Title: Comparison of treatment of incomplete abortion with misoprostol by physicians and midwives at district level in Uganda: a randomised controlled equivalence trial

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Introduction

Unsafe abortion contributes substantially to the global burden of maternal mortality and morbidity.\(^1\) Majority of unsafe abortions occur in low-income countries where induced abortion is restricted and the unmet need for contraception is high.\(^2\) Sub-Saharan Africa caters for the highest rates of unsafe abortion and global maternal mortality.\(^3\)

Emergency treatment of complications from unsafe abortion and spontaneous abortion, post-abortion care (PAC), is identified as an effective intervention to decrease maternal mortality.\(^4\) The PAC model consists of emergency treatment of abortion related complications and post abortion contraceptive counselling and provision.\(^5\) The prostaglandin E1 analogue misoprostol has been suggested as an effective tool in treatment of incomplete abortion.\(^6\)-\(^8\) International studies have compared and found no significant difference in effectiveness between treatment of incomplete abortion with misoprostol, and surgical treatment with Manual Vacuum Aspiration (MVA).\(^9\)-\(^12\) In low resource settings misoprostol in PAC is a simplified, cost effective and resource saving alternative to surgical interventions.\(^10\)

The lack of physicians in many low-income countries limits women’s access to PAC.\(^13\) In Africa the shortage of trained health care providers is greatest in rural and remote areas where maternal mortality and morbidity is highest.\(^14\) In Uganda, where unsafe abortion constitutes a serious public health issue, physicians are scarce and few midwives receive PAC training,\(^15\) restricting access to care. *Task shifting* is a process of delegating tasks, when appropriate, to less specialized health care providers. It has been identified as a way of increasing access and productivity,\(^16\) and to contribute to the building of cost effective and equitable health care services.\(^17\),\(^18\) Optimizing the use of midwives would be a pragmatic response to the shortage of physicians at district level in Uganda and a strategy to decrease maternal mortality.\(^18\)

Despite the proven effectiveness and safety of misoprostol treatment of incomplete abortion and the known advantages of task shifting, the involvement of midwives in diagnosing and treating incomplete abortion with misoprostol has not been systematically evaluated in any low resource setting. In this trial, we aimed to assess whether diagnoses and treatment of first trimester incomplete abortion with misoprostol provided by a midwife is equally effective and safe as that provided by a physician.

Methods

*Trial design and participants*
The study was designed as a multicentre randomised controlled equivalence trial conducted at district level in six health care facilities in six districts in rural, peri-urban and urban settings in central Uganda. The study protocol and trial followed the CONSORT guidelines for non-inferiority and equivalence randomised trials. The study was conducted between April 2013 and July 2014. The study was not masked. Inclusion criteria were women with signs of incomplete abortion (i.e. bleeding and contractions during pregnancy, opening cervix and no expulsion). Exclusion criteria were complete abortion, known allergy to misoprostol, a uterine size of more than 12 weeks of gestation, suspected ectopic pregnancy, unstable hemodynamic status and shock, signs of pelvic infection and/or sepsis. The health care facilities selected for inclusion were equipped to provide basic and emergency obstetric services and were estimated to have sufficient staff and caseload in order to be part of the study. The procedure and the instruments were pilot tested at Mulago Hospital, the national referral hospital in Kampala. Only minor revision was made to the instruments before recruitment started in the current study. The first month was considered the run in period where the facilities were given time to set the routine for screening, enrolment and follow up. This was supervised and supported closely by the study coordinator. An interim report was also sent to WHO following the run in phase. No changes were made to the data collection tool or the recruitment process and thus the run in period was included in the analysis. The study was developed and coordinated by researchers at the WHO research centre at Karolinska Institutet, Stockholm, and Mulago Hospital/Makerere University, Kampala. The study was approved by the Scientific and ethical review group at the Reproductive Health and Research Department, WHO, Geneva. Ethical approval was further obtained from the Research Ethics Committee, Makerere University, Dnr: 2012-129, Uganda National Council for Science and Technology Dnr: HS 1314 and the Swedish regional ethical review board at Karolinska Institutet Dnr: 2013/2;9.

