

2 METHODS

2.1 Structure of the Studies

Two studies were performed at the Groote Schuur Maternity Centre and Mowbray Maternity Hospital, Cape Town, South Africa. The head of the department of obstetrics and gynaecology at Groote Schuur Hospital is Professor Zephne M. van der Spuy. The principal investigator of research is Professor Dr. J. Anthony. The supervision and guidance of these two studies were conducted by Dr. Paul le Roux.

In Germany, the thesis was supervised by Professor Dr. med. K. Vetter, head of the department of obstetrics at Vivantes Klinikum Neukölln, Berlin.

The hospitals mentioned above handle 10,000 of the province's 28,000 births annually. Mowbray Maternity Hospital is a secondary and Groote Schuur Hospital a tertiary perinatal facility. The population is almost entirely coloured or black.

Prior to the commencement of the study, the research proposal received the approval of the University of Cape Town Ethics Committee.

All inductions were carried out on an inpatient basis. The study protocol included a 20 minute cardiotocographic (CTG) recording before commencing induction of labour. A standardised vaginal examination for Bishop score evaluation and measurement of frequency of contractions were performed each time before the induction agent was admitted. All patients underwent continuous cardiotocographic monitoring. Labour and delivery were managed as usual.

Augmentation was performed at the discretion of the attending clinician if cervical dilatation was less than 1 cm in 2 hours once in active labour, in case of onset of active labour with 3 strong contractions in 10 minutes, and once the cervix was favourable at a dilatation of the cervix of 4 cm or more. Two methods of augmentation were used: Amniotomy and a standard oxytocin infusion which was increased half hourly from 2mU/min to a maximum of 12 mU/min until adequate contractions were achieved.

Analgesia was given to the patient on request and at the discretion of the labour ward staff. Opioid analgesia, entonox gas (50% nitrous oxide and 50% oxygen) and epidural anaesthesia were available.

In the case of early labour, when the patient was not expected to deliver within three hours, 10 mg to 15 mg morphine was given intramuscular for pain relief if required.

Upon onset of labour, the preferred method was a regional neural conduction blockade by continuous epidural analgesia using analgetic drugs such as Fentanyl®.

The other option was inhalation analgesia with entonox via face mask and demand valve.

Patients in late labour which were expecting to deliver within two hours could not receive epidural analgesia and were therefore given 3 to 5 mg morphine by slow intravenous injection over 10 minutes.

2.1.1 Part I – Misoprostol versus Dinoprostone

Between April 1999 and November 2000, patients were randomised to the trial if they presented with:

- ◆ an indication for induction of labour
- ◆ willingness to participate in the study
- ◆ singleton foetus
- ◆ cephalic presentation
- ◆ gestational age of 34 weeks or more
- ◆ Bishop score of less than 7
- ◆ unruptured membranes
- ◆ no evidence of fetal distress in cardiotocographic monitoring
- ◆ no progressive painful contractions being present.

Exclusion criteria were:

- ◆ age less than 18 years
- ◆ previous cesarean section
- ◆ parity greater than 4
- ◆ twins
- ◆ breech presentation
- ◆ intrauterine death
- ◆ fetal anomaly
- ◆ contraindications for induction of labour

Women meeting the inclusion criteria were included after written informed consent was obtained. Eligible subjects were assigned to an induction method after opening a sequentially numbered opaque envelope in which written instructions were given concerning the drug to be

given. The envelopes were equally distributed to the two hospitals. Half of the envelopes contained cards for the oral study group, divided between oral misoprostol (n=120) and the dinoprostone control group (n=120), the other half for the vaginal study group, divided between vaginal misoprostol (n=120) and the dinoprostone control group (n=120).

Among the 573 patients randomised to the trial during the study period, 93 had to be excluded from the analysis for protocol violations. 480 subjects remained for the analysis.

The reasons for exclusion were clerical errors (n=65), ignored exclusion criteria (n=18), administration of an incorrect dose (n=5), under age (n=2), cesarean section after randomisation before the first dose of prostaglandin could be given (n=2), and one patient withdrew from the study.

The 120 patients recruited in each arm was based on a sample size calculation of the results shown in a prior pilot study.

