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Research Article

The First International Guideline for Oxytocin Safely Decreased Oxytocin Amount During Cesarean Section: A Single-Institution Retrospective Analysis

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ABSTRACT

Purpose: It is routine to administer oxytocin following delivery of the neonate during cesarean section. However, there are many kinds of administration methods. Heesen *et al.* published an international consensus statement in 2019 on the use of uterotonic agents, including oxytocin during cesarean section [1]. Our institution adapted the guideline-based oxytocin infusion method. We verified the validity of the new approach after one year.

Methods: A single-center retrospective study of consecutive patients who underwent cesarean section with a new protocol or the conventional manner from November 2019 to December 2020 was conducted. The primary endpoint was a significant difference in the amount of intraoperative hemorrhage and the total oxytocin amount. Secondary endpoints included differences in the incidence of intraoperative complications.

Results: The study included 174 patients: 66 in the new protocol group and 108 in the conventional group. There was a statistically significant difference between the two groups for oxytocin amount (new protocol 4.2 [3.2-5.9] vs. conventional 5.0 [5.0-10] IU, $p<0.01$) with equivalent intraoperative hemorrhages (new protocol 558 [337-963] vs. conventional 683 [484-1012] g, $p=0.08$). There was no significant difference in the incidence of nausea.

Conclusion: The new guideline-based oxytocin administration safely decreased the intraoperative oxytocin amount in our institution.

Introduction

It is our routine to administer oxytocin following delivery of the neonate during cesarean section. However, there are many kinds of administration methods; intramuscular injection, bolus, continuous intravenous administration, and intramyometrial injection; that is, the standard protocol in an institution is entirely different from that in another institution. The World Health Organization published a new recommendation on uterotonics for postpartum hemorrhage prevention after vaginal delivery [2]. After that, Heesen *et al.* published an international consensus statement on the use of uterotonic agents, including oxytocin during cesarean section in 2019 [1]. Our institution adapted the guideline-based oxytocin infusion protocol after some discussion between the anaesthesiology and obstetrics departments. One year after the change in the oxytocin administration protocol, we verified the validity of the new method.

Methods

The institutional review board in Asahi General Hospital approved this single-center retrospective study (Jan. 19th, 2021; #2021011911), and this study was registered in UMIN Clinical Trial Registry (Link) (UMIN000042952) prior to data collection. We collected information on consecutive patients receiving cesarean delivery from November 2019 to December 2020 from the electric medical and anaesthesia records. Exclusion criteria included the allergy to oxytocin, placenta previa, placental abruption, and undergoing simultaneous other surgeries except for partial salpingectomy. The patients were divided

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into two groups: group N for the patients with the new protocol and group C for the patients with our conventional oxytocin administration methods (Table 1). The primary endpoint was a significant difference in the amount of intraoperative hemorrhage and the total oxytocin amount. Secondary endpoints included differences in the incidence of intraoperative oxytocin-related complications. Statistical analyses were performed with R version 4.0.2 using the Mann-Whitney test and Fisher's exact test. All data were processed as non-Gaussian distributions, and the normality test was not performed.

Table 1: The oxytocin protocols.

	Group N		Group C
Initial dose	[Elective C/S] ●Bolus 1 IU i.v. plus ●2.5-7.5 IU/h	[Intrapartum C/S] ●3 IU i.v. over 30s plus ●7.5-15 IU/h	●5 IU, mix into the ongoing infusion bottle
Additional dose	●3 IU i.v. over 30s, when required after 2min. ●Consider second-line agents.		●5 IU, mix into the next infusion bottle, whenever required. ●5 IU intramyometrial injection, when the surgeon required.

C/S: Cesarean Section.

Table 2: Patient backgrounds.

	Group N (n=66)	Group C (n=108)	P value
Age [y]	35 [30-38]	33 [30-37]	0.25
Height [cm]	158 [154-162]	158 [155-162]	0.99
Weight before delivery [kg]	63 [57-73]	65 [60-73]	0.22
Weight before pregnancy [kg]	54 [48-62]	55 [50-62]	0.43
Emergent/urgent case	24 (34%)	50 (44%)	0.20
Gestational weeks	38 [37-38]	38 [36-38]	0.99
Graviditas (G)	2 [1-3]	2 [1-3]	0.75
Parturition (P)	1 [0-1]	1 [0-1]	0.98
Complication			
PIH	2 (3%)	11 (10%)	0.08
Intramyometrial myoma	2 (3%)	10 (9%)	0.12
Arrested labor	6 (9%)	12 (11%)	0.67

The data are shown in medians [interquartiles] or numbers (percentage). There was no significant difference between groups in patient backgrounds.
PIH: Pregnancy-Induced Hypertension.

