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CLINICAL INVESTIGATION **Cervix**

RANDOMIZED TRIAL OF ORAL MISOPROSTOL TREATMENT FOR CERVICAL RIPENING BEFORE TANDEM APPLICATION IN CERVIX CANCER

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Purpose: To investigate the efficacy of oral misoprostol administered to facilitate tandem application to the cervix as a part of brachytherapy in patients with cervical cancer.

Methods and Materials: Eighty patients with cervical cancer who had been planned to undergo brachytherapy at Dr. Lütfi Kırdar Kartal Training and Research Hospital were evaluated in a double-blind, prospective, randomized trial. Patients were divided randomly into two groups of 40 patients. The first and second groups received 400 μg of misoprostol orally and placebo, respectively, 3 h before tandem application. The two groups were compared 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.

Results: Of all cases, 63.6%, 16.3%, 10%, 6.3%, 2.5%, and 1.3% were Stage IIB, IIIB, IIIA, IVA, IIA and IIC, respectively. Mean (±SD) age (range) was 49.3 ± 13.1 (25–83) years and 56.6 ± 13.2 (30–78) years in the study and control groups, respectively ($p = 0.015$). Age at first intercourse, diameter of tumor, parity, amount of bleeding at first tandem application, and length of endometrial cavity measured by hysterometer were not significantly different between the two groups. Pain score was significantly higher in the control group ($p < 0.001$). Application was significantly easier in the study group compared with controls ($p < 0.001$). Average size of initial Hegar dilators used for cervical dilatation was significantly higher in the study group compared with controls ($p = 0.017$).

Conclusion: Administration of misoprostol 400 μg orally for cervical ripening before tandem application facilitates the procedure, increases patient tolerability and comfort, and may decrease complication rates. © **2011 Elsevier Inc.**

Cervical cancer, Brachytherapy, Cervical ripening, Misoprostol.

INTRODUCTION

Intracavitary brachytherapy and external-beam radiotherapy (EBRT) are two methods, supplemental to each other, in radical treatment of cervical cancer. In particular, optimized intracavitary treatment plays a significant role in the management of pelvic tumors (1–3). In modern practice, pelvic EBRT followed by intracavitary brachytherapy is performed at most centers. Brachytherapy is a form of conformal dose escalation and decreases the risk of residual tumor and pelvic relapse (4, 5). The use of brachytherapy in the treatment of cervical cancer has increased worldwide since its initial introduction more than 100 years ago. Its efficacy and success are attributable to its ability to deliver high doses of radiation to a localized area, with relative sparing of adjacent normal tissues.

Complications encountered during the procedure are partly related to difficulties in cervical dilatation. Owing to distortion of the cervical canal or obliteration, tandem insertions can be difficult, even in the hands of experienced physicians. The emphasis has largely been on detecting uterine perforations and myometrial penetrations to avoid unnecessary acute physical side effects of treatment, such as bleeding, infection or abscess formation, pain, and pelvic discomfort (1).

The incidence of these complications can be reduced if the cervix is ripened before the procedure. It may also reduce the incidence of complications during the procedure and is therefore recommended in a number of guidelines (6, 7). It was shown that misoprostol is also effective at priming in nonpregnant women (8). Cervical priming is recommended by several evidence-based guidelines before surgical abortion,

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dilatation and curettage, hysteroscopy, and intrauterine device insertion. It is effective in pregnant as well as in nonpregnant women, although the results in postmenopausal women are conflicting. Misoprostol is the best-suited prostaglandin for a number of reasons: 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. Various doses, routes, and time intervals between misoprostol application and the intervention have been evaluated. A single dose of 400 μg given sublingually (oral) or vaginally 3 h before the intervention has given the best efficacy with the least side effects (9). Higher doses or longer intervals do not improve the effect on the cervix. Pain is a frequent side effect but usually responds well to nonsteroidal anti-inflammatory drugs. Other side effects are rare (9).

The aim of the present study was to evaluate the efficacy of 400 μg of misoprostol, administered orally, on cervical ripening before tandem application procedures. These results should provide further conclusions concerning the usefulness of misoprostol in clinical practice.

METHODS AND MATERIALS

This study was conducted prospectively between March 2005 and February 2007 at the Oncology Department of the Dr. Lütfi Kırdar Training and Research Hospital. A total of 80 women with cervical cancer, who underwent primary radical radiotherapy (EBRT and intracavitary brachytherapy) for cervical cancer in our clinic, were eligible for study recruitment. The institutional ethics review committee approved the study, and informed consent was obtained before participation.

