GSC Advanced Research and Reviews

eISSN: 2582-4597 CODEN (USA): GARRC2

Cross Ref DOI: 10.30574/gscarr

Journal homepage: https://gsconlinepress.com/journals/gscarr/

(RESEARCH ARTICLE)

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The effectiveness of oral misoprostol compares to intravenous oxytocin in enhancing labor in primigravida: A comparative study

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GSC Advanced Research and Reviews, 2024, 20(02), 077–087

Publication history: Received on 02 June 2024; revised on 19 July 2024; accepted on 22 July 2024

Article DOI: https://doi.org/10.30574/gscarr.2024.20.2.0256

Abstract

Background: Augmentation of labor addresses uterine inertia in primigravidae, with oxytocin being preferred. Misoprostol offers cost-effective, convenient alternatives, making it a cost-effective option.

Objective: The study evaluates the effectiveness and safety of misoprostol oral solution vs. oxytocin for primigravida augmentation.

Methodology: A randomized comparative study was conducted on primigravida in active labor in Osogbo metropolis, using three hospitals as study sites. The study included two arms: oxytocin-augmented and misoprostol-oral solution. Events in labor with fetal/maternal outcomes were monitored and documented. Appropriate statistical tests and presentations were applied, p value was set at <0.05

Result: A study of 159 patients on each arm of Oxytocin (oxy) and misoprostol (miso) was conducted, with the majority aged between 20-35 years (64.47%). The onset of adequate contractions interval was 8.73 and 9.03 minutes in Oxy and Miso arm, respectively while vaginal delivery intervals were 4.69 and 4.47 hours in the Oxy and Miso arms, respectively. Fetal Heart Rate abnormalities were more in the Miso arm but did not affect fetal outcomes. There was no significant difference in maternal outcomes, with vaginal delivery rate, caesarean section rate, postpartum hemorrhage reported estimated blood and Birth weight (p>0,005). Most neonates had a good APGAR score at birth. Stillbirth and intrauterine fetal death were not recorded. Vomiting was the only symptom with a significant more in the miso arm (p-value= 0.033),

Conclusion: Misoprostol, a 20mcg oral solution, is effective and safe for augmentation of labor in primigravidae during active labor phases, with side effects like vomiting.

Keywords: Oxytocin; Misoprostol; Augmentation of labour; Primigravida

1. Introduction

Augmentation of labour has been a proven means of overcoming uterine inertia in order to achieve vaginal delivery, especially the nulliparous (1,2) Abnormal labour (labour dystocia) may lead to serious complications including death of patients and their babies (3) Drugs to increase the frequency and strength of contractions have often been used in such birth process, examples are: misoprostol and oxytocin (4).

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Misoprostol is an inexpensive and stable drug that stimulates uterine contractions, but it can have serious and even life-threatening side-effects (5). Therefore, the dose has to be carefully adjusted. Titration refers to the process of adjusting the dosage of a medication on the basis of frequent monitoring to achieve the best outcomes (6) Titrated misoprostol could be effective in treating delayed progress in labour and as an alternative to oxytocin which is harder to store and is given intravenously by infusion (7). Oxytocin is a natural nonapeptide hormone stored at the posterior pituitary gland and effects the contractility of the uterus. (8). It is a tested drug of choice for augmentation of labour over the years with proven results. It is however not without some limitations. ((9). It is expected to be stored under cold temperature for best result to be achieved (10). Evaluations of these two essential obstetric drugs have been on for several years for different usages (11), however, there are limited studies that compare the effectiveness and certain obstetric outcomes of these drugs. In resource poor countries, there is paucity of information concerning safety and protocol concerning the usage of misoprostol in labour (12). The majorly feared side effects of misoprostol, uterine rupture and its related complications are mostly seen in the multiparous, scarred uterus and injudicious uses of these two drugs coupled with poor intrapartum surveillances (11).

Important uncertainties still exist on the safety and acceptability of titrated oral solution of misoprostol compared with intravenous oxytocin regimens in women with dystocia following spontaneous onset of labour (13).

Proper storage of oxytocin for effective pharmacologic action is a great challenge because of poor electricity supply in the tropic, compared to the stability of misoprostol at room temperature which is easily achievable in our environment coupled with high cost of oxytocin to cheaper price of misoprostol (14).

