The Effectiveness and Safety of Misoprostol in the Termination of Molar Pregnancies in Comparison to Conventional Methods

MOLAR GEBELİKLERİN SONLANDIRILMASINDA MİSOPROSTOL'UN ETKİNLİĞİNİN VE GÜVENİLİRLİĞİNİN KONVANSİYONEL METODLARLA KARŞILAŞTIRILMASI

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Summary

Objective: To determine the safety and efficiency of prostaglandin E1 (misoprostol) in the termination of mole hydatidiform in comparison to hysterectomy and suction curettage.

Material and Methods: From May 1997 to August 2000 42 women who were diagnosed as mole hydatidiform by ultrasonographic examination and serum βhCG measurement. After establishment of the diagnosis, patients were divided into three groups and treated as follows at Harran University Faculty of Medicine, Department of Obstetric and Gynecology. 8 women (Group I) were treated by simple hysterectomy, 16 women (Group II) underwent suction curettage and 18 women (Group III) received prostaglandin E1 to remove the mole hydatidiform. In this group once Bishop score was determined by a sterile speculum, the patients were administered 800mg (four tablet of 200mg for each) misoprostol (Cytotect, Searle) intravaginally in the posterior fornix. Two additional doses of 800mg misoprostol were repeated at 6th and 12th hours if no change in Bishop score was noted. Three methods were compared in terms of complication rates including hemorrhage, postevacuation respiratory insufficiency, persistent trophoblastic disease, toxemia of pregnancy, infection and the need of blood transfusion.

Results: In Group I, one patient received 3 units of blood transfusion. None of the patients in this group developed postmolar trophoblastic disease and had toxemia of pregnancy. Two patients (25%) developed infection after the operation. In Group II, four patients received a total of 10 units of blood transfusion, two patients (12.5%) in this group developed postmolar trophoblastic disease and infection was noted in two patients (12.5%) one of which was present at admission and the other after abortion, three patients (18.75%) had toxemia of pregnancy. In one patient uterine perforation occurred, diagnosed by laparoscopy and managed conservatively. Two patients experienced acute pulmonary insufficiency (12.5%). In Group III, four patient (22.22%) received

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Özet

Amaç: Mol hidatidiformun tedavisinde prostoglandin E1 analoğunun (misoprostol) etkinliğini ve güvenilirliğini araştırarak, histerektomi ve "suction" küretaj ile karşılaştırmak.

Materyel ve Metod: Mayıs 1997 ve Ağustos 2000 tarihleri arasında ultrasonografik olarak ve βhCG ölçümü ile tanı konulan 42 hasta araştırmaya dahil edildi. Tanının histopatolojik olarak doğrulanmasını takiben, hastalar 3 gruba ayrılarak Harran Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Kliniği'nde tedavi edildi. Fertilite arzusu olmayan üreme dönemini tamamlamış olan I. grupta yer alan 8 hastaya histerektomi uygulanırken, fertilite arzusu olan II. grupta yer alan 16 hastaya "suction" küretaj, üçüncü grupta yer alan 18 hastaya ise prostoglandin E1 uygulandı. Bu grupta steril bir spekulum ile Bishop skoru değerlendirildikten sonra, 800mg (200mg 4 tablet) misoprostol (Cytotect, Searle) arka fornikse uygulandı. Bishop skorunda değişme oluşmamış ise 6.cı ve 12.ci saatlerde doz iki kez 800mg olarak tekrarlandı. Tedavi grupları; transfüzyon gereksinim, toksemi, solunum yetmezliği, kanama, enfeksiyon ve persistan trofoblastik hastalık açısından karşılaştırıldı.

