ORIGINAL ARTICLE

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The Importance of Hemoperitoneum and Retrospective Analysis of Tubal Ectopic Pregnancy Cases Treated in Our Clinic

Kliniğimizde Tedavi Edilen Tubal Ektopik Gebelik Olgularında Hemoperitonumun Önemi ve Retrospektif Analizi

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ABSTRACT

Introduction: *The aim of our study is to analyze retrospectively outcomes of tubal ectopic pregnancy treated in clinic and to highlight the significance of hemoperitoneum.*

Material and Methods: *Between January 2012 and August 2013, 86 women who were diagnosed with and treated for tubal ectopic pregnancy (EP) at this single-center clinic were enrolled in this study. Age, timing of the previous menstrual cycle, levels of human chorionic gonadotropin (hCG), size and presence of tubal EP masses, the fetal cardiac activity, and the methods of treatment were assessed and compared. The presence of hemoperitoneum and important factors in the choice of treatment were investigated.*

Results: *The patient's average age was 29.1±5.7 (16-41) years. The average level of β-hCG was 4448,5±8351,9 IU/L. 14 patients (16.3%) underwent laparatomy, 5 patients (5.8%) to laparoscopy, and 15 patients (17.4%) to expectant management. 46 patients (53.5%) received methotrexate (MTX) treatment, whereas laparoscopy and laparatomy were performed on 1 patient (1.2%) and 5 patients (5.8%), respectively, due to the failure of MTX treatment in 6 patients. The initial -hCG level (p=0.004), existence of abdominal bleeding (p=0.03), the size of ectopic pregnancy mass (p=0.005), and presence of fetal cardiac activity (p=0.001) were all detected to be statistically significant when compared to MTX therapy of tubal EP. The success rate of single dose MTX treatment was calculated as 69.5%*

Conclusion: *Presence of hemoperitoneum may be a risk factor for the decision to treat MTX because of surgical intervention. One of the alternative treatment for tubal EP is MTX therapy.*

ÖZET

Amaç: *Çalışmamızın amacı klinikte tedavi edilen tubal ektopik gebeliğin sonuçlarını retrospektif olarak incelemek ve hemoperitonumun önemini vurgulamaktır.*

Gereç ve Yöntemler: *Bu çalışma Ocak 2012 ile Ağustos 2013 tarihleri arasında tek merkezli kliniğimizde tubal ektopik gebelik (EP) tanı ve tedavisi yapılan 86 olgu dahil edildi. Yaş, son adet tarihi, insan koryonik gonadotropin (β-hCG) düzeyi, tubal EP kitlelerinin büyüklüğü ve varlığı, fetal kardiyak aktivite ve tedavi metotları değerlendirildi ve karşılaştırıldı. Tedavi yöntemleri için hemoperiton varlığı ve tedavi yöntemlerinin başarısını etkileyen faktörler araştırıldı.*

Bulgular: *Olguların yaş ortalaması 29,1±5,7 (16-41) yıl idi. Ortalama β-hCG düzeyi 4448,5±8351,9 IU/L idi. 14 olguya (%16.3) laparatomi, 5 olguya (%5.8) laparoskopi, 15 olguya (%17.4) ekspektan tedavi uygulandı. Metotreksat (MTX) tedavisi 46 olguya (%53,5), MTX tedavisi başarısızlığı nedeniyle 1 olguya (%1,2) laparoskopi, 5 olguya (%5,8) laparatomi uygulandı. Tubal EP'nin MTX tedavisi ile karşılaştırıldığında, başlangıç β-hCG düzeyi (p=0,004), intraabdominal kanama varlığı (p=0,03), ektopik gebelik boyutu (p=0,005) ve fetal kalp aktivite varlığı (p<0,001) gibi cerrahi metodu etkileyen faktörler istatistiksel olarak anlamlı bulundu. Tek doz MTX tedavisinin başarı oranı %69.5 idi.*

Sonuç: *Tedavi yöntemlerinde hemoperitonyumun varlığı MTX tedavisi için cerrahi tedaviye yol açan bir risk faktörü olabilir. MTX tedavisi tubal EP'de cerrahi tedaviye alternatif yöntemlerden biridir.*

