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A study of how safe and how well different doses of oral Misoprostol induce labour in pregnant women in Papua New Guinea

Submission date
28/07/2016

Recruitment status
No longer recruiting

Registration date
08/08/2016

Overall study status
Completed

Last Edited
23/08/2022

Condition category
Pregnancy and Childbirth

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
In Papua New Guinea (PNG), many women die from pregnancy related complications or their babies may become ill or die if pregnancy is not cared for well and delivery is not supervised. If a women goes past her due date or has a long-term health condition (such as high blood pressure), it may be necessary for health workers to help speed up the process of labour to save the baby or the mother (induction of labour). Induction of labour is an important procedure in caring for pregnant women all over the world, but there is currently standardised way of doing it. In PNG, a drug called misoprostol is widely used for the induction of labour in PNG and other resource-limited countries as it is cheap, safe to store at room temperature, and is easy for women to take. Despite this, currently there are not enough appropriate guidelines on which dose to use. The aim of this study is to compare the safety and effectiveness of a lower dose and higher dose of misoprostol in the induction of labour.

Who can participate?
Pregnant women aged between 18 and 44 who are overdue (past their expected date of delivery), have a condition that puts them and their baby at risk, such as blood pressure problems, or any other medical problems warranting induction of labour.

What does the study involve?
Participants are randomly allocated to one of two groups. Those in the first group start off taking four doses of 25ml misoprostol every two hours. If labour doesn't begin, the dose in then increased to 50ml every two hours for four doses and then repeated at 50ml every two hours for four hours. If after this the women do not go into labour, after 24 hours rest, the women is given 50ml every two hours for eight hours. Those in the second group start off taking four doses 12ml misoprostol every two hours, which is increased to 25ml every two hours for four doses and then 50ml every two hours for four hours. If the women do not go into labour then they are given 50ml every two hours for eight doses after a 24 hour rest. For participants in both groups, if after they have taken all of the misoprostol doses they are still not in labour, then an

alternative method of labour induction is used. Women in both groups are observed over the four weeks following birth to monitor for any negative side effects, and the number who successfully give birth are recorded.

What are the possible benefits and risks of participating?
Patients who participate in this study will benefit from the care provided by the study team as part of monitoring for drug safety and effect. The study will be conducted with the intention to treat these patients, so with their involvement, they benefit directly from this process as continuing pregnancy might pose complications to both the mother and the baby. The risks involved such as caesarian section, if induction of labor fails, is not really a risk of the study, but in fact part of standard management practices in obstetrics. Uterine or womb rupture as a result of misoprostol use is very rare especially with lower doses as used in the present study. Others such as tummy upset or diarrhea are considered minor and rare risk factors of misoprostol.

Where is the study run from?
Modilon Hospital (Papua New Guinea)

When is the study starting and how long is it expected to run for?
May 2016 to March 2019

Who is funding the study?
Hope Specialist Health Care Ltd (Papua New Guinea)

Who is the main contact?
Dr John Bolnga

Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
MRAC 16.17

Study information

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

Study objectives
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.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Medical Research Advisory Committee of Health Department of Papua New Guinea (MRAC), 25 /05/2016, ref: # 16.17

Study design
Single-centre open-label randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Induction of Labour to terminate pregnancy after third trimester with specific indications in Obstetrics practice

Interventions
Based on computer-generated block randomization, eligible patients will be allocated 1:1 to the standard treatment group or to the low dose oral misoprostol intervention group. Allocated treatments will be concealed in sealed numbered envelopes which will be opened in sequence by study medical or nursing staff only after enrolment and the specified treatment administered. A tablet of Cytotec (misoprostol) comes in 200mcg, therefore a solution of 1mcg /ml is made by dissolving 1 tablet (200mcg) of cytotec 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 at 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 below separately.

Standard Treatment Arm:
Participants initially recieve 25mls (25mcg) of cytotec every 2 hours for 4 doses which will be equal to 100mls (100mcg) in 8 hours. The dose is then increased to 50mls (50mcg) every 2 hours for 4 doses (if there is no progression in labour) which will be equal to 200mls (200mcg) in 8 hours. If the patient has not yet gone into labour, another 50mls (50mcg) of cytotec every 2 hours for 4 doses, equivalent to 200mls (200mcg) in 8 hours, will be administered. The total

dosage will now be 500mls (500mcg) in 24 hours. This would complete the first cycle. If no labour progression is achieved after the first cycle, the patient would be allowed to rest for 24 hours, then a repeat of the induction process, commencing at 50mcg (50mls) every 2 hours for 8 doses which will be equivalent to 400mls (400mcg) in 16 hours will be recommenced. If there is still no progression in the second cycle, participants will further undergo Foley's catheterization with the intention to treat while those failing induction would undergo caesarean section.

