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Research Report

Effect of misoprostol on type 3 transformation zone of the cervix among Cameroonian women

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ABSTRACT

Background: Type 3 transformation zone (TZ) of the cervix has been shown to be associated with a four to five-fold increased risk of missed precancerous/cancerous lesions. The aim of this study was to evaluate the effect of intravaginal misoprostol on the TZ among women with Type 3 TZ in Cameroon.
Materials and methods: A single dose of vaginal misoprostol (400 mcg or 600 mcg) was administered as part of the plan of care for women with Type 3 TZ during cervical cancer screening. The primary outcome was successful conversion from Type 3 TZ to Types 1 or 2 TZ. Descriptive analysis was performed using chi-square and Fisher's exact tests.
Results: Among the 90 of 107 (84.2%) women who returned for re-evaluation of the cervix, 43 (47.8%, 95% CI: 0.36%-0.60%) had conversion of Type 3 TZ to Types 1 or 2. Women who received misoprostol 600 mcg were more likely to have their Type 3 TZs converted to Types 1 or 2 than women receiving 400 mcg ($p = 0.037$).
Conclusion: Misoprostol converted approximately 50% of Type 3 TZ to Types 1 or 2 in Cameroon. Misoprostol is feasible in converting Type 3 TZ to Types 1 or 2 among Cameroonian women.

1. Introduction

Women undergoing regular cervical cancer screening with visual inspection with acetic acid (VIA) and visual inspection with Lugol's iodine (VILI) with Type 3 transformation zone (TZ) of the cervix have up to a four to five-fold increased risk of missed precancerous or cancerous lesions (Qianwen et al., 2019; Manga et al., 2021). Therefore, Type 3 TZ of the cervix poses a challenge in cervical cancer screening programs that rely solely on VIA/VILI. The TZ is the most important portion of the cervix to be examined during cervical cancer screening with VIA/VILI because it is the area where most cervical precancers and cancers originate (Luyten et al., 2015; O'Connor et al., 2014).

Compared to other cervical cancer screening techniques, VIA/VILI are easier to perform, cheaper, and do not require any sophisticated equipment (WHO, 2014). The World Health Organization (WHO), for several years, endorsed VIA as a primary screening test for cervical cancer in low-and-middle income countries (LMICs). In 2021, WHO has recommended the human papilloma virus (HPV) testing as preferred screening in all settings, although VIA remains an option (WHO, 2021). However, it may take decades for VIA/VILI programs in LMICs to transition to HPV testing due to costs and logistics. Furthermore, even in the HPV testing era, VIA is still required as a triage test for those positive for oncogenic HPV in many settings (WHO, 2021). Therefore, VIA will remain an important primary or adjunctive component of cervical cancer screening program in LMICs.

In high-income countries, women with Type 3 TZs undergoing cervical cancer screening usually undergo endocervical curettage (ECC) to sample the portion of the TZ that has been driven into the internal

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cervical canal (Gage et al., 2003). In LMICs, obtaining pathological results from endocervical sample has been quite challenging, typically because there are fewer pathologists and they might not have the experience or equipment to adequately analyze samples from ECC. Thus, a feasible solution for women with Type 3 TZ is needed in LMICs.

Misoprostol is a prostaglandin E1 analogue that causes ripening of the cervix with softening and dilation. It is commonly used in obstetrics to induce labor or treat missed/incomplete first trimester miscarriage (Abubeker et al., 2020; Wu et al., 2017.) Thus, misoprostol has to be used with caution among women of reproductive age and pregnancy has to be adequately ruled out.

Intra-vaginal misoprostol 200–400 mcg has been evaluated in converting Type 3 TZ to Types 1 or 2 and the results appear promising, though none of the studies had adequate sample size (Wu et al., 2017). In addition, none of these previous studies were done in Africa where the burden of cervical cancer is high and where VIA is widely used (Manga et al., 2022). The aim of this study was to evaluate the effect of the use of misoprostol on the TZ among women with Type 3 TZ in Cameroon. We also examined dose and side effects.