The International Federation of Gynecology and Obstetrics classification was used for clinical staging (10). Pain was measured by visual analogue scale (0 = no pain, 1–5 minimum pain, and 6–10 = severest pain imaginable) (11).

Patients were randomly assigned to the following treatment regimens (by A.M.): the study group (n = 40) received 400 μg of misoprostol (Cytotec; Ali Raif, Istanbul, Turkey) orally, 3 h before tandem application; the control group received placebo before tandem application. Both patients and physicians were blinded.

The amount of bleeding was graded by the physician as either absent (no bleeding), minor (bleeding not requiring any intervention), moderate (bleeding that stops by pressure application for 5 min), or heavy (bleeding that stops by suturing or pressure application for 2 h). Sizes of the initial Hegar dilator were recorded for each patient. Physicians graded the procedure as easy, moderate, or difficult according to size of the initial Hegar dilator, subjective perception of rigidity of cervix, and subjective difficulty level of tandem insertion. Tandem application procedures were performed by the same physician (K.C.).

Intracavitary brachytherapy was initiated after pelvic EBRT and was performed without anesthesia. The high-dose-rate accelerated Curietron ^{60}Co (Theratron 780, MDS Nordion, Ontario, Canada) afterloading system was used in intracavitary applications until February 2, 2000; since then the high-dose-rate accelerated ^{192}Ir-based Gammamed device (Gammamed, MDS Nordion-Gammamed, Hahn, Germany) has been used. In our clinic intracavitary brachytherapy is applied by a ^{137}Cs-supplied Curietron device (CIS Bio International, Gif-Sur-Yvette, France) with a reference dose at 0.5 cm. Three different tandem applicators, consisting of one flat and two curved applicators, were used in the ^{60}Co Curietron. The angles of the curved tandems were 15° and 30°, and the external diameter was 6 mm. The total tumor dose (24 Gy) was administered to point A in three fractions. Two tandem applicators, one flat and one curved, were used in the Gammamed device. The angle of the curved tandem applicator was 20°, and the external diameter was 3 mm. The optimization of application was controlled by X-ray films or fluoroscopy.

Results are presented as the mean ± SD (range) for quantitative variables and frequency (percentage) for qualitative variables. Data were analyzed by the Student's t test for normally distributed data and the Mann-Whitney U test for skewed data. Discontinuous data were analyzed by χ^2 test. A paired-samples t test was used for intragroup analysis. A p value of <0.05 was considered statistically significant.

RESULTS

Patient characteristics are summarized in Tables 1 and 2. The median patient age by group was a statistically significant factor. Means (±SD) of age were 49.3 ± 13.1 (25–83) years and 56.6 ± 13.2 (30–78) years in the study and control groups, respectively (Student's t test: p = 0.015) (Table 2). Most of the patients (63.8%) had Stage IIB disease (Table 1). Operative complications were not encountered in any of the patients.

No statistical differences were detected between two groups in mean age at first intercourse, parity, length of endometrial cavity measured by hysterometer, and tumor diameter (Table 2). In 75% of all cases there was either no or minor bleeding. There was no statistically significant difference between two groups in terms of amount of bleeding during and after tandem application. (Mantel-Haenszel test: p = 0.688) (Table 3).

Mean pain score was significantly higher in the control group compared with the study group (χ^2 test: $p < 0.001$) (Table 4). In the control group 67.5% of patients felt severe pain, whereas in the study group this proportion was only 20% (Table 4). Physicians subjectively expressed that tandem insertion was easier in the study group (Mantel-Haenszel test: $p < 0.001$) (Table 5). The difference between the two groups was striking: physicians expressed that insertion was easy in 80% of patients in the study group, whereas in 67.5% of the control group insertion was difficult. The mean size of initial Hegar dilator was significantly higher in the study group compared with the control group (χ^2 test: p = 0.017) (Table 6).

Table 1. Distribution of patients according to clinical stage

Stage	n	%
IIA	2	2.5
IIB	51	63.6
IIC	1	1.3
IIIA	8	10
IIIB	13	16.3
IVA	5	6.3
Total	80	100

Table 2. Patient characteristics

Characteristic	Misoprostol group (n = 40)	Control group (n = 40)	p
Age (y)	49.3 ± 13.1	56.6 ± 13.2	0.015*
Age at first intercourse (y)	17.8 ± 3.7	17 ± 2.1	0.194*
Parity	4.3 ± 2.8	4.7 ± 2.2	0.341†
Length of endometrial cavity (cm)	5.7 ± 0.8	5.8 ± 0.8	0.541*
Tumor diameter (cm)	4.7 ± 1.3	4.6 ± 1.2	0.720*

Values are mean ± SD.
* Student's t test.
† Mann-Whitney U test.