Sonuçlar: Birinci grupta bir hastaya 3 ünite kan transfüzyonu yapıldı. Birinci gruptaki hiçbir hastada postmolar trofoblastik hastalık ve gebelik toksemisi izlenmedi. İki hastada (%25) histerektomiyi takiben enfeksiyon gözlendi. İkinci grupta yer alan 4 hastaya toplam 10 ünite kan transfüzyonu yapılırken, 2 hastada (%25) postmolar trofoblastik hastalık, 2 hastada da (%12.5) enfeksiyon, 3 hastada da (%18.75) gebelik toksemisi izlendi. Bir hastada uterus perforasyonu oluştu, laparoskopik olarak tanı doğrulandı ve konservatif olarak tedavi edildi. İki hastada (%12.5) akut pulmoner yetmezlik izlendi. Üçüncü grupta 4 hastaya (%22.22) toplam olarak 9 ünite kan transfüzyonu yapıldı. İki (%11.11) hastada tanı konulma anında enfeksiyon izlenirken, üç hastada (%16.66) postmolar trofoblastik hastalık oluştu. Üç hastada (%16.66) gebelik toksemisi mevcuttu. Bu grupta yer alan hiçbir hastada pulmoner yetmezlik izlenmedi. Bu hastalardan 6'sına (%33) üçüncü doz misoprostol'e rağmen molar gebelik boşalmadığı için "suction" küretaj uygulandı. Molar gebeliği atamayan 3 hastada

a total of 9 units of blood transfusion. Three patients (16.66%) developed post molar trophoblastic disease, two patients (11.11%) had infection at admission and three patients (16.66%) had toxemia of pregnancy. None of these patients experienced acute pulmonary insufficiency. Six of these patients (33%) failed to deliver the mole after the third dose of vaginal misoprostol and underwent suction curettage of uterus. Three of six patients who failed to deliver the mole developed uncontrolled bleeding and needed emergent blood transfusion and suction curettage.

Conclusion: This study points out that, misoprostol may be used in the termination of molar pregnancy with close observation and with subsequent revision curettage.

Key Words: Mole hydatidiform, Hysterectomy, Suction curettage, Misoprostol

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Karar: Bu çalışma, molar gebeliğin sonlandırılmasında yakın takip ve revizyon küretaj ile misoprostol uygulanabilirliğine dikkat çekmektedir.

Anahtar Kelimeler: Mol hidatidiform, Histerektomi, "Suction" küretaj, Misoprostol

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Gestational trophoblastic neoplasia is among one of the rarely encountered human malignancies that can be cured even in the presence of widespread metastasis. It includes a spectrum of interrelated tumor, mole hydatidiform, invasive mole, placental cite trophoblastic tumor, and choriocarcinoma that has a varying propensity for local invasion and metastasis (1). Mole hydatidiform literally means a shapeless mass of watery vesicles. Mortality rate associated with mole hydatidiform decreased from 15% to 1.5 % in 1930's by the advent and application of oxytocin in the treatment and safety of blood transfusion (2).

The techniques used to remove mole hydatidiform include; sharp or suction curettage, induction of labor with oxytocin or prostaglandins and hysterotomy or hysterectomy (3). In 1966 Bransdes et al. first reported the use of suction evacuation curettage for molar pregnancy (4). Since then this form of management has become the primary method for terminating molar pregnancies.

Recently, the application of prostaglandins in the termination of normal and abnormal pregnancies has been a very common procedure. Misoprostol (Cytotec, Searle), a methyl ester of prostaglandin E1 that is additionally methlylated at C-16, which is being marketed as to prevent and/or to treat peptic ulcer disease, has been shown in several studies to be an effective myometrial stimulant of the pregnant uterus (5,6) by selectively binding to EP-2 /EP-3 prostanoid receptors (7).

Material and Methods

From May 1997 to August 2000, 42 women who were diagnosed as mole hydatidiform by ultrasonographic examination and βhCG measurement, all of which was confirmed by histopathologic evaluation, was included in the study. After establishment of the diagnosis, the patients were divided into three groups and treated as follows at Harran University Faculty of Medicine, Department of Obstetric and Gynecology.

Group I included 8 patients whose ages were over 40 years and who did not have fertility desire. Hysterectomy was the selected procedure to perform in this group of patients.

