The evaluation of misoprostol-related tachysystole in normal and high risk pregnancies

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Summary

Objective: To determine whether misoprostol-related tachysystole is due to the cumulative effect of the drug.

Methods: A group of preeclamptic patients were chosen and data were compared to non-preeclamptic patients to prove the hypothesis. Among 90 patients evaluated, 45 were preeclamptic while 45 were non-preeclamptic. Six out of 43 preeclamptic patients were diagnosed as having HELLP syndrome. All patients were induced by 50 μg of misoprostol applied to the posterior vaginal fornix with 4-hour intervals for a maximum of three times.

Results: Two patients from both groups were left out of the study leaving 86 patients to evaluate. The number of misoprostol tablets used in the preeclamptic group was significantly higher (2.32±0.64 preeclamptic vs 1.81±0.76 tablets non-preeclamptic group; [p=0.001]) , while the number of women giving birth after only one tablet of misoprostol was significantly lower (2/24 preeclamptic vs. 14/32 non-preeclamptic group [p=0.006, OR 0.116; 95% CI 0.02-0.58]). Although the frequency of tachysytolic patterns observed was different between the two groups, (35% preeclamptic vs 16% non-preeclamptic) this difference was not statistically significant (p=0.082). It is important to note that an increase of only one case having tachysystole in the preeclamptic group would have converted this difference to significant.

Conclusion: Relatively hard induction of labor in preeclamptic patients leads to an increase in the amount of misoprostol used and hence to an increased incidence of tachysystole secondary to the cumulative effect of the drug. These findings seem to support our hypothesis and prove the presence of the cumulative effect of misoprostol.

Key words: Misoprostol; Tachysystole; High risk pregnancy; HELLP syndrome.

Introduction

Throughout pregnancy, the cervix with its rich collagen and glycosaminoglycan content acts as a barrier protecting the fetus from the outer environment. This strong barrier effaces and dilates by an unknown mechanism as pregnancy progresses towards term [1]. This process is defined as cervical ripening.

When there is a need to terminate pregnancy due to arising obstetric or medical problems, there is a need to initiate and to speed up this ripening process. Induction of labor, especially in nulliparous and preterm pregnancies, is a failure without the completion of cervical ripening. In pregnant women with Bishop scores less than four, the rate of abdominal delivery approaches 60% [2]. Aware of this fact, obstetricians have tried many ways to initiate cervical ripening. The ideal method is one with the least maternal and fetal side-effects and which shortens the duration of labor the most, hence decreasing the number of complications. Today, the most suitable agents used for this purpose are prostaglandins. Prostaglandins not only ripen the cervix but also increase myometrial contractility while inducing endogenous oxytocin secretion.

Prostaglandins were first used orally in 1968 but due to their high side-effect profile they have lost their popularity [1]. After trials by many different routes (oral, topical, systemic) intracervical PGE2 gel (dinoprostone) is used for inducing cervical ripening today. In Turkey, it is the only preparation that can legally be used for this purpose in pregnant women. The main disadvantage of dinoprostone is the high price. For a country like Turkey, whose citizens are not wealthy, it is very expensive since the gel is used at least two or three times per patient.

Misoprostol is a synthetic PGE1 analogue, which is available in tablets containing 200 μg of active product, and it is marketed in Turkey for use in the prevention of gastric ulcer (acts by inhibiting gastric acid secretion). From 1990 and on, it has been used in a totally different field, first for abortion and then to establish ripening and to induce labor in term pregnancies.

To investigate misoprostol and its effects, first used by Neto and colleagues [3] for induction of labor in 1987, a lot of prospective randomized studies have been performed. In these studies, researchers evaluated the effects of misoprostol on term pregnancies and/or on pregnancies that were beyond 35 weeks of gestation using dinoprostone in the control groups. Sanchez-Ramos and colleagues [4] published a meta-analysis gathering up their results on misoprostol use in 1997. This meta-analysis and other studies performed claim that misoprostol is an ideal agent for labor induction and cervical ripening. Other advantages are its easy application, stability in room temperature and inexpensive price. Tachysystole and hyperstimulation, negative effects on fetal heart rate pattern and increased abdominal delivery rates are its main disadvantages.

In most studies performed by using misoprostol, study groups were composed of patients with no apparent risks. Even in studies involving a large number of preeclamp-

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tic patients, details like severity of preeclampsia or an accompanying IUGR are omitted. In two randomised studies using misoprostol, arising tachysystole and hyperstimulation have been attributed to the cumulative effect [5] of and/or a sensitivity [6] to the drug.

