Treatment for primary postpartum haemorrhage (Review)

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ABSTRACT

Background
Primary postpartum haemorrhage (PPH) is one of the top five causes of maternal mortality in both developed and developing countries.

Objectives
To assess the effectiveness and safety of pharmacological, surgical and radiological interventions used for the treatment of primary PPH.

Search strategy
We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 October 2006).

Selection criteria
Randomised controlled trials comparing pharmacological, surgical techniques and radiological interventions for the treatment of PPH.

Data collection and analysis
We assessed studies for eligibility and quality, and extracted data, independently. We contacted authors of the included studies for more information.

Main results
Three studies (462 participants) were included. Two placebo-controlled randomised trials compared misoprostol (dose 600 to 1000 mcg) with placebo and showed that misoprostol use was not associated with any significant reduction of maternal mortality (two trials, 398 women; relative risk (RR) 7.24, 95% confidence interval (CI) 0.38 to 138.6), hysterectomy (two trials, 398 women; RR 1.24, 95% CI 0.04 to 40.78), the additional use of uterotonics (two trials, 398 women; RR 0.98, 95% CI 0.78 to 1.24), blood transfusion (two trials, 394 women; RR 1.33, 95% CI 0.81 to 2.18), or evacuation of retained products (one trial, 238 women; RR 5.17, 95% CI 0.25 to 107). Misoprostol use was associated with a significant increase of maternal pyrexia (two trials, 392 women; RR 6.40, 95% CI 1.71 to 23.96) and shivering (two trials, 394 women; RR 2.31, 95% CI 1.68 to 3.18).

One unblinded trial showed better clinical response to rectal misoprostol compared with a combination of syntometrine and oxytocin. We did not identify any trial dealing with surgical techniques, radiological interventions or haemostatic drugs for women with primary PPH unresponsive to uterotonics.

Authors' conclusions
There is insufficient evidence to show that the addition of misoprostol is superior to the combination of oxytocin and ergometrine alone for the treatment of primary PPH. Large multi-centre, double-blind, randomised controlled trials are required to identify the best drug combinations, route, and dose of uterotonics for the treatment of primary PPH. Further work is required to assess the best way of managing women who fail to respond to uterotonics therapy.

PLAIN LANGUAGE SUMMARY

Treatment for primary postpartum haemorrhage needs more research

After a woman gives birth, womb muscles contract, clamping down on the blood vessels and helping to limit bleeding when the placenta has detached. If the muscles do not contract strong enough, postpartum haemorrhage (very heavy bleeding) can occur, which can be life-threatening. These situations are common in resource-poor countries, and maternal mortality is about one hundred times higher than in resource-rich countries. It is a serious problem that requires effective treatments which might avert the use of surgery to remove the womb (hysterectomy), often the last treatment option. The earlier treatment options include drugs to increase muscle contractions (such as ergometrine, oxytocin and prostaglandins), surgical techniques (such as tying off or blocking the uterine artery), radiological interventions (such as blocking of the main artery to the womb using gel foams), and haemostatic drugs (such as tranexamic acid and recombinant activated factor VII). The review identified three trials involving 462 women that assessed treatment with the drug misoprostol, but there were no trials about the effects of surgical techniques, radiological interventions or haemostatic drugs. One small trial showed a possible benefit of rectal misoprostol compared with standard combination of ergometrine and oxytocin. However, more research is needed before newer drugs, like misoprostol, can be tried as a first-line drug treatment to be sure that maternal mortality is not increased and to further assess the possible impact of adverse side-effects like shivering, nausea and headaches.

BACKGROUND

Some half a million women die annually across the world from causes related to pregnancy and childbirth (UNICEF 1996; WHO 1990). Approximately one quarter of these deaths are caused by complications of the third stage of labour, i.e. bleeding within the first 24 hours after delivery (Abou Zahr 1991). This type of haemorrhage is known as primary postpartum haemorrhage. In the developing world, the risk of maternal death from postpartum haemorrhage (PPH) is approximately one in 1000 deliveries (Abou Zahr 1991). In the United Kingdom (UK), the risk of death from obstetric haemorrhage is about one in 100,000 deliveries (DoH 1998).

Physiology

The uterus is composed of a unique interlacing network of muscle fibres known as 'myometrium'. The blood vessels that supply the placental bed pass through this latticework of uterine muscle (Baskett 2000). Myometrial contraction is the main driving force for both placental separation and haemostasis through constriction of these blood vessels. This blood-saving mechanism is known as the 'physiological sutures' or 'living ligatures' (Baskett 2000). The active management of the third stage of labour enhances the physiological process and is shown to be associated with a two-fold reduction in the risk of PPH and less need for blood transfusion (Prendiville 2002). Furthermore, the physiological increase in the clotting factors during labour helps to control blood loss after separation of the placenta. A blood loss up to 500 ml at delivery is regarded as 'physiologically normal'. It is part of the normal mechanism that brings the mother's blood parameters to their normal non-pregnant levels, and a healthy pregnant woman can cope with it without any difficulty (Gyte 1992; Ripley 1999).

Definition

Traditionally, primary PPH is defined as bleeding from the genital tract of 500 ml or more in the first 24 hours following the delivery of the baby (Cunningham 1993). Alternative cut-off levels of 600 ml (Beischer 1986), 1000 ml (Burchell 1980), 1500 ml (Mousa 2002), a substantial fall in the haematocrit or the need for blood transfusion (ACOG 1998; Combs 1991) have also been suggested. Under estimation of blood loss following delivery is a common problem. The diagnosis is usually made subjectively and many cases remain undetected (Pritchard 1962). Primary PPH with a loss greater than 1000 ml occurs in one to five per cent of vaginal deliveries in high-income countries (Combs 1991; Jouppila 1995; Stones 1993).

Causes and risk factors

Lack of efficient uterine contraction (uterine atony) is the commonest cause of primary PPH. Other aetiological factors include retained parts of the placenta and vaginal or cervical tears. Uterine rupture, clotting disorders and uterine inversion are extremely rare, but often very dramatic causes of heavy bleeding. Risk factors for primary PPH include first pregnancy (Gilbert 1987; Hall 1985), maternal obesity (Aisaka 1988), a large baby (Stones 1993), twin pregnancy (Combs 1991), prolonged or augmented labour (Gilbert 1987), and antepartum haemorrhage. High multiparity does not appear to be a risk factor, either in high- or low-income countries, even after control for maternal age (Drife 1997; Stones 1993; Tsu 1993). Despite the identification of risk factors, primary PPH often occurs unpredictably in low-risk women.

Complications

The most important consequences of severe PPH include hypovolaemic shock, disseminated intravascular coagulopathy (DIC), renal failure, hepatic failure and adult respiratory distress syndrome (Bonnar 2000). In low-income countries, poor nutritional status, lack of easy access to treatment, and inadequate intensive care and blood bank facilities are additional contributing factors that lead to the high morbidity and mortality rates in these countries. As there has been no universally accepted definition of PPH, the exact incidence of complications is unknown (Gilstrap 1994).

Management of primary postpartum haemorrhage

Treatment for primary PPH requires a multidisciplinary approach. After exclusion of lower genital tract lacerations, in the majority of cases, the bleeding is due to uterine atony. Uterotonics that increase the efficiency of uterine contraction, including ergometrine

and oxytocin, were introduced as a first-line therapy for atonic PPH since the 19th century. Women who continue to bleed would require further assessment and interventions, "second-line therapy", to control the bleeding.

