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Effect of melatonin on postpartum hemorrhage in vaginal delivery: a prospective randomized double-blind study

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ABSTRACT

Background. The similarities between the melatonin and oxytocin signaling could promote myometrium contractility. We conducted this study to determine the effect of melatonin on the bleeding during and after vaginal delivery.
Methods. The current double-blind randomized clinical trial was conducted on 140 pregnant women at term with labor pain. Subjects in the melatonin group received three sublingual doses of melatonin from labor room staff as follows: 6 mg in 7 cm dilatation, 3 mg after delivery of the fetus and 3 mg one hour after the delivery. The same schedule was conducted for the subjects in the placebo group by giving the placebo. The hemoglobin levels before and 24 hours after vaginal delivery, the hemodynamic variables were recorded.
Results. There was a significant difference between the groups regarding the mean of hematocrit changes in the melatonin (3.59 ± 2.89) and placebo (5.29 ± 3.19) groups (P = 0.001). The mean variation of systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) show a significant difference among two groups of the study (P = 0.021, P = .020 and 0.001, respectively).
Conclusions. The sublingual of melatonin to pregnant women with labor pain could reduce the amount of blood loss after the vaginal delivery. Furthermore, melatonin could provide hemodynamic stability.

SOMMARIO

Contesto. Le somiglianze tra il signaling di melatonina e ossitocina potrebbero promuovere la contrattilità del miometrio. Abbiamo condotto questo studio per determinare l'effetto della melatonina sul sanguinamento durante e dopo il parto vaginale.
Metodi. L'attuale studio clinico randomizzato in doppio cieco è stato condotto su 140 donne in gravidanza a termine con dolore del travaglio. I soggetti nel gruppo della melatonina hanno ricevuto tre dosi sublinguali di melatonina dal personale della sala travaglio come segue: 6 mg con una dilatazione di 7 cm, 3 mg dopo il parto e 3 mg un'ora dopo il parto. Lo stesso programma è stato condotto per i soggetti nel gruppo placebo somministrando il placebo. Sono stati registrati i livelli di emoglobina prima e 24 ore dopo il parto vaginale e le variabili emodinamiche.
Risultati. C'era una differenza significativa tra i gruppi per quanto riguarda la media dei cambiamenti dell'ematocrito nei gruppi melatonina (3,59 ± 2,89) e placebo (5,29 ± 3,19) (P = 0,001). La variazione media della pressione sanguigna sistolica (SBP), della pressione sanguigna diastolica (DBP) e della frequenza cardiaca (HR) mostra una differenza significativa tra i due gruppi dello studio (P = 0,021, P = .020 e 0,001, rispettivamente).
Conclusioni. La somministrazione sublinguale di melatonina alle donne in gravidanza con dolore del travaglio potrebbe ridurre la quantità di perdita di sangue dopo il parto vaginale. Inoltre, la melatonina potrebbe fornire stabilità emodinamica.

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Key words
Melatonin; hemorrhage; vaginal delivery; postpartum hemorrhage.

INTRODUCTION

Postpartum hemorrhages still one of the main causes of maternal death. Oxytocin is routinely prescribed by obstetricians to prevent and treat postpartum hemorrhages due to uterine atony after delivery. However, it may be insufficient for prevention of postpartum hemorrhage (PPH), for example in patients who have hepatorenal disease, psychotic disorders, chronic anemia, allergy to melatonin, long-term antidepressant or analgesic drug use. Oxytocin may cause severe cardio-vascular complications, such as hypotension, due to vasodilation, especially in high doses (1). Melatonin, N-acetyl-5-methoxy tryptamine, is a methoxyindole derived from tryptophan and totally secrets by hypophysis. Melatonin secrets rhythmically every day and stimulates by the suprachiasmatic nucleus of the hypothalamus. This hormone almost exists in all tissues (with or without receptor) of mammalian; this hormone acts as growth hormone and antioxidant (2). Melatonin can regulate circadian rhythm; it is sedative, pain reliever and has anti-inflammatory and anti-oxidant effects which encourage obstetricians to prescribe it (2). It is hypothesized that melanin and oxytocin could cause augmenting the overnight contractions of term uterus. In other word, melatonin synergizes with oxytocin to promote contractility of human myometrial smooth muscle cells (3, 4). It is reported that melatonin levels increase in maternal blood, amniotic fluid and urine of pregnant women throughout pregnancy, reaching a peak at term (5). The beneficial effect of melatonin in placental and fetal well-being is reported (5-9). Melatonin specially causes the circadian rhythms and helps fetal growth and neurogenesis, while no adverse fetal or neonatal outcomes have been reported. Furthermore, it is shown melatonin repairs the injury with regrowth of axons and possesses neonatal cerebral protection and it could induce the condition to reestablish periventricular white matter which may be associated with the enhancement of learning ability (5-9). In previous study, it is shown premedication of patients with 6 mg sublingual melatonin statistically reduced the amount of blood loss after lower segment cesarean section, which may not be clinically meaningful (10).

