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Evaluation of Dynamic Thiol /Disulfide Homeostasis and Ischemia- Modified-Albumin Levels in Cord Blood of Newborns to Patients with Oxytocin-Induced Labor

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Abstract

The aim of this study is to evaluate both dynamic thiol-disulfide and ischemia modified albumin (IMA) levels in cord blood of newborns to patients with oxytocin-induced labor. A total of 30 pregnant women who underwent medical labor induction with oxytocin were compared with 30 women whose labor progressed spontaneously without any kind of induction. The dynamic thiol-disulfide balance was determined by a new colorimetric method. IMA levels were analyzed using the albumin cobalt binding test. It was found that TAS and TOS levels were lower and OSI levels were higher in the oxytocin-induced group compared to the controls. Native and total thiol levels were found lower while disulfide levels found higher in oxytocin-induced group respect to the control. IMA levels were found significantly different between the patient and control subjects. We indicated that formation of disulfide leads to decrease antioxidant capacity in newborns of oxytocin-induced patients. Dynamic thiol-disulfide homeostasis may contribute to the monitoring of oxidative stress (OS) in infants of oxytocin-induced patients and the follow-up of diseases that may arise due to OS.

Key Words: Newborn, Oxidative stress, Ischemia-modified albumin, Thiol-disulfide homeostasis, Oxytocin induction

Oksitosin ile İndüklenen Doğumu Olan Hastalarda Yeni Doğanların Kordon Kanındaki Dinamik Tiyol/Disülfid Homeostazisi ve İskemi-Modifiye-Albümin Düzeylerinin Değerlendirilmesi

Özet

Bu çalışmanın amacı oksitosine bağlı doğum eylemi olan hastalarda yenidoğanların kordon kanındaki hem dinamik tiyol-disülfid hem de iskemi modifiye albümin (IMA) düzeylerini değerlendirmektir. Oksitosin ile tıbbi doğum indüksiyonu yapılan toplam 30 hamile kadın, doğumu herhangi bir indüksiyon olmaksızın kendiliğinden ilerleyen 30 kadınla karşılaştırıldı. Dinamik tiyol-disülfit dengesi, yeni bir kolorimetrik yöntemle belirlendi. IMA düzeyleri ise albümin kobalt bağlama testi kullanılarak analiz edildi. Oksitosin ile indüklenen grupta kontrollere göre TAS ve TOS seviyelerinin daha düşük ve OSI seviyelerinin daha yüksek olduğu bulundu. Oksitosin ile indüklenen grupta kontrol grubuna göre native ve toplam tiyol seviyeleri daha düşük, disülfid seviyeleri daha yüksek bulundu.IMA seviyeleri hasta ve kontrol grupları arasında anlamlı olarak farklı bulundu. Oksitosin ile indüklenen hastaların yenidoğanlarında disülfid oluşumunun antioksidan kapasitede azalmaya yol açtığını belirttik. Dinamik tiyol-disülfid homeostazı, oksitosin ile indüklenen hastaların bebeklerinde oksidatif stresin (OS) izlenmesine ve OS'ye bağlı ortaya çıkabilecek hastalıkların takibine katkı sağlayabilir.

Anahtar Kelimeler: Yenidoğan, Oksidatif stres, İskemi ile modifiye edilmiş albümin, Tiyol-disülfid homeostazı, Oksitosin indüksiyonu

