RESEARCH ARTICLE

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Oxytocin and endothelial dysfunction in pregnant Woman

Hakan Gocer[1*], Özlem Kayacık Günday[2], Mustafa Unal[3]

1 Medical Park Hospital Cardiology Department, İzmir, Turkey

2 KTO Karatay University Medicana Medical Faculty Hospital, Department of Obstetrics and Gynecology, Konya, Turkey ***orcid id:*** *orcid.org/0000-0002-9249-679X; email: drozlemgunday@gmail.com*

3 Bicard Clinic, Cardiovascular Surgery, Bishkek, Kyrgyzstan; ***orcid id:*** *orcid.org/0000-0001-6640-6298; email: uunalmustafa@gmail.com*

*Corresponding Author: Dr. Hakan Gocer, Medical Park Hospital Cardiology Department, İzmir, Turkey.

orcid id: orcid.org/ 0000-0003-3295-1145, Mobile: +90533 5761821, email: hgocer@gmail.com

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Abstract

Objective: Oxytocin is frequently used medication in obstetrics and is synthesized in the brain. The effect of Oxytocin is mediated by Oxytocin receptors which are present in both the heart and large vessels. In our study we try to estimate the effect of Oxytocin on endothelium by means of flow mediated shear stress with an ultrasonography. There is no study in this field. **Method:** The seventy-six healthy pregnant women, whose average age was (26.2 ± 1.3), were admitted to our clinic hospital to labor. Exclusion criteria were high blood pressure, presence of documented arteriosclerotic heart and peripheral diseases, open heart or vascular surgery, diabetes, vasoactive medication usage, planned caesarean section. Informed consent obtained from all women. Whenever indicated, Oxytocin infusion was initiated at a rate of 3mIU/min and increased to the maximum dose of Oxytocin (42ml/min). Flow mediated vasodilatation was evaluated before and after Oxytocin infusion via a high-resolution ultrasonography. And then all measurements were compared with statistically. **Result:** All results were statistically compared before and after the infusion of Oxytocin. It was found that endothelial-dependant brachial artery vasodilatation was significantly improved after Oxytocin infusion ($p<0.001$). Also flow-mediated dilatation of brachial artery was found positively correlated with the given dose of Oxytocin ($r=1.847$, $p<0.001$). **Conclusion:** Oxytocin had positive impact on the vasodilatory functions of endothelium. In which was showed via Flow Mediated Vasodilatation with ultrasonography in the study. This positive improvement of endothelial function can be related to increase of nitric oxide and atrial natriuretic peptide's amount. These mediators can play positive role in fetus and woman's well being and blood supply. The Oxytocin selection for induction of labor should be made with having regard to its positive impact on endothelium.

Keywords: Oxytocin, Induction, Flow Mediated Vasodilatation, Ultrasonography.

INTRODUCTION

Oxitocine is synthesized in the supra-optic and para-ventricular nucleus of the hypothalamus [1]. And reduced synthesis of oxitocine in the hypothalamus was reported in hypertensive rats [2] and was correlated with etiology of hypertension in those animals [3]. The background of oxitocine in the cardiovascular system was discovered by experiments on atrial natriuretic peptide (ANP) released into the circulation during experimental blood volume expansion. Oxytocin action and signaling are mediated by Oxytocin receptors, which are present in both the heart and large vessels [4,5].

Oxytocin is one of the most frequently used vasoactive medications in obstetrics [6]. One known effect of its use is the improvement in uterine contractions [7]. Oxytocin is widely used in modern obstetric practice to increase uterine activity, in cases in which the labor process has failed, with the aim to enable it to progress to a vaginal delivery [8]. The use of oxytocin has been indicated for the treatment of labor dystocia, as it may reduce the rates of cesarean sections [9].

Flow mediated vasodilatation (FMD) was developed a non-

invasive method to evaluate early changes in vascular function in systemic arteries by using an ultrasound. It is expressed as a percentage change of the arterial diameter from the baseline diameter. FMD has been extensively used in clinical research and it is currently considered a standard for a noninvasive assessment of conduit artery endothelial function [10-13].