The use of melatonin as an anxiolytic agent has been studied in several humans and animals (2, 11), but to the best of our knowledge, this study is the first in which the effect of melatonin has been estimated on the amount of blood loss after vaginal delivery. Hence, the current randomly controlled clinical trial aimed to evaluate the effect of melatonin on the amount of bleeding during and after vaginal delivery.

METHODS

Following Ethics Committee approval and informed patients' consent, 154 pregnant females whose age ranged between 18-40 years with American Society of Anesthesiologists (ASA) physical status of I or II who had been referred to the hospital due to spontaneous labor pain and were the candidates for vaginal delivery were recruited in a prospective, double-blinded randomized controlled trial in 2014-2015. The patients were randomly allocated to one of the two groups to receive either three sublingual doses of melatonin from labor room staff as follows: 6 mg in 7 cm dilatation, 3 mg after delivery of the fetus and 3 mg one hour after the delivery. The same schedule was conducted for the subjects in the control group by giving the placebo. Exclusion criteria were significant coexisting conditions such as hepatorenal disease, psychotic disorders, chronic anemia (hemoglobin Hb < 10 g/dl) cardiovascular disease, allergy to melatonin, long-term antidepressant or analgesic drug use, any risk factor associated

with an increased risk of postpartum hemorrhage, labor dystocia, distended uterus (macrosomia and multiple births), chorioamniotite and parity > 4, administration of uterine relaxants (halogenated anesthetic agents, beta-adrenergic agonist (sympathomimetic) and $MgSO_4$), those who were under the induction of labor and patients who needed blood transfusions (after receiving the required blood) excluded from the study. Also, subjects who needed other drugs besides oxytocin to control postpartum bleeding, those who undergone cesarean or even needed blood transfusions were excluded from the study. Consolidated Standards of Reporting Trials (CONSORT) recommendations for reporting randomized, controlled clinical trials were charted (**figure 1**). The randomization was commenced using computer-generated random numbers in the closed opaque envelopes. The allocation was achieved by a resident physician who was out of the project and the drugs given by a nurse non-involved in the study. The obstetrician was blinded to the patient's group allocation, and a blinded observer recorded the study data. According to the routine protocol in the delivery section of our Hospital, all of patients received intravenous infusion of oxytocin 20 units of oxytocin in 1 L of ringer lactate with speed of 1000 CC/h immediately after clamping the umbilical cord. The main outcome measures were the estimated of blood loss at vaginal delivery and change in hemoglobin levels. Since the difference of Hb provides a more accurate assessment of actual blood loss during vaginal delivery, than visual estimation, we determined the hemoglobin value before and 24 h following the vaginal delivery. Apgar score and hemodynamic variables after delivery were recorded. Sample size was calculated based on the change in hemoglobin level before (Hb1) and 24 h after vaginal delivery (Hb2) in a pilot sample of 20 patients. Considering 90% power and 5% error, the sample size was determined to be 60 cases in each group. We included 70 patients in each group to allow for dropouts and protocol violations. Data were analyzed using SPSS (SPSS 15.0, SPSS Inc., Chicago, IL, USA). Continuous variables were tested for normal distribution by the Kolmogorov–Smirnov test. Student's t test and paired t test were used for variables with normal distribution. Chi-square test was used to compare qualitative variables between