Appropriate management of a primigravida in labour have a significant bearing in subsequent pregnancies and prevention of primary cesarean section is a major means to reduce caesarean section rate worldwide (15). therefore, management of labour dystocia which is common in primigravida with timely augmentation is pivotal in achieving successful vaginal delivery (16).

Objectives

To determine the effectiveness of 20ug oral solution of misoprostol against standard dose of oxytocin in augmentation of labor in primigravidae.

- *Specific objectives*
    - To determine duration of labor after commencement of misoprostol compared to oxytocin.
    - To determine the influence of misoprostol on the characteristics of labor /side effects compared to oxytocin group.
    - To determine the influence of misoprostol compared to oxytocin on the feto-maternal outcome of labour.

2. Material and method

2.1. Study site

The study site is Osogbo township. This is a multicenter study which comprises secondary and tertiary health facilities namely, the Obstetrics and Gynaecology department of LAUTECH Teaching hospital, Osogbo, the Labour ward unit of Osun state specialist hospital Asubiaro, Osogbo and Our lady of Fatima specialist hospital, Jaleyemi, Osogbo. The study was conducted between Nov 2017 and May 2018.

2.2. Study design

This was a randomized comparative study which aims at evaluating the effectiveness and safety of oral solution of 20ug misoprostol against standard dose of oxytocin in primigravida in established active phase of labour in these hospitals in Osogbo. Randomization was done electronically using a computer generated (randonizerpro software) numbers into two arms. Patients were recruited into two arms, one for augmentation with misoprostol while other was for oxytocin. For every primigravida in labour, after adequate counseling and written consent taken, when there is need for augmentation of labour (due to inadequate contractions i.e less than 3 contractions in 10-minute lasting less than 40 seconds in active phase of labour between 4 - 8 cm) a ballot was taken from the provided box which allocated them into either misoprostol arm or oxytocin arm. Prior to the commencement of the research, in-house training was given to the research assistants with a weekly in each study centres: My research assistants were midwives, medical officers, house officers and Registrars in peadiatrics and labour wards. These set of people were also involved in recruitment of patients, monitoring of labour , administration of appropriate medications in labour, delivery of baby and immediate

care of the neonate (Apgar scoring) among others. The profoma were later filled and collated before manual data entry into SPSS 21 and further data management was done.

2.3. Inclusion Criterion

All primigravida in active phase of labour (4 to 8 cm) that has inadequate uterine contractions after obtaining written informed consent.

2.4. Exclusion Criteria

The study excluded patients with advanced labor, asthma, scarred uterus, reactive hepatitis, retroviral infection, cervical ripening/induction of labor with misoprostol, indication for caesarean section, patient on cervical ripening/ induction of labour with misoprostol or allergic to misoprostol.

2.5. Protocol design

Protocol for usage of misoprostol arm: there must be no contraindication to usage of misoprostol and no exclusion criteria present. Twenty microgram of misoprostol was prepared by dissolving 200ug of a misoprostol tablet (Cytotec) in a sterile water of 40mls volume, this was allowed to dissolve, stirred and 4mls of this prepared solution which now contain 20ug was administered orally to patient at 2 hours interval for 4 maximum doses (80ug in 8 hours) until adequate contraction was achieved. When patient vomited within 6 minutes of administration a repeat dose was given with antiemetics.

Protocol for usage of Oxytocin arm was managed using the departmental protocol, starting with 5IU of oxytocin in 500mls saline solution, at 15 dpm (4miu) and increased by 15 dpm every 30 minutes until adequate contractions was achieved or maximum dose of 32miu was reached.

These protocols were clearly and boldly written then pasted conspicuously in the labour wards for prompt guide.

Cardiotocographic (CTG) monitoring was ensured for both arms along with partographic monitoring. In absence of CTG monitoring, electronic sonocaid was used in some cases. Fetal heart rate was monitored using CTG or Sonocaid (Hand held doppler). Normal fetal heart rate is between 120 to 160 bpm. When fetal heart was less than 120 bpm but change to normal range within 20 minutes with or without intervention it was regarded as transient bradycardia, while persistent bradycardia was fetal heart rate less than 120bpm despite all available interventions instituted. Likewise, fetal heart rate greater than 160 bpm but change to normal range within 20 minutes with or without intervention was as regarded transient tachycardia, while persistent Tachycardia was fetal heart rate greater than 160bpm despite all available interventions instituted. Hyperstimulations is the presence of greater than six (6) uterine contractions in 10 minutes or a single contraction lasting more than 2 minutes with features of persistent fetal heart rate abnormalities.

