

Inflammatory and oxidative alterations of water immersion and epidural analgesia during the labor

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Abstract

Objective: Water immersion and epidural analgesia are both pain relief methods used to perceive less pain during the labor process. There are concerns about the maternal and fetal outcomes, although studies presented no significant complication directly related to these methods. We aimed to compare the IL-1 and 6 levels, Total serum oxidant (TOS), antioxidant (TAS) and catalase levels of births with epidural analgesia, water immersion and conventional birth without analgesia.

Material and Methods: A total of 88 patients were included in the study (The water immersion group included 29 patients, while the epidural analgesia and control group included 30 and 29 patients respectively). Umbilical cord IL-1, IL-6, catalase, TAS, TOS levels, neonatal Apgar scores, duration of birth process and demographic data were compared between three groups

Results: There was no significant difference between the three groups in terms of age, Body mass index (BMI), gravidity, parity, gestational week, and birth weight ($p>0.05$). TOS and IL-6 levels were significantly lower in epidural group than others ($p=0.031$, $p=0.019$ respectively). Apgar scores were significantly lower in epidural group ($p<0.001$).

Conclusion: The water immersion and epidural analgesia were found to have no adverse effect on oxidative status and infection parameters of women.

Key words: Analgesia, Epidural, Labor Pain, Interleukins, Oxidative stress, Waterbirth

Introduction

Increasing cesarean rates worldwide made popular noninterventional methods such as water immersion (1-3). There is a debate on the routine use of water during labor in the world due to the lack of sufficient data evaluating the potential risks and benefits of the method. American College of Obstetricians and Gynecologists (ACOG) recommended that water immersion during the first stage of labor could be offered to patients without obstetrical risk factors between 37+0 and 41+6 weeks of gestation (4). Still, birth should occur on the land, although there is no proven evidence that water birth had harmful obstetric effects (4). Water immersion during the delivery presents the positive birth experience, movement free environment, reduced need of pharmacologic pain relief methods, reduced stress on pelvic muscle and tissue to let the baby settle down the birth way quickly (5). Opponents of the process present the debate focusing on the concerns about the maternal and fetal infection risk (6). The risk of the previously used tube as a source of infection, the effect of warm water to provide the organisms suitable environment to live, the skin, vagina, and anal parts of a submerged

woman are assumed to be the potential infection sources. However, studies advocate that there is no proven risk for maternal or fetal infection (7, 8).

Epidural analgesia is an effective, safe, and prevalent used pain management method during labor. The frequency of using epidural analgesia during labor became more popular in the world by years (9). Epidural analgesia defines injecting local anesthetics into the epidural space. The method presents effective pain relief, safe and satisfying labor progress and outcome, minimal maternal and fetal effects (9).

Complications related to drugs, the technique of an inexperienced person, or the effects of neuraxial analgesia are the drawbacks of the method (10). Hypotension, pruritus, unsufficient analgesia (failure of neuraxial analgesia), headache in case of accidental dural puncture, breastfeeding difficulties, nerve damage, epidural hematoma, and infection are the most frequent complications (11-15).



Pregnancy is known to be a period characterized by increased oxidative stress due to the increased oxygen demand of the fetus and mother. However, it becomes more exaggerated by some of the pregnancy complications such as preeclampsia, preterm labor, and diabetes mellitus (16, 17). Labor is also known to be associated with increased oxidative stress due to the uterine contractions (18). Ischemia and reperfusion because of contractions are accused of increased oxidative stress (19). Several factors may affect the oxidative status of mother and fetus; however, studies show no difference in terms of oxidative stress between the modes of delivery (cesarean vs. vaginal) (20). These studies suggest that different mechanisms are altering oxidative status during labor. Catalase is one of the most important antioxidant defense enzymes. Increasing hydrogen peroxide results in decrease catalase levels (21). TOS, TAS levels are the other markers of oxidative balance (22).

Cytokines such as interleukin-1 (IL-1), and interleukin-6 (IL-6) are detected in the amniotic fluid during the healthy pregnancy (23). The level of these cytokines tends to increase during labor. However, the levels are determined much higher in case of infection (23).

In this prospective study, we aimed to compare the catalase status, TOS, TAS, IL-1, and IL-6 levels of the patients who labored with epidural analgesia, water immersion, and conventional birth.

Material and Methods

The study was conducted at XX University, XX hospital department of Obstetrics and Gynecology, antenatal clinic. The ethical committee has approved the study protocol (48/2018*). We collected the blood samples after taking written informed consent from the patients.

