EFFICACY AND SAFETY OF LABOR INDUCTION BY ORAL VERSUS VAGINAL MISOPROSTOL: A RANDOMIZED CONTROLLED CLINICAL TRIAL

ABSTRACT

Background: Laborinduction is one of the most common practices in obstetrics in developed countries. But, in developing countries, its prevalence is low. This study seeks to compare the efficacy and safety of oral versus vaginal Misoprostol in an area with limited resource.

Patients and Methods: This is a single-blind, randomized controlled clinical trial, conducted at Kisangani, from September 1, 2022 to February 01, 2023. We had the approval of the ethics committee of Kisangani University. Data collection was prospective. The sample was 177 patients, in term mono-fetal pregnancy, in cephalic presentation and fetal heart rate (FHR) within the norms. Fifty micrograms of Misoprostol were administered either orally or vaginally every six hours. The data were encoded on an Excel 2013 sheet and analyzed using EPI INFO and SPSS software.

Results: Labor was induced after 6.18±4.11 h for oral Misoprostol versus 4.03±1.99 h for the vaginal route (p=0.00). The duration of labor was 10.85±3.59 h for the oral route, 9.39±2.55 h for the vaginal route. The time from the first dose to delivery was 16.88±6.11 h for the oral route, 13.03±3.32 h for the vaginal route. The delivery rate within 24 hours was 98.9% (87/88) for the vaginal route and 88.8% (79/89) for the oral route (p=0.00). The rate of caesarean section was 6.7% for the oral route, 12.5% for the vaginal.

Conclusion: Misoprostol is effective both orally and vaginally. Administered vaginally, it is associated with a reduction in the duration of labor, while it improves maternal and perinatal prognosis.

Keywords: Labor induction; Misoprostol; Efficacy; Safety; Kisangani.

I. INTRODUTION

Labor induction is an artificial interruption of the course of pregnancy before spontaneous induction with the aim of reducing maternal and perinatal morbidity and mortality [1,2]. It is successful when a vaginal birth is obtained within 24 hours and should only be performed if it appears that in terms of health, the mother or the newborn will benefit from a more favorable outcome than if the birth had been later [3].

According to the World Health Organization (WHO) [4], the labor induction rate in developed countries is on average 25%, 11.4% in Latin America and 12.1% in Asia. In Sri Lanka, the labor induction rate is 35.5% [5] and in the United States of America it is 25% [6]. In Africa, the rate varies between 1.4-6.8% with an average of 4.9% [7]. In Nigeria, a study

found a rate of 16.7% in a tertiary hospital in Lagos [8]. However, In Eastern Region of DRC, at Kisangani, the rate of labor induction is 3.36% [9].

To induce labor, we use either mechanical technique such as membrane stripping, transcervical placement of a Foley catheter with or without extraamniotic saline infusion, breast stimulation with a breast pump, acupuncture or amniotomy, either drug methods such as oxytocin solution, prostaglandins or intra-amniotic injection of hypertonic saline [10].

However, labor induction may be associated with a risk of failure to induce labor, and like any other intervention, have adverse effects such as hyperkinesia, hypertonia, uterine hyperstimulation, fetal distress, pre-rupture or uterine rupture, cesarean section, postpartum hemorrhage, and in rare cases, fetal or maternal death [11].

WHO recommends the use of oxytocin solution, prostaglandins or amniotomy to induce labor [12]. Synthetic prostaglandins have been widely used over the past 20 years in the induction of labor due to their greater efficacy [13,14]. Synthetic prostaglandins used in obstetrics are analogues of prostaglandin E2 (Dinoprostone) and analogues of prostaglandin E1 (Misoprostol).

Misoprostol is stable at ambient temperature and can be administered sublingually, buccally, orally or vaginally to induce labor [15]. WHO [12] recommends the use of Misoprostol at low doses and monitoring of the parturient by the cardiotocogram to detect early pathological changes in the fetal heart rate (FHR), hyrkinesia, hypertonia or uterine hyperstimulation which can lead to uterine rupture.

WHO [10] and the International Federation of Gynecologists and Obstetricians (FIGO) [16] recommend doses of 25 migrograms (µg) vaginally every 6 hours or 25 µg orally every 2 hours to induce labor. However, there is no evidence on the optimal number of doses to be administered to increase the rate of vaginal delivery, the same is true for the frequency of doses and the route of administration[17].

