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ORIGINAL ARTICLE

The timing of intravenous oxytocin administration is crucial to minimize perioperative blood loss during first-trimester suction curettage for missed abortion

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Abstract

Background: Oxytocin is commonly used to reduce blood loss during suction curettage for missed abortion. However, the potential of oxytocin to mitigate blood loss in early pregnancy remains controversial. Based on the hypothesis that the "timing" of oxytocin administration may be a critical factor, we investigated whether the timing of intravenous (IV) administration is associated with reduced perioperative blood loss during first-trimester suction curettage for missed abortion.

Methods: The medical charts of 146 patients with ultrasound-confirmed first-trimester missed abortion who underwent suction curettage with IV oxytocin administration were retrospectively reviewed.

Results: Among the patients, 67 received 10 IU of IV oxytocin before suction curettage (early-oxytocin administration group), while 79 patients received 10 IU of IV oxytocin after suction curettage (late-oxytocin administration group). The demographic features between the two groups did not significantly differ. However, there was a lower proportion of nulliparous patients in the early-oxytocin administration group than in the late-oxytocin administration group (38.8% vs 60.8%, $p = 0.006$). The perioperative blood loss amount was significantly lower in the early-oxytocin administration group than in the late-oxytocin administration group (60 [range: 50–100] vs 100 [range: 30–250] mL, $p = 0.001$). Moreover, the multivariate logistic regression analysis showed that the early-oxytocin administration group had a lower risk for a perioperative blood loss amount of ≥100 mL than the late-oxytocin administration group (0.23 [range: 0.10–0.55], $p = 0.001$); a gestational age of 9–12 weeks ($p = 0.009$) was found to be associated with an increased risk for a perioperative blood loss amount of ≥100 mL.

Conclusion: Compared with late-oxytocin administration, early-oxytocin administration could reduce perioperative blood loss during first-trimester suction curettage for missed abortion. However, the results require further investigation.

Keywords: First trimester; Missed abortion; Oxytocin; Perioperative blood loss; Suction curettage

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1. INTRODUCTION

Oxytocin is a potent uterotonic agent that enhances the uterine tone and contractility and is commonly used for labor induction and postpartum hemorrhage management.[1–9] The response of a target tissue relies on the concentration of the circulating hormone and affinity and concentration of tissue receptors.[10] Notwithstanding, considering that oxytocin contracts the uterine smooth muscle and increases the uterine tone, many clinicians favor its use during surgical evacuation for missed abortion to attempt to minimize blood loss and reduce the risk for uterine perforation.[11–15] However, the blood loss-mitigating potential of oxytocin during first-trimester surgical evacuation for missed abortion remains controversial. Although the definite causes contributing to the conflicting data are still unknown, we hypothesized that the "timing" might be a critical factor based on the significant variation of the appropriate timing of oxytocin

administration intraprocedurally. To date, most studies have not specified the timing when oxytocin should be administered.[12–15] Additionally, clinicians use various medications to prevent or treat hemorrhage during surgical evacuation, and scant evidence is available to guide abortion providers on the use of drugs to decrease hemorrhage during surgical procedures for abortion.[16] Therefore, identifying a specific timing of oxytocin administration to mitigate blood loss is urgently needed.

Although suction curettage is generally considered safe, it can cause significant morbidity and mortality when complications occur[17–19] and result in deterioration of women's reproductive health and possible economic or social problems.[20] Notably, pregnancies complicated by life-limiting malformations, such as trisomy 18 and 13, are frequently associated with placental abnormalities,[21–25] and excessive hemorrhage may also occur during suction curettage. Such cases should be treated with caution and managed appropriately if antenatally diagnosed. Additionally, unlike many reports,[14,15] intravenous (IV) oxytocin is widely administered during suction curettage in Taiwan.[21,22,24] However, the practice details of oxytocin administration markedly differ among facilities.[21,22,24] Hence, this study aimed to clarify the role of the "timing" of oxytocin administration in reducing blood loss during first-trimester suction curettage.