2.6. Data collections

A labor event performance/outcome sheet proforma was used.

2.7. Data analysis

All information obtained from the profoma was entered manually into statistical package for social sciences (SPSS) version 21.

3. Result

3.1. Socio-demographic distribution / obstetric data

Three hundred and twenty-eight patients were recruited but 10 opted out leaving a sample size of 318. The response rate was 99.37%. Five hundred and fifty-nine patients in each arm,

Majority of the participants were within 20-35 years (64.47%), 97.5 % of the patients had a formal education while teenage pregnancy rate was about 3%. Majority of the respondents were married (89.31%) and booked 82.38%. At recruitment 45.28 % had cervical dilatation of 5cm (Table 1).

3.2. Effect of Augmentation -

Onset of Augmentation- adequate contractions interval, was 8.73 ± 2.03 compared to 9.03 ± 1.72 minutes in Oxy and. Miso arm respectively (p=0.988) while Vaginal Delivery interval (in hours) was 4.69 ± 1.99 and 4.47 ± 1.64 in Oxy and Miso Arm respectively (p=0.9911). Table 2 The fetal outcomes measured were the birth weight and asphyxia; The birth weight was not statistically significant between the two study arms (Table 2). Majority of the neonates had a good APGAR score at birth. Stillbirth and Intrauterine fetal death were not recorded throughout this study due to the intrapartum fetal surveillances deployed. (Table 2)

Significant proportion of the Misoprostol group (57.9%) had fetal heart rate abnormality compared to the Oxytocin group (37.7%). The observation was statistically significant (X2= 12.999, p-value = < 0.001) but has no effect on the fetal outcome. (Table 3).

There was no difference in the maternal outcomes; vaginal delivery rate was 93.1% and 94.9% in Oxy and Miso arm respectively. The caesarean section rate was 6.9% vs.5.0% (Oxy vs. Miso), no postpartum hemorrhage reported, estimated blood loss was 284.15 ± 20.17 and 334.72 ± 24.67 for Oxy and Miso arm respectively, p-value of 0.051. Vomiting is the only symptom with a significant p-value of 0.033(Table 4).

Transient bradycardia occurs in 67% in the misoprostol group compared with 33% respectively, while transient tachycardia occurs in 855 and 89% in misoprostol and oxytocin group respectively. Common mediation used was analgesic, antiemetic and antipyretics. There was no statistically difference in the proportion of respondents who used the drugs in both arms (Fig 1) In addition, persistent tachycardia occurs in 40% and 44% of the misoprostol and oxytocin group respectively while the uterine hyper stimulation was 2% in both arms. The differences in both arms were not significant (fig 2)

4. Discussion

The major aim of this study was to evaluate the effectiveness and safety profile of oral misoprostol when it is being used to achieve successful vaginal delivery with no adverse effect to fetus and mother when compared to oxytocin (which has been the standard drug of choice for augmentation) in primigravida with inadequate contractions. The outcomes measured were Augmentation - Onset of adequate contractions interval, Augmentation – Vaginal Delivery interval, Fetal heart abnormalities, hyperstimulation, maternal outcomes such as mode of delivery, estimated blood loss and uterine rupture, adverse maternal symptoms such as: fever, vomiting and watery stool, fetal outcomes such as: Asphyxia, IUFD/ fresh still birth and fetal birth weight.

Table 1 Socio demographic distribution/Obstetric data

Variables	Frequency(n=319)	Percentage (%)
Age groups(years)		
≤19	10	3.15
20 – 24	44	13.84
25 – 29	205	64.47
30 – 34	56	17.61
≥35	3	0.93
Educational status		
None	8	2.52
Primary	14	4.40
Secondary	140	44.03
Tertiary	156	49.05
Marital status		
Single	34	10.69

Married	284	89.31
Booking status		
Booked	262	82.39
Unbooked	56	17.61
Cervical dilation at recruitment		
4cm	134	42.14
5cm	144	45.28
6cm	26	8.18
7cm	10	3.14
8cm	4	1.26
Gestational age		
37-38	12	3.77
>38-39	104	32.70
>39-40	96	30.19
>40-41	98	30.82
>41-42	8	2.52

