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Clinical trial

Effects of transcutaneous electrical nerve stimulation applied at different frequencies during labor on hormone levels, labor pain perception, and anxiety: A randomized placebo-controlled single-blind clinical trial

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ABSTRACT

Introduction: There are various non- pharmacological methods for decreasing labor pain which is acute and severe. One method is Transcutaneous Electrical Nerve Stimulation (TENS). This study investigated the effects of TENS applied at different frequencies during labor on hormone levels, labor pain perception and anxiety. The overall aim was to determining the most effective TENS frequency and pulse width.

Methods: This randomized-controlled single-blind experimental study included 56 pregnant women who were hospitalized in the delivery unit of a public hospital in Adana, Turkey between 20th of June 2020 and 19th of August 2020. Women were randomized into 4 groups: active TENS 1 (100 Hz and 100 μs) ($n = 14$); active TENS 2 (80–100 Hz and 350 μs) ($n = 14$); placebo group ($n = 14$); control group ($n = 14$). TENS therapy was initiated at the active phase of the first stage of labor, when cervical dilation was 4 cm, and administered for 30 min. Data were collected using the Personal Information Form, the Labor Monitoring Form, the Visual Analogue Scale (VAS), the State Anxiety Scale (STAI-S), and Biochemical Hormone Tests.

Results: The participants in the active TENS 2 group demonstrated a significant increase in their oxytocin and endorphin levels ($p<0.01$) and a significant decrease in post-test plasma cortisol, labor pain perception, and anxiety levels ($p<0.01$) compared to active TENS 1, placebo, and control groups.

Conclusions: High-frequency TENS application decreased labor pain perception and anxiety levels more significantly than stable frequency TENS, via effects on the release of oxytocin, endorphin and cortisol, which have positive contributions to labor.

Trial registration: ClinicalTrials.gov.ID: NCT04851938 was registered on the 2nd of March 2020.

1. Introduction

Labor is a natural and healthy process that is regulated by the release of specific hormones [1,2]. Labor pain, which forms an integral part of this natural process, is classified as a most severe and acute pain [3,4]. Methods used for managing labor pain are categorized under pharmacological and non-pharmacological methods [4–9]. Non-pharmacological methods are generally utilized in labor as a part of midwifery practices [10–14] due to factors such as easy implementation, ease of learning, cost-effectiveness, absence of any medication, reduced risks in terms of maternal and fetal health, and lack of allergic reactions [10,11]. Transcutaneous Electrical Nerve Stimulation (TENS) is a non-pharmacological method used for managing labor pain [15,16]. The use of TENS at optimum frequency in the labor process is considered to have positive contribution to maternal and infant health by triggering the release of hormones that have effects on labor and decreasing pain perceptions and anxiety levels. Besides, randomized-placebo-controlled feature of the study is believed to provide midwives, nurses and physicians with important evidence for the management of labor.

The analgesic effect of TENS in labor can be explained by two different mechanisms. The first mechanism relies on gate-control theory [15–17]. The gate control theory is based on the stimulation of Aβ nerve fibers that prevent nociceptive stimulation and activate anti-nociceptive systems. Since these nerve fibers transmit pain signals due to the TENS stimulus from the myometrium faster than nerve fibers, the signals reach the hypothalamus earlier. This makes transmission of pain to thin fibers

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difficult. Due to the blockage of nerve stimulation transmitting pain information, the body does not comprehend the pain and its severity [18,19]. The second mechanism for the analgesic effect of TENS is on hormone release. TENS stimulation formed with low density and high-frequency electrical pulses causes the release of endogenous opioids from the brain [17–21]. Release of opioids such as endorphin and oxytocin create an analgesic effect that can provide relief from labor-related pain [15–16].

Anxiety is a compliance mechanism associated with how individuals cope with a dangerous or distressing situation [22]. Anxiety experienced during labor may increase the severity of labor pain, prolong the duration of labor, cause operative labor, and have negative effects on the fetus and the newborn [22,23]. The use of TENS during labor may slow down the release of cortisol in the body, thereby decreasing the anxiety level [21,24,25]. To date, two studies have investigated the effect of TENS applied at different frequencies on labor pain as well as labor duration [26,27]. However, no studies in the published literature have investigated the effects of TENS applied at different frequencies on hormone levels, anxiety, and cervical dilation.

The aim of this study was to determine what was the most effective TENS frequency applied during labor by assessing hormone levels, labor pain perception and anxiety. It was conducted as a randomized, placebo-controlled, single-blind clinical trial.