For the calculation, the two dinoprostone control groups with 120 patients each were combined for better understanding.

Patients randomised to the oral misoprostol arm were given 50 µg (one half of a 100 µg tablet) orally 6-hourly up to a maximum of 4 doses (over 24 hours) until the cervix was effaced and 4 cm dilated with adequate uterine contraction frequency of three or more contractions in 10 minutes. Rupture of membranes did not influence the continuation. In case of slow progress, i.e., a cervical dilatation rate of less than 4 cm in 4 hours and less than three contractions in 10 minutes, augmentation was performed with amniotomy and a standard oxytocin infusion as previously mentioned.

In the vaginal misoprostol arm, 50 µg misoprostol was inserted into the posterior fornix 6-hourly for a maximal period of 24 hours. If spontaneous rupture of membranes occurred further doses were given vaginally with a sterile technique to reduce the risk of infection.

Further management was identical to that in the oral misoprostol arm.

The controls were managed according to the hospital's established induction protocol: Prandin®, a 1 mg dinoprostone E₂ vaginal gel, was inserted into the posterior fornix. If the cervix was still unfavourable for amniotomy after 6 hours, a second dose was applied. Six hours after the second dose of Prandin® amniotomy was performed. An oxytocin infusion was started if there were no regular uterine contractions.

If amniotomy was not possible after the second dose of Prandin®, the clinician had the choice to proceed with a cesarean section for failed induction of labour or, if the health of the fetus and the mother was not endangered, to wait until the 24 hour period was completed, provided that there was appropriate monitoring.

2.1.2 Subgroup Analysis of Part I

The subgroup analysis compared the groups of interest with respect to the main outcome measures. The patients' data were analysed comparing multiparae to nulliparae and women presenting with an initial Bishop score <4 or ≥ 4 .

The outcome variables of interest in the subgroup analysis were reduced to the following points:

- ◆ the success rate of deliveries within 24 hours
- ◆ induction to delivery interval
- ◆ mode of delivery without time limit
- ◆ indications for cesarean section
 - fetal distress
 - failed induction of labour
- ◆ fetal outcome measures
 - low Apgar scores
 - admission to neonatal intensive care unit (NICU)
 - incidence of hypoxic ischemic encephalopathy

2.1.3 Part II - Vaginal and Oral Misoprostol versus Oral Misoprostol

A small pilot study of 40 patients was planned. Four protocol violations occurred while conducting the study. To reach the target number of 40 patients, 4 additional patients had to be randomised.

All of the cases had to present with nulliparity, requirement for induction of labour, a gestational age of 37 or more weeks, a single viable foetus in vertex presentation with a Bishop score of less than 7 and unruptured membranes.

Patients who presented with any one of the following were ineligible: non-reassuring foetal heart rate (FHR) tracing, progressively painful contractions, fetal anomaly, previous uterine surgery, known hypersensitivity to prostaglandins, age less than 18 years, or regular contraindications.

The outcome variables of interest were the same as in Part I (cf. Chapter 2.1.1).

44 women were randomly selected and assigned to one of two equally large groups according to a computer generated table for the study. At presentation for induction, the protocol and potential risks and benefits were explained before obtaining written consent.

Allocation of each consenting patient to the induction method was determined at the time of induction by opening the next sequentially numbered envelope. 22 patients were randomised to vaginal and oral misoprostol and 22 to oral misoprostol.

Patients who were randomised to the vaginal and oral group were initially given 50 µg misoprostol vaginally, the subsequent 2 doses were applied orally at four-hourly intervals.

Those randomised to the oral regimen received three doses of 50 µg misoprostol 4-hourly until active labour was achieved. A maximum of three doses could be given in each group.

Further treatment with misoprostol was stopped when the cervix was effaced and 4 cm dilated with 3 regular, strong uterine contractions in 10 minutes and the labour rate was assessed as usual. Spontaneous rupture of membranes did not influence further application. In case of slow progress, augmentation was performed by amniotomy and a standard oxytocin infusion.

As there were less than 100 patients in both groups, decimal numbers were excluded as being imprecise.