Intervention and procedure

Eligible providers for participation were physicians and midwives involved in PAC at the different facilities. The health care providers were trained according to a standardized PAC training module. The five-day training programme focused on diagnosing incomplete abortion, treatment with misoprostol and MVA, and contraceptive methods and counselling. A number of midwives at each facility were trained to be research assistants in the study and were responsible for eligibility screening and enrolment of participants. The midwives conducted clinical assessments and were responsible for the follow up visits including...
assessed abortion status at follow up, gave contraceptive counselling and provided MVA when necessary. Clinical procedures for all enrolled women followed medical treatment of incomplete abortion according to WHO and the International Federation of Gynaecology and Obstetrics (FIGO) guidelines. Women admitted with signs of incomplete abortion was screened based on self reported Last Menstrual Period (LMP) and symptoms. Clinical signs of incomplete abortion included lower abdominal pain or cramping, vaginal bleeding, an open cervical os, a history of amenorrhoea and sometimes partial expulsion of products of conception. Eligible women who consented to participation were randomly allocated to a midwife (intervention) or a physician (standard care/control) for diagnosis and treatment. The clinical assessment included: (i) history taking, including LMP, obstetric and gynaecological history, and contraceptive history; (ii) general physical examination; (iii) pelvic examination including any signs of genital infections, cervical status, bleeding, and size of the uterus. Ultrasound was not systematically used. Each participant was given one single dose of 600mcg misoprostol orally. In addition they were offered analgesics in the form of Ibuprofen or Paracetamol, and oral antibiotics according to national guidelines for PAC. For monitoring purposes, participants were advised to stay at the clinic for four hours after swallowing the misoprostol tablets. Before discharge all women were offered contraceptive counselling and provided with a follow up date. Participants were given detailed information regarding bleeding, pain expected, and abnormal symptoms following treatment (fever and foul smelling vaginal discharge) and were informed about the importance of seeking care if such symptoms occurred. A separate protocol was used to record adverse events. The women were offered reimbursement for travel as an incentive to come for FU within the trial.

Outcomes

Primary and secondary outcomes were measured by research assistants at a follow up visit, 14 days + 2 weeks (within 14 to 28 days), after the initial visit. The primary outcome was complete abortion not requiring surgical intervention within 14 to 28 days of the initial treatment. The clinical assessments of the primary outcome were; (i) physical examination (pulse, blood pressure and temperature); (ii) pelvic examination including cervical status and bimanual examination of uterine size. Secondary outcomes included: (i) bleeding; (ii) pain; (iii) and un-scheduled visits. Measurements of secondary outcomes were: (i) the intensity of bleeding in relation to normal menstruation using a symptom diary card; (ii), and pain.
experienced following treatment, using a visual analogue scale (VAS).

Sample size
The sample size was calculated with the objective of showing two-sided equivalence assuming that the rate of incomplete abortions could be four per cent and would apply to both types of providers. A predefined acceptable difference in completion rate between the two providers ranged between -4% to +4%. To establish equivalence, with a power of 80% and two-sided 95% CI, the sample size becomes 452 per arm. Compensating for 10% loss to follow up gave a total sample size of 994.

Randomisation
The randomisation was 1:1 conducted in blocks of 12 and was stratified for study site. A computer random number generator was used to generate a list of codes from 1 to 994 and each code was linked to one of the two study groups. Sequentially numbered, opaque, sealed envelopes, each containing a random allocation, were prepared at the coordinating centre, and later opened in consecutive order by the research assistants after obtaining written consent.

Data management was organised locally at the coordinating centre at Mulago Hospital. Study protocols were collected and data entered continuously throughout data collection. The study coordinator checked protocols for accuracy, corrected protocols after discussion with research assistants, and conducted continuous process evaluation. The study coordinator also provided support and guidance to the providers throughout the study period.

Statistical analyses
Background characteristics and categorical outcomes were presented using descriptive statistics. The intergroup comparison was done using a generalized linear mixed-effects model with group as a fixed effect and health care facility as a random effect. The confidence interval for the risk difference was estimated using 1000 bootstrap simulations. In addition, the adjusted risk difference was estimated where the model was extended with the following fixed effects: age (<25 vs. 25+), marital status (single vs. married/cohabiting), education (none/primary vs. secondary/tertiary), number of pregnancies (1 vs. >1), and parity (0-para vs. multipara). The adjusted risk difference was estimated as the predicted risk difference at the average of all included covariates. Equivalence between the two study groups can be stated if the 95% CI of the risk difference lies completely within the pre-determined limits of equivalence (-4% to 4%). The intention-to-treat (ITT) population was defined as all
randomised patients with data concerning the primary outcome, excluding patients who had withdrawn consent. The per-protocol (PP) population is a subset of the ITT population excluding women with major protocol violations (e.g. cross-overs). Analysis of the primary outcome was made by PP analysis using generalized linear mixed-effects model to estimate the risk difference between the groups. P-values ≤0·05 were considered statistically significant. Data was entered in EpiData 3.1 and analysed using Stata version 13. Statistical analysis of the primary outcome was analysed using the Ime4 package in R version 3·0·1. Safety data were viewed descriptively without any formal statistical testing and there were no changes to the study design following the pilot phase. We have uploaded the study protocol to the Karolinska Institutet website: http://ki.se/en/people/krigem. The trial is registered at ClinicalTrials.org NCT 01844024.

