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ORIGINAL ARTICLE

Efficacy of methylergometrine during the early puerperium: a randomized double-blind placebo-controlled clinical trial

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ABSTRACT

Objective: To determine if oral methylergometrine administration during the first 10 d following spontaneous vaginal delivery has any beneficial effect on the increase of hemoglobin levels.

Methods: This was a parallel group double-blind placebo-controlled clinical trial conducted at single center university hospital in Italy. Participants were puerperal women, who delivered singleton gestation with spontaneous vaginal delivery at term. Participants were randomized into a 1:1 ratio to receive either 0.125 mg methylergometrine *per os* twice a day or placebo for 10 d. Hemoglobin levels were recorded on the day of delivery and after 10 d. The primary outcome was the variation in hemoglobin levels between the first and the 10th day of treatment.

Results: From December 2012 to October 2015, 220 agreed to take part in the study, underwent randomization, and were enrolled and followed-up. Of the randomized women, 110 (50%) were randomized to the methylergometrine group and 110 (50%) to the placebo group. No women were excluded after randomization or lost to follow-up (100%). We found no significant difference in the median variation of hemoglobin levels between the intervention and the placebo group

Conclusions: The use of 10 d oral methylergometrine in puerperal women was not associated with any benefit in the variation of hemoglobin levels from delivery to 10 d after delivery.

KEY MESSAGE

Methylergometrine in puerperal women was not associated with any benefit.

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KEYWORDS
Bleeding; breastfeeding; hemoglobin; maternal mortality; postpartum hemorrhage

Introduction

Methylergometrine is an ergot derivative belonging to the group of oxytocic drugs, which enhance uterine motility. Parenteral administration of these agents during the third stage of labor has been shown to be effective in reducing the maternal blood loss [1]. In this setting, the use of methylergometrine or oxytocin leads to comparable effects [1].

Only few studies have investigated the routine use of prophylactic methylergometrine during the puerperium for reducing bleeding during the postnatal period [2–10]. A Cochrane meta-analysis reported that "there was insufficient evidence to support the use of prophylactic oral methylergometrine given after delivery" [7], concluding that large, well-designed, placebo-controlled randomized clinical trials are warranted.

Thus, the hypothesis of this trial was that in puerperal women the use of 10-days prophylactic oral methilergometrine would reduce bleeding during the postnatal period.

Materials and methods

Study design and participants

This was a single-center parallel group randomized clinical trial of puerperal women, who delivered singleton gestation with spontaneous vaginal delivery at term, and who were randomized to receive either methylergometrine or placebo at University of Naples "Federico II" (Naples, Italy) from December 2012 to October 2015.

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The trial was approved by the local ethics committee (Prot. No. 75/10 approved on 23.06.2010). All participants in the trial provided written informed consent.

Inclusion criteria were 18–50 years of age, spontaneous vaginal delivery at term, singleton gestations, low risk pregnancy, fetal weight between 2800 and 3800 g, hemoglobin levels the day of the delivery >10 g/dL.

Exclusion criteria were: high-risk pregnancy (e.g. hypertension disorder, cardiovascular disease, IUGR), preterm delivery, operative delivery, prior cesarean delivery, history of postpartum hemorrhage in a prior pregnancy, retained placenta at delivery, severe perineal trauma (either third- or fourth-degree laceration) at delivery, episiotomy at the time of delivery, unknown or ≤10 g/dL hemoglobin levels the day of the delivery, established postpartum hemorrhage (i.e. blood loss >500 mL) at the time of delivery.

Eligible women were those who delivered singleton gestation at term with spontaneous vaginal delivery. Consented women were randomized soon after the delivery. All randomized women received a complete blood count 2 h and 10 d after delivery. All included women received active management of the third stage of labor, as per our protocol. Active management of the third stage of labor included prophylactic oxytocin and controlled cord traction, as these interventions have been proven to be effective and are considered standard of care [11–14].

Randomized women received either 0.125 mg methylergometrine *per os* twice a day for 10 d starting 12 h after delivery, or placebo. The capsules were identical regarding color, shape, size, and packing. The methylergometrine were manufactured by Novartis Farma SpA. The placebo was prepared by Pierrel Research IMP, Cantù, Italy.

Randomization and masking

Eligible participants were randomly allocated in a 1:1 ratio to either methylergometrine or placebo. Women were randomized by a web-based system. The randomization sequence was prepared by an independent statistician. Clinicians did not have advance access to the randomization sequence. Participants, outcome assessors, data collectors, and data analysts were blinded to the allocated treatment group. Assessment of the outcomes and outcome collection were made by clinicians not involved in the clinical trial and reported in a form with only the trial ID as identifier. The data analyst was blind until the entire analysis was completed.