The sample population was three hundred and eighteen (318) which is higher than the calculated sample size (300), this is within the range of the two previous randomized studies evaluating these drugs where about 213 and 350 primigravidae were recruited (17,28,39,40). Larger proportion (64.47%) of the patients were 20 -35 years, which is also similar to a study done (18) and this correlate with most statistics values of age of primigravida both in the tropics and worldwide. The mean maternal age in this study was (27.48 ± 2.58 vs. 26.56 ± 3.39 years) in similar to the figure of age of primigravida in European countries and USA which has risen from 23 years to 27 years (19). Factors such as academic pursuit along with cultural, financial challenges account for this upward trend in maternal age of primigravida (18). Less than 1% of the participants were elderly primigravidae, this corroborate the known fact about reduction in fertility rate due to ovarian aging in women beyond the age of 35years in women (20). Teenage primigravida accounted for 3.15%, though this is lower than the reported value reported in the north-central part of the country this may be due to the location of the study centers which is an urban setting (21). Very few (2.5%) of the patients had no formal education, this might be attributed to the location of the study which is the city capital and this shows significant improvement towards achievement of SDG goal 348. About 8 in 10 patients had antenatal care, this showed an increase ANC attendance compared other studies (22, 23).

Table 2 Comparism of Sociodemographic Characteristics and Obstetric Data Between the Study Arms

Variables	**Oxy Arm**		**Miso Arm**		**Df**	**Statistical Test**	**p- value**
	Frequency (%)		**Frequency (%)**				
					1		
Marital status							
Single	15	15 (4.7)	19	(6.0)		**X^2= 1.861**	**0.256**
Married	144	144 (45.3)	140	(44.0)			
Educational status					**1**		
Non-Tertiary	83	83 (52.2)	79	(49.7)		**X^2 = 4.003**	**0.129**
Tertiary	76	76 (47.8)	80	(50.3)			

Booking status				**1**		
Booked	24	24 (15.1)	32 (20.1)		**X^2 = 1.387**	**0.239**
Unbooked	135	135 (84.9)	127 (79.9)			
Cervical dilation at recruitment Mean ± SD	5.20 ± 1.63		5.32 ± 1.90	4	t test = 5.771	0.252
Maternal Age Mean ± SD	27.48 ± 2.85		26.56 ± 3.39	4	t test = 6.102	0.192
Gestational age Mean ± SD	287± 5 days		282± 3 days	2	t test = 4.704	0.081

The Augmentation - Onset of adequate contractions interval was 8.73 ± 2.03 vs. 9.03 ± 1.72 minutes in Oxy vs. Miso arm. This is in line with onset of action of these two drugs according to their pharmokinetic (24) (25). Augmentation – Vaginal Delivery interval (in hours) was 4.69 ± 1.99 and 4.47 ± 1.64 in Oxy and Miso Arm respectively, there is a shorter duration in Miso Arm but with no statistical differences (26). A similar duration was reported in the study done in China with an average interval of about 5.2 hours, 20mcg was used in that study has it was used in this study (27). The rate of cervical dilation was 1.37 and 1.52 cm per hour in Oxy and Miso arm respectively this is similar to the findings of the work done in Ilorin (28) with a value of 1.76cm/ hour in primigravida (29) this also falls within the range of the popular known value of 1- 1.5cm / hour in primigravida in active phase of labour (30), This may be attributed to the synergic effect of misoprostol on enhancing contractility of uterus and softening of cervix (2,31).

