USE OF MISOPROSTOL IN EVACUATION OF THE UTERUS IN INCOMPLETE ABORTION

A thesis submitted in part fulfillment for the degree of Masters of Medicine (Obstetrics and Gynecology), of the University of Nairobi.

By

Dr. Peter Igogo, MB,Ch.B. (University of Nairobi)

November 2009

DECLARATION

This thesis is my original work and has not been presented for a degree in any other university

Dr Peter Igogo,

M.MeD Student, Department of Obstetrics and Gynecology, University of Nairobi

Signed.....Date.....12. 11. 2009.....

CERTIFICATE OF SUPERVISION

This is to certify that the thesis presented in this book was researched upon by Dr Peter Igogo under my guidance and supervision and that the thesis is submitted with my approval.

Professor J G Karanja,
MB,Ch.B, M.MeD (Obs/Gyn),
Associate Professor and consultant Obstetrician and Gynecologist
Department of Obstetrics and Gynecology,
University of Nairobi at Kenyatta National Hospital

Signed.....Date.....13.11.2009

Dr. Tamooh S H
MB,Ch.B, M.MeD(Obs/Gyn)
Specialist Obstetrician and Gynecologist
Kenyatta National Hospital and Hon. Lecturer, University Of Nairobi

Signed.....Date 13.11.2009

CERTIFICATE OF AUTHENTICITY

This is to certify that this thesis is the original work of Dr Peter Igogo, M.MeD student, registration number H58/7212/06 in Obstetric and Gynecology department (2006-2010). The research was carried out in the department of Obstetric and Gynecology, School of Medicine, College of Health Sciences, University of Nairobi. It has not been presented to any other University for award of a degree.

Signed.....**Date**.....

Prof Koigi kamau,

Associate Professor of Obstetric and Gynecology,

Consultant Obstetrician and Gynecologist,

Chairman,

Department of Obstetric and Gynecology,

University of Nairobi.

DEDICATION

This work is dedicated to my dear wife Felistus and my children Collins, Mary and Lucy Anne, my mother and the memory of my late father, James Igogo.

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I humbly thank God almighty for His abundant love and guidance that enabled me to do and finish this work.

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List of Abbreviations

MVA	manual vacuum aspiration
KNH	Kenyatta national hospital
KSH	Kenyan shilling
CPGH	Coast Provincial General Hospital
WHO	World Health Organization
OBS/GYN	Obstetric/Gynecology
PRDH	Port Reitz District Hospital
D&C	Dilatation and curettage
USD	United States of America Dollar
CAC	Comprehensive abortion care
LTF	Loss to follow up
RHRA	Reproductive Health And Rights Alliance
KOGS	Kenya Obstetrical and Gynecological Society
ERC	Ethics and Research Committee

OPERATIONAL DEFINITIONS OF KEY TERMINOLOGIES

Abortion-is defined as the expulsion or extraction from its mother of an embryo or fetus weighing 500gm or less when it is not capable of independent survival. This is approximated to 22 weeks of gestation.

Incomplete Abortion-This is when the entire products of conception are not expelled and part of them are left in the uterine cavity. This is the commonest type amongst women hospitalized for abortion complications.

Unsafe Abortion-WHO defines unsafe abortion as a procedure of terminating an unwanted pregnancy either by persons lacking the necessary skills or in an environment lacking the minimum basic medical standards or both.

MVA (Manual Vacuum Aspiration)-This is the standard surgical treatment of incomplete abortions in which a canula and a hand-held aspirator are used to create vacuum for effective uterine aspiration of products of conception.

Misoprostol-This is a prostaglandin E1 analogue initially developed for prevention and treatment of gastric ulcers resulting from chronic administration of non- steroidal anti-inflammatory drugs (NSAIDs). It has many potential applications in obstetric and gynecologic practice e.g. treatment of early pregnancy failures including blighted ovum, incomplete and missed abortions as well as induction of labor and prevention and treatment of post partum hemorrhage.

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ABSTRACT

Background: Manual vacuum aspiration (MVA) has evolved to be the standard surgical method of evacuating the uterus in incomplete abortion. However, the procedure requires surgical training and there are cost related issues regarding its sustainability. Several studies have shown that misoprostol could be a safe, effective, acceptable and more affordable alternative method. By exploring this avenue of management, diversity of treatment methods may be achieved and enable provision of CAC services in lower health care settings.

Objectives: To compare the safety, efficacy and acceptability of sublingual misoprostol as compared to manual vacuum aspiration for treatment of incomplete abortion.

Study design: This was a randomized clinical trial.

Setting: Coast Provincial General Hospital and Port Reitz District Hospital Mombassa.

Methodology: Between December 2008 and July 20009, a total of 260 women with clinically diagnosed incomplete abortion with uterine size of up to 12 weeks gestation were randomized to either 600μg sublingual misoprostol or MVA. The women were followed for a minimum of seven days in order to asses whether the abortion was complete.

Main outcome measure: Completeness of uterine evacuation as indicated by history and lack of active bleeding and closed cervical os.

Results: Success was high in both MVA and misoprostol arms (100% & 93.8% respectively, p=0.012). Side effects such as heavy bleeding, nausea, pain/cramps, fever/chills were more in the misoprostol arm though the pain score was higher in the MVA arm (p=<0.001).More women in the misoprostol arm reported being either satisfied or very satisfied compared to satisfaction rates in the MVA arm (96.9% & 79.3% respectively, p=<0.001). More women in the misoprostol arm said they would choose the method again and would recommend the method to a friend compared with those in the MVA arm.

Conclusion: Misoprostol is as effective as MVA in treating incomplete abortion of up to 12 weeks uterine size. The acceptability of misoprostol appears higher. Given the many known advantages of misoprostol over MVA in poor resource settings, misoprostol should be promoted as an option of treating women with incomplete abortion.

INTRODUCTION

Background information

Abortion is the expulsion or extraction from its mother of an embryo or fetus weighing 500gm or less when it is not capable of independent survival (WHO).This is approximated to 22 weeks gestation. Abortion is classified into either spontaneous or induced. Spontaneous abortion is either isolated or recurrent and can be threatened, inevitable, complete, incomplete, missed or septic. Induced abortion is either legal or illegal. When the entire products of conception are not expelled and part of them are left in the uterine cavity, it is called incomplete abortion .This is the commonest type amongst women hospitalized for abortion related complications. Any abortion associated with clinical evidence of infection of the uterus is called septic abortion (15).

Early pregnancy loss is among the most widely experienced medical conditions in the world. Up to 20% of recognized pregnancies miscarry and perhaps 25% of women will experience miscarriage at some point in their lives. Beyond this, however there approximately 40-50 million induced abortions worldwide each year resulting in about 78,000 deaths world wide each year. There figures are naturally not reliable due to stigma attached to abortions and clandestine nature of the process. About 13% of the pregnancy related deaths worldwide are attributed to unsafely induced abortion. WHO defines unsafe abortion as a procedure of terminating an unwanted pregnancy either by persons lacking the necessary skills or in an environment lacking the minimum medical standards, or both. 90% of unsafe abortions are in the developing countries comprising 13% of all maternal deaths. In some African countries, unsafe abortion contributes as high as 35-50% of all maternal deaths (1).