2. METHODS

2.1. Patients

This study was conducted in accordance with the Declaration of Helsinki and approved by our Institutional Review Board. This retrospective observational study was conducted from October 2019 to November 2020. The requirement for patient consent was waived because of the retrospective study design. One hundred fifty-one women with ultrasound-confirmed first-trimester missed abortion underwent ultrasound-guided suction curettage (Fig. 1). Nine patients were excluded from the study owing to the following reasons: prior anticoagulant treatment or history of coagulopathy (n = 3), multiple gestations (n = 1), and prior misoprostol treatment (n = 5). Finally, 146 patients were included in the analysis. They were divided into two groups based on their medical records: early and late-oxytocin administration groups. As current evidence does not specify the appropriate timing of oxytocin administration, surgeons administer oxytocin early or late based on their routine practice and clinical experiences. Herein, the early-oxytocin administration group (n = 67) received IV oxytocin (10 IU) immediately after cervical dilatation and before suction curettage. In contrast, the late-oxytocin administration group (n = 79) received IV oxytocin (10 IU) immediately after suction curettage. The primary outcome was perioperative blood loss during the procedure, while the secondary outcomes were the numbers of patients who received blood transfusions and uterine perforations. Furthermore, since first-trimester surgical evacuation is rarely associated with excessive perioperative blood loss, a perioperative blood loss amount of ≥100 mL was defined as excessive blood loss.[17,18,26] The risk factors associated with a perioperative blood loss amount of ≥100 mL were also analyzed.

2.2. Surgical procedure and perioperative blood loss evaluation

Two surgeons performed the procedures. Before the procedures, missed abortion was double-confirmed by the absence of fetal heartbeats on ultrasound. After sedation, the vagina was dilated using a speculum to allow clear visualization of the cervix and disinfected with a povidone-iodine solution. The bladder was inflated with 350 mL isotonic sodium chloride solution to visualize the uterus using transabdominal ultrasound. Thereafter, the cervix was grasped using a long Allies clamp at the anterior lip and dilated using a Hegar dilator up to number 12.[27–29] The early-oxytocin administration group received IV oxytocin infusion after cervical dilatation and before suction curettage. In contrast, the late-oxytocin administration group received IV oxytocin infusion immediately after suction curettage. Oxytocin was administered as follows: 10 IU in 500 mL D5W infused for 1 hour.

Ultrasound-confirmed sac removal at the end of the procedure. After complete gestational tissue evacuation, the final perioperative blood loss amount was recorded based on the fluid collected in the suction bottle. A strainer was used to separate

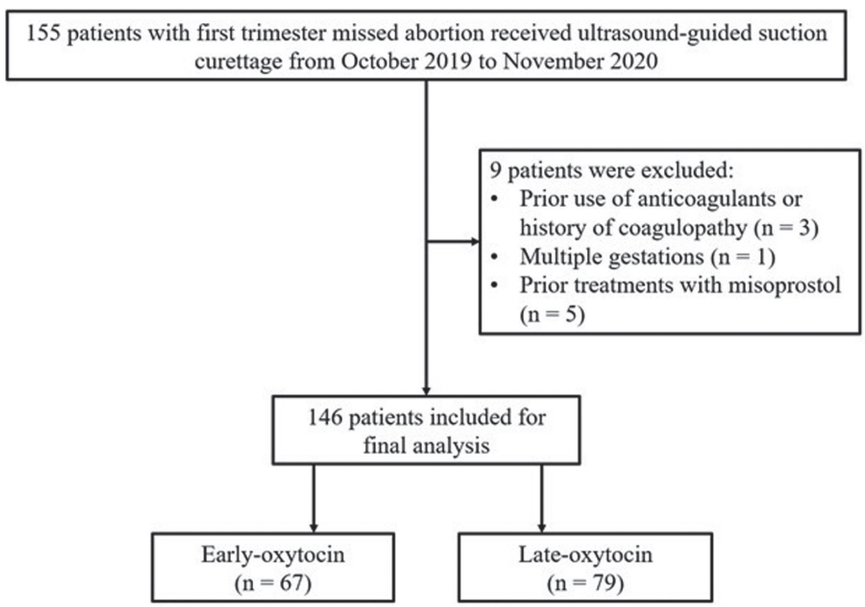

Fig. 1 Flow diagram of the inclusion and exclusion criteria for the retrospective analysis of early-oxytocin and late-oxytocin, representing the subjects receiving intravenous oxytocin before and after suction curettage, respectively.

the products of conception and blood to measure the blood volume precisely. Surgical gauze and other blood-soiled materials were collected to quantify blood loss. The surgical duration was also documented. Routine postoperative prescription included a short course of antibiotic prophylaxis (prophylactic use of first-generation cephalosporin) and 1- or 2-day oral postoperative nonsteroidal anti-inflammatory drugs for analgesia.

