

ORIGINAL ARTICLE

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As the number of cesarean sections increases, does the combined use of oxytocin and methylergonovine during the procedure affect postpartum hemorrhage? **Kemal Dinc***Erzincan Binali Yildirim University, Department of Obstetrics and Gynaecology, Erzincan, Türkiye*

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**Abstract**

In this study, we sought to demonstrate the benefit of postpartum hemorrhage prophylaxis treatment and the superiority of methylergonovine-oxytocin combination over oxytocin in terms of hemodynamic stability and amount of bleeding during cesarean section. In this retrospective study, 400 patients who had a cesarean section in the same clinic were divided into two groups and included in this study. The first group consisted of nulliparous patients (n=141) who gave birth by cesarean for the first time and the second group consisted of multiparous patients (n=259) who gave birth by cesarean section before. Then both main groups; women who received only oxytocin infusion in the intraoperative and postoperative periods were divided into (monotherapy group), women who received methylergonovine and oxytocin therapy in the intraoperative and postoperative periods were divided into 2 more subgroups (combined group). For comparison, samples for preoperative and postoperative complete blood counts were obtained from all patients in each group. When the postoperative Hb levels of nulliparous pregnant women were compared, it was seen that the decrease in Hb levels was less in the group that received methylergonovine in addition to oxytocin ($p=0.031$). Similarly, Hb decrease was observed less in the group given methylergonovine in addition to oxytocin in multiparous pregnant women ($p=0.045$). The group that received methylergonovine in addition to oxytocin provided more hemodynamic stability in both the nulliparous and multiparous cesarean section groups, which we divided according to the number of cesarean sections, compared to the group that received oxytocin; significantly reduced the level of bleeding. We think that this form of treatment will also reduce the risk of uterine atony; therefore (if there is no coronary disease) we recommend it to be used under spinal anaesthesia.

Keywords: Cesarean section, hemoglobin, methylergonovine, oxytocin, postpartum hemorrhage**Introduction**

Postpartum hemorrhage (PPH) is the most prominent cause of maternal morbidity and mortality worldwide and is also a preventable condition [1]. Although, by definition, it is accepted as bleeding more than 500ml after vaginal delivery and more than 1000 ml after cesarean in the literature, PPH causes the real bleeding to be ignored and makes it difficult to use in the clinic [2]. The most common complications observed in the first seven days after birth are bleeding from the abundance, hypertension and infection [3]. The most common cause of postpartum hemorrhage

is uterine atony bleeding, which occurs due to the inability of the uterus to contract properly after delivery [4]. Compared with vaginal delivery, the incidence of uterine atony is increased, especially during and after cesarean section [5]. It is still an important cause of maternal morbidity and mortality in both developing and developed countries [6].

Uterotonic drugs are used in prophylaxis to prevent PPH. Oxytocin, which is used for this purpose, is used as the first choice uterotonic drug to prevent and treat uterine atony [5]. Oxytocin exerts its therapeutic effect by contracting the uterus. This effect depends on the quantity and quality of the receptors on the uterus. In cases where this effect is not sufficient, other uterotonic drugs with different mechanisms can be administered instead of or in addition to oxytocin [7]. Methylergonovine is used as a second-line uterotonic agent in the prevention and treatment of PPH in cases where oxytocin is insufficient [5]. Methylergonovine is an ergot

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alkaloid that causes strong myometrial contractions. However, intravenous administration sometimes causes transient but severe blood pressure elevation [4]. According to some studies, the combination of methylergonovine and oxytocin has been shown to be more beneficial than oxytocin in preventing PPH [8]. However, due to the negative side effects of methylergonovine, it is used less frequently today to prevent PPH. The reason for this is that methylergonovine can cause a significant increase in morbidity and mortality due to its strong vasospasm [9].

The primary aim of this study was to investigate the efficacy of methylergonovine-oxytocin combination compared to oxytocin in cesarean section groups and to compare the methylergonovine-administered group with the oxytocin-administered group in terms of hemodynamic stability and bleeding amount.

Material and Methods

This study was planned and completed in accordance with the Declaration of Helsinki. Each participant provided detailed information and written informed consent was obtained about the study. Our study was approved by the university ethics committee (Ethics Committee Date: 29.04.2020, Issue: 05/26).