In Kenya, as in most other Africa countries, unsafe abortions are believed to contribute in large part to the unacceptably high maternal death rates and a burden to hospital budgets, time and space. It is estimated that 300,000 abortions occur in Kenya annually. The total estimated annual direct cost of treating incomplete abortions presenting to public hospitals is approximately KSH 18.4 million with about KSH 11.5 million (62% of total) being spent on treating unsafe abortions(1).

Therefore finding safe, effective, acceptable and affordable means of treating incomplete abortions is a priority, especially for facilities in low resource settings.

Originally the treatment of choice for first trimester abortions was surgical uterine evacuation with dilatation and curettage (D&C). This was subsequently replaced by MVA, which was found to be just as effective, but cheaper and with fewer adverse effects. Unfortunately, MVA is not always available in low resource settings, as it requires special equipment and training for its use. There is also difficulty in maintaining and adequate stock of MVA equipment and supplies. Also in Kenya only doctors and specially trained nurses/midwives and clinical officers can provide MVA service. According to the report on human resource mapping and verification finding published in 2006, 70.4% of all medical staff works in hospitals, leaving the remainder to work in health centers and dispensaries. Also doctors represent only 3.4% of health workers and are concentrated in cities and towns (14). Therefore MVA has not been able to achieve its promise as a sustainable treatment of incomplete abortion.

There is therefore need to come up with an alternative method of uterine evacuation which can be applied by low cadre health care providers with no surgical skills of MVA.

MISOPROSTOL

There has been increasing interest in the use of misoprostol for medical evacuation especially in low resource settings. It is a prostaglandin E_1 analogue, which was developed in 1973 for prevention or treatment for peptic ulcer disease caused by prostaglandin synthetase inhibitors. It has many potential applications in obstetric and gynecological practice. These include:

1) Cervical priming before gynecological procedures -endometrial biopsy, Hysteroscopy, hysterosalpingogram, dilatation and curettage, manual vacuum aspiration, and dilatation and evacuation.
2) Medical management of incomplete and inevitable abortion, missed abortion, blighted ovum and intrauterine fetal death.
3) Therapeutic termination of pregnancy in first and second trimester.
4) Induction of labor.
5) Prevention and treatment of post-partum hemorrhage.

Advantages

Misoprostol is inexpensive costing about KSH.50-70 per one 200µg tablet of the original cytotec. There is also a generic (isovent 200) registered in Kenya for obstetric and gynecological use and is selling at KSH.22.The drug is stable even at room temperature, is easy to store and does not require refrigeration.

It is rapidly absorbed via various routes of administration hence enhancing patient convenience and it can also be self administered.

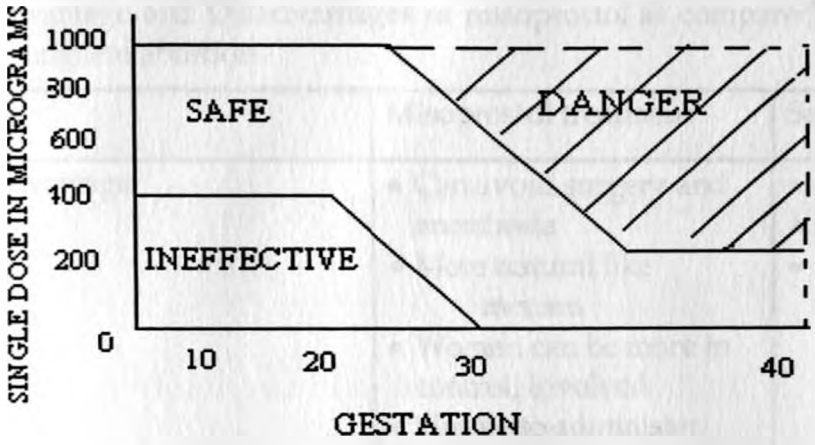
Side effects

1) Fetal death
2) Uterine rupture
3) Diarrhea
4) Abdominal pains/cramps
5) Nausea/vomiting
6) Fever/chills

Side effects such as nausea, vomiting, diarrhea, fever and chills are usually mild, lasting less than 24 hours and rarely require any therapy. The more serious side effects of misoprostol such as uterine rupture and fetal death occur when wrong doses are used .It is important therefore to use the correct dose of misoprostol and for the right indication.

Figure A

Ineffective, safe and dangerous dose of misoprostol at pregnancy.



Contraindications

The drug is contraindicated in patients with known allergy to misoprostol or other prostaglandins, confirmed or suspected ectopic pregnancy and patients with hemorrhagic disorder or concurrent anticoagulant therapy (12)

Table A: Advantage and disadvantages of Misoprostol and MVA

Advantage and Disadvantages of misoprostol as compared to surgical treatment of incomplete abortion		
	Misoprostol treatment	Surgical treatment
Advantage	• Can avoid surgery and anesthesia • More natural like menses • Women can be more in control, involved • Simple to administer • In-patient care not needed	• quicker • provider controlled • women can be less involved
Disadvantages	• bleeding cramping and more side-effects • waiting, uncertainty	• invasive and painful • small risk of uterine or cervical injury • small risk of infection • loss of privacy, autonomy

LITERATURE REVIEW

Misoprostol has been shown to effectively treat incomplete abortion in at least 19 studies with success ratio ranging from 13-100% but most slowing efficacy with misoprostol regimens at about 90 %.For example in the weeks trial, a single dose of 600μg of oral misoprostol performed slightly better than MVA (96.3 & 91.5%) when used to treat 317 women with incomplete abortion at a teaching hospital in Kampala Uganda. Rates of satisfaction were similarly high for both treatments. Unfortunately, nearly 1/3rd of participants did not return for follow up in this trial and therefore outcome was not available for them (4).

The 600μg dose of misoprostol administration is based on two earlier dose finding studies conducted in Thailand and Vietnam (16). While some studies have employed vaginal route of administration, the majority of the studies have employed the oral route of administration. Sublingual misoprostol seems to be slightly more effective than oral route with peak serum levels being achieved faster and therapeutic levels are maintained longer. Furthermore there are women who find vaginal administration more invasive and less acceptable than oral or sublingual route and there is an unconfirmed possibility that this route may be associated with greater rates of infection (19, 20, 21, and 22).

Similar study was done in Kagera regional hospital in Bukuba Tanzania. It was a randomized control trial in which 300 women with clinical diagnosis of incomplete abortion and uterine size ≤ 12 weeks were recruited, 150 in each arm. The main outcome measures were incidence of successful abortion, incidence of adverse effects and patient satisfaction. Success was very high in both arms (misoprostol 99%, MVA 100%).Main adverse effects were higher in the misoprostol arms, although the mean pain score was higher in the MVA arm. More women very satisfied in the misoprostol group (75%) than with MVA (55%) (P=0.001) and a higher proportion of women in the misoprostol arm said they would recommend the treatment to a friend (95% & 75% P< 0.001) (6).

Similar study done in Jose Macamo hospital in Maputo Mozambique, involving 270 women showed success rates of 100% & 91 % for MVA and misoprostol respectively (P=0.002).Women in MVA arm reported fewer side effects but higher pain scores. Women

who received misoprostol were significantly more likely to be very satisfied with the treatment and willing to choose the method again (5).

Another study done in Burkina Faso West Africa, involving 447 women showed success rates of 94.5% & 99.1% RR=0.95(95% CI 0.92-0.99).Majority indicated that treatment's adverse effects were tolerable 72.9% misoprostol & 75.8% MVA. Majorities were "Satisfied" or "very satisfied" with the method (96.8% misoprostol &97.7%MVA) and would recommend the method to a friend misoprostol 94.5%, MVA 85.2% (7).