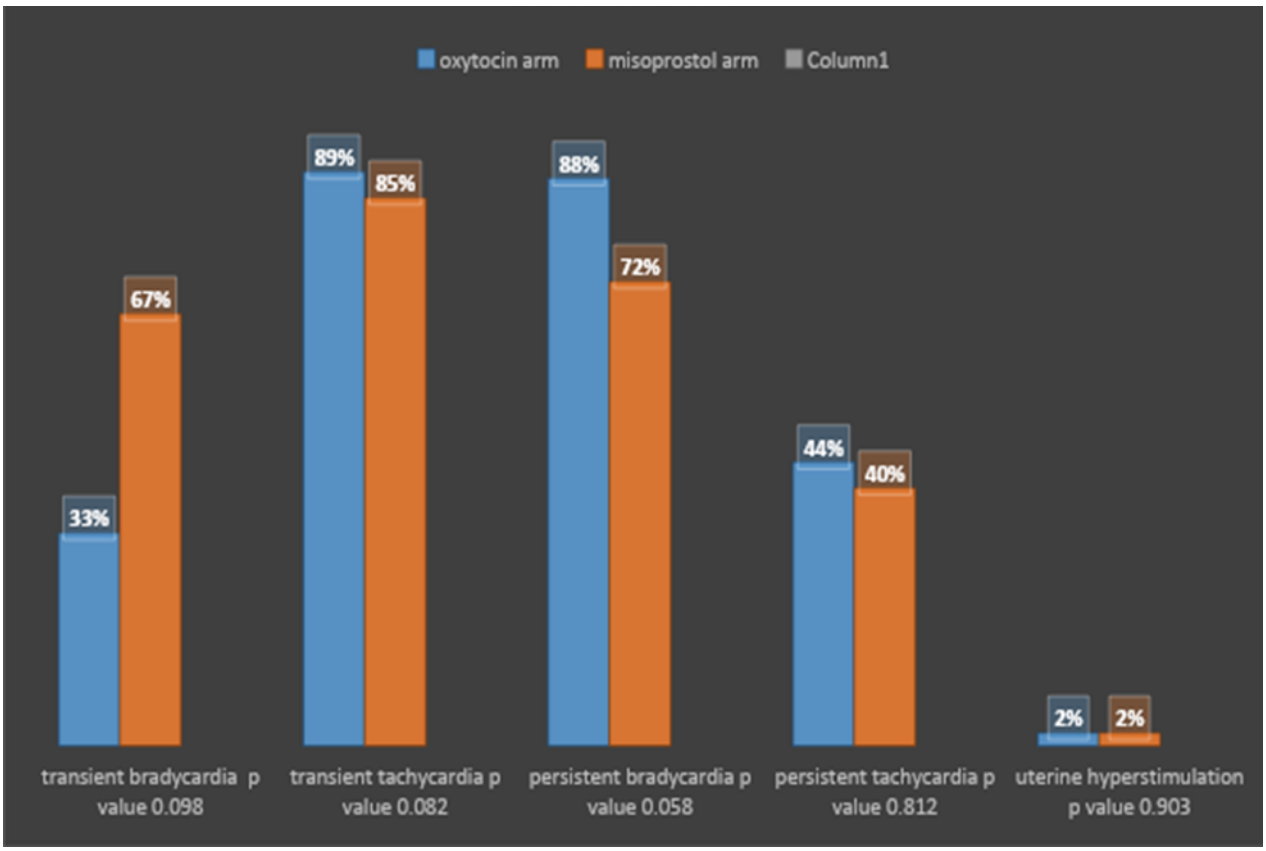

Figure 1 The fetal heart rate abnormalities

The occurrence of fetal heart rate (FHR) abnormalities is significant in this study, this finding was also reported in several studies where Misoprostol was used in labour either as induction agent or augmentation agent. FHR abnormalities is one of the known side effects of misoprostol (32-34) however, it has no significant effect on the feto-maternal outcomes. Majority of the fetal heart abnormalities were self-abated (transient) even the Hyperstimulation

rate were very minimal and equal in both study arms (2% each), and this was also reported in the studies (35, 36). No need for surgical intervention in any of the participant secondary to FHR abnormalities (37).

