SIDE-EFFECTS OF ORAL MISOPROSTOL IN THE THIRD STAGE OF LABOUR — A RANDOMISED PLACEBO-CONTROLLED TRIAL

G Justus Hofmeyr, V Cheryl Nikodem, Marinda de Jager, Andrew Drakely

Background. Misoprostol, an inexpensive, stable, orally active prostaglandin analogue, has been suggested for use in the prevention of postpartum haemorrhage. Potential side-effects, however, need to be quantified.

Objective. To compare the rate of postpartum shivering and pyrexia following oral misoprostol 600 µg and placebo.

Design. A double-blind placebo-controlled trial. Women in labour were randomly allocated to receive either misoprostol 600 µg orally or placebo after delivery. Conventional oxytocics were given immediately if blood loss was thought to be more than usual. Side-effects were recorded. Postpartum blood loss in the first hour was measured by collection in a special flat plastic bedpan.

Setting. The labour ward of an academic hospital in Johannesburg, with 7 000 deliveries per annum.

Main outcome measures. Shivering and pyrexia.

Results. The groups were well matched. Misoprostol use was associated with more shivering (44% versus 11%, relative risk (RR) 4.03, 95% confidence interval (CI) 2.85 - 5.70), pyrexia ≥ 37.8°C (38% v. 6%, RR 6.23, CI 3.89 - 9.97), 1-hour systolic blood pressure ≥ 140 mmHg (33% v. 25%, RR 1.32, CI 1.03 - 1.70), and diastolic blood pressure ≥ 90 mmHg (10.5% v. 3.0%, RR 3.44, CI 1.67 - 7.11). There were no other significant differences. The study was not designed to be large enough to assess a difference in blood loss ≥ 1 000 ml (9% v. 9.7%, RR 0.93, CI 0.56 - 1.53). Possible effects on blood loss may have been obscured by the lesser use of additional oxytocics in the misoprostol group (14% v. 18%, RR 0.78, CI 0.54 - 1.13).

Department of Obstetrics and Gynaecology, Coronation Hospital and Effective Care Research Unit, University of the Witwatersrand, Johannesburg

G Justus Hofmeyr, MRCOG
V Cheryl Nikodem, MCur
Marinda de Jager, MCur
Andrew Drakely, MB ChB

Conclusions. This study has shown the association of postpartum oral misoprostol 600 µg with shivering, pyrexia and hypertension. The increased blood pressure, as for the trend towards increased abdominal pain, may be secondary to the uterotonic effect of misoprostol. Large randomised trials are needed to assess the effectiveness of misoprostol in the prevention of postpartum haemorrhage, against which the disadvantages demonstrated here can be weighed.

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The use of misoprostol, an inexpensive, stable, orally active prostaglandin analogue, for the prevention of postpartum haemorrhage, was first reported in 1996.[1] If effective, this therapy would have profound implications for the health of childbearing women worldwide. A limiting factor may be side-effects of misoprostol.[2] In a preliminary randomised trial, we observed shivering in 19% of puerperal women who received oral misoprostol 400 µg, compared with 5% of those who received placebo treatment.[3] As shivering was not a primary outcome of the latter study, underreporting may have occurred. We have therefore conducted a prospective, randomised, placebo-controlled trial specifically to assess the side-effects of misoprostol use after delivery.

Patients and methods

The study protocol was approved by the Committee for Research on Human Subjects of the University of the Witwatersrand. Women in labour at Coronation Hospital, Johannesburg, were asked to participate in the study, and to sign informed consent. Baseline data were recorded. Immediately after delivery the women were asked to swallow three tablets directly from the next in a series of numbered, opaque test tubes, with a sip a water. The tablets were either misoprostol 200 µg or placebo tablets similar in size and colour but not shape. Efforts to obtain identical placebo tablets were unsuccessful. This method of blinding proved to be effective. The containers were ordered according to a computer-generated random sequence, in balanced blocks of 18. The placenta was removed by cord traction once the uterus was palpated to have contracted firmly.