Most of the studies conclude that misoprostol is as effective as MVA in treating incomplete abortion at uterine size of up to 12 weeks. They recommend that given many practical advantages of misoprostol over MVA in low resource settings, Misoprostol should be more widely available for treatment of incomplete abortion in the developing world.
Most of the studies involving misoprostol have been carried out in developed or middle income countries. Some studies have been carried out in low income countries such as Uganda, Tanzania, Mozambique and Burkina Fasso but no such study has been carried out in Kenya. Therefore the study was designed to fill a gap in literature by testing sublingual administration of misoprostol for treatment of incomplete abortion in hospital settings in a low income country.

JUSTIFICATION/RATIONALE

Unsafe abortions contribute to about 78,000 deaths per year worldwide. Many times that number of women experience serious morbidity. Most of these cases are found in developing countries. MVA is currently the standard surgical procedure for treating incomplete abortion .However it requires technical training for its use and also carry the risk of iatrogenic infection and surgical injury. It also requires special equipment which has to be processed before use. Therefore finding safe, effective, acceptable and affordable alternative of treating incomplete abortion is a priority especially for facilities in low resource settings .Such an alternative method would offer women right of choice which is fundamental. It is on this basis that this study seeks to establish the effectiveness of sublingual misoprotol as compared to MVA in management of incomplete abortion. This would influence policy on management of incomplete abortion by promoting misoprostol as an alternative method.

RESEARCH QUESTION

Is sublingual misoprostol as safe, effective, and acceptable as manual vacuum aspiration for the treatment of incomplete abortion?

OBJECTIVES

Broad objective

To determine the effectiveness, safety and acceptability of sublingual misoprostol for management of incomplete abortion.

Specific objectives

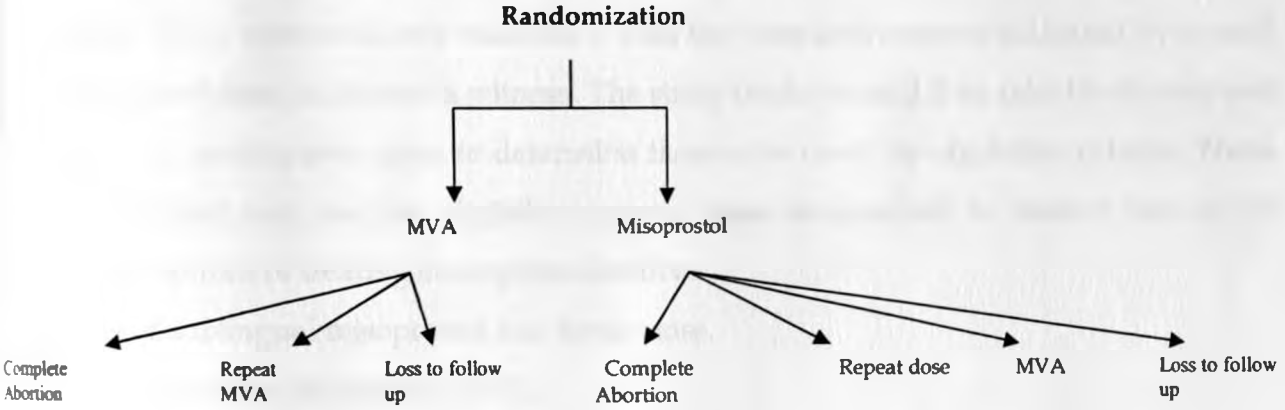
1) To compare success rates of sublingual misoprostol versus MVA in the management of incomplete abortions.
2) To compare the incidence of adverse events between the 2 arms
3) To compare the acceptability between the 2 treatment arms.

METHODOLOGY

Study design

This was a randomized clinical trial in which 260 women with clinical diagnosis of incomplete abortion were randomized to either sublingual misoprostol or MVA for the treatment of incomplete abortion, 130 participants in each arm.

Figure 1: Summary of Overall Design



Study sites

This study was done at Coast Provincial General Hospital (CPGH) and Port Reitz District Hospital (PRDH) both in Mombasa Kenya. CPGH is the regional referral hospital for Coast province of Kenya with a busy obstetric and gynecological unit. An average of 60 MVA is performed per month. Port Reitz hospital performs about 50 MVA per month most being referrals from health centers and dispensaries. In both hospitals, MVA procedures are performed by trained medical officers, trained nurses/midwives and trained clinical officers.

Sampling procedure

The study participants were getting the standard care at the facilities until the time of allocation. The standard care included the comprehensive medical history, history of previous pregnancies, past medical history, onset and the amount of per vaginal bleeding, and the events related to the onset of bleeding.

Systemic enquiry was then done and the physical examination which included the general examination and taking the vital signs, Systemic examination of respiratory, cardiovascular

and central nervous system. Per abdomen examination would then be done particularly noting any area of tenderness and the uterine size.

Pelvic examination including inspection, digital exam to check whether the cervical os is open or closed and bimanual exam to determine the uterine size and position and adnexal mass or tenderness.

Women presenting with incomplete abortion were offered the option of participating in the study. Those who answered in affirmative were given the informed consent form to read and sign. Those who could not read had it read for them and consent indicated by a mark on the consent form in front of a witness. The study doctor would then take the history and examine the participants again to determine those who meet the eligibility criteria .Those who consented and met the eligibility criteria were randomized to receive one of the following options of treating incomplete abortions:

1. 600µg of sublingual misoprostol as a single dose.
2. Manual vacuum aspiration (MVA).

Since ultrasound is not routinely done to diagnose incomplete abortion in our set up, the diagnosis of incomplete abortion was made based on history of amenorrhea, vaginal bleeding and finding an open cervical os on examination.

Papers were printed, 65 indicating misoprostol and 65 indicating MVA. The papers were then inserted in opaque envelopes which were sealed and sequentially numbered 1-130.This was done for each hospital and was done by the data manager who was not directly involved in managing the patients. This was done to ensure that the study was blinded to both the investigators and the study participants up to the time that the envelope was opened. Once the participant met the eligibility criteria, the study staff would open the next envelope in the sequence and allocate the woman to the indicated treatment arm. The study from this point was no longer blinded.

Those women who declined participation into the study or did not meet the eligibility criteria received the standard care offered at the hospitals without discriminating them.

Inclusion criteria

Participants were eligible for the study if they:-

1) Had confirmed incomplete abortion with uterine size not exceeding 12 weeks gestation.

2) Were 18 years or older
3) Lived within the hospitals' geographical area of coverage i.e. within 20kms from the hospital
4) were haemodynamically stable i.e. systolic blood pressure not<100mmhg, pulse rate not >100/min
5) General good health
6) Were willing to return for follow up

Exclusion criteria

Participants were excluded if they:

1) had signs of septic abortion with at least one of the following: 1.foul smelling par vaginal discharge 2.fever of >38 degrees centigrade 3.uterine tenderness
2) had a known allergy to misoprostol and prostaglandins
3) had known or suspected ectopic pregnancy

Sample size calculation

The sample size, n, was calculated using the variables from a similar study by C. Bique et al using the following formula from the book primer of biostatistics by Stanton. A. Grantz 2005(13)

$$n = \frac{A\left[1 + \sqrt{1 + 4\delta}\right]^2}{4d^2}$$

Where $A = [Z\alpha/2\sqrt{2P(1-P)} + Z1 - B\sqrt{P_1(1-P_1) + P_2(1-P_2)}]$

$$P = \frac{P_1 + P_2}{2}$$

n = sample size

$Z\partial/2$ = (2 tailed) table of value at 95% confidence interval = 1.96

Z (1 - B) = power of the test = 1.28

P = average success rate.