2. Materials and methods

2.1. Setting and procedure

We conducted a retrospective cohort study of women with Type 3 TZs who received intravaginal misoprostol during cervical cancer screening in the Cameroon Baptist Convention Health Services (CBCHS) Women's Health Program (WHP). The Institutional Review Boards (IRBs) of CBCHS and University of Alabama at Birmingham (UAB) provided IRB approvals. The CBCHS is a large faith-based healthcare organization that runs a system of 94 health facilities located in nine of the 10 regions of Cameroon (http://www.cbchealthservices.org). The CBCHS implemented the WHP in 2007 principally to fight against cervical cancer. The WHP has become the most comprehensive cervical cancer prevention program in Cameroon and it runs in 12 of the CBCHS facilities (DeGregorio et al., 2017; DeGregorio et al., 2016). For a decade, the program relied principally on visual inspection with acetic acid and Lugol's iodine (VIA/VILI) enhanced by digital cervicography (DC), and it has been described in detail in our previous work (Manga et al., 2015; Manga et al., 2020). Beginning in 2020, the program uses human papilloma virus (HPV) testing as the primary screening test for women 30 years and above and those who are found to be HPV-positive are triaged to VIA/VILI-DC. Based on the available evidence of the effect of misoprostol on the transformation zone (TZ), WHP began offering the use of misoprostol intravaginally to enhance visualization of the TZ among women with Type 3 TZs as part of clinical practice in March 2020.

Data from women seen at six WHP sites were included in this analysis (EtougEbe Baptist Hospital and Ekoumdoum Baptist Hospital in Yaoundé, Mboppi Baptist Hospital in Douala, Nkwen Baptist Health Center in Bamenda, Mutengene Baptist Hospital and Kribi Baptist Health Center). Additionally, from July to October 2020, WHP partnered with Horizons Femmes (HF), a non-governmental organization that caters to the health needs of female sex workers (FSWs), to screen 1000 FSWs for oncogenic HPV types, cervical cancer, and four sexually transmitted infections; Chlamydia trachomatis, Neisseria gonorrhea, Trichomonas vaginalis, and Mycoplasma genitalium. They were screened at the HF drop-in center in Bafoussam, Yaoundé, and Douala. These patients were also offered misoprostol if Type 3 TZ was seen. In premenopausal women, pregnancy was ruled out from history of last menstrual period and in cases of uncertainty such as missed or delayed periods, the misoprostol was not administered. The misoprostol was inserted at the end of the VIA/VILI-DC screening after removal of the vaginal speculum. Its purpose was further explained to the woman using the photograph of her cervix and showing how her squamo-columnar junction (SCJ) had migrated into the endocervix beyond view (Type 3 TZ) making her screening results inadequate and the potential of misoprostol to enable complete visualization of the TZ. The patient had to be available for rescreening within two hours or the next day, otherwise the drug was not administered. Some women waited for at least two hours and had their rescreening before going home while others went away and returned hours later or the following day. During the re-screening, the same VIA/VILI-DC procedure was performed. Side effects, including lower abdominal pain, nausea/vomiting, fever, diarrhea, were documented in addition to changes in the extent of visualization of the TZ type and any new lesions seen.

All women seen by the CBCHS WHP team with Type 3 TZs who received misoprostol were included in the current analysis. We excluded those who were unable to return to the clinic for re-examination at least two hours later or the next day. The data sources were the WHP clinic records including a dedicated misoprostol reporting form. The misoprostol record included date and time of administration, dose, date and time of re-screening, changes in visualization of the TZ and SCJ at re-screening, and side effects. The changes in the TZ were categorized into no change (Type 3), change to Type 1 or 2. Demographic information was captured in our routine WHP enrollment form.

The primary outcome for this study was the successful conversion from Type 3 to Types 1 or 2 TZs after treatment with intravaginal misoprostol (i.e., the proportion of all those with Type 3 TZ who developed Type 1 or 2 TZ) after misoprostol. The secondary outcomes were successful detection of abnormal VIA/VILI-DC result at re-screening that was not identified at the time of initial screening, change in percentage of SCJ visualized after misoprostol, and reported side effects. We also explored differences in outcomes by dose of misoprostol received and timing of re-screening associated with successful conversion of Type 3 TZs.

We provided descriptive statistics (frequency and percentage) for the overall patient cohort, including age, occupation, menopausal status, HIV status, parity, and time from administration to re-screening. We determined the frequency of successful detection of cervical lesions post conversion (frequency and percentage) with any dosage of misoprostol. We evaluated whether certain relevant factors (age, menopausal status, parity, time from administration to re-screening) were associated with successful conversion or successful detection. Chi-square tests of association and Fisher's exact test, as relevant, were used to compare proportions and Wilcoxon rank test for median for time to conversion (median, IQR).

