Safety and efficacy of oral misoprostol for the induction of labor in Papua New Guinean women: low dose regimen versus standard treatment regimen

STUDENT

John Bolnga, *MBBS, DipOG, MMed (OG),A.MRANZCOG*

Consultant Obstetrician and Gynaecologist, Modilon Hospital, Madang

SUPERVISORS

Moses Laman, *BMSc, MBBS, DCH, MMSc, PhD*

Senior Clinical Research Fellow, PNGIMR, Madang

Glen Mola, *MBBS, DipPH, FRANZCOG,FRCOG, OL,CSM*

Professor of Obstetrics and Gynaecology, UPNG, Port Moresby

Safety and efficacy of oral misoprostol for the induction of labor in Papua New Guinean women: low dose regimen versus standard treatment regimen

By

John W Bolnga

Submitted as a requirement to enroll in the Medical Doctorate Degree at the School of Medicine and Health Sciences, University of Papua New Guinea

Contents

BACKGROUND AND BRIEF LITERATURE REVIEW

Induction of labour (IOL) refers to stimulation of contraction before the spontaneous onset of labour to bring an end to pregnancy when the benefits of giving birth at that time outweigh the risks of the induction process [1]. Labour induction is one of the most frequent medical procedures in pregnant women. It is a major intervention in the normal course of pregnancy with the potential to set in motion a cascade of events, leading to delivery of the baby. Some of the indications for IOL include: post-term pregnancy, ruptured membranes with chorioamnionitis, severe pre-eclampsia, pre-labour rupture of membranes without labour, gestational hypertension, non-reassuring fetal status and various other maternal medical conditions such as hypertension and diabetes [1].

In developing countries like Papua New Guinea (PNG) where maternal and perinatal mortality and morbidity remains high [2],coupled with limited capacity to maintain effective monitoring, prolonging pregnancy in the face of impending complications can result in severe adverse outcomes for both the mother and her baby. It is therefore imperative that IOL forms an essential part of obstetrics care and management in PNG.

The techniques available to induce labour have changed overtime. Current regimes using intravenous oxytocin and prostaglandins have been shown to be effective in inducing labour [3]. Whilst Dinoprostone, a prostaglandin E2 agent, is widely used in industrialized countries and approved by the Food and Drug Administration (FDA)[4], its high cost and instability at room temperature limits its usefulness as a cost-effective agent particularly in developing countries. Furthermore, oxytocin used alone without priming and ripening of the cervix has been increasingly associated with failed IOL and high rates of caesarian section [5]. On the other

hand, misoprostol, a prostaglandin E2 analogue has gained much popularity in the last decade in many developing countries including PNG, as an effective IOL agent. Compared to other prostaglandins, misoprostol has several potential advantages. It is stable at room temperature, inexpensive and can be given via several routes (oral, vaginal, sublingual and buccal).

It is possible that the oral route of administration of misoprostol reduces the risk of severe adverse events such as uterine hyperstimulation and rupture compared to other routes of administration such as the vaginal route. However, currently there is not enough evidence to prove this possibility because of the high rates of heterogenicity between studies comparing the vaginal and oral routes of misoprostol administration [1]. Although a lot of studies comparing the vaginal and oral misoprostol routes of administering misoprostol have been conducted [1, 6], there is still a need for more intervention trials comparing various dose regimens of oral misoprostol. Additionally, there is still a lack of data globally from randomized controlled trials to determine the best dose to ensure optimal safety and efficacy of oral misoprostol [1, 6-8].

In view of these, in the present study, we aim to investigate the safety and efficacy of two different regimens of oral misoprostol as part of a randomized controlled trial at Modilon Hospital in Madang Province.

AIMS AND HYPOTHESIS

General aim

To conduct a 2-year open label randomized control trial to determine the safety and efficacy of two different dose regimens of oral misoprostol in inducing labour in Papua New Guinean women in their third trimester of pregnancy.