P1 = success rate for one arm of treatment (100% for MVA group)

P2 = success rate for 2nd arm of treatment (91% for Misoprostol group)

$\partial = P_1 - P_2 = 1 - 0.91 = 0.09$

$A = [1.96 \sqrt{2 (\times 0.955) (0.045)} + 1.28 (1 (1\text{-}1) + 0.91 (0.09)]^2$

$= 0.883$

Therefore $n = 0.88 [1 + \sqrt{1 + 4 \times 0.09}]^2$

$$\frac{0.88}{4 \times 0.09^2}$$

= 130 for each arm.

Based on the above formula, the sample size was calculated to be 130 participants for each treatment group.

INSTRUMENTS AND PROCEDURES

The study was conducted by the principal investigator under the guidance of two supervisors Prof Karanja and Dr Tamooh. The study team also included one medical officer and nursing officer for each participating hospital. The consultant obstetrician/gynecologists at the two study sites also supervised the study.

The two medical officers and the two nurses were trained on the study protocol before the study commenced. The principal investigator and the two medical officers would enroll the study participants, obtain informed consent and randomize eligible participants into either of the treatment arms.

The drugs were bought and kept in a locked cabinet and the key kept by the study nurse.

Those participants randomized to MVA arm were evacuated immediately. The procedure was said to be complete when no more blood was aspirated and bubbles were observed in the syringe and there was gritting sound with the cervix forming a tight grip on the canula. The patients would be observed for about one hour then discharged on analgesics and prophylactic antibiotics while those in the misoprostol arm were given 600µg of misoprostol sublingually and advised to swallow the remainder after keeping the tablets under the tongue for about 30minutes.They would then be discharged on analgesics and antibiotics.

In both arms, the telephone contacts of the participants were taken and they were given contacts of the study staff in order to call in case of any complications.

The study participants would be asked to come back for follow up seven days after the initial treatment and during this visit they would be reviewed by history and physical examination for the completeness of the procedure i.e. absence of lower abdominal pains and active par vaginal bleeding and on examination, finding a closed cervical os..

If during the follow up visit the abortion was found to be complete, the woman would be released from the study and if it was found to be incomplete, they would be given the option of immediate surgical evacuation or repeat dose of misoprostol and further follow up after one week.

The one week follow up was very crucial in this study and the following measures were put in place to ensure high follow up rate:

1. Eligibility criteria included only those participants who were willing to come for follow up.
2. Patients coming from outside the geographical area of the hospitals coverage were excluded from the study.
3. Intensive counseling was done to the study participants.
4. Transport cost was reimbursed at a flat rate of KSH 200 during the one week follow up visit. The participants were informed about this.
5. The telephone numbers of the study participants or close relatives were taken in order to remind them of the return date.

STUDY OUTCOMES

The primary outcome was achievement of complete uterine evacuation following initial treatment (either misoprostol or MVA).

Other outcomes were:

Incidence of adverse events assessed by observation after administration of misoprostol or conducting MVA and at the exit interview. These included:

1. Intensity of pain. A visual analogue scale in which 7 circles ranging in size from small(no pain) to large(intense pain) were used to measure pain level.(18)

2. Amount of bleeding.
3. Presence of infection at follow up visit –assessed clinically.
4. Any other complication

DATA MANAGEMENT AND PROCESSING

Data was collected using coded entry data forms. The study forms were completed by the staff at the study site and reviewed by the principal investigator for completeness and data quality.

Data analysis was done using the Statistical Package for the Social Sciences, Version 12(SPSS 12).

Chi-square tests were used to analyze categorical data and t tests used for continuous data (also using SPSS).

ETHICAL CONSIDERATION

This was a randomized controlled trial on use of sublingual misoprostol in evacuation of the uterus in incomplete abortion. Whichever method which was used has been found to be safe and effective as established in research done as shown in literature review.

The participants in the misoprostol arm who presented with signs of incomplete abortion during the one week follow up, were offered the option of immediate surgical evacuation or repeat dose of misoprostol.

Approval was sought from KNH Ethics and Research committee and the hospital management boards of CPGH and Port Reitz Hospital.

Informed consent was obtained from the study participants.

The participants were assured of confidentiality and the filled in questionnaires were kept in safe custody by the principal investigator.

Patients who declined participation in the study received the standard care without discrimination.

TIME FRAME

The study was carried out between December 2008 and August 2009.

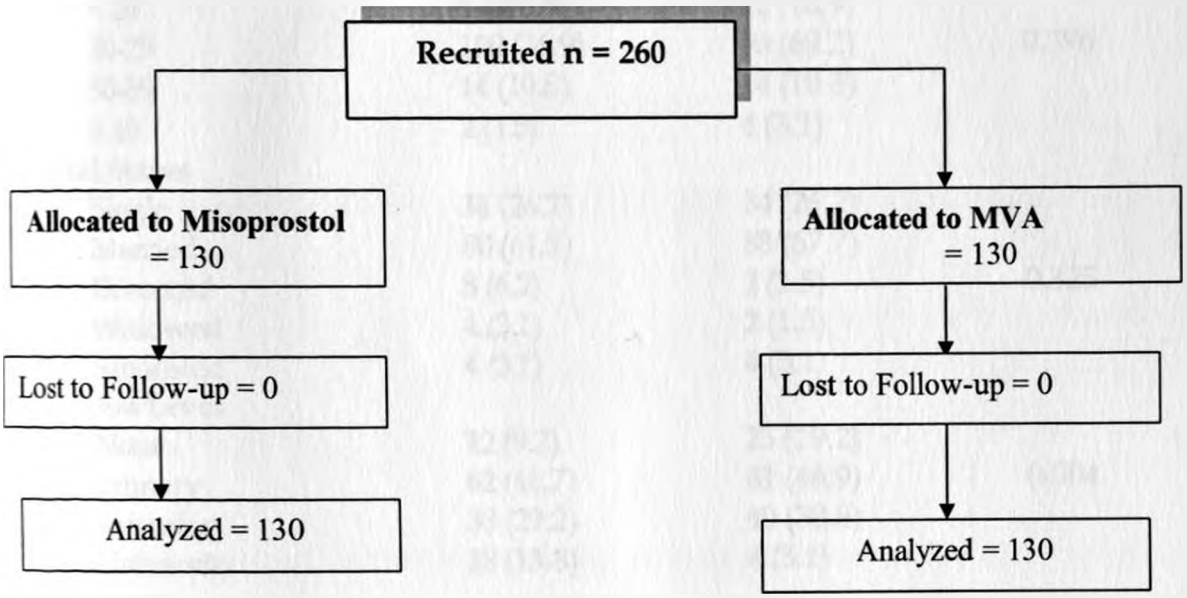
STUDY LIMITATIONS

1. Ultrasound was not routinely used to diagnose incomplete abortion and women with complete abortion with open cervical os may have been included in this study leading to selection bias. However the diagnosis of incomplete abortion is usually clinical and the study was meant to depict what happen in real life situations.
2. Studies have shown 50% success rates with expectant management of incomplete abortion and therefore the one week follow up with misoprostol arm may fall in this category.
3. Recall bias: the one week follow up involved filling questionnaire based on the participants experience and this may have introduced recall bias.