Low dose of Misoprostol is well tolerated, but its use after previous cesarean section is associated with a high rate of uterine rupture [18]. Misoprostol can be associated with hyperkinesia, hypertonia, uterine hyperstimulation, FHR disorders and this depends on the dose and route of administration, which may be accompanied by an emergency cesarean section then that the latter might not be indicated [19].The Misoprostol available in our environment is 200 µg, hence the difficulty of dividing it by eight in order to obtain the dose

of 25 µg as recommended by WHO [12] and FIGO [16], and several structures of health do not have a cardiotocogram for monitoring parturients and fetuses during labor.

This is why we would like to compare the efficacy and safety of the labor induction by 50 µg of oral Misoprostol versus 50µg in vaginal route in under-equipped health structures, and assess the maternal and perinatal prognosis.

II. PATIENTS AND METHODS

It is a single-blind, randomized controlled clinical trial written according CONSORT guidelines. Data collection was prospective from September 1, 2022 to February 01, 2023.

This multi-site study was carried out at the University Clinics of Kisangani, at the Kabondo General Referral Hospital, Alwaleade and Saint-Joseph Referral Health Center, in Kisangani, Tshopo Province, Democratic Republic of Congo (DRC). This study had the approval of the ethics committee of Kisangani University toand is registered in Panafrican Clinical Trial Registry (PARC) to identification number PACTR202208496861650.

The study population was pregnant women with full term pregnancy admitted to one of the maternity wards of the selected health structures and having followed the prenatal consultations there. The sample consisted of 177 pregnant women, 89 for oral Misoprostol and 88 for vaginal route.

Were included, nulliparous, primiparous and multiparous who controlled their date of last menstruation, and who had a term progressive pregnancy, mono-fetal, with FHR in the standards (110-160 beats per minute), cephalic presentation, without medical or obstetric indication of labor induction and having signed the informed consent.

Were excluded, pregnant women who had already delivery more than five times, twin pregnancy, hypertensive disorders, diabetes, presentation other than cephalic, FHR anomaly before onset, large pregnant uterus, placenta previa, scarred or fibromyomatous uterus, anomalies of the maternal pelvis and cases of fetal death.

Data collection was done during prenatal consultations by trained midwives or nurses, who towards the end of the third trimester informed the pregnant women about the study explaining the advantages and disadvantages of labor induction. At term pregnancy, patients who met the inclusion criteria and signed the informed consent were selected to participate in the study.

In the operational setting, the socioeconomic parameters were evaluated according to the score of Traissac et al [20], large pregnant uterus was a fundal height ≥ 36 centimeters, uterine hyperstimulation was the association or not of hyperkinesia or uterine hypetonia.

Prolonged latency phase was when a dilation of four centimeters could not be achieved eight hours after the onset of uterine contractions.

The delivery bleeding was a difference ≥ 1g / dl between the initial hemoglobin levels taken before the onset of labor compared to the controlled hemoglobin level taken two hours after delivery.

We induced labor by Miso® 200 made by Mylan Laboratories Ltd. Gujarat. India. Lot No 9415A009A (INN: Misoprostol).

After evaluation of the socio-demographic and clinical parameters, 50µg of Misoprostol was administered either orally with a cup of water every six hours until effective uterine contractions were obtained, without exceeding three doses, or by vaginal route following the same frequency and dose. Drug administration was stopped when the parturient reached three uterine contractions per ten minutes or four centimeters cervical dilation. If after three doses the labor did not start, the induction of labor was considered to have failed and the pregnant woman was given an appointment after 24 hours to restart the induction by administering the drug by the same route, same dose and frequency.

The primary outcomes were the time from drug administrations to uterine contractions, labor time, and vaginal delivery rate. For secondary outcomes, the course of labor as well as the maternal and perinatal prognosis was assessed. Items to assess maternal prognosis were hyperstimulation, uterine pre-rupture or rupture, rate of cesarean sections and delivery hemorrhage. For the perinatal prognosis, FHR disorders were evaluated which was monitored using the Pinard fetoscope, meconium staining of the amniotic fluid, Apgar score at the first, fifth and tenth minutes, need for neonatal care.

As side effects we looked for diarrhea, vomiting, chills and fever.

Data was collected using the standard protocol including socio-demographic, gyneco-obstetrical parameters, the elements of labor monitoring, the delivery route and elements related to the maternal and perinatal prognosis.