Keywords:
Ectopic pregnancy
Hemoperitoneum
Methotrexate
Surgery

Anahtar Kelimeler:
Ektopik gebelik
Hemoperitonyum
Metotreksat
Cerrahi

INTRODUCTION

Ectopic pregnancy, also known as abnormal localized pregnancy, occurs when the blastocyst implants outside of the uterine cavity (1). Approximately 95% of EP are localized in the different parts of the fallopian tubes (2). EP accounts of 2% of all pregnancies and is an important cause of maternal morbidity and mortality (3). EP is diagnosed with early term with both high-resolution ultrasonography and quantitative assessment of β-hCG. After the blastocyst develops, usually in the sixth to ninth gestational weeks, the tension of the fallopian tube wall increases and unilateral lower abdominal pain occurs. After the fallopian tube ruptures, intraabdominal bleeding may lead hematoperitoneum and hemorrhagic shock, also. Hemoperitoneum is common in EP, but it may also be seen in the absence of falopian tube rupture. In the presence

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of hemorrhage in the abdominal cavity, the incidence of tubal rupture is only 50% to 62% (4, 5). Ultrasound examination of fallopian tube of EP in women with abdominal hemorrhage is not certain contraindication for MTX or expectant treatment. The presence of any degree of hemoperitoneum accurately supports neither falllopian tube rupture nor hemodynamic instability. In more than 80% of confirmed EP ruptured or unruptured, fluid accumulation in the cul-de-sac can be detected (5, 6). Compared with stable women, women with unstable hemodinamics have significantly more free blood accumulations in the cul-de-sac and lower hemoglobin levels (7). Mortality is now very rare, accounting for 0.05 % of cases (8).

Up to now, studies have been reported the important role of hemoperitoneum in predicting the effect of MTX treatment (9-12). These studies show that the predictive value of hemoperitoneum is weak. However, some studies have shown that MTX treatment is contraindicated in the presence of hemoperitoneum (13-16). However, the presence of hemoperitoneum in women diagnosed with EP is an important risk factor for failure of MTX treatment (17) and should be carefully examined. The purpose of this study is to present the importance of hemoperitoneum and retrospective analysis of tubal ectopic pregnancy cases treated in our clinic.

MATERIAL AND METHODS

This retrospective study analyzed 86 women diagnosed and treated for tubal EP in our clinic between January 2012 and August 2013. All patients provided written informed consent before MTX administration or surgical treatment. The Committee of Ethics for Research in Kahramanmaras Sutcu Imam University approved this study with decision no 2013/08-1 on May 16, 2013.

The patient files were analysed retrospectively. Patient's age, complaints, last menstrual date, β-hCG level, the presence of hemoperitoneum, the size and the presence of EP masses and fetal cardiac activity by transvaginal ultrasound and treatment procedures were evaluated. The size of EP and the presence of hemoperitoneum described as the presence of echogenic free fluid (18) in the cul-de-sac or above the level of the uterine fundus or around the ovaries (19) are detected via ultrasound examinations.

Table 1: The characteristics of 52 women treated with MTX.

Characteristic	Value
Age-yr	29.2 ± 5.9 (16-41)
Gravidity no	2.6 ± 1.2 (1-5)
Parity no	1.1 ± 1.0 (0-3)
Free fluid in the cul-de-sac no (%)	22 (47.8)
Fetal cardiac activity no (%)	2 (4.3)
Identified ectopic mass no (%)	49 (94.2)
Serum β- β-hCG level mIU/ml	2483.4 ± 3728.5 (92-16514)
Serum progesterone level ng/ml	6,81 ± 5.4 (2-18)
Ectopic mass in size-cm	1.4 ± 0.9

EP was firstly considered in women refered for pelvic pain, vaginal bleeding and delayed menstrual cycle. Then non-tubal EP patients were excluded. Patients both referred for tubal EP or tubal EP and hemoperitenoum detected by ultrasound were evaluated a careful clinic examination for the presence or absence of an acute abdomen (rebound tenderness) and hemodynamic instability (hypotension, tachycardia and consciousness disability). The inclusion criterias for MTX treatment include absence of fetal cardiac activity, tubal EP, size of EP less than 4 cm, suitability for the follow-up and maximum three doses and criterias for surgery include acute abdomen and/ or hemodynamic instability, tubal EP and MTX treatment failure. Exclusion criteria include for MTX treatment include hepatic or renal failure, thrombopenia, anemia, non-tubal EP, an acute abdomen or a hemodynamic instability and criterias for surgery intervention include non-tubal EP and refuse MTX treatment.