RESULTS

Overall, between December 2008 and August 2009,130 women were randomized to receive sublingual misoprostol and 130 women were randomized into the MVA arm. There was no loss to follow up as shown in the flow chart below.

Flow chart



Participant characteristics

Table 1: Base line characteristics of the study participants

Characteristics	Participants		p-value
	Misoprostol (n=130)	MVA (n=130)	
Age (in years)			
< 20	14 (10.8)	22 (16.9)	
20-29	100 (76.9)	90 (69.2)	0.396
30-39	14 (10.8)	14 (10.8)	
≥ 40	2 (1.5)	4 (3.1)	
Marital Status			
Single	34 (26.2)	34 (26.2)	
Married	80 (61.5)	88 (67.7)	
Divorced	8 (6.2)	2 (1.5)	0.325
Widowed	4 (3.1)	2 (1.5)	
Separated	4 (3.1)	4 (3.1)	
Education Level			
None	12 (9.2)	25 (19.2)	
primary	62 (41.7)	61 (46.9)	0.004
secondary	38 (29.2)	40 (30.8)	
University	18 (13.8)	4 (3.1)	
Occupation			
Student	8 (6.2)	4 (3.1)	
H/wife	62 (47.7)	88 (67.7)	
S/employed	40 (30.8)	14 (10.8)	0.001
Civil servant	6 (4.6)	8 (6.2)	
Other	14(10.8)	16(12.3)	
Parity			
< 2	24 (18.5)	18 (13.8)	
2-4	88 (67.7)	90 (69.2)	0.527
> 4	18 (13.8)	22 (16.9)	
Gestation			
Up to 8 weeks	21 (16.2)	16 (12.3)	0.375
More than 8 weeks	109 (83.8)	114 (87.7)	

Table 1 shows that there was no statistically significance difference in the mean age and the marital status between the two treatment arms. Most participants were aged 20-29 years (73%) and most were married (65%). Most study participants had primary level of education (47%) and most of them were housewives (50%). The mean parity was 3.0 and 3.3 for misoprostol and MVA arm respectively and the mean gestational age was 9.4 for misoprostol and 9.9 for MVA group. In these two parameters, there was no statistically significant difference between the two treatment arms. In general, table one show that the two treatment arms were comparable in most baseline characteristics.

Table 2: **Efficacy of the Method of Evacuation Used by study site**

	Method		
Efficacy	Misoprostol (N=130)	MVA (N=130)	p-value
All sites	122 (93.8%)	130 (100.0%)	***0.012***
Site			
1	60 (92.3%)	65 (100.0%)	0.846
2	62 (95.3%)	65 (100.0%)	0.949

Table 2 shows that the success rates for the misoprostol and MVA arm were high at 93.8% and 100% respectively. While this difference is statistically significant (p value=0.012), there does not appear to be a clinically significant difference between the two treatment arms. MVA was 100% successful in the two study sites while misoprostol was 92.3% successful in site 1 and 95.3% in site2.

Eight (8) women had incomplete abortion during week one follow up and 6 of them preferred immediate surgical evacuation while one woman in the misoprostol arm was diagnosed with septic abortion .She was admitted, started on intravenous antibiotics and evacuated and soon after discharged in a stable condition. One participant presented with heavy bleeding at the one week follow up with signs of moderate anemia. The study doctor performed surgical evacuation and was discharged with oral haematinics and antibiotics.

EXPERIENCE WITH SIDE EFECTS

Table 3: Pain Score by Method of Evacuation Used

Pain score	Method		p-value
	Misoprostol (N=130)	MVA (N=130)	
1	2 (1.5%)	0	
2	77 (59.2%)	5 (3.8%)	
3	33 (25.4%)	2 (1.5%)	
4	16 (12.3%)	6 (4.6%)	***<0.001***
5	0	23 (17.7%)	
6	2 (1.5%)	86 (66.2%)	
7	0	8 (6.2%)	

At the follow up visit, all women were asked to give their individual assessments of the worst amount of pain experienced during and after the treatment .The pain level was measured with a seven -point likert scale; a visual analogue scale which was developed by the study team containing seven circles of increasing size with the smallest circle representing no pain and the largest circle representing the worst pain imaginable. They were asked to indicate by putting a mark on the pain scoring scale.

Table 3 shows that women randomized to MVA reported a significantly higher pain score compared those in the misoprostol arm (p=<0.001).

Figure 2: Pain Score (N = 260)

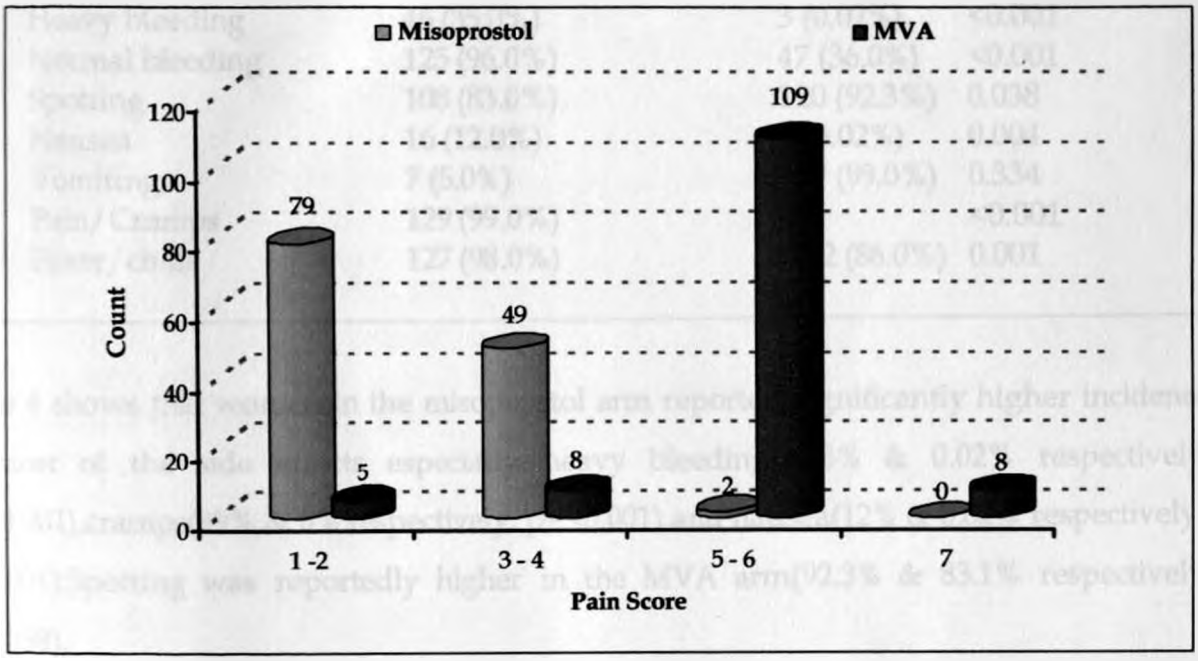


Table 4: **Reported Side Effects by Method of evacuation used**

Side effects	Method		p-value
	Misoprostol (N=130)	MVA (N=130)	
Heavy bleeding	46 (35.0%)	3 (0.02%)	<0.001
Normal bleeding	125 (96.0%)	47 (36.0%)	<0.001
Spotting	108 (83.0%)	120 (92.3%)	0.038
Nausea	16 (12.0%)	3 (0.02%)	0.004
Vomiting	7 (5.0%)	129 (99.0%)	0.334
Pain/Cramps	129 (99.0%)	0	<0.001
Fever/chills	127 (98.0%)	112 (86.0%)	0.001

Table 4 shows that women in the misoprostol arm reported significantly higher incidence of most of the side effects especially heavy bleeding(35.3% & 0.02% respectively, p=<0.001),cramps(99% & 0% respectively, p=<0.001) and nausea(12% & 0.02% respectively , p=0.004).Spotting was reportedly higher in the MVA arm(92.3% & 83.1% respectively, p=0.038).