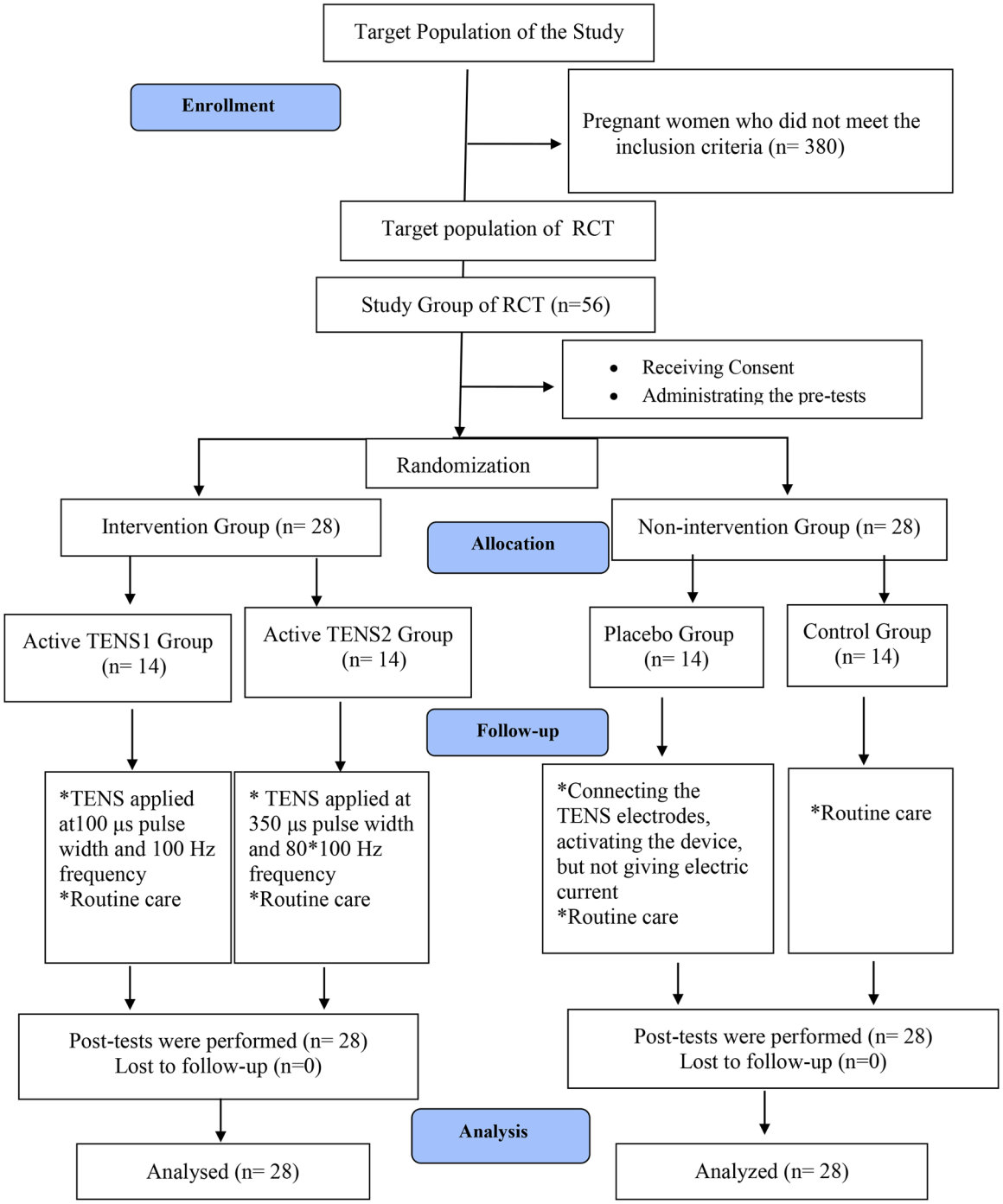


Fig. 1. CONSORT flowchart.

2. Materials and methods

2.1. Study design

This study was conducted as a randomized placebo-controlled single-blind clinical trial to investigate the effects of TENS applied at different frequencies during labor on hormones such as oxytocin, endorphin and cortisol that play an active role in labor, labor pain perception, and anxiety and to determine the most effective frequency and pulse width.

2.2. Participants and setting

The study was conducted between the 20th June 2020 and 19th August 2020. The target population of the study were pregnant women who were accepted to the delivery room of a maternity hospital for labor. Blood samples collected from the participants could be stored for a maximum of 2 months at −80 °C. Therefore, the target population of the study was 500 primipara women who applied to the hospital for vaginal delivery over a period of two months. Of these 500 participants, 380 were excluded from the study according to the exclusion criteria. The final target population of the randomized clinical trial included 120 participants. After obtaining informed consent, 56 participants were randomly assigned to one of 4 groups, active TENS 1 ($n = 14$), active TENS 2 ($n = 14$), placebo ($n = 14$) or control ($n = 14$) using block randomization [28] (Fig. 1).

The inclusion criteria were as follows: aged 18 years or above, having a vaginal delivery, having a cervical dilatation of 4 cm and over, having a healthy single fetus and head presentation, speaking Turkish and being able to communicate, agreeing to participate in the study, and no history of a high-risk pregnancy. Exclusion criteria were as follows: undergoing induction of labor via exogenous oxytocin hormone, use of analgesia/anesthesia during labor, having a planned cesarean section, having skin damage, skin disease, contraction anomaly in the parts to which TENS would be applied, having epilepsy, wearing a cardiac pacemaker or cardiac defibrillator, and having prior experience of TENS. The participants were provided information about alternative treatments, their responsibilities during the study, and the potential benefits and risks of TENS. The midwives who aided the participants during labor had at least a 10 years of experience in midwifery and delivery. The study included individuals who agreed to participate in the study and met the inclusion criteria. Each new participant who was recruited was monitored for the study upon application for delivery and was referred to the postpartum care clinic. These participants were monitored by the responsible researcher and assistant researcher until delivery and later when they were taken to the postpartum care unit.

2.3. Sample size estimation

Before intervention, a pilot study was conducted with 10 participants. The sample size of the study was calculated using G*power 3.1.9.6 in repeated measures ANOVA approach (inter-groups effects). An analysis of the studies in the literature indicated a high effect size of intergroup differences. Therefore, calculations included high Cohen's effect size ($f = 0.40$) [29]. Accordingly, for two repeated measures design belonging to four groups, the minimum sample size to be assessed for the study was calculated as 56 (14 participants in each group) using 0.80 power (1-β error probability), α=0.05 error probability, $f = 0.40$ effect size [29,30].

2.4. Randomization

Selection bias was controlled by random assignment of participants and concealment of randomization. In this regard, random assignment to the active TENS 1, active TENS 2, placebo and control groups was performed by a statistician who was blind to the participants' names and characteristics. The Personal Information Form was administered by the responsible researcher to 56 participants who were included in the study after their consent was received. The responsible researcher also performed the pre-test administration of the related forms. Block randomization was performed by an independent statistician for forming the four comparison groups. Initially, six combinations of four letters were formed using "A", "B", "C", and "D" for the randomization of 56 participants. Random numbers generated on a computer were utilized for choosing random permute blocks (four blocks of equal proportions). Block randomization was completed by having a random assignment of six combinations 14 times [28]. The letters A, B, C, and D were assigned to active TENS 1, active TENS 2, placebo and control groups, respectively.