An important observation that we encounterd in our clinical practice was the hard induction of labor in preeclamptic patients. Although it can be argued theoretically that preeclamptic cases are easier to induce, we have been thinking the opposite for quite a while; however to prove and evaluate our point of view objectively, we did not design a study until seeing the results of a study by Xenakis and colleagues [7] which supported our view of the issue. In this study, it is concluded that failed induction is more common in preeclamptic patients independent of Bishop scores, gestational week, and the severity of preeclampsia.

While organizing our study, we hypothesized that during the induction of preeclamptic patients the number of misoprostol tablets used would increase and thus, might lead to an increment in the incidence of tachysystole due to the cumulative effect of misoprostol.

Hence, in this study we tried to test the hypothesis that induction of labor would be harder in preeclamptic patients using misoprostol and since the time interval between the first misoprostol dose and delivery would tend to be longer, incidence of tachysystole due to the cumulative effect of the drug would be more common. Apart from this hypothesis, we tried to evaluate the effects of misoprostol on high-risk patients, and how fetal parameters like fetal heart rate pattern and arterial cord blood values are affected in patients who have been prediagnosed as having IUGR and HELLP syndrome.

Materials and Method

Our study group was composed of 90 pregnant women, all over 35 weeks of gestation and meeting the criteria listed below. They were admitted to Istanbul Medical Faculty Obstetrics Clinic between December 1998 and May 1999 and termination of pregnancy was indicated for different obstetric and non-obstetric reasons.

Inclusion criteria included: 1) Singleton gestation; 2) Cephalic presentation; 3) Bishop score <4; 4) Normal fetal heart rate pattern. Exclusion criteria were: 1) Non-vertex presentation; 2) Multiple gestation; 3) Post-term pregnancy; 4) Bishop score ≥4; 5) Estimated fetal weight more than 4500 g; 6) Evidence of cephalopelvic disproportion; 7) Unexplained vaginal bleeding; 8) Previous abdominal delivery; 9) Grandmultipara; 10) Any contraindication to receiving prostaglandins (eg. cardiovascular disease).

One hundred and fourteen pregnant women were given information about the study and 90 of them entered the study by signing an informed consent form. The study was approved by the Ethics Committee of the University of Istanbul Faculty of Medicine.

Of 90 patients, 45 were preeclamptic and 45 were non-preeclamptic. All patients received 50 μg of misoprostol tablets applied to the posterior vaginal fornix with 4 hour intervals for a maximum of three times. Misoprostol in 50 μg tablet form was prepared by Istanbul University, Istanbul Medical Faculty Pharmacology Unit by using 200 μg tablet form of the drug. While using misoprostol, the application was halted if the Bishop score was 5 or more. Taking the frequency of uterine contractions into account, oxytocin infusion was initiated if needed by the attending physician. To evaluate the effect of uterine contractions by oxytocin on cervical dilatation, oxytocin infusion was begun 12 hours after the first dose of the induction agent if the patient was not in active labor (defined as uterine contractions causing progressive cervical dilatation) even after receiving three tablets of misoprostol. Oxytocin infusion was prepared by adding 10 IU of oxytocin into a 1,000cc 5% Dextrose-Ringer lactate solution and started at a rate of 2 mU/min. Until the uterine contractions were one in three minutes, the infusion rate was increased 2 mU/min every 15 minutes. Maximal oxytocin infusion rate was set as 16 mU/min. Once the patient entered the active phase, labor was handled with general obstetric rules. If the fetal membranes were intact, artificial rupture of the membranes was performed when either cervical dilatation was 4-5 cm and effacement over 70%.

Tachysystole was defined as more than five uterine contractions in two consecutive 10-minute intervals, while hypersystole was defined as a single contraction lasting more than 2 minutes. Hyperstimulation syndrome was defined as the appearance of nonreassuring fetal heart rate monitoring patterns during tachysystole and/or hypersystole. Nonreassuring fetal heart rate monitoring patterns are defined as persistent or recurring episodes of moderate or severe variable decelerations, late decelerations or prolonged fetal bradycardia or a combination of decreased beat-to-beat variability and a decelerative pattern. Vaginal lavage was carried out in patients with tachysystole and/or hyperstimulation. In cases with persistent tachysystole and non-rhythmic contractions of the uterus even after lavage, tocolysis was begun by ritodrine infusion.