ACCEPTABILITY AND SATISFACTION

Table 5: Acceptability and satisfaction by Method of evacuation Used

	Method		
	Misoprostol (N=130)	MVA (N=130)	p-value
Acceptability of side effects			
No side effect	12 (9.2%)	8 (6.2%)	
Easily Tolerable	93 (70.8%)	13 (10.0%)	
Effects Tolerable	22 (16.9%)	99 (76.2)	<0.001
Bad	4 (3.1%)	10 (7.7%)	
Satisfaction			
Very Satisfied	69 (53.1%)	8 (6.2%)	
Satisfied	57 (43.8%)	95 (73.1%)	<0.001
Unsatisfied	4 (3.1%)	24 (18.5%)	
Would choose the method again			
Yes	114 (87.7%)	30 (23.1%)	<0.001
No	16 (12.3%)	100 (76.9%)	
Would recommend the method			
Yes	118 (90.8%)	32 (24.6%)	<0.001
No	12 (9.2%)	98 (75.4%)	

Table 5 shows that although the women in the misoprostol arm experienced a greater number of side effects than the MVA arm, they were more likely to report these side effects as easily tolerable (70.8% & 10% respectively, p<0.001).Women in the misoprostol arm were almost eight times more likely to be very satisfied with the treatment as compared with the MVA arm (53.1% & 6.2% respectively, p<0.001). 87.7% of the participants in the misoprostol arm would choose the method again compared to 23.1% in the MVA arm which is statistically significant (p<0.001).More than 90% in the misoprostol arm indicated that they would recommend the method to a friend (misoprostol=90.8%, MVA=24.6, p<0.001).

DISCUSSION

This study shows that although MVA is significantly more effective than sublingual misoprostol in management of incomplete abortion (100% & 93.8% respectively, p=0.012), it has a role in management of incomplete abortion especially in resource poor settings where MVA skills may be lacking. The 100% success rate for MVA can be attributed to the Ministry of Health policy of training health care providers up to the level of nurses on how to perform MVA and there are adequate resources for training and retraining in most health institutions. One major advantage of MVA is that it is quicker and the provider is able to remove the products of conception from their attachment. Misoprostol on the other hand stimulate the myometrium to contract and expel the products of conception which takes longer. Biochemical mechanism of misoprostol in uterine evacuation cannot be ruled out and this is an area that requires more research and ascertainment. The high success rate in the misoprostol arm is in consistent with other studies using 600μg of misoprostol (Chung et al 1995;Shwerkerela et al 2007; Clark et al 2007; Rizi et al 2006).In a study done in Uganda (Weeks trial);misoprostol was found to be effective in 96.3% of the cases with no serious adverse effects reported. There are other studies done in Tanzania, Bukina Fasso and Mozambique which shows that misoprostol is highly effective. This shows that misoprostol can be offered in a sub-Saharan hospital setting.

The study confirms misoprostol's strong safety profile with only 2 users presenting with unexpected adverse effects i.e. septic abortion and severe hemorrhage. Although women in the Misoprostol arm experienced more adverse effects, they did not find these adverse effects difficult to tolerate perhaps because, in comparison with the women in the MVA arm, they experienced lower levels of pain. Side effects such as bleeding, abdominal cramps and nausea are all known and expected side effects of misoprostol and women should be counseled about them. These side effects such as bleeding and abdominal cramps are the mechanism of action of misoprostol as compared to MVA where the clinician aspirates the products of conception. The side effects are usually transient and rarely require treatment.

One more success story about this study is the 100% follow up rates. In comparison a study done in Uganda in which one third of the women in the misoprostol arm did not return for their next scheduled visit while one done in Tanzania had no loss to follow up. The high follow up rate can be attributed to the strict eligibility criteria followed, proper counseling,

use of mobile phone to remind the participants of the return date and the reimbursement of bus fare on the date of follow up.

In this study, a higher proportion of women reported heavy bleeding in comparison to other studies using 600µg of oral misoprostol. New evidence which came up after this protocol was developed, indicate that a lower dose of 400µg is recommended when sublingual route of administration is used and this can explain the higher proportion of heavy bleeding reported in this study.

This study shows a higher pain score in the MVA arm compared to the pain score in similar studies. This can be attributed to lack of proper guidelines in pain management during MVA procedure at the two hospitals .Improvement of pain management e.g. Para cervical block can improve on satisfaction and acceptability of MVA in management of incomplete abortion.

In this study, a higher percentage reported being very satisfied and satisfied with misopostol (96.9%) and 90.8% indicated that they would recommend the method to a friend. These figures are similar to those reported in other studies (Shwekerela, 2007; Dao, 2007; Weeks, 2005; Bique, 2007).

CONCLUSION

1. Sublingual misoprostol is nearly as effective as MVA in treatment of incomplete abortion.
2. Sublingual misoprostol is an acceptable method of treating incomplete abortion.
3. Sublingual misoprostol is a safe and simple method of treating women with incomplete abortion.

RECOMMENDATIONS

1) With minimal training, primary health care facilities who are less equipped with personnel and equipment to perform MVA could potentially treat women with incomplete abortions using misoprostol.
2) Larger local studies using a smaller dose of sublingual misoprostol (400µg) should be carried out.
3) Misoprostol should be included in Kenya National Essential Drug list to make it widely available for comprehensive abortion care (CAC) programs.
4) The findings of this study together with others should be used to influence health care policy by promoting misoprostol as a simple, feasible alternative to MVA in managing patients with incomplete abortion.

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Appendix 1: PATIENT INFORMATION AND CONSENT FORM.

The study is -The use of misoprostol in evacuation of uterus in incomplete abortion.

Study investigator-Dr Igogo Peter.K. M.Med student dept of Obs/Gyn University of Nairobi. Cell phone number-0721410870

Supervisors 1.Prof Karanja J.G cell phone number 0722513881

2.Dr Tamooh S.H Cell phone number 0722752143

Ethical committee chairperson (KNH)-Prof K.M.Bhatt TEL-0202726300

RESEARCH STATEMENTS

The purpose of this consent form is to give you information about the study. The information will help you to decide whether to be in the study or not. Please read the form carefully you may ask questions about the purpose of the research, what we would ask you to do, the possible risks and benefits, your rights as a volunteer and anything else about the research or this form that is not clear. When we have answered all of your questions, you can decide if you want to be in the study or not. This process is called **informed consent**. If you wish we will give you a copy of this form for your records.