Our study was retrospectively planned and performed by scanning the files of 400 women who gave birth by cesarean section under spinal anesthesia in a regional Training and Research Hospital between January 2015 and January 2019. Inclusion criteria; age, 18-45; Pregnant women with cesarean section with a pregnancy greater than ≥ 34 weeks were included. Patients diagnosed with preeclampsia, patients receiving blood transfusion during pregnancy, patients with coagulation disorders, patients with anemia Hb < 7 g/dL, and patients with ischemic heart disease, cerebrovascular disease, and peripheral disease were excluded from the study. Vascular disease: Additional pregnant women with ischemic heart findings evaluated by an internist with electrocardiogram test (ECG) in the preoperative period were excluded from the study. Severe postpartum hemorrhage (SPPH) was defined as any of the following: Clinically, PPH (estimated blood loss ≥ 1000 ml) or Hb levels between pre- and post-cesarean section ≥ 3 g/dl, or need for blood transfusion [10].

Our study universe was divided into 2 main groups. The first group consisted of nulliparous patients (n=141) who gave birth by cesarean for the first time, and the second group consisted of multipar patients (n=259) who gave birth by cesarean section before. Then, both main groups were divided into 2 more subgroups according to the type of treatment as women who received oxytocin infusion only (monotherapy group) and women who received methylergonovine + oxytocin treatment (combined group) (Figure 1).

During the cesarean section, intravenous oxytocin infusion was administered to both groups in 500 mL ringer lactate, 20 units of 333 ml per hour and 1 L of ringer lactate 30 units per hour, 333 ml per hour, immediately after the placenta was removed. In addition, 0.2 mg methylergonovine was administered intramuscularly to the combined group during cesarean section, within the first minute after removal of the placenta, and at the 3rd hour postoperatively. When methylergonovine is administered intramuscularly, the duration of action is approximately 3 hours [11]. Preoperatively and 24 hours after surgery, all study participants were monitored

and their progress was recorded [12]. In all patients, hourly blood pressure and pulse, urine output and vaginal bleeding were routinely checked to determine PPH in the postoperative period. The blood hemoglobin levels were assessed using the Beckman method.

Statistical analysis

Statistical analysis was performed using SPSS 22.0 program (SPSS Inc., Chicago, IL, USA). A Student's t-test was used for between-group comparisons of parameters for evaluation of study data, which included descriptive statistical methods (Mean, Standard Deviation, Median, Frequency, Ratio, Minimum, and Maximum) and comparisons of quantitative data. Mann-Whitney U test was used for the comparison of the non-parametric variables. Paired samples t-test was used for preoperative and postoperative comparisons of normally distributed parameters. Significance was evaluated at the level of $p < 0.01$ and $p < 0.05$.

Results

The mean age of the patients participating in the study was 27.8 ± 4.9 years. Of the patients, 141 (35.25%) were nulliparous (pregnant women who gave with cesarean section birth for the first time), and 259 (64.75%) were multiparous (those who have more than one cesarean section). The study population was divided into two main groups, nulliparous and multiparous, and then divided into 2 subgroups as monotherapy and combined group, and the effect of methylergonovine was examined (figure 1). In the nulliparous patient group; When the mean age of the monotherapy subgroup and the combined subgroup were compared, the difference between them was not statistically significant ($p = 0.762$). Mean preoperative Hb levels in nulliparous women were different between monotherapy and combined treatment groups ($p = 0.039$). When compared in terms of postoperative Hb values in the nulliparous group, the Hb level of the combined treatment group was significantly higher than the monotherapy group ($p = 0.031$). These results show that the decrease in mean Hb level is less in nulliparous patients who received methylergonovine in addition to treatment in the postoperative period (Table 1).

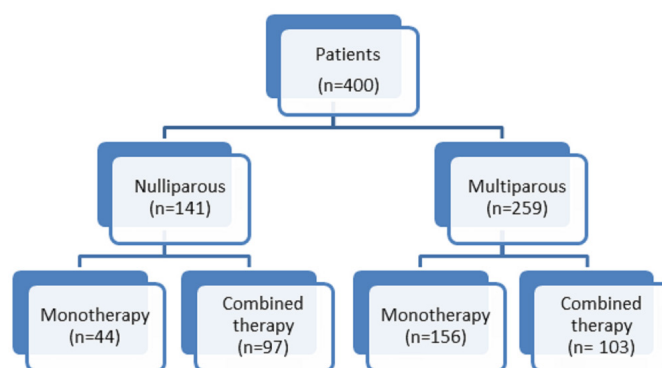


Figure 1. Working diagram

In multiparous women, preoperative mean Hb levels were similar in monotherapy and combined therapy groups ($p = 0.818$). In the postoperative period, the difference in mean Hb levels between the combined treatment and monotherapy groups in multiparous women was statistically significant, and the decrease in Hb was less in the combined group ($p = 0.045$). These results show that in both nulliparous and multiparous patients, there was less reduction

in postoperative Hb in the combined treatment group compared to the monotherapy group (Table 1).