Intervention Arm:
Participants initially recieve 12mls (12mcg) of cytotec every 2 hours for 4 doses, equivalent to 48mls (48mcg) in 8 hours. Then it will be increased to 25mls (25mcg) every 2 hours for 4 doses which will be equal to 100mls (100mcg) in 8 hours. If the patient does not go into labour, then another 50mls (50mcg) of cytotec every 2 hours for 4 doses, equivalent to 200mls (200mcg) in 8 hours, will be administered. This would bring the total dosage within 24 hours to 348mls (348mcg), completing the first cycle. If no progression in labour is achieved after the first cycle, the patient would be allowed to rest for 24 hours. In cycle two, induction will be repeated, commencing at 50mcg (50mls) every 2 hours for 8 doses which will be equivalent to 400mls (400mcg) in 16 hours. If there is still no progression in the second cycle, participants will further undergo Foley's catheterization with the intention to treat while those failing induction would undergo caesarean section.

There will be a follow up in four weeks after delivery or post-partum period to see if there are any long term side effects or any complication that may have occurred with both the mother and the baby. All participants will be asked to return in four weeks after delivery as required. The parameters to check for the baby will include any infection morbidity, whether there was any neonatal death and if baby was thriving well. The mother will be followed up to ascertain her acceptability of the trial, any infection morbidity and or any hemorrhage and any other residual problem.

Intervention Type
Drug

Drug/device/biological/vaccine name(s)
Misoprostol

Primary outcome(s)
Proportion of women who have a successful live vaginal delivery without any severe adverse events is determined by monitoring and caring for the mother and baby until delivery is achieved with no complications leading to perinatal and maternal mortality and morbidity during the course of the study.
Adverse events include:
1. Failed induction necessitating cesarean section
2. Maternal death
3. Retained placenta
4. Perinatal death
5. Neonatal admission to special care nursery

Key secondary outcome(s))
1. Proportion of successful live births delivered vaginally within 24 hours is measured by the number of deliveries born without complications or severe adverse events from a total of those induced in both the treatment and intervention arms
2. Proportion of mothers requiring Foley's catheterization is measured by the number of women

who did not progress to vaginal delivery with the use of misoprostol and were subjected to Foleys catheterization, compared to those that were successfully induced. This proportion will be taken from the number using Foleys Catheter over the total that was induced
3. Proportion of mothers requiring oxytocin augmentation is measured by the number of study patients who are having prolonged labour and therefore clinically assessed to require assistance with intravenous oxytocin that subsequently results in delivery of the baby. This proportion will be taken from the number augmented with intravenous oxytocin over the total that was induced
4. Neonatal Apgar scores ≤7 at 5 minutes post-delivery is measured by the Apgar Scoring System which takes into consideration the appearance of the baby, the color of the newborn baby, the pulse of the baby, grimacing of the face and respiration rate at the time of delivery to 5 minutes
5. Maternal and neonatal adverse events will be investigated by interviewing the patient using standard case reporting forms and doing clinical examinations on both the baby and the mother to determine if they have any complication related to the trial during the peripartum period as well as at 4 weeks post-discharge

Completion date
30/03/2019

Eligibility

Key inclusion criteria
1. Able to complete study informed consent procedures, to understand the benefits of the study and the potential risks and benefits associated with study participation
2. Aged between 18 and 44 years
3. Willing to undergo clinical assessment, including cervical assessments to establish the Bishop score (cervical readiness or softness and dilatation).
4. Willing to come back after four weeks for follow up progress and check up.
5. Third trimester singleton pregnancies in women over 18 years old
6. Bishops score of less than 6
7. Cephalic presentation
8. Hemoglobin concentration of more than 8g/dL

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
Female

Total final enrolment
262

Key exclusion criteria
1. Multiple pregnancies confirmed with ultrasound examination
2. Previous caesarian sections or other conditions that required surgery on the uterus with uterine scar
3. Chronic illness such as TB, renal failure, other malignancies and heart disease
4. Hemoglobin of less than 8g/dL with symptomatic anemia
5. Unstable or abnormal lie with malpresentation
6. Any high risk cases that require immediate caesarian sections

Date of first enrolment
01/06/2016

Date of final enrolment
20/08/2018

Locations

Countries of recruitment
Papua New Guinea

Study participating centre
Modilon Hospital
P.O.Box 2119
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Sponsor information

Organisation
Papua New Guinea Institute of Medical Research

ROR
https://ror.org/01x6n0t15

Funder(s)

Funder type
Industry

Funder Name
Hope Specialist Health Care Ltd

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated and/or analysed during this study will be included in the subsequent results publication.

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		01/03/2021	20/04/2021	Yes	No
Protocol file		21/02/2016	23/08/2022	No	No