3. Results

From March to October 2020, 2,146 women were seen for cervical cancer screening at the six Women's Health Program (WHP) participating sites and 953 women at Horizons Femmes (HF) centers. A total of 107 women with Type 3 TZs received intravaginal misoprostol at doses of either 400 mcg (n = 37, 25.2%) or 600 mcg (n = 70, 65.4%). After excluding 17 women who did not return at least two hours later or the next day for rescreening, a total of 90 women were retained for analysis (Fig. 1). Most of the women who received 400 mcg of misoprostol were seen at the WHP clinics and returned for re-evaluation in two hours while most of those who received 600 mcg were FSWs screened at HF clinics who returned the next day for re-evaluation.

There were 37 women receiving 400 mcg, and 70 women receiving 600 mcg. Among the 400 mcg group, 40% (95% CI: 0.25%-0.58%) women had successful conversions. Among the 600 mcg group, 62.5% (95% CI: 0.46%-0.76%) women had successful conversions. In total, among the 90 women who returned for re-evaluation, 43 (47.8%, 95% CI: 0.36–0.60) had their Type 3 TZs converted to Types 1 or 2. Of these 43 women, 1 (2.3%, 95% CI: 0.003–0.14) woman had a positive lesion at re-screening which was eligible for loop electrosurgical excision procedure (LEEP). The LEEP was done and the histopathological report was CIN2 (high-grade lesion).

The participants' characteristics according to Type 3 TZ conversion

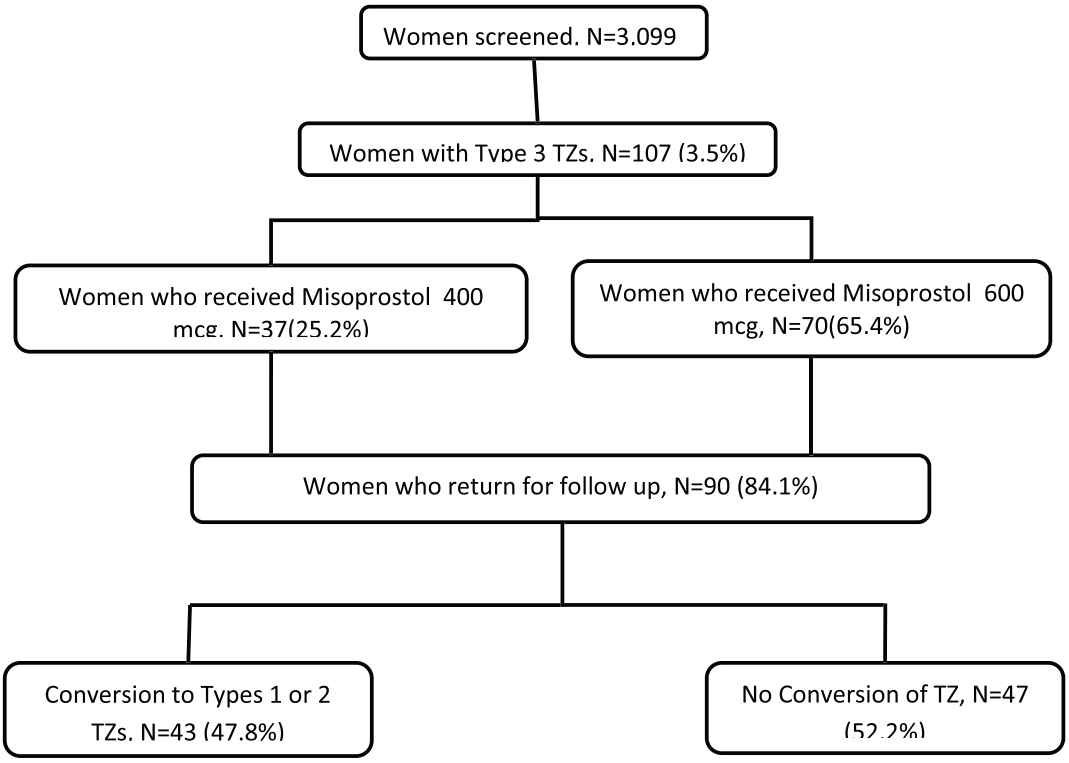

Fig. 1. Algorithm.

are shown in Table 1. Female sex workers (FSWs) were more likely to have their Type 3 TZs converted with intravaginal misoprostol than women of other professions ($p = 0.003$). Women who received misoprostol 600 mcg were more likely to have their Type 3 TZs converted to Types 1 or 2 (63.8%) compared to women who received 400 mcg (36.2%; $p = 0.037$). However, median time at re-screening was 2.6 (2.2–4.0) hours for women who received 400 mcg and 23.8 (21.3–25.9) hours for those who received 600 mcg ($p < 0.0001$).

