BMC Pregnancy and Childbirth

RESEARCH

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Effect of topical magnesium sulfate on labor duration and childbirth experience: a randomized controlled trial

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Abstract

Background Magnesium sulfate is used topically to reduce the duration of labor in some regions of the country. However, there is insufficient evidence about its effectiveness. This study aimed to determine whether topical magnesium sulfate reduces labor duration and improves childbirth experience (primary outcomes).

Methods In this randomized controlled trial, the participants were 98 women with low-risk, singleton, and full-term pregnancies admitted to a teaching hospital in Iran. They were randomly assigned to the intervention group (receiving 50% magnesium sulfate) or the control group (receiving distilled water) stratified by parity and onset of labor. The participants, interventionists, and data collectors were blinded. During the vaginal examination at the beginning of the active phase of labor, 10 mL of magnesium sulfate or distilled water was poured on the cervix of the uterus. Data collection was performed by the researcher with continuous monitoring up to two hours post-delivery and follow-up at 4–5 weeks postpartum. The Childbirth Experience Questionnaire 2.0 was used to examine childbirth experience. We performed a modified intention-to-treat analysis, excluding those whose outcome of interest could not be assessed. Independent-samples t-tests were used to compare the groups in terms of the mean of the primary outcomes.

Results Participant recruitment took place between December 2021 and December 2022. Thirty-three percent were primiparous and 37% had induced labor. Three women in the intervention group and seven in the control group underwent emergency cesarean sections. All 49 women assigned to each group were included in the analysis of labor duration outcome, while one and two women were excluded from the analysis of childbirth experience score due to loss to follow-up. In the intervention group, compared to the control group, the mean duration of the intervention until delivery was significantly shorter (1.59 vs. 2.93 h; MD -1.34, 95% CI [-1.88 to -0.79]) and the childbirth experience score was higher (3.1 vs. 2.3, MD 0.84; 95% CI [0.59 to 1.08]).

Conclusions According to the results of this trial, pouring 10 mL of 50% magnesium sulfate on the cervix at the beginning of the active phase of labor probably reduces labor duration and improves the childbirth experience.

Trial registration Ethics Committee of Tabriz University of Medical Sciences: IR.TBZMED.REC. 1400.726. Iranian Registry of Clinical Trials: IRCT20100414003706N40 Registration date: 21/11/2021 (https://en.irct.ir/trial/58323).

Keywords Labor, Dystocia, Magnesium sulfate, Childbirth experience, Labor duration

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Background

Labor dystocia or prolonged labor occurs in approximately 21% of all live births [1]. It is associated with some complications for both mothers and infants, including higher rates of cesarean section and chorioamnionitis for mothers [2], a lower 5-min Apgar score, and the need for mechanical ventilation for infants [3]. Prolonged labor is also associated with lower maternal satisfaction and a more negative childbirth experience [4, 5]. The experience of childbirth has a significant impact on women's lives. A positive childbirth experience is associated with relaxation and increased maternal-infant attachment [6]. In contrast, a negative childbirth experience is associated with feelings of helplessness [7], depression [8], postponing future births, possibly never wanting to have another child, and choosing a cesarean section [9]. Therefore, it is important to identify interventions that can safely shorten the active phase of labor and improve the childbirth experience.

Currently, various pharmacological and nonpharmacological approaches are used for the active management of labor [10]. Oxytocin is one of the most frequently prescribed medications to shorten the active phase [11]. However, there is insufficient evidence regarding the optimal dosage of oxytocin during the active phase [12]. Additionally, oxytocin can increase the risk of severe postpartum bleeding [13], uterine hyperstimulation [14], and non-reassuring fetal heart rate. Therefore, its routine use is not recommended. To improve maternal and fetal outcomes, the benefits and harms of its use should be weighed [15].

In some regions of the country,experimentally, one of the drugs recommended to facilitate dilation of the cervix in the active phase is the use of magnesium sulfate locally (by pouring it on the cervix) [16]. Magnesium sulfate is one of the most commonly used drugs in obstetrics, mainly as an anticonvulsant drug [17]. It is usually administered intramuscularly or intravenously, but it can also be used topically [16]. It has been reported that Lamicel consisting of polyvinyl alcohol polymer compressed sponges containing up to 500 mg of magnesium can soften and dilate the cervix by extracting fluid from the cervical tissue and collagenolytic in the cervical stroma, and some of the effects are due to magnesium [18]. However, a clinical trial comparing the effects of Lamicel with and without magnesium sulfate failed to show the positive effect of magnesium sulfate on facilitating labor [19].A clinical trial showed a 0.6-h reduction in the median length of the active phase of labor with intravenous infusion of magnesium sulfate compared to normal saline (placebo) in women with mild preeclampsia,but this difference was not statistically significant [20]. Also, a few trials have shown that pouring magnesium sulfate on the cervix significantly shortens the active phase [16, 21] and the latent phase [22] of labor in primiparous women.