PURPOSE, BENEFITS AND POSSIBLE RISKS

We are conducting a study to test a new alternative method to treat incomplete abortion. The standard treatment has been surgical evacuation we call MVA. The alternative method involves use of 3 tablets that you will place below the tongue. Each woman will be assigned to one of the methods by chance meaning that you cannot decide the method you want nor will the doctor decide the method you will be in the study. The study doctor will ask you questions related to your presenting condition then conduct examination you including pelvic examination.

If you are assigned to the surgical evacuation method, you will receive the standard care at this hospital. The procedure is usually short but may uncomfortable. You may experience pain /cramps during the procedure which is usually transient. Thereafter you may experience bleeding from birth canal similar to menses for a few days up to one week. You will be given pain killers and antibiotics to prevent any infection after the procedure. You will be required to come to the hospital after one week for review. You can call the telephone numbers provided or come to the hospital any time you experience complications even before the return date. This procedure is successful in approximately 98% to 100%.The procedure will prevent you from excessive bleeding and other complications related to abortion like infection and chronic pelvic pain.

If you are assigned to the non surgical method, you be required to take 3 pills below the tongue in the hospital. You will be observed at the hospital for a short time. You may experience nausea, vomiting or diarrhea after taking the pill but this will be mild and transient. When you go home, you will experience slightly heavy bleeding similar to heavy menses and abdominal clamps/pain similar to painful periods. You may also experience fever and chills which are related to the pills and will soon go away. You will be required to come back to the hospital for review after one week. If after one week the procedure is incomplete we will offer you an alternative between repeat dose of the pill or immediate surgical evacuation. You may call the telephone numbers provided or visit the hospital any time you experience complication. The benefits of this method of treatment are:

1. The success rates are 66- 99% according to similar studies which are comparable to the surgical evacuation.
2. You will avoid surgery.

3. The study will help us come up with an alternative method of treating incomplete abortion which is safe, effective and affordable.

Your name will not appear anywhere in the study documents .The information you provide Will be kept in strict confidence and will only be accessible by the study staff. Your Participation in this study is voluntary and you will not be denied standard care at this Hospital if you decline participation."

Signature of the investigator.....date.....

PARTICIPANTS STATEMENTS

I voluntarily agree to participate in the study on the use of misoprostol in the evacuation Of the uterus in incomplete abortion.

I have been informed that the information obtained will be treated with outmost of confidentiality and my treatment will not be compromised if I decline participation or withdrawal from the study.

I have had a chance to ask questions and if I have questions later I can ask the researcher. If I have questions about my rights as a research participant, I can call the ethical review committee at Kenyatta National Hospital on telephone number 020726300.

Signature of the participant.....date.....

HABARI KWA MGONJWA NA CHETI CHA KUKUBALI KUSHIRIKI KATIKA

UTAFITI

Huu ni utafiti wa matumizi ya dawa, misoprostol kwa wamama ambao wamevunja mamba

Mtafiti mkuu ni Dr Igogo P.K,daktari na mwanafunzi wa maswala yanayohusu uzazi,chuo kikuu cha Nairobi.Nambari ya simu :0721410870

Mwenyekiti wa kamati ya utafiti KNH-Prof K.M.Bhatt nambari ya simu -0202726300

MAELEZO YA UTAFITI

Maana kuu ya hii cheti cha kukubali ni kukupasa wewe mshirika habari kuhusu huu utafiti.Haya maelezo yatakuwezesha kuamua kama utakubali kushiriki au la.Tafadhari yasome maelezo haya kwa utaratibu.Unaweza kuuliza maswali kuhusu maana ya huu utafiti,yale mambo tutakayo kwambia ufanye,faida na adhari kwako,haki zako na jambo lingine lote ungetaka kujua juu ya huu utafiti.Wakati ambapo tumejibu maswali yako yote,utaamua kushiriki kwenye utafiti ama la.Tunaweza kukupatia nakara ya cheti hii kama ungependa.

SABABU NA NA MANUFAAYA HUU UTAFITI

Sababu hasa ya kufanya huu utafiti ni kuchunguza matumishi ya dawa, misoprotol kwa wamama ambao wamevunja mimba.Tutalinganisha dawa hii na njia inayotumika sasa ambayo ni kusafisha kizazi kwa wamama ambao wamevunja mimba ya miezi mitatu ama chini yake.Hii dawa kulingana na utafiti iliofanywa,imedhibitishwa kuwatibu hawa wamama na tena kwa sababu bei yake iko chini,inapatikana kwa urahisi,ni rahisi kutumia,inafaa sana huku kwetu ambako tuna raslimali kidogo.Utakuwa kwa moja wapo

wa njia hizi pili kwa bahati na sibu na daktari hatakuchagulia njia ya matibabu.Ikiwa utakuwa kwa njia ya kusafishwa,unaweza kusikia uchungu lakini itaisha punde tu utakapomalisiwa.Baadaye utapewa madawa ya uchungu nay a kuzuia maradhi.Ikiwa utakuwa kwa njia ya kutumia tembe,utapewa ndawa uweke chini ya ulimi kisha ukae kidogo kwenye hospitali ukiangaliwa.Baada ya kutumia madawa unaweza kusikia kutapika,njoto kwa mwili au maumivu ya tumbo ambayo itaisha muda mfupi baadaye.Utavunja ndamu zaidi kidogo ya zile za hedhi.Ikiwa una shida ingine yeyote unaweza kutupigia simu ama ututembelee hospitali wakati wowote.Kwa njia sote mbili, utatakiwa kurundi hospitalini baada ya siku saba kuonekana vile unaendelea.Habari tutazopata kwako tutaziweka siri na hakuna mutu mwingine atajurishwa.Habari hii itawekwa kwa faili yako ya kutibiwa.Jina lako halitatumika utafiti huu utakapochapishwa.

Sahihi ya mtafiti.....tarehe.....

CHETI CHA KUKUBALI KUSHIRIKI KWENYE UTAFITI

Mimi ninakubali kushiriki katika utafiti wa matumizi ya dawa, misoprostol kwa wamama ambao wamevunja mamba.

Nimeelezwa kwamba habari zangu zitawekwa siri naya kwamba matibabu yangu hayataadhiriwa kama nitakataa kushiriki ama nitajiondoa kwenye utafiti.

Nimekuwa na nafasi ya kuuliza maswali na kama nina maswali mengine,ninaweza kuuliza watafiti wakati wowote.

