Cancer Therapy & Oncology
International Journal
ISSN: 2473-554X

Juniper Publishers
key to the Researchers

Research Article
Volume 27 Issue 3 - October 2024
DOI: 10.19080/CTOIJ.2024.25.556220

Cancer Ther Oncol Int J

Enhancing Cervical Preparation with Misoprostol in Brachytherapy

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Submission: September 17, 2024; **Published:** October 09, 2024

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Abstract

Abstract: Intracavitary brachytherapy is indispensable while treating carcinoma cervix. Negotiating the cervical Os is the key step while performing ICRT. Our institutional experience concludes that prescribing oral prostaglandin before the procedure facilitates dilating the Os making the procedure easier and less time consuming. It is cost effective and valuable in a nation with limited resources.

Purpose: To evaluate the efficacy of oral misoprostol in facilitation tandem application to the cervix during brachytherapy in patients with cervical cancer.

Methods and Materials: 306 patients with cervical cancer who had been planned to undergo brachytherapy at our institute were evaluated in a retrospectively from 2013-2019. All patients treated with radical radiation therapy undergoing intra-cavitary or interstitial brachytherapy were analyzed. All patients received 200 mg of misoprostol on the day prior and on the day of the procedure before tandem application. The entire group was analyzed in terms of age, stage and size of Hegar dilators used for cervical dilatation.

Results: Of all cases, 4% were Stage IB3 ,6% were Stage IIA, 12%% stage IIB, 10% stage IIIA ,29 % stage IIIB, 24% stage III C and 15 % stage IVA respectively. Mean (±SD) age (range) was 48 (25-68) years. Application was significantly easier in the entire group and the average size of initial Hegar dilators used for cervical dilatation was higher. Of the entire group there was only one case of severe cramping pain abdomen after consumption of misoprostol. In 9 cases (2.94%) Cervical Os was non-negotiable despite the usage of Misoprostol,6 cases in interstitial brachytherapy and 3 of intracavitary brachytherapy. There were 3 cases (0.98%) of uterine perforation identified on the planning CT scan.

Conclusion: Misoprostol administration for cervical ripening before brachytherapy facilitates the procedure, increases patient tolerability and comfort, and may decrease complication rates like inadvertent uterine perforation or false tract formation. It is also cost effective as it reduced the number of cases requiring systemic or regional anesthesia.

Keywords: Intracavitary therapy; ICRT; Cervical Os dilation; Misoprostol; Brachytherapy; Cervix cancer

Introduction

Brachytherapy is an integral component in the treatment of carcinoma cervix [1]. It is the most conformal technique of radiation due to its ability to deliver high doses of radiation to a localized area, with relative sparing of adjacent normal tissues. Identification and dilatation of cervical canal is a key step in intracavitary brachytherapy for carcinoma cervix. The difficulties in cervical dilatation can lead to several complications including bleeding, infection, abscess formation and uterine perforation. There is a reported incidence of 1.75-13% of uterine perforation during intracavitary brachytherapy. Uterine perforation occurs more frequently in patients with anatomical distortions of the cervix and/or cervical stenosis due to advanced disease, post irradiation fibrosis and previous cone biopsy. Other predisposing factors include retroverted/retroflexed and extremely anteverted/anteflexed uterus. It is not uncommon to find intense fibrosis in patients who have also received neoadjuvant chemotherapy. Owing to distortion of the cervical canal or obliteration, tandem insertions can be difficult, even to professionals with expertise [2].

A variety of techniques have been adopted to facilitate and ensure an accurate placement of the uterine tandem during brachytherapy applicator insertion. These include postoperative plain films or computerized tomography, intraoperative transabdominal or transrectal ultrasound guidance at the time of placement [1,3-6]. When postoperative techniques are used to confirm perforation, it necessitates a second visit to the operating room, a second general anesthetic, as well as a treatment delay that may impact negatively upon central control rates in the long term. Intraoperative techniques have their limitations as well, particularly in the obese patient and at times no availability of such techniques in certain centers. With difficult insertions, direct endoscopic evaluation at the time of tandem insertion is the only means of knowing definitively the location of the tandem prior to leaving the operating room. The complications can be reduced if the cervix is ripened before the procedure and is therefore recommended in several guidelines for dilatation of non-pregnant cervix also.