A. First-line therapy or uterotonics

1. Ergometrine

John Stearns (Stearns 1822) was the first to emphasis the use of ergots for PPH. Earlier, he wrote describing ergot's action: "It expedites lingering parturition ... The pains induced by it are peculiarly forcing … . In most cases you will be surprised with the suddenness of its operation" (Stearns 1808). Moir 1932 noticed that administration of aqueous ergot extract by mouth is associated with dramatic and vigorous uterine contractions, which were described as the 'John Stearns effect'. In 1935, Dudley and Moir were able to isolate the pure crystallized substance from the water soluble extract of ergot that was responsible for the 'John Stearns effect' and they called it 'ergometrine' (Dudley 1935). The isolation of a new water-soluble extract of ergot was announced almost simultaneously from three other centres: in America (Davis 1935), UK (Thompson 1935) and Switzerland (Stoll 1935). It turned out to be the same substance. The Americans called their preparation ergonovine and the Swiss used the name ergobasine.

2. Oxytocin

In 1953, Vincent Du Vigneaud (Du Vigneaud 1953) identified the structure of oxytocin and was able to synthesise the hormone. By the 1980s several randomised controlled trials and their meta-analyses confirmed the effectiveness of active management of the third stage in reducing PPH (Prendiville 2002). While the use of oxytocin is usually free of adverse effects, the use of ergometrine may be associated with nausea, vomiting, and hypertension (ACOG 1998).

3. Prostaglandins

By the 1970s, the prostaglandin F2 alpha series was discovered by Sune Bergstrom, among others (Bergstrom 1962). The 15-methyl analogue of prostaglandin F2 alpha has been reported to have a high success rate if used alone (88%) or in combination with other uterotonic agents (95%) (Oleen 1990). Prostaglandin administration could be associated with unpleasant side-effects including vomiting, diarrhoea, hypertension, and fever (Oleen 1990). In the majority of cases, these oxytocic drugs will control bleeding but if not, surgical intervention must be considered.

Second-line therapy

1. Surgical interventions

Porro (Porro 1876) was the first to describe caesarean hysterectomy to prevent death from uterine haemorrhage. Active attempts have been made to introduce other conservative procedures to avoid hysterectomy including the use of uterine packing, Foley catheter, and artery ligation. Uterine packing, using several yards of wide gauze placed inside the uterine cavity, fell out of favour in the 1950s as it was thought to conceal haemorrhage and cause infection (Eastman 1950). However, this technique has re-emerged in the 1980s and 1990s after these concerns were not confirmed (Maier 1993). A transcervical catheter with larger bulb could be used as a useful alternative to uterine packing (Gilstrap 1994; Johanson 2001). Close observation of the uterine size and the general condition of the woman is mandatory as significant bleeding may occur distally to the bulb (Alamia 1999).

Ligation of the uterine artery or its main supply (internal iliac artery) may be considered in selected cases (AbdRabbo 1994; Jouppila 1995). However, the latter may be technically difficult and is only successful in less than 50% of cases (Clark 1985). Uterine compression sutures have recently been described (B-Lynch 1997; Cho 2000; Hayman 2002) including a suture that runs through the full thickness of both uterine walls (anterior and posterior). When tied, the suture allows tight compression of the uterine walls and stops the bleeding (Mousa 2001). Single or multiple stitches may be inserted at the same time and, according to the shape, they may be called brace suture (B-Lynch 1997), simple brace (Hayman 2002), or square sutures (Cho 2000). Although thought to be effective in selected cases, unexpected occlusion of the uterine cavity with subsequent development of infection (pyometra) has been reported (Ochoa 2002). The choice of the type of surgical intervention depends on several factors, paramount of which is the experience of the surgeon. Other factors include parity and desire for future children, the extent of the haemorrhage, and the general condition of the woman (ACOG 1990).

2. Radiological embolisation

Selective radiological embolisation of the bleeding vessel may be a therapeutic option in centres where interventional radiologists are available and the bleeding is not life threatening (ACOG 1998; Mitty 1993). The technique includes femoral artery puncture followed by selective stepwise catherisation of pelvic arteries. Gelfoam (gelatin) pledgets are the most commonly used material in cases of emergency embolisation with a potential for recanalisation three weeks later (Pelage et al., 1999). Pelage and colleagues evaluated the role of selective arterial embolisation in thirty-five patients with unanticipated PPH (Pelage 1999). Bleeding was controlled in all except one who required hysterectomy for re-bleeding five days later. All women who had successful embolisation resumed normal menstruation. Fever, contrast media renal toxicity, and leg ischaemia are rare but reported complications of this procedure (ACOG 1998).

3. Haemostatic drugs

Haemostatic drugs, including tranexamic acid (As 1996) and recombinant activated factor VII (rFVIIa) (Moscardo 2001), have been used for the treatment of intractable haemorrhage unresponsive to first- and second-line therapies.

Rational for the review

The quest for fast, effective and safe interventions in cases of major PPH is the focus of this review. Other relevant published Cochrane reviews are Prendiville 2002, which compares active with expectant

third stage management; Gulmezoglu 2000 and Elbourne 2002, which both consider the role of different prophylactic uterotonics (prostaglandin, and syntometrine compared to oxytocin, respectively) in the third stage management; Carroli 2002, which looks at the role of umbilical vein injection for the treatment of retained placenta; and Alexander 2002, which is examining drug treatment for secondary PPH. The current review will focus primarily on atonic primary PPH. Management of haemorrhage due to laceration of the genital tract will be outside the scope of the current review.

OBJECTIVES

To determine the effectiveness and safety of pharmacological, surgical and radiological interventions used for the treatment of primary postpartum haemorrhage.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All randomised controlled trials of treatment of primary postpartum haemorrhage (PPH). We excluded quasi-randomised controlled trials.

Types of participants

Women after delivery following a pregnancy of at least 24 weeks' gestation with a diagnosis of primary PPH, regardless of mode of delivery (vaginal or caesarean section) or other aspects of third stage management. Initially, our protocol stipulated that only studies where primary PPH was defined by a blood loss greater than 500 mls should be included. As it may be difficult to have an accurate measurement of blood loss before recruitment, we have expanded our inclusion criteria to include trials in which PPH was defined in one of the following ways:
(1) women with a blood loss of 500 ml or more; and/or
(2) women with primary PPH requiring blood transfusion and/or blood products; and/or
(3) women with a clinical diagnosis of primary PPH (as defined by trialists)

Exclusion criteria

(1) Women with postpartum haemorrhage with a gestational age less than 24 weeks
(2) Women with a blood loss less than 500 mls, or who fail to meet any of the criteria listed above

Types of intervention

Eligible interventions included:
(i) first-line uterotonics therapy (drugs that encourage uterine contractility such as ergometrine, oxytocin, and prostaglandins);
(ii) surgical interventions such as uterine packing or intrauterine catheter insertion, artery ligation, uterine compression sutures and/or hysterectomy;
(iii) haemostatic agents that influence the clotting cascade (tranexamic acid and rFVIIa);
(iv) interventional radiology (X-ray guided embolisation).

We planned subgroup analyses to take into consideration mode of delivery (caesarean versus vaginal delivery) and whether the intervention was used alone or in combination. For uterotonic drugs, we planned subgroup analyses according to the dose and route.

Main comparisons include the following interventions.