Group II included 16 patients in the reproductive age and demanded fertility to be preserved. In this group suction curettage was performed. After achievement of intratracheal anesthesia, the cervix was gently dilated to allow passage of a 12-14 mm canula just through the internal cervical os. The anesthetic agents causing uterine wall relaxation were not used in order to avoid perforation. Continuous oxytocin infusion and uterine massage were used simultaneously with suction curettage to make uterus contracted and to improve hemostasis. After suction curettage had been completed, a sharp curret tegemex was used to completely remove the trophoblastic tissue. These tissues were submitted separately for pathologic examination.

Group III included 18 patients of reproductive age and as group II who desired to remain fertile. In this group once Bishop score was determined by a sterile speculum, the patients were administered 800mg (four tablet of 200mg for each) misoprostol (Cytotect, Searle) intravaginally in the posterior fornix. Two additional doses of 800mg misoprostol were repeated at 6th and 12th hours if no change in Bishop score was noted. No more than three doses was repeated. Each patient in this group received pretreatment with both an antiemetic (metoclopramid) and an anti-diarrheic (loperamid). If abortion was not achieved within 18 hours of the therapy, then vacum aspiration was performed (Table 1).

A large-for-dates uterus was arbitrarily considered to be a large-for-dates if the uterine size was 4 weeks larger than the predicted uterine size according to the last menstrual period. Similarly, a uterine size 4 weeks smaller than the predicted gestational week was considered as small-for-dates. If the uterine size was between these two ranges, it was interpreted as consistent with dates. Additionally for

Table 1. Clinical characteristics of the patients

		Group I n = 8	Group II n = 16	Group III n = 18
Mean Age		43.4	24.1	26.7
Mean uterine size	(weeks)	16.2	18.3	17.8
Consistent with dates	n / %	4 / 50%	1 / 6.25%	2 / 11.11%
Large for dates	n / %	2 / 25%	12 / 75%	14 / 77.77%
Small for dates	n / %	2 / 25%	3 18.75%	2 / 11.11%
Fertility desire		-	+	+

Table 2. Complications encountered

Complication	Group I, n = 8 n / %	Group II, n=16 n / %	Group III, n=18 n / %
Postmolar trophoblastic disease	- / 0%	2 / 12.5%	3 / 16.66%
Infection	2 / 25%	2 / 12.5%	2 / 11.11%
Toxemia	- / 0%	3 / 18.75%	3 / 16.66%
Blood transfusion	1 / 12.5%	4 / 25%	4 / 22.22%
Pulmonary insufficiency	- / 0%	2 / 12.5%	- / 0%
Uterine perforation	- / 0%	1 / 6.25%	- / 0%

clinical purposes, detection of a uterus at or above the level of the umbilicus, provided evidence as the presence of a pregnancy consistent with a gestation of > 20 weeks.

Baseline arterial blood gas was obtained in the view of the risk of trophoblastic embolization. A diagnosis of respiratory insufficiency was based on clinical findings as tachypnea, hypoxia, chest X-ray changes consistent with pulmonary edema and need for supplemental oxygen as evidenced by arterial blood gas measurements. Infection was considered in the presence of a temperature above 38.3°C. Post molar trophoblastic disease was diagnosed on the basis of existence of a plateau in serum βhCG levels for 3 weeks (four values) or existence of a rise in serum βhCG levels over a 2-weeks period (three values) or the detection of metastasis.

Results

Group I. Eight women underwent hysterectomy as the primary therapy for hydatidiform mole. The mean age of these women was higher than the other two groups (43,4 years versus 24.1 and 26.7 respectively). The mean uterine size in this group was 16 weeks gestational age, ranging from 13 to 20 weeks. Four of them (50%) were consistent with dates, two of them (25%) were large-for-dates and two of them (25%) were small-for-dates. One patient received three units of blood transfusion. None of the patients in this group neither developed postmolar trophoblastic disease nor had toxemia of pregnancy. Two patients developed infection after the operation and treated as such with implementation of intravenous antibiotics.