Specific aims

- To compare the safety and efficacy profiles of low dose titrated oral misoprostol commencing at 12mcg at baseline compared to a standard treatment regimen commencing at 25mcg.
- To determine maternal labour outcomes in women who undergo IOL with low dose compared to the standard treatment regimen by documenting the proportion of adverse and severe adverse events that may occur.
- To determine perinatal outcomes in the babies of women who undergo IOL with low dose compared to standard dose by documenting the proportion of adverse and severe adverse events that may occur.

Hypothesis

Misoprostol has the potential to cause dose dependent adverse effects such as uterine hyperstimulation and rupture that may lead to adverse and/or severe adverse labour outcomes. Therefore, the ideal oral misoprostol IOL regimen should be one that utilises a low dose. In the present study, we hypothesis that a regimen commencing with a lower dose of oral misoprostol administered at 12mcg per dose and

gradually increased to a maximum of 50mcg per dose over 24 hours will have a non-inferior efficacy and safety profile in inducing labour compared to a regimen that is administered at 25mcg per dose at baseline and gradually increased to a maximum of 50mcg per dose within 24 hours.

METHODS

Study Site

Modilon General Hospital is an established provincial hospital that has well over 3000 deliveries in a year and has an average induction rate of 3-5%. It has an obstetrician, registrars and midwives to assist with the study. It has an operating theater facility that can be used to perform emergency caesarian sections and/or any other operative procedures that may be required to manage patients undergoing IOL.

Study design

The present study will be an open-label randomized controlled trial. Based on computer-generated block randomization, eligible patients will be allocated 1:1 to the standard treatment group (see Figure 1) or to the low dose oral misoprostol group (Figure 2). Allocated treatments will be concealed in sealed numbered envelopes which will be opened in sequence by study medical or nursing staff and the specified treatment administered.

Oral misoprostol protocol

A solution of 1mcg/ml is made by dissolving 1 tablet (200mcg) of misoprostol in 200mls of tap water. The solution will be measured and given in titrated doses as per the two different protocol requirements. The misoprostol solution will be kept at the nurse's station at room temperature

and discarded if not completed within 24hrs. Each dose, either commencing 12mls (12mcg/ml) or 25mls (25mcg/ml) will be given at an interval of 2 hours and doses incremented accordingly in the two different arms as outlined in Figures 1 and 2. This is in accordance with WHO recommendations of time-interval between each oral misoprostol dose [9].

Standard Treatment Arm

- 25mls(25mcg) every 2 hours for 4 doses - 100mls (100mcg) in 8 hours then
- 50mls(50mcg) every 2 hours for 4 doses - 200mls (200mcg) in 8 hours then
- 50mls(50mcg) every 2 hours for 4 doses - 200mls (200mcg) in 8 hours

Total = 500mls (500mcg) in 24 hours

- If no progression in the first cycle, rest for 24 hours, then repeat 50mcg(50mls) every 2 hours for 8 doses =400mls(400mcg) in 16 hours.
- If no progression in the second cycle, participants will further undergo Foley's catheterization with the intention to treat as shown in figure 1, while those that are already in labour but needing assistance with contractions may undergo augmentation with oxytocin.

Intervention Arm

- 12mls (12mcg) every 2 hours for 4 doses - 48mls (48mcg) in 8 hours then
- 25mls (25mcg) every 2 hours for 4 doses - 100mls (100mcg) in 8 hours then
- 50mls (50mcg) every 2 hours for 4 doses - 200mls (200mcg) in 8 hours

Total = 348mls (348mcg) in 24 hours

- If no progression of labour, rest for 24 hours, then

  Repeat 50mls (50mcg) every 2 hours for 4 doses =200mls(200mcg) in 8 hours

  Repeat 50mls (50mcg) every 2 hours for 4 doses =200mls(200mcg) in 8 hours

  Total = 400mls (400mcg) in 16 hours

- If no progression in the second cycle, participants will further undergo Foley's catheterization with the intention to treat as shown in Figure 2 while those that are already in labour but needing assistance with contractions may undergo augmentation with oxytocin.