(a) First-line therapy with uterotonics
1. Uterotonics versus control or placebo
2. One uterotonic versus another uterotonic

(b) Second-line therapy (where women in both arms receive conventional therapy with uterotonics)
1. Additional uterotonic verus other treatment, or versus control or placebo
2. Uterine packing or balloon tamponade (for example, Foley or, hydrostatic catheter) versus other treatment, or versus control or placebo
3. Vessel ligation versus other treatment, or versus control or placebo
4. Hysterectomy versus other treatment, or versus control or placebo
5. Uterine compression sutures (for example, brace or square) versus other treatment, or versus control or placebo
6. Radiological embolisation versus other treatment, or versus control or placebo
7. Haemostatic drugs versus other treatment, or versus control or placebo

Types of outcome measures

Main outcomes
1. Maternal mortality
2. Serious maternal morbidity (admission to intensive care, renal or respiratory failure)
3. hysterectomy (provided that it is not part of the intervention under investigation)

Secondary outcomes

(i) Outcome measures related to blood loss
4. Blood loss 500 ml or more after enrolment
5. Blood loss 1000 ml or more after enrolment
6. Mean blood loss (ml)
7. Continued vaginal bleeding or unsatisfactory response (however determined by the trialist) without need for further treatment
8. Blood transfusion
9. Duration from randomisation to cessation of bleeding or obtaining satisfactory response (as determined by the trialist)

10. Co-interventions (medical, surgical or both)
11. Maternal haemoglobin concentration (Hb) less than 6 grams/decilitre 24 hours to 48 hours postpartum

(ii) Other
12. Days in hospital
13. Iron therapy in the puerperium
14. Secondary PPH (vaginal bleeding after 24 hours to 42 days following delivery)
15. Interventions to control secondary PPH (medical, surgical, or both)
16. Hospital readmission and number of days in hospital
17. Failure to continue breastfeeding at discharge from hospital and at 42 days of delivery
18. Side-effects of therapy (such as headache, vomiting, injuries)
19. Economic outcomes
20. Maternal dissatisfaction with therapy
21. Quality of life including physiological activity, social and emotional changes

Assessment of blood loss could vary between trials. It is expected that the measurement of blood and blood clots in jars and the weighing of linen are likely to be more precise than clinical judgement. The latter is known to underestimate blood loss (Pritchard 1962). The way of reporting the amount of loss as 'greater than' or 'greater than or equal to' a certain cut-off level (for example, greater than 500 mL or greater than or equal to 500 ml) may affect the total reported amount of blood loss especially when this amount is estimated. Also, it should be taken into consideration that hysterectomy could be a method of intervention and co-intervention as well as an outcome measure.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

We searched the Cochrane Pregnancy and Childbirth Group Trials Register by contacting the Trials Search Co-ordinator (31 October 2006).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:
(1) quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
(2) monthly searches of MEDLINE;
(3) handsearches of 30 journals and the proceedings of major conferences;
(4) weekly current awareness search of a further 37 journals.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Search strategies for identification of studies' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are given a code (or codes) depending on the topic. The codes are linked to review topics. The Trials Search Co-ordinator searches the register for each review using these codes rather than keywords.

We did not apply any language restrictions.

METHODS OF THE REVIEW

Selection of studies
We assessed for inclusion all potential studies we identified as a result of the search strategy. There was no disagreement between the review authors.

Assessment of methodological quality of included studies
We assessed the validity of each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2005). Methods used for generation of the randomisation sequence is described for each trial.

(1) Selection bias (allocation concealment)
We assigned a quality score for each trial, using the following criteria:
(A) adequate concealment of allocation: such as telephone randomisation, consecutively numbered sealed opaque envelopes;
(B) unclear whether adequate concealment of allocation: such as list or table used, sealed envelopes, or study does not report any concealment approach;
(C) inadequate concealment of allocation: such as open list of random number tables, use of case record numbers, dates of birth or days of the week.

(2) Attrition bias (loss of participants; for example, withdrawals, dropouts, protocol deviations)
We assessed completeness to follow up using the following criteria:
(A) less than 5% loss of participants;
(B) 5% to 9.9% of loss of participants;
(C) 10% to 19.9% loss of participants;
(D) more than 20% loss of participants.

(3) Performance bias (blinding of participants, researchers and outcome assessment)
We assessed blinding using the following criteria:
(A) blinding of participants (yes/no/unclear);
(B) blinding of caregiver (yes/no/unclear);
(C) blinding of outcome assessment (yes/no/unclear).

Data extraction and management
We designed a form to extract the data. HA Mousa extracted the data onto prespecified data sheets. Z Alfirevic checked the data. There were no discrepancies. We used Review Manager software (RevMan 2003) to double enter all the data.

Measures of treatment effect
We carried out statistical analysis using Review Manager software (RevMan 2003). We used a fixed-effect meta-analysis for combining data in the absence of significant heterogeneity if trials were sufficiently similar. Where heterogeneity was significant (I^2 greater than 50%), random effects were used.

Dichotomous data
For dichotomous data, we presented the results as summary relative risks with 95% confidence intervals.

Continuous data
For continuous data, we used the weighted mean difference if outcomes were measured in the same way between trials. We used the standardised mean difference to combine trials that measured the same outcome, but used different methods.

Available case analysis
We analysed data on all participants with available data in the group to which they were allocated, regardless of whether or not they received the allocated intervention.

Assessment of heterogeneity
We applied tests of heterogeneity between trials, if appropriate, using the I^2 statistic.

Subgroup analyses
We conducted planned subgroup analyses classifying whole trials by interaction tests as described by Deeks 2001. We considered subgroup analyses by mode of delivery (caesarean versus vaginal delivery) and whether the intervention was used alone or in combination. For uterotonic drugs, we considered subgroup analyses by dose and route.

DESCRIPTION OF STUDIES

Three misoprostol trials (462 participants) are included.

First-line therapy or uterotonics
Four studies were identified and considered for inclusion in this review. Of these, one was excluded (Japan 1976) because the trial included women with blood loss less than 500 ml and the trial report did not allow analysis based on treatment allocation ('intention to treat'). South Africa 2001 compared rectally administered misoprostol versus oxytocics (combined syntometrine and oxytocin infusion) for the treatment of primary postpartum haemorrhage (PPH) defined as blood loss greater than 500 ml. The main objective of the study was to assess the effectiveness of the randomly selected drug to stop PPH within 20 minutes. Two studies compared misoprostol with placebo when bleeding persisted despite routine treatment with conventional uterotonics (Gambia 2004; South Africa 2004).

Second-line therapy including surgical, radiological and haemostatic drugs
None identified.

For details of included and excluded studies, *see* the tables of 'Characteristics of included studies' and 'Characteristics of excluded studies'.

METHODOLOGICAL QUALITY

The South Africa 2001 trial described clearly the random generation method and allocation concealment using consecutively numbered, sealed, opaque envelopes. It was a single-blinded study as obstetricians were aware of the type of drug been given while women and midwives were not. The trial authors indicated that single blinding was mainly for safety "to prevent over-dosage and to know what had been given in case of need of additional drugs". There was no description of the method of measurement of blood loss or the management of the third stage of labour. The authors have been contacted for more information. There was postrandomisation withdrawal of only one woman (1/32) in the misoprostol arm. The study was terminated after an interim analysis revealed an 80% difference between the two treatment arms for the prespecified outcome measure (effectiveness at stopping postpartum haemorrhage within 20 minutes of trial drugs administration). The trial is prone to assessment bias, as physicians were aware of the treatment given. Only four outcome measures were adequately reported (hysterectomy, persistent vaginal bleeding following randomisation, medical and surgical co-interventions). Other reported outcome measures, including disseminated intravascular coagulopathy, blood transfusion, length of in-patient stay, and drug side-effects, were reported as "p value of significance" without any numbers or percentages.