Group II. In this group of 16 patients in which suction curettage was performed, the mean uterine size was 18,3 weeks gestational age, ranging from 13 to 24 weeks. Only 1 uterus (6.25%) was consistent with dates. 12 (75%) were large for dates and 3 (18.75%) were small-for-dates. Four patients received a total of 10 units of blood. Two patients in this group developed postmolar trophoblastic disease. Infection was diagnosed in two patients, one of which was diagnosed at the admission and the other emerged after the abortion. Three patients had toxemia of pregnancy. During the procedure uterine perforation was encountered in one patient in which the diagnoses was also approved by laparoscopy and managed conservatively. Two patients experienced acute pulmonary insufficiency both of which also received blood transfusion and had toxemia of pregnancy. All of the patients in whom complication was experienced had uterine size of > 20 weeks.

Group III. Eighteen women received misoprostol therapy for termination of molar pregnancy. Six (33.33%) of these patients failed to expulse the trophoblastic tissue in spite of the third dose of intravaginal misoprostol and underwent suction curettage of the uterus. Three of the six patients who failed to deliver the mole, developed uncontrolled bleeding and needed urgent blood transfusion. The size of uterus of these three patients ranged from 20 to 24 weeks. The mean uterine size in this group was 17.8 weeks gestational weeks ranging from 14 to 22 weeks. Two of them (11.11%) were consistent with dates, 14 of them (77.77%) were large-for- dates and 2 of them (11.11%) were small-for-dates. Four patients received a total of 9 units of blood transfusion. Three patients (16.66%) devel-

oped post molar trophoblastic disease. Two patients (11.11%) also had infection at admission and three patients (16.66%) had toxemia of pregnancy. None of these patients experienced acute pulmonary insufficiency. Among the patients with a large-for- dates uterus, seven of them experienced complication all of which had a uterine size of > 20 weeks (Table 2).

Discussion

The termination of mole hydatidiform has long been a challenging gynecological problem around the world. Both surgical and non-surgical modalities have been associated with significant complications. Even it is sometimes associated with serious complications such as perforation and severe hemorrhage, suction evacuation curettage of the uterus has been the most widely applied modality for the treatment of mole hydatidiform. Oxytocin administration is often insufficient to induce effective uterine contractility in these patients (8).

Recently, many clinical studies using prostaglandin analogues in labor induction and medical abortion indicate that administration of prostaglandin analogues may offer advantages over the conventional methods used for termination of molar pregnancy. Although, there has been great interest on the use of prostaglandins for terminating hydatidiform mole, this had not gained widespread acceptance. The most feared subject is that the induction of uterine contraction against an undilated cervix could theoretically increase the risk of hematogeneous trophoblastic dissemination (3). Additionally, it was recommended that this method may have the potential of causing an incomplete evacuation and significant blood loss subsequently performing suction curettage inevitable (9).

Patients with respiratory insufficiency present a striking clinical picture and it is difficult to pinpoint the precise cause. The factors typically considered to be responsible are trophoblastic emboli, fluid overload, cardiac failure due to toxemia of pregnancy, hypertyroidism and tromboembolism. A serious complication of a molar pregnancy is massive trophoblastic embolization which can lead to acute cardiorespiratuory failure and subsequently death (10). A more frequent complication is acute pulmonary edema which is reported to vary between 11 to 22% of the cases (11). Several observations suggest that the symptoms are related to deportation of the trophoblastic tissue that occludes small vessels which causes pulmonary hypertension. The first observation is trophoblastic embolism which appears to be common even in normal pregnancy ,although it usually does not become clinically manifest (12). Second, large mononuclear and multinucleoted cells were recovered from samples of pulmonary artery blood aspirated from patients with mole hydatidiform in whom significant hemodynamic instability or pulmonary compromise did not occur (13). And the third, trophoblastic tissue was identified in pulmonary artery blood samples of women with molar pregnancy complicated by hypoxemia (14) Trophoblastic embolization that is severe enough to cause pulmonary symptoms is quite rare and seems to be related with the amount of tissue deported. Clearly, the patients at the greatest risk are those with uterus greater than 16 weeks gestational age. Schlerth et al. reported that acute pulmonary insufficiency is more common after evacuation of a uterus greater than 16 weeks or larger, and pulmonary complications was reported in up to %15 of women with hydatidiform moles of 20 weeks gestational age or greater (9).