Outcome measures were: 1) First Bishop score; 2) Indications for caeserean section; 3) Time interval between first misoprostol dose and delivery (mean duration of labor); 4) Mean number of misoprostol used; 5) Number of patients requiring one misoprostol for vaginal delivery; 5) Number of patients requiring oxytocin; 6) Incidence of tachysystole and hyperstimulation; 7) Incidence of reassuring fetal heart rate pattern; 8) Birth weight; 9) Number of newborns with Apgar scores less than 7 at 1 and 5 minutes; 10) Arterial cord blood pH.

Preeclampsia was diagnosed and classified according to the ACOG's criteria [8]. HELLP syndrome was defined to be present when platelet counts were <100,000/mm^3, LDH >600 U, AST >70 U, and total bilirubin >1.6 mg/dl. Data of patients having HELLP syndrome were recorded separately because this was the first study about induction of labor using misoprostol in patients with HELLP syndrome.

On the basis of the research of Wing and Buser, sample size was calculated assuming a 36.7% tachysystole in preeclamptic patients with 50 μg misoprostol and 8% in non-preeclamptic patients. The type I error was 0.05 and the power was 80%. Thirty-eight patients were required in each treatment group with this scenario.

Data were recorded using Microsoft Access 97 and statistical analysis was performed by using SPSS® 8.0 for Windows. Student's *t*-test, Mann-Whitney U, and Fisher's exact tests were used during analysis. Data on differences in age, gestational age, mean duration of labor, average number of misoprostol tablets used, birth weight, arterial cord blood pH were analysed by using the Student's *t*-test; data on the number of patients with premature rupture of membrane (PROM), incidence of reassuring fetal heart rate monitoring patterns, the route of delivery, the incidence of tachysytole and hyperstimulation, the

number of patients who delivered vaginally after only one misoprostol dose, the difference between Apgar scores <7 were analysed with the Fisher's exact test. Bishop scores were analysed with the Mann-Whitney U test. A p value of <0.05 was regarded as significant.

Results

Although 90 patients participated in the study, two of 45 preeclamptic and two of 45 non-preeclamptic patients were left out because of deviations from the study protocol. As a result, data of 86 patients, 43 preeclamptic and 43 non-preeclamptic, were evaluated.

Table 1. — *Indications for induction of labor in the preeclamptic group.*

Indications	n	%
Preeclampsia	21	49
Preeclampsia-Intrauterine growth restriction	7	16
Preeclampsia-Intrauterine growth restriction-Oligohydramnios	5	12
Preeclampsia-HELLP syndrome	3	7
Preeclampsia-Intrauterine growth restriction-HELLP syndrome	2	5
Preeclampsia-Premature rupture of the membranes	2	5
Preeclampsia-Premature rupture of the membranes-HELLP syndrome	1	2
Preeclampsia-Oligohydramnios	1	2
Preeclampsia-Oligohydramnios-HELLP syndrome	1	2
Total	43	100%

Table 2. — *Indications for induction of labor in the non-preeclamptic group.*

Indications	n	%
Oligohydramnios	19	44
Premature rupture of the membranes	9	21
Chronic hypertension	8	19
Intrauterine growth restriction	2	5
Intrauterine growth restriction-Oligohydramnios	2	5
Intrauterine growth restriction-Chronic hypertension	1	2
Gestational diabetes	1	2
Abnormal antepartum test results	1	2
Total	43	100%

Indications for induction of labor in both groups are detailed in Tables 1 and 2. The characteristics of the study population were not different between the two groups. The number of patients detected with PROM between the two groups was also not statistically different (3/43 preeclamptic vs. 9/43 non-preeclamptic group [p=0.117, Odds Ratio [OR] 0.28; 95% Confidence Interval [CI] 0.07-1.33]).

For labor induction, an average of 2.32±0.64 misoprostol tablets were used in the preeclamptic group while 1.81±0.76 tablets were used in the non-preeclamptic group and the difference was statistically significant (p=0.001). While two of the preeclamptic patients needed only one misoprostol tablet for vaginal delivery, this number was 14 for the non-preeclamptic patients. The difference was also statistically significant (2/24 preeclamptic vs 14/32 non-preeclamptic group [p=0.006, OR 0.116; CI 0.02-0.58]) Mean duration of labor in the preeclamptic group was significantly longer than in the non-preeclamptic group (833.37±423.61 min preeclamptic vs 656.74 ± 344.12 min. non-preeclamptic group; [p=0.037]).

The rate of abdominal delivery was 44% (19/43) in the preeclamptic group and 21% (9/43) in the non-preeclamptic group. The difference was statistically significant. (p=0.037, OR 2.99, 95% CI 1.15-7.73). In contrast, the number of caesarean sections performed due to fetal distress was not statistically different between the two groups (Table 3).