The Gambia 2004 and South Africa 2004 trials were double-blinded studies. However, the authors of the former trial felt that blinding may have been compromised due to differences in the size of the misoprostol tablets and the placebo. Both of them used active management of the third stage of labour and they measured blood loss after administration of the trial drug. In South Africa 2004, six out of 244 data sheets did not have pack numbers completed and could not be included in analysis. In the Gambia 2004 trial, there were no withdrawals after enrolment.

RESULTS

A. First-line therapy or uterotonics
The results are based on three misoprostol trials (462 participants). There were no disagreements in applying the selection criteria and data extraction that required further discussion or consultation.

(i) Misoprostol versus oxytocin/ergometrine
South Africa 2001 compared rectal misoprostol 800 microgram with a combination of intramuscular syntometrine injection and oxytocin infusion. There was no record of maternal mortality or

serious maternal morbidity. However, there was insufficient evidence for reliable conclusions about the possible effect on the need for surgical co-interventions (excluding hysterectomy) and hysterectomy. The use of misoprostol was noted to be superior to syntometrine/oxytocin in subjective cessation of haemorrhage within 20 minutes (64 women; RR 0.18, 95% 0.04 to 0.76) and significant reduction in the number of women who required additional uterotonics (one trial, 64 women; RR 0.18, 95% CI 0.04 to 0.76).

(ii) Misoprostol versus placebo (two trials)

South Africa 2004 used misoprostol 1000 microgram and Gambia 2004 used misoprostol 600 microgram. There were three cases of maternal mortality in the misoprostol arm of the South Africa 2004 trial (two trials, 398 women; pooled relative risk (RR) 7.24, 95% confidence interval (CI) 0.38 to 139)). There were five cases of hysterectomy; two in the placebo group of Gambia 2004 and three in the misoprostol arm in South Africa 2004 (two trials, 398 women; RR 1.24, 95% CI 0.04 to 40.78). Despite the relatively small numbers of hysterectomies, heterogeneity was statistically significant and the results were analysed using random effects.

Misoprostol use was associated with a significant reduction in blood loss of 500 ml or more after enrolment (two trials, 397 women; RR 0.57, 95% CI 0.34 to 0.96). However, the additional use of uterotonics (two trials, 398 women; RR 0.98, 95% CI 0.78 to 1.24), blood transfusion (two trials, 394 women; RR 1.33, 95% CI 0.81 to 2.18), and evacuation of retained products (one trial, 238 women; RR 5.17, 95% 0.25 to 107) did not differ between the two groups after enrolment.

The use of misoprostol was associated with a statistically significant increase in both maternal pyrexia (two trials, 392 women; RR 6.40, 95% 1.71 to 23.96) and shivering (two trials, 394 women; RR 2.31, 95% CI 1.68 to 3.18). However, maternal headache (one trial, 160 women; RR 0.65, 95% 0.27 to 1.60) and nausea (one trial, 160 women; RR 0.62, 95% 0.15 to 2.49) did not differ between the two groups.

B. Second-line surgical, x-ray guided embolisation or haemostatic drug therapy

None identified.

DISCUSSION

We identified only three clinical trials of uterotonic therapy that fulfilled our inclusion criteria; one evaluated misoprostol as an alternative to conventional first-line therapy, the other two as an additional adjuvant therapy. All three trials examined the place of misoprostol in the management of primary PPH. Overall the number of included women was too small to evaluate the effect on maternal mortality, serious maternal morbidity and hysterectomy. Therefore, there is at present insufficient evidence to draw any conclusion about the effectiveness and safety for either first- or second-line therapy. Large double-blind, multi-centred, randomised controlled trials are needed to evaluate the effect on the primary outcome measures; however, the inability to obtain informed consent from critically ill patients may make it difficult to recruit participants. Clinicians should be encouraged to conduct such trials provided that they are able to follow agreed procedures for getting consent from critically ill patients and ensure that recruitment does not interfere with standard management.

In our meta-analysis, placebo-controlled, randomised controlled trials showed a less dramatic effect in the use of misoprostol than previously thought (Abdel-Aleem 2001; Adekanmi 2001; O'Brien 1998; Oboro 2003). That may be due to three reasons. Firstly, in all previous reports, blood loss was subjectively assessed, while in the current two placebo-controlled trials, blood loss was measured objectively. Secondly, lack of blinding in previous studies may have affected the perception of effectiveness. Thirdly, variation in the route and dose of the administration of misoprostol may reflect variations in plasma therapeutic levels. Current evidence from the analysis of pharmacodynamic studies (Abdel-Aleem 2003; Andolina 2003; Danielsson 1999; Khan 2003; Tang 2002; Zieman 1997) suggests that the oral and sublingual routes have the advantage of rapid onset of action, while the sublingual, vaginal and rectal routes have the advantage of prolonged activity and greater bioavailability (Hofmeyr 2005). However, many clinicians might question the feasibility and effectiveness of using the sublingual route in an unstable or unconscious patient and the vaginal route in the presence of a significant vaginal bleeding.

The use of misoprostol was not associated with any significant reduction in any of the prespecified primary outcome measures. Of the three parameters used for the assessment of blood loss, misoprostol use was associated with a significant reduction of blood loss of 500 ml or more after enrolment (RR 0.57, 95% CI 0.34 to 0.96). However, the additional use of uterotonics, blood transfusion, and the evacuation of retained products did not differ between the two groups after enrolment. There were three cases of maternal mortality in the misoprostol arm of the South Africa 2004 trial. Despite the small number of patients recruited, results should be interpreted with great caution, and future large randomised trials should address the safety of the use of misoprostol in women with a major primary PPH.

The relative risk reduction of 43% of blood loss of 500 ml or more was similar in the two misoprostol placebo-controlled trials, despite a lower dosage in the Gambia 2004 trial. Somewhat surprisingly, this reduction was not associated with any significant reduction in mean blood loss, the additional use of uterotonics, surgical interventions, or blood transfusion. The review was underpowered to assess maternal mortality and other outcomes including serious maternal morbidity and surgical interventions and, therefore, future large multicentre randomised control studies, using a fixed dose and route of administration, are required to assess efficacy and safety.

South Africa 2001 was not large enough to evaluate the effects of rectal misoprostol on maternal mortality, serious maternal morbidity or hysterectomy rates in women with primary PPH. Compared with syntometrine and oxytocin infusion, rectal misoprostol administration provided better control of PPH and less need for medical co-interventions. The generalisation of the results (external validity) is somewhat limited because the adverse outcomes, like 'treatment failure', were susceptible to biased ascertainment. It is possible that a misoprostol enthusiast may have been more inclined to start additional treatment in women who were not assigned to receive rectal misoprostol, thus inflating the numbers of 'treatment failures' in the control group. Furthermore, the authors performed an interim analysis after 12 months (30 recruited women), which, according to the authors, showed that "misoprostol performed best". The trial was continued but it is unclear whether this information was shared with the clinicians participating in the trial. One cannot rule out the possibility that postrandomisation management and outcome assessment was influenced by the knowledge of interim results. It would be prudent to regard the results of the South Africa 2001 trial as 'preliminary' and 'encouraging' and urge other trialists to use rectal misoprostol as one of the treatment arms in future trials.

