Experimental
&
Clinical Article

The Effect of Different Doses of Intraamniotic Digoxin on the Timing of Fetal Demise in Second Trimester Medical Abortions

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ABSTRACT

OBJECTIVES: The World Health Organization recommends feticide for termination of pregnancy after 20 weeks of gestation, and the Royal College of Obstetricians & Gynecologists after 21 weeks and 6 days. Digoxin is a commonly used feticidal agent. This retrospective study aimed to show the effect of different doses of digoxin on the timing of fetal demise when used for feticide.

STUDY DESIGN: Our retrospective cohort study included 57 patients who underwent feticide by routine intra-amniotic digoxin 0.75 mg or 1 mg between 2016 and 2018 at the Ataturk University Medical Faculty Research Hospital. The patients were administered undiluted digoxin 0.75 mg (3 ccs) or 1 mg (4 ccs) with a 20-gauge spinal needle inserted through the amniotic membrane. After digoxin administration, the fetal heartbeat was monitored every hour by ultrasound, and recorded.

RESULTS: In this retrospective study, we reviewed the data of 61 patients who underwent feticide by intra-amniotic digoxin 0.75 mg and 1 mg. Digoxin 3 ccs (n=23) and digoxin 4 ccs (n=34). The two groups were not significantly different in terms of age, gestational week, and termination indications. We reviewed the medical records of all subjects and noted any side effects.

CONCLUSIONS: In our study, we investigated the effect of different doses of intra-amniotic digoxin on the fetal demise in accordance with the literature. Despite our small sample size, we conclude that a higher dose of digoxin will reduce the time to asystole and minimize the mental burden of the procedure on the patient.

Keywords: Digoxin, Feticide, Medical abortion

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Introduction

Approximately 35-40 abortions are performed per 1,000 women worldwide. This number is 25% higher in countries of low socioeconomic status compared to high-income countries. Globally, medical abortion is mostly performed before 13 weeks; however, in Ethiopia, second-trimester abortions are also allowed (1). A recent study from Northern Ethiopia reported that the prevalence of second-trimester abortion was 19.2% (2). The reasons behind delayed abortion included irregular menstruation, economic difficulties, lack of information, and delayed diagnosis of pregnancy. Moreover, increased gestational age at the time of medical abortion was associated with increased transient fetal survival rates (1). On the other hand, the widespread use of ultrasonography and perinatal genetic diagnosis in high-income countries allows for the increased prenatal diagnosis of fetal anomalies. This development has resulted in a recent increase in demand for the termination of pregnancies. The recommended gestational limit for feticide is 18-22 weeks (3). The World Health Organization (WHO) recommends feticide for termination of pregnancy after 20 weeks of gestation, and the Royal College of Obstetricians & Gynecologists after 21 weeks and 6 days (1,4). Feticide is the induction of fetal death before expulsion from the uterus. Digoxin is a pharmacological agent commonly used for feticide. Intraamniotic digoxin is widely used for feticide before the termination of pregnancy (5). There are few studies on its safety and efficacy. A small-scale study ad-

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ministered digoxin 1 mg to 8 patients and reported that maternal serum digoxin levels did not increase, maternal coagulation factor levels did not change and no maternal cardiac side effects were observed (6). On the other hand, some authors argue that feticide accelerates the termination process (7,8). The induction period is shorter after fetal demise compared to normal pregnancies. This is ascribed to factors such as endogenous prostaglandins and maceration. Since maceration will contribute to the softening of fetal tissues and cranium, the tissues can be expelled through an undilated cervix (3). However, a randomized controlled study demonstrated that maceration did not significantly change the duration of delivery (9). One study showed that estimated blood loss was reduced in 15 patients with placenta previa who underwent feticide compared to patients who did not, and argued that uterine blood flow is decreased after feticide (10). Although digoxin has been widely used since the 1980s, there is still no consensus on the dose or the method of administration (4). This retrospective study aimed to show the effect of different doses of digoxin on the timing of fetal demise when used for feticide.