All women were counselled about possible EP risks and treatment methods. All EP who had hemodynamic stability, not an acute abdomen, accepted MTX treatment protocols and suitable for MTX were administered single-dose MTX treatment (50 mg/m2) (20). Tanaka et al. first used MTX therapy in clinical use for the treatment of EP (21). Other women that had a clinic instability, an acute abdomen, refused MTX treatment and not suitable were performed salpingostomy or salpingectomy by laparoscopy or laparatomy.

The indications for MTX treatment were absence of fetal cardiac activity, size of EP less than 4 cm and suitability for the follow-up. MTX protocols contraindications include hepatic or renal failure, thrombopenia, anemia, an acute abdomen or a hemodynamic instability (17). The day 1 of the protocol was accepted as a day of injection. Plasma β-hCG levels were assessed on days 4 and 7. If β-hCG levels decreased more than 15% between day 4 and 7, weekly follow-up continued until they decreased below 5 mIU/mL. If they decreased less than 15% between day 4 and 7 or between weekly β-hCG levels, the MTX injection was administered again until maximum three doses. If they did not decrease after three injections or the presence of acute abdomen or hemodynamic instability during MTX treatment, treatment protocols were accepted failure and surgical intervention was recommended and performed.

Possible factors which are available for treatment procedure were compared. Outcomes of treatment methods and factors affecting the success of medical and surgical treatments were investigated.

Statistical analysis

Statistical analysis was performed by SPSS 16.0 version. Kolmogorov-Smirnov test is used to evaluate the uniformity of the distribution of continuous variables. The results of data are presented as mean, standard deviation (SD), frequency and percentages for categoric variables. In statistical analysis Mann Whitney test was used the to compare quantitative variables, Fisher's

Table 2: Distributions of maternal ages, parity, size of EP and mean gestational age in tubal EP treated with MTX.

		Cases		Successful	
		n =52	%	n	%
Maternal Age	15- 24	12	23.1	12	100
	25- 34	25	48.1	19	76
	35- 45	15	28.8	14	93.3
Parity, n	0-1	31	59.6	27	87.1
	2-3	20	38.5	18	90.0
	≥4	1	1.9	1	100
Gestational Week	0-4	9	17.3	9	100
	4-6	15	28.8	13	86.7
	>6	28	53.8	23	82.4
Size of EP mass, (cm)	0-2	34	65.4	34	100
	2-3	11	21.2	10	90.9
	3-4	3	5.8	1	33.3
	≥4	4	7.7	0	0

test and X2-test for qualitative variables. Categoric variables, such as treatment failure were described using frequency distributions and are presented as numbers and percentages. Roc analysis was used for sensitive and specificity. Logistic regression analysis was used to model failure and odds ratio was estimated with 95% confidence intervals. Significance was determined as $p < 0.05$.

RESULTS

A total of 86 women with tubal EP were treated in our clinic (Figure 1). The mean age of the patients was 29.1±5.7 (16-41) years. The characteristics of 52 women who received with MTX for tubal EP are shown in Table 1. In the patient files, no severe side effects were observed in any of the patients who were given mtx treatment and only mild compliants such as abdominal pain in 3 patients, nausea in 5 patients were recorded.

The success rate of MTX is 100% among women under 25 age, 76% between 25 and 34 ages, and 93.3% between 35 and 45 ages. MTX success rate of MTX increases with the increase in maternal parity. The gravida number rate of women receiving MTX treatment is 1 to 6 times, 59.6% of primiparas (n=31), 38.5% of 2-3 parities (n=20), and 1.9% of more than 4 parities (n=1). The overall success in MTX treatment was in multiparous women. The mean gestational age at diagnosis was 6.1 weeks (Table 2). Among 86 women with tubal EP, 63 (73.2%) had ectopic masses and 38 (44.2%) had free fluid within coagulated blood or clots in the cul-de-sac, which was limited to the pelvic cavity and was detected by transvaginal ultrasound. Mean size of tubal EP was measured as 1.6±1.3 cm. The diagnosis success rate of MTX decreased with the increase in the size of tubal EP 46 patinents ($p<0.001$) (Figure 2). The highest success rate of MTX occurs in women with a tubal EP in the size of 0 to 2 cm (%100). Of them, laparatomy was performed to 14 patients (16.3%), laparoscopy to 5 patients (5.8%), expectant management to 15 patients (17.4%). Inclusion criteria for MTX treatment were included in 52 women, only 46 patients (53,5%) were given MTX, 1 patients (1,2%) underwent laparascopy, and 5 patients (5,8%) failed due to MTX treatment and underwent laparatomy.