A total of 88 patients were included in the study. The water immersion group consisted of 29 patients, while the epidural analgesia and control group included 30 and 29 patients. The study is planned as a prospective study. Patients were selected randomly from the patients who requested for epidural analgesia or water immersion for pain relief and meet the following criterias to be included to the study: All of the participants were pregnant Turkish women with the term (between 37+0 and 41+0 gestational weeks), vertex presented, singleton pregnancies without identified obstetric risk factors. Exclusion criteria from the study are diagnosed physical or mental illness, multiple pregnancies, any kind of diagnosed disease and obstetric complication, drug use, smoking, membrane rupture more than 6 hours, any identified evidence of active infection (including active genital herpes and Human papillomavirus), active vaginal bleeding, previous uterine surgery, suspicion of the macrosomic fetus, pregnancies of assisted reproductive techniques and fetal distress. Demographic data and obstetric history were collected from the patient records.

The place for water immersion was the standard ovoid tube bath with filtered water at the temperature of 34-36 °C. The tub was cleaned with chlorine tablets for each patient. A culture was taken from the floor and walls of the bath after

cleaning procedure. Every patient is allowed to enter the tub after getting a negative culture result. The water immersion group included 29 patients who were submerged during the first stage of labor when the labor was active. The active phase of the labor was defined as 6cm cervical dilatation with intense, regular uterine contractions. Labor was completed without labor induction, or any kind of analgesic drugs and birth occurred on the land. Vital signs and fetal heart rates were controlled at regular intervals. For the epidural group, an anesthetist performed epidural analgesia in charge of request and confirmation of the patients. Epidural analgesia was performed by using 100 mcg fentanyl and 10 mg Marcaine (5%). Repeat dose was administrated every one and a half hours if needed. The Control group consisted of the patients who had no pain relief method during labor. After the birth, cord blood about 5-10 cm³ was taken from the umbilical artery and centrifuged at 5000 r.p.m for ten minutes. Sera was transferred to Eppendorf tube to be stored at -80 °C until the time for analyses.

Assay for catalase: Catalase measurement was made by using the Human CAT (catalase) ELISA kit (Fine Test/Wuhan Fine Biotech Co., Ltd) at ELISA reader branded MRC UT6100. All the results were reported as pg/mL. Intra-assay and inter-assay Coefficient Variation (CV%) were <8% and <10% respectively.

Assay for IL-1 and IL-6: IL-1 and IL-6 measurement was made by using Human interleukin 1 Alpha (IL-1 alpha) and Human interleukin 6 (IL-6) ELISA kit (Fine Test/Wuhan Fine Biotech Co., Ltd) at ELISA reader branded MRC UT6100. All the results were reported as pg/mL. Intra-assay and inter-assay Coefficient Variation (CV%) were <8% and <10% respectively.

Assay for TAS and TOS: Total oxidant status (TOS) was measured spectrophotometric method by using the measurement kit of Rel Assay Diagnostic. Measurements were made with the Heales mb530 device, and all the results were reported as µmol/L. The normal range for human sera was reported as between 4.00 and 6.00 µmol/L. Intra-assay and inter-assay Coefficient Variation (CV%) were <3.9% and <3.2% respectively.

Total antioxidant status (TAS) was measured spectrophotometric method by using the measurement kit of Rel Assay Diagnostic. Measurements were made with the Heales mb530 device, and all the results were reported as mmol/L. The normal range for human sera was reported as between 1.20 and 1.50 mmol/L. Intra-assay and inter-assay Coefficient Variation (CV%) were <3.3% and <2.8% respectively.

Statistical Analysis

Data analysis was performed by using IBM SPSS Statistics version 17.0 software (IBM Corporation, Armonk, NY, USA). Whether the distributions of continuous variables were normally or not is determined by the Kolmogorov-Smirnov test. The Levene test examined the assumption of homogeneity of variances. Descriptive statistics for continuous variables were expressed as mean ± SD or median (25th – 75th) percentiles, where appropriate. A

number of cases and percentages were used for nominal data. While the Kruskal Wallis test evaluated the continuous variables in which parametrical test assumptions were not met, otherwise, the mean differences among groups were compared by One-Way ANOVA. When the p-values from the Kruskal Wallis test or One-Way ANOVA were statistically significant, Dunn-Bonferroni or posthoc Tukey HSD test was used to know which group differs from which others. Nominal data were analyzed by Pearson's χ^2 or Likelihood ratio test, where applicable. A p-value of less than 0.05 was considered statistically significant.