Management of the enrolled women

A complete blood count was performed 2 h and 10 d after delivery. A total of 5 mL blood was collected in EDTA Vacutainer® Tubes from each patient. All specimens were processed using an Automated Hematology Analyzer (Advia 2120i, Siemens Healthcare, Berlin, Germany) within 30 min of the blood being drawn. A transabdominal ultrasound with calculation of uterine volume was performed 1 d and 10 d after delivery. All the ultrasound scans were performed on a Voluson 730 Expert machine using a convex probe RealTime 4D and a 4–8 MHz transducer (GE Healthcare, Chalfont St Giles, United Kingdom). The uterus was assessed in the transverse and the sagittal plane and its volume was calculated according to the ellipse formula [(length × transverse diameter × fundal anteroposterior diameter)/3 × 0.5233].

Outcomes

The primary outcome was the variation in hemoglobin levels between the first and the 10th day of treatment.

The prespecified secondary outcomes were the variation in uterine volume between the first and the 10th day of treatment, and the incidence of postpartum endometritis. Endometritis was defined as temperature greater than 37.5 °C with one or more symptoms or signs: uterine tenderness, maternal tachycardia greater than 100 bpm, purulent or foul-smelling cervical discharge or maternal leukocytosis greater than 12,000 cells/mL^3.

Sample size calculation

The calculation of the sample size was based on the following considerations: in the 10 d following a spontaneous vaginal delivery, hemoglobin level shows usually an increase of approximately 1.5 g/dL with a SD of ±3, in comparison with immediate postpartum values.

From a clinical point of view, we would consider useful a treatment that allows an increase of hemoglobin 1.5 g/dL greater than placebo.

We determined that a sample size of 220 (110 per group) patients would provide a power of 80% with a two-sided type 1 error of 5%.

Statistical analysis

Data are shown as means, or as number (percentage). Univariate comparisons of dichotomous data were performed with the use of the Chi-square test with continuity correction. Comparisons between groups were performed with the use of the *T*-test to test group

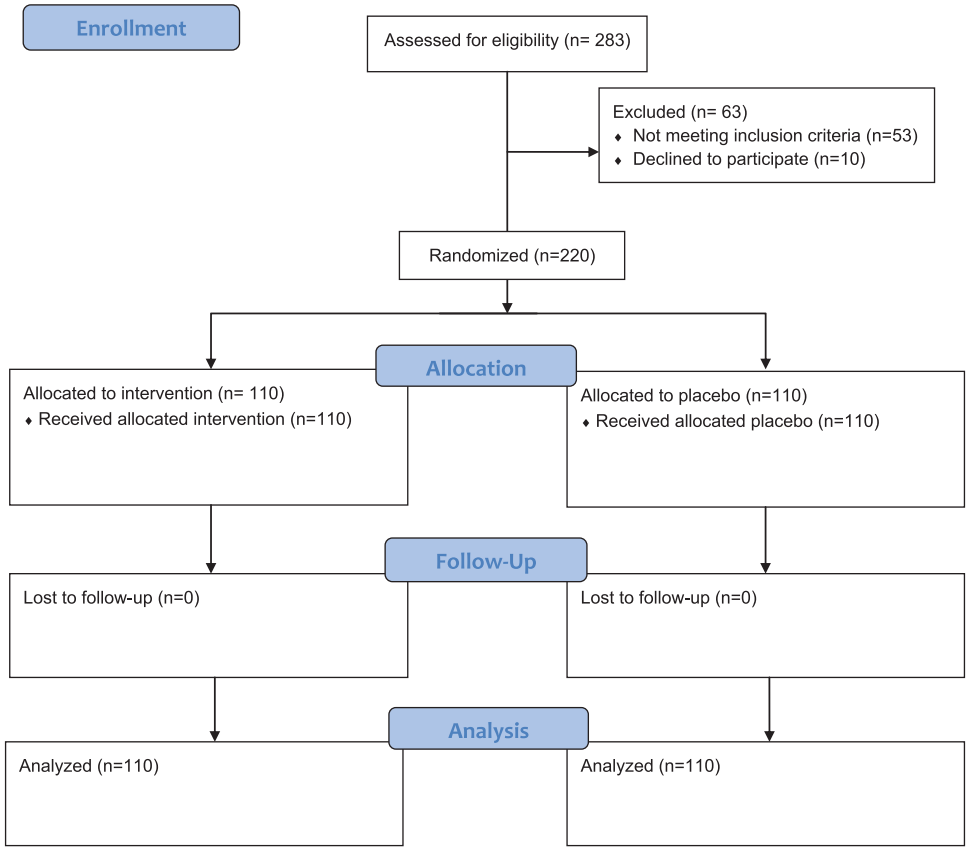

Figure 1. Study flow chart.

means by assuming equal within-group variances. The primary analysis was an intention to treat comparison of the treatment assigned at randomization. A two-sided *p* value less than .05 was considered significant. Statistical analysis was performed using statistical package for social sciences (SPSS, Chicago, IL) v. 19.0 (IBM Inc., Armonk, NY).