We found no studies examining the effect of magnesium sulfate on the childbirth experience. Therefore, given the lack of evidence, we aimed to determine the effect of topical magnesium sulfate on labor duration and childbirth experience.

Methods

Study design and participants

This is a single-center, double-blind, two-parallel-arm, randomized superiority trial. Participants, interventionists, care providers, and data collectors were unaware of the type of intervention administered to each participant. Participants were women aged 18 to 39 years with full-term live and singleton pregnancies (gestational age 37 to 42 weeks). They were primiparous or had one or two previous natural births without a history of cesarean sections. The participants had been admitted to the maternity ward of Taleghani Hospital in Tabriz, Iran. Other eligibility criteria were estimated fetal weight ranging from 2500 to 4000 g, cephalic presentation and fetal head station between -2 and zero, and cervical effacement between 40 and 70%. Exclusion criteria were insufficient literacy to fill out the questionnaires; previous history of infertility; known serious medical conditions (e.g. severe anemia [hemoglobin levels below 7] or blood, heart, and lung diseases, connective tissue, and smooth muscle disorders); high-risk pregnancies (e.g., placental abruption, placenta previa, intrauterine growth retardation (IUGR)); known fetal abnormalities; absolute or relative contraindications for vaginal delivery, including cephalopelvic disproportion (CPD) as determined by the attending physician; and fetal heart rate abnormalities during the preintervention phase. Only about 70 women have a vaginal birth in the hospital (study area) every month. We expected at least 50% of them to be ineligible (based on the participant eligibility criteria) and to have only one or two eligible participants at a time. Careful management of two eligible participants simultaneously by the principal investigator (PI [SR, first author, midwife with eight years of clinical expertise]), who had no other responsibilities in the delivery room, was reasonable.

Recruitment, randomization and blinding

The participants were selected consecutively when the investigator was present at the hospital, usually for 48–72 consecutive hours per week. If more than two women were eligible at a time, we recruited two women, based on hospital admission time, so that the PI could best manage all her duties. Most of the time, there was only one eligible participant.

In the early stage of labor, at the earliest opportunity after a woman's admission to the labor department, the PI briefly described the purpose and methodology of the study to potentially eligible women. Women willing to participate in the study were assessed for eligibility criteria using a checklist. Then, the trial objectives and methods were explained in more detail to eligible women and they were asked to read and sign the informed consent. They had enough time to read the consent form and ask any questions they had. After that, the baseline assessment was done. The participants were allocated into either the intervention group, which received magnesium sulfate, or the control group, which received a placebo (distilled water) at the beginning of the active phase of labor. The allocation sequence was determined using a software program (www.random.org) employing stratified block randomization with a block size of four, and an allocation ratio of 1:1. Stratification was conducted based on parity (primiparous/multiparous) and labor onset (spontaneous/induced). The research team couldn't obtain visually indistinguishable ampoules of magnesium sulfate and distilled water. To address this challenge, we purchased 50% magnesium sulfate produced by Yara Teb Samen Pharmaceutical Company (Iran) and distilled water produced by Shahid Ghazi Pharmaceutical Company (Iran) from the domestic pharmaceutical market and identical 10-mL prefilled syringes containing either 10 mL of magnesium sulfate or distilled water were prepared. To ensure the allocation concealment, sequentially numbered opaque, sealed envelopes were used. Each envelope contained two prefilled syringes of magnesium sulfate or distilled water (the second syringe was prepared for reuse in cases of rupture of the amniotic membrane shortly after pouring the contents of the first syringe).The sequence generation and envelope preparation were performed by a person not involved in recruitment, intervention administration, care provision, or data collection.

At the beginning of the active phase of labor, after writing the woman's name on the envelopes, the envelopes were opened sequentially. The recruitment and allocation of participants into the groups were conducted by the PI.

Interventions

The onset of the active phase of labor, characterized by 4–5 cm of dilatation and regular uterine contractions, was determined through the utilization of the Partograph and confirmed by a vaginal examination conducted by the PI. At the beginning of this phase, using the prefilled syringe, 10 mL of 50% magnesium sulfate or distilled water was poured on the cervix from the sides of the fingers during the vaginal examination so that the entire cervix was covered with it. To increase absorption, the participant was asked to lie on the bed for 30 min following the intervention. In cases of rupture of the amniotic sac within 30 min after administering the medicine, after the end of the amniotic sac liquid leakage, the intervention was repeated using the other prefilled reserved syringe.

The PI implemented the study interventions. The conventional birth attendants provided routine care, including monitoring and managing the various stages of labor, to all participants.

Outcomes and data collection

The primary outcomes were the duration of the intervention to delivery of the fetus, and the total score of childbirth experience. The PI assessed the duration through direct observation. Childbirth experience was determined using the childbirth experience questionnaire (CEQ-2).