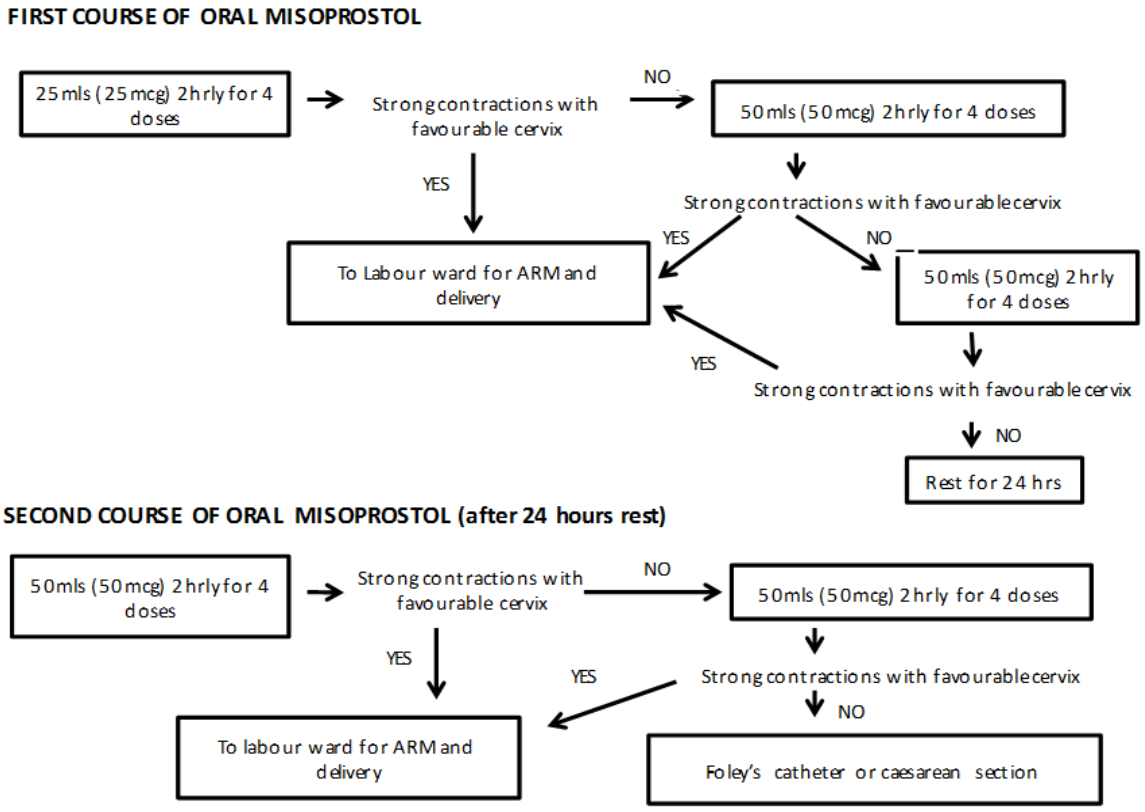

Figure 1: Standard Treatment Protocol for oral misoprostol induction of labour at Modilon Hospital.