Changes in the endothelium, including endothelial dysfunction, are essential for the initiation and progression of atherosclerosis [14]. Albeit there were a lot of proof about relationship of oxytocin and cardiovascular system in some studies [15,16]. There were no studies in relationship with oxitocine and endothelial vasomotion. Because of that, we aimed to demonstrate the effect of oxytocin on the endothelium via FMD in healthy women before and after spontaneous labor with oxytocin induction in our study. All women were evaluated with ultrasonography before and after oxytocin infusion and measurements were compared with statistically.

METHOD

The 76 healthy women in their first pregnancy were admitted to our clinic hospital to elective spontaneous labor. All subjects were informed and signed written consent prior to their enrollment. The institutional Ethics Committees of Bicard Clinic approved the study protocol. This study was conducted according to the latest version of Helsinki Declaration. The average age on the day of delivery was (26.2 ± 1.3), ranging from 19 to 36 years old. Exclusion criteria were documented arteriosclerotic heart and peripheral diseases, open heart or vascular surgery, diabetes, vasoactive medication usage, planned caesarean section. Operative vaginal delivery was conducted for obstetric indications. Maternal and fetal monitoring was done every 15 minutes. Pelvic examination was carried out before induction of labor and 2–4 times per hour depending on the initial pelvic findings, onset of adequate uterine contractions, or whenever indicated. Cardiotocography was used as and when indicated. After 5 min of rest before oxytocin infusion, the brachial artery was located above the elbow, and a longitudinal image of 6 to 8 cm was taken as the resting scan. A blood pressure cuff was placed on the forearm and inflated to 300 mm Hg for 4.5 min. The cuff was deflated, and after ~1 min, the second or FMD scan was obtained, which represents the endothelial-dependent dilation due to shear-induced endothelial nitric oxide production. 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. After delivery, endothelial functions were evaluated by means of same protocol with ultrasography. The percent diameter changes for FMD, other parameters of vasomotion and the given total dose of oxytocin were calculated in relation to its respective scans. Then all measurements statistically calculated and compared.

STATISTICAL ANALYSIS

The statistical package SPSS (Statistical Package for the Social Sciences, version 17.0, SSPS Inc, Chicago, Ill, USA) was used for statistical analysis. Continuous variables were expressed as means ± standard deviation. Categorical variables were expressed as the total number (percentage). All continuous variables were evaluated with the Kolmogorov–Smirnov normality test to show their distributions. Continuous variables with normal distributions were compared using the unpaired Student *t*-test and ANOVA with the Tukey's post-hoc test. Continuous variables with abnormal distributions were compared using the Mann–Whitney *U* test and ANOVA with the Tukey's post-hoc test. For categorical variables, the chi-square test was used. Values of $P < 0.05$ were considered statistically significant for all tests.

The relationship between the oxytocin infusion dose and parameters of FMD were examined by Pearson's correlation analysis.

RESULTS

The demographic characteristics of the groups were as presented in Table 1. All results were statistically compared before and after infusion of Oxytocin. FMD namely endothelial-dependant brachial artery vasodilatation before induction of labor was (6.39 ± 0.35 %) and significantly improved shortly after with oxytocin infusion (11.03 ± 0.82 %, p<0.001) Also increase in peak blood flow was statistically significantly improved after infusion of oxitycin (354.7 ± 6.8ml/min, 629 ± 8.7ml/min, p<0.001) respectively. And there was statistically meaningful increase in base line arterial diameters after oxytoycin infusion (3.28 ± 0.14 mm, 4.12 ± 0.13 mm, p=0.003) and blood flow (199.5 ± 5.4 ml/min, 287 ± 5.9 ml/min, p= 0.012) respectively (Table 2). Parameters of the FMD; Baseline arterial diameter (r=0.711, p<0.001) and blood flow (r=1.012, p<0.001), increase in peak blood flow during flow mediated hyperemia (r=1.125, p<0.001), flow-mediated dilatation of brachial artery (r=1.847, p<0.001) was found positively correlated with the given total dose of oxytocin (Table 3).