2.5. Blinding

Blinding was performed for the participants, output measures (blood sample analysis and laboratory results), statistics, and reporting. Individuals who agreed to participate in the study did not know which group they would be assigned to. As the participants did not know their group assignment, this was a single-blind trial. Data collection was performed by two people, the responsible researcher and assistant researcher. The responsible researcher was blinded to the groups and ensured that consent was received from the participants. The responsible researcher also administered the pre-test to the participants who agreed to participate in the study. The assistant researcher (who performed the interventions and cervical dilatation measurements) communicated with the statistician who carried out the randomization immediately before the interventions started. The assistant researcher carried out the interventions after learning about the group information, and along with performing the post-tests. These processes were not shared with other individuals who were involved in the study. Blood sample analysis was performed by two laboratory technicians who were not involved in the study. Analyses were performed as "A", "B", "C", and "D" coded groups, without the knowledge of whether they represented the intervention or control groups. Reporting of laboratory results of the samples was performed by an independent medical biologist who was blinded to study details and the coding of the groups. Data input (entering data on pre and post-tests) was carried out by a midwife who was not involved in the research and had no knowledge of the intervention and control groups, using "A", "B", "C", and "D" codes. Data analysis and drafting of the research report were performed by an independent statistician. Blinding was carried out for output measures, statistics, and drafting the research report. This way, detection bias and statistical bias were regulated. After completion of the statistical analysis and drafting of the study report, the coding for the intervention and control groups was explained to the coder by the responsible researcher.

2.6. Interventions

2.6.1. Intervention groups

TENS therapy was initiated at the active phase of the first stage of labor, when cervical dilation was 4 cm. The TENS device utilized in this study was Cefar Rehab 2pro®. The assistant researcher programmed the TENS unit and was the only researcher who knew whether the TENS was in the active or placebo mode. Two pairs of electrodes of 5 × 9 cm size were placed in the participants' paravertebral region at T10–L1 and S2–S4 levels. A total of 4 electrodes (in a sterile package) was used for each participant. For the active TENS 1 group, the TENS tool was set at a 100 μs pulse width and 100 Hz frequency. For the active TENS 2 group, the device was set at double phase 350 μs pulse width and 80–100 Hz frequency. TENS was administered to the participants in the intervention group for 30 min. The intervention groups were then administered routine care.

2.6.2. Non-invasive groups

For the participants in the placebo group, two pairs of TENS

electrodes were placed similarly to the intervention group at the active phase of the first stage of the labor when cervical dilation was 4 cm. The participants in this group were connected to the TENS electrodes for 30 min, the tool was activated, but no electric current was given. The placebo group was then administered routine care. The participants in the control group were not connected to TENS, and were given routine care by the midwives attending to these patients in the delivery room.

2.7. Data collection

Pre-test data were collected at the active phase of the first stage of labor, when cervical dilation was 4 cm, while the post-test data were collected 30 min later. Data collection was carried out using the Personal Information Form, the Labor Monitoring Form, the Visual Analogue Scale (VAS), the State Anxiety Scale (STAI-S) and biochemical hormone tests. Data collection was carried out by the responsible researcher and the assistant researcher. The responsible researcher received participant consent without any knowledge of the groups and performed the pre-test of the participants who agreed to participate in the study. The assistant researcher, communicated with the statistician who carried out the randomization and learned about the groups right before starting the interventions for each participant. The frequency and parameters of the TENS device were set according to the group description. Post-tests were performed after TENS administration was carried out for 30 min. These processes were not shared with the other individuals who were involved in the study.

The Personal Information Form was prepared by the researchers based on the related literature [10,11,13,24,26,27]. The form was composed of 11 questions that collected data on age, education level, working status, income level, presence of health insurance, place of living, family type, gestational week, whether the current pregnancy was planned, whether the individual participated in antenatal classes, and anxiety about labor.

VAS (Visual Analogue Scale) was utilized to evaluate the severity of the pain. VAS is a 10 cm line with horizontal and vertical lines that start with "no pain" and ends with "worst pain possible". Pain assessment was performed according to the numerical values indicated in each section [31]. The assessment of the VAS score was completed in three stages: (1) before the intervention, (2) at the 10th minute of the intervention, and (3) at the 30th minute of the intervention. None of the participants used any analgesics throughout the period when the pain results were assessed, starting from when they were admitted to the hospital and after the intervention. This enabled data collection from all participants without any side effects associated with analgesics.

The Hormone Values Monitoring Form was developed to monitor hormone levels of the study participants. Five ml blood samples were taken from the participants just before starting the TENS application and 30 min later when the TENS application was ceased and evaluated for oxytocin, endorphin, and cortisol levels. Since each of the four groups were composed of 14 individuals and blood samples were collected twice from each participant, a total of 112 tubes of blood sample were collected. The samples taken were put in jelly tubes using an injector. The tubes were inverted a few times and kept in an upright position for around 15–20 min at room temperature until the clotting process was completed, then centrifuged for ten minutes at 3000 rpm. The serum samples thus obtained were aliquoted in 1.5 ml locked Eppendorf tubes, and the participants' rotation numbers and groups were written on the tubes. The tubes were then put in the Eppendorf storage boxes and kept in a −80 °C freezer until the analysis. Blood sample analysis was performed by two laboratory technicians who were unrelated to the study. Analyses were performed as A", "B", "C" and "D" coded groups, without the knowledge of whether they represented intervention or control groups. Reporting the laboratory results of the samples was performed by an independent medical biologist who was blinded to the conditions of the study and the coding of the groups.

STAI-S (State Anxiety Inventory), which was developed by Spielberg et al. (1970) to measure normal and abnormal levels of state anxiety, was adapted to Turkish by Öner and Le Compte (1983) [32]. The 20-item STAI-S is composed of (1) never, (2) sometimes, (3) often, (4) almost always according to the intensity levels of emotions or behaviors. The scale has 10 reverse statements. These statements include items 1,2, 5,8,10,11,15,16,19 and 20. The scores obtained from the STAI-S theoretically range from 20 to 80. Higher scores indicate greater anxiety, with 0–19 points indicating "no anxiety", 20–39 points "mild anxiety", 40–59 points "moderate anxiety" and 60–79 points "severe anxiety". In the validity and reliability study, the Cronbach's alpha coefficient of the inventory was found to be between 0.94 and 0.96. [33]. In our study, the Cronbach's alpha coefficient of the scale was determined as 0.86 in the first follow-up.