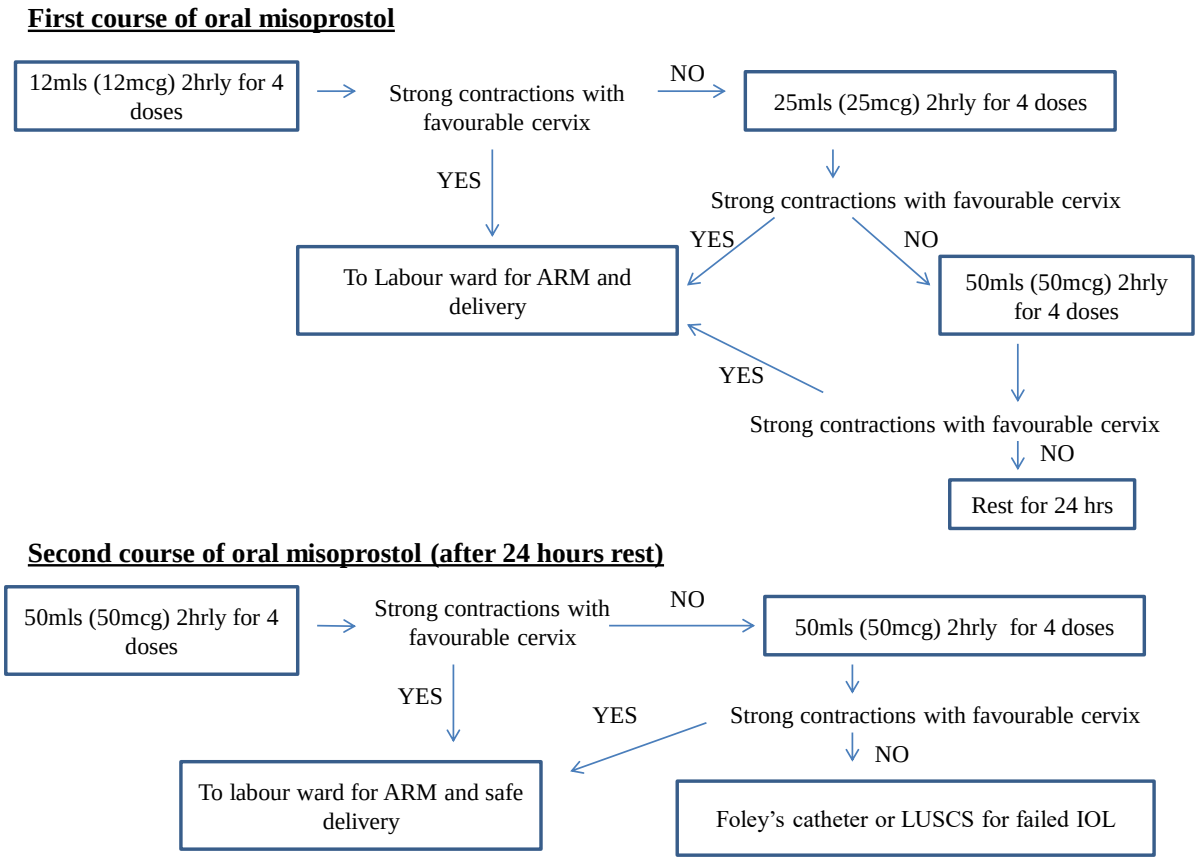

Figure 2: Intervention arm for oral misoprostol induction of labour at Modilon Hospital

Primary endpoint

The primary outcome measured would be the proportion of women who have a successful live vaginal delivery without any severe adverse event including: i) failed induction necessitating cesarean section, ii) maternal death, iii) retained placenta, iv) perinatal death, and/or v) neonatal admission to special care nursery.

Secondary endpoints

Secondary endpoints measured will include the proportion of successful live births delivered vaginally i) within 24 hours, ii) the proportion of mothers requiring Foley's catheterization, iii) the proportion of mothers requiring oxytocin augmentation, iv) Neonatal Apgar scores ≤7 at 5 minutes post-delivery, and v) reported maternal and neonatal adverse events at 4 weeks post-discharge.

Inclusion and Exclusion Criteria

All women who deliver at Modilon Hospital must fulfill the following study criteria prior to enrollment:

- Third trimester singleton pregnancies in women over 18 years old
- Bishops score of less than 6
- Cephalic presentation
- Hemoglobin concentration of more than 10g/dL
- Signed written informed consent

Women excluded will include:

- Twin or multiple pregnancies
- Women under 18 years old
- Unstable or abnormal lie

- Previous caesarian section
- Any high risk mothers needing immediate caesarian section

Clinical procedures

As per our labour induction study protocol, all women will be thoroughly screened to ensure those enrolled fulfill the above mentioned criteria. Baseline clinical data (including sociodemographic information, past obstetrics particulars, BMI) as well as laboratory data will be collected for all women. Haemoglobin will be measured using the coulter counter analyzer (ACT. Diff PAK, Beckman's coulter). Hepatorenal function investigations will be performed if indicated. Urinalysis and baseline glucose investigations will also be performed.

Patient follow-up

All women who participate in this trial will be asked to return at 4 weeks post-discharge. At this time, general puperum care will be arranged for the study participants and their babies. All adverse events or complications will be documented and treated accordingly. The participants' acceptability and satisfaction level considering their involvement in the trial will also be evaluated.