The secondary outcomes were: intensity of pain experienced during labor after the intervention, the Bishop score one hour after the intervention, duration of the second and third stages of labor, levels of hemoglobin and hematocrit after delivery, fear of childbirth one hour after the intervention, postpartum childbirth fear, and birth satisfaction. We had planned to assess the Bishop score and fear of childbirth at labor two hours after the intervention. However, at the beginning of data collection, we realized some participants might deliver before the two-hour time-point, and some will be too distressed to answer the DFS items accurately. Therefore, we decided to change the assessment time to one hour of intervention.

Data for the secondary outcomes were collected using a 10-cm visual analog scale (VAS), Bishop score form, Delivery Fear Scale (DFS), Wijma delivery expectancy/experience questionnaire-version B (W-DEQ-B), and Birth Satisfaction Scale-Revised (BSS-R). Additionally, a sociodemographic questionnaire and a checklist of side events and fetal heart rate changes (using continuous fetal heart rate monitoring from the time of participant recruitment to delivery) were completed.

The PI collected all the data through various methods, including direct observation of the labor process from recruitment to two hours after delivery of the fetus, interviewing participants, questioning care providers, and reviewing hospital files. Also, a visit was performed 12–24 h after delivery, before the participant was discharged from the hospital. In addition, 4–5 weeks after delivery, a follow-up was conducted using a phone call or WhatsApp messaging platform.

We used a psychometrically validated Persian version of the scales to assess the outcomes.

Some other measures to increase the quality of collected data were: 1) using short, simple, and easily administered scales to assess outcomes during the active phase of labor (VAS and DFS); and 2) not introducing a new scale in the active phase of labor to the participants and explaining the scales to them before the start of the active phase of labor and asking women to answer the questions between uterine contractions. Below, a description of each tool is provided.

The CEQ-2 was used to evaluate the childbirth experience 4–5 weeks after delivery. This scale comprises 23 items, 20 of which are 4-option Likert items ranging from completely agree (score 4) to completely disagree (score 1). The remaining three items are transformed from 100 mm VAS-scale to categorical values: 0–40 is encoded as 1, 41–60 as 2, 61–80 as 3, and 81–100 as 4. Negative items (experiencing severe pain, fatigue, dread, and poor memory) were scored inversely. The total score obtained from the mean score of the items ranges from 1 to 4, and higher scores indicate a more positive childbirth experience [23]. The Persian version of this scale has already been validated in our research setting [24]. Its internal consistency using Cronbach's alpha for the total score in that study was 0.93 [25]. In the present study, it was 0.94.

The assessment of labor progression involved documenting the precise timing of events including the onset of the active phase of labor, initiation of the intervention, rupture of the amniotic sac, delivery of the fetus, and delivery of the placenta. Additionally, the investigator recorded the characteristics and frequency of uterine contractions at baseline, medications administered during hospitalization, the type of delivery, Apgar scores, and any measures taken to resuscitate the newborn.

The Bishop score was assessed at baseline and one hour following the intervention. The interrater reliability of the score was determined by examining ten women by the PI and another experienced midwife at approximately a 10-min interval. The correlation coefficient between the scores was 0.93.

Pain intensity was assessed using a 10-cm VAS scale at baseline, and one, two, and three hours after the intervention (in the case of no delivery). The beginning and end of this linear scale are indicated by the numbers 0 (no pain) and 10 (the most severe pain) [26]. When had no contraction (between contractions), the women were asked to specify the pain intensity during their most recent uterine contraction on the line.

Hemoglobin and hematocrit levels were measured once in the first hour of the woman's admission to the hospital (as a routine of the hospital) and again 12–24 h after delivery by collecting a 2 mL venous blood sample. By analyzing the blood of ten women in the laboratory of the sampling site and the laboratory of one of the most reputable laboratories in the city, the reliability of these test results was determined to be 1.00 for hemoglobin and 0.97 for hematocrit.

Fear of childbirth during labor was evaluated using the DFS at baseline and one hour after the intervention. This 10-item scale has scores ranging from 1 (do not agree at all) to 10 (completely agree) for each item (some items are scored in reverse) and from 0 to 100 for the overall scale [27]. Cronbach's alpha coefficient for the Persian psychometric version of this scale in Iran was 0.77 [28]. In the present study, it was 0.73 for the baseline assessment and 0.91 for the one hour after.

The W-DEQ-B was used to evaluate postpartum fear 2 h and five weeks after delivery. The WDEQ-B comprises 33 six-point Likert items with scores ranging from 0 (not at all) to 5 (extremely) for each item. Some items are scored inversely. The total score of this scale, calculated by adding the scores of each item, ranges from 0 to 165, with higher scores indicating a higher fear of childbirth [29]. Internal consistency of the total scale using Cronbach's alpha 0.94 for the Persian version used for the validation in Iran [30]. In the present study, it was 0.89 for 2 h after delivery and 0.95 for five weeks after delivery.