The Labor Monitoring Form monitored the date and hour of the onset of labor pain, the onset of the active phase, duration of labor, and time of separation of the placenta. During the labor process, the related parts of the form were filled by the responsible researcher and the assistant researcher.

2.7.1. Laboratory analyses

Laboratory analyses of the samples were carried out after the data collection was completed. The analysis of the samples was carried out at the Balcalı Health Application and Research Center of the Medical Faculty of Çukurova University. Enzyme-linked Immunosorbent Assay (ELISA) Kits were used for oxytocin (Cloud-Clone Corporation catalog no: CEB052Ge 96 Tests) and endorphin (Cloud-Clone Corporation catalog no: CEA806Hu 96 Tests), while Direct Immunoenzymatic Assay Kit (DiaMetra Corporation catalog no: DKO001) was used for cortisol analysis. The kits were used manually. The samples to be analyzed were taken out of the −80 °C freezer and kept at 4 °C for 12 h followed by 2 h at room temperature. Meanwhile, the samples were numbered again so that they could be analyzed, and the kits were brought to room temperature. The kits were utilized as per manufacturer's instructions and the hormone levels were calculated from the colorimetric readings carried out in a microplate reader at 450 nm.

2.8. Statistical analysis

Analyses were performed using IBM SPSS V25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp) software and R Studio [34]. Normality of distribution was evaluated in the groups before the analyses. Parametric analyses were carried out in cases where normal distribution assumptions were met and nonparametric tests were used in cases where normal distribution assumptions were not met. Continuous variables were presented using mean, standard deviation, median, minimum, and maximum values. Assessment of the categorical variables was carried out using chi-square analysis. Comparison of two independent two groups was carried out with independent sample *t*-test/Mann Whitney U test, and comparison of two dependent groups was carried out using dependent sample *t*-test/Wilcoxon test. In cases when normal distribution assumptions were met, a one-way ANOVA test was used for multiple groups mean comparisons, and the Kruskal Wallis H test was used for multiple group median comparisons in a nonparametric approach; Bonferroni and Dunn tests were carried out for posthoc comparisons. Analysis of the repeated measures was carried out using a non-parametric test L1-FD-L1 design for repeated measures in a factorial design. In the parametric approach, intragroup, intergroup, and group x time interaction was analyzed using the repeated-measures ANOVA test. Statistical significance was considered at the level of $p<0.05$ and corrected test statistics were presented in posthoc comparisons.

2.9. Ethical considerations

The study was evaluated by the Çukurova University Faculty of Medicine Non-interventional Research Ethics Committee and approved

with a decision dated 14th of February 2020, meeting number 90 and decision number 80. The data collection phase of the study was performed in line with the Declaration of Helsinki. Permission was obtained from the Adana Seyhan State Hospital of the T. C. Ministry of Health, which is under the Adana Provincial Health Directorate hospital affiliated to Adana Local Health Authority, and informed consent was received from the participants. A Clinical Trials protocol registration was carried out for the study ("ClinicalTrials.gov.ID: NCT04851938"). CONSORT-2017 criteria (Fig. 1) were taken into consideration while drafting the study report [35].

3. Results

Of the participants, 37.5% were 20 years old or younger, 42.9% had primary school education, 92.9% were unemployed, 71.4% had medium income level, 50% had health insurance, 62.5% lived in a town, 75% had an extended family, 64.3% planned their current pregnancy, 91.1% received care during pregnancy, 91.1% did not participate in antenatal classes, and 71.4% felt anxious about labor (Table 1).

No significant differences were found between the groups in their education level, working condition, income level, health insurance, place of living, family type, whether the pregnancy was planned, whether the participant received care during pregnancy, whether antenatal classes were attended, and feeling anxious about labor. Hence, the distribution of the descriptive characteristics was found to be similar, independent and homogenous between the groups (Table 1).

The average age of the participants was 22.02±3.13 years (min 18 years, max 30 years), and the average gestational week was 38.27±0.55 (min 38 weeks, max 40 weeks). The groups demonstrated no statistically significant differences in age (years) and gestational week ($p>0.05$). The groups were found to be similar, independent and homogenous for these characteristics (Table 2).

No statistically significant differences were detected in the average oxytocin level of the participants between the groups ($p = 0.304$); however, intra-group ($p<0.001$) and group x time interaction ($p<0.001$) were found to have statistically significant differences. Therefore, intra-group and inter-group comparisons were analyzed independently. The mean pre-test oxytocin levels were found to be similar between the groups ($p = 0.955$), while the post-test mean oxytocin levels were significantly different between the groups ($p = 0.003$). Posthoc comparisons of mean oxytocin levels indicated statistically significant differences between active TENS 1 and active TENS 2 ($p<0.001$), active TENS 1 and placebo ($p<0.001$) and active TENS 1 and Control Group ($p<0.001$). Intra-group comparisons showed that the post-test levels were significantly higher in all groups. The post-test oxytocin level of the Active TENS 2 group was found to be significantly higher in comparison to active TENS 1, placebo and control groups (Table 3). The effect size of these differences is (d(group)=0.068; d(time)= 0.824; d(group*time) =0.803).

The mean endorphin levels were found to be statistically significantly different between the groups ($p<0.001$), within the groups ($p<0.001$) and group x time interaction ($p<0.001$). Therefore, intra-group and inter-group comparisons were analyzed independently. The mean pre-test endorphin levels were similar between the four groups ($p = 0.936$) and no significant differences were found in the inter-group post-test average endorphin levels ($p<0.001$). Posthoc comparisons indicated statistically significant differences in average endorphin levels between active TENS 1 and active TENS 2 ($p<0.001$), active TENS 1 and placebo ($p<0.001$) and active TENS 1 and control groups ($p<0.001$). The post-test mean endorphin levels were found to be significantly high in active TENS 1, active TENS 2 and placebo groups, and significantly low in the control group. The post-test endorphin level of the Active TENS 2 group was found to be significantly higher in comparison to active TENS 1, placebo and control groups (Table 3). The effect size of these differences was (d(group)=0.250; d(time)= 0.435; d(group*time) =0.668).