Within a minute after delivery, linen soiled with amniotic fluid was removed, a fresh, disposable absorbent linen saver sheet with plastic backing was placed under the woman, and a low-profile wedge-shaped plastic 'fracture' bedpan was slid under her buttocks. When active bleeding had stopped, any blood clots were expressed from the uterus, the bedpan was removed and a sanitary towel was applied. The blood in the bedpan was measured in a measuring jug. One hour after delivery, any bloodstained linen savers and sanitary towels were placed in a plastic bag and weighed in grams. The known dry weight of the linen savers and sanitary towels was subtracted to give the approximate volume of blood in millilitres. This was added to the measured blood volume from the bedpan to give the total measured blood loss in the first hour after delivery.

Because conventional oxytocics were not given routinely, the protocol required that close observation be maintained, and conventional therapy be given immediately if the bleeding was considered to be more than usual. The caregiver could choose to use intramuscular Syntometrine 1 ampoule or oxytocin 10 IU, or in more severe cases an intravenous infusion of oxytocin 20 IU in 1 000 ml saline.

All data were entered onto a database (EpiInfo 6) for analysis. The randomisation code was broken only after entry and checking of data. Comparisons were by the chi-square test with Yates' correction or Fisher's exact probability test if any cell was < 5, and relative risks with Taylor Series 95% confidence intervals.

Results

There were no withdrawals after randomisation and all outcomes were analysed in the allocated group.

The randomisation process was successful in producing well-matched groups (Table I). The outcome variables are shown in Table II. Shivering, pyrexia ≥ 37.8°C and hypertension were significantly more common in the misoprostol group. There was somewhat less frequent use of conventional oxytocics in the misoprostol group.

Table I. Comparison of baseline variables between women randomly allocated to receive misoprostol 600 µg or placebo for third stage of labour management

	Misoprostol	Placebo
Number	300	300
Age (years)	26.6 (5.6)	27.4 (5.8)
Primiparous	94 (31%)	85 (28%)
Parity 4+	10 (3.3%)	7 (2.3%)
Episiotomy/tear	146 (49%)	141 (47%)
Birth weight (grams)	3 047 (528)	3 076 (528)

Results are expressed as mean values (standard deviation) or numbers (%). There were no statistically significant differences.

Discussion

The use of placebo treatment was considered acceptable by the University Ethics Committee, specifically within the context of a research environment in which blood loss was closely and accurately monitored, and conventional oxytocics were administered as soon as blood loss was thought to be more

Table II. Comparison of outcome variables between women randomly allocated to receive misoprostol 600 µg or placebo for third stage of labour management

	Misoprostol		Placebo				
	No. of women observed	No. of women with negative outcomes (%)	No. of women observed	No. of women with negative outcomes (%)	RR	95% CI	*P*-value
Primary outcomes							
Shivering	300	133 (44)	300	33 (11)	4.03	2.85 - 5.70	0.0000
Temperature ≥ 37.8°C	299	114 (38)	294	18 (6.1)	6.23	3.89 - 9.97	0.0000
Temperature ≥ 40°C	299	1 (0.3)	294	0 (0)	—	—	1.00
Secondary outcomes							
Nausea	300	5 (1.7)	300	1 (0.3)	5.00	0.59 - 42.5	0.22
Vomiting	300	4 (1.3)	300	2 (0.7)	2.00	0.37 - 10.8	0.68
Diarrhoea	300	1 (0.3)	300	1 (0.3)	1.00	0.06 - 15.9	1.00
Abdominal pain	300	47 (15.7)	300	31 (10.3)	1.52	0.99 - 2.32	0.07
Blood pressure at 1 hour	300	2 (0.7)	300	2 (0.7)	1.00	0.14 - 7.05	1.00
Systolic ≥ 140 mmHg	299	100 (33)	296	75 (25)	1.32	1.03 - 1.70	0.04
Diastolic ≥ 90 mmHg	296	31 (10.5)	296	9 (3.0)	3.44	1.67 - 7.11	0.0006
Blood loss ≥ 1 000 ml	300	27 (9)	299	29 (9.7)	0.93	0.56 - 1.53	0.88
Additional oxytocic needed	300	42 (14)	300	54 (18)	0.78	0.54 - 1.13	0.22
Third stage ≥ 30 min	299	6 (2)	300	3 (1)	1.99	0.50 - 7.87	0.50
Manual removal of placenta	300	2 (0.7)	300	2 (0.7)	1.00	0.14 - 7.05	1.00
Blood transfusion	299	1 (0.3)	300	2 (0.7)	0.50	0.05 - 5.50	1.00

Results are expressed as numbers (%).
RR = relative risk; CI = confidence interval.