When the groups were examined in terms of preoperative and postoperative Hb differences, the pre-postop Hb difference was less in the combined group than in the monotherapy group in

nulliparous patients ($p=0.047$). Similarly, when the multiparous patient group was examined, the pre-postop Hb difference was found to be less in the combined group ($p=0.012$) (Figure 2). According to these results, adding methylergonovine to the treatment in both nulliparous and multiparous patient groups reduces the pre-postop Hb difference.

Table 1. Comparison of Hb levels preoperatively and postoperatively between multiparous and Nulliparous subgroups in both therapy groups

Treatment	Nulliparous		p^*	Nulliparous Multiparous		p^*
	Monotherapy (n=44)	Combined (n=97)		Monotherapy (n=156)	Combined (n= 103)	
Age	25.9±5.0	26. 2±5.6	0.762	28.4±4.4	29.0±4.5	0.300
Hb preop	11.8±1.7	12.4±1.7	0.039	11.9±1.4	11.9±1.3	0.818
Hb post	10.2±1.5	11.0±1.5	0.031 ^a	10.4±1.3	10.6±1.3	0.045 ^a
p	<0.001	<0.001		<0.001	<0.001	

* Comparison of combine and oksitosin groups. a adjusted according to pre measurement

Table 2. Measurements of platelet values preoperatively and postoperatively in patients treated with combined therapy (methylergonovine and oxytocin) and in patients treated with oxytocin alone

	Nulliparous		p	Multiparous		p
	Monotherapy	Kombine		Monotherapy		
PLT pre	256.7±68.2	244.0±62.4	0.275	227.7±57.9	237.9±73.3	0.216
PLT post	224.0±66.5	211.2±52.8	0.550 ^a	198.0±55.3	203.6±65.0	0.398 ^a
p	<0.001	<0.001		<0.001	<0.001	

Comparison of methergine + and methergine – groups in *Nulliparous group and in **multiparous group. ***p values of pre-post comparisons. a adjusted according to pre measurement.

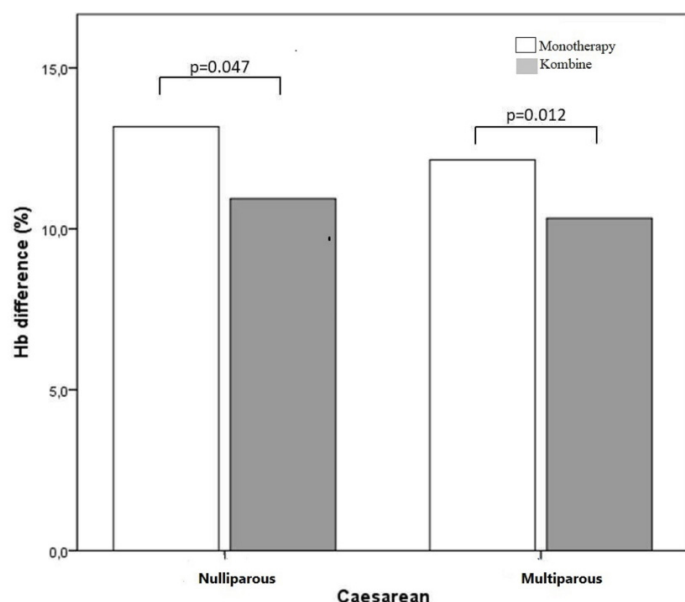


Figure 2. Percentage change in Hb levels according to groups

When the number of cases with massive bleeding requiring blood transfusion and the study population are divided into two main groups as monotherapy and combined group; 14 (7%) in the monotherapy group and 17 (8.5%) in the combined group. These values were statistically similar ($p=0.575$).

In terms of platelet levels, it was not found statistically significant between combined and monotherapy subgroups in nulliparous and

multiparous pregnancies before and after surgery ($p>0.05$ in all groups). However, the difference between pre- and postoperative platelet levels was statistically significant in all subgroups ($p<0.001$) (Table 2).

