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Original Article

The effect of oxytocin on atrial and ventricular repolarization parameters of surface 12-lead ECG

Oksitosinin yüzey 12-derivasyon elektrokardiyografi (EKG) 'de atriyal ve ventriküler repolarizasyon parametrelerine etkisi

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Abstract

Aim: The purpose of this study is to evaluate whether oxytocin has effect on surface ECG or not. Although some of the studies demonstrated that oxytocin can change ventricular repolarizaton in the rats, there are no studies of human about all repolarization parameters. We were aimed to demonstrate the effect of oxytocin on both ventricular and atria depolarization parameters.

Material and Methods: We planned cross-sectional study. The Seventy- five patient, who were their last trimester and nulipar and admitted to hospital for spontaneous labor, were included to this study All patients' informed consent were obtained. A 12-lead ECG was recorded for each woman twice at 12 hour before oxytocin infusion at rest while in the supine position and shortly after from labor and upon cessation of oxytocin infusion. Recordings were acquired at a paper speed of 50 mm/s, with 1 mV/cm standardization. The Tp-e interval was defined as the interval between the peak and end of the T wave, measurements of the Tp-e interval were performed from precordial leads, and the Tp-e/QTc ratio and P wave dispersion, QTc was calculated from these measurements. All results were calculated and compared with statistically

Results: There were statistically significant differences in the Tp–e interval and Tp-e/QTc ratio and other parameters before and after oxytocin infusion , the maximum QTc, minimum QTc, and QTc dispersion values, P wave dispersion and other parameters of repolarization were significantly higher after labor compared to the before labor.

Conclusion: Although study population was small and arrhythmic potential of oxytocin was evaluated with surface ECG. The repolarization parameters were increased in women with oxytocin infusion during their labor. To obtain these repolarization parameters are easy and usage of these parameters as a cardiac arrhythmic risk factor are logical.

Key words: Oxytocin; cardiac arrhythmias; repolarization parameters; electrocardiography.

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Öz

Amaç: Bu çalışma ile amacımız, oksitosinin yüzey EKG'yi etkileyip etkilemediğini değerlendirmektir. Bazı çalışmalarda oksitosinin sıçanlarda ventriküler repolarizasyonu değiştirebileceğini göstermesine rağmen, farklı repolarizasyon parametreleri hakkında insan çalışmaları yoktur. Oksitosinin hem ventriküler hem de atrial depolarizasyon parametreleri üzerindeki etkisini göstermek amaçlanmıştır.

Gereç ve Yöntemler: Kesitsel bir çalışma planladık. Son trimester ve nulipar olan ve spontan doğum için hastaneye başvuran yetmiş beş hasta çalışmaya alındı. Tüm hastaların bilgilendirilmiş onamı alındı. Her kadın için 12 saatte iki kez EKG, yatar pozisyonda, istirahatte oksitosin infüzyonu almazken, doğumdan kısa bir süre sonra ve oksitosin infüzyonunun kesilmesinden sonra kaydedildi. Kayıtlar, 50 m / s kağıt hızında, 1 mV / cm standardizasyonu ile alındı. Tp-e aralığı T dalgasının tepe noktası ve sonu arasındaki aralık olarak tanımlandı. Tp-e aralığının ölçümleri precordial lead'lerden gerçekleştirilmiş ve Tp-e / QTc oranı ve P dalga dispersiyonu, QTc'den hesaplandı. Tüm sonuçlar hesaplandı ve istatistiksel olarak karşılaştırıldı.

Bulgular: Tp-e aralığı ve Tp-e / QTc oranı ve diğer parametrelerde oksitosin infüzyonu öncesi ve sonrası, maksimum QTc, minimum QTc ve QTc dağılım değerleri, P dalga dispersiyonu ve diğer repolarizasyon parametreleri arasında istatistiksel olarak anlamlı farklar vardı.