2.3. Statistics

The demographics and clinical characteristics between the groups were compared using Fisher's exact test for categorical variables or an independent sample t-test for continuous variables. The blood loss amount was not normally distributed and was therefore compared between the groups using the Mann-Whitney *U* test. The blood loss amount was dichotomized into two subgroups (<100 vs ≥100 mL). The perioperative blood loss amount and numbers of patients who received blood transfusions and uterine perforations were compared between the groups using Fisher's exact test. Univariate and multivariate logistic regression analyses were used to evaluate the risk factors for a blood loss amount of ≥100 mL. All tests were two-tailed, and statistical significance was set at $p < 0.05$. Data analyses were conducted using IBM SPSS for Windows version 25 (IBM Corp., Armonk, NY, USA).

3. RESULTS

3.1. Patients

Among the 146 patients, 67 and 79 receiving IV oxytocin (10 IU) before and after suction curettage were included in the early and late-oxytocin administration groups, respectively. No significant differences were found in the clinical characteristics, including age, body mass index (BMI), prior dilatation and curettage, previous uterine surgeries (myomectomy or cesarean section), history of coagulopathy, and dichotomized gestational age (6–8 vs 9–12 weeks), between the groups (Table 1). Notably, the proportion of nulliparous women was significantly higher in the late-oxytocin administration group than in the early-oxytocin mL group (60.8% vs 38.8%, $p = 0.006$).

Table 1

Comparative demographic characteristics of early-oxytocin and late-oxytocin subjects

Variables	Early-oxytocin (n = 67)	Late-oxytocin (n = 79)	*p*
Age (year)	35.4 ± 5.8	35.9 ± 5.6	0.619
Body mass index (kg/m^2)	23.0 ± 3.8	23.7 ± 5.0	0.419
Nulliparous			
Yes	26 (38.8)	48 (60.8)	0.006
No	41 (61.2)	31 (39.2)	
Prior dilation and curettage			
Yes	12 (17.9)	12 (15.2)	0.412
No	55 (82.1)	67 (84.8)	
History of coagulopathy			
Yes	2 (3.0)	0 (0.0)	0.209
No	65 (97.0)	79 (100.0)	
Previous uterine surgery			
Yes	9 (13.4)	11 (13.9)	0.563
No	58 (86.6)	68 (86.1)	
Gestational age (weeks)			
6–8	47 (70.1)	58 (73.4)	0.399
9–12	20 (29.9)	21 (26.6)	

Early-oxytocin and late-oxytocin groups represent subjects receiving intravenous oxytocin (10 IU) before and after suction curettage.
Data are presented as frequency (percentage) or mean ± standard deviation.

3.2. Clinical outcomes

Table 2 displays the clinical outcomes, including the perioperative blood loss amount, numbers of patients who received blood transfusions and uterine perforations, and surgical duration. The median perioperative blood loss amount was 60 (interquartile range: 50–100) and 100 (interquartile range: 30–250) mL in the early and late-oxytocin administration groups, respectively. The Mann-Whitney *U* test showed that perioperative blood loss was more significant in the late-oxytocin administration group than in the early-oxytocin administration group ($p = 0.001$). After dichotomization of the blood loss amount into two subgroups, the incidence of a blood loss amount of ≥100 mL was significantly higher in the late-oxytocin administration group than in the early-oxytocin administration group (73.4% vs 35.8%, $p < 0.001$). Four (5.1%) and zero patients in the late and early-oxytocin administration groups required blood transfusion, respectively, although the difference was not significant ($p = 0.083$). No uterine perforation was noted in either group. Additionally, the surgical duration was not significantly different between the groups (18.6 ± 11.2 vs 20.8 ± 13.8 minutes, $p = 0.291$).

