approved the use of misoprostol tablets, initially in hospital and clinic settings, for the prevention and treatment of postpartum haemorrhage.[38]

In a study in Indonesia, researchers trained community volunteers to provide women with information about the prevention of postpartum haemorrhage with misoprostol, distributed the medication to the women, and provided follow-up support. The community-based approach was noted as being safe and acceptable to the women.[39]

Our results suggest that within a district health setting, the use of misoprostol and a calibrated blood-collection drape can effectively be integrated into local practice acceptable to midwives, women and their families. Use of misoprostol may be especially beneficial in locales where only expectant management is the standard of care. However, in our study, blood loss was reduced by 18·3% in the misoprostol group, compared with a reported 22% reduction with oxytocin in expectant management in a hospital setting.[40] Our study was done in a low-risk population of women and cannot necessarily be generalised to high-risk pregnancies where referral is usually recommended.

Injectable oxytocin remains the drug of choice for prevention of postpartum haemorrhage in a hospital-based setting, but it is not feasible for resource-poor areas where most births take place out of hospital settings. Our results show that oral misoprostol is safe, effective, and inexpensive ($1·00 per 600 µg dose) for women giving birth in low-resource settings, and is currently the only available pharmacological option for preventing postpartum haemorrhage and reducing postpartum blood loss in these communities.[7,11,22,41]

Contributors

All authors helped draft the manuscript and undertook the analysis and interpretation of data; R J Derman, B S Kodkany, S S Goudar, S E Geller, V A Naik, M B Bellad, S S Patted, A Patel, and S A Edlavitch contributed to the study design; R J Derman, B S Kodkany, S S Goudar, S E Geller, V A Naik, M B Bellad, S S Patted, T Hartwell, and N Moss assisted with data acquisition; S A Edlavitch, T Hartwell, and H Chakraborty provided statistical expertise; R J Derman, B S Kodkany, S E Geller, A Patel, and N Moss were responsible for obtaining funding; R J Derman, B S Kodkany, S S Goudar, S E Geller, V A Naik, M B Bellad, S S Patted, A Patel, N Moss provided administrative, technical or material support; R J Derman, B S Kodkany, S S Goudar, S E Geller, V A Naik, M B Bellad, S S Patted, T Hartwell, and N Moss supervised the study.

Conflict of interest statement
We declare that we have no conflict of interest.

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