Sonuç: Çalışma popülasyonu küçük olmasına rağmen, yüzeysel EKG ile oksitosinin aritmik potansiyeli değerlendirilmiştir. Repolarizasyon doğum sırasında oksitosin infüzyonu olan kadınlarda artmıştır. Bu repolarizasyon parametrelerinin ortaya çıkması kolaydır ve kardiyak aritmi için risk faktörü olarak kullanımları mantıklıdır.

Anahtar kelimeler: Oksitosin; kardiyak aritmi; repolarizasyon parametreleri; elektrokardiyografi.

Introduction

Oxytocin is a hormone made in a part of the brain called the hypothalamus that causes the uterus to contract and milk to be released into the milk ducts of the breast during breastfeeding. A synthetic form of oxytocin can be given as a drug to induce labor contractions or make them stronger (1).

Oxytocin has some cardiac arrhythmic side effects in its label; it is safe and widely used medication in obstetric field. These known side effects were listed below, for example: it has been reported in that oxytocin infusion can prolong QTc intervals (2) and triggered ventricular arrhythmia during cesarean section under spinal anesthesia. (2,3) Also a large and transient QTc interval prolongation has also been documented after oxytocin administration during a first-trimester-induced abortion curettage under general anesthetics (4). In all the human studies referenced above, anesthetics were present, which could complicate the interpretation of QTc effects, because anesthetics can alter ventricular repolarization through a direct effect upon myocardial electrophysiology (5) or by an interaction with oxytocin. To understand if oxytocin could prolong QT and QTc intervals independent of anesthetics (6), evaluated the effect of oxytocin on QT and QTc intervals in both conscious male and female rabbits. The results revealed that QT and QTc intervals were prolonged in male and female conscious rabbits by administration of oxytocin. That study demonstrated that oxytocin prolonged ventricular repolarization independent of anesthesia and suggested that rabbit heart is a good model for translating the QTc findings of oxytocin in human.

To assess the effect of oxytocin on cardiac repolarization directly, this peptide was evaluated for its ability to prolong QT intervals in the isolated rabbit heart (IRH), and on action potential duration (APD) in human ventricular myocytes. The IRH model has been used for cardiac safety assessment to evaluate the propensity of small molecule drugs to cause QT interval prolongation and arrhythmia (7), and it has demonstrated sensitivity to detect QT prolongation induced by BeKm-1, a specific peptide inhibitor of the hERG channel (8).

Therefore, this isolated whole heart model can detect QTc prolongation caused by small or large molecules inhibitors that directly interfere with cardiac repolarization. In addition, APD recorded in ventricular myocytes is another sensitive model for predicting effects on the QT interval in vivo (9,10).

It can be see above oxytocine arrhythmic effects have been studied mainly in animal experiments, isolated heart models and limited human studies. Because of that, we decided to evaluate oxytocin's effect on atrial and ventricular repolarization parameters in a healthy pregnant women

surface electrocardiography (ECGs). Our study aimed to determine the risk of arrhythmia by calculating the electrocardiographic Ventricular repolarization parameters (P-wave duration, QT interval, T peak-to-end interval, Tp-e/QT ratio, QTc) and atrial repolarization parameter (P wave dispersion). All measurements were carried out before and after oxytocin infusion and compared with statistically..

Material and Methods

All consecutive pregnant women with normal heart functions in their last trimester according to last menstrual period and ultrasonographic measurements were admitted to the Department of Obstetrics and Gynecology of bicard clinic were considered eligible for the this study.

Those with multiple pregnancies, hypertension, diabetes mellitus, gestational diabetes, pre-eclampsia, eclampsia, previous history of pregnancy-induced hypertension, family history, any immunologic-rheumatologic disease, abnormal renal, hepatic, or thyroid function tests, atrial fibrillation, complete or incomplete bundle branch block, ST–T abnormalities, the use of any drugs that could affect Tp-e or QT interval, U waves or negative T waves, p wave dispersion on ECG, and electrolyte imbalances were excluded from the this study.