Comparing side effects between the 400 mcg and the 600 mcg doses of misoprostol, more mild and moderate nausea were reported in the 600 mcg group ($p = 0.007$). Few cases of severe abdominal pains were reported only in the 600 mcg group but none in the 400 mcg group ($p < 0.001$).

4. Discussion

Among women who received 400–600 mcg of misoprostol for Type 3 TZ, we observed a conversion proportion of approximately 50% and a previously missed clinically significant lesion was observed in 2.3% of those who converted. Significantly more women who received 600 mcg appeared to convert from Type 3 to Types 1 or 2 TZ, but the results are difficult to interpret as the median time to re-screening was over 20 hours later in that group compared with those who received 400 mcg. Overall, misoprostol was well tolerated in the study group although more side-effects were observed with 600 mcg.

Our findings for conversation rate overall are consistent with prior studies in which the response rate to single dose intravaginal misoprostol (200 mcg or 400 mcg) was 20–79% within 4–6 hours (Pergialiotis et al., 2015; Aggarwal et al., 2006; Thanapprapasr et al., 2010; Tungmunsakulchai, 2010). However, these were four small, non-powered, randomized control trials (RCTs) in which the rate of conversion in the control groups ranged from 0% to 20%. A major difference is that our study was a retrospective cohort reporting our preliminary experience with clinical implementation while the described studies were RCTs. The 600 mcg of misoprostol, although consistent with clinically approved doses (Abubeker et al., 2020), was higher than the doses used in prior trials. We anticipated higher conversion rates but since more women who received 600 mcg were FSWs who elected to return the next day rather than wait for same-day re-screenings, we are unable to tease the effect of dose from duration of misoprostol placement using our data. Furthermore, even though the doses were well tolerated overall, 600 mcg was associated with more side effects than the 400 mcg. In a Norwegian study in which women were administered up to 1000 mcg of misoprostol intravaginally, the side effects were also well tolerated (Oppegaard et al., 2010) suggesting that the drug is safe even at high doses when administered intravaginally.

We reported a 2.3% of high-grade lesion (CIN 2) diagnosed after conversion which would have been otherwise missed. Treatment by Loop Electrosurgical Excision Procedure (LEEP) per program protocol was administered. In high-income countries, women with Type 3 TZs undergo endocervical curettage (ECC) to sample the portion of the TZ beyond view. ECC is able to diagnose cervical lesions which would have been otherwise missed (Gage et al., 2003), In one study, of the 40 patients who were randomized into misoprostol and placebo groups in the ratio 1:1, only 4 patients in the misoprostol group underwent ECC compared to 13 patients in the placebo group (Aggarwal et al., 2006). Furthermore, consistent with our findings, in cases where ECC has been done on women with Type 3 TZs, the prevalence of significant lesions diagnosed that would have been otherwise missed ranged from 1.01% to 14.4% (Gage et al., 2003; Liu et al., 2017). However, ECC requires histopathology services and always more than one visit (enhancing loss to follow up). Therefore, it is not typically available in Cameroon and many LMICs.

We acknowledge several weaknesses in our study. First, the data reflects clinical experience and does not include a contemporary comparison group without misoprostol as may be available from a clinical trial, thus the true efficacy of misoprostol is not reported. However, we would expect few if any patients who do not receive misoprostol to return with a conversion in the same time interval of two hours to one day. Second, 17 women (15.9%) with Type 3 TZs who received misoprostol

Table 1
Demographic characteristics of Participants According to Type 3 TZ Conversion (N = 90).