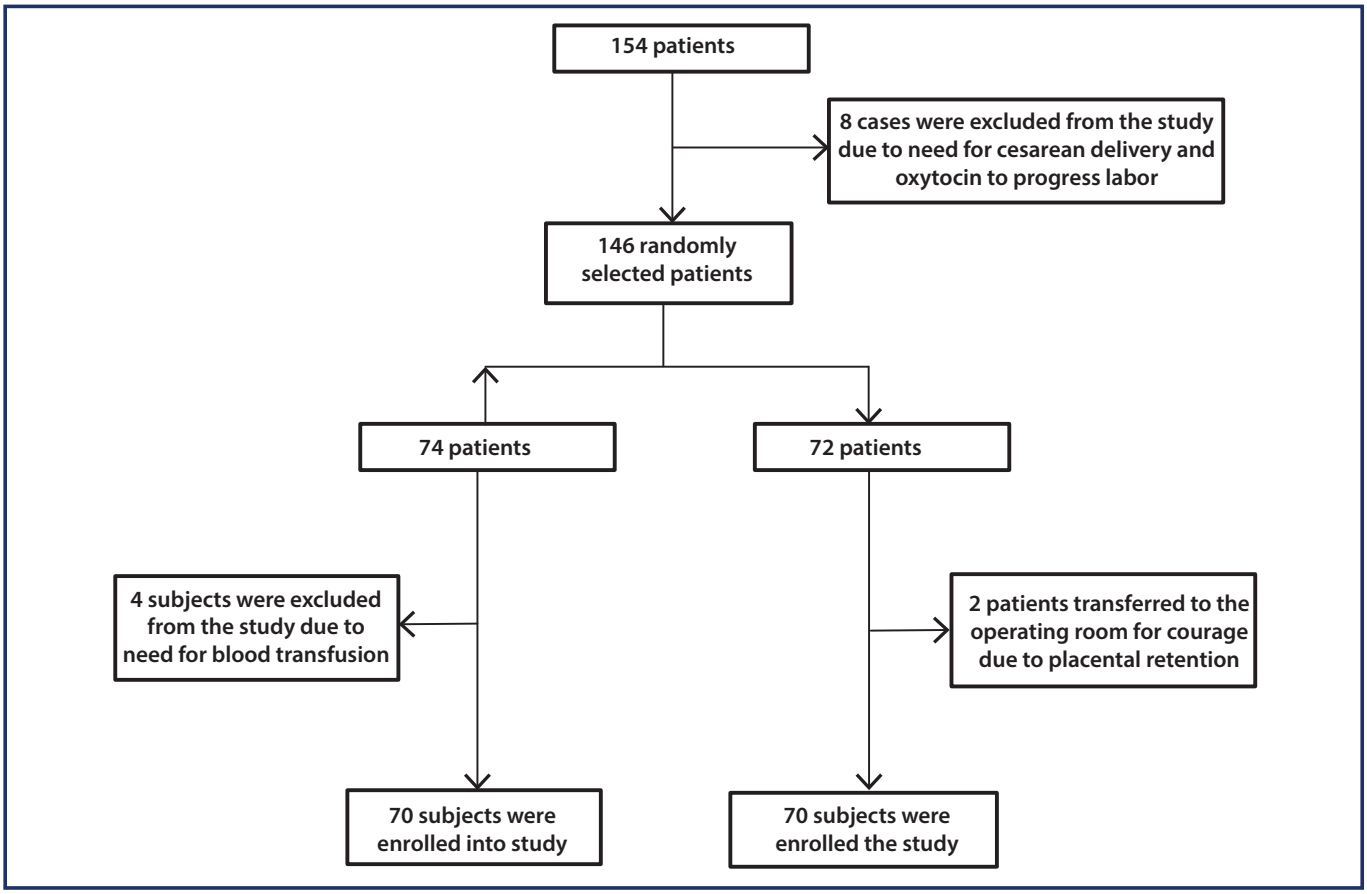

Figure 1. *Consort Flow diagram.*

groups. The P values of less than 0.05 were considered significant.

RESULTS

One hundred and fifty-four patients were recruited in the study of which 14 were excluded due to logistic reasons or other factors violating the study protocol (**figure 1**). **Table I** shows the mean age of the subjects in the intervention and the control groups was 26.19 ± 4.72 and 25.41 ± 4.74 years old, respectively (**table I**). As shown in **table I**, no significant difference was observed between the groups regarding the level of hemoglobin during the time of labor; while there was a significant difference in this regard after labor between the groups (11.53 ± 1.19 g/dL in the intervention and 11.05 ± 1.32 g/dL in the control groups) (P = 0.002). The mean variations of Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and heart rate (HR) were defined as the difference between the highest and the SBP, DBP and heart rate in each patient and compared between the groups. **Table II** shows that difference of SBP (P = 0.028) and DBP (P = 0.022) variation between two groups were significant. Also, as shown in **table II** the difference of mean HR variation between two groups were significant (P < 0.001). All new borns in our study were free of any adverse effect. The Apgar scores at first (P = 0.891) and five (P = 0.576) minutes after delivery in the two groups were statistically similar.

Table I. *Comparing the main outcomes between the Groups.*

Report	Group		P value
	Melatonin (n = 70)	Placebo (n = 70)	
	Mean ± SD	Mean ± SD	
Age (year)	26.19 ± 4.72	25.41 ± 4.74	.337
GA (week)	39.06 ± 1.04	39.04 ± 0.08	.928
Hemoglobin in labor (g/dl)	12.80 ± 1.04	12.65 ± 1.08	.417
Hemoglobin 24 h after delivery (mg/dl)	11.53 ± 1.19	11.05 ± 1.32	.026
HCT in labor (%)	37.56 ± 2.81	37.36 ± 2.67	.676
HCT after delivery (%)	33.96 ± 3.55	32.06 ± 3.70	.002
Change in HCT%	3.5929	5.2971	.001
Change in Hemoglobin (mg/dl)	1.2743	1.6057	.055
apgar1	8.79 ± 0.58	8.77 ± 0.64	.891
apgar5	9.91 ± 0.28	9.89 ± 0.32	.576
Placental removal (min)	2.08 ± .47	2.08 ± .47	1

Values are presented as mean ± SD.