The BSS-R was completed 12–24 h after delivery. It is a 10-item Likert scale with a 5-point item format. The scale ranges from 0 (strongly disagree) to 4 (strongly agree) for each item, with four items scored in reverse. The total score is calculated by adding up the scores of all items, with a higher score indicating a higher level of satisfaction [31]. The Persian version of the scale has already been validated in our research setting, demonstrating an internal consistency of 0.96 when assessed 12–24 h after delivery and 0.91 when assessed 40–45 days after delivery [4]. In the present study, the consistency was 0.77.

The side events checklist was completed by direct observation and review of mother and infant records. The listed events were uterine tachysystole; mild, moderate, and severe vaginal bleeding; maternal adverse events after delivery (such as transfer to the operating room or intensive care unit); rashes and skin irritation; itching; perineal tear; cervical tear and admission of the infant to the neonatal intensive care unit (NICU). It also included an open question to record any other side events.

The face and content validity of the questionnaires, excluding the validated scales, was determined using the opinions of ten experts. The experts included obstetrics and gynecology specialists and midwives from the faculty members of the Tabriz University of Medical Sciences.

Sample size

The sample size was calculated using G-Power software, considering both primary outcomes. Considering the mean and standard deviation of the duration of the active

phase until delivery of the fetus in the control group in a similar study [16] (M1 = 4.2, SD1 = 2.0), a decrease of at least 30% in the mean of this duration with the intervention [M2 = 2.94] and SD2 = SD1, it was determined that a sample size of 41 women in each group is necessary to achieve 80% power and a two-tailed significance level of 0.05. Based on the childbirth experience variable, taking into account the mean and standard deviation of the childbirth experience score (M1 = 59.6, SD1 = 12.7) [32] in the control group, assuming a 15% increase in the mean score as a result of the intervention (M2 = 68.5), with the same variability (SD2 = SD1), a two-tailed significance level of 0.05, and power of 90%, the sample size was determined to be 44 individuals. Considering a possible attrition rate of 10%, 49 individuals were considered for each group.

Data analysis

The data were analyzed using SPSS version 24 software. The Kolmogorov–Smirnov test results confirmed the normality of the distribution of quantitative data by the groups. Independent-samples t-tests were used to compare the groups in terms of the primary outcomes and the secondary outcomes with no baseline assessments. Univariate General Linear Model tests were used to assess the differences between groups regarding the mean of quantitative outcomes adjusted for the baseline values. As primary planned analyses, all randomized women were analyzed in the allocated group, excluding only those who could not be followed up to assess the outcomes. As an additional unplanned analysis, we also analyzed the data on the primary outcomes excluding those who had cesarean sections to see how sensitive the results are to inclusion or exclusion of such cases. The reasons for such a decision were: 1) in this trial, the number of emergency cesarean sections in the intervention group was less than in the control group, 2) the duration of labor in cesarean sections could not be assessed in the same way as with vaginal deliveries, 3) the experience of childbirth in women with emergency cesarean section is usually less positive than those with vaginal delivery [4].

Results

Of the 254 women assessed for eligibility, 104 were eligible. Six of these eligible women declined to participate in the study. All 49 women randomized to each group were carefully monitored until their discharge from the hospital. One participant from the intervention group and two participants from the control group were lost to follow-up at 4–5 weeks after delivery (Fig. 1). Three participants from the intervention group and seven participants from the control group had emergency cesarean section. Its main reasons in the magnesium sulfate group were fetal heart rate disorders (2 cases) and arrest of fetal descent (1 case), and in the control group, the main reasons were fetal heart rate disorders (3 cases), arrest of fetal descent (2 cases), fetal distress due to amniotic fluid contamination with meconium (1 case), and umbilical cord prolapse (1 case). Due to the rupture of the amniotic sac less than half an hour after the intervention, the reserve syringe was used for four participants, all of whom were from the magnesium sulfate group.

There were small differences between the groups in terms of some of the baseline characteristics (age, income, oxytocin use). The mean age of the women was 26.8 years (SD = 5.2). The gestational age was 39.3 weeks (SD = 1.0). Approximately one-third (33%) of the women were primiparous, and 37% had induced labor (Table 1). The mean neonatal birth weight in the magnesium sulfate group was 3278 g (SD 423) and that in the control group was 3246 g (SD 415).

There were no notable differences between the intervention and control groups in the drugs used to affect the progress of labor, from the beginning of the intervention to the time of delivery; i.e. oxytocin 5 units in 500 mL serum (84% vs. 80%), pethidine (6% vs. 10%), remifentanil (21% vs. 16%), promethazine (10% vs. 8%), and hyoscine (10% vs. 10%).