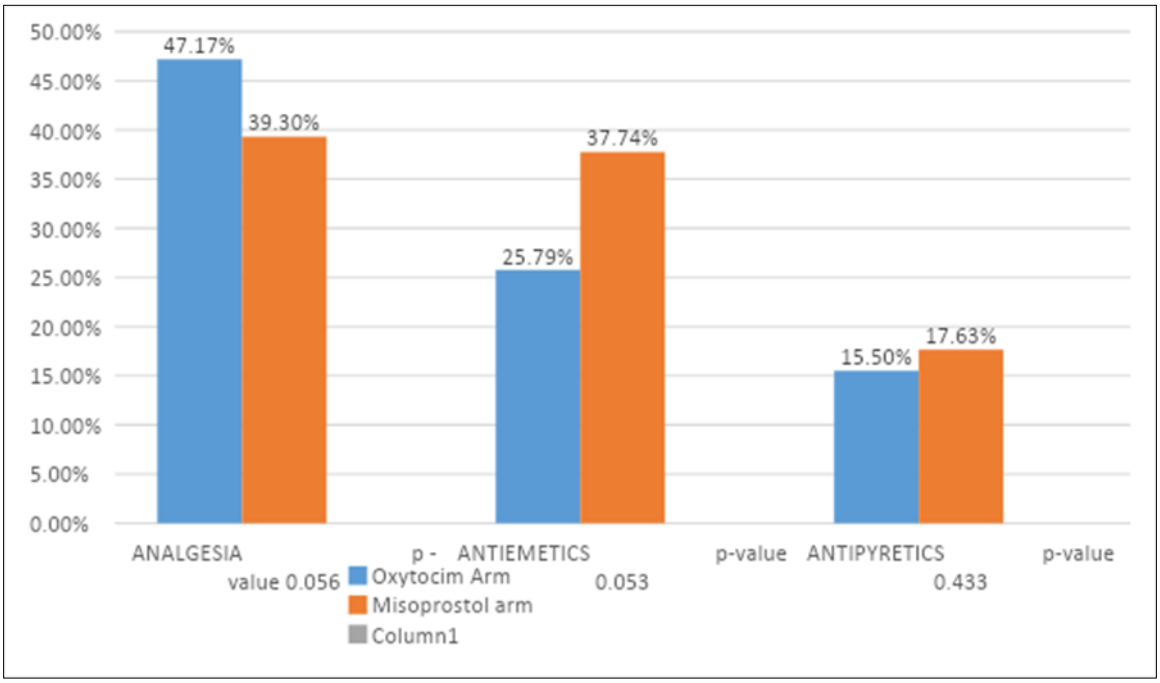

Figure 2 Common Medications Administered Intrapartum in both Study Arms

The common adverse symptoms (Figure 1) seen were fever/ chills, vomiting and loose stool; these are similar to the side effects profile of both drugs (25) Vomiting is the only symptom with a significant. The oral route of administration of Misoprostol used in the study coupled with some intrapartum medications (Pentazocine and Pethidine for pain control in labour) also increase the vomiting tendency and may account for this significance. However, fever/ chills and loose stool have respectively. These symptoms were also reported in previous studies but there were no statistical differences reported, epidural was the labour analgesia used in those studies unlike this where opiates with emetics tendency was the main labour analgesia (35)

Table 3 The Augmentation-Adequate Contractions Interval in Study Arms (Onset Interval) in Minutes

	MEAN ± SD			
	Oxytocin	**Misoprostol**	**T test**	**p-value**
Augmentation-adequate contractions interval in Study arms (onset interval) in minutes.	8.73 ± 2.03	9.03 ± 1.72	1.205	0.988
The augmentation-delivery interval in the study arms (in hours).	4.69 ± 1.99	4.47 ± 1.64	3.403	0.911
Birth weight groups (kg)	3.54 ± 0.36	3.64± 0.36	0.226	0.721
APGAR score at birth	8.41±0.66	8.44 ± 0.17	0.806	0.451
Estimated blood loss (mls)	284.15 ± 20.17	334.72 ± 24.67	3.912	0.051

Over 90 % in each arm had a successful vaginal delivery which is the main aim of augmentation of labour. Caesarean section rate overall in this study was 6% while in the arms (Oxy vs. Miso: 6.9% vs. 5.0%) was found. This is lower than the reported values of 11% vs. 10 % in Oxy and Miso arm respectively in the study done in USA (17). This finding is also in sharp contrast to the high Caesarean section rate of about 30% reported in the tropics (40). However, this study was done only in primigravidae which could have limited the rate of surgical intervention in labour and majority of the participants were booked with proper assessment prior onset of labour. Positional Cephalopelvic disproportion was the only indication for Caesarean section done in this study.

The mean estimated blood loss (mls) in both arms of the study was not significant, although the estimation was a subjective estimation using the visual inspection with perineal pad estimation, though this method of estimation has also been found to be effective in quantification of blood loss in obstetric practice (38,39) No single case of postpartum hemorrhage was reported because all the patients were managed actively in third stage of labour nor uterine rupture incidence during this study (16). This is due to stringent intrapartum surveillances deployed and low dose of misoprostol was used unlike when high dose of misoprostol was administered (40).

