論文の内容の要旨

論文題目

Does oxytocin administration during the first and second stages of labor increase the risk of postpartum hemorrhage? A case-control study at the National Maternity Hospital in El Salvador

（分娩第 1 期・第 2 期のオキシトシン投与は、産後多出血のリスクを増大させるか？エルサルバドル国立産科病院における症例対照研究）

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Introduction

More than 300,000 women die each year due to complications of pregnancy, and approximately 99% of these deaths occur in developing countries. Postpartum hemorrhage (PPH) is a major cause of obstetric complications, and it accounts for ≥ 25% of all maternal deaths. The most common causes of PPH are failed uterine contraction after delivery and genital tract trauma, which account for 70% and 20% of all PPH cases, respectively. Several risk factors have been postulated to increase the risk of PPH among pregnant women. For example, retained placenta and a prolonged third stage of labor exhibit strong associations with PPH in both developed and developing countries. It has also been reported that the administration of oxytocin during the first and second stages of labor can increase the risk of PPH if the oxytocin is utilized improperly. However, there is little research from developing countries regarding the association between the risk of PPH and labor induction and augmentation. In addition, only a few studies have investigated the association between PPH and the specific level of exposure to oxytocin during labor induction or augmentation.

An observational study has reported that the prevalence of PPH in El Salvador is extremely high (30.3%), compared to the global prevalence of PPH (6.1%). As the reason for the high prevalence of PPH in El Salvador is unclear, an analysis of the risk factors for PPH is urgently needed. This study aimed to investigate the risk factors for PPH, while focusing on the association between the level of oxytocin exposure during the first and second stages of labor and the risk of PPH.

Methods

We conducted a case-control study among patients who delivered at the National Maternity Hospital (a top referral, tertiary hospital in the capital of El Salvador) between April 1 and June 30, 2014. The inclusion criteria were women who underwent vaginal delivery after an uncomplicated pregnancy at a gestational age of ≥ 35 weeks. Women with singleton or multiple pregnancies (≥ 2 fetuses), cephalic presentation, or mild complications were also included. The exclusion criteria were caesarean section delivery, intrauterine fetal death, antenatal hemorrhage, hematological disorders, and severe complications. The cases were defined as women who had a measured

postpartum blood loss of ≥ 500 g, and the controls were defined as women who had a measured postpartum blood loss of < 400 g and had not received a blood transfusion. The cases and controls were enrolled sequentially according to the time of delivery.

We collected explanatory data regarding socio-demographic characteristics, obstetric and pregnancy history, duration of labor, location of the bleeding site, neonatal characteristics, and birth outcomes from the subjects' medical records. The level of exposure to oxytocin during the first and second stages of labor was of special interest, and the quantitative data regarding oxytocin administration was categorized as low or high levels of oxytocin exposure. The variables that were related to oxytocin exposure included the total dose of oxytocin, maximal infusion rate, duration of infusion, and time at the maximal infusion rate.

All data were analyzed using SPSS for Windows (version 17.0, IBM/SPSS Inc., Chicago, IL), and a p-value of < 0.05 was considered statistically significant. The case and the control groups were compared using the chi-square test for categorical variables, and all tests were two-tailed. The risk of PPH was then compared to the risk among the women who did not receive oxytocin during the first and second stages of labor using multivariate analysis, which was adjusted for the potential confounders that were identified in the bivariate analyses ($p < 0.05$ in the chi-square test).

The study design was approved by the Ethics Committee of the Graduate School of Medicine at the University of Tokyo, Japan, and by the Ethics Committee for Health Research of the National Maternity Hospital of El Salvador.

Results

Based on our inclusion and exclusion criteria, 263 women with PPH and an equivalent number of controls were enrolled. Bivariate analysis revealed that 11 of the 30 variables exhibited a significant association with PPH. These included parity ($p = 0.006$), patients who were referred from another health facility ($p = 0.015$), prolonged time for a postpartum medical procedure ($p = 0.001$), uterine atony ($p < 0.001$), episiotomy ($p = 0.001$), perineal tears ($p = 0.006$), vaginal laceration ($p = 0.003$), birth weight ($p < 0.001$), birth height ($p = 0.005$), blood transfusion after delivery ($p = 0.003$), and anemia in the postnatal period ($p = 0.017$).

Multivariate analysis was then performed to assess the relationship between the level of oxytocin exposure and the risk of PPH. Among the study subjects, 9 (1.7%) women underwent labor induction, 104 (19.8%) women underwent labor augmentation, and 413 (78.5%) women gave birth spontaneously. In the National Maternity Hospital, two kinds of uterotonics are used (oxytocin and misoprostol). Among the 9 women whose labor was induced, oxytocin was used for 2 patients and misoprostol was used for 7 patients, while oxytocin was used for all 104 women whose labor was augmented. For our analysis, the induced labors could not be combined with the augmented labors, as a greater amount of oxytocin was inevitably required to induce vaginal delivery. Therefore, as only two labors were induced using oxytocin (our variable of interest), all 9 women with induced labors were excluded from the analysis. Thus, data from 257 women in the case group and 260 women in the control group were analyzed. Oxytocin

was administered during labor in 24.1% of the cases and in 16.2% of the controls. After adjusting for the variables that were significantly associated with PPH in the bivariate analysis (parity, uterine atony, episiotomy, perineal tears, vaginal laceration, birth weight, and birth height), no significant association between labor augmentation and the risk of PPH was observed (adjusted odds ratio [OR]: 1.50, 95% CI: 0.91–2.46).