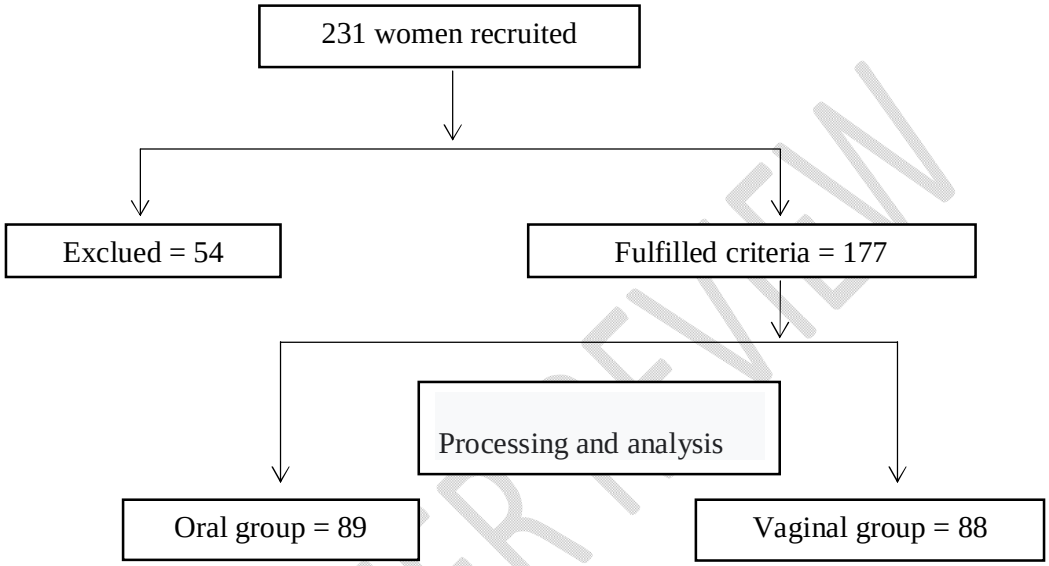
The data collected was encoded on an Excel 2013 sheet and analyzed using the EPI INFO

Version 7.2.2.6 software and SPSS Statistics 20.

III. RESULTS

Graphic 1. Flow diagram.

Fig 1- Schematic representation of women studied



As shown in **Fig.1,** 231 patients were eligible for labor induction. However, 54 were excluded including 16 who had refused to sign the informed consent, and 38 did not meet the inclusion criteria including 8 patients for hypertensive disorders, 6 for scarred uterus, 5 for large pregnant uterus, 12 patients who already had delivered more than 5 times, and 7 for surgical pelvis. We selected 177 patients who met the criteria and who agreed to participate in the study, including 89 for oral Misoprostol and 88 for the vaginal route.

Table 1. Socio-demographic factors

	Oral Misoprostol (n=89)	**Vaginal Misoprostol (n=88)**	*p*-value
Age (years)means± SD	23.73±6.29	25.62±7.24	0.23
< 20	28 (31.5)	30 (34.1%)	
20-34	51 (57.3%)	41 (46.6%)	
≥ 35	10 (11.2%)	17 (19.3%)	
Marital Status			0.34
Married	72 (80,9%)	69 (78.4%)	
Single	17 (19,1%)	19 (21.6%)	

Profession			
Pupil/Student	26 (29.2%)	27 (30.7%)	0.84
Without	43 (48.3%)	38 (43.2%)	
Salaried	8 (8.9%)	10 (11.4%)	
Informal sector	12 (13.6%)	13(14.7%)	
Socio-economiclevel			0.83
Low	45 (50.6%)	47 (53.4%)	
Medium	40 (44.9%)	36 (40.9%)	
High	4 (4.5%)	5 (5.7%)	
Education level			0.52
Illiterate	5 (5.6%)	4 (4.5%)	
Primary	27 (30.3%)	22 (25.0%)	
Secondary	45 (50.6%)	43 (48.9%)	
Superior	12 (13.5%)	19 (21.6%)	

As shown in **Table 1**, the majority of the patients were married, aged 20-34 years, with a average of 23.73±6.29yearsfor oral group vs 25.62±7.24 for vaginal group, without profession 43 (48.3%) vs 38 (43.2%), of low socioeconomic level 45 (50.6%) vs 47 (53.4%) and of secondary education level 45 (50.6%) vs 43 (48.9%). The two groups are comparable because there was no significant difference from these parameters.

Table 2. Gyneco-obstetrical parameters

Parameters, means ± SD	**Oral Misoprostol**	**Vaginal Misoprostol**	*p*-value
Parity	0.73±1.12	1.11±1.29	0.07
Nulliparous	61 (68,5%)	49 (55,7%)	
Primiparous	19 (21,4)	19 (21,6%)	
Multiparous	9 (10,1)	20 (22,7%)	
BMI (Kg/m^2)	25.62±2.81	26.45±3.59	0.13
< 25	53 (59.6)	45 (51.1%)	
≥ 25	36 (40.4)	43 (48.9%)	

As shown in **Table 2**, the majority of patients was nulliparous, and had a BMI < 25 kg / m. The difference was not significant statistically in the two groups.