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INTRODUCTION

Induction of labor (IOL) is one of the most frequently performed obstetric procedures in the world and its use is increasing worldwide (Marconi, 2019). According to WHO's data on maternal and perinatal health, consisting of approximately 300,000 births in 24 countries; it has been shown that induction of labor is applied in 9.6% of deliveries. It has been found that induction of labor is an independent risk factor for labor complications and is associated with increased fetal and maternal morbidity and mortality (Rydahl, Eriksen, & Juhl, 2019). Oxytocin is the most common drug used to induce and facilitate labor (Giri et al., 2022) Infusion of oxytocin can have harmful effects on both mother and fetus (Alchalabi, Obeidat, Jallad, & Khader, 2006). Studies have shown that induction of labor with induction may create an oxidative stress source on the newborn and accordingly increase the systemic oxidative stress load (Saugstad, 2005). Oxygen utilization in tissues increases due to the increased requirements of both the mother and the newborn during pregnancy, and despite increased antioxidants as a defense mechanism, the placenta is the main source of oxidative end products during pregnancy (Karacor et al., 2017). Under normal conditions, free radicals and antioxidant molecules are in a balance, which is defined as oxidative balance, and when free radicals increase more than normal, the balance is disrupted and shifted to the free radical side is defined as OS (Ozcan, Erdal, & Yonden, 2015; Özcan et al., 2015). The increase in oxidative stress causes permanent damage to nucleic acids, proteins and cell membranes, resulting in functional loss and death of the cell (Özcan et al., 2015). Increased OS is associated with many diseases and is responsible for the pathogenesis of these diseases (Cakirca G, 2018; Erdal, Ciftciler, Tuncer, & Ozcan, 2022; O. Ozcan et al., 2018; Erdal et al., 2022; Erdal, Demirtas, Tuncer & Ozcan, 2022). Thiols are compounds containing sulfhydryl groups and they transform into disulfide structures under oxidative stress. Therefore, they are the primary target of reactive oxygen species. The plasma thiol pool is mostly composed of albumin thiols and low molecular weight thiols (Otal, Kahraman, Haydar, & Erel, 2021). Dynamic thiol disulfide balance is vital for the organism and has been shown to be associated with many diseases (Cakirca G, 2018; Demirtas, & Erdal, 2022; Erdal et al., 2022; M. A. Eryilmaz et al., 2019; Otal et al., 2021; Demirtas & Erdal, 2022). Ischemia-modified albumin damages the N-terminal end of albumin as a result of increased oxidative stress, reducing the binding capacity of albumin. This modified form of albumin is called IMA (Bar-Or, Curtis, Rao, Bampos, & Lau, 2001). The aim of the present study was to investigate dynamic thiol disulfide balance and IMA levels in cord blood of newborns in patients with receiving oxytocin-induced labor.

MATERIALS AND METHODS

Patient and Control Groups

Thirty pregnant women who were followed up in the Obstetrics and Gynecology outpatient clinic of Aksaray University Training and Research Hospital between February 2022 and April 2022 were included in the study. The control group consisted of 30 healthy women individuals whose labor progressed spontaneously without any kind of induction with no statistically significant difference in terms of gender and age.

Written medical informed consent was obtained from the all participants included in the study in accordance with the terms of the Helsinki declaration of ethical issues. All routine laboratory parameters of the patients; hemoglobin, platelet, neutrophil, lymphocyte, hematocrit, urea creatinine, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT) values and demographic data; Age, gravida, parity, abortion numbers, birth weight, baby gender and APGAR scores were recorded. In the present study, pregnant women who had additional diseases, were included in the risky pregnancy category such as preeclampsia and eclampsia, had any intrauterine anomaly or growth retardation (IUGR), had multiple pregnancies, and gave birth before the 37th gestational week were excluded from the study.

Sample Collection of the Study

Whole blood samples were collected both from the oxytocin-induced and control groups. Then, samples were centrifuged at 1500 x g for 10 min. After this procedure, all working samples were separated into Eppendorf tubes and stored in a refrigerator at -20°C until the time of the assay.

Oxytocin protocol

Low-dose oxytocin infusion was started in patients with expiration, premature rupture of membranes, oligohydramnios, or in cases where the continuation of pregnancy was risky. Oxytocin infusion was prepared at a concentration of 10mU/ml by placing 10U in 1000ml isotonic and started at 1.0 mU/min. Oxytocin was increased by 1mU every 15 minutes to create regular contraction. When 3-4 contractions lasting 45-60 seconds were achieved in ten minutes, the oxytocin infusion dose was fixed.

Biochemical Measurements

TAS and TOS measurements

Total oxidant status (TOS) and total antioxidant status (TAS) levels were measured spectrophotometrically based on method developed by Erel (Erel, 2005). Oxidative stress index (OSI). OSI (arbitrary unit) =TOS (μmol H_2O_2 Eq/L)/TAS (μmol Trolox Eq/L) ×100 were calculated.