The average cortisol level was found to be statistically similar between the groups ($p = 0.212$); significant differences, however, were found within the group ($p<0.001$) and in group x time interaction ($p<0.001$). Therefore, intra-group and inter-group comparisons were analyzed independently. The mean pre-test ($p = 0.042$) and post-test ($p = 0.002$) cortisol levels were found to be statistically different between the groups. Posthoc comparisons between the groups suggested a significant difference in the pre-test cortisol levels between active TENS 2 and placebo group ($p = 0.041$). The mean pre-test mean cortisol level of the active TENS 2 group was significantly higher than the placebo group. A statistically significant difference in the post-test cortisol levels was

Table 1
Descriptive characteristics of the participants ($N = 14$).

Characteristics		Active TENS 1 (n=14)	Active TENS 2 (n=14)	Placebo Group (n=14)	Control Group (n=14)	Total (n=14)	Test statistics; p value
Age groups	20 years or younger	8 (57.1)	3 (21.4)	4 (28.6)	6 (42.9)	21(37.5)	X^2=6.152 p=0.406
	24 years or older	6 (42.9)	11 (78.6)	10 (71.4)	8 (57.1)	35 (62.5)	
Education Level	Primary school	7 (50.0)	7 (50.0)	6 (42.9)	4 (28.6)	24 (42.9)	X^{2*}=6.020 p=0.432
	Secondary school	4 (28.6)	3 (21.4)	7 (50.0)	8 (57.1)	22 (39.3)	
	High school	3 (21.4)	4 (28.6)	1 (7.1)	2 (14.3)	10 (17.9)	
Employment	Working	1 (7.1)	1 (7.1)	1 (7.1)	1 (7.1)	4 (7.1)	X^{2*}=0.610 p=1.000
	Not working	13 (92.9)	13 (92.9)	13 (92.9)	13 (92.9)	52 (92.9)	
Income Level	Good	5 (35.7)	2 (14.3)	3 (21.4)	1 (7.1)	11 (19.6)	X^{2*}=6.926 p=0.291
	Medium	8 (57.1)	9 (64.3)	11 (78.6)	12 (85.7)	40 (71.4)	
	Low	1 (7.1)	3 (21.4)	0 (0.0)	1 (7.1)	5 (8.9)	
Presence of Health Insurance	Yes	6 (42.9)	8 (57.1)	8 (57.1)	6 (42.9)	28 (50.0)	X^2=1.143 p=0.815
	No	8 (57.1)	6 (42.9)	6 (42.9)	8 (57.1)	28 (50.0)	
Place of Living	City	4 (28.6)	4 (28.6)	3 (21.4)	2 (14.3)	13 (23.2)	X^{2*}=2.634 p=0.901
	Town	7 (50.0)	9 (64.3)	9 (64.3)	10 (71.4)	35 (62.5)	
	Village	3 (21.4)	1 (7.1)	2 (14.3)	2 (14.3)	8 (57.1)	
Family Type	Nuclear	5 (35.7)	2 (14.3)	3 (21.4)	4 (28.6)	14 (25.0)	X^{2*}=1.919 p=0.733
	Extended	9 (64.3)	12 (85.7)	11 (78.6)	10 (71.4)	42 (75.0)	
Having planned the current pregnancy	Yes	7 (50.0)	12 (85.7)	9 (64,3)	8 (57.1)	36 (64.3)	X^2=4.356 p=0.302
	No	7 (50.0)	2 (14.3)	5 (35.7)	6 (42.9)	20 (35.7)	
Having received care during pregnancy	Yes	12 (85.7)	11 (78.6)	14 (100.0)	14 (100.0)	51 (91.1)	X^{2*}=4.979 p=0.150
	No	2 (14.3)	3 (21.4)	0(0.0)	0 (0.0)	5 (8.9)	
Having participated in antenatal classes	Yes	2 (14.3)	3 (21.4)	0 (0.0)	0 (0.0)	5 (8.9)	X^{2*}=4.979 p=0.150
	No	12 (85.7)	11 (78.6)	14 (100.0)	14 (100.0)	51 (91.1)	
Feeling anxiety about labor	Yes	9 (64.3)	10 (71.4)	13 (92.9)	8 (57.1)	40 (71.4)	X^{2*}=5.130 p=0.183
	No	5 (35.7)	4 (28.6)	1 (7.1)	6 (42.9)	16 (28.6)	

*X^2: Chi-square test, $p<0,05$ Significance Level.

Table 2
Comparison of the means of descriptive characteristics of the participants according to group ($N = 56$).

Characteristics	Active TENS 1 (n=14)	Active TENS 2 (n=14)	Placebo Group (n=14)	Control Group (n=14)	Total (n=56)	Inter-groups Comparisons
	$\widetilde{X}$ [min − max]	$\widetilde{X}$ [min − max]	$\widetilde{X}$ [min − max]	$\widetilde{X}$ [min − max]	$\widetilde{X}$ [min − max]	
Age	21.0[18–27]	22.9 [19–30]	22.8 [18–30]	21.4[18–24]	22.02[18–30]	KW=3.251 p=0.354
Gestational Week	38.2 [38–39]	38.5 [38–40]	38.1 [38–39]	38.1 [38–40]	38.2[38–40]	KW=5.889 p=0.117

KW: Kruskal Wallis test, NA: Not applicable, $p<0.05$ Significance.

detected between the active TENS 1 and control group ($p = 0.005$) and active TENS 2 and placebo group ($p = 0.006$). Intra-group comparisons revealed a statistically significant decrease in post-test cortisol levels in the active TENS 1 and active TENS 2; the post-test cortisol levels were significantly high in the control group and placebo group. The post-test cortisol level of the active TENS 1 and active TENS 2 groups was found to be significantly lower than the placebo and control groups (Table 3). The effect size of these differences is (d(group)=0.082; d(time)= 0.323; d (group*time)=0.766).