Table 3. Comparison of the efficacy of misoprostol

Parameters	Oral Misoprostol	Vaginal Misoprostol	Relative Risk (RR) 95% CI	*p*-value
		Primaryresults		
Induction-uterine contractions (hrs) : means ± SD	6.18 ± 4.11	4.03 ± 1.99	-	
≤ 12 hrs	81 (91.1%)	88 (100.0%)		0.00*
> 12 hrs	8 (8.9%)	0 (0.0%)		
Duration of labor (hrs) except in case of cesarean section	10.85±3.59	9.39±2.55	-	
≤ 8 hrs	21/83 (25.3%)	26/77 (33.8%)		0.29
9-16 hrs	52/83 (66.7%)	50/77 (64.9%)		0.44
>16 hrs	10/83 (12.1%)	1/77 (1.3%)		0.01*
Induction-deliverydelay (hrs)	16,88±6,11	13,03±3,32		
≤ 12 hrs	28 (31.5%)	44 (61.1%)	1.49 [1.07-2.08]	0.01*
≤ 24 hrs	79 (88.8%)	87 (98,9%]	1.91 [1.49-2.44]	0.00*
> 24 hrs	10 (11.2%)	1 (1.1%)	0.52 [0.41-0.67]	0.00*
Number of doses at delivery				
Delivery at dose 1	26 (29.2%)	42 (47.7%)	1.51 [1.07-2.13]	0.01*
Delivery at dose 2	47 (52.8%)	43 (48.9%)	0.92 [0.69-1.24]	0.30
Delivery at dose 3	13 (14.6%)	2 (2.3%)	0.54 [0.42-0.70]	0.01*
Delivery after 3 doses	3 (3.4%)	1 (1.1%)	0.66 [0.37-1.19]	0.19
Sideeffects				
Chills	3 (3.4%)	0 (0%)	0.49 [0.43-0.57]	0.06
Diarrhea	1 (1.1%)	0 (0%)	0.50 [0.43-0.58]	0.25

*****Significantdifference

As shown in **Table 3**, uterine contractions occurred on average after 6.18±4.11 hrs in oral group versus 4.03±1.99 hrs in vaginal group and the difference was significant (*p*=0.00). The delivery rate beyond sixteen hrs was 12.1% (10 patients) for the oral route and the difference was significant (*p*=0.01) compared to the vaginal route 1.3% (1 patient). Vaginal Misoprostol caused more delivery within twelve to twenty-four hrs and the difference was significant compared to the oral route (*p*=0.01 and *p*=0.00 respectively).

Oral misoprostol resulted in 10 (11.2%) delivery after 24 hrs, and the difference was significant (*p*=0.00) compared to vaginal route 1 (1.1%). After the first dose, 42 (47.7%) patients delivered for vaginal Misoprostol versus 26 (29.2%) for the oral route and the difference was significant (*p*=0.01), RR 1.5, 95% CI 1.07-2.13. The majority of patients who reached the third dose received oral Misoprostol 13 (14.6%) versus 2 (2.3%) vaginally and the difference was significant (*p*=0.01).

Table 4. Comparison to the course of labor and maternal prognosis

Parameters	Oral Misoprostol	Vaginal Misoprostol	RR 95% CI	*p*-value
		Secondaryresults		
Number of doses				
Means ± SD	97.19 ± 41.54µg	76.71 ± 27.28µg		
≤ 3	86 (96,6%)	87 (98,9%)	1,51 [0,84-2,71]	0,19
> 3	3 (3,4%)	1 (1,1%)		
Failure induction	3 (3.4%)	0 (0.0%)	0.49 [0.43-0.57]	0.06
Prolongedlatency phase (> 8hrs)	12 (13.6%)	0 (0.0%)	0.47 [0.39-0.55]	0.00*
Hyperstimulation	4 (4.5%)	7 (7.9%)	1.41 [0.64-3.12]	0.18
Delivery route			1.5 [0.76-2.85]	0.10
Vaginal delivery	83 (93.3%)	77 (87.5%)		
Cesarean section	6 (6.7%)	11 (12.5%)		

*****Significantdifference

As shown in **Table 4**, the prolonged latency phase had occurred in 12 (13.6%) of patients in oral group and the difference was significant (p = 0.00) compared to the vaginal group where no case had been recorded. The rate of uterine hyperstimulation was 7.9% in vaginal group versus 4.5% in oral group, RR 1.41, 95% CI 0.64-3.32.