Role of the funding source
Funder of the study was UNDPA/UNFPA/WHO/World bank special programme of research, development and research training in human reproduction, WHO, Geneva, the Swedish research council (521-2009-2605), Karolinska Institutet and Dalarna University. The authors designed this investigator-initiated trial. Funders of the study were not involved in the design, data collection, analysis or interpretation of the results. All authors have had full access to the data collected in the study. The corresponding author had final responsibility for the decision to submit the manuscript for publication.

Results
A total of 1108 women with symptoms of incomplete abortion were assessed for eligibility, of whom 89 were ineligible and nine women declined participation. A total of 1010 women were randomly assigned to the intervention (506 to midwife and 504 to physician). Eleven women (four in the midwife group and seven in the physician group) were excluded. In the midwife group, one woman had missing values for endpoint analysis, two women had a gestational age of >12 weeks and one was excluded because of withdrawn consent. In the physician group, two women did not receive misoprostol after clinical examination thus the intervention was discontinued, one woman was not eligible (septic and gestational age unknown), and two had missing values for the endpoint analysis. In addition, two women allocated to physicians were classified as protocol violations (e.g. cross-overs) as they were assessed by midwives when there was no physician available. One of the crossovers returned with complete abortion and one was lost to follow up. After exclusion of these 11 cases the total number of women that
received the intervention was 502 in the midwife group and 497 in the physician group. Table 1 shows the socio-demographic background and reproductive history of participants, including women lost to follow up. The baseline characteristics among participants were balanced with no major difference between the two groups with regard to socio-demographic background or reproductive history. The mean duration of gestational age based on clinical examination was 8.8 weeks (range 1-12 weeks) (Table 1).

One crossover was not considered enough to affect the results in a separate ITT analysis, as the PP population would be almost identical as the ITT population. Total loss to follow up was 44 (4.5%) of whom 30 (5.9%) were in the midwife group and 14 (2.8%) in the physician group. Thereby, a total of 955 women, 472 women in the midwife group and 483 women in the physician group, were included in the PP analysis (Figure 1).

Participating providers had similar background characteristics although physicians had longer work experience in PAC (Table 2). The women lost to follow up had a lower gestational age based on clinical exam compared with women who came back for follow up. Otherwise there was no difference in socio-demographics or reproductive history in the group of women lost to follow up compared with those who were not (Suppl Table 1).

**Primary outcome**

The overall proportion of complete abortion was 96.2%. The proportion of women with complete abortion among midwives and physicians was 95.8% (n=452) and 96.7% (n=467) respectively. The model based risk difference for midwife versus physician group was -0.79% (95% CI -2.90 to 1.35) (Table 3). The total number of incomplete abortions was 20 (4.2%) for midwives and 16 (3.3%) for physicians. All women with incomplete abortion (n=36) required surgical treatment and were evacuated with MVA after completing the follow up assessment. No serious adverse events were recorded.

**Secondary outcomes**

The majority (83.8%) reported bleeding less than or similar to normal menstrual bleeding following treatment. Mean number of days bleeding was 5 (range 1-16). Women evaluated pain following treatment, using VAS, with a mean score of 3.6 (range 0-10). The number of women reporting unscheduled visits was 30 (6.4%) in the midwife group and 18 (3.7%) in the physician group. Vaginal bleeding and abdominal pain were reported as reasons for the
unscheduled visits (Table 4). There were no significant differences in secondary outcomes between the groups. Reported side effects following treatment were nausea, vomiting, abdominal pain, chills and fever and were similar in both groups (Suppl Table 2).

**Discussion**

Diagnosis and treatment of first trimester incomplete abortion with misoprostol by midwives was equally effective and safe as when provided by physicians. Women with signs of incomplete abortion, seeking care at district level in Uganda who were diagnosed and treated by a midwife did not experience a higher complication rate compared with women treated by a physician. Our findings will be useful to scale up women’s access to safe PAC in low resource settings and thus contribute to a decrease in maternal mortality and morbidity.

Midwifery led interventions have been shown to be associated with efficient use of resources and to have a positive impact on health outcomes. Implementation of effective and sustainable models of care, such as optimizing the midwifery role, is central in order to reduce maternal mortality and morbidity. Other RCT studies from settings with liberal abortion laws show that provision of pregnancy termination using MVA and medical abortion is equally safe and effective when provided by midwives as when provided by physicians. These results are further confirmed in a systematic review, although the evidence is limited.