SAFETY MONITIORING AND QUALITY ASSUARANCE

Interim analysis

We will perform an interim analysis after the first 30 participants in each arm have been

enrolled. This analysis will be examined by the Data and Safety Monitoring Committee comprising of: Prof Francis Hombhanje (Director of Health Research, Divine Word University), Dr Frank Kapipi (independent onsite Obstetrician, Modilon Hospital), Prof John Vince (UPNG, Paediatrician), Dr Leanne Robinson (PNGIMR, Head of Vector Borne Unit), and Dr Stephan Karl (WEHI, Melbourne – scientist and statistician).

This committee will review the results of the interim analysis and decide on the progress of the study. The three criteria to be used will include **i)** drug related adverse events >25% documented within 72 hours post-administration of treatment, **ii)** severe adverse events >10% documented within 72 hours post-administration of treatment, and/or **iii)** >25% adverse events reported at 4 weeks post-discharge.

The second interim analysis will be performed after 80 patients in each arm of the trial have been enrolled. All study protocols will be adhered to at all times and any deviation to the study protocols will not be administered without appropriate ethical approval.

SAMPLE SIZE CALCULATION

If there is a true difference in favour of the experimental treatment of 5%, then 236 patients (118 per treatment arm) will be required to be 90% sure that the upper limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) will exclude a difference in favour of the standard group of more than 5%.

DATA ANALYSIS PLAN

Per-protocol pre-specified analyses will include study participants with complete delivery data available to compare primary and secondary outcomes by treatment arms. Two-sample comparisons for normally-distributed variables will be performed using the Student's *t*-test, for non-normally distributed variables by Mann Whitney U-test, and for proportions by Fisher's exact test. Safety and tolerability to determine the rate of adverse events will be assessed from the incidence of symptoms/signs during the in-patient period until discharge and at 4 weeks post-discharge using Poisson regression. Unless otherwise stated, all *P*-values will be two-tailed with 0.05 taken as significant.

ETHICAL ISSUES

We have experience in conducting research in this setting [10-12] and do not anticipate that we will be encountering serious ethical issues during the conduct of this study. However, some ethical issues that we may confront include:

- **Age of consent**: Because teenage pregnancy is common in our setting, we will ensure only women over the age of 18 are eligible for inclusion in this study.
- **Written Informed Consent Procedures**: Women who fulfil the selection criteria for induction of labour and are eligible and willing to participate in the trial will be asked to complete formal written informed consent procedures that will include face-to-face discussion with the investigator or designated staff member of the clinical trial team who will then explain key study objectives, procedures, potential risks and benefits in more

detail. This will include a clear explanation that participation in this trial is entirely voluntary, and that withdrawal is possible at any time without having to give a reason.

- **Patients' autonomy**: We are aware of the challenges involved when clinical research is integrated with patient care in resource-limited settings such as ours [13]. However, the study protocol will be adhered to at all times and no deviation to the study protocol will be entertained without proper ethical approval.
- **Patient confidentiality**: Each study participant will be assigned a study code and we will separate the patients name from the information and samples collected. We will be very careful about the information that we collect, ensuring this information is made available only to the doctors or nurses providing patient-care.

CANDIDATURE TIMELINE

The time as proposed by the University of Papua New Guinea By Law No:37 governing the Degree of Doctor of Medicine-Part 2 states that candidates admitting to the degree by presentation of a thesis would be required to complete 3-5 years. Therefore, I would like to complete my MD within 3 years.

During the 3 years of this MD program (2016-2018), I will spend most of the time continuing in my capacity to do clinical work and conduct these studies as part of continued professional education and research. I will spend some time to supervise, coordinate and train the staff about the study protocol and methods on a daily basis.