Two of our patients had pulmonary insufficiency after four hours from the suction curettage. It can not be concluded as the method of evacuation took role in the occurrence of respiratory insufficiency. Because both patients had toxemia and transfused a total of six units of blood. Additionally these two patients had a uterine size greater than 20 weeks. Interestingly, none of the 18 patients who received misoprostol developed this problem despite uterine stimulation is believed to may cause trophoblastic embolism.

The use of oxytocin has been criticized by Braga and Chun, who suggested that these drugs might promote embolization of molar vesicles and increase the risk of residual trophoblastic disease (15). However, this argument is only theoretical. In Singapore where oxytocin was used to be applied (it has been replaced by prostaglandins), residual trophoblastic disease or coriocarcinoma were developed in 14,8% of the patients, which is comparable to the rates reported elsewhere (16). In our study, five patients developed postmolar trophoblastic disease, two of which was treated by suction curettage and three was treated by misoprostol. It was reported that medical induction with prostaglandins has two to three-fold risk of persistent trophoblastic disease (17,18). Flam et al. reported that 61.7% of the patients in whom medical intervention was implemented, developed persistent trophoblastic disease, which was 35,2% in the control group (19). However when corrected for uterine size (>15weeks), it was observed that medical method had been used equally in both groups. In our study four of the five patients (80%) developed postmolar trophoblastic disease had a uterine size >20 weeks, and the other (25%) had a uterine size of 18 weeks. Therefore we conclude that the risk of residual disease is not increased by oxytocin or prostaglandins and the development of persistent trophoblastic disease depends more on the uterine size than the method of uterine evacuation.

Four women who received misoprostol and failed to deliver molar pregnancy required a total of 9 units of blood transfusion, four women who underwent suction curettage received 10 units of blood transfusion and one women who underwent hysterectomy needed 3 units of blood transfusion. It is difficult to conclude from these results whether any mode of evacuation takes advantages over the others in terms of decreasing blood loss. However, evacuation by prostaglandins with a fear of sudden uncontrollable bleeding during stimulation seems justifiable, since three of the patients who failed to deliver molar pregnancy developed uncontrollable bleeding after the third dose of misoprostol.

In the light of this observation, patients intended to be treated by prostaglandins require close observation for a relatively longer duration of an average induction-abortion time of 8.3 hours (range, 5 to 12 hours). On the other hand, the average time required for complete evacuation of the uterus by suction curettage was 30 minutes ranging from 15 to 45 minutes.

Elective hysterectomy was performed in 8 women who completed childbearing. The mean age in this group was higher than the others (43,4 years versus 24.1 and 26.7 respectively). For older patients, this may be the treatment of choice if fertility is not desired. Town et al. reported that the risk of persistent trophoblastic disease might be as high as 37% for patients over 40 years depending on the selected treatment modality (20). With hysterectomy, the risk of persistent trophoblastic disease was reported to decrease from 20% to 3,5% (21-23). In our study, none of the patients who underwent hysterectomy neither developed persistent trophoblastic disease nor experienced acute pulmonary complication. Bearing these specific facts in mind hysterectomy continues to be a legitimate option for management of mole hydatidiform.

The results of the present study indicate that use of misoprostol in termination of mole hydatidiform does not increase the risk of hemorrhage, pulmonary trophoplastic embolization and persistent trophoblastic disease. But when considering this modality, close follow up of these patients are mandatory because of the risk of uncontrollable hemorrhage. It may be used as an alternative treatment of mole hydatidiform in patients with fertility desire, with close surveillance during stimulation and requires subsequent revision curettage anyway in all cases. As a result medical induction with misoprostol, prior to surgical evacuation of mole hydatidiform is an advisable procedure.

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