Our study is, to our knowledge, the first RCT conducted to evaluate the involvement of midwives diagnosing and treating women for incomplete abortion with misoprostol at district level, in a low resource setting. The overall complete abortion rate in our study was 96.2% similar to results in previous studies (range 94.4-99). Decentralization of misoprostol use in PAC has been found successful in a similar setting, where ultrasound is not routinely used and physicians are scarce, consistent with our findings. In Uganda, the majority of physicians work in the central urban region serving less than one third of the population. As a response, task shifting is already taking place but often without clear policies, planning, monitoring and evaluation. A recent qualitative study at district level in Uganda reports midwives as the main providers, including complicated cases due to the absence of physicians. However, both physicians and midwives revealed a lack of adequate skills and expressed a need for in-service training. Misoprostol was also reported to be rarely used in PAC due to limited availability and treatment guidelines at the health facilities. Results from this study provide scientific evidence that support task shifting in PAC and may be used in the
development and implementation of policies and standard care guidelines in Uganda, and
other similar low resource settings.

The Ugandan health system costs in treating women with incomplete abortion, often caused
by unsafe abortion, is substantial, and so is the cost for the individual women and their
families. A task shift to midwives in providing treatment of incomplete abortion with
misoprostol at district level will increase women’s access to safe PAC where it is needed
most. It has the potential to reduce the workload on the already overstretched health care
providers, save resources, and reduce the cost of unsafe abortion, at an individual and societal
level. In order to achieve these changes, an increase in misoprostol use in PAC is essential
and supplies at district level must be ensured. The authors suggest that PAC is incorporated in
basic midwifery education curricula in order to safeguard a future workforce with PAC skills.

Safe and effective task shifting between midwives and physicians also requires in-service
training in PAC for both professional cadres, based on updated evidence based guidelines.
The strengths of our study are its randomised design, low rate of loss to follow up, and
adequate power for detection of the primary outcome. One limitation is that several facilities
were involved and the standard of care might have differed between the facilities. However,
this is also a strength of the trial since the intervention was successful irrespective of the local
clinical standard of care. The involved providers’ clinical experiences of PAC ranged between
0-28.5 years (median 3.7) and differed between midwives and physicians. However, the
analyses between facilities showed no cluster effect on equivalence result. The larger loss to
follow up in the midwife group compared with the physician group is a limitation. Physicians
have a higher status than midwives in Uganda. Hence, this result could be interpreted as a
consequence of women feeling more inclined to return for follow up after being treated by a
physician. It could also be a consequence of individual differences in providers’ ability to
explain the importance of the follow up visit. The lost to follow up analysis did not show any
statistically significant differences except for gestational age. Women who were lost to follow
up had a significantly lower gestational age compared with women who returned for follow
up (Suppl Table 1).
Panel: Research in context

Systematic Review

Our literature review was conducted primarily in PubMed and included keywords: ”post abortion care”, ”incomplete abortion”, ”misoprostol”, ”midwives”, “non-physicians” and ”midlevel providers”. We have reviewed scientific publications aiming to assess midwives’ involvement in treating incomplete abortion with misoprostol in low resource settings. Existing evidence in relation to the topic is based on one observational study describing misoprostol use in post abortion care provided by nurse-midwives. However, no randomised controlled trial has evaluated the effectiveness and safety of midwives diagnosing and treating incomplete abortion with misoprostol.

Interpretation

Findings from our study show that midwives with a standardized training programme can independently diagnose incomplete abortion and successfully treat women with misoprostol at district level in a low resource setting. Our trial builds on previous scientific evidence showing that medical treatment with misoprostol and surgical treatment with Manual Vacuum Aspiration (MVA) for treatment of incomplete abortion is equally effective. Non-physician’s involvement in medical abortion has been evaluated to be safe in low resource settings. Our findings further support existing evidence concerning the use of misoprostol and fill an important knowledge gap regarding midwives’ competencies as main providers of post abortion care using misoprostol at district level.

Conclusion

Midwives are able to safely diagnose and treat first trimester incomplete abortion with misoprostol at district level in Uganda. The findings are of relevance to low resource settings but could also have implications for other settings where access to PAC is limited due to shortages in human resources. Scaling up midwives’ involvement in PAC at district level would increase women’s access to safe and effective treatment of incomplete abortion and thereby avoid severe complications that may lead to maternal mortality and morbidity.

Contributors

MKA developed the protocol and study design, directed implementation of the study, the data analyses and was lead author together with AC. AC participated in the implementation of the
study, in data collection and analysis of the study. SA was the coordinator for the facilities included in the study and participated in data collection, analysis and report writing. NMT was the statistician of the study and coordinated the data management, participated in analysis and report writing. EF took part in the study design, participated in analysis and report writing. JB was the local principal investigator and responsible for the overall supervision of the trial and participated in the implementation of the study, data analysis and report writing. KGD was the principal investigator, contributed to the study conception and was responsible for the overall supervision of the trial and participated in the study design, implementation of the study, data analysis and report writing. All involved authors have had access to the data, commented on the manuscript drafts and approved the final version submitted.

**Conflict of interests**

We declare that we have no personal or financial conflicts of interests.

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