After evaluation of bishop score and decision of induction, which was based to obstetric reasons, was made. The oxytocin infusion was initiated at a rate of 3 mIU/min and was increased every 30 minutes by 3 mIU/min until regular contractions at a rate of 3–5 contractions/10min were achieved. The maximum dose of oxytocin was 42 mIU/min. Infusion of oxytocin was incremental until 4–6cm cervical dilation, which, along with 3–5 contractions in 10 minutes, marked the active stage of labor. At cervical dilatation of 4–6 cm, amniotomy was performed in those with intact membranes

A 12-lead ECG (AT-102, Schiller AG, Baar, Switzerland) was recorded for each woman only once at a point in 12 hour before labor at rest while in the supine position. Recordings were acquired at a paper speed of 50 mm/s, with 1 mV/cm standardization. We improved our accuracy using calipers and magnifying lenses. The onset of the P wave was defined as the first atrial deflection from the isoelectric line, and the offset was the return of the atrial signal to the baseline. The maximum and minimum P wave duration were measured and their differences were defined as the P dispersion. The QT interval was measured from the beginning of the QRS complex to the end of the T wave and corrected for the heart rate using the Bazett formula:$cQT=QT\sqrt{(R-R\ interval)}$.

The Tp-e interval was defined as the interval between the peak and end of the T wave, measurements of the Tp-e interval were performed from precordial leads, and the Tp-e/QTc ratio was calculated from these measurements.

Statistical analysis

Statistical analysis was performed using SPSS 21 (SPSS Inc., Chicago, Illinois). In the interim statistical analysis of the study, the sample size was calculated according to the QTc interval and a sample size of 75 patients would be required with 80% power and the conventional 2-sided type 1 error of 5%. Data were tested for normality of distribution using the Kolmogorov-Smirnov test. Continuous variables were presented as means followed by the standard deviation and categorical variables as frequencies and percentages. Continuous variables between the two groups were compared using Student's t test for normally distributed data and the Mann–Whitney U test for data that was not normally distributed. Categorical parameters were evaluated by chi-squared ($\chi 2$) test. A two-tailed $P \leq 0.05$ was considered significant.

Results

The obstetric and demographic characteristics of the women were as presented in Table-I, and study population. Laboratory tests results were summarized in Table-II. There were no statistically significant discrepancies. But there were statistically significant differences in the QTc, Tp–e interval and T-e/QTc ratio and P wave dispersion before and after oxytocin infusion , the maximum QTc, minimum QTc, and QTc dispersion, P-wave dispersion values were significantly higher after oxytocin infusion compared to the before oxytotin infusion (Table III). But we did not observe any cardiac arrhythmia during and after oxytocin infusion ($P<0.01$).

Table-1: Characteristics of the study population	
Maternal age, years	36.5 ± 2.9
Gestational week	37.6 ± 3.2
BMI, kg/m^2	28.4 ± 3.9
Heart rate, bpm	92.7 ± 10.2
Systolic BP, mmHg	112.4 ± 9.5
Diastolic BP, mmHg	76.1 ± 7.2

Table 2. Laboratory tests results of the study population at assessment.	
Hemoglobin (g/dl)	11.3 ± 1.4
Platelet (×103) – /µL	252.6 ± 56.2
WBC	10108 ± 2312
BUN (mg/dl)	15.3 ± 3.1
Creatinine (mg/dl)	0.38 ± 0.09
Sodium (mEq/L)	139.4 ± 1.4
LVEF (%)	55 ± 2.9
Potassium (mEq/L)	4.1 ± 0.9

Table 3: The electrocardiographic-repolarization findings before and after oxytocin infusion in the study population.