Maternal pyrexia was prevalent in the misoprostol, placebo-controlled trials (Gambia 2004; South Africa 2004). In South Africa 2004 (200 orally, 400 sublingually and 400 rectally), 3/114 women had pyrexia greater than 40 °C. In Gambia 2004 (200 orally and 400 sublingually), 2/79 women had pyrexia greater than 39 degrees °C, but none greater than 40 °C. Future studies should examine the use of a minimum clinically effective dosage with the least side-effects.

The questions relating to the management of women with major primary PPH unresponsive to first-line uterotonic therapy remain largely unanswered. In the absence of randomised controlled trials, clinicians are left to make their own judgement on the best combination of surgical, radiological and/or pharmaceutical interventions that should be used to control the bleeding. Although many will question the use of a placebo arm in women with primary PPH, it should be considered for evaluation of second-line interventions. Such trials are scientifically superior and ethical provided that every effort is made to ensure that the administration of the placebo does not delay the standard treatment and does not put women at additional risk.

AUTHORS' CONCLUSIONS

Implications for practice

The current evidence is not robust enough to recommend replacing the combination of oxytocin and ergometrine with misoprostol for the first-line treatment of primary PPH. Also, more safety data are needed if misoprostol is to be used as an adjuvant therapy to oxytocin and ergometrine when other alternative methods are not available, or for certain groups of women who are awaiting second-line therapy, or for those awaiting transfer to hospital following home deliveries. A system of "adverse event registration" should be used to identify serious maternal morbidity and mortality associated with the use of misoprostol in clinical practice.

The variation in dose regimens between the three different studies made it difficult to draw clear conclusions regarding the most effective dose or route. The use of higher doses (greater than 600 mcg) should be balanced against maternal side-effects. Potential routes of administration include oral, sublingual, rectal, or a combination of these. Clinicians should be aware that the feasibility and effectiveness of the sublingual and vaginal routes might be limited in unconscious participants and in those with heavy vaginal bleeding.

There is no clear evidence regarding the management of women who failed to respond to first -line uterotonics therapy. However, every attempt should be made to use conservative surgical techniques, radiological interventions, and/or haemostatic drugs, to avoid hysterectomy.

Implications for research

Future randomised controlled trials are required to identify the best drug combinations, route, and dose of uterotonics, especially misoprostol, for the treatment of primary PPH. Ideally, the trials should be double-blinded to minimise the risk of bias in the assessment of the outcomes. More importantly, trials should be large enough to assess maternal morbidity and mortality. Another area of interest would be interventions for control of primary PPH following home deliveries, particularly in developing countries.

Currently, there are no randomised data on the effectiveness of intrauterine misoprostol, but recent reports suggest that it may be effective (Adekanmi 2001; Oboro 2003) and, therefore, further research would be justified. More pharmacological data are needed, particularly relating to the rectal and intrauterine routes of administration, and the interaction between misoprostol and other oxytocics.

Three areas would be of interest for future research in women with primary PPH unresponsive to uterotonics. Firstly, further work is needed to identify the most effective tamponade procedures and uterine haemostatic suturing techniques in women with major postpartum haemorrhage. Secondly, haemostatic drugs like rFVIIa and tranexamic acid have been considered in patients with major haemorrhage in obstetrics and other specialties in an attempt to control massive haemorrhage. Finally, the benefits of interventional radiology in women at increased risk of bleeding during delivery, and those who bleed following childbirth, should be critically evaluated in randomised trials. Both first-line uterotonics and second-line surgical intervention trials can be conducted in both developed and developing countries.

POTENTIAL CONFLICT OF INTEREST

Z Alfirevic has received financial support from Novo Nordisk to investigate recombinant activated factor VII (rFVIIa) as a potential treatment for massive postpartum haemorrhage.

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TABLES

Characteristics of included studies

Study	Gambia 2004
Methods	Next in a series of randomised treatment packs in opaque envelopes with 3 tablets of misoprostol 200 mcg or placebo.
Participants	160 women who delivered vaginally with measured postpartum blood loss of 500 ml or more within one hour of delivery and inadequate uterine contraction thought to be the possible factor. Exclusion criteria included women who delivered by caesarean section if blood loss was less than 500 ml in first hour following vaginal delivery, if gestational age was less than 28 weeks, or if inadequate uterine contraction was not thought to be the causative factor for PPH.
Interventions	Routine active management of third stage of labour with oxytocin 10 IU or syntometrine 1 ampule (5 ml). All participants had standard management of PPH (rubbing the uterus, commencing intravenous infusion, administering oxytocics, delivering the placenta if undelivered, and emptying the bladder). Trial tablets (misoprostol 200 mcg or placebo) were administered: 1 orally and 2 sublingually.
Outcomes	Primary outcome: additional blood loss after enrolment.

Characteristics of included studies (*Continued*)

	Secondary outcomes: frequency and severity of side-effects, additional blood loss of 500 ml or more after enrolment, clinical complications (blood transfusion, hysterectomy), and haemoglobin level at 12-24 hours after delivery.
Notes	Blinding may have been compromised by non-identical placebos.
Allocation concealment	A – Adequate

Study	**South Africa 2001**
Methods	Random allocation by sealed sequentially numbered envelopes. No blinding.
Participants	64 women with primary PPH > 500 ml in two centres. Women with hypertension at recruitment, cardiac abnormalities, ongoing severe asthma, connective tissue disorders, haemorrhage due to obvious genital tract trauma. Any contraindications to prostaglandin therapy were excluded.
Interventions	Syntometrine + syntocinon intravenous infusion + 4 placebo tablets per rectum versus 800 mcg (4 tablets) misoprostol per rectum + a placebo normal saline 2 ml intramuscular injection + placebo crystalloid intravenous infusion.
Outcomes	Effectiveness to control PPH within 20 minutes of administration.
Notes	Single-blinded study as obstetricians were aware of the type of drug been given while women and midwives were blinded. No mention of: (a) drugs used in the third stage; (b) measurement of blood loss. Outcome measures for the following factors were reported as p value only: (a) DIC; (b) blood transfusion; (c) length of hospital stay; (d) drug side-effects.
Allocation concealment	A – Adequate

Study	**South Africa 2004**
Methods	Next in a series of treatment packs containing 5 tablets of independently prepared, ordered in computer-generated random sequence and numbered consecutively. The packs contained either placebo or misoprostol 5 x 200 mcg.
Participants	244 women with bleeding more than expected at least 10 minutes after delivery that thought to be due to uterine atony and requiring additional uterotonic therapy.
Interventions	Routine active management of the third stage of labour with oxytocin 10 units or syntometrine one ampule soon after birth. All participants were given all the routine treatment for PPH (intravenous infusion, uterotonics, etc) from a special 'PPH Trolly'. Trial tablets (misoprostol 200 mcg or placebo) were administered: 1 orally, 2 sublingually and 2 rectally.
Outcomes	Primary outcome: (1) measured blood loss 500 ml or more in 1 hour after enrolment; (2) mean measured blood loss in 1 hour after enrolment; (3) haemoglobin level day 1 after birth < 6 g/dl or blood transfusion; (4) side-effects (pyrexia 38.5 degrees celsius or more, moderate or severe shivering 1 hour after enrolment). Secondary outcomes: (1) blood loss 1000 ml or more in 1 hour after enrolment; (2) blood transfusion. (3) haemoglobin level 1 day after birth < 8 g/dl or blood transfusion; (4) additional uterotonic given after enrolment; (5) manual removal of the placenta; (6) evacuation of retained products of conception; (7) hysterectomy; (8) maternal death.