3.3. Risk factors for perioperative blood loss

The univariate and multivariate logistic regression analyses revealed the risk factors for a perioperative blood loss amount of ≥100 mL (Table 3). The multivariate logistic regression analysis showed that a gestational age of 9–12 weeks (odds ratio: 4.35, 95% confidence interval: 1.45–13.07, $p = 0.009$) was associated with a higher risk for a blood loss amount of ≥100 mL. Notably, oxytocin administration before suction curettage significantly reduced the risk for a blood loss amount of ≥100 mL (odds

Table 2

Clinical outcomes of the 146 subjects with early-oxytocin and late-oxytocin administration

Variables	Early-oxytocin (n = 67)	Late-oxytocin (n = 79)	*p*
Median perioperative blood loss (mL)	60 [50, 100]	100 [30, 250]	0.001
Perioperative blood loss (mL)			
<100	43 (64.2)	21 (26.6)	<0.001
≥100	24 (35.8)	58 (73.4)	
Blood transfusion (n)	0 (0.0)	4 (5.1)	0.083
Uterine perforations (n)	0	0	
Operation time (minutes)	18.6 ± 11.2	20.8 ± 13.8	0.291

The early-oxytocin and late-oxytocin groups represent subjects receiving intravenous oxytocin (10 IU) before and after suction curettage.
Data represents frequency (percentage) or median [25 percentile, 75 percentiles].

Table 3

Univariate and multivariable logistic regression analysis of risk factors associated with perioperative blood loss ≥ 100 mL

	Univariate		Multivariate	
	OR (95% CI)	*p*	OR (95% CI))	*p*
Age (year)	1.04 (0.98–1.10)	0.196	1.02 (0.94–1.10)	0.669
BMI (kg/m^2)	1.07 (0.98–1.17)	0.126	1.08 (0.97–1.20)	0.175
Nulliparous	1.17 (0.61–2.26)	0.631	1.69 (0.66–4.34)	0.277
Prior dilation or curettage	1.37 (0.56–3.37)	0.495	1.69 (0.50–5.69)	0.400
Previous uterine surgery	0.95 (0.37–2.45)	0.910	1.04 (0.28–3.85)	0.949
Gestational age (9–12 weeks)	2.03 (0.95–4.35)	0.067	4.35 (1.45–13.07)	0.009
Early-oxytocin administration	0.20 (0.10–0.41)	<0.001	0.23 (0.10–0.55)	0.001

BMI = body mass index; CI = confidence interval; OR = odds ratio.

ratio: 0.23, 95% confidence interval: 0.10–0.55, $p = 0.001$) after adjustments for other covariates.

4. DISCUSSION

Whether oxytocin administration is needed in patients with first-trimester missed abortion treated with suction curettage remains unclear. Intramuscular (IM) oxytocin injection (10 IU) before curettage can diminish blood loss and reduce the uterine perforation risk.[15] IM oxytocin immediately administered after cervical dilatation before curettage has been reported to yield the lowest complication rate and less hemorrhage.[14] However, a randomized controlled clinical trial did not show the benefits for uterine contraction of uterotonic agents, such as syntocinon or ergometrine, for spontaneous abortion compared with those without uterotonic agents.[30] A randomized controlled study showed no statistically significant difference between the nonoxytocin and the oxytocin-administered groups on postoperative blood loss during surgical termination of first-trimester pregnancy.[31] Accordingly, oxytocin has been recommended to not be routinely administered during uterine evacuation in early pregnancy.[32] However, in our hospital, oxytocin is routinely administered during first-trimester suction curettage for missed abortion, regardless of the timing.

In theory, oxytocin receptor expression is dependent on the pregnancy status and gestational age; expression in the uterine myometrium is extremely low in the nonpregnant uterus compared with that in the pregnant uterus, increases from the early trimester to the late trimester, and plateaus at term.[33–35] However, this concept was challenged by Japanese scholars. Den et al[36] showed no significant difference in the myometrial oxytocin receptor concentration throughout pregnancy; the oxytocin-specific binding affinity increased from 18.3% in the first trimester to 35.6% at term. Therefore, the low expression or reduced specific binding affinity of oxytocin and oxytocin receptors in the uterine myometrium in the first trimester can be considered a theoretical reason to debate the usefulness of oxytocin administration for early-pregnancy termination procedures.