	After Oxytocin Infusion	Before Oxytocin Infusion	P-value
Maximum QTc interval (ms)	413.9 ± 21.9	383.2 ± 13.5	< 0.001
Minimum QTc interval (ms)	399.8 ± 13.8	312.1 ± 11.4	<0.001
QTc dispersion (ms)	27.1 ± 6.7	17.7 ± 8.3	<0.001
Tp-e interval (ms)	99.3 ± 12.1	69.9 ± 12.1	<0.001
Tp-e/QTc ratio	0.27 ± 0.04	0.13 ± 0.12	<0.001
P dispersion (ms)	18.9 ± 7.7	12.1 ± 6.1	<0.001

Discussion

The major finding of our study was the atrial and ventricular repolarization parameters of surface ECGs were significantly higher in women after oxytocin infusion than before infusion ($p<0.001$). Which proved that in our study in pregnant women without any disease might be legitimate to obtained ECG parameters from surface ECG to evaluate arrhythmic tendency.

Oxytocin is a hormone that causes contractions of the uterus. It can be used to start labor or to speed up labor that began on its own. Contractions usually start in about 30 minutes after oxytocin is given (11-13). The use of oxytocin has been indicated for the treatment of labor dystocia, as it may reduce the rates of cesarean sections (14, 15). Oxytocin has a proven strong effect on uterine muscle via oxytocin receptors. And it was demonstrated that oxytocin receptors are widely separated throughout other body tissues (15-17). Also oxytocin effects on cardiovascular system were demonstrated via a lot of studies. The oxytocin was also shown to have transient negative inotropic and chronotropic effects on perfused isolated dog right atria in a mechanism independent of Atrial Natriuretic Factor release and mediated by nitric oxide production and acetylcholine release at cardiac parasympathetic postganglionic neurons (18-20).

The electrocardiogram is a common, simple medical tool used for predicting arrhythmogenic risk in clinical practice. The QT interval and its correction by heart rate (QTc), QT interval dispersion, and recently published markers such as the Tp-e interval and Tp-e/QTc ratio have been proposed as markers for predicting the development of malign cardiac arrhythmia and recommended as alternatives for the risk stratification of sudden cardiac death in women with several medical conditions (21- 23).

We demonstrated that in our study oxytocin disturbed both ventricular and atrial repolarizaton within therapeutic dose range. We observed ECG chances related to oxytocin infusion from surface ECG. The ventricular repolarization parameters, which shows tendency to arrhythmias in ventricular myocardium, Tp-e/QTc ratio, (QTc), QT interval dispersion, Tp-e interval in addition to this also atrial repolarization parameter (P wave dispersion) were statistically increased after oxytocin infusion ($p< 0.001$). However we did not observe any critical arrhythmia during and after oxytocin infusion except rare VPC (ventricular premature contraction). It should be consider that all our study population was healthy women without any cardiac problem beforehand. Because that they were not bias to any rhythm disturbance. It should be consider when oxytocin used in patients with cardiac problems. Surface ECG parameters which are related to atrial and ventricular arrthymias should be evaluated during and after oxytocin infusion inpatients with pre-diagnosed cardiac diseases. And there is a need for further studies about arrhythmias in patient with heart disease during oxytocin infusion. And we assessed these ECG parameters only after and before oxytocin infusion not during infusion. Some kind of algorithms must be advanced for evaluation of cardiac arrhythmia potential during ECG monitorization. If we can develop algorithms which continuously monitorize and analyze repolarization parameters we can successful in preventing arrhythmias during usage of this kind of medication. Also in our study was used surface ECG to evaluate the tendency of cardiac arrhythmias. Advanced electro physiologic and clinical methods can be used to demonstrate the arrhythmic potential of oxytocin.

Conclusion

In conclusion, although study population was small and arrhythmic potential of oxytocin was evaluated with surface ECG. The repolarization parameters were increased in women with oxytocin infusion during their labor. To obtain these repolarization parameters are easy and usage of these parameters as a cardiac arrhythmic risk factor are logical. Furthermore, the other parameters except QT measurements, which we were used in this study as a marker of arrhythmic bias, can be used to detailed observation of atrial and ventricular arrhythmic tendency. Also further studies should be carried out in this area.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

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