Five patients in the study group (12.5%) had transient subfebrile fever (tympanic measurements between 37°C and 37.7°C), which did not last longer than 3 h in any of these 5 patients. We did not encounter any other complication that may be attributable to the use of misoprostol.

DISCUSSION

It has been reported that intracavitary brachytherapy plays a significant role in the management of pelvic control in cervical cancer (1, 2). The significance of intracavitary brachytherapy in multivariate analysis was first shown in the study by Hanks *et al*. (12). In that study, a 24% decrease in the relapse rate was determined for the 4-year period after the application of intracavitary brachytherapy in Stage III patients. Similar results have been reported in other studies (4, 5, 13).

The objective in intracavitary brachytherapy is to optimize management of application. However, some difficulties are experienced in daily practice. For example, it is much more difficult to place implants in older patients because of anatomic distortion and tissue atrophy (2, 14). Moreover, development of fibrosis after EBRT predisposes to retraction, obstruction, and deviation of the cervical canal (15). These can cause difficulties in sounding and/or dilating the cervix, leading to underdosing of the tumor and delivery of more than the optimal dose to surrounding normal tissues (13).

As is the case in other uterine interventions, cervical dilatation affects the success of tandem application. Bimanual examination of flexion and version status of the uterus and measurement of the angle between collum and corpus and length of collum and uterine cavity are also effective. Tandem application is actually easier if the procedure is performed under ultrasound guidance (16). Although we are aware of all these factors, difficulties in cervical dilatation may cause an increase in complication rates and a decrease in optimal benefit in daily practice and may even render the procedure impossible.

Table 3. Amount of bleeding during or after tandem application

	Misoprostol group		Control group		Total	
Parameter	n	%	n	%	n	%
Absent	14	35	9	22.5	23	28.8
Minor bleeding	16	40	21	52.5	37	46.2
Moderate bleeding	7	17.5	9	22.5	16	20
Heavy bleeding	3	7.5	1	2.5	4	5

Mantel-Haenszel test: $p = 0.688$.

Table 4. Perception of pain (visual analogue scale) during the procedure

	Misoprostol group		Control group		Total	
Score	n	%	n	%	n	%
Absent (0)	10	25	2	5	12	15
Minimum (1–5)	22	55	11	27.5	33	41.2
Severe (6–10)	8	20	27	67.5	35	43.8

χ^2 test: $p < 0.001$.

Our search in PubMed for the keywords ''tandem AND misoprostol'' and ''brachytherapy AND misoprostol'' revealed no study in literature that evaluates the use of misoprostol for cervical ripening before tandem application.

Cervical priming is especially helpful as a means of pain reduction and can be used either in addition to, or instead of, local anesthesia. In a study by Saxena *et al*. (17) of women undergoing surgical termination of pregnancy, priming with vaginal misoprostol (with no additional analgesics) was compared with a paracervical block (with no priming). This study showed that women who received misoprostol reported significantly less pain at the time of mechanical dilatation of the cervix. Our study also shows that pain scores were significantly lower during tandem application in the study group compared with the control group.

Perrone *et al*. (18) have shown that misoprostol-treated patients 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 at the 3-h pretreatment interval. In our study, physicians expressed that intervention was easier in the study group compared with controls (Mantel-Haenszel test: $p < 0.001$).

In contrast to the obstetric literature, there are limited data available regarding the use of misoprostol in nonpregnant patients for gynecologic indications. Preutthipan and Herabutya (19, 20) and Ngai *et al*. (8) showed that misoprostol

Table 5. Subjective expression of difficulty level of tandem insertion by physicians

	Misoprostol group		Control group		Total	
Difficulty level	n	%	n	n	%	n
Easy	32	80	3	7.5	35	43.8
Moderate	3	7.5	10	25	13	16.2
Difficult	5	12.5	27	67.5	32	40

Mantel-Haenszel test: $p < 0.001$.

Table 6. Sizes of initial Hegar dilators

	Misoprostol group		Control group		Total	
Size	*n*	%	*n*	%	*n*	%
3	18	45	30	75	48	60
4	17	42.5	9	22.5	26	32.5
5	5	12.5	1	2.5	6	7.5

χ^2 test: $p = 0.017$.

significantly increased cervical dilatation and decreased both cervical resistance and the need for additional cervical dilatation before hysteroscopy.

In two studies by Preutthipan and Herabutya (19, 20), 200 μg of misoprostol or placebo was placed vaginally 9 to 10 h before hysteroscopy in nulliparous patients, and cervical priming effects were then evaluated before diagnostic hysteroscopy and before operative hysteroscopy. Misoprostol enhanced cervical dilatation, reduced the need for cervical dilatation before hysteroscopy, decreased the operating time, and reduced the frequency of complications (cervical tears).