Although the current evidence supporting the benefits of oxytocin administration for early-pregnancy termination procedures is indeterminate, numerous physicians still favor routine oxytocin administration during surgery, including those in Taiwan.[37] Additionally, one case report in Taiwan even successfully used oxytocin antagonists to manage threatened abortion at 15 weeks of gestational age.[38] Furthermore, although Beeby and Morgan Hughes did not observe any benefit of oxytocin in reducing blood loss during early-pregnancy termination procedures, they still recommended its use when excessive hemorrhage is anticipated.[30] Although another study failed to observe the benefits of oxytocin in reducing hemorrhage during first-trimester surgical termination, it did not assess perioperative blood loss during the procedure.[31] Thus, the role of oxytocin in reducing the risks for bleeding and surgical complications must be reinvestigated. Accordingly, an ongoing clinical trial attempts to clarify the oxytocin receptor expression and myometrial oxytocin receptor function in the nonpregnant and pregnant (crossing over three trimesters) uterine myometria via ultrasound-guided core needle biopsy of myometrial tissue samples from anesthetized women immediately following surgical abortion and from controls (NCT03907735).[39]

Our study showed that early-oxytocin administration reduced the median perioperative blood loss amount and the risk for a perioperative blood loss amount of ≥100 mL compared with late-oxytocin administration during first-trimester suction curettage for missed abortion. These results can be partly explained by the interaction between oxytocin and its receptors. Oxytocin is metabolized by the liver and kidneys.[3] When administered via the IV route, it binds to receptors within the myometrium to facilitate uterine contractions within seconds or minutes, with a half-life of 2 to 4 minutes.[3,40,41] Therefore, if oxytocin is administered after suction curettage, the myometrial tone may not increase during the procedure, which may be associated with unwanted perioperative blood loss. Although contemporary pieces of evidence suggest that compared to term, oxytocin receptors are relatively lower in the early gestational age, our study showed that early-oxytocin administration (before suction curettage) may still have a certain degree of impact on the uterine wall allowing smooth muscle contraction. Similarly, 5 to 10 IU of oxytocin is routinely administered through the IV route for surgical termination of first-trimester pregnancy in Norwegian hospitals.[31] IV synthetic oxytocin (syntocinon) could induce adequate uterine contraction and reduce hemorrhage during first-trimester suction curettage compared with IV saline treatment.[42] IV oxytocin administration may also significantly shorten the instillation-to-abortion time.[43] Additionally, Salomy et al showed IV oxytocin infusion following intraamniotic administration of prostaglandin F2alpha shortens injection to abortion time in mid-trimester abortion.[44] Oxytocin may be one of the most effective and safe alternatives to misoprostol and PGE2 for mid-trimester induced[45] and missed abortions.[46] Taken together, our findings are supported by various reports on the preference of the IV over the IM route in terms of efficacy, with no evidence of additional safety concerns and a comparable side effect profile.

Notably, oxytocin possesses an intrinsic antidiuretic effect and therefore can increase water reabsorption from the kidneys and may lead to hyponatremia, headache, vomiting, drowsiness, or convulsions when continuously infused.[3] Hence, medical providers should be cautious of the possibility of water intoxication, particularly when oxytocin is administered continuously via infusion. However, IM oxytocin administration is not recommended owing to the occurrence of a more extended uterine response (3–5 minutes) following injection, which might be too late to salvage perioperative blood loss. Herein, the proportion of nulliparous women was significantly higher in the late-oxytocin administration group than in the early-oxytocin administration group. This is almost certainly attributed to the small number of enrolled patients and retrospective study design. Additionally, current shreds of evidence have not demonstrated that nulliparous status is associated with perioperative blood loss during early pregnancy missed abortion procedures.