Results

Two hundred thirty-seven patients received cesarean section between November 2019 and December 2020. Fifty-two patients were excluded because of incomplete records after data collection. Eleven patients were excluded because of placenta previa and placental abruption. Sixty-six patients received oxytocin in the new protocol and 108 patients received it in the conventional method. The last patient in the conventional method was in September 2020, because each anaesthesiologist in the department gradually adapted to the new guideline. There was no significant difference in patient backgrounds (Table 2). Most of the patients received spinal anaesthesia; 4 in Group N (6%) and 4 in Group C (4%) received general anaesthesia because of immediate cesarean sections. There was no failed spinal anaesthesia. There was a statistically significant difference between the two groups for intraoperative oxytocin amount (group N 4.2 [3.2-5.9] vs. group C 5.0 [5.0-10] IU, $p<0.01$) (Figure 1). There was no significant difference in intraoperative hemorrhage (group N 556 [323-955] vs. group C 680 [481-1016] g, $p=0.08$) (Figure 2). For secondary outcomes, the amount of urine was significantly different (group N 100 [46-200] vs. group C 95 [0-100] mL, $p=0.02$). For oxytocin-related complications, there was no significant difference in the incidence of nausea. Other symptoms such as headache, ST change, and chest pain had not been recorded. Some surgery-related outcomes showed significant differences between groups; the durations of anaesthesia and surgery and the amount of mineral solutions (Table 3).

Table 3: Intraoperative variables.

	Group N (n=66)	Group C (n=108)	P value
Anaesthesia [min]	71 [61-82]	76 [67-88]	<0.01*
Spinal/General	62/4	110/4	0.48
Surgery [min]	48 [42-59]	54 [48-61]	<0.01*
Solutions			
Mineral [mL]	650 [275-650]	425 [200-660]	0.02*
Colloid [mL]	1000 [663-1000]	925 [500-1000]	0.07

Oxytocin [IU]	4.2 [3.2-5.9]	5 [5-10]	<0.01*
Hemorrhage [g]	558 [337-963]	683 [484-1012]	0.08
Urine [mL]	100 [46-200]	95 [0-100]	0.02*
Nausea	12 (17%)	22 (19%)	0.99

The data are shown in medians [interquartiles] and numbers (percentage). Statistically different P values were marked with asterisks.

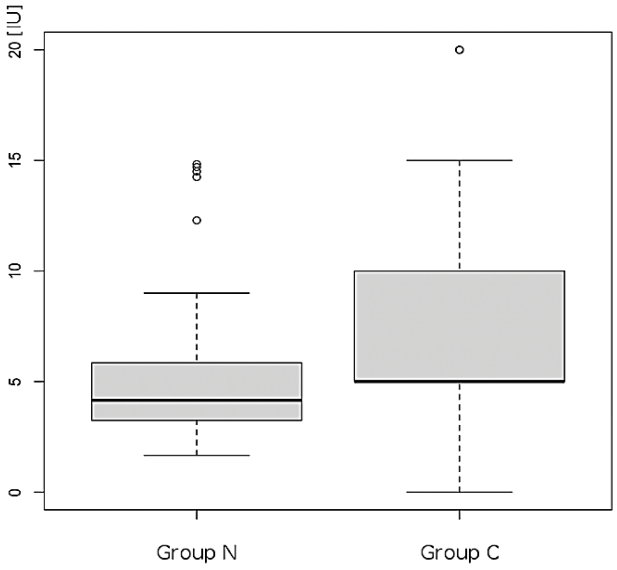

Figure 1: The amount of oxytocin consumed intraoperatively.
There was a significant difference in the oxytocin amount (group N 4.2 [3.2-5.9] vs. group C 5 [5-10] IU, p<0.01).