The VAS measure median showed no statistically significant differences when compared between ($p = 0.659$) and within (0.287) groups; however, the group x time interaction showed significant differences ($p<0.001$). Therefore, intra-group and inter-group comparisons were analyzed independently. The VAS measure median values showed no statistically significant difference with VAS 1 ($p = 0.073$) and VAS 2 ($p = 0.569$) measures between the groups; however, a significant difference was found in the VAS 3 measure ($p = 0.004$) between the groups. Posthoc comparisons indicated a significant difference between the median of active TENS 2 and control groups ($p = 0.003$). The median of the control group was found to be significantly higher. active TENS 2 was found to be more effective in decreasing labor pain; moreover, the labor pain of the participants who were administered active TENS 1 was significantly lower (Table 4, Fig. 2). The effect size of these differences was (d(group)=0.031; d(time)= 0.062; d(group*time) =0.641).

Pre-test and post-test mean scores of STAI-S showed no significant differences in intra-group, inter-group, and group x time interactions($p = 0.186$); statistically significant differences, however, were detected in the intra-group mean scores ($p<0.001$) and group x time interaction ($p<0.001$). The pre-test mean scores was found to be similar between the groups ($p = 0.051$); the post-test mean scores were found to be significantly different ($p<0.001$). Paired comparisons indicated statistically significant differences between active TENS 1 and active TENS 2 ($p = 0.003$), active TENS 1 and control group ($p<0.001$) and placebo and control group ($P = 0.033$) (Table 4). The effect size of these differences is (d(group)=0.102; d(time)= 0.224; d(group*time) =0.755).

The differences in the median time of the duration of stages of labor were analyzed using a non-parametric test for repeated measures in a factorial design. Accordingly, while a statistically significant difference was detected between ($p<0.001$) and within groups ($p<0.001$), the group x time interaction was not significant ($p = 0.512$). Analysis of the duration of labor stage according to groups revealed a statistically significant decrease in the duration of all stages of labor in the TENS group. Inter-group analyses showed that the duration of labor stages of the participants who were administered active TENS 2 was significantly lower in comparison to active TENS 1, control, and placebo groups (Table 5). The effect size of these differences is (d(group)=0.274; d (time)= 0.973; d(group*time) =0.159).

A statistically significant difference was detected in post-test cervical dilation (X^2=14.175; $p = 0.003$) between the groups. Bonferroni corrected paired comparisons revealed significant differences between the active TENS 2 group, and the placebo and control groups. Post-test cervical dilation of the Active TENS 2 group was significantly higher in comparison to the placebo and control groups (Table 5).

4. Discussion

The main purpose of the current study was to investigate the effects of TENS on the levels of oxytocin, endorphin and cortisol, which play an active role in labor as well as perceived labor pain and anxiety level, and determine the most effective TENS frequency and pulse width.

TENS applied at different frequencies was found to increase the oxytocin level, which contributed to the progress of labor. However, it was found that in comparison to stable frequency, TENS applied at a higher frequency and pulse width (80- 100 Hz and 350 μs) could increase the oxytocin level significantly. These results indicate that the use of high-frequency and pulse TENS during labor could be an effective implementation in increasing the level of oxytocin. A review of the current literature indicates that no studies have investigated the relationship between non-pharmacological methods for alleviation of labor pain and oxytocin levels. Farra et al. [36] reported that the need for exogenous oxytocin for labor induction was significantly lower in participants who were administered TENS in comparison to the placebo group. The use of TENS during labor is considered to decrease the need for exogenous oxytocin by increasing the endogenous oxytocin levels [36].

TENS applied at different frequencies was also seen to increase the levels of endorphin, again positively contributing to the progress of labor. The use of TENS in a higher frequency and pulse width (80- 100 Hz and 350 μs) increased the endorphin level significantly in comparison to stable frequency (100 Hz and 100 μs) and the placebo group. Báez-Suárez et al. [26,27] reported that high-frequency TENS was more effective in decreasing labor pain. Although these two studies did not evaluate the relationship between TENS and endorphin levels, the results are similar to the present study in emphasizing the potential analgesic effect of endorphin released more effectively at high frequency and density [26,27].

The application of TENS at different frequencies could reduce the cortisol levels during labor. Specifically, TENS applied at higher frequency and pulse width (80- 100 Hz and 350 μs) could reduce the cortisol level statistically significantly. Anxiety levels are known to increase during the labor process, which may increase the release of cortisol. The increase in the cortisol level may exacerbate stress and anxiety even further via positive feedback, creating a vicious circle [37,38]. The current study found that this vicious circle could be broken by applying TENS, which could reduce the cortisol levels and thereby regulate the process of natural labor. To our knowledge, no study to date has investigated the effect of TENS applied during labor on cortisol levels. Hanafy et al. reported a significant level of decrease in the plasma cortisol levels of patients with pudendal pain who were administered TENS [39].

The level of perception of labor pain was also reduced with TENS applied at different frequencies. The application of TENS at high frequency and pulse width (80- 100 Hz and 350 μs) could significantly reduce the perception of labor pain in comparison to TENS with stable frequency (100 Hz and 100 μs) and placebo. Several studies have previously reported the effect of TENS on labor pain [25-27,36,40–42] and support the data from the current study. A significant decrease was reported in pain density in the TENS active groups. Of note, the methodology used in the previous studies differed from the methodology of the present study [25-27,36,40-43]. Two studies that applied TENS at different frequencies [26,27] reported that high frequency was more effective in decreasing labor pain, but stable frequency also decreased labor pain significantly [26,27].

Anxiety levels were found to be reduced with TENS applied at

Table 3
Intra-group and inter-group comparison of pre-test and post-test hormone levels of the participants ($N = 56$).