The majority of patients delivered vaginally, including 83 (93.3%) for the oral route versus 77 (87.5%) for the vaginal route. However, the cesarean section rate was 11 (12.5%) for the vaginal route versus 6 (6.7%) for the oral route, RR 1.5, 95% IC 0.76-2.85.

Table 5. Comparison to perinatal prognosis

Parameters	Oral Misoprostol	Vaginal Misoprostol	RR 95% CI	*p*-value
		Secondaryresults		
FHR disorders	5 (5.6%)	8 (9.1%)	1.33 [0.65-2.69]	0.19
Meconium staining of amniotic fluid	6 (6.7%)	15 (17.1%)	1.86 [0.93-3.72]	0.02*
Apgar Score				
Apgar < 7 1st minute	8 (8.9%)	13 (14.8%)	1.36 [0.77-2.40]	0.92
Apgar < 7 5th minute	0 (0)	0 (0)	-	-
Neonatal care	4 (4.5%)	8 (9.1%)	0.65 [0.29-1.46]	0.12
Stillbirth	0 (0)	0 (0)	-	-

*****Significantdifference

As shown in **Table 5**, by the vaginal route, the rate of meconium staining of the amniotic fluid was 17.1% (15) for vaginal Misoprostol versus 6.7% (6) for the oral route, RR. 1.86, 95% IC 0.93-3.72, and the difference was significant (p = 0.02). The low Apgar level at the first minute was 14.8% (13) for the vaginal route versus 8.9% (8) for the oral route, RR 1.36, 95% CI 0.77-2.40.

IV. DISCUSSION

4.1. Misoprostol administration and time to uterine contractions

Uterine contractions occurred on average after 6.18±4.11 h for oral Misoprostol versus 4.03±1.99 h for the vaginal route. The rate of occurrence of uterine contractions during the first three doses, which corresponds to 12 hours from the start of Misoprostol administration, was 91.1% for the oral route versus 100% for the vaginal route, (p=0.00). This reflects that vaginally Misoprostol triggered uterine contractions faster than orally. This is consistent with the results of a study who compared 25µg Misoprostol vaginally versus 50µg orally which he administered every six hours found that the duration of onset of uterine contractions was prolonged for the oral route (7.5±4.4h) versus 6.6±3.6 for the vaginal route (p=0.1)[21]. However, in another study, authors administered 50µg Misoprostol every 4 hours and found a delay in onset of uterine contractions of 4.2±0.66h for the oral route versus 5.06±1.1h for the vaginal route[22]. These results are thought to be due to a shorter interval between doses (4h) because vaginally Misoprostol has a slow absorption and a lower peak plasma level than oral administration [23]. Thus, with oral administration, and at closer intervals, Misoprostol can stimulate uterine contractions earlier than when administered vaginally.

4.2. Misoprostol Administration and Duration of Labor

The mean duration of labour excluding caesarean section was 10.85±3.59 h for oral Misoprostol versus 9.39±2.55 h for the vaginal route. However, with oral Misoprostol, 12.1% of patients had a labour duration >16 hours vs. 1.3% with vaginal Misoprostol (p=0.01). These data are almost similar to those found in a study which were 8.4±0.92h for the oral route vs 9.2±1.5h for the vaginal route[22]. In another study, authors compared 25µg Misoprostol vaginally every 2h vs 50µg peros every 6h and found a mean duration of 31h vs 41h respectively[24]. Hence, the duration of labour would be shorter when Misoprostol is administered vaginally. However, a study found a mean duration of 21.02±16.9 h for the oral route vs 23.95±54.28 for the vaginal route (p=0.47)[25]. The duration of labour was longer for the vaginal route in this study because they started with 25µg Misoprostol for the first intra vaginal dose and increased the dose to 50µg if uterine contractions were not effective whereas with the oral route they started directly with 50µg. However, another study found that the duration of induction of labour in the active phase was shorter for vaginal than for oral Misoprostol and the difference was significant[26].

The majority of pregnant women delivered within 24 hours of induction of labour, 88.8% for the oral route versus 98.9% for the vaginal route (p=0.00). a study found a 24 hour delivery

rate of 44.9% for the oral route vs 53.5% for the vaginal route (p=0.27)[25]. This reflects that the 50µg Misoprostol every 6 hours protocol is effective both orally and vaginally, but the vaginal route is statistically more effective. However, another study found a 24-hour delivery rate of 88.2% for the oral route vs. 85.7% for the vaginal route when inducing labour with 25µg Misoprostol peros every 2 hours vs. 25µg vaginally every 6 hours with a maximum duration of 24 hours[27]. This high rate of delivery within 24 hours for oral Misoprostol is thought to be related to the shorter dosing interval for this route.