The mean β-hCG of women receiving MTX treatment was

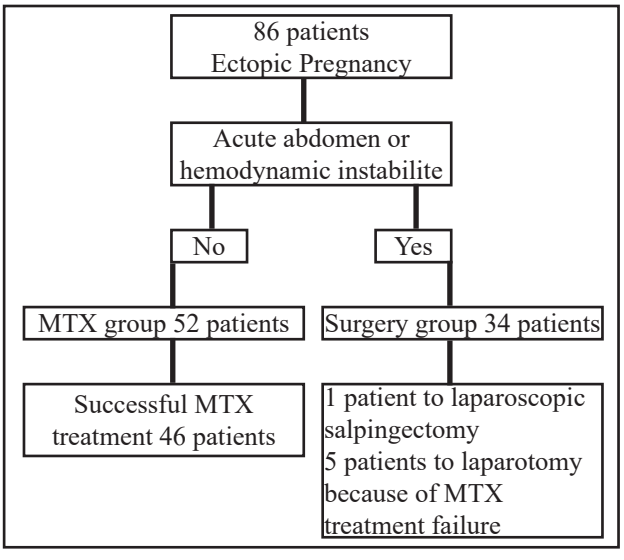

Figure 1: Flow chart of EP patients management

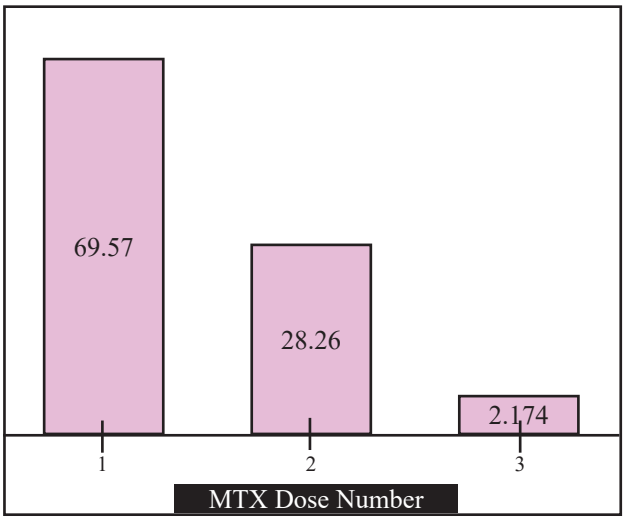

Figure 2: Administration doses in women treated with MTX successfully.

Table 3: Possible factors affecting MTX success in EP

Factor	MTX treatment		
	Successful (n= 46)	Failure (n=6)	p
Age-y	29 ± 6.1	30 3 ± 3.7	0.6
Parity-no	1 ± 1	1.3 ± 1.5	0.7
Serum ß-β-hCG level-mIU/ml	1637.8 ± 2755.6	8966.1 ± 4056.1	<0.001
Serum progesterone level-ng/ml	5.3 ± 0.6	12.6 ± 6.5	0.7
Size of ectopic mass-cm	1.3 ± 0.1	3.8 ± 0.4	<0.001
Free fluid in cul-de-sac -no (%)	21 (45.6)	1 (2.1)	0.10
Fetal cardiac activity-no (%)	-	2 (4.3)	<0.001

* mean ±SD

Table 4: Possible factors affecting management of surgical and MTX treatment.