Incidence of hyperstimulation was not different between the two groups. Although the number of tachysytole periods observed was different between the two groups, this difference was not statistically significant (Table 3). The number of nonreassuring fetal heart rate patterns observed during labor between the two groups was also not different.

Birth weight and number of newborns with Apgar scores less than 7 at 1 and 5 min were not different between the two groups. Measured arterial cord blood pH was significantly lower in preeclamptic cases. However, mean pH value of these fetuses was found to be above the accepted fetal acidosis cut-off level in our clinic (7.150).

Six (one being postpartum) out of 43 preeclamptic patients were diagnosed as having HELLP syndrome. Data on those patients are detailed in Table 4. Four of the patients were delivered by the abdominal route and in three of them the cause was fetal distress. In all three, fetal distress was diagnosed after the application of a 2nd dose of misoprostol.

Discussion

When used for cervical ripening and induction, misoprostol is an effective agent. The most important side-effect is tachysystole. The incidence of tachysystole increases directly proportional to the dose, although reported percentages in many studies differ even with the same dose of misoprostol used. The fellowing are the results of studies using 50 µg vaginal misoprostol: 7.8% Buser 1997 [9]; 8% Surbek 1997 [10]; 13.7% Carlan 1997 [11]; 21.3% Sanchez-Ramos 1998 [12]; 32.8% Farah 1997 [13]; 36.7% Wing 1995 [5].

Up to now, studies have mainly focused on the effectiveness of misoprostol rather than its side-effects. In two studies by Wing and colleagues [5, 6], it was proposed that tachysystole was due to the cumulative effect of the drug and/or a hypersensitivity reaction to the drug. Taking this point into consideration, we tried to prepare a model which would help us show whether tachysystole was primarily due to the cumulative effect or not. We decided to perform this study on preeclamptic patients like in Xenakis' *et al.* study [7]. They compared the results of induction in preeclamptic and normal pregnant patients and concluded that failed induction was five more times likely to be seen in preeclamptic patients. This was especially true for patients with Bishop scores

Table 3. — *Demographic characteristics and outcome measures of study population.*

	Preeclamptic group (n=43)	Non-preeclamptic group (n=43)	*p*	*t*	Odds Ratio 95% CI*
Age (years)	26.02±4.45	27.81±5.95	0.118	1.579	
Nulliparous	29/43 (67.4%)	25/43 (58.1%)	0.27		1.801 0.75-4.32
Gestational age	38.72±1.72	39.37±1.81	0.091	1.707	
Bishop score	2.58±0.49	2.69±0.51	0.211		
Cesarean deliveries	19/43	9/43	0.037§		2.991 1.15-7.73
– Fetal distress	11/43	5/43	0.164		2.613
– Failed induction	5/43	3/43	0.713		1.754 0.39-7.85
Mean duration of labor	833.37±423.61	656.74±344.12	0.037§	2.122	
Mean number of misoprostol used	2.32±0.64	1.81±0.76	0.001§	3.366	
Number of patients requiring one misoprostol for vaginal delivery	2/24	14/32	0.006§		0.116 0.02-0.58
Number of patients requiring oxytocin	23/43	13/43	0.048§		2.65 1.09-6.43
Hyperstimulation	5/43	7/43	0.756		0.67 0.19-2.32
Tachysystole	15/43	7/43	0.082		3.36 0.13-1.01
Nonreassuring fetal heart rate	18/43	14/43	0.503		1.49 0.61-3.59
Birth weight (g)	2980.9±682.9	3155.58±476.7	0.173	1.375	
Apgar score <7					
– 1 min	13/43	7/43	0.201		2.22 0.78-6.29
– 5 min	3/43	0/43	0.241		7.51 0.37-150.21
Arterial cord blood pH	7.204±0.13	7.269±0.06	0.05§	2.927	

*CI: Confidence Interval; §: Statistically significant

Table 4. — *Analysis of the patients with HELLP syndrome.*

Age	Parity	Gestational age (wk)	Diagnosis	Type of delivery	Indications for cesarean delivery	Nonreassuring FHR*	Birth weight (g)	Apgar score 1 min	Apgar score 5 min	Arterial cord blood pH
26	0	36	Preeclampsia HELLP, PROM**	Cesarean	Fetal distress	Yes	2100	4	8	7186
24	0	36	Preeclampsia, HELLP	Cesarean	Fetal distress	Yes	2050	5	7	7093
21	0	36	Preeclampsia, HELLP IUGR	Cesarean	Failed induction	No	1760	7	1	7375
35	1	37	Preeclampsia, HELLP, IUGR***	Vaginal		Yes	1650	5	7	7211
30	0	39	Preeclampsia, HELLP	Vaginal		No	3100	8	9	7310
22	0	36	Preeclampsia, HELLP, IUGR	Cesarean	Fetal distress	Yes	1350	4	7	6980