Results

Table 1 demonstrates the comparison of demographic, maternal, and fetal characteristics regarding groups. There was no significant difference between the three groups in terms of age, Body mass index (BMI), gravidity, parity, gestational week, and birth weight ($p>0.05$). Duration of 2nd phase, duration of 3rd phase, and delivery duration were not statistically different between three groups ($p>0.05$).

There was a statistically significant difference between the three groups in terms of 1st and 5th minutes APGAR scores. APGAR scores of the epidural group at 1st and 5th minutes were significantly lower than the water and control group ($p<0.001$ and $p<0.001$ respectively). There was no statistically significant difference between water and control groups ($p>0.999$) (Table 1).

The statistically significant difference between groups was found for the TOS level ($p=0.031$). The TOS level was found significantly lower in the epidural group than in the control group ($p=0.044$). No significant difference was found between water and epidural groups and water and control groups ($p>0.974$ and $p=0.077$, respectively) (Table 2). The IL-6 level was found significantly different between the three groups ($p=0.019$). The difference was that the level of IL-6 was lower in the epidural group than in the control group ($p=0.038$). No significant difference was found between water and epidural groups and water and control groups ($p>0.999$ and $p=0.051$, respectively) (Table 2). In the study, there was no significant difference between the three groups in terms of TAS, IL-1, and catalase levels ($p>0.05$) (Table 2).

Table 1: Demographical, maternal and fetal characteristics, and labor durations of groups

	Water (n=29)	Epidural (n=30)	Control (n=29)	p-value
Age (years)	28 (26-29)	27 (26-29)	27 (26-29)	0.710†
BMI (kg/m ²)	28.4 (24.5-31.2)	28.8 (26.0-30.6)	29.3 (27.6-33.5)	0.343†
Gravidity	2 (2-3)	2 (2-3)	2 (2-2)	0.698†
Parity	1 (1-1)	1 (1-2)	1 (1-1)	0.686†
Gestational week	38.0 (38.0-39.0)	39.0 (38.0-39.2)	38.0 (38.0-40.0)	0.899†
Birth weight (g)	3400 (3175-3600)	3375 (3150-3650)	3400 (3175-3625)	0.733†
1 st min APGAR	8 (8-9) ^a	7 (6-7) ^{a,b}	9 (8-9) ^b	<0.001†
5 th min APGAR	10 (10-10) ^a	8.5 (8-9) ^{a,b}	10 (10-10) ^b	<0.001†
Duration of 2 nd phase	10.0 (6.0-10.0)	10.0 (5.0-10.0)	10.0 (7.0-12.5)	0.552†
Duration of 3 rd phase	10.0 (8.0-10.0)	10.0 (8.75-10.0)	10.0 (8.5-10.0)	0.882†
Delivery duration	3.0 (2.1-4.5)	2.3 (1.9-4.0)	2.5 (2.0-3.7)	0.608†

While, the descriptive statistics were expressed as median (25th – 75th) percentiles for continuous variables, otherwise number of cases and (%) were used for nominal data, † Kruskal Wallis test, a: Water vs Epidural ($p<0.001$), b: Epidural vs Control ($p<0.001$).

Table 2: The results of biochemical measurements

	Water (n=29)	Epidural (n=30)	Control (n=29)	p-value
TAS	1.24 (0.86-1.66)	1.08 (0.86-1.38)	1.05 (0.85-1.57)	0.536†
TOS	4.89±0.48	4.86±0.55	5.20±0.59	0.031 ‡
CAT	0.15 (0.12-0.26)	0.13 (0.10-0.35)	0.17 (0.15-0.25)	0.091†
IL-1	4.07 (2.70-7.37)	4.58 (2.85-11.50)	5.48 (4.32-9.54)	0.163†
IL-6	9.07 (6.08-26.66)	8.87 (4.75-29.71)	13.32 (11.62-19.33)	0.019 †

While the descriptive statistics for continuous variables which parametrical test assumptions were not met were expressed as median (25th – 75th) percentiles, otherwise mean ± SD were used. † Kruskal Wallis test, ‡ One-Way ANOVA

Discussion

This prospective study aimed to compare the oxidative markers (TAS, TOS, and catalase) and infection markers (IL-1 and IL-6) during the labor with water immersion, epidural anesthesia used as pain relief methods, and conventional labor without pain control. Results demonstrated that labor with epidural anesthesia and water immersion is associated with lower TOS and IL-6 levels compared to the control group. Duration of labor was not different between three groups.