Misoprostol is a synthetic prostaglandin E1 analog. It is extensively absorbed, and undergoes rapid de-esterification to its free acid, which is responsible for its clinical activity. It has a short half-life, few side effects, it is stable at room temperature, it is relatively cheap, and the dosage can easily be adjusted according to the clinical need [2]. Various doses, routes, and time intervals between misoprostol application and the intervention have been evaluated .A single dose of 400mg given sublingually (oral) or vaginally 3 h before the intervention or 200 microgram at 12 hours interval (oral or vaginal) can give reasonable ripening [7]. Higher doses or longer intervals do not improve the effect on the cervix. Pain is the most frequent side effect which can be treated with nonsteroidal anti-inflammatory drugs [7].

Misoprostol has been extensively studied in reproductive health. It is known to be effective for priming in nonpregnant women [8]. It is widely recommended for the treatment of missed and incomplete miscarriages, the induction of abortion, and cervical preparation before uterine instrumentation, induction of labor and postpartum hemorrhage prophylaxis and treatment [7-9]. Its efficacy in postmenopausal women is conflicting. Cervical preparation prior to brachytherapy to facilitate the identification and negotiation of the cervical Os was adopted at our center in August 2013. The aim was to decreasing chances of false tract formation and uterine perforations. The current study analyses all the cases treated after cervical ripening with misoprostol administered orally prior to brachytherapy so as to provide insight regarding usefulness of misoprostol in clinical practice.

Methods and Materials

This analysis was conducted retrospectively for patients of carcinoma cervix treated between Sept 2013 and October 2019 at the Radiation Oncology at a tertiary care cancer center. This study included 306 patients of carcinoma cervix stage II A to IV A. All patients received Radical concurrent chemo-radiation followed by 3 sessions of BT (with or without anesthesia) or Interstitial brachytherapy under spinal epidural anesthesia. The informed consent was obtained for the procedure from all patients. The International Federation of Gynecology and Obstetrics classification was used for clinical staging. Since the FIGO staging was revised in 2018 so the staging was based on revised staging system in patients treated 2018 onwards. Pre-brachytherapy MRI was performed if deemed necessary, especially in case of interstitial implants. Tablet Misoprostol 200 microgram was administered orally at bed time prior to procedure and early morning on the day of the Brachytherapy for cervical dilatation at-least 3 h before tandem application. Intravaginal Misoprostol pessary insertion was also done in some cases, but they were not included for analysis.

Intracavitary brachytherapy (ICRT) was initiated after pelvic EBRT and was performed with anesthesia till Dec 2014. Thereafter with a good cervical dilatation achieved by misoprostol, in subsequent cases ICRT was performed under mild sedation with Fortwin and Phenargen. The high-dose-rate accelerated microselectron HDR V3 after loading system was used in intracavitary applications. Standard procedures for ICRT were performed Cervical Os was localized dilated with Hegar's dilator if required, length of uterine canal was measured with sound and appropriate intrauterine tandem were inserted(Three different tandem applicators, consisting of three curved applicators ;the angles of the curved tandems were 15, 30. & 45 and the external diameter was 3.2 mm). The two ovoids were selected based on individual anatomy. Adequate packing with Betadine soaked gauze packs was done.

The total tumor dose (21 Gy) was administered to point A in three fractions in ICRT and 27.5 Gy in 5 fractions was delivered in Interstitial brachytherapy. The ICRT planning was done by 2D or 3D CT scan-based planning, but interstitial brachytherapy underwent only 3D CT based planning. The amount of bleeding was retrieved from the operative notes was graded by the physician as either absent (no bleeding), minor (bleeding not requiring any intervention < 10 cc), moderate (bleeding that stops by pressure application for 5 min 20-30c), or heavy (bleeding that stops by suturing or pressure application for 2 h/> 50cc). Sizes of Hegar dilator dilatation required prior to insertion of the intrauterine tandem were also retrieved from the records for each patient.

Results & Observations

A total of 306 patients underwent brachytherapy after cervical ripening in study duration. Misoprostol was administered during 819 ICRT sessions and 31 interstitial brachytherapy sessions. Patient characteristics are summarized in Table 1. Patient age ranged from 38-68 years and median age was 48 years. Most of the patients (29%) had Stage IIIB disease (Table 1). All patients were examined under sedation/anesthesia (Table 2).

How to cite this article: Kanika Sood S, Satinder K, Neha A, Aditi T, Manisha H. Enhancing Cervical Preparation with Misoprostol in Brachytherapy. Canc Therapy & Oncol Int J. 2024; 27(4): 556220. DOI: 10.19080/CTOIJ.2024.27.556220

Table 1: Patient Characteristics - stage.