The mean interval between the first dose and delivery was longer (16.88±6.11 h) for oral misoprostol versus 13.03±3.32 h for the vaginal route. A study found an interval of 16.47h (4-28h) for the oral route vs 6h (3.24-26.32h) for the vaginal route and the difference was significant (p=0.0033)[15]. Vaginally administered Misoprostol is fast acting as it is close to the body and cervix, but is slowly eliminated from the maternal body hence its bioavailability is longer compared to oral administration where it has to be absorbed from the gastrointestinal tract, undergo the first hepatic pass where it is catabolised, binds to plasma proteins and only its free form will be active (Misoprostol acid) [23]. However, another study administered 50µg every 6h for the oral route vs 25µg every 6h for the vaginal route and found a shorter interval for the oral route (22.6±17.22h) vs 25.5±54.25h for the vaginal route but the difference was not significant (p=0.47)[25]. Similarly, a study found an interval of 18.48±2.01h for the oral route vs 22.82±2.50h for the vaginal route (p=0.00)[27]. This proves that Misoprostol administered at shorter intervals by the oral route would be more effective than by the vaginal route.

Vaginal Misoprostol resulted in more deliveries within twelve to twenty-four hours and the difference was significant compared to the oral route (p=0.01 and p=0.00 respectively).in a studyalso found that vaginally administered Misoprostol resulted in more deliveries within 24 hours (90.4%) versus 72.5% when administered orally[26]. Another study found a delivery rate of 13.8% for the oral route vs. 17.4% for the vaginal route within 12 hours (p=0.64), and 44.9% for the oral route vs. 53.5% for the vaginal route within 24 hours (p=0.27)[25]. Hence, vaginal Misoprostol is more effective and results in a higher rate of delivery within 24 hours than the oral route.

Oral Misoprostol resulted in 10 (11.2%) deliveries after 24 hours, and the difference was significant (p=0.00) compared to the vaginal route 1 (1.1%). A study found a delivery rate within 48 hours of 64.1% for the oral route vs 66.9% for the vaginal route and the difference was not significant[25]. This would be related to the low doses (25µg) of vaginal Misoprostol

with which they started the induction and only administered 50µg in the absence of effective uterine contractions, hence the number of doses was increased and the duration of labour prolonged. Another study conducted in nulliparous women and gave one group 50µg of Misoprostol orally every 4 hours up to 3 doses and the other group 200µg of Misoprostol in the posterior vaginal fornix which was removed after at least 3 uterine contractions or 4 cm cervical dilatation, and found a 24-hour delivery rate of 44.1% for the vaginal route vs. 14.1% for the oral route (p=0.001)[28]. Hence, continuous administration of Misoprostol by the vaginal route improves its effectiveness.

4.3 Adverse events in relation to the routes of administration of Misoprostol

Adverse events were only noted with oral administration of Misoprostol, including: chills 3 (3.4%) and diarrhoea 1 (1.1%). A study found a rate of nausea of 10.9% for the oral route versus 0% for the vaginal route, RR 27.07 at 95% CI, 1.17-465.7[29]. Similarly, another study found a diarrhoea rate of 1.7% for vaginal Misoprostol vs. 0% for oral (p=0.16), nausea rate of 9.3% for vaginal vs. 9.6% for oral (p=0.73) and a vomiting rate of 14.0% for vaginal vs. 17.4% for oral (p=0.18)[25]. This suggests that the oral route would have more side effects on the gastrointestinal tract than the vaginal route, however the difference is not significant compared to the oral route. The low rate of adverse events is thought to be related to the low dose of Misoprostol (50µg) administered in our study which is extremely lower than the optimal dose in terms of occurrence of side effects (400µg) [30].

4.4. Number of doses of Misoprostol administered

Administered orally, 86 (96.6%) patients received a maximum of 3 doses versus 87 (98.9%) for the vaginal route (p=0.19), RR 1.51, 95% CI 0.84-2.71. Similarly, in a study, authors used the protocol of 50µg Misoprostol taken every 4 hours up to a maximum of 6 doses and found that 85% of patients received a maximum of 3 doses for the oral route versus 84% for the vaginal route and the difference was not significant[31]. In another study author found a rate of 5.88% of patients who received a single dose of Misoprostol orally vs. 11.54% vaginally, 15.69% for 3 doses orally vs. 19.23% vaginally, but 11.77% for six doses orally vs. 5.77%

vaginally[15]. This reflects that the number of doses administered was lower when inducing labour with Misoprostol vaginally compared to orally.