Characteristics	Conversion to Type 1 or 2 N=43	No Conversion N=47	Total	P Value
Age				0.242
<30	13 (27.7)	6 (14.0)	19 (21.1)	
30–49	25 (53.2)	25 (58.1)	50 (55.6)	
≥50	9 (19.1)	12 (27.9)	21 (23.3)	
Menopausal Status				0.408
Yes	17 (37.0)	17 (46.0)	34 (41.0)	
No	29 (63.0)	20 (54.0)	49 (50.0)	
Marital Status				0.368
Married	10 (21.7)	13 (35.1)	23 (27.7)	
Single	30 (65.2)	19 (51.4)	49 (59.0)	
Others	6 (13.0)	5 (13.5)	11 (13.3)	
Educational Level				0.291
0–7 years	12 (30.0)	16 (48.5)	28 (38.4)	
8–14 years	21 (52.5)	13 (39.4)	34 (46.6)	
15–17 years	5 (12.5)	4 (12.1)	9 (12.3)	
≥18 years	2 (5.)	0 (0)	2 (2.7)	
Occupation				0.003
Sex worker	33 (70.2)	14 (37.8)	7 (56.0)	
Others	14 (29.8)	23 (62.2)	37 (44.0)	
HIV Status				0.582
Positive	14 (31.1)	14 (36.8)	28 (33.7)	
Negative	31 (68.9)	24 (63.2)	55 (66.3)	
Parity				0.164
0	12 (25.5)	5 (12.8)	17 (19.8)	
01-Feb	12 (25.5)	12 (30.8)	24 (27.9)	
03-Apr	11 (23.5)	16 (41.0)	27 (31.4)	
≥5	12 (25.5)	6 (15.4)	18 (20.9)	
Dosage				0.037
400 mcg	17 (36.2)	25 (58.1)	42 (46.7)	
600 mcg	30 (63.8)	18 (41.9)	48 (53.3)	

did not return for re-evaluation. Thus, we cannot determine the status of their conversion. Third, there may be variability in practice between health workers at the sites (mainly nurses) in their interpretation of Type 3 TZ and conversions. This reflects clinical practice and we did not conduct any quality control. Finally, the dose and time to re-examination was not standardized and varied from two hours to the next day depending on the patient's preference and availability. Therefore, we are unable to tease out the important roles of dose and duration of placement. The major strength of our study is that it is among the first studies to report the clinical experience using misoprostol for conversion of Type 3 TZ in Africa. It highlights some of the challenges for cervical cancer screening programs including failure to follow-up within a short time period.

Transforming a Type 3 TZ to Types 1 or 2 during cervical cancer screening is very important to identify hidden lesions which would have been otherwise missed (Pergialiotis et al., 2015). In our previous work in Cameroon, we have observed women with Type 3 TZs who received reassuring cervical cancer screening results but returned to clinic in one to two years with invasive cervical cancer (ICC) (Manga et al., 2021). Conversion of Type 3 TZ to Types 1 or 2 has not been given adequate attention as evident in the limited number studies in the medical literature. Although oral and intravaginal estradiol have also been tried in converting Type 3 TZ to Types 1 or 2 with promising results (Beniwal et al., 2016; Saunders et al., 1990; Piccoli et al., 2008), their multi-dose regimen over 5–10 days increases cost and makes compliance difficult (Aggarwal et al., 2006). However, misoprostol is administered in single dose which is an added advantage (Pergialiotis et al., 2015). Secondly, misoprostol is included on the 2019 WHO Essential Drug List, making it widely available and affordable in LMICs compared to estradiol (WHO, 2019). Therefore, misoprostol is more feasible for use in converting Type 3 TZ to Types 1 or 2 in LMICs. Misoprostol has maximum absorption within four to six hours after intravaginal insertion. Although women have to wait few to several hours after misoprostol administration, most evaluation can be completed in a single visit, which supports the "see-and-treat" approach of cervical cancer screening recommended for LMICs by WHO.

5. Conclusion

Our data demonstrate that the use of misoprostol is feasible in LMICs to convert Type 3 TZ to Types 1 or 2 and expose lesions which would have been otherwise missed and is well tolerated. Doses of 400mcg or 600mcg may be used as it is not clear that the higher dose is associated with better conversion rates adjusted for duration of placement. Future studies should include clinical trials with adequate sample sizes in LMICs, especially in sub–Saharan Africa where the burden of cervical cancer is higher. Such studies should address the role of different types of screening methods and groups for whom misoprostol is most effective.

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Informed Consent

The IRB waived requirements for informed consent because the study was based on review of secondary data.

Institutional Review Board (IRB) Statement

This research was granted expedited and except approval by the Cameroon Baptist Convention Health Services IRB2021-04 and an IRB waiver by the University of Alabama at Birmingham.

Informed Consent Statement

Not applicable.

CRediT authorship contribution statement

Simon M. Manga: Conceptualization, Methodology, Writing – original draft. **Margaret I. Liang:** Methodology, Writing – original draft, Writing – review & editing. **Yuanfan Ye:** Formal analysis, Writing – review & editing. **Jeff M. Szychowski:** Formal analysis, Writing – review & editing. **Kathleen L. Nulah:** Data curation. **Alan T. Tita:** Writing – review & editing. **Isabel Scarinci:** Writing – review & editing. **Warner K. Huh:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

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