I hope to complete the proposed study by 2017 and to perform data analysis and write up in 2018. My detailed candidature timeline is proposed below:

2016

- **January** Submit Draft Research Proposal
- **February** Literature Review
- **February** Submit corrected draft Research Proposal to supervisors
- **March** Enrol for MD Program and submit Final Research Proposal
- **March-April** Submit for Ethical Approval from MHEC, MRAC, UPNG SMHS Ethics committee and register the trial
- **April** Commence data collection
- **June** Start Preliminary data entry and continue literature review
- **Augu**st Continue research and data entry
- **September** Perform interim analysis on the first 30 participants (each arm)
- **October** Continue literature research and start writing background of thesis
- **November** Start writing methodology of the thesis
- **December** -Start writing 2016 annual report

2017

- **February** Submit 2016 annual report to UPNG , SMHS post graduate office
- **March** Continue writing thesis background and methodology
- **May** Aim to have recruit 80 participants in each arm and to perform the second interim analysis
- **June** Continue writing methodology of thesis and data entry
- **November** Required number for the study (236 in total) to be completed

- **December** Start writing 2017 Annual Report

2018

- **February** Submit 2017 annual report to UPNG SMHS postgraduate office
- **February** Start preamble of thesis and do data cleansing
- **March** Data analysis and results entry
- **May** Write the Discussion
- **June** Commence collating draft of background, methods, results and discussion and have the first draft of thesis ready for submission to MD supervisors
- **August** Submit first draft of thesis to MD supervisor for correction
- **October** Submit second draft of thesis to MD supervisor for final review
- **November** Submit final draft of MD thesis for examination

ETHICAL APPROVAL

The study will obtain ethical clearance from Modilon General Hospital Ethics Committee (MHEC), UPNG SMHS Ethics committee, Medical Research Advisory committee of Papua New Guinea (MRAC) and the trial will be registered with International Standard Randomized Control Trial(ISRCTN) Registry and attain a RCT number. It will be conducted under Good Clinical Practice guidelines and monitoring and safety evaluation will be performed by an independent Data and Safety Monitoring Committee.

REFERENCES

1. Alfirevic Z, Aflaifel N, Weeks A: **Oral misoprostol for induction of labour**. *The Cochrane database of systematic reviews* 2014, **6**:CD001338.
2. Mola G, Kirby B: **Discrepancies between national maternal mortality data and international estimates: the experience of Papua New Guinea**. *Reproductive health matters* 2013, **21**(42):191-202.
3. Mozurkewich EL, Chilimigras JL, Berman DR, Perni UC, Romero VC, King VJ, Keeton KL: **Methods of induction of labour: a systematic review**. *BMC pregnancy and childbirth* 2011, **11**:84.
4. Dodd JM, Crowther CA, Robinson JS: **Oral misoprostol for induction of labour at term: randomised controlled trial**. *BMJ (Clinical research ed)* 2006, **332**(7540):509-513.
5. Alfirevic Z, Kelly AJ, Dowswell T: **Intravenous oxytocin alone for cervical ripening and induction of labour**. *The Cochrane database of systematic reviews* 2009(4):CD003246.
6. Kundodyiwa TW, Alfirevic Z, Weeks AD: **Low-dose oral misoprostol for induction of labor: a systematic review**. *Obstetrics and gynecology* 2009, **113**(2 Pt 1):374-383.
7. WHO: **WHO Global Survey on Maternal and Perinatal Health. Induction of labour data**. In. Geneva: WHO press; 2011.
8. WHO: **WHO recommendations for induction of labour**. In.: Geneva; 2010.
9. Gulmezoglu AM, Souza JP: **WHO recommendations for induction of labour**. In.; 2011.
10. Bolnga JW, Hamura NN, Umbers AJ, Rogerson SJ, Unger HW: **Insights into maternal mortality in Madang Province, Papua New Guinea**. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics* 2014, **124**(2):123-127.
11. Bolnga JW, Morris M, Aipit J, Laman M: **Maternal and perinatal mortality in resource-limited settings**. *The Lancet Global health* 2015, **3**(11):e672.
12. Hamura NN, Bolnga JW, Wangnapi R, Horne AW, Rogerson SJ, Unger HW: **The impact of tubal ectopic pregnancy in Papua New Guinea--a retrospective case review**. *BMC pregnancy and childbirth* 2013, **13**:86.
13. Laman M, Pomat W, Siba P, Betuela I: **Ethical challenges in integrating patient-care with clinical research in a resource-limited setting: perspectives from Papua New Guinea**. *BMC medical ethics* 2013, **14**:29.