	Medical treatment n=46	**Surgery treatment n=19**	**p**
Age-y	29.1 ± 6.2	30.5 ± 4.6	0.5
Graviditiy-no	2.6 ± 1.2	2.7 ± 1.5	0.5
Parity-no	1 ± 1	1.5 ± 1.2	0.1
Progesterone level-ng/ml	5.3 ± 4.6	6.8 ± 4.4	0.07
Serum ß-β-hCG level-mIU/ml	1637.8 ± 2755.6	9647.2 ± 12856.2	0.004
Gestational week	5.7 ± 2.0	6.3 ± 1.9	0.4
Free fluid in cul-de-sac -no (%)	21	15	0.03
Fetal cardiac activity-no (%)	-	8	‹0.001
Size of ectopic mass-cm	1.3 ± 0.9	2.3 ± 1.3	0.005

2798.4 ± 611 IU/L (95 % CI, 1572-4024.8 IU/L, median value 906 IU/L), 1571,7 (range 377-2795) for a single dose of MTX, 2114 IU/L (range 702-3525) for two doses of MTX and 1546 IU/L for three doses of MTX. β-hCG level cutt off value of 3035 IU/L for MTX treatment of EP had 75 percent sensitivity and 88.9% spesifity when compared to surgical and medical treatment and this β-hCG level was accepted a risk factor for MTX treatment.

Our clinic's overall treatment success rate was 88.5% (46/52) with 32 patients receiving a single dose, 13 patients receiving two doses, and one patient receiving three doses (Figure 1). Single-dose methotrexate treatment, on the other hand, showed a success rate of 69.5% (32/46). Six patients required surgical intervention as a result of MTX treatment failure.

Table 3 shows possible factors affecting tubal EP MTX success. The β-hCG levels, ectopic mass size and the presence of fetal cardiac activity for methotrexate therapy success were found statistically significant (p<0.001). However, initial β-hCG levels (p=0.004), presence of hemoperitenoum (p=0.03) and the presence of fetal cardiac activity (p<0.001) and EP size (p=0.005) were found to statistically significant factors affecting surgery management compared to MTX treatment for tubal ectopic pregnancy were detected statistically significant (Table 4). The presence of hemoperitoneum for management surgery and MTX treatment was found a significantly important factor (OR 4.2 (CI % 95 1.14;10.05), p=0.01).

DISCUSSION

Ectopic pregnancy is a big problem of pregnant women in early pregnancy terms. Decision on expectant, medical treatment or surgical treatment with transvaginal ultrasound, serum β-hCG level and clinic course of patients have a crucial role. In the first assessment, an experienced physician with a transvaginal ultrasound exam diagnoses 76 percent of EP and 91 percent of EP before surgery (22). This retrospective analysis of tubal EP and the absence of follow-up losses in our clinic was critical. In this study, we showed that using transvaginal ultrasound, we were able to detect 82.1% of EP.

MTX therapy is a widely used treatment method in the treatment of ectopic pregnancy. The feature of MTX in the treatment of ectopic pregnancy, is a folic acid analogue that acts as an antagonist by binding to dehydrofolate reductase, resulting in low tetrahydrofolic acid levels. Therefore, MTX is often used as an antineoplastic, immunosuppressive, and anti-inflammatory agent that inhibits cell proliferation and protein synthesis by suppressing the metabolism of cytostatics, as well as purine bases and nucleic acids (23).

Bonin et al. 2017 and Hemly et al. 2014 showed that the presence of clinic symptoms such as lower abdominal pain and uterine bleeding before treatment not affected treatment results (3, 24). Our study showed that when hemodynamic stability was, the clinic symptoms consisted of lower abdominal pain, abnormal uterine bleeding or the presence of hemoperitoneum don't have affected the treatment results. Because, these kind of complaints may be normally and seems as adverse or effect of MTX treatment.

Hemoperitoneum was not found to be a significant independent factor in determining MTX success or failure (p=0.10), but it was found to be a significant factor in the management of surgical and MTX treatment (p=0.01). If a patient has hemoperitoneum by ultrasonography but does not have an acute abdomen or hemodynamic instability, surgical techniques should be considered (25). The presence of hemoperitoneum increased the likelihood of surgical intervention with an OR of 4.0 when the surgical method and MTX treatment for EP management were examined (CI % 95 1.14;14.05).