The average dose of Misoprostol by the oral route was 97.19± 41µg versus 76.71, ± 27.28µg by the vaginal route. In a study, authors induced labour with 50µg of Misoprostol every 4 hours and found a mean administered tablet of 2.5±1.3 for the oral route versus 2.0±1.1 for the vaginal route (p=0.02)[32]. Misoprostol administered vaginally would be associated with a reduction in the number of doses compared to the oral route. In another study authors found a mean dose of 257µg ±144µg[28]. These high doses would be related to the fact that on the first day they administered 50µg every 4 h up to a maximum of 3 doses. However, in case of failure, the next day they administered 100µg of Misoprostol every 4 hours without exceeding 300µg. It is recommended not to exceed 150µg of Misoprostol per 24 hours when inducing labour in a full term pregnancy due to possible maternal and perinatal complications [1,23].

4.5. Failure rate of induction and prolonged latency phase in relation to the route of administration of Misoprostol

The failure rate was 3.4% (3 patients) and this was only found with oral Misoprostol induction of labour. In a study authors found a failure rate of 4.3% for the vaginal route vs. 11% for the oral route (95% RR CI 0.39[0.15-1.02])[33]. In another study, authors administered 50µg Misoprostol every 4 hours with a maximum of six doses and found a failure rate of 25.49% for the oral route vs 9.62% for the vaginal route and the difference was significant (p=0.0426)[15]. This indicates that there is a higher risk of failure when inducing labour with oral Misoprostol. However, In another studyfound a failure rate of 5% for the oral route versus 6% for the vaginal route and this would be related to the close interval of 50µg of Misoprostol every 4 hours for both routes which may potentiate the efficacy of the oral route[22].

Prolonged latency occurred in 12 (13.6%) patients when inducing labour with oral Misoprostol and the difference was significant (p=0.00) compared to the vaginal route where no cases were recorded. This is related to the protocol of 50µg of Misoprostol orally every six hours as its absorption and elimination is rapid by this route compared to the vaginal route [26,33]. Thus, WHO [12] and FIGO [16] recommend doses of 25µg Misoprostol orally every two hours versus 25µg vaginally every six hours until effective uterine contractions are achieved. In a study authors found a time interval from induction to onset of active phase of 6 hours for vaginal Misoprostol versus 9.25 hours for oral Misoprostol and the difference was

significant (p=0.0049)[15]. However, in another study authors inducing labour with 100µg Misoprostol to be taken every 4 hours for the oral route versus every 6 hours for the vaginal route found a mean duration of 7.5±4.2 hours for the oral route versus 7.3±4.1 for the vaginal route and the difference was not significant (p=0.87)[34]. Hence, Misoprostol per os administered at 100µg would reduce the rate of prolonged latency phase.

4.6. Maternal prognosis in relation to the route of administration of Misoprostol

The rate of uterine hyperstimulation was 4.5% for the oral route versus 7.9% for the vaginal route, RR 1.41 at 95% CI 0.64-3.12, but the difference was not significant (p=0.18). in a study, authorsfound a uterine hyperstimulation rate of 2% for the oral route versus 14% for the vaginal route. A study [15] used the protocol of 50µg Misoprostol administered every four hours up to a maximum of six doses and found no cases of hyperstimulation or uterine rupture compared to both groups. In another study,the rate of uterine hyperstimulation were 4.8% for the oral route versus 9.4% for the vaginal route but the difference was not significant (p=0.27)[25]. However, a study found a uterine hyperstimulation rate of 9% for oral Misoprostol versus 5% for the vaginal route[31]. This rate is thought to be related to the 4-hour interval between doses of 50µg Misoprostol, which potentiates the efficacy of oral Misoprostol, but also its adverse effects.

In our study, we did not have any cases of uterine rupture. Several other studies that used the maximum dose of 50µg Misoprostol did not find any cases of uterine rupture [15,25,33]. This indicates that the 50µg dose of Misoprostol is well tolerated by parturients. Howevera study [26] compared the two routes using a protocol of 50µg every 4 hours until effective uterine contractions were achieved and found a 0.5% rate of uterine rupture that occurred in a patient with a scarred uterus and induction was done with Misoprostol vaginally. This suggests that induction of labour with per os Misoprostol would be safer than vaginal induction.

4.7. Route of delivery after induction of labour with Misoprostol

The rate of vaginal delivery was 83 (93.3%) when Misoprostol was administered orally versus 77 (87.5%) for the vaginal route and the difference was not significant (p=0.10). a study [26] found a vaginal delivery rate of 74% for the oral route versus 94% for the vaginal route. They induced labour in patients with medical indications for induction including gestational hypertension, IUGR, gestational diabetes and oligohydramnios. And another study [15] found a vaginal delivery rate of 74.5% for the oral route versus 90.4% for the vaginal route and the difference was significant (p=0.0462). This indicates that by inducing labour with

Misoprostol in the same doses, the vaginal route offers a better chance of achieving vaginal delivery regardless of the indication. In our study we obtained a higher rate of vaginal delivery for the oral route than for the vaginal route because at the same dose and frequency, vaginal Misoprostol increases the risk of caesarean delivery more than oral Misoprostol.