Measurement of Thiol / disulfide Levels

Thiol/disulfide levels were determined by automated spectrophotometric method as previously described by Erel and Neselioglu (Erel & Neselioglu, 2014). Disulfide levels were determined by dividing the difference obtained by subtracting native thiols from total thiols by two.

Measurement of IMA Levels

Ischemia Modified Albumin (IMA) levels were analyzed by using albumin cobalt binding test developed by Bar-Or et al (Bar-Or et al., 2001). The results were expressed as absorbance units (ABSU).

Statistical Analysis

SPSS 22 (SPSS Inc., Chicago, IL, USA) program was used for statistical analysis. The Shapiro-Wilk test was used to determine whether the data showed normal distribution. Comparison of the data that was not normally distributed was determined by the Mann-Whitney U test. 0.05 was considered statistically significant.

RESULTS

This study consisted of 60 people, including 30 oxytocin-induced and 30 control groups, were included in the present study. There was no significant difference between the groups in terms of age and gender (Table 1).

Table 1. Demographic features of oxytocin-induced group and control.

Parameter	Oxytocin-induced (n=30) Mean ± SD	Control (n=30) Mean ± SD	$p^{¥}$
Age (years)	28.6 ± 5.3	28.9 ±5.1	0.82
Gravity	3 (1-7)	3 (1-6)	0.42
Parity	1 (0-4)	1 (0-3)	0.91
Gestational age(week)	39.4 ± 0.68	39.2 ± 0.65	0.26
Birthweight (g)	3470 ± 511	3577 ± 320	0.34
Apgar scores at 1st min	8 (7-9)	8 (6-9)	0.15

¥: Student t -test

Demographic data of pregnant women including age, gravity, parity, gestational age, birthweight and Apgar scores of newborns are shown in Table 1.

Table 2: Biochemical parameters of study and control groups.

Parameter	Oxytocin-induced Mean (n=30) (min-max)	Control Mean (n=30) (min-max)	$p^{§}$
Hemoglobin (g/dL)	12.8 (9.9-14.5)	12.7 (10.1-14.7)	0.923
Neutrophile (%)	8.5 (5.1-15.0)	8.7 (4.1-14.1)	0.734
Lymphocyte (%)	2.1 (0.8-2.9)	2.2 (1.3-3.4)	0.193
Hematocrit (%)	37.5 (31.1-41.6)	37.9 (31.7-44.1)	0.549
Platelet (x 10^3/µL)	227.6 (135-344)	252.6 (160-379)	0.107
MCV (fL)	86.1 (75-93)	83.8 (69.3-93.8)	0.154
Glucose (mg/dL)	85.1 (68-114)	91.4 (62-116)	0.025
Urea (g/L)	16.6 (7-24)	17.3 (12-25)	0.683
Creatinine (mg/dL)	0.47 (0.32-0.63)	0.54 (0.39-0.80)	0.010
ALT (U/L)	10.9 (5.7-27.8)	11.6 (6-21.5)	0.796
AST (U/L)	23.6 (13-42)	24.2 (13-61)	0.363

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, MCV: Mean Corpuscular Volume, §: Man-Whitney U test

The biochemical parameters of the study and control groups are shown in Table 2. Glucose and creatinine were statistically significant in the oxytocin-induced and control groups. Among the biochemical parameters, glucose and creatinine were found to be significantly different between the study and control groups. No statistically significant difference was found in the study and control groups among other parameters. Native and total thiol levels were found to be significanlty lower in the oxytocin-induced group compared with the control subjects ($p<0.05$). However, disulfide levels were higher in the patient group compared with the control group ($p= 0.073$). Disulfide/native, disulfide/total and native/total levels were higher but not statistically significant between the patient and control groups respectively ($p=0.274$; 0.280; 0.223). Moreover, we found TAS levels were statistically significant

between patient and control groups ($p<0.05$). However, TOS and OSI levels were not significanlty different between study and control groups ($p>0.05$). In addition, serum IMA levels were significantly different between patient and control groups ($p <0.05$, Table 3).