Primary outcomes

In the magnesium sulfate group compared to the control group, intervention to delivery duration was significantly shorter (1.59 vs. 2.93 h; MD -1.34, 95% CI -1.88 to -0.79), and the total score of the childbirth experience was significantly higher (3.1 vs. 2.3; MD 0.84, 95% CI 0.59 to 1.08) (Table 2). In the additional unplanned analysis, excluding those who had cesarean deliveries, the results changed only slightly to 1.57 versus 2.83 h; MD -1.26, 95% CI -1.89 to -0.67 regarding intervention to delivery duration and 3.1 versus 2.4; MD 0.75, 95% CI 0.49 to 1.01 regarding the total score of the childbirth experience.

Key secondary outcomes

In the group receiving magnesium sulfate, there was a statistically significant increase in the mean Bishop score one hour after the intervention compared to the control group ($P < 0.001$). In addition, the mean pain intensity one hour ($P = 0.003$) and three hour after the intervention ($P = 0.040$), as well as the mean fear score one hour after the intervention ($P < 0.001$), two hours after delivery ($P = 0.018$), and 4–5 weeks after delivery ($P < 0.001$) in the magnesium sulfate group were significantly lower than those in the control group.

Although the pain intensity scores at 2 h after the intervention in the magnesium sulfate group were lower than those in the control group, the differences were

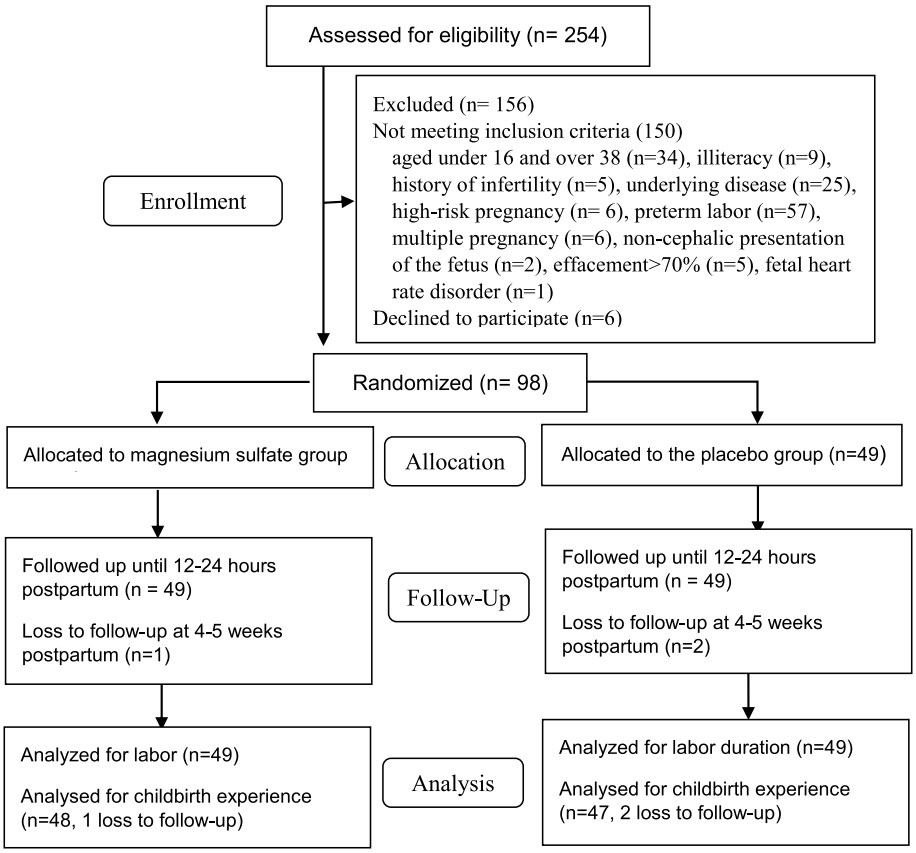

Fig. 1 Flow diagram of participants

not statistically significant ($P=0.116$). Furthermore, no statistically significant difference was observed between the two groups in terms of the mean length of the second ($P=0.94$) and third ($P=0.29$) stages of labor, as well as the birth satisfaction score ($P=0.19$), hemoglobin level ($P=0.30$), and hematocrit level ($P=0.21$) assessed at 12–24 h after delivery (Table 3).

Additional secondary outcomes

These outcomes have not been registered in the trial registration form. However, we had a plan to assess them. The mean time interval between the intervention and rupture of the amniotic fluid sac (among those who had an intact sac at the time of the intervention) was significantly shorter in the magnesium sulfate group than in the control group (63 vs. 125 min, $P=0.001$). Additionally, the magnesium sulfate group had significantly greater rates of high or very high overall satisfaction with pain relief in the first stage of labor (38.8% vs. 16.3%) and the second stage (32.6% vs. 16.3%) (both $P<0.01$).