Results

From December 2012 to October 2015, 220 women agreed to take part in the study, underwent randomization, and were enrolled and followed-up (Figure 1). Of the randomized women, 110 (50%) were randomized to the methylergometrine group and 110 (50%) to the placebo group. No women were excluded after randomization or lost to follow-up (100%).

Table 1 shows the baseline demographic and clinical characteristics for each group. The two groups were similar in terms of maternal demographics.

After 10 d, no significant differences were found in the variation in the hemoglobin level or in the variation of the uterine volume between the two groups (Table 2). No cases of endometritis were reported in either group.

Discussion

This randomized double-blind placebo-controlled clinical trial showed that use of 10-d prophylactic oral methylergometrine in puerperal women was not associated with any benefit in the variation of hemoglobin levels from delivery to 10 d after delivery. Strengths of the study included the use of placebo as control, the study design, and the blinding of participants and personnel. We achieved exactly our trial registry planned sample size of 220 women, with no over, or under-recruitment, 100% follow-up and 100% compliance with treatment allocation in both groups.

Few studies have been performed on the use of methylergometrine during puerperium. Klug et al. [4]. and Arabin et al. [2] did not found any benefit in the prophylactic oral use of methylergometrine in the early puerperium. They also found that this intervention was associated with an increased incidence of severe uterine cramps, endometritis, and pelvic pain [2]. Iatrakis et al. [5] compared single dose versus multiple doses of methylergometrine after delivery, finding a reduction in the rate of endometritis in the intervention group. Our trial concurred with the prior literature and provided evidences that prophylactic oral use of methylergometrine in the early puerperium was not associated with

Table 1. Characteristics of the included women.

	Methylergometrine ($n = 110$)	Placebo ($n = 110$)
Age (year)	31 ± 2.9	31 ± 3.1
Parity	0–3	2 (0–3)
Smoking	17 (15.5%)	16 (14.5%)
Perineal lacerations		
First-degree	23 (20.9%)	22 (20.0%)
Second-degree	17 (15.5%)	17 (15.5%)
Birthweight (g)	3310 ± 352	3285 ± 361
BMI	23.5 ± 5.0	23.2 ± 4.5
Gestational age at randomization (weeks)	39.5 ± 0.1	39.4 ± 0.1

Data are shown as mean ± standard deviation or as median (range) or as number (percentage).

Table 2. Primary and secondary outcomes.

Placebo ($n = 110$)	Methergine ($n = 110$)	p Value[a]
Hemoglobin after 2 h		
12.1 ± 1.0	12.3 ± 0.8	.32
Hemoglobin after 10 d		
12.1 ± 1.0	12.2 ± 0.8	.64
Variation of hemoglobin levels (g/dL)[a]		
−0.1	−0.2	.53
[−0.174; 1.109]	[−0.227; 0.018]	
Uterine volume after 24 h		
651.7 ± 167.2	651.9 ± 154.1	.12
Uterine volume after 10 d		
321.4 ± 89.4	329.2 ± 103.9	.63
Variation of uterine volume (cm^3)		
−315.2	−309.0	.64
[−358.5; −305.5]	[−342.4; −300.0]	

[a]Primary outcome.

any benefits. Notably, ergot derivatives may also induce coronary spasm [8,10,15]. Serious ischemic cardiac events related to these drugs are rare and have most often been described after intravenous use. However, recently, at least two cases of myocardial infarction after oral administration of methylergometrine have been reported [8,10]. Therefore, a judicious use of ergot alkaloids seems mandatory.

Conclusions

In conclusion, the use of 10-d prophylactic oral methylergometrine in puerperal women was not associated with any benefit in the variation of hemoglobin levels.

Ethics approval

The study was approved by the human subjects committee at University of Naples "Federico II".

Disclosure statement

No potential conflict of interest was reported by the authors.

Costantino Di Carlo, the lead author, affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. He had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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