Stage	Number(%)
IB3	12(4)
IIA	18(6)
IIB	37(12)
IIIA	30(10)
IIIB	89(29)
IIIC1	49(16)
IIIC2	25(8)
IVA	46(15)

Table 2: Types of brachytherapy procedure.

Type of Anesthesia/Sedation	Number of brachytherapy sessions
Spinal Epidural	31 Interstitial brachytherapy
General Anesthesia	Intracavitory 25
Spinal Anesthesia	Intracavitory 18
Sedation with fortiwn phe-nargen	Intracavitory 232

120 patients had no disease identifiable, and 186 patients had residual disease confined to cervix at the time of brachytherapy (Table 3). Uterocervical length was estimated by uterine sound. The tandem insertion was easier after misoprostol intake. The mean size of initial Hegar dilator was easily achieved to 12 Fr in more than 60 % cases (Table 4) There was no requirement of cervical dilation in 12 patients, where uterine tandem could be directly inserted after estimation of uterocervical length. In 97 patients (33%) the cervical os was easily negotiated but minimal cervical dilatation was required. There was no impact of age on cervical dilatation. The ease of insertion of tandem was similar across all age groups. The cervical os was nonnegotiable despite usage misoprostol in 9 patients. Of these 6 patients had gap of more than 2 weeks between completion of external RT to first brachytherapy procedure. (Table 5) In these 9 patients interstitial implant without uterine tandem placement was undertaken.

Table 3: Findings at the time of brachytherapy.

EUA findings	Number (%)
No residual disease - Os Negotiable	117(38.2%)
No residual Disease - Os Non-Negotiable	3(0.98%)
Residual Disease- Os Negotiable	180(58.8%)
Residual Disease - Os Non-negotiable	6(1.96%)

Table 4: Hegar's dilator size for Negotiation of cervical Os.

Initial Hegar's dilator Number (Double ended)	Number
3mm(9Fr)	97(33%)
4mm(12Fr)	188(63.3%)
5mm(15Fr)	9(3%)
6mm(18Fr)	3(.34%)

Table 5: Interval between external beam radiation therapy and brachytherapy.

Interval from EBRT	Number
1 week	235(77%)
>1 week	46(15%)
>2 weeks	17(5.5%)
>3weeks	8(2.6%)

The ICRT planning was done by 3D planning after acquiring CT scan in 171 cases (62.2%) and X ray-based planning was undertaken in 104 cases (37.8%). All cases of interstitial brachytherapy underwent CT based planning. Operative complications included vaginal tear (one patient) and uterine perforation 3 patients. In 91.4% of all cases there was either no or minor bleeding during and after tandem application. Rest of the cases where moderate bleeding was encountered were after removal of the interstitial applicator (Table 6). Misoprostol was tolerated well. One out of 306 patients reported complaints of cramping pain in lower abdomen after administration of Misoprostol. Pain was managed with antispasmodic agents. She did not receive Misoprostol in subsequent sessions of brachytherapy. We did not encounter any other complication that may be attributable to the use of misoprostol.

Table 6: Grades of bleeding.

Bleeding Grade	Number
No	62(20.2%)
Minor	218(71.2%)
Moderate	26(8.5%)
Heavy	Nil

Discussion

Intracavitary brachytherapy is an important pillar in the management of cervical cancer. But the successful brachytherapy implant is affected by many factors including the stage of disease at presentation, presence of residual disease at time of brachytherapy and treatment induced fibrosis [10]. Post External Beam Radiation Therapy (EBRT) fibrosis can cause retraction ,obstruction or deviation of the cervical canal [11]. Additionally, it is difficult to place implants in older patients because of anatomic

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distortion and tissue atrophy [11]. Such complexities can lead to under dosing of the tumor and also increase the risks of inadvertent uterine perforation [12].

As is the case in other uterine interventions, cervical dilatation affects the success of tandem application. Tandem application is easier if the procedure is performed under ultrasound guidance [13]. Cervical priming is also helpful as a means of pain reduction and can be used either in addition to, or instead of, local anesthesia. of women undergoing surgical termination of pregnancy. Priming with vaginal misoprostol (with no additional analgesics) was compared with a paracervical block (with no priming) in a study by Saxena et al. [14]. They demonstrated that women who received misoprostol reported significantly less pain at the time of mechanical dilatation of the cervix.