Measures	Active TENS 1 (n=14)	Active TENS 2 (n=14)		Placebo Group (n=14)		Control Group (n=14)		Inter-groups comparisons	Comparisons for Repeated Measures	Effect Size (%95)	
	$\overline{X} \pm SS$	Test Statistics, p	$\overline{X} \pm SS$	Test Statistics, p	$\overline{X} \pm SS$	Test Statistics, p	$\overline{X} \pm SS$	Test Statistics, p			
Oxytocin Level Pre-test[a]	383.96 ±95.16	t=−7.940 p<0.001	380.23 ±89.06	t=−11.721 p<0.001	385.55 ±92.62	t=−9.260 p<0.001	389.18 ±93.89	t=−2.180 p=0.048	F*=0.022 p=0.995	Group: F=1.243 p=0.304 Time: F=239.309 p<0.001 Group x Time: F=69.477 p<0.001	Group η^2: 0.068****Time η^2: 0.824****Group*Time η^2: 0.803
Post-test[b]	448.04 ±106.16		529.1 ±103.72		407.1 ±92.23		396.8 ±94.1		F*=5151 p=0.003		
Endorphin Level Pre-test[a]	527.78 ±77.66	t=−14.502 p<0.001	530.14 ±80.56	t=−6.190 p<0.001	514.03 ±85.05	t=−8.437 p<0.001	533.75 ±101.35	t=3.406 p=0.005	F*=0.139 p=0.936	Group: F=5.788 p=0.002 Time: F=40.006 p<0.001 Group x Time: F=34.886 p<0.001	Group η^2: 0.250****Time η^2: 0.435****Group*Time η^2: 0.668
Post-test[b]	580.07 ±73.96		728.84 ±121.6		532.38 ±79.89		486.9 ±84.7		F*=18.258 p<0.001		
Cortisol Level Pre-test[a]	361.9 ±72.85	t=6.284 p<0.001	441.96 ±94.94	t=8.977 p<0.001	347.33 ±102.44	t=−1.045 p=0.315	375.15 ±93.01	t=−6.506 p<0.001	F*=2.927 p=0.042	Group: F=1.552 p=0.212 Time: F=24.766 p<0.001 Group x Time: F=56.624 p<0.001	Group η^2: 0.082****Time η^2: 0.323****Group*Time η^2: 0.766
Post-test[b]	312.68 ±78.74		315.48 ±83.56		358.32 ±96.91		434.03 ±101.55		F*=5.455 p=0.002		

t: Dependent Sample t-test, F*: One-way ANOVA test, F: Repeated measures ANOVA test, $p<0.05$ Significance level.
a: Pre-intervention plasma level, b: Post-Intervention plasma level.

Table 4
Intra-group and inter-group comparisons of pre-intervention and post-intervention VAS ve STAI-S mean scores ($N = 56$).

Measures	Active TENS 1 (n=14) $\overline{X} \pm SS$	$\widetilde{X}[min - max]$	Active TENS 2 (n=14) $\overline{X} \pm SS$	$\widetilde{X}[min - max]$	Placebo Group (n=14) $\overline{X} \pm SS$	$\widetilde{X}[min - max]$	Control Group (n=14) $\overline{X} \pm SS$	$\widetilde{X}[min - max]$	Inter-Groups Comparisons	Comparisons for Repeated Measures	Effect Size (% 95)
VAS 1 Pre-test [a]	7.2±2.3	7 [3–10]	7.7±2.6	9 [3–10]	5.29 ±2.67	4.5 [1–10]	5.93 ±2.81	5.5 [2–10]	KW=6.953 p=0.073	Group: WTS=1.603 p=0.659 Time: WTS=2.499 p=0.287 Group x Time: WTS=157.2 p<0.001	Group η^2: 0.031 Time η^2: 0.062 Group*Time η^2: 0.641
VAS 2 Post-test[b]	5.86 ±2.8	5.5 [2–10]	6±2.48	7.5 [2–8]	6.07 ±2.76	5.5 [1–10]	7.14 ±2.41	7 [3–10]	KW=2.015 p=0.569		
VAS 3 Post-test[c]	5.7±3.0	5 [2–10]	3.8±2.1	5 [0–6]	6.9±2.9	7 [1–10]	7.9±2.3	8.5 [4–10]	KW=13.316 p=0.004		
DKÖ Pre-test[a]	48.14 ±11.03	t=3.322 t=0.006	50.36±9	t=8.983 p<0.001	45.07 ±8.16	t=−0.269 p=0.792	40.64 ±9.34	t=−8.656 p<0.001	F*=2.781 p=0.051	Group: F=1.665 p=0.186 Time: F=15.275 p<0.001 Group*Time: F=52.053 p<0.001 Time η^2: 0.224 Group*Time η^2: 0.755	Group η^2: 0.102
DKÖ Post-test[b]	40.57 ±6.86		30.93 ±6.28		45.43 ±6.63		52.86 ±7.94		F*=24.450 p<0.001		

* t: Dependent Sample t-test, F*: One-way ANOVA test, F: Repeated measures ANOVA test, $p<0.05$ Significance level.
a: Pre-intervention.
b: Measured at 10th minute of the intervention.
c: Measured at the 30th minute of the intervention.