Sahihi ya mshiriki.....tarehe

Appendix 2: Study Questionnaire

USE OF MISOPROSTOL IN EVACUATION OF THE UTERUS IN INCOMPLETE ABORTION

PART ONE

A-IDENTIFICATION

1-Serial number ( )

2-Registration number ( )

B-SOCIAL DEMOGRAPHIC DATA

1-Age in completed years ( )

2-Marital status:

1=single 2=married 3=divorced 4=widowed 5=separated

3-Highest level of education:

1=none 2=primary school 3=secondary school 4=university/college

4-Occupation:

1=student 2=house wife 3=self employed 4=civil servant 5=others

C-OBSTETRIC/GYNAECOLOGICAL HISTORY

1-Parity ( )

2-Gravidity ( )

3-Gestation (complete weeks) ----------

4-History of previous abortion:

1=yes 2=no

D CLINICAL SIGNS (before the procedure)

1-Temperature>37 degree celcius:

1=yes 2=no

2-Pulse rate:

1=<60 beats per minute

2=60-100 beats per minute

3>100 beats per minute

3- Lower abdominal tenderness:

1=yes 2=no

4-Fowl smelling par vaginal discharge:

1=yes 2=no

E ELIGIBILITY CHECK LIST

1 open cervical os or past/present history of vaginal bleeding

1=yes 2=no

2Uterine size equals or less than 12 weeks

1=yes 2=no

3Willing to come for the follow up visit

1=yes 2=no

4 known medical contraindication to misoprostol or prostaglandins

1=yes 2=no

F. ELLIGIBILITY AND METHOD SELECTION

1. Is the client eligible for treatment 1=yes 2=no
2. Has she given informed consent 1=yes 2=no
3. Treatment arm 1=misoprostol 2=MVA

PART TWO

G-EFFICACY AND SIDE EFFECTS

1-Loss to follow up:
1=yes 2=no

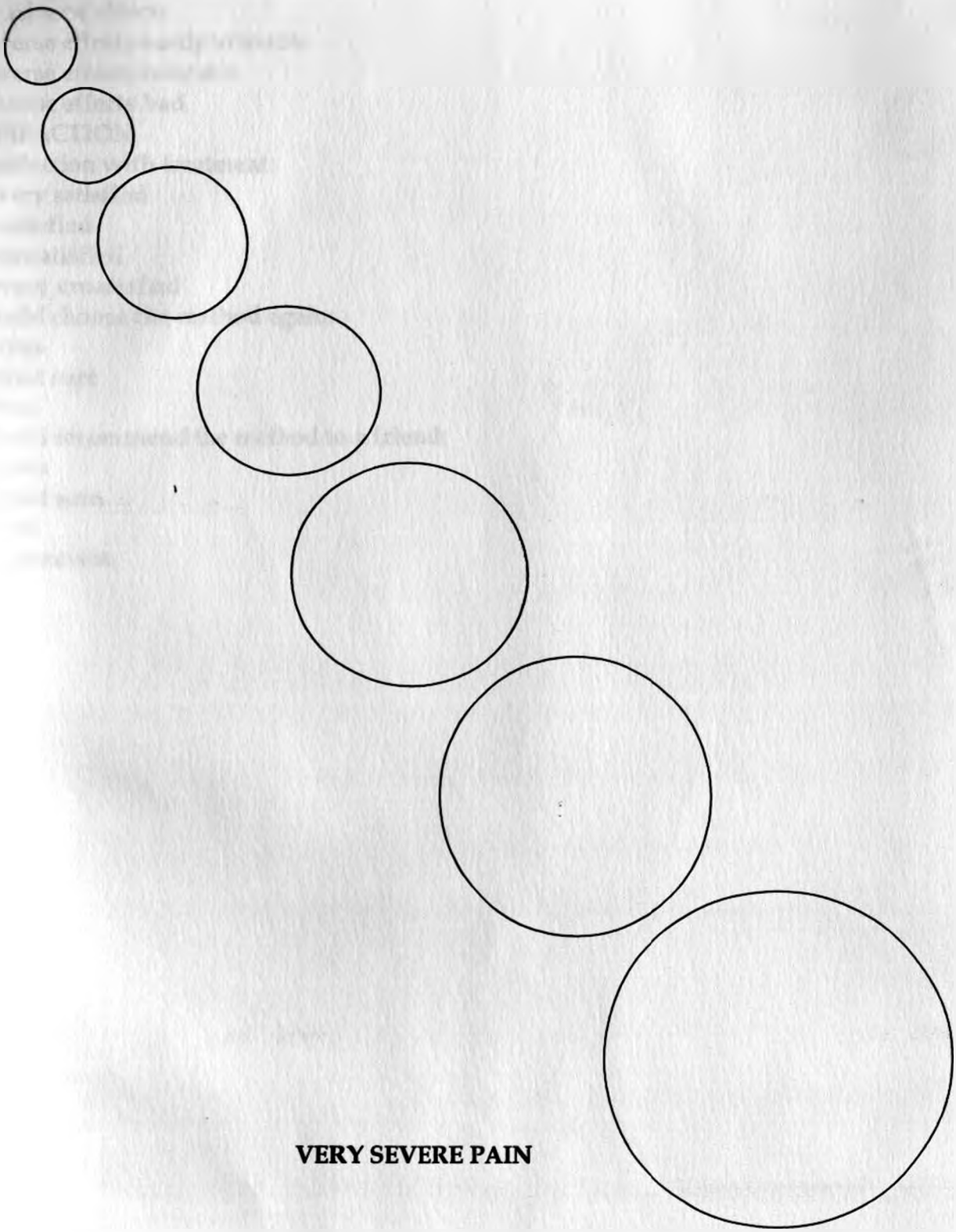
2-Succesful uterine evacuation :(from history and physical examination)
1=yes 2=no

3-Type of failure:
1=medically necessary after initial treatment
2=patient prefer immediate MVA
3=clinician prefer immediate MVA

4-Side effects reported (multiple entries are possible)
1=heavy bleeding(>menses)
2=normal bleeding(=menses)
3=spotting(<menses)
4=nausea
5=vomiting
6=pain/cramps
7=fever/chills
8=others

5-Pain score (ask the patient to place a mark on one of the circles below which correspond to the maximum level of pain which she associates with the treatment given)

NO PAIN



VERY SEVERE PAIN

H -TOLERABILITY OF SIDE EFFECTS:

1=no adverse effects

2=adverse effects easily tolerable

3=adverse effects tolerable

4=adverse effects bad

G-SATISFACTION

1-Satisfaction with treatment:

1=very satisfied

2=satisfied

3=unsatisfied

4=very unsatisfied

2-Would choose the method again:

1=yes

2=not sure

3=no

3-Would recommend the method to a friend:

1=yes

2=not sure

3=no

H-Any comment:

Appendix 3: Letter of Approval

KENYATTA NATIONAL HOSPITAL
Hospital Rd. along, Ngong Rd.
P.O. Box 20723, Nairobi.
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP", Nairobi
Email: KNHplan@Ken.Healthnet.org

Ref: KNH/UON-ERC/ A/115

12th November 2008

Dr. Igogo P. K.
Dept. of Obs/Gynae
School of Medicine
University of Nairobi

Dear Dr. Igogo

Research Proposal: "Use of Misoprostol in Evaluation of the Uterus in incomplete abortion" (P106/05/2008)

This is to inform you that the Kenyatta National Hospital Ethics and Research Committee has reviewed and **approved** your above revised research proposal for the period 12th November 2008 –11th November 2009.

You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given. Clearance for export of biological specimen must also be obtained from KNH-ERC for each batch.

On behalf of the Committee, I wish you fruitful research and look forward to receiving a summary of the research findings upon completion of the study.

This information will form part of database that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Yours sincerely

PROF. A N GUANTAI
SECRETARY, KNH/UON-ERC

c.c. Prof. K.M. Bhatt, Chairperson, KNH-ERC
The Deputy Director CS, KNH
The Dean, School of Medicine, UON
The Chairman, Dept. of Obs/Gynae, UON
Supervisors: Dr. Prof. J. G. Karanja, Dept.of Obs/Gynae, UON
Dr. H. Tamooh, Dept.of Ob/sGynae, UON