2.2 Implementing Regulations of the Studies

2.2.1 Bishop Score

In this system for cervical assessment, a score of 0 to 3 is assigned for dilatation, effacement, consistency, position of the cervix and station of the vertex in centimetres above the ischial spine²⁰⁸.

In these studies the modified Bishop Score with a maximum score of 13 was used.

Score	0	1	2	3
Dilatation of the cervix (cm)	0	1 or 2	3 or 4	5 or more
Length of cervical canal (cm)	>2	2-1	1-0.5	<0.5
Consistency of cervix	Firm	Medium	Soft	
Position of cervix	Posterior	Central	Anterior	
Station of presenting part	3	2	1 or 0	Below

Table 2-1: Modified Bishop score²⁰⁸.

2.2.2 In Case of Adverse Events

Planned treatment of tachysystole and hyperstimulation included change in maternal position to the left lateral position.

Tachysystole without abnormal fetal heart tracing on cardiotocographic monitoring was observed constantly and induction was continued as usual.

In the event of abnormal uterine activity, such as tachysystole, was noted on the CTG recording with evidence of fetal distress, the situation was managed according to the usual labour ward protocol; initially a bolus of 10 µg intravenous Hexoprenaline (Ipradol®) was applied. The maintenance dose was 150 µg in 1000 ml at 10 to 20 to 40 drops per minute. The dosage was decreased as contractions disappeared.

Maternal or fetal deterioration with the need to perform a cesarean section before 24 hours from the start of induction was recorded.

To determine tachysystole and hyperstimulation syndrome on the CTG tracing, all fetal graphs were reviewed post-delivery. In cases where tachysystole was present the fetal heart rate tracing was investigated for fetal heart rate abnormalities as a result of tachysystole.

To classify the monitoring strips, the following terminology was used:

- ◆ Tachysystole was defined as at least five contractions in 10 minutes for two consecutive 10-minute periods.
- ◆ A hyperstimulation syndrome was defined by the presence of uterine contraction abnormalities associated with pathological fetal heart rate pattern.

In case of failure of induction after 24 hours, the situation of the patient was re-evaluated by the attending physician.

2.2.3 Outcome Measures

The primary outcome measures were success of the regimen within 24 hours, the time interval from induction to delivery and the cesarean section rate.

The specific maternal outcome measures were maternal side effects, maternal complication rate, maternal analgesia requirements, the indications for cesarean section and the incidence of failed induction.

On the fetal side tachysystole and fetal heart rate abnormalities were noted on CTG and the liquor was examined for meconium staining. The neonatal outcome was evaluated by Apgar score \geq or <7 at 5 minutes, arterial cord pH assessment, the incidence of admission to a neonatal intensive care unit and the incidence of hypoxic ischemic encephalopathy.

If active labour had not commenced after 24 hours this was considered failed induction of labour.

For documentation, a questionnaire was used to evaluate demographic data reflecting age, gravidity, parity, gestational age of induction, indication for induction, as well as maternal and fetal outcome parameters mentioned above (cf. Chapter 11.3.3, page 132)

2.2.4 Data Analysis

Randomisation was performed with computer generated randomisation techniques.

All parameters were summarised and reported as descriptive statistics. The data were summarised by adequate methods: continuous data by means of summary statistics (N, mean, median, percentiles with quartiles corresponding to $Q1=25\%$ and $Q3=75\%$) and categorical data by means of relative and absolute frequencies or contingency tables.

All demographic data, clinical history and baseline characteristics of the patients included in the study were represented by a treatment group. The compatibility between the two treatment groups regarding demographic and other baseline data were assessed using standard statistical techniques.

Statistical analysis was performed using Microsoft Excel and SPSS. Entry characteristics and outcome variables were analysed using the Chi-square test, Fisher exact test, Student *t* test Mann-Whitney *U*- and Kruskal-Wallis-Test, as appropriate. Throughout all analyses the tests were two-tailed and $P < 0.05$ was considered statistically significant.

For better surveillance the outlier are not shown in boxplot figures.

In the main study as well as in the subgroup analysis, the percentages are given with one digit behind the decimal point as there have been no more than 120 and 240 patients in the groups.