In our study, the caesarean section rate was 6.7% for the oral route versus 12.5% for the vaginal route, RR 1.5 at 95% CI 0.76-2.85 for vaginal Misoprostol but p=0.10. A study [33] found a caesarean section rate of 30.2% for the oral route versus 31.9% for the vaginal route (RR 1.06, 95% CI 0.7-1.5). Another study [25] found a caesarean rate of 32.9% for the oral route versus 31.4% for the vaginal route (p=0.21). This high caesarean rate in this studies was related to the body mass index of the patients which was on average 33.54 kg/m2. In both groups reflects that a BMI $\geq$ 25kg/m2 is associated with prolonged duration of labor which may indicate a caesarean section [35].

4.8. Perinatal prognosis in relation to route of administration

The rate of pathological changes in BCF (fetal heart sounds) was 5.6% for the oral route versus 9.1% for the vaginal route, RR 1.33 at 95% CI 0.65-2.69. A study [25] found that neonatal acidemia (umbilical artery pH < 7.0) was common with vaginal Misoprostol reflecting hypoxia, and the difference was significant (p=0.04) compared to the oral route. Hence, the vaginal route would increase the risk of occurrence of fetal distress. However, another study[26] found a rate of 20% of pathological changes in the FHR for the oral route versus 10% for the vaginal route. These high rates are thought to be related to the fact that they induce labour in medically indicated patients whose hypertensive disorders had a rate of 84% for the oral route versus 86% for the vaginal route.

The rate of meconium staining of the amniotic fluid (AF) was 6.7% for the oral route versus 17.1% for the vaginal route, RR 1.86 at 95% CI (0.93-3.72) (p=0.02). A study [28] also found a meconium staining rate of 33.8% for the vaginal route versus 18.5% for the oral route, RR 2.38, 95% CI 1.32-4.29 (p=0.004). This further reflects that the risk of fetal distress is higher when inducing labour with Misoprostol vaginally. However, another study [15] monitoring partients by cardiotocography, found a rate of meconium staining of the LA of 1/51 for the oral route vs 1/52 for the vaginal route (p=0.899). These almost similar rates would be related to the electronic monitoring of the parturient that detects early signs of fetal distress that indicated caesarean sections at a rate of 25.5% for oral Misoprostol versus 9.6% for vaginal Misoprostol (p=0.0462).

The Apgar score < 7 at the first minute was 8 (8.9%) for oral versus 13 (14.8%) for vaginal, RR 1.36 at 95% CI 0.77-2.40 (p=0.92). Note that at five minutes postpartum, the Apgar score was ≥ 7 for both routes. A study [27] also found an Apgar rate <7 at 5 minutes of 1.2% for the oral route versus 2.4% for the vaginal route, RR 0.49, 95% CI 0.05-6.65. Another study [25] found an Apgar rate <7 at the first minute of 16.2% for the oral route vs 21.5% for the vaginal route (p=0.16). At five minutes, they found an Apgar < 4 of 1.2% and 2.7% pH < 7.0 at the umbilical artery only for the vaginal route; and Apgar < 7 of 2.4% for the oral route vs. 1.7% for the vaginal route with p=0.69. This would suggest that the risk of low Apgar at 5 minutes is more related to induction of labour with vaginal Misoprostol.

The rate of neonatal management was higher with vaginal Misoprostol induction 9.1% vs. 4.5% for oral induction (p=0.12). A study [28] found a neonatal management rate of 3.0% for oral versus 4.5% for vaginal induction and p=0.83. Another study [33] who only induced labor in nulliparous women, found a neonatal management rate of 9.3% for the oral route vs 11.2% for the vaginal route with RR 1.2 at 95% CI 0.60-2.4. Hence the risk of neonatal resuscitation is higher when inducing labour with vaginal Misoprostol compared to the oral route.

V. CONCLUSION

Labor induction with misoprostol is effective both orally and vaginally. Its use at low doses in under-equipped settings may be recommended due to its ease of storage and administration and the wide range of routes of administration. Misoprostol administered vaginally is more effective because it reduces the time to onset of uterine contractions and the duration of labor. Orally, Misoprostol improves maternal and perinatal prognosis by reducing the risk of complications.

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