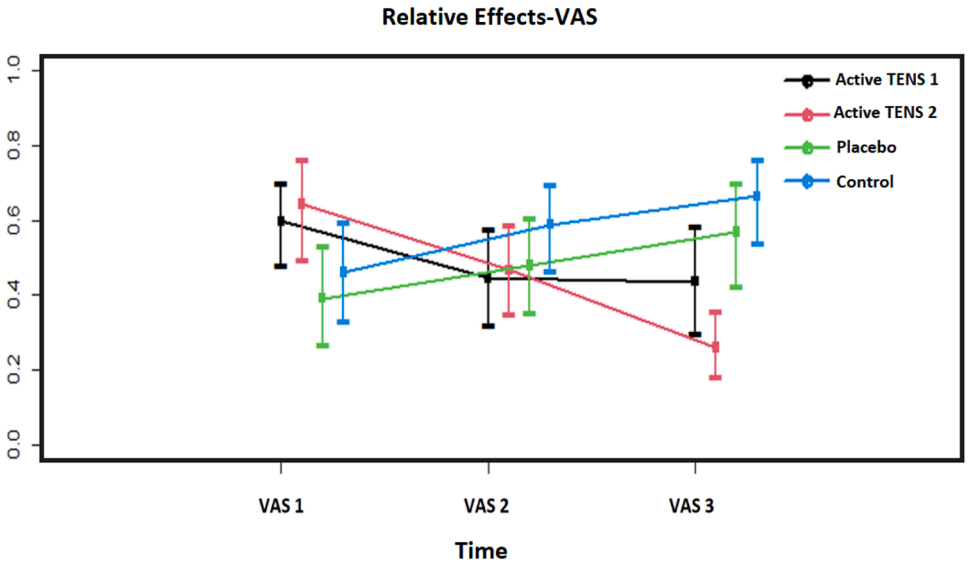


Fig. 2. Changes in the participants' pre-intervention and post-intervention VAS mean scores in groups by time.

different frequencies. TENS at a higher frequency and pulse width (80-100 Hz and 350 μs) significantly decreased the mean STAI-S score. This was expected, since higher frequency TENS could enhance the release of endorphin, decreased labor pain and decrease the cortisol level, all of which could alleviate stress and contribute towards the decrease in STAI-S scores. Karlinah et al. [40] reported that TENS decreased labor pain by increasing endorphin release and decreased anxiety and fear in the labor process in case of what?

A significant decrease in the duration of the stages of labor was also found with the application of TENS. Again, TENS applied in a higher frequency and pulse width (80- 100 Hz and 350 μs) could significantly decrease the duration of the stages of labor. The reduction in plasma oxytocin level, regulation of uterine contractions, and an increase in the push power with the use of TENS was likely to have contributed to the decrease in the duration of labor. Njogu et al. reported a statistically significant decrease in the duration of labor in comparison to the

Table 5
Intra-group and inter-group comparisons of the participants' labor process ($N = 56$).

	Active TENS 1 (n=14)		Active TENS 2 (n=14)		Placebo (n=14)		Control Group (n=14)		Inter-group Comparisons	Comparisons for Repeated Measures	Effect Size (%95)
	$\tilde{X}$ [*min* – *max*]	Test statistics; p	$\tilde{X}$ [*min* – *max*]	Test statistics; p	$\tilde{X}$ [*min* – *max*]	Test statistics; p	$\tilde{X}$ [*min* – *max*]	Test statistics; p			
Labor Stage Durations											
Duration of Stage I	560.5 [475–755]	FT=28.000 p<0.001	515.5 [360–750]	FT=28.000 p<0.001	662 [540–990]	FT=28.000 p<0.001	666.5 [540–980]	FT=28.000 p<0.001	**KW=13.629 p=0.003**	Group: WTS=68.322 p<0.001	Grup η^2: 0.274
Duration of Stage II	44 [32–63]		41 [30–60]		45 [33–75]		55 [44–82]		**KW=15.070 p=0.002**	Time: WTS=2129.8 p<0.001	Zaman η^2: 0.973
Duration of the Separation of Placenta	9.5 [8–10]		8 [7–10]		12 [8–15]		12.5 [10–20]		**KW=29.286 p<0.001**	Group*Time: WTS= 5.253 p=0.512	Grup*Zaman η^2: 0.159
Cervical Dilation Measures											
Pre-test[a]	4 [4–4]	W=−2.392	4 [4–4]	W=−3.095	4 [4–4]	W=−2.271	4 [4–4]	W=−2.000	NA	NA	
Post-test[b]	4.5 [4–8]	p=0.017	6 [4–8]	p=0.002	4 [4–6]	p=0.023	4 [4–5]	p=0.046	**KW=14.175 p=0.003**		

FT: Friedman test statistics, W: Wilcoxon test statistics, KW: Kruskal Wallis test statistics, WTS: Wald-type statistics, $p<0.05$ Significance level.
a: Pre-intervention measures.
b: Post-intervention measures.

placebo group when TENS was applied in the active phase of labor [41]. Baez-Suarez et al. reported a decrease the duration of the second stage of labor upon the administration of TENS in comparison to the placebo group [27]. Another similar study also supports the findings of the current study [41].

The level of cervical dilation was found to be affected significantly with the use of TENS, with higher frequency and pulse width (80- 100 Hz and 350 μs) being significantly more effective in increasing cervical dilation. To our knowledge, no published study to date has assessed the effect of TENS on the level of cervical dilation during labor. The increase in cervical dilation was most likely due to an increase in the levels of oxytocin and endorphin with the use of TENS.

5. Limitations of this study

This study has some limitations that need to be considered while interpreting the results. First, the study was conducted on primipara pregnant patients who gave birth at a single center. Therefore, the results can be generalized only for this group. Multi-centered studies including larger sample groups are needed to address this limitation. A second limitation is the lack of postpartum follow-up on the use of TENS.

6. Conclusions

Labor is a painful process. TENS is a non-pharmacological, efficient and reliable option for decreasing pain during labor. The application of TENS at a higher frequency was found to be more effective than stable frequency. Hormone levels were affected and anxiety levels decreased with a decrease in pain during labor, which is considered to enable a positive labor experience. Therefore, high-frequency TENS should be recommended for use by midwives during delivery. Despite the results obtained in this study, we should not forget the presence of many factors that could affect pain.

CRediT authorship contribution statement

Rukiye Sulu: Research idea, design, organization, data collection, data analysis and interpretation, literature review, writing the article, critical reading, supervision. **Meltem Akbaş:** Research idea, design, organization, data collection, data analysis and interpretation, literature review, writing the article, critical reading. **Salih Çetiner:** Sample analysis and interpretation of the findings, critical reading.

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Declaration of Competing Interest

The authors declare no conflicts of interest with respect to the authorship and/or publication of this article.

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Data availability

Any additional information can be obtained from the corresponding author on request.

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