In our study we did not assess pain scores but due to a good cervical dilatation seen in the first 15 patients we attempted the subsequent ICRT insertions in mild sedation without anesthesia. The safe insertion of brachytherapy implant after cervical ripening without anesthesia and brought down the cost of the procedure to half the estimated expenditure in comparison to the procedures performed with anesthesia thereby increasing the cost effectiveness. It is of importance in our country as most patients of cervical cancer belong to lower socio economical strata with limited financial resources.

Many studies have shown that misoprostol significantly increased cervical dilatation and decreased both cervical resistance and the need for additional cervical dilatation before hysteroscopy [7, 8,9,15,16]. Few of these studies had placed misoprostol vaginally 9-10 hours prior to the procedure [16]. Misoprostol enhanced cervical dilatation and reduced the requirement for dilatation thereby reducing the operating time & frequency of cervical tears. Oral Misoprostol for cervical priming has been established randomized controlled study of nulliparous women [17]. In these studies authors found that the cumulative force required to dilate the cervix was significantly less and that the mean cervical dilatation was significantly greater in the misoprostol group [8]. In our study also oral misoprostol was preferred, although we have attempted misoprostol pessaries in selected cases which we have excluded in this analysis. The role of misoprostol pessary has to be studied as it is not evident whether radiation changes impact the absorption of Misoprostol via vaginal route.

Patients treated with misoprostol had significantly ($p < 0.01$) increased baseline cervical dilatation and significantly ($p < 0.05$) decreased cumulative force required for cervical dilatation compared with the placebo group in a study by Perrone et al. [17]. In our analysis also the tandem insertion was facilitated by usage of misoprostol. In our experience also the intervention was easier after usage of misoprostol. We did not encounter a false tract formation as the cervical Os was easily identifiable. We had only 3 cases of uterine perforation identified on planning CT scan. In these 3 cases the tandem was projecting through the fundal region and through anterior uterine wall. Although there may be an under-reporting of uterine perforations in our series as in 37.8% patients the brachytherapy planning was X ray Based. Uterine perforations cannot be identified in 2 D based radiation planning. We also had one case of vaginal tear, but this was unrelated to cervical dilatation. The tear was located in mid vagina lateral wall and was attributed to the friable vaginal mucosa.

Cepni et al also evaluated the use of misoprostol for cervical ripening before tandem application in patients of carcinoma cervix after delivery of external radiation in a prospective, randomized trial. They randomized 40 patients into two groups one group received 400 mg of misoprostol orally and the other placebo 3 hours prior to tandem application. They compared the groups in terms of age, diameter of tumor, parity, age at first intercourse, amount of bleeding and pain at first tandem application, length of endometrial cavity measured by hysterometer, and size of Hegar dilators used for cervical dilatation. They reported that in 75% cases there was either no or minor bleeding with no statistical difference between the 2 groups. The Mean pain score was significantly higher in the control group compared with the study group ($p < 0.001$). The ease of tandem insertion was subjectively expressed to be better in the study group by the physicians. (Mantel-Haenszel test: $p < 0.001$) (Insertion was easy in 80% of patients in the study group & on the contrary in 67.5% of the control group insertion was difficult). Also, the mean size of initial Hegar dilator was significantly higher in the study group compared with the control group ($c2$ test: $p = 0.017$). Our study has also shown that the mean size of initial Hegar dilator was greater than the cases we had performed previously. Although this was a retrospective study and there was subjectivity in the documentation.

The study by Cepni et al transient subfebrile fever (tympanic measurements between 37° C and 37.7°C) lasting for less than 3 h was reported in Five patients in the study group (12.5%). No case of low-grade fever was reported in in our study. As a protocol, prescribe antibiotics and analgesics post brachytherapy which can mask such episodes of fever. They did not encounter any other complication that may be attributable to the use of misoprostol [2]. But we noted one case of cramping pain abdomen noted after consumption of misoprostol. This was managed with Non-Steroidal Anti-Inflammatory Drugs. Misoprostol induced pain is the most common side effect noted elsewhere in literature [18]. There was an impact of duration of gap between the external radiation and brachytherapy due to post radiation fibrosis in the endocervical region. Six of the nine patients where cervical Os could not be negotiated was attributed to the fibrosis due to the delay in brachytherapy.