Table 4 Association of Maternal outcome in each the Study Arms

Variable	Oxy arm frequency (%)	Miso arm frequency (%)	X^2	Df	p-value
Duration in Active phase					
<2 hours*	10 (3.1)	5 (1.6)	5.9324	2	0.051
2 – 8 hours	139 (43.7)	151 (47.5)			
>8hours**	10 (3.1)	3 (0.9)			
Fetal heart rate abnormalities					
Yes	60 (37.7)	92 (57.9)	12.9055	1	<0.001**
No	99 (62.3)	67 (42.1)			
Symptoms (response) **Fever/chills**					
Yes	80 (50.3)	78 (49.1)	0.0503.	1	0.823
No	79 (49.7)	81 (50.9)			
Vomiting					
Yes	68 (42.8)	87 (54.7)	5.0113	1	0.033
No	91 (57.2)	72 (45.3)			
Loose stool					
Yes	26 (16.4)	23 (14.5)	0.2171	1	0.641
No	133 (83.6)	136 (85.5)			
Mode of delivery					
SVD	146(91.8)	150(88.7%)	0.861	2	0.650
Operative delivery	2(1.3)	11(6.5%)			
Caesarean section	11(6.9)	8(4.7%)			

The fetal outcomes determined in this study were asphyxiation and birth weight. The birth weight was not statistically significant between the two study arms. Larger proportions of the two study arms have a mean birth weight of 3.38 ± 0.24 kg in Oxy arm and 3.46 ± 0.22 kg in Miso arm. Majority of the birth weight are within 3.0 – 4.0 kg which is in consonance with the reported value of birth weight in primigaivda in Nigeria (29). Macrosomic babies (>4kg) were reported in both arms of this study with no significant difference, all were delivered via vaginal route with no feto-maternal complication, they were not diagnosed prior delivery, this buttress the point that in some selected primigravidae with suspected macrosomia can have vaginal delivery with no complication. Majority of the neonates had a good APGAR score at birth and very few had mild asphyxia that was managed by observation at mother side.

Stillbirth and Intrauterine fetal death were not recorded throughout this study due to the intrapartum fetal surveillances deployed. Analgesia uptake was high in both arms of the study (47.17% and 39.3% in Oxy and Miso arm respectively) with no significance differences, this study shows a higher analgesia usage in labour in the low resource setting/ tropics compare to previous studies done in the tropics where its usage is very low and the ideal analgesia for labour is epidural which was readily made available in other comparative studies (40). Poor pain management in labour accounted for the attrition rate of 3.15% with equal proportion from each arm. Those that opted out were mainly due

to inadequate pain management in labour coupled with some cultural taboos about labour experience. Epidural analgesia is the gold standard for pain management in labour, however it could not be provided for all patients in this study due to cost, personnel availability and non-acceptance by few, these factors are common in the tropics it was also reported in a study done in Owo, Ondo state South West, Nigeria (40).

Antiemetic uptake was higher in Miso arm than Oxy arm but no significant difference with no adverse effect on feto-maternal outcomes, antipyretic uptake was the least out of the intrapartum medications used, it has no significant difference. All these medications have no demonstrable adverse effect on the course of labour nor on the feto-maternal outcome

5. Conclusion

Twenty mcg oral solution of Misoprostol is as effective and safe as Oxytocin for augmentation of labour in primigravidae in active phase of labour. Though, there was significant vomiting (side effects) with the use of oral misoprostol but this is ameliorable to readily available medications with no adverse effect to the mother and fetus.

Compliance with ethical standards

Acknowledgments

We extend our gratitude to all the members of staff in the hospitals

Disclosure of conflict of interest

This study has no conflict of interest with anybody/bodies, person/persons, company/companies nor organization

Author's Contributions

Study conception: OEA AFA, JK, AF and KA, Data collection: OEA and KA; Data analysis and interpretation: OEA, AFA and JF; Manuscript drafting by OEA and proof reading by AAN. All authors reviewed and approved the revised manuscript.

Statement of ethical approval

Ethical approval was obtained from the Ethics and Research Ethics Committee of the University of Osun Teaching Hospital Osogbo Osun state (LTH/EC/2017/03/294).

Statement of informed consent

Participation was voluntary, and informed consent was obtained from participants. Share upon reasonable request Data Sharing Policy. The data is presently unavailable in the public domain because authors do not have permission to share data yet. So, data would be made available only on request.

Funding

The authors exclusively provided the funding for the study.

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