DISCUSSION

Based on the data found in our study, we concluded that sublingual administration of melatonin to pregnant women with spontaneous labor pain could reduce the amount of blood loss after the vaginal delivery, although it may not be clinically meaningful. The estimation of blood loss during vaginal delivery remains a challenge. The measuring blood loss during the third stage of labor by visual estimation is inaccurate. The effectiveness of quantitative blood loss measurement on clinical outcomes has not been demonstrated. A more precise measurement of blood loss is hemoglobin concentration (Hb) in venous blood sampling. The difference of Hb provides a more accurate assessment of actual blood loss than visual estimation. However, to avoid of bias in this research, patients who needed blood transfusions, additional uterotonic agents, or surgical interventions were considered as exclusion factors. The results of present study partially are consistent with the results of previous study by Khezri *et al*., which conducted on patients undergoing cesarean section under spinal anesthesia (10). However, there were no differences regarding the hemodynamic conditions between the groups in the study by Khezri *et al*. The current study reported more stable hemodynamic conditions regarding the systolic and diastolic blood pressure ranges in the intervention group, in such a way that the changes were lower in the intervention group compared with those of the control group. The more stable hemodynamic variables in the current study in the melatonin group are a valuable finding. However, these effects may be dose-dependent. In

Table II. *Changes in hemodynamic variables.*

	Group		
	Melatonin	placebo	P value
Change Systolic blood pressure (mmHg)	4.1429	7.0000	.028
Change Diastolic blood pressure (mmHg)	2.1429	5.0000	.022
Change Heart rate (bpm)	1.4000	- 3.5143	.000

Values are presented as mean ± SD; SBP; systolic blood pressure (mmHg); DBP: diastolic blood pressure; HR; heart rate (bpm). The mean variation of MAP and HR was defined as the difference between the highest and the lowest mean arterial pressure and heart rate in each patient.

current study, we use the higher dose of melatonin compared to Khezri *et al*. study (10). This finding is consistence with the result obtained in the Ismail's (2) and Gupta's (12) studies in which a significant decrease in mean arterial pressure (MAP), after melatonin premedication, was reported. This effect may be related to the modulatory effect of melatonin on the cardiovascular function. Moreover, the hemodynamic effect of melatonin may be attributed to its anxiolytic actions. The underlying mechanism is probably the synergy between melatonergic and GABAergic systems. It also has analgesic effects as observed by various investigators and this may also contribute to the hemodynamic stability (2, 12).
According to the studies by Sharkey *et al*. (3) and Kumari *et al*. (4), the similar structures of melatonin and oxytocin receptors in vitro showed that free calcium increase in platelets after exposure to melatonin. Considering the role of calcium to control bleeding and the role of melatonin on increasing the amount of intracellular free calcium in platelets, it can be concluded that calcium-mediated melatonin can decrease bleeding (4). Calcium also plays a role in deformation, adhesion and aggregation of platelets (4, 13-15). Finally, calcium, in physiological concentrations, can improve platelet aggregations. Therefore, it can be concluded that the possible role of melatonin on blood restriction results from increasing the hemostatic activities in platelet aggregations (4, 13-15). Accordingly, changes in the level of hematocrit in the intervention group were lower than those of the control group, and hemostatic processes in the current study were performed more effective and finally led to decrease of bleeding. Furthermore, hemodynamic effect of melatonin can be considered as one of the explanation causes of bleeding reduction in the current study. The current study is the first trial which showed the effectiveness of melatonin on decreasing the level of bleeding in vaginal delivery. However, it is far too early to reach any definitive conclusions. Future studies are necessary to evaluate the effect of melatonin on the level of bleeding in vaginal delivery.

CONCLUSIONS

According to the results of the current study, it can be concluded that the sublingual administration of melatonin to pregnant women with spontaneous labor pain could reduce the amount of blood loss after the vaginal delivery. Furthermore, melatonin could provide hemodynamic stability. So, using melatonin, as a supplementary agent in vaginal deliveries is explainable due to favorable hemostatic and hemodynamic effects.

CONTRIBUTORS

The first author of this paper is Ezatossadat Haj SeyedJavadi, Associate Professor of Qazvin University of Medical Science, which responsible for conception and design of study. Mahor Kamali, Resident of Obstetrics and Gynecology as done acquisition of data and drafting the manuscript. Ameneh Barikani, Associate Professor of Community and preventive medicine who analyzed and interpreted the data and reviewed the manuscript. Professor Marzieh Beigom Khezri, Professor of Qazvin University of Medical Science, is the corresponding authors of this paper which responsible for conception and revising the manuscript critically for important intellectual content. Fatemeh Lalooha, Associate Professor of Qazvin University of Medical Sciences who cooperated in drafting and reviewing the manuscript.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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