Limpscomb et al. (1999) showed that the presence of hemoperitoneum in the cul-de-sac for medical treatment in EP was not an essential factor of success in a study of 350 women treated with MTX for tubal EP. Our study and Potter et al. study both reported similar results (9, 10). However, the existence of fetal cardiac activity, initial serum β-hCG level, and size of EP mass were all significant predictors. Orozco et al. (2015), Bonin et al. (2017) and Beguin et al. (2020), like this study, found that maternal age was not an important predictor of MTX treatment management (3, 16, 26). Hemoperitonoum's sensitivity and specificity were 0.63 and 0.76, respectively, in a study of 93 women treated with MTX (11). However, we discovered that its sensitivity and specificity were respectively 53.3% and 48.8%. Hemoperitenoum was not ruled out as a contraindication for a cautious EP approach in this investigation.

According to Potter et al. (2003), serum β-hCG levels on admission were the most critical risk factor in tubal EP management of for MTX success (10). Otherwise, a retrospective cohort study showed that the success of MTX treatment was not associated to maternal age, β-hCG level on admission and gestational age. But, gestational age after MTX treatment was found statistically significant at time of surgery intervention. For MTX treatment, EP size, fetal cardiac activity, and the presence of hemoperitoneum through ultrasound were not significant (27). The participants in this retrospective analysis were separated into two groups: group 1 (MTX before surgery) and group 2 (MTX after surgery) (surgery only). Clinic data, such as the number of groups, B-hCG levels higher than group 2, fetal heart activity rate, free fluid, and the existence of hemoperitonum between two groups, differed from literature data.

Beguin et al. study reported that on MTX treatment administration for EP more than β-hCG level of 4000 IU/L needed surgical intervention and this β-hCG level was shown a risk factor of failure of MTX treatment. The β-hCG cut off value for MTX success was described as 2439 IU/L, with a sensitivity of 66%, with a spesifity of 93,3% (16). In this study, we found that β-hCG level cutt off value of 3035 IU/L for MTX treatment of EP had 75 percent sensitivity and 88.9% spesifity when compared to surgical and medical treatment and this β-hCG level was accepted a risk factor for MTX treatment. Helmy et al. reported success rates and cut off values for the β-hCG levels of 2121 IU/L, Orozcu et al. reported below 1000 IU/L, while Marret et al. reported more than 2000 IU/L (24, 26, 28).

While we reported a 69 percent success rate of MTX treatment after single dose to treat EP, an overall success rate of 88 percent, according to other studies such as Bonin et al. (2017), Levin et al. (2019), Barbier et al. (2019), Beguin et al. (2020) and Sindiani et al. (2020), MTX treatment for EP have had a success rate of 65 to 95 percent (3, 16, 29-31). The success rate of our MTX tratment for EP was found to be similar to that seen in the literature. Althought the authors disagree on the cut-off β-hCG level for MTX treatment of EP in literature (28), when MTX treatment was received, β-hCG levels greater than 5000 IU/L should not be considered (15). According to a study by Beguin et al., EP patients with β-hCG level greater than 4000 IU/L required surgical intervention, and this β-hCG level was found to be a risk factor for MTX treatment failure.

Despite the fact that hemoperitoneum is a negative factor in MTX treatment, the success rate of MTX treatment has been found to be high, and hence, hemoperitoneum is not a certain contraindication to MTX treatment. The presence of hemoperitoneum on an ultrasound exam should be considered a significant factor when deciding whether to treat with MTX or surgery.

The study's limitations are that is retrospective, that the study group is small, and that hemoperitoneum is described quantitatively. Clinic examination, initial β-hCG levels, ectopic mass size, fetal cardiac activity and hemoperitoneum are the most predictive factors of MTX or surgical management for tubal EP treatment on admission in our clinic.

However, patient's clinical examination is normal, the most predictive factors for the success of MTX are the initial β-hCG level, ectopic mass size, fetal cardiac activity and the presence of hemoperitoneum. This situation shows that if patient's clinic exam is normal, the presence of hemoperitoneum is not an important risk factor of treatment choice. However, the analysis of patients undergoing surgery because of they refused MTX treatment or was suspected of being lost to follow-up in this study is a controversial issue. In addition, the patient's treatment choice and rejection is a natural right.

CONCLUSION

The presence of hemoperitoneum in treatment methods may be a risk factor for MTX treatment, leading to surgical treatment. MTX treatment is one of alternative method to surgical treatment in tubal EP

Conflict of Interest: No conflict of interest was declared by the authors

Ethics: The Committee of Ethics for Research in Kahramanmaras Sutcu Imam University approved this study with decision no 2013/08-1 on May 16, 2013.

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