Notes	6/244 data sheets did not have pack numbers completed and were excluded from the analysis. No abnormal outcomes were observed in any of the excluded group except 1 case of shivering and 1 of blood transfusion. No information given regarding allocation group. Authors were contacted to clarify amount of blood loss before recruitment and they have provided the following information. (1) The trial was planned as a PPH treatment trial to assess the effect of misoprostol over and above routine treatment of PPH. (2) The entry criteria were intended to identify women who had PPH requiring additional treatment. No blood loss criterion was included, as clinically we diagnose PPH on the basis of ongoing abnormal bleeding irrespective of the volume lost so far. Thus, all the participants, in the opinion of the attending clinician, had abnormal bleeding requiring treatment. It is likely that, in most cases, this would have been more than 500 ml, but we do not have these data. (3) 10 minutes was the minimum time after delivery, but in most cases the time was longer (in the 3 cases of maternal mortality, enrolment ranged between 85 and 140 minutes after delivery).
Allocation concealment	A – Adequate

DIC: disseminated intravascular coagulopathies
IU: international units
PPH: postpartum haemorrhage

Characteristics of excluded studies

Study	Reason for exclusion
Japan 1976	The study consists of 2 parts. The first part was a retrospective analysis of data prior to the clinical trial. The clinical trial compared the effects of prostaglandin F2 alpha and ergot derivatives on the amount of blood loss in women who suffered PPH as blood loss > 400 ml in primiparas and > 300 ml in multiparas. Thirteen women were randomised to receive ergot derivatives and 46 women received prostaglandin F2 alpha by one of the following routes: (i) gluteal intramuscular; (ii) intravenous infusion; (iii) transabdominal intramyometrial; (iv) transvaginal intramyometrial. The method of randomisation was not reported. We were unable to extract the data according to the allocated groups in order to perform an 'intention-to-treat' analysis.

PPH: postpartum haemorrhage

Characteristics of ongoing studies

Study	Villar 2006
Trial name or title	Misoprostol to treat postpartum hemorrhage (PPH): a randomized controlled trial (Argentina, Egypt, South Africa, Thailand and Viet Nam)
Participants	Women delivering vaginally with clinically diagnosed PPH thought to be due to, or contributed to, by atonia requiring additional uterotonics
Interventions	Misoprostol or placebo in addition to routine treatment for PPH
Outcomes	Primary outcome: incidence of greater than or equal to 500 ml of measured blood loss at 60 minutes after enrolment
Starting date	1 May 2005
Contact information	Dr J Villar villarj@who.int
Notes	

Characteristics of ongoing studies (*Continued*)

ANALYSES

Comparison 01. Misoprostol versus oxytocin/ergometrine

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Hysterectomy	1	64	Relative Risk (Fixed) 95% CI	0.33 [0.01, 7.89]
02 Persistent haemorrhage	1	64	Relative Risk (Fixed) 95% CI	0.18 [0.04, 0.76]
03 Additional uterotonics	1	64	Relative Risk (Fixed) 95% CI	0.18 [0.04, 0.76]
04 Surgical co-interventions (excluding hysterectomy)	1	64	Relative Risk (Fixed) 95% CI	1.00 [0.15, 6.67]

Comparison 02. Misoprostol versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Hysterectomy	2	398	Relative Risk (Random) 95% CI	1.24 [0.04, 40.78]
02 Additional uterotonics	2	383	Relative Risk (Fixed) 95% CI	0.98 [0.78, 1.24]
03 Surgical co-intervention (excluding hysterectomy)	0	0	Relative Risk (Fixed) 95% CI	Not estimable
04 Blood loss 500 ml or more after enrolment	2	397	Relative Risk (Fixed) 95% CI	0.57 [0.34, 0.96]
05 Blood loss 1000 ml or more after enrolment	2	397	Relative Risk (Fixed) 95% CI	0.65 [0.17, 2.44]
06 Average blood loss after enrolment	2	397	Weighted Mean Difference (Fixed) 95% CI	-19.10 [-58.68, 20.48]
07 HB < 6 or blood transfusion	2	386	Relative Risk (Fixed) 95% CI	1.15 [0.73, 1.82]
08 Shivering	2	394	Relative Risk (Fixed) 95% CI	2.31 [1.68, 3.18]
09 Nausea	1	160	Relative Risk (Fixed) 95% CI	0.62 [0.15, 2.49]
10 Headache	1	160	Relative Risk (Fixed) 95% CI	0.65 [0.27, 1.60]
11 Maternal pyrexia (38.5 degrees celsius or more)	2	392	Relative Risk (Fixed) 95% CI	6.40 [1.71, 23.96]
12 Manual removal of the placenta	2	398	Relative Risk (Fixed) 95% CI	0.59 [0.17, 1.98]
13 Maternal death	2	398	Relative Risk (Fixed) 95% CI	7.24 [0.38, 138.60]
14 Evacuation of retained product of conception	1	238	Relative Risk (Fixed) 95% CI	5.17 [0.25, 106.55]
15 Blood transfusion	2	394	Relative Risk (Fixed) 95% CI	1.33 [0.81, 2.18]

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Rectal; Ergonovine [administration & dosage]; Hysterectomy; Maternal Mortality; Misoprostol [administration & dosage]; Oxytocics [administration & dosage]; Oxytocin [administration & dosage]; Postpartum Hemorrhage [drug therapy; surgery; *therapy]; Randomized Controlled Trials

MeSH check words

Female; Humans; Pregnancy

COVER SHEET

Title Treatment for primary postpartum haemorrhage

Authors	Mousa HA, Alfirevic Z
Contribution of author(s)	Hatem Mousa assessed trial eligibility, extracted the data and co-wrote the review. Zarko Alfirevic verified the trial eligibility, data extraction and co-wrote the review.
Issue protocol first published	2001/3
Review first published	2003/1
Date of most recent amendment	15 November 2006
Date of most recent SUBSTANTIVE amendment	14 November 2006
What's New	November 2005 Search updated. We identified two new trials: Gambia 2004; South Africa 2004.
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	31 October 2006
Date authors' conclusions section amended	Information not supplied by author
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GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Misoprostol versus oxytocin/ergometrine, Outcome 01 Hysterectomy

Review: Treatment for primary postpartum haemorrhage

Comparison: 01 Misoprostol versus oxytocin/ergometrine

Outcome: 01 Hysterectomy

Study	Misoprostol n/N	Oxytocin/ergometrine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 2001	0/32	1/32		100.0	0.33 [0.01, 7.89]
Total (95% CI)	32	32		100.0	0.33 [0.01, 7.89]
Total events: 0 (Misoprostol), 1 (Oxytocin/ergometrine)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.68 p=0.5					

Analysis 01.02. Comparison 01 Misoprostol versus oxytocin/ergometrine, Outcome 02 Persistent haemorrhage

Review: Treatment for primary postpartum haemorrhage

Comparison: 01 Misoprostol versus oxytocin/ergometrine

Outcome: 02 Persistent haemorrhage

Study	Misoprostol n/N	Oxytocin/ergometrine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 2001	2/32	11/32		100.0	0.18 [0.04, 0.76]
Total (95% CI)	32	32		100.0	0.18 [0.04, 0.76]
Total events: 2 (Misoprostol), 11 (Oxytocin/ergometrine)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.35 p=0.02					

Analysis 01.03. Comparison 01 Misoprostol versus oxytocin/ergometrine, Outcome 03 Additional uterotonics