Table 3: Thiol-disulfide homeostasis parameters of the study and control groups.

Parameter	Oxytocin-induced Mean (n=30) (min-max)	Control Mean (n=30) (min-max)	$p^{\S}$
Total thiol (µmol/L)	382.1 (310-482)	402.1 (325-487)	0.023
Native thiol (µmol/L)	344.8 (280-432)	365.8 (296-466)	0.040
Disulfide (µmol/L)	19.8 (11.5 -34)	17.4 (5-33)	0.073
Disulfide / Native thiol	5.53 (3.2-10.4)	5.1 (1.6-9.5)	0.274
Disulfide /Total thiol	4.93 (2.9-8.6)	4.5 (1.5-7.9)	0.280
Native thiol /Total thiol	90.1 (82.7-94.1)	90.9 (84.1-96.9)	0.223
IMA (ABSU)	1.02 (0.47-1.78)	0.84 (0.47-1.28)	0.008
TAS (nmol Troloks/L)	1.38 (1.03-1.88)	1.62 (0.9-2.37)	0.019
TOS (µmol H2O2 Equiv./L)	7.8 (5.4-12.3)	8.04 (4.4-12.0)	0.478
OSI	0.58 (0.36-1.04)	0.51 (0.22-0.83)	0.131

IMA: Ischemia -modified albumin, TAS: Total antioxidant status, TOS: Total oxidant status, OSI: Oxidative stress index, §: Man-Whitney U test

DISCUSSION

We demonstrated that thiol levels were significantly lower in patients with oxytocin-induced group than control subjects. However, disulfide levels were significantly higher in patients with oxytocin-induced group with respect to controls. Our study also revealed that IMA levels were statistically significant in patient group compared to the controls. We also demonstrated that serum TAS and TOS levels were lower in patients with oxytocin-induced group than control subjects. However, OSI levels were higher but not statistically different in patient group compare to the controls. In the present study, the ratios of disulfide/natural, disulfide/total and natural/total thiol levels were also evaluated between the control and patient groups, and no statistically significant difference was found. IMA levels were higher in the oxytocin-induced group than that of the controls.

During pregnancy, which is a physiological state in which metabolic processes take place, the oxygen requirement of the tissues increases. The increase in the amount of oxygen leads to an increase in the production of free radicals, causing OS (Özcan et al., 2015). Thiols play an important role in the elimination of oxidative stress in cells and are composed of sulfur and hydrogen atoms attached to a carbon atom (Erdal, Ciftciler, Tuncer, & Ozcan, 2022). When exposed to thiol oxidation, they transform into disulfide structures, which is an indication of an early cellular response to OS. The disulfide structures are reduced back to thiol groups and thus dynamic thiol- disulfide equilibrium is achieved.

Karacor et al. showed that TAS and TOS values were statistically different in the induction group than that of the controls. They concluded that induction with oxytocin during labor increases OS and accordingly, antioxidant mechanisms occur. They also revealed that oxytocin induction did not have a negative effect on labor (Karacor et al., 2017). In another study, Korkmaz et al. investigated the effects of oxytocin on thiol/disulfide and malondialdehyde/glutathione homeostasis in stressed rats. They reported that native thiol levels changed statistically significantly as a result of both stress and oxytocin application. They also showed that disulfide levels of the control group decreased as a result of oxytocin administration. They hypothesized that endogenous oxytocin increasing methods and/or the application of exogenous oxytocin can be considered as a protective measure in order to prevent the stress-induced increase in oxidant stress, which plays a very important role in the pathogenesis of various stress-related diseases (Korkmaz, Onal, Alisik, Erel, & Pehlivanoglu, 2020). Another study conducted with Eryılmaz et al. indicate that there was no significant difference in maternal and cord blood thiol/disulfide homeostasis in pregnant women whose labor was induced by oxytocin compared to women who gave birth spontaneously without any labor induction. They found that the native and total thiol levels increased in the group that received oxytocin, but there was no statistically significant difference compared to the control group. However, they found disulfide levels slightly lower in oxytocin-induced group compared to the controls. They concluded that induction of labor with oxytocin did not significantly change thiol-disulfide levels and it was safe for both mother and fetus (O. G. Eryilmaz, Kansu-Celik, Erel, & Erdogan, 2017). In the present study, native and total thiol levels were found to be significantly lower in the oxytocin-induced group compared with the control subjects. However, disulfide levels were higher in the patient group with respect to the controls. We concluded that the decrease in serum thiol levels in the group receiving oxytocin may be due to the continued depletion of sulfhydryl-containing antioxidant molecules to remove reactive oxygen species (ROS).