The efficacy of misoprostol for cervical priming was also supported by a randomized controlled study of nulliparous women who received 400 μg oral misoprostol 12 h before diagnostic hysteroscopy. In that study, the 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. There were no differences in operating times, complication rates, or side effects between the misoprostol and control groups (8). Our study has also shown that the mean size of initial Hegar dilator was greater in the study group compared with controls; neither important complications nor adverse effects were noted.

CONCLUSION

If we consider the pain reduction, maintenance of dilatation, and facile application, we may conclude that misoprostol, which is proven to be beneficial in cervical maturation before both obstetric and gynecologic interventions, provides increased tolerability and patient comfort, as well as facilitation of tandem application.

REFERENCES

1. Lanciano RM, Won M, Coia LR, *et al*. 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* 1991;20:667–676.
2. Corn BW, Hanlon AL, Pajak TF, *et al*. Technically accurate intracavitary insertions improve pelvic control and survival among patients with locally advanced carcinoma of the uterine cervix. *Gynecol Oncol* 1994;53:294–300.
3. Perez CA, Carmel HM, Kuske RR, *et al*. Radiation therapy alone in the treatment of carcinoma of uterine cervix: A 20-year experience. *Gynecol Oncol* 1986;23:127–140.
4. Paley PJ, Goff BA, Minudri R, *et al*. The prognostic significance of radiation dose and residual tumor in the treatment of barrel-shaped endophytic cervical carcinoma. *Gynecol Oncol* 2000; 76:373–379.
5. Eifel PJ, Thoms WW Jr., Smith TL, *et al*. The relationship between brachytherapy dose and outcome in patients with bulky endocervical tumors treated with radiation alone. *Int J Radiat Oncol Biol Phys* 1994;28:113–118.
6. World Health Organization. Safe abortion: Technical and policy guidance for health systems. Geneva: WHO; 2003.
7. Royal College of Obstetricians and Gynaecologists. The care of women requesting induced abortion: Evidence-based clinical guideline. London: RCOG Press; 2004. Vol. 7.
8. Ngai SW, Chan YM, Liu KL, *et al*. Oral misoprostol for cervical priming in non-pregnant women. *Hum Reprod* 1997;12:2373–2375.
9. Fiala C, Gemzell-Danielsson K, Tang OS, *et al*. Cervical priming with misoprostol prior to transcervical procedures. *Int J Gynaecol Obstet* 2007;99:168–171.
10. Creasman WT. New gynecologic cancer staging. *Gynecol Oncol* 1995;58:157–158.
11. Breivik H, Borchgrevink PC, Allen SM, *et al*. Assessment of pain. *Br J Anaesth* 2008;101:17–24.
12. Hanks GE, Kerring DF, Kramer S. Pattern of care outcome studies: Results of the national practice in cancer of the cervix. *Cancer* 1983;51:959–967.
13. Perez CA, Fox S, Lockett MA, *et al*. Impact of dose in outcome of irradiation alone in carcinoma of the uterine cervix: Analysis of two different methods. *Int J Radiat Oncol Biol Phys* 1991;21: 885–898.
14. Dusenbery KE, Carson LF, Potish RA. Perioperative morbidity and mortality of gynecologic brachytherapy. *Cancer* 1991;67: 2786–2790.
15. Rotmensch J, Waggoner SE, Quiet C. Ultrasound guidance for placement of difficult intracavitary implants. *Gynecol Oncol* 1994;54:159–162.
16. Sahinler I, Cepni I, Oksuz CD, *et al*. Tandem application with transvaginal ultrasound guidance. *Int J Radiat Oncol Biol Phys* 2004;59:190–196.
17. Saxena P, Salhan S, Sarda N. Role of sublingual misoprostol for cervical ripening prior to vacuum aspiration in first trimester interruption of pregnancy. *Contraception* 2003;67:213–217.
18. Perrone JF, Caldito G, Mailhes JB, *et al*. Oral misoprostol before office endometrial biopsy. *Obstet Gynecol* 2002;99:439–444.
19. Preutthipan S, Herabutya Y. A randomized controlled trial of vaginal misoprostol for cervical priming before hysteroscopy. *Obstet Gynecol* 1999;94:427–430.
20. Preutthipan S, Herabutya Y. Vaginal misoprostol for cervical priming before operative hysteroscopy: A randomized controlled trial. *Obstet Gynecol* 2000;96:890–893.