Material and Method

Our retrospective cohort study included 57 patients who underwent routine intra-amniotic administration of digoxin 0.75 mg or 1 mg for feticide between 2016 and 2018 at the Ataturk University Medical Faculty Research Hospital. Our study was granted ethical approval by the ethics committee (B.30.2.ATA.0.01.00/01.10.2020/08/59). The study included patients aged between 17 and 44 years who required termination of pregnancy due to fetal anomalies, including central nervous system anomalies, cardiac anomalies, neural tube defects, and omphalocele. Gestational age ranged between 16 and 24 weeks. The patients were known not to have digoxin allergy. After giving informed consent, the patients were administered undiluted digoxin 0.75 mg (3 ccs) or 1 mg (4 ccs) with a 20-gauge spinal needle inserted through the amniotic membrane. Performing the procedure under ultrasonography prevents myometrial, placental, and venous administration. However, there is no data regarding the benefit or significance of digoxin administration to these sites (11). The procedure was performed by the same experienced perinatology team trained in amniocentesis. Twenty-three patients were administered digoxin 0.75 mg and 34 patients were administered digoxin 1 mg. We recorded data concerning demographic characteristics, chronic diseases, digoxin dose, and time from digoxin administration to fetal demise. In patients where digoxin was contraindicated, pregnancy was terminated by intracardiac potassium chloride injection. These patients were excluded from the study. After digoxin administration, the fetal heartbeat was monitored every hour by ultrasound, and recorded. No further doses were administered to any subject. After the absence of fetal heartbeat was confirmed, misoprostol 400-600 mcg was administered vaginally for induction. We reviewed the medical records of all subjects and noted any side effects.

All statistical analyses were carried out by using SPSS version 20.0. Normality assessment was made with the Kolmogorov- Smirnov test. Age and gestational age were analyzed with the Student's t-test. Indications of termination were analyzed with the Pearson chi-square and Kolmogorov–Smirnov test. Fetal asystole time was analyzed by survival analysis using the Kaplan-Maier method and compared with the Log-rank test. All tests were performed as two-tailed tests, and $p<0.05$ was accepted as statistically significant.

Results

In this retrospective study, we reviewed the data of 61 patients who underwent feticide by intra-amniotic digoxin 0.75 mg and 1 mg. 4 patients were excluded due to missing data. For the remaining 57 patients with complete data, the demographic characteristics, termination indications, and time to fetal demise according to digoxin dose are presented in table I. The mean age of the subjects was 27 years, and the mean gestational age was 21 weeks. The patients were divided into two groups: digoxin 3 ccs (n=23) and digoxin 4 ccs (n=34). The two groups were not significantly different in terms of age, gestational week, and termination indications. However, the time to fetal demise was significantly different for the digoxin 0.75 mg group and the digoxin 1 mg group (p=0.011). The time from digoxin administration to fetal demise was 17±9 hours for the digoxin 0.75 mg group and 11±8 hours for the digoxin 1 mg group. Table II compares pregnancy termination indications of the two groups. Accordingly, digoxin was administered due to neural tube defects in 33 patients, due to central nervous system anomalies in 6 patients, severe cardiac anomalies in 4 patients, omphalocele in 3 patients, genetic reasons in 4 patients, anhydramnios in 2 patients, and other reasons (e.g. Congenital pulmonary airway malformation, Meckel-Gruber syndrome, diaphragm hernia) in 5 patients. Indications for pregnancy termination were not significantly different for the two groups. Among the 11 patients with anencephaly, 8 were administered 4 ccs, and 3 were administered 3 ccs of digoxin. Time to fetal death was longer in patients with anencephaly in both groups compared to other indications.

Table I: *Characteristics of the study cohort*

	Digoxin dose		Total
	3 cc	4 cc	
NTD, n (%)	10 (43)	23 (68)	33 (57.8)
CNS, n (%)	4 (7.0)	2 (3.5)	6 (10.5)
CHD, n (%)	3 (5.2)	1 (1.7)	4 (7.0)
Anhydramnios, n (%)	1 (1.7)	1 (1.7)	2 (3.5)
Omphalocele, n (%)	2 (3.5)	1 (1.7)	3 (5.2)
Others, n (%)	1 (1.7)	4 (7.0)	5 (8.7)
Genetic, n (%)	2 (3.5)	2 (3.5)	4 (7.0)
Total, n (%)	23 (40.3)	34 (59.6)	57 (100)

NTD: Neural tube defects, CNS: Central nervous system, CHD: Congenital heart disease