We also showed disulfide/native, disulfide/total and native/total levels were higher but not statistically significant between the patient and control groups. Moreover, TAS levels were found to be statistically significant between the patient and control groups ($p<0.05$). However, TOS and OSI levels were not found significanlty different between two groups ($p>0.05$). In addition, IMA levels were found to be statistically different between the patient and control groups. We hypothesized that increased IMA levels may be related to oxidative stress and functional decrease of the antioxidant defense system.

CONCLUSION

In conclusion, these findings show that oxidant and antioxidant balance is disturbed. It was found that while disulfide levels increased in oxytocin-induced patients, native and total thiol levels were decreased. This might indicate that formation of disulfide leads to decrease antioxidant capacity in patients with oxytocin-induced. Increased IMA levels demonstrate that antioxidant capacity decreases with the increase of oxidative stress. We think that increased IMA levels change due to the increase in ROS production under OS. Dynamic thiol-disulfide homeostasis may contribute to the monitoring of oxidative stress in infants of oxytocin-induced patients and the follow-up of diseases that may arise due to OS

Competing of Interest: The authors declare that this study received no financial support and there are no conflicts of interest.

Ethics approval

The present study was approved by the Aksaray University Clinical Research Ethics Committee (protocol number: 11-SBKAEK).

REFERENCES

Alchalabi, H. A., Obeidat, B. R., Jallad, M. F., & Khader, Y. S. (2006). Induction of labor and perinatal outcome: the impact of the amniotic fluid index. *Eur J Obstet Gynecol Reprod Biol, 129*(2), 124-127. doi: 10.1016/j.ejogrb.2005.10.039

Bar-Or, D., Curtis, G., Rao, N., Bampos, N., & Lau, E. (2001). Characterization of the Co(2+) and Ni(2+) binding amino-acid residues of the N-terminus of human albumin. An insight into the mechanism of a new assay for myocardial ischemia. *Eur J Biochem, 268*(1), 42-47. doi: 10.1046/j.1432-1327.2001.01846.x

Cakirca, G., C. M., Erdal H, Neselioglu S, Erel O, Basarali MK, Cakirca TD. (2018). Investigation of thiol/disulfide homeostasis in familial mediterranean fever patients. *Clin Anal Med, 9*(3), 231-234. doi: 10.4328/JCAM.5789

Demirtas, M.S., Erdal H . Evaluation of thiol-disulfide homeostasis and oxidative stress parameters in newborns receiving phototheraphy. *J Investig Med*. doi: 10.1177/jim-10815589221140594

Demirtas, M. S., Erdal H (2022) Evaluation of Thiol Disulfide Balance in Adolescents With Vitamin B12 Deficiency. DOI: https://doi.org/10.21203/rs.3.rs-1318028/v1

Erdal, H., Özcan, O., Turgut, F., Neşelioğlu, S., Erel Ö. (2022). Evaluation of dynamic thiol-disulfide balance and ischemia modified albumin levels in patients with chronic kidney disease. *MKÜ Tıp Dergisi*. 2022;13(47):237-242. https://doi.org/10.17944/mkutfd.947113

Erdal, H., Ciftciler, R., Tuncer, S. C., Ozcan, O. (2022). Evaluation of dynamic thiol-disulfide homeostasis and ischemia-modified albumin levels in patients with chronic lymphocytic leukemia. *J Investig Med*. doi: 10.1136/jim-2022-002568