Side events

There were 12 first-degree perineal tears in the magnesium sulfate group and 11 in the control group, but no cervical tears. No cases in the magnesium sulfate group and two cases in the control group required manual removal of the placenta. There was one case of uterine tachysystole and one case of itching in the control group, two cases of mild postpartum bleeding in the magnesium sulfate group and two cases in the control group, and one case of transfer to the operating room to drain the hematoma of the episiotomy repair site in the magnesium sulfate group (she was discharged in good general condition). One infant in the magnesium sulfate group and three infants in the control group required neonatal resuscitation (oxygen administration only), and five infants in the magnesium sulfate group and seven infants in the control group were transferred to the NICU within the first 24 h of delivery. All infants had a five-minute Apgar score of 9 or 10.

Table 1 Baseline characteristics of participants by study group

Characteristics	Magnesium Sulfate (n = 49)	Placebo (n = 49)
Age (years), Mean (SD)	25.9 (5.0)	27.8 (5.2)
Education (years), n (%)		
1–5	12 (24.5)	8 (16.3)
6–8	14 (28.6)	20 (40.8)
9–12	19 (38.8)	16 (32.7)
University	4 (8.2)	5 (10.2)
Household income, n (%)		
Much less than enough	4 (8.2)	2 (4.1)
Slightly less than enough	11 (22.4)	12 (24.5)
Enough	34 (69.4)	35 (71.4)
Occupation, housewife, n (%)	47 (95.9)	49 (100)
Not using addictive substances, n (%)	48 (98.0)	47 (95.9)
Body mass index (kg/m^2), Mean (SD)	24.3 (3.5)	23.8 (4.4)
Gestational age (weeks), Mean (SD)	39.3 (1.0)	39.2 (1.0)
Nulliparity, n (%)	16 (32.7)	16 (32.7)
Interval of current and previous delivery, (years), Mean (SD)[a]	5.0 (2.3)	6.0 (3.0)
Unintended pregnancy, n (%)	12 (24.5)	14 (28.6)
Satisfied with the gender of the fetus, n (%)	44 (89.8)	46 (93.9)
Attendance at birth classes, yes, n (%)	8 (16.3)	4 (8.2)
Induced labor, n (%)	18 (36.7)	18 (36.7)
Drugs used during labor before the intervention, n (%)		
Oxytocin (5 IU/500 mL serum)	38 (77.6)	35 (71.4)
Misoprostol (50 µg, sublingual)	0 (0)	1 (2)
Pethidine	7 (14.3)	8 (16.3)
Remifentanil	0 (0)	1 (2.0)
Promethazine	9 (18.4)	10 (20.4)
Hyoscine	4 (32.7)	3 (24.5)

[a] For multiparous cases (33 women in each group)

Table 2 Comparison of the groups in terms of primary outcomes

Outcomes	Magnesium Sulfate		Placebo		Comparison between groups	
	n	Mean (SD)	n	Mean (SD)	MD (95% CI)	*P* value [a]
Intervention to delivery duration (h)[b]	49	1.59 (1.05)	49	2.93 (1.62)	-1.34 (-1.88 to -0.79)	< 0.001
Total score childbirth experience (1–4)[c]	48	3.1 (0.5)	47	2.3 (0.7)	0.84 (0.59 to 1.08)	< 0.001

SD standard deviation; *MD* mean difference; *CI* confidence interval

[a] Independent-samples t-test

[b] Analyzed for those who had vaginal delivery

[c] Assessed using Childbirth Experience Questionnaire 2.0 (CEQ2); the higher the score, the more positive the experience; 1 case of magnesium sulfate group and 2 cases of placebo group were excluded from the analysis due to loss to follow-up

Discussion

To our knowledge, this is the first trial to examine the effect of topical magnesium sulfate on the childbirth experience and one of the few to examine the effect of this intervention on the duration of the active phase of labor. This study showed that topical use of magnesium sulfate decreased the duration of the active phase of labor and enhanced the positive childbirth experience.