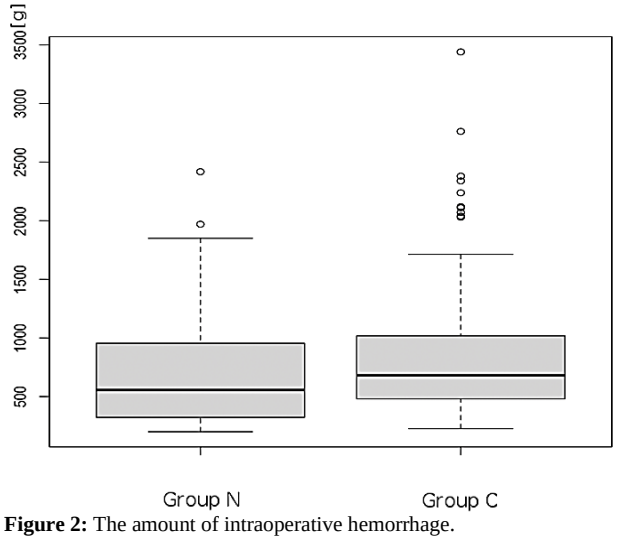

Figure 2: The amount of intraoperative hemorrhage.
There was no significant difference between the two groups for intraoperative hemorrhage.

Discussion

Oxytocin has been widely used after delivery from the 1950s-1960s to prevent postpartum hemorrhage [3]. The newest WHO recommendation for uterotonic agents, including oxytocin, was published in 2018-2019 [2]. Several years after the clinical application to vaginal delivery, oxytocin was applied to cesarean sections. However, there had been no guideline or international standard protocol for oxytocin administration after delivery during cesarean section until Heesen *et al.* published a global consensus statement in 2019 [1]. The guideline-based oxytocin administration in our institution showed a lesser amount of oxytocin with equivalent amount of intraoperative hemorrhage. The guideline suggests that the oxytocin receptor desensitization against oxytocin can happen when the uterine has already been exposed to oxytocin. Therefore, a greater amount of oxytocin should be administered in intrapartum C/S (Table 1).

The amniotic fluid volume sometimes affects the intraoperative hemorrhage volume count. However, the hemorrhage is counted after suctioning most of the amniotic fluid when the cesarean section is performed before amniorrhexis in our daily practice. Therefore, the oligoamnios or hydramnios did not affect the hemorrhage volume in our hospital. The amount of hemorrhage can be affected by hemodilution after a large amount of mineral or colloid solutions. There was a difference in the mineral solution amount administered intraoperatively. However, group C had less amount of mineral solution with more amount of hemorrhage. Both the duration of anaesthesia and surgery were shorter in group N. The shorter surgery could have decreased intraoperative hemorrhage. The change in the obstetric team members in April 2020 could have affected the duration of the surgery. The intraoperative urine amount was different between groups. The records are retrospective, and the patient could not have necessarily entered the operating room after voiding. Therefore, the recorded urine amount should have been the total of the residual urine and actual intraoperative urine excretion. However, oxytocin has a structural analogy with antidiuretic hormone, and excessive oxytocin administration could cause water retention in a dose-dependent manner [1, 4]. Less intraoperative oxytocin in group N might have been favourable for avoiding oxytocin-dependent water retention.

Although there was no significant difference in the incidence of nausea in this study, oxytocin causes dose-dependent nausea and vomiting [5]. However, this secondary outcome was statistically underpowered. Further, ideally, a prospective randomized study is warranted. Oxytocin causes rapid vasodilatation leading to hypotension after administration [6]. Therefore, a larger amount of oxytocin can cause more frequent nausea and vomiting.

The limitation of the study is the administration and discontinuation of oxytocin infusion. The administration of oxytocin with the new guideline necessitates extra syringe pump for continuous infusion. The preparation of the oxytocin solution syringe was time-consuming at first, especially in urgent situation. And the guideline originally recommends that the discontinuation of oxytocin infusion be considered 2-4 hour after the start of the administration. However, the infusion is discontinued at the end of cesarean section surgery in our institution in the present situation, avoiding the extra burden of ward staff. Too early discontinuation can increase postpartum hemorrhage.

Conclusion

The new guideline-based oxytocin administration for cesarean section significantly decreased intraoperative oxytocin amount with an equivalent amount of intraoperative hemorrhage in our institution.

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