Table II: *Comparison of pregnancy termination indications.*

	Total	3cc (0.75 mg) (n=23)	4cc (1 mg) (n=34)	*p*
Age	27±6	26±4	28±7	0.208
Gestational age (weeks)	21±3	20±3	21±2	0.637
Indication of termination				0.07
Noral tube defect	33(58)	10(43)	23(68)	
Others	24(42)	13(57)	11(32)	
Time between digoxin and US detection of cardiac asystole (hours)	13±9	17±9	11±8	0.011

Discussion

Considering the mental impact of the smallest chest movement of an aborted fetus on the mother and the medical staff, we believe that feticide before expulsion is preferable during the termination of pregnancy. Although the clinical benefits are yet to be proven, many clinicians prefer feticide before second-trimester medical abortions. A survey of 126 patients who preferred feticide before medical abortion indicated that 29% of patients believed that feticide would facilitate the procedure, and 19% believed that the termination would be less painful after feticide (9). However, a study compared placebo and feticide by digoxin 1 mg and did not find a difference in the duration of the procedure (12). A study of 20 women who underwent feticide before medical abortion reported both positive and negative responses concerning feticide (13). Some patients took a dim view of feticide due to not wanting to carry the dead fetus until medical abortion, or a fear of needles, whereas some patients indicated feeling relieved knowing that the fetus would not be alive upon delivery.

A retrospective study from the British Pregnancy Advisory Service including 548 patients found that feticide with potassium chloride lasted 8 minutes, resulted in a mere 3.5-minute reduction in the duration of the procedure, and that feticide was associated with a more painful procedure and an increased risk of atony (14). Another study demonstrated that intraamniotic or intrafetal administered 0.125-1 mg digoxin had no side effects (15). The maximum digoxin dose in this study of 1795 patients was 1 mg, and no adverse effects were reported. Intrafetal administration utilized a dose of 0.5 mg, and it was shown that lower doses of digoxin were effective with intrafetal administration (12). We believe that the intra-amniotic administration of digoxin is more comfortable for the mother. In Muslim countries, stopping the heart by giving potassium directly can be a stress factor for the clinician. So digoxin appears to be a better option. Also, our review revealed that KCL or intrafetal digoxin administration was not performed in our clinic. In our study, we investigated the effect of different doses of intra-amniotic digoxin on the fetal demise in accordance with the literature. In our study, the mean time to fetal demise was longer in the digoxin 0.75 mg group compared to the digoxin 1 mg group. We found that the maximum time of fetal demise was 41 hours in a patient who was administered intraamniotic digoxin 0.75 mg for hydrocephalus diagnosis. The minimum time to fetal demise was 2 hours in two patients where termination was indicated due to hydrocephalus and anhydramnios who were administered digoxin 1 mg. The reason for the short duration of fetal death in patients with anhydramnios may be the lack of dilution of digoxin. The prolonged time to fetal demise in anencephaly may be due to impaired fetal swallowing or dilution of digoxin. Among the 11 patients with anencephaly, 8 were administered 1 mg, and 3 were administered 0.75 mg of digoxin, and the maximum time to fetal demise was 28 hours for digoxin 0.75 mg, and 16 hours for digoxin 1 mg. Hence, intrafetal digoxin could have been administered in these patients. A randomized study reported that fetal mortality was not significantly different for digoxin 1 mg and digoxin 1.5 mg, indicating that the administration of digoxin >1 mg is unnecessary. However, this study did not specify the time to fetal demise (7). A dose-ranging series showed that fetal asystole was achieved the next day in 100% of the cases that were administered digoxin 1 mg intrafetal, whereas this rate was 96.4% for digoxin 0.5 mg (15). This study is partially consistent with our results. Another large case series reported that fetal asystole was successfully achieved in 99.7% of patients who were administered digoxin 1 mg (16).

In our study, fetal asystole was successfully achieved within 24 hours in 86.9% of the patients in the digoxin 3 cc (0.75 mg) group and 97% of the digoxin 4 cc (1 mg) group. A further dose could have been administered in the presence of a fetal heartbeat after 24 hours. This would have allowed the investigation of the effects of repeat doses on time on fetal demise and side effects.

Despite our small sample size, we conclude that a higher dose of digoxin will reduce the time to asystole and minimize the mental burden of the procedure on the patient. The literature does not report any side effects for the administration of digoxin 1.5 mg. Further studies with larger samples can prospectively compare digoxin 1 mg and 1.5 mg.

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