Table 3 Comparison of the groups in terms of the secondary outcomes

Outcomes	Magnesium Sulfate		Placebo		Comparison between groups	
	n	Mean (SD)	n	Mean (SD)	MD (95% CI)	*P* value
Pain intensity (0–10)[c]						
Baseline	49	7.0 (2.6)	49	6.1 (2.3)	0.9 (-0.08to1.9)	0.071[a]
1 h after the intervention[*]	33	7.4 (2.4)	45	8.8 (1.9)	-1.5 (-2.4 to -0.5)	0.003
2 h after the intervention[*]	12	7.7 (1.7)	33	8.7 (1.9)	-1.0 (-2.2 to 0.2)	0.116
3 h after the intervention[*]	7	7.1 (3.0)	22	9.1 (2.0)	-2.1(-4.1 to -0.1)	0.040
Bishop score (0–13)[b]						
Baseline	49	4.9 (0.9)	49	4.8 (0.9)	0.08 (-0.3 to 0.4)	0.663[a]
1 h after the intervention	49	12.0 (1.5)	49	10.0 (2.3)	2.0 (1.2 to 2.8)	< 0.001
Labor duration (min)						
Second stage[d]	46	17.4 (14.6)	42	17.7 (14.7)	-0.2 (-6.5 to 5.9)	0.935 [a]
Third stage	49	6.3 (4.3)	49	7.2 (4.3)	-0.9 (-2.6 to 0.8)	0.293 [a]
Delivery Fear Scale (DFS) (10–100)[c]						
Baseline	49	52.7 (15.2)	49	51.4 (16.1)	1.4 (-4.9 to 7.6)	0.666[a]
1 h after the intervention	49	44.2 (22.3)	49	67.0 (19.5)	-23.1 (-31.1 to -15.2)	< 0.001
Wijma Delivery Expectancy/Experience- B (WDEQ-B) (0–165)[c]						
2 h after delivery	49	59.2 (25.6)	49	71.2 (23.5)	-12.0 (-21.8 to -2.1)	0.018[a]
5 weeks after delivery	48	47.8 (27.1)	47	85.1 (28.3)	-37.3 (-48.6 to -26.0)	< 0.001[a]
Birth satisfaction scale- revised (BSS-R)[c], (0–40)	49	24.9 (6.0)	49	23.2 (6.3)	1.6 (-0.8 to 4.1)	0.189[a]
Hemoglobin (mg/dL)						
Baseline	49	12.6 (1.4)	49	12.4 (1.2)	0.3 (-0.3 to 0.8)	0.322[a]
12–24 h after delivery	49	11.7 (1.4)	49	11.3 (1.3)	0.2 (-0.2 to 0.6)	0.302
Hematocrit (%)						
Baseline	49	37.3 (3.4)	49	36.6 (2.5)	0.7 (-0.5 to 1.9)	0.243[a]
12–24 h after delivery	49	34.6 (3.5)	49	33.7 (3.1)	0.7 (-0.4 to 1.8)	0.213

SD standard deviation; *MD* mean difference; *CI* confidence interval

[a] Independent t-test, Univariate General Linear Model tests adjusted for the baseline values for the other comparisons

[b] The higher score indicates the more ripening of the cervix. The Bishop score was considered 13 for the cases that had normal vaginal delivery in less than 1 h (16 cases from the magnesium sulfate group, 4 cases from the placebo group)

[c] Higher scores indicate greater pain/fear and satisfaction with the childbirth experience

[*] Those who gave birth before the evaluation time were excluded from the analysis

[#] All (those who had vaginal or cesarean section) were included in the analyses, except the ones lost to follow-up (1 case from the magnesium sulfate group, 2 from the placebo group)

[d] Analyzed for those who had a normal delivery

The result regarding the positive effect of magnesium sulfate on reducing the duration of the active phase of labor is consistent with the results of previous trials conducted by Heydari et al. in Tehran [16] and Fakour et al. in Rasht [21], Iran. Similar to the current trial, Heydari et al. [16] performed the intervention only once, at the beginning of active labor. However, Fakour et al. [21] performed the intervention three times (at dilatations of 5–6, 7–8, and 9–10 cm) by pouring 10 mL of magnesium sulfate or distilled water on the cervix each time. The almost identical effect (average reduction of 1 to 1:30 h) in these studies may indicate that the use of multiple doses will not have a significant effect on this outcome. To conclude in this field, it is necessary to conduct trials to compare magnesium sulfate in a single application with multiple applications.

The previous trials [16, 21] were conducted on primiparous women, while the current trial was conducted on both primiparous and multiparous women with up to two deliveries. The limited sample size of the present study prevented us from conducting a subgroup analysis to examine the interaction effect of parity and the intervention. However, the similarity between effect sizes in the present study and previous trials may suggest that birth history has no interaction effect. It is recommended, however, that the interactive effect of having a

history of delivery on the effect size be investigated in future trials or a review of trials.

The results of the present study regarding the effect of magnesium sulfate on improving childbirth experience may be related to the effect of the intervention in reducing the duration of the active phase of labor. Previous research has also shown a negative correlation between the duration of labor and the childbirth experience score [5]. However, it should be considered that other variables, such as pain reduction, could also have influenced this finding.

The results of the secondary outcomes of the current study can generate hypotheses for further investigation in future studies. However, due to the increased error due to multiplicity, it is impossible to accurately comment on them in this study. Below is a brief explanation of some of them.

Consistent with the trial conducted by Heydari et al. [16], the present investigation showed that magnesium sulfate had no significant effect on the duration of the second and third stages of labor. However, the results of Fakour et al. trial showed that administration of magnesium sulfate was associated with a shorter second stage of labor. This effect is probably related to the more frequent (three times) use of magnesium sulfate in the trial of Fakour et al.