Preoperative and postoperative electrocardiogram (ECG) findings and blood pressure changes of patients with intraoperative chest pain and palpitations were compared. There was no ST elevation or ST depression on ECG in symptomatic patients. Similarly, heart rate (80-100/min) and blood pressure (<140/90 mm/Hg) were within normal limits in symptomatic patients.

Discussion

Cesarean section is the most widely used surgical method in obstetrics today. Unfortunately, women who deliver by cesarean section (CS) have a higher risk of postpartum hemorrhage than women who deliver vaginally. In addition, even if maternal death due to PPH is prevented, it brings a great cost increase to health services due to reasons such as blood transfusion, hysterectomy, and the need for additional care [13].

The aim of this study was to demonstrate that the methylergonovine-oxytocin combination is more effective than a standard oxytocin protocol in the prophylaxis of postpartum hemorrhage. The use of uterotonic drugs to prevent PPH in the third stage of labor is recommended by WHO to all women who have given birth. Among the drugs used for this purpose, oxytocin is the first highly recommended uterotonic drug[14]. Prophylactic use of oxytocin results in an approximately 40% reduction in the incidence of

PPH [15]. Methylergonovine is a semi-synthetic derivative of the ergot alkaloid, which causes vasoconstriction of uterine vascular smooth muscle. However, due to the negative side effects of methylergonovine, it is rarely used to prevent PPH. Because of its significant vasospasm effect, methylergonovine can cause increased morbidity and death. Consequently, it should not be used in patients at risk for ischemic heart disease, peripheral vascular disease, or diabetes [9]. The dose and procedure for administering oxytocic drugs during C/S are still controversial. According to some studies, the combination of methylergonovine and oxytocin is more effective than oxytocin alone in preventing PPH [16,17,18].

Our study was supported by the above literature, and it was concluded that the methylergonovine-oxytocin combination was more effective than oxytocin alone [16,17]. In our study, we showed that the rate of severe anemia after cesarean section was 2.75%. This result we found was similar to ours found in a study (2%) conducted in India [19] with severe anemia on the second day (cut-off hemoglobin level < 8 g/dl) and 3% [20] in a German study. After birth, Şentürk et al. [9] showed that the use of combination methylergonovine-oxytocin infusion during intraoperative cesarean section significantly reduced the amount of postpartum hemorrhage with no adverse effects. In addition, in accordance with the literature, no side effects were observed in individuals who received methylergonovine prophylaxis during our study [9]. The main strength of our study is that it divides the study population into 2 main groups, nulliparous and multiparous, according to the number of cesarean sections, and divides these groups into 2 more subgroups, monotherapy group and combined group, according to treatment modalities. Another important strength of our study was that it used Hb concentration difference as an objective method to measure PPH. The most objective way to accurately assess blood loss after cesarean section is the difference between pre- and post-operative Hb concentration, and this method is widely used to analyze blood loss after PPH [21]. It is difficult to measure blood loss during cesarean section, especially with amniotic fluid. In addition, blood is collected through compresses during surgery and it becomes more difficult to determine the amount of blood loss. Therefore, blood loss is often underestimated [9,22].

The main flaw of our study is the lack of a randomized, double-blind study that would provide a high level of evidence to evaluate the efficacy of methylergonovine and oxytocin in avoiding PPH. Our study showed that postoperative Hb reduction was lower in both the primiparous and multiparous combined groups treated with methylergonovine compared to the subgroup using oxytocin. Although methylergonovine is not preferred in many centers due to its negative effects in PPH prophylaxis, it has been shown in many publications that ergometrine does not cause adverse outcomes in pregnant women compared to other uterotonic drugs [23]. According to our literature review, this is the first study to examine the efficacy of metiergonovine-oxytocin combined therapy against routine oxytocin use in preventing postpartum bleeding in pregnant women with both nulliparous and multiparous cesarean sections.

Conclusion

Routine use of methylergonovine-oxytocin infusion during cesarean section significantly reduced the amount of postpartum hemorrhage in both primiparous and multiparous cesarean sections. In addition, the use of methylergonovine-oxytocin to

prevent postpartum hemorrhage is as safe and effective as other uterotonic treatments. For postpartum hemorrhage prophylaxis, this combination can be used as uterotonic therapy in pregnant women without cardiac risk factors. We believe that this procedure will also reduce the risk of uterine atony, but future prospective studies are required to confirm this assumption.

Conflict of interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure

The authors declare that they have received no financial support for the study.

Ethical approval

Our study was approved by the ethics committee of the university (Ethics Committee Date: 29.04.2020, Number: 05/26).

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