Review: Treatment for primary postpartum haemorrhage

Comparison: 01 Misoprostol versus oxytocin/ergometrine

Outcome: 03 Additional uterotonics

Study	Misoprostol n/N	Oxytocin/ergometrine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 2001	2/32	11/32		100.0	0.18 [0.04, 0.76]
Total (95% CI)	32	32		100.0	0.18 [0.04, 0.76]

Total events: 2 (Misoprostol), 11 (Oxytocin/ergometrine)

Test for heterogeneity: not applicable

Test for overall effect z=2.35 p=0.02

Analysis 01.04. Comparison 01 Misoprostol versus oxytocin/ergometrine, Outcome 04 Surgical co-interventions (excluding hysterectomy)

Review: Treatment for primary postpartum haemorrhage

Comparison: 01 Misoprostol versus oxytocin/ergometrine

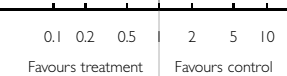
Outcome: 04 Surgical co-interventions (excluding hysterectomy)

Study	Misoprostol n/N	Oxytocin/ergometrine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 2001	2/32	2/32		100.0	1.00 [0.15, 6.67]
Total (95% CI)	32	32		100.0	1.00 [0.15, 6.67]

Total events: 2 (Misoprostol), 2 (Oxytocin/ergometrine)

Test for heterogeneity: not applicable

Test for overall effect z=0.00 p=1



Analysis 02.01. Comparison 02 Misoprostol versus placebo, Outcome 01 Hysterectomy

Review: Treatment for primary postpartum haemorrhage

Comparison: 02 Misoprostol versus placebo

Outcome: 01 Hysterectomy

Study	Misoprostol n/N	Placebo n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Gambia 2004	0/79	2/81		49.6	0.21 [0.01, 4.20]
South Africa 2004	3/117	0/121		50.4	7.24 [0.38, 138.60]
Total (95% CI)	196	202		100.0	1.24 [0.04, 40.78]

Total events: 3 (Misoprostol), 2 (Placebo)

Test for heterogeneity chi-square=2.74 df=1 p=0.10 I^2 =63.5%

Test for overall effect z=0.12 p=0.9

Analysis 02.02. Comparison 02 Misoprostol versus placebo, Outcome 02 Additional uterotonics

Review: Treatment for primary postpartum haemorrhage

Comparison: 02 Misoprostol versus placebo

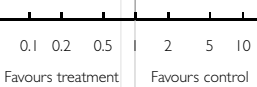
Outcome: 02 Additional uterotonics

Study	Misoprostol n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Gambia 2004	3/79	5/81		7.3	0.62 [0.15, 2.49]
South Africa 2004	63/111	63/112		92.7	1.01 [0.80, 1.27]
Total (95% CI)	190	193		100.0	0.98 [0.78, 1.24]

Total events: 66 (Misoprostol), 68 (Placebo)

Test for heterogeneity chi-square=0.49 df=1 p=0.49 I^2 =0.0%

Test for overall effect z=0.17 p=0.9



Analysis 02.04. Comparison 02 Misoprostol versus placebo, Outcome 04 Blood loss 500 ml or more after enrolment

Review: Treatment for primary postpartum haemorrhage

Comparison: 02 Misoprostol versus placebo

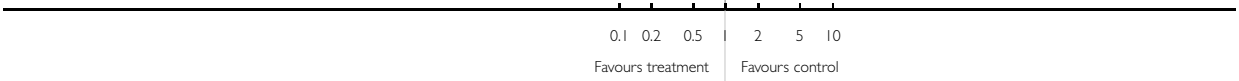
Outcome: 04 Blood loss 500 ml or more after enrolment

Study	Misoprostol n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Gambia 2004	13/79	23/81		67.7	0.58 [0.32, 1.06]
South Africa 2004	6/117	11/120		32.3	0.56 [0.21, 1.46]
Total (95% CI)	196	201		100.0	0.57 [0.34, 0.96]

Total events: 19 (Misoprostol), 34 (Placebo)

Test for heterogeneity chi-square=0.00 df=1 p=0.95 I^2 =0.0%

Test for overall effect z=2.12 p=0.03



Analysis 02.05. Comparison 02 Misoprostol versus placebo, Outcome 05 Blood loss 1000 ml or more after enrolment

Review: Treatment for primary postpartum haemorrhage

Comparison: 02 Misoprostol versus placebo

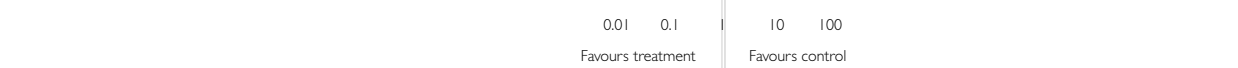
Outcome: 05 Blood loss 1000 ml or more after enrolment

Study	Misoprostol n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Gambia 2004	2/79	5/81		90.9	0.41 [0.08, 2.05]
South Africa 2004	1/117	0/120		9.1	3.08 [0.13, 74.76]
Total (95% CI)	196	201		100.0	0.65 [0.17, 2.44]

Total events: 3 (Misoprostol), 5 (Placebo)

Test for heterogeneity chi-square=1.23 df=1 p=0.27 I^2 =18.5%

Test for overall effect z=0.63 p=0.5



Analysis 02.06. Comparison 02 Misoprostol versus placebo, Outcome 06 Average blood loss after enrolment

Review: Treatment for primary postpartum haemorrhage

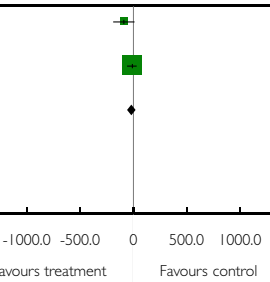
Comparison: 02 Misoprostol versus placebo

Outcome: 06 Average blood loss after enrolment

Study	Misoprostol N	Misoprostol Mean(SD)	Placebo N	Placebo Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Gambia 2004	79	325.00 (264.00)	81	410.00 (397.00)		14.4	-85.00 [-189.23, 19.23]
South Africa 2004	117	168.00 (163.00)	120	176.00 (173.00)		85.6	-8.00 [-50.78, 34.78]
Total (95% CI)	196		201			100.0	-19.10 [-58.68, 20.48]

Test for heterogeneity chi-square=1.79 df=1 p=0.18 I^2 =44.3%

Test for overall effect z=0.95 p=0.3



Analysis 02.07. Comparison 02 Misoprostol versus placebo, Outcome 07 HB < 6 or blood transfusion

Review: Treatment for primary postpartum haemorrhage

Comparison: 02 Misoprostol versus placebo

Outcome: 07 HB < 6 or blood transfusion

Study	Misoprostol n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Gambia 2004	12/79	12/81		41.7	1.03 [0.49, 2.14]
South Africa 2004	20/110	17/116		58.3	1.24 [0.69, 2.24]
Total (95% CI)	189	197		100.0	1.15 [0.73, 1.82]

Total events: 32 (Misoprostol), 29 (Placebo)

Test for heterogeneity chi-square=0.16 df=1 p=0.69 I^2 =0.0%

Test for overall effect z=0.60 p=0.6

Analysis 02.08. Comparison 02 Misoprostol versus placebo, Outcome 08 Shivering

Review: Treatment for primary postpartum haemorrhage

Comparison: 02 Misoprostol versus placebo

Outcome: 08 Shivering

Study	Misoprostol n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Gambia 2004	23/79	8/81		21.0	2.95 [1.40, 6.19]
South Africa 2004	63/116	30/118		79.0	2.14 [1.50, 3.04]
Total (95% CI)	195	199		100.0	2.31 [1.68, 3.18]