Table 1: Subject characteristics

Age, yr	26.2 ± 1.3
Height, cm	165.6±1.7
Body mass, kg	68.7 ± 2.3
BMI, kg/m2	24.5± 0.5
Systolic BP, mmHg	114 ± 2
Diastolic BP, mmHg	71 ± 1
Mean BP, mmHg	89 ± 1
Heart rate, beats/min	66± 3
Total cholesterol, (mg/dl)	198 ±9
Glucose, (mg/dl)	98 ± 6

Table 2: Brachial Arterial Data of Flow mediated vasodilatation. (Endothelial-dependent dilation)

	BEFORE OXITOYCIN INFUSION	**AFTER OXITOYCIN INFUSION**	**P-VALUE**
Baseline arterial diameter(mm)	3.28 ± 0.14	4.12± 0.13	0.003
Baseline blood flow (ml/min)	199.5± 5.4	287± 5.9	0.002
Increase in peak blood flow during flow mediated hyperemia (%)	354.7±6.8	629 ±8.7	<0.001
Flow-mediated dilatation of brachial artery (%)	6.39± 0.35	11.03±0.82	<0.001

Table 3: Correlation analysis between the total infusion dose of Oxytocin and flow mediated parameters

Variables	All patients	
	*r	*p
Baseline arterial diameter(mm)	0.711	< 0.001
Baseline blood flow (ml/min)	1.012	< 0.001
Increase in peak blood flow during flow mediated hyperemia (%)	1.125	< 0.001
Flow-mediated dilatation of brachial artery (%)	1.874	< 0.001

DISCUSSION

The endothelium is recognized as an endocrine and vasoactive organ that acts to maintain vascular homeostasis regulating the vascular tone and structure. The endothelial cells synthesize a variety of mediators among them; the main agent is the nitric oxide, a potent vasodilator [17-19].

There is no study about showing relationship of endothelial dysfunction and oxytocin but there are a lot of studies about FMD and pregnancy, pre-eclampsia, eclampsia. Also, it was showed that, some treatments like estrogen therapy in postmenopausal women is associated with lower the risk of cardiovascular events, and the augmented release on endothelium-derived nitric oxide by estrogens has been suggested to be one of the mechanisms for the cardio protective effects [20-23].

Oxytocin has a proven strong effect on uterine muscle via oxytocin receptors. And it was demostrated that oxytocin receptors are widely separated throughout other body tissues [23,24]. Also, oxytocin effects on cardiovascular system was

demonstrated via a lot of studies oxytocin was also shown to have transient negative inotropic and chronotropic effects on perfused isolated dog right atria in a mechanism independent of ANP release and mediated by nitric oxide production and acetylcholine release at cardiac parasympathetic postganglionic neurons [25-27]. Exogenous oxytocin administration has direct negative chronotropic effects [28]. Slowing of the heart rate leads to a decrease in myocardial consumption of oxygen and nutrients, and an increase in subendocardial blood flow per beat that may improve regional contractile function [29].

We evaluated endothelial vasomotor functions before and after oxytocin infusion in our study. Also, a lot of studies demonstrated that physiological levels of oxytocin have been shown to protect against oxidative stress and to reduce Hydrogen Peroxide-stimulated Nicotinamide Adenine Dinucleotide Phosphate-dependent superoxide activity in vascular cells, monocytes, and macrophages [26]. This activity of oxytocin was compatible with our findings. We found that there was strong positive correlation between given dose of oxytocin and all flow-mediated vasodilatation parameter (Table 3). In addition to this, other Brachial Arterial Data showed us statistically significant improvement in endothelial vasodilatation parameters after Oxytocin infusion (Table 2).

Our study was demonstrated that endothelial functions improved after Oxytocin infusion via just ultrasonography but we did not demonstrate the underlying exact mechanisms and molecular interactions of this effect. In which may be related with nitric oxide, ANP and other mediators. Because of that there is a need for further studies about nitrate mediated vasomotion, which shows vascular muscles function during vasodilatation, and the molecular basis of the effect on endothelium of Oxytocin.

As a result of this study, FMD and blood flow during flow mediated shear stress was better after oxytocin infusion than before infusion. This proved that Oxytocin has not only effect of uterine and myocardial muscle also has effect on endothelium. And it can be easily demonstrated via FMD with ultrasonography.

CONCLUSION

Oxytocin had fruitful effect on the vasodilatory functions of endothelium. In which was showed easily via FMD with ultrasonography in the study. This positive improvement of endothelial function can be related to increase of nitric oxide and atrial natriuretic peptide's amount. These mediators can play positive role in fetus and woman's wellbeing and blood supply. The selection of oxytocin for induction of labor should be made with having regard to its positive impact on endothelium. Also, oxytocin can be used various arteriosclerotic disorders as a medication. All these scopes require further molecular and clinical researches.

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