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Conclusion

Misoprostol has been used in cervical preparation for abortions, dilatation and curettage procedures. Its efficacy and safety are well established. Its utilization during brachytherapy reduces the need of imaging modalities during applicator insertion. Prevents false tract formation which may occur due to undue pressure while negotiating a fibrosed cervical canal. This is one of the largest series report so far in literature of utilizing misoprostol for cervical dilatation. Oral misoprostol is a safe and effective means of cervical dilatation for brachytherapy in carcinoma cervix. It is a cost effective especially in centers where facility of ultrasonography during brachytherapy applicator insertion is not available and especially holds potential for the developing nations with limited resources.

References

1. Barnes EA, Thomas G, Ackerman I, Barbara L, Letourneau D, et al. (2007) Prospective comparison of clinical and computed tomography assessment in detecting uterine perforation with intracavitary brachytherapy for carcinoma of the cervix. Int J Gynaecologic Cancer 17(4): 821-826.
2. Cepni Kimia, Sule Gul, Ismail Cepni, Onur Güralp, Veysel Sal, et al. (2011) Randomized trial of oral misoprostol treatment for cervical ripening before tandem application in cervix cancer. Int J Radiat Oncol Biol Phys 81(3): 778-781.
3. Davidson MRM, D'Souza DP, Yuen J, Murray T, Derrah LI, et al. (2007) Does intraoperative ultrasound guidance benefit routine intracavitary cervical carcinoma brachytherapy? Int J Radiat Oncol Biol Phys 69: S403-S404.
4. Rotmensch J, Waggoner SE, Quiet C (1994) Ultrasound guidance for placement of difficult intracavitary implants. Gynecol Oncol 54(2): 159-162.
5. Granai CO, Doherty F, Allee P, Ball HG, Madoc-Jones H, et al. (1990) Ultrasound for diagnosing and preventing malplacement of intrauterine tandems. Obstetr Gynecol 75(1): 110-113.
6. Fiala C, Gemzell-Danielsson K, Tang OS, Hertzen von H (2007) Cervical priming with misoprostol prior to transcervical procedures. Int J Gynaecol Obstet 99: 168-171.
7. Wing DA, Gaffaney CA (2006) Vaginal misoprostol administration for cervical ripening and labor induction. Clin Obstet Gynecol 49(3): 627-641.
8. Sääv I, Stephansson O, Gemzell-Danielsson K (2012) Early versus delayed insertion of intrauterine contraception after medical abortion-a randomized controlled trial. PloS one.
9. Lanciano RM, Won M, Coia LR, Hanks GE (1991) Pretreatment and treatment factors associated with improved outcome in squamous cell carcinoma of the uterine cervix: A final report of the 1973 and 1978 patterns of care studies. Int J Radiat Oncol Biol Phys 20(4): 667-676.
10. Rotmensch J, Waggoner SE, Quiet C (1994) Ultrasound guidance for placement of difficult intracavitary implants. Gynecol Oncol 54(2): 159-162.
11. Dusenbery KE, Carson LF, Potish RA (1991) Perioperative morbidity and mortality of gynecologic brachytherapy. Cancer 67(11): 2786-2790.
12. Sahinler I, Cepni I, Oksuz CD, Kimia C, Seluck K, et al. (2004) Tandem application with transvaginal ultrasound guidance. Int J Radiat Oncol Biol Phys 59: 190-196.
13. Saxena P, Salhan S, Sarda N (2003) Role of sublingual misoprostol for cervical ripening prior to vacuum aspiration in first trimester interruption of pregnancy. Contraception 67(3): 213-217.
14. Preutthipan S, Herabutya Y (1999) A randomized controlled trial of vaginal misoprostol for cervical priming before hysteroscopy. Obstet Gynecol 94: 427-430.
15. Preutthipan S, Herabutya Y (2000) Vaginal misoprostol for cervical priming before operative hysteroscopy: A randomized controlled trial. Obstet Gynecol 96(6): 890-893.
16. Perrone JF, Caldito G, Mailhes JB, et al. (2002) Oral misoprostol before office endometrial biopsy. Obstet Gynecol 99(3): 439-444.
17. Allen R, O'Brien BM (2009) Uses of misoprostol in obstetrics and gynecology. Rev Obstetr Gynecol 2(3): 159.
18. Ali Tauseef, Sahaj P, Aafreen K, Shalu V, Sumit G, et al. (2022) Use of misoprostol before tandem application for intracavitary brachytherapy in patients of carcinoma cervix: An institution study. J Cancer Res Therap 18(6): 1569-1571.

DOI: 10.19080/CTOIJ.2024.27.556220

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