Total events: 86 (Misoprostol), 38 (Placebo)

Test for heterogeneity chi-square=0.60 df=1 p=0.44 I^2 =0.0%

Test for overall effect z=5.12 p<0.00001

Analysis 02.09. Comparison 02 Misoprostol versus placebo, Outcome 09 Nausea

Review: Treatment for primary postpartum haemorrhage

Comparison: 02 Misoprostol versus placebo

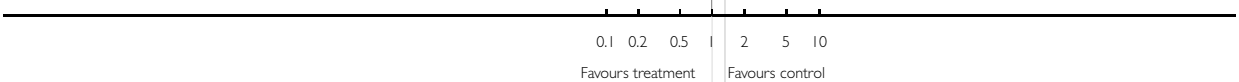
Outcome: 09 Nausea

Study	Misoprostol n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Gambia 2004	3/79	5/81		100.0	0.62 [0.15, 2.49]
Total (95% CI)	79	81		100.0	0.62 [0.15, 2.49]

Total events: 3 (Misoprostol), 5 (Placebo)

Test for heterogeneity: not applicable

Test for overall effect z=0.68 p=0.5



Analysis 02.10. Comparison 02 Misoprostol versus placebo, Outcome 10 Headache

Review: Treatment for primary postpartum haemorrhage

Comparison: 02 Misoprostol versus placebo

Outcome: 10 Headache

Study	Misoprostol n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Gambia 2004	7/79	11/81		100.0	0.65 [0.27, 1.60]
Total (95% CI)	79	81		100.0	0.65 [0.27, 1.60]
Total events: 7 (Misoprostol), 11 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.93 p=0.4					

Analysis 02.11. Comparison 02 Misoprostol versus placebo, Outcome 11 Maternal pyrexia (38.5 degrees celsius or more)

Review: Treatment for primary postpartum haemorrhage

Comparison: 02 Misoprostol versus placebo

Outcome: 11 Maternal pyrexia (38.5 degrees celsius or more)

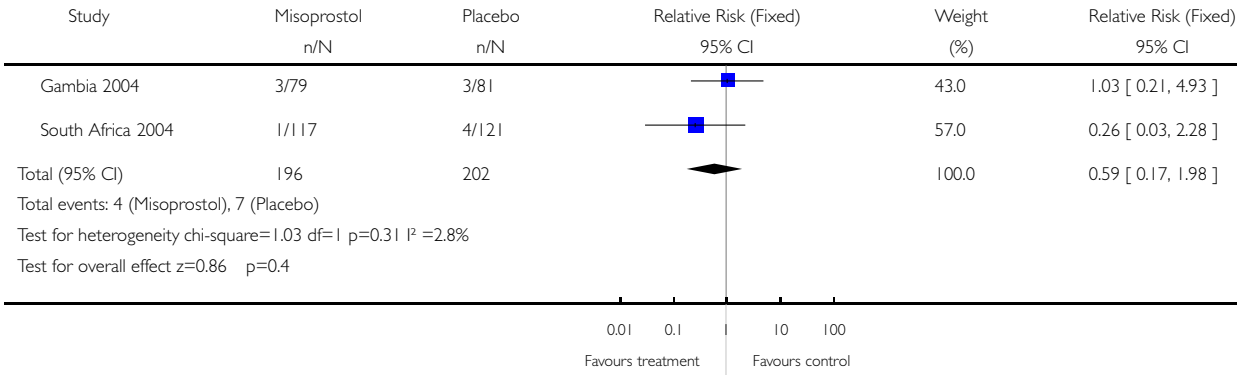
Study	Misoprostol n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Gambia 2004	4/79	0/81		20.1	9.23 [0.50, 168.57]
South Africa 2004	11/114	2/118		79.9	5.69 [1.29, 25.12]
Total (95% CI)	193	199		100.0	6.40 [1.71, 23.96]
Total events: 15 (Misoprostol), 2 (Placebo)					
Test for heterogeneity chi-square=0.08 df=1 p=0.77 I^2 =0.0%					
Test for overall effect z=2.76 p=0.006					

Analysis 02.12. Comparison 02 Misoprostol versus placebo, Outcome 12 Manual removal of the placenta

Review: Treatment for primary postpartum haemorrhage

Comparison: 02 Misoprostol versus placebo

Outcome: 12 Manual removal of the placenta

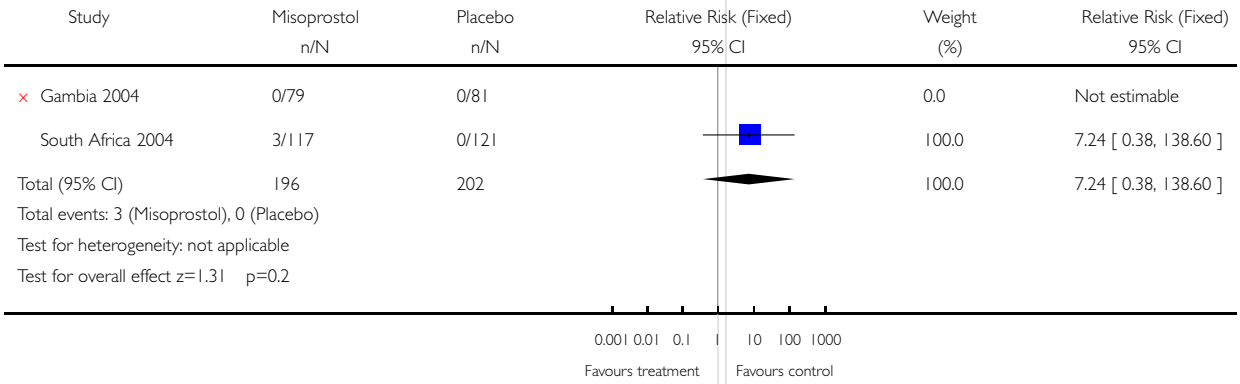


Analysis 02.13. Comparison 02 Misoprostol versus placebo, Outcome 13 Maternal death

Review: Treatment for primary postpartum haemorrhage

Comparison: 02 Misoprostol versus placebo

Outcome: 13 Maternal death



Analysis 02.14. Comparison 02 Misoprostol versus placebo, Outcome 14 Evacuation of retained product of conception

Review: Treatment for primary postpartum haemorrhage

Comparison: 02 Misoprostol versus placebo

Outcome: 14 Evacuation of retained product of conception

Study	Misoprostol n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 2004	2/117	0/121		100.0	5.17 [0.25, 106.55]
Total (95% CI)	117	121		100.0	5.17 [0.25, 106.55]
Total events: 2 (Misoprostol), 0 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.06 p=0.3					

Analysis 02.15. Comparison 02 Misoprostol versus placebo, Outcome 15 Blood transfusion

Review: Treatment for primary postpartum haemorrhage

Comparison: 02 Misoprostol versus placebo

Outcome: 15 Blood transfusion

Study	Misoprostol n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Gambia 2004	12/79	9/81		37.6	1.37 [0.61, 3.06]
South Africa 2004	19/115	15/119		62.4	1.31 [0.70, 2.45]
Total (95% CI)	194	200		100.0	1.33 [0.81, 2.18]
Total events: 31 (Misoprostol), 24 (Placebo)					
Test for heterogeneity chi-square=0.01 df=1 p=0.94 I^2 =0.0%					
Test for overall effect z=1.14 p=0.3