According to the WHO reports, there is an increasing trend for cesarean sections worldwide (24). Turkey has the highest cesarean rate of any Organisation for Economic Co-operation and Development (OECD) country with 531.4/1000 live birth/per year (25). Patients' request due to the fear of labor pain is one of the most important preventable reason for increasing cesarean rate (26). Several pain relief methods are being studied to prevent the use of C-section that is performed to escape from labor pain (27).

The main goal of clinicians is to present a safe and painless birth experience to the patients. For this purpose, several pharmacological and non-pharmacological approaches were defined. Non-pharmacological methods for labor analgesia include massage, audio-therapy, hydrotherapy, acupuncture, acupressure, hypnosis, and transcutaneous electrical nerve stimulation (TENSE) (28). Pharmacologic methods consist of inhalation analgesia, opioids, and neuraxial analgesia (28). The advantages and drawbacks of these methods need to be well defined to ensure maternal and fetal safety. Cluett et al. published a comprehensive data of water immersion during the labor process in 2018 (8). The study did not show an impact of water immersion during the first stage of labor on maternal and neonatal adverse outcomes. Although there is a minor negative effect on birth mode and perineal tears, water immersion perceives less pain, and anesthesia requirement prominently decreases (8).

Studies are supporting the concerns about the increased risk of maternal and fetal infection during the water immersion (7, 29). The fecal contamination and the effect of warm water for microbial colonization are assumed as significant concerns. Thöni et al. demonstrated that labor water was contaminated with *E.coli* after the water immersion, although the infection rate did not increase (30). *Legionella* and *Pseudomonas* infection of newborns are also reported after the water immersion (31, 32). Fehervary et al. presented the study evaluating the microbial colonization after the water immersion, water birth, and conventional land birth. Maternal and neonatal infections were not different between groups, although the microorganisms of vaginal flora were present in the ear and palate of newborns (33). There was no significant difference between maternal and fetal infection rates with water immersion in the systemic review of Cluett et al. (8). Our data demonstrated that significant infection, fever, and NICU admission were not determined in all groups. The maternal temperature, leucocyte count, and CRP levels did not show a significant difference ($p>0.05$). IL-6 levels are significantly lower in water immersion and epidural groups than conventional land birth (epidural group < water immersion < control group).

The presentations of infection of neuraxial anesthesia are epidural abscess and meningitis. These complications are infrequent with an incidence of 3/100.000 (8). In our study population, there was no infection following epidural anesthesia. IL-6 levels are significantly lower in the epidural group than the water immersion and control group, while IL-1 levels are not significantly different.

The effect of water immersion on the oxidative status of mother and fetus is under debate in literature. Wilinska et al. demonstrated that oxidative status is not affected by the mode of delivery (34). However, Sert et al. demonstrated that cumulative oxidative stress is higher in the water immersion group than in the control group (35). We found that the TOS level is significantly lower than the control group suggesting that water immersion presents lower oxidative stress to mother and newborn than conventional birth. A few data are evaluating the effect of epidural anesthesia on the oxidative stress of mother and neonate.

Compagnoni et al. assessed the level of coenzyme Q10 in a vaginal birth, spinal, and general anesthesia (36). Coenzyme Q10 is an antioxidant molecule and is found to be higher in spinal anesthesia than general anesthesia (36). Similarly, we found that the TOS level as an oxidative stress marker was the lowest in the epidural group. Our results supported that risk of adverse outcomes related to oxidative stress is low with epidural anesthesia.

The study of Leighton et al. evaluated the effect of epidural anesthesia on the neonatal outcome (37). The study showed that the method used for labor analgesia does not impact neonatal Apgar scores (37). Our study demonstrated that there was a statistically significant difference between the three groups in terms of 1st and 5th minutes APGAR scores. APGAR scores of the epidural group at 1st and 5th minutes were significantly lower than the water and control group. There was no statistically significant difference between water and control groups. The mean 1st and 5th minutes Apgar scores for the epidural group were 7 and 8.5, respectively. The decrease in Apgar score did not affect the NICU need and wellbeing of the newborns, although the difference was significant. There was no Apgar score of less than 6 in our study. Apgar scores of water immersion were not different from conventional birth, comparably the meta-analyze of Cluett et al. (8). The lower Apgar scores might be associated with the effect of fentanyl diffusing from epidural space to the maternal blood, placenta (38). Fentanyl might have adverse effects on neonatal respiratory system (38).

Conclusion

Water immersion and epidural anesthesia presented a chance for less painful labor to women and used all over the world. Our study is an essential contribution to the possible adverse effects of pain relief methods, water immersion, and epidural anesthesia. When used for labor pain control, the techniques seem to be safe in terms of oxidative results, infection, and neonatal outcomes.

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