brisk than usual. Placebo use has also been considered acceptable in a recent Swedish trial.[4]

Two previous reports[1,2] have suggested that postpartum misoprostol causes shivering in as many as 60% of women, but these studies lacked the control groups necessary to quantify this effect. After completing the current study, we participated in a World Health Organisation multicentre pilot trial comparing misoprostol 600 µg and 400 µg and Syntocinon 10 units intramuscularly.[5] Although different cut-off points were chosen, both trials documented a clear thermogenic effect of puerperal misoprostol. In only one case in the current trial did the temperature exceed 40°C, and in no case was the temperature problematic. However, it is most important that clinicians be aware of this side-effect to avoid unnecessary investigation or treatment of 'unexplained' postpartum pyrexia.

This is the first randomised trial to show an increase in postpartum hypertension with misoprostol. As misoprostol in non-pregnant hypertensive patients is associated with slight lowering of blood pressure,[6] the most likely explanation for this finding is that blood pressure was increased as a result of increased uterine contractility. Physiological studies have demonstrated a clear uterotonic effect of misoprostol in the puerperium.[7] Similarly, the near-significant increase in abdominal pain is likely to reflect increased uterine contraction.

One possible method of reducing side-effects of misoprostol in the third stage of labour is use of the rectal route.[8,9]

No conclusions should be drawn from the lack of a significant reduction in postpartum haemorrhage in this study, firstly because the numbers studied were not adequate to detect a modest reduction, and secondly because the ready use of conventional oxytocics, which were required more frequently in the control group, is likely to have obscured any benefit from misoprostol. The potential benefit of misoprostol may be greater in an environment in which conventional oxytocics are not available.

CONCLUSIONS

This study has quantified certain side-effects of postpartum misoprostol. It is essential for clinicians who use misoprostol in the postpartum period to be aware of these side-effects. Very large randomised trials, such as the trial currently being undertaken by the World Health Organisation, are needed to determine the effectiveness of oral misoprostol in the prevention of postpartum haemorrhage, against which the disadvantages of the side-effects documented in this study can be weighed.

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References

1. El-Rafaey H, O'Brien P, Morafa W, Walder J, Rodeck C. Misoprostol for third stage of labour. *Lancet* 1996; **347:** 1257.
2. El-Refaey H, O'Brien P, Morafa W, Walder J, Rodeck C. Use of oral misoprostol in the prevention of postpartum haemorrhage. *Br J Obstet Gynaecol* 1997; **104:** 336-339.
3. Hofmeyr GJ, Nikodem VC, de Jager M, Gelbart BR. A randomised placebo controlled trial of oral misoprostol in the third stage of labour. *Br J Obstet Gynaecol* 1998; **105:** 971-975.
4. Nordstrom L, Fogelstam K, Fridman G, Larsson A, Rydhstroem H. Routine oxytocin in the third stage of labour: a placebo controlled trial. *Br J Obstet Gynaecol* 1997; **104:** 781-786.
5. Lumbiganon P, Hofmeyr J, Gulmezoglu AM, Pinol A, Villar J. Misoprostol dose-related shivering and pyrexia in the third stage of labour. *Br J Obstet Gynaecol* 1999; **106:** 304-308.
6. Kailasam MT, Lin MC, Cervenka JH, *et al.* Effects of an oral pGE1 agonist on blood pressure and its determinants in essential hypertension. *J Hum Hypertens* 1994; **8:** 515-520.
7. Chong YS, Chua S, Arulkumaran S. Can oral misoprostol be used as an alternative to parenteral oxytocics in the active management of the third stage of labour? A preliminary study of its effect on the postpartum uterus (Abstract). The Royal Australian and Royal New Zealand Colleges of Obstetricians and Gynaecologists 1997 Combined Scientific Meeting, Brisbane 28 April - 2 May 1997.
8. Bamigboye A. Merrell DA, Mitchel R, Hofmeyr GJ. Randomised comparison of misoprostol with Syntometrine for management of third stage labor. *Acta Obstet Gynecol Scand* 1998; **77:** 178-181.
9. Bamigboye AA, Hofmeyr GJ, Merrell DA. Rectal misoprostol in the prevention of postpartum hemorrhage: a placebo-controlled trial. *Am J Obstet Gynecol* 1998; **179:** 1043-1046.

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