*FHR: Fetal heart rate; **PROM: Premature rupture of the membranes; ***IUGR: Intrauterine growth retardation.

less than or equal to three. In addition, preeclamptic patients were two times more likely to have an abdominal delivery when compared to normal pregnant patients. Xenakis *et al.*, using PGE_2 gel for cervical ripening, did not mention the frequency of gel use, total amount of gel used and the mean duration of labor in his study [7]. We hypothesized that more misoprostol tablets would be used in the preeclamptic group in our study because they would respond to the drug slower and hence we would encounter tachysystole more frequently. When estimating the sample size, we used the highest tachysystole rate reported with 50 μg misoprostol for the preeclamptic group (36.7%, Wing 1995), and lowest rate for the normal group (7.8%, Buser 1997). We left post-term pregnant patients out of the study and only compared the data concerning pregnant women who were at least in their 36th week of gestation. Although there were cases with PROM in both groups, the number of cases were similar.

Our results, unlike Xenakis' *et al.* study [7], showed that there was no difference in the number of patients with Bishop scores less than or equal to three, in whom abdominal delivery was performed due to failed induction. We observed that oxytocin and misoprostol were more frequently used in our preeclamptic group of patients.

In our study, we used an average of 2.32 tablets of misoprostol in preeclamptic patients and 1.81 tablets in non-preeclamptic patients for induction of labor. While 17 cases (39%) of the non-preecamptic group delivered after only one misoprostol tablet, this number was four (9%) for the preeclamptic group; mean duration of labor was significantly longer in the preeclamptic group. Although tachysystole was more frequent in the preeclamptic group (35% vs 16%), as we hypothesized, the difference was not statistically significant. It is important to note that an increase of only one case of tachysystole in the preeclamptic group would have made the difference significant.

An important point to emphasize is the high rate of abdominal deliveries in our study. Tachysystole and nonreassuring fetal heart rate monitoring patterns seemed to be the causes of this situation. Thus the effect of misoprostol on fetal heart rate monitoring patterns should be thoroughly evaluated. It has been proposed in several studies that misoprostol increases the rate of abdominal delivery by adversely affecting fetal heart rate. First, Buser reported the rate of nonreassuring fetal heart rate pattern to be 34.1% and abdominal delivery to be 35.5% (27/76 cases). In 70% of these 27 cases the reason for cesarean section was pathologic fetal heart rate. In the study published in 1999 by Kolderup and colleagues [14], fetal bradycardia and late decelerations were observed in 41% of patients using 50 μg misoprostol and cesarean section was performed because of fetal distress in 20% of these patients. In our study, the abnormal fetal heart rate pattern was 32.5% in the non-preeclamptic and 41% in the preeclamptic group and the abdominal delivery rate for fetal distress was 11.6% and 25.5%, respectively. Buser *et al.* linked the effect of misoprostol on FHR to increased "excessive uterine activity". Due to the adverse effects of misoprostol, the rate of abdominal deliveries will be increased especially when dealing with high-risk patients. Although 25 μg instead of of 50 μg of misoprostol may be a solution, reported results on incidence of tachysystole and nonreassuring FHR with this dose are quite variable.

Our study is the first one to use misoprostol in cervical ripening and labor induction in pregnant women with HELLP syndrome. Six cases with HELLP syndrome were evaluated. Of these, 67% (4/6) delivered abdominally and in three of them the reason was fetal distress. The diagnosis in all three was made after the application of the 2nd misoprostol tablet.

We believe that tachysystole is more frequent in patients who are hard to induce and these types of patients are higher in number among the preeclamptic. Different results reported on the rate of tachysystole with the same misoprostol dose used may be explained by this observation. The result of our study seems to support our hypothesis. The clinician, especially in preeclamptic patients with low Bishop scores, must bear in mind that more misoprostol tablets will be needed for cervical ripening and tachysystole will be seen more often due to the cumulative effect of the drug. It is still debated and not clear whether these findings affect the reported high rates of nonreassuring FHR patterns and abdominal deliveries. Up to now, studies with misoprostol have compared the drug with other prostaglandin preparations or tried to set an optimal dose for the drug. In future, the studies should focus on the unwanted clinical effects, like tachysystole, of misoprostol and the possible reasons. Our study was carried out based on this objective although the results are debatable.

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