Erdal, H., Demirtas, M. S., Tuncer, S.C., Ozcan O (2022).Thiol/disulfide homeostasis as a new oxidative stress marker in patients with neonatal transient tachypnea. Ann Clin Anal Med 2022, doi: 10.4328/ACAM.21457

Erel, O. (2005). A new automated colorimetric method for measuring total oxidant status. *Clin Biochem, 38*(12), 1103-1111. doi: 10.1016/j.clinbiochem.2005.08.008

Erel, O., & Neselioglu, S. (2014). A novel and automated assay for thiol/disulphide homeostasis. *Clin Biochem, 47*(18), 326-332. doi: 10.1016/j.clinbiochem.2014.09.026

Eryilmaz, M. A., Kozanhan, B., Solak, I., Cetinkaya, C. D., Neselioglu, S., & Erel, O. (2019). Thiol-disulfide homeostasis in breast cancer patients. *J Cancer Res Ther, 15*(5), 1062-1066. doi: 10.4103/jcrt.JCRT_553_17

Eryilmaz, O. G., Kansu-Celik, H., Erel, O., & Erdogan, S. (2017). Thiol/disulfide parameters as a novel oxidative marker in medical labor induction with oxytocin. *Horm Mol Biol Clin Investig, 29*(2), 61-65. doi: 10.1515/hmbci-2016-0032

Giri, T., Jiang, J., Xu, Z., McCarthy, R., Halabi, C. M., Tycksen, E., Palanisamy, A. (2022). Labor induction with oxytocin in pregnant rats is not associated with oxidative stress in the fetal brain. *Sci Rep, 12*(1), 3143. doi: 10.1038/s41598-022-07236-x

Karacor, T., Sak, S., Basaranoglu, S., Peker, N., Agacayak, E., Sak, M. E., Gul, T. (2017). Assessment of oxidative stress markers in cord blood of newborns to patients with oxytocin-induced labor. *J Obstet Gynaecol Res, 43*(5), 860-865. doi: 10.1111/jog.13263

Korkmaz, H., Onal, D., Alisik, M., Erel, O., & Pehlivanoglu, B. (2020). The impact of oxytocin on thiol/disulphide and malonyldialdehyde/glutathione homeostasis in stressed rats. *Biol Chem, 401*(11), 1283-1292. doi: 10.1515/hsz-2020-0190

Marconi, A. M. (2019). Recent advances in the induction of labor. *F1000Res, 8*. doi: 10.12688/f1000research.17587.1

Otal, Y., Kahraman, F. A., Haydar, F. G., & Erel, O. (2021). Dynamic thiol/disulfide homeostasis as oxidative stress marker in diabetic ketoacidosis. *Turk J Med Sci, 51*(2), 743-748. doi: 10.3906/sag-1904-55

Ozcan, O., Erdal, H., Ilhan, G., Demir, D., Gurpinar, A. B., Neselioglu, S., & Erel, O. (2018). Plasma Ischemia-Modified Albumin Levels and Dynamic Thiol/Disulfide Balance in Sickle Cell Disease: A Case-Control Study. *Turk J Haematol, 35*(4), 265-270. doi: 10.4274/tjh.2018.0119

Ozcan, O., Erdal, H., & Yonden, Z. (2015). İskemi-reperfüzyon hasari ve oksidatif stres ilişkisine biyokimyasal bakiş. *Mustafa Kemal Üniversitesi Tıp Dergisi, 6*(23), 27-33. Doi: 10.17944/mkutfd.54113

Özcan O, E. H., Çakırca G, Yönden Z (2015). Oxidative stress and its impacts on intracellular lipids, proteins and DNA. *J Clin Exp Invest, 6*(3), 331-336. doi: 10.5799/ahinjs.01.2015.03.0545

Rydahl, E., Eriksen, L., & Juhl, M. (2019). Effects of induction of labor prior to post-term in low-risk pregnancies: a systematic review. *JBI Database System Rev Implement Rep, 17*(2), 170-208. doi: 10.11124/JBISRIR-2017-003587

Saugstad, O. D. (2005). Oxidative stress in the newborn--a 30-year perspective. *Biol Neonate, 88*(3), 228-236. doi: 10.1159/000087586