The univariate and multivariate logistic regression analyses in our study did not reveal a varying risk for blood loss among the women with different BMI. Women with a higher BMI are generally at increased risks for pregnancy-associated complications, including conditions requiring cesarean delivery, preeclampsia, gestational diabetes, macrosomia and stillbirth, than those with a normal BMI.[47–53] Class 3 obesity (BMI of ≥40 kg/m^2) might increase the risk for complications, including hemorrhage, need for repeated evacuation, uterine perforation, cervical laceration, and reintervention in second-trimester procedures.[54] However, Benson et al[55] evaluated the relationship between obesity and surgical abortion-related complications and found that a higher BMI is not an independent predictor of abortion-related complications after adjusting for age, gestational age, and prior cesarean delivery. Based on these findings,[47–55] the association between increased BMI and the risk for complications during surgical abortion remains inconclusive, which agrees with our findings.

In addition to the timing of oxytocin administration, our multivariate logistic regression analysis revealed that a gestational age of 9 to 12 weeks was associated with a significantly high risk for a blood loss amount of ≥100 mL ($p = 0.009$). Furthermore, the association between a higher gestational age and the risk

for hemorrhage during abortion procedures has been well documented.[56–62] Surgical abortion before 7 weeks of gestation is generally considered safe[63]; however, from 9 weeks of gestation, the perioperative blood loss amount increases. A significant blood loss amount for every 2 weeks of gestation increase ($p < 0.005$) has been reported.[13] Interestingly, a Georgian population-based study found that compared with dilatation and curettage, the vacuum aspiration was associated with reduced risks of postabortion hemorrhage and fever, and a gestational age greater than 10 weeks did not turn out to be a predictive factor for immediate postabortion complications.[64] However, the rate of complications and number of retained products of conception could decrease using intraoperative ultrasound guidance during uterine evacuation procedures.[65] Similarly, neither uterine perforation nor reinterventions were noted in both groups in our study, indicating that the procedure was safe under ultrasound guidance. Theoretically, owing to its uterotonic effects, oxytocin can increase the uterine tone, further reducing the risk for uterine perforation during surgical evacuation procedures. Previously, Whitehouse et al[66] found no significant difference in the frequency of intervention to control hemorrhage between their IV-administered oxytocin (30 IU) and placebo groups among second-trimester women (18–24 weeks of gestation) who underwent surgical evacuation; however, the median blood loss amount and hemorrhage frequency were found to be lower in the oxytocin group, favoring the IV route of oxytocin administration.

The strengths of this study are as follows. First, we used a uniform infusion rate for oxytocin, considering that the infusion rate can influence perioperative blood loss. Second, we proposed a useful and easy technique to mitigate blood loss associated with first-trimester surgical interventions for abortion. In the United States, the Supreme Court overturned Roe v. Wade on June 24, 2022, and most states are expected to severely restrict abortion.[67,68] This will have a deleterious impact on residency training in obstetrics and gynecology in the United States.[69,70] Residents will lose the opportunity to enhance their abilities on miscarriage management and uterine evacuation. Therefore, similar to dealing with any high-risk pregnancy,[71–75] developing a strategy to avoid undesired complications of abortion is warranted and urgently needed, since morbidity and possible mortality will follow if inadequate and unprepared procedures are performed. Meanwhile, the limitations of this study include the possible imprecision in estimating the perioperative blood loss amount, even after cautiously following a strict protocol. Furthermore, gynecological surgeons were not blinded to the timing of oxytocin administration because of the retrospective study design. However, to our knowledge, very few studies have investigated the impact of oxytocin administration timing during first-trimester suction curettage for missed abortion. Owing to lack of clarity on oxytocin's contribution to mitigating perioperative blood loss, we suggested the timing of oxytocin administration may be one of the causes contributing to an uncertain role in the reduced bleeding during the early trimester missed abortion procedure. Taken together, we demonstrated that IV oxytocin administration before suction curettage might be beneficial in women with first-trimester missed abortions. Although arguably, the oxytocin receptor expression might be low in early pregnancy, a larger randomized controlled trial is needed to confirm the impact of oxytocin on early-pregnancy abortion surgeries.

In conclusion, oxytocin administration before suction curettage could reduce perioperative blood loss during first-trimester suction curettage for missed abortion. A gestational age of 9 to 12 weeks is associated with an increased risk for a perioperative blood loss amount of >100 mL compared with a gestational age of 6 to 8 weeks.

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