While a significant linear trend was observed in the duration of oxytocin infusion ($p = 0.090$) and the time at the maximal infusion rate ($p = 0.048$), no linear trend was observed for the total oxytocin dose ($p = 0.104$) or the maximal infusion rate ($p = 0.095$). When each category of oxytocin exposure and the risk of PPH was compared, only the high level of oxytocin exposure in time at the maximal rate was significantly associated with an increased risk of PPH (adjusted OR: 2.29, 95% CI: 1.05–5.01). Based on this data, there was insufficient evidence to indicate a clear dose-response relationship between the categorized oxytocin exposure and the risk of PPH.

In contrast, in the final logistic regression model, four variables were independently related to an increased risk of PPH. These significant associations were observed between the risk of PPH and uterine atony (adjusted OR: 31.61, 95% CI: 3.88–257.27), second- to fourth-degree perineal tears (adjusted OR: 5.12, 95% CI: 1.40–19.16), vaginal laceration (adjusted OR: 3.26, 95% CI: 1.22–8.75), and episiotomy (adjusted OR: 1.95, 95% CI: 1.29–2.94).

Lastly, the direct causes of PPH among the 263 cases were classified. Among these subjects, the primary etiology of PPH was traumatic bleeding (including perineal tears, cervical laceration, vaginal laceration, and episiotomy) in 200 (76.0%) cases, followed by a combination of uterine atony and genital tract trauma in 23 (8.7%) cases, and atonic bleeding in 6 (2.3%) cases. In 34 (12.9%) cases, the etiology of PPH was unspecified.

Discussion

This case-control study was performed to identify the risk factors for PPH, specifically by focusing on the association between the level of exposure to oxytocin and the risk of PPH. Although previous studies have indicated that the administration of oxytocin during the first and second stages of labor was a risk factor for PPH, with ORs ranging from 1.4 to 2.2, the present study did not reveal a significant association between labor augmentation and the risk of PPH. Furthermore, no clear dose-response relationship was observed when the oxytocin dosage was categorized as low or high levels of exposure. A possible explanation for these results is differences in each individual's oxytocin receptor sensitivity (in the uterine muscle). For example, among women who are highly responsive, oxytocin is effective at a low rate of infusion. In contrast, other women are less responsive to oxytocin, and must receive oxytocin at a high rate of infusion.

Despite the ambiguous study results, we believe that our results may explain the reason for the high prevalence of PPH in El Salvador (30.3%), relative to the global prevalence of PPH (6.1%). Our results indicate that severe perineal tears, vaginal laceration, and episiotomy were significantly associated with the increased risk of PPH (approximately 5-fold, 3-fold, and 2-fold, respectively). Although uterine atony exhibited a strong

association with PPH (adjusted OR: 30.91), when the causes of PPH in the 263 cases were classified, atonic bleeding was observed only in 2.3% of the cases, and a combination of uterine atony and genital tract trauma was only observed in 8.7% of the cases. Surprisingly, traumatic bleeding was responsible for 76.0% of the PPH cases. These results are unique, as our data are markedly different from the findings of a previous study, which reported that uterine atony and traumatic bleeding was responsible for 70% and 20% of PPH cases, respectively.

Previous studies have reported that labor induction and augmentation, as well as episiotomy, increased the risk of genital tract laceration. Additional studies have reported that higher doses of oxytocin decrease the time to delivery, compared to the time for lower doses. After evaluating the results of our study and the previous studies, it appears that an excessive dose of oxytocin may excessively shorten the delivery time, thereby leading to cervical, vaginal, and perineal laceration, due to the rapid decent of the fetal head before the birth canal has sufficiently softened. A comparison of previous studies reveals that the mean maximal rate of oxytocin infusion is higher in El Salvador, compared to the rates that are used in France and the USA. Therefore, the increased incidence of perineal and vaginal tears in the case group may be explained by a high rate of oxytocin infusion. In contrast, a lower dose was associated with a prolonged duration of oxytocin infusion, which appears to cause oxytocin-induced desensitization that appears at approximately 4.2 hours, possibly inducing uterine fatigue and uterine atony.

This study revealed that several factors were related to each other and contributed to the elevated risk of PPH. As traumatic bleeding could be the consequence of oxytocin use during the first and second stages of labor, further detailed analysis regarding this issue is needed. Given the fact that traumatic bleeding was responsible for 76.0% of the Salvadoran PPH cases and that El Salvador has an extremely high prevalence of PPH (30.3% vs. 6.1% globally), the current standard strategy of preventing PPH by focusing on the third stage of labor (AMTSL), with little regard for the first and second stages of labor, appears to be somewhat futile in reducing the prevalence of PPH. Although AMTSL appears to have effectively reduced the risk of uterine atony to a certain extent, as only 2.3% of Salvadoran women were complicated with PPH in this context, the effect of AMTSL on the risk of PPH is not well understood. Therefore, it is recommended that further studies should be conducted, and that healthcare personnel should be educated regarding the known risks of PPH, as well as the risks that are related to labor induction and augmentation.