The current study's results that magnesium sulfate significantly reduced pain one and three hours after the intervention are consistent with those of the trial by Fakour et al. [21]. Also, according to a review of interventional and observational studies, the analgesic effect of intrathecal or epidural magnesium administration during labor has been documented with moderate certainty of evidence [33]. It was impossible to investigate the pain intensity at all planned time points for a substantial number of participants because they had already given birth before the time points. The limited sample size, especially in the intervention group, maybe a reason for the lack of a statistically significant effect on pain intensity at the two hours following the intervention.

The strengths of this study include low risk of biases such as selection bias (due to the study's proper randomization process), performance and detection biases (due to the double-blind design), and reporting bias (due to the complete reporting of results of all primary and secondary outcomes and preplanned data analyses). Also, the few (only three) losses to follow-up regarding the outcome of the childbirth experience reduce the risk of attrition bias in this result. Although we assessed the outcome of intervention to delivery duration in all participants, the relatively higher number of emergency cesarean sections in the control group compared to the sulfate group (7 vs. 3) may have influenced the effect of the intervention on the outcome of the duration of labor. The 30-min cut-off for asking the participants to lie down on the bed following the intervention, as well as for repeating the intervention in case of membrane rupture was based on the recommendations of the previous trials [16, 22], due to the lack of scientifically approved cut-off. The best cut-off should be investigated in future studies. The administered medicine may leak while repositioning the participants on the bed or when sneezing or coughing. Therefore, it is recommended to use gauze or small pads impregnated with magnesium sulfate or distilled water or cervical dilators impregnated with these substances in future studies.

The relatively high eligibility criteria and the fact that the study was conducted in only one teaching hospital may limit the generalizability of its findings. Previous trials assessing the effect of the intervention have also been conducted in Iranian teaching hospitals. As reported in the results, several medicines affecting the progress of labor are abundantly used in Iranian delivery wards for women in labor. Such conditions in the study setting may have influenced the findings. Therefore, future studies should be conducted in diverse settings and with fewer eligibility requirements to maximize the generalizability of the results.

Although we assessed and reported the frequency of cesarean section, Apgar score of less than seven at five minutes, NICU admission, and other adverse events by groups in this trial, it was not possible to examine the effect of the intervention on such key outcomes, due to the need for a large sample size. Detailed investigation and reporting of these key outcomes and adverse events are also necessary in future studies. Systematic reviews and meta-analyses performed on such data from individual trials can draw conclusions regarding the effect of the intervention on such outcomes. Additionally, we did not assess the long-term effects of the intervention in this study which should be investigated in future studies.

Conclusions

According to the results of this trial, pouring 10 mL of 50% magnesium sulfate on the cervix at the beginning of the active phase of labor probably reduces the duration of labor and improves the positive childbirth experience. If these results are confirmed by additional studies in different contexts and we obtain high-certainty evidence about the efficacy and safety of this method, its use as a low-cost method applicable to all levels of birth attendants will significantly help to facilitate vaginal delivery and make it pleasant.

Abbreviations

DFS	Delivery Fear Scale
WEDQ-VB	Wijima Delivery Expectancy Questionnaire Version B

BSS-R	Revised Scale of Satisfaction with Delivery
FOC	Fear of childbirth
ART	Assisted reproductive technology
BMI	Body mass index
VAS	Visual Analog Scale
MD	Mean difference
SD	Standard deviation

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12884-024-06831-2.

Supplementary Material 1.

Acknowledgements
This report has been extracted from a research project of the thesis of an MSc student in midwifery. We thank all women who participated in this study, as well as the Clinical Research Development Unit, Taleghani Hospital, Tabriz University of Medical Sciences, Tabriz, Iran for their kind support and the staff of the hospital for their cooperation.

Authors' contributions
SMAC and SR: conception and design of the study, analysis, and interpretation of data, manuscript writing. SR, SM: acquisition of data for the work. MM, SM: Design of the work. All authors contributed essentially to the manuscript editing, final approval of the last version, and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding
This work was supported by the Research Vice-Chancellor of Tabriz University of Medical Sciences, Iran [Grant no 68196]. Sakineh Mohammad-Alizadeh-Charandabi received this grant. The funding center had no role in the study design, collection and analysis of data, writing of this manuscript, or decision on where to submit the manuscript.

Availability of data and materials
The dataset supporting the conclusions of this article is included within the article (and its additional file).

Declarations

Ethical approval and consent to participate
This trial was approved (IR.TBZMED.REC.1400.726) by the Committee of Medical Ethics of Tabriz University of Medical Sciences (October 25, 2021) and registered at the Iranian Center for Clinical Trial with the IRCT20100414003706N40 code (21/11/2021). We obtained informed written consent from all participants before their recruitment. We designed and conducted this study following the Helsinki Declaration.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interest

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Received: 24 September 2023 Accepted: 14 September 2024
Published online: 30 October 2024

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