A Comparative Study between Oxytocin Intravenous Bolus versus Oxytocin Intravenous Bolus and Infusion for Control of Blood Loss at Elective Cesarean Section

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ABSTRACT
Background: One of the most crucial steps taken to stop postpartum hemorrhage (PPH) is to take a uterotonic medication as soon after delivery.
Objective: Our main objective was to determine which method was better for controlling intraoperative and early postoperative bleeding after an elective Cesarean section (CS) whether intravenous (IV) oxytocin bolus or oxytocin bolus with infusion.
Patients and methods: Randomized controlled study that included 214 women who were scheduled for an elective Cesarean section after 38 weeks were divided into two equal groups and given an IV slow bolus oxytocin 5 IU and a placebo infusion (500 ml of normal saline over 4 hours) (Control group) or an IV slow bolus oxytocin 5 IU and an oxytocin infusion (40 IU in 500 ml of normal saline over 4 hours) (Study group). Following fetal delivery, all patients were administered the study medication.
Results: The need for additional uterotonic was statistically higher in group A than in group B 26 (24.3%) versus 14 (13.1%). While the estimated blood loss was statistically insignificant between both groups (691.9 ± 233.6 ml in group A versus 543.1 ± 179.4 ml in group B
Conclusion: Following IV oxytocin slow bolus during an elective Cesarean section, an additional oxytocin infusion was not superior to IV oxytocin slow bolus alone in reducing the operative blood loss but it may reduce the postoperative need for additional uterotonic
Keywords: Postpartum hemorrhage, Oxytocin, Cesarean section. Third stage.

INTRODUCTION
The loss of 500 ml of blood or more, through the vaginal tract, in the 1st 24 hours after a baby is born, is the conventional definition of primary PPH. PPH can range from 500–1000 ml to more than 1000 ml. Majors could be classified as severe (more than 2000 ml) or moderate (1000–2000 ml). Definitio...
LMP or first trimester US.

Exclusion criteria: Women with previous instances of major obstetric hemorrhage in the past, those who are risky for PPH [prior PPH, placenta previa/accreta and those with an oversizd uterus (twin pregnancy, polyhydramnios & uterine fibroid), more than three Cesarean sections and patients who experience trial of labor or preterm labor were not included in the trial.

METHODS
1- Informed consent: All participants gave their informed consent after being made mindful of the reason for and nature of the study.

2- All participants underwent the following:
- Detailed history taking: Including personal, present, past, family, surgical, medical, menstrual, obstetric history regarding number of previous CS, previous pregnancy outcome and complications.
- General examination: Including vital signs measurements and BMI.
- Abdominal and vaginal examination: Obstetric abdominal examination “Leopold maneuvers”. The gravid uterus is methodically palpated using the Leopold procedures. It is employed to ascertain the fetus’s engagement, presentation, and position in pregnancy. Vaginal examination to assess cervical dilatation, cervical consistency, presenting part and stage of head descend.
- Abdominal ultrasound: When the patient was admitted, an abdominal ultrasound was performed to assess the volume of amniotic fluid, grade, placental site, gestational age, fetal viability, and wellbeing. Identification of any obstetric issues, such as multiple gestations, placenta previa, and congenital defects.
- Routine pre-operative investigations: Including RH, CBC, coagulation profile, liver function tests and kidney function tests.
- Intra operative: Spinal anesthesia was administered using a standardized anesthetic approach. Prior to spinal anesthesia, patients underwent an intravenous 500 mL crystalloid bolus. The CS surgical technique was standardized. Surgeons were instructed to follow standard operating protocol, which calls for a continuous two-layer suturing of the uterine incision following a transverse lower segment CS and not to deliver the uterus for closure unless clinically necessary.

The following are prime instances of active labor stage three management: (8):
- Cutting and clamping the umbilical cord shortly after delivery.
- After cord clamping, either a placebo infusion (0.9% saline solution, 500 ml) or an oxytocin infusion (40 IU in 500 ml of 0.9% saline) is administered as a gradual IV bolus over a period of 4 hours.
- Providing regulated stress on the umbilical cord and concurrently providing counter-pressure through the abdomen to the uterus.

- Post operative: Following delivery, cases were monitored in the recovery area and operating theater to guarantee infusion ongoing continuity and detect uterine atony, early lochial discharge development, postpartum bleeding, and any oxytocin adverse effects. Serial clinical examinations, blood pressure, pulse, and UOP measures were also performed. Hemoglobin and hematocrit were measured 24 hours after delivery with a full blood count (a drop of more than 20% in hemoglobin is considered severe anemia) (9).

Ethical consideration: Ethical Committee of Faculty of Medicine, Cairo University provided its approval to the work. All participants gave informed consents after receiving a brief but comprehensive description of the study’s goals, potential benefits, and assurances that there would be no costs to their health. Participants were not required to stay, and they might leave at any moment. For the duration of the research, the Helsinki Declaration was followed.

Statistical analysis
Using IBM SPSS (Statistical package for social research) version 24 for Windows (Chicago, USA), data were coded, calculated, and then analyzed. Frequency tables were used to display qualitative data as numbers and percentages. Standard deviation (SD) was used to portray quantitative data as mean ± SD. To examine the relationship between categorical variables, Chi-square test was used. In four-cell tables, if the expected cell count was fewer than five, the Fisher Exact Test was used. The Mann-Whitney U test (z) was used for analyzing two independent non-normally distributed continuous variables, and the Paired samples t-test was used to compare two dependent groups of parametric data. The independent sample t-test was used to test the association between normally distributed continuous variables in two independent groups. A statistically significant P-value ≤ 0.05 and a highly significant P-value ≤ 0.01.

RESULTS
214 singleton pregnant women who had at least 38 full weeks of gestation and an elective CS were divided into two groups: Following an intravenous (IV) slow bolus oxytocin (5 IU) and placebo infusion (0.9% saline solution 500 ml over 4 hours) for group (A) and an oxytocin infusion (40 IU in 500 ml 0.9% saline over 4 hours) for group (B).

Table (1) showed that the mean age (30.6 ± 5.4 versus 29 ± 5.6 years), the mean GA (38.46 ± 0.64 versus 38.49 ± 0.58 weeks), the mean gravidity (3.17 ± 0.995
versus 3.2 ± 1.09), the mean parity (1.97 ± 0.916 versus 1.94 ± 0.97), the mean number of previous CS (1.66 ± 0.764 versus 1.71 ± 0.75) and the mean BMI (34.7 ± 3.12 versus 34.16 ± 3.12).

Table (1): Comparison between study groups according to baseline characteristics (n=214)

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Group A (n=107)</th>
<th>Group B (n=107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.6 ± 5.4</td>
<td>29.00 ± 5.6</td>
</tr>
<tr>
<td>GA (weeks)</td>
<td>38.46 ± 0.64</td>
<td>38.49 ± 0.58</td>
</tr>
<tr>
<td>Gravidity</td>
<td>3.17 ± 0.995</td>
<td>3.2 ± 1.09</td>
</tr>
<tr>
<td>Parity</td>
<td>1.97 ± 0.916</td>
<td>1.94 ± 0.97</td>
</tr>
<tr>
<td>Number Previous CS</td>
<td>1.66 ± 0.764</td>
<td>1.71 ± 0.75</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>34.7 ± 3.12</td>
<td>34.16 ± 3.12</td>
</tr>
</tbody>
</table>

Major obstetric hemorrhage was statistically significant higher in group (A) than in group (B) [17 (15%) versus 6 (5.7%) with p-value 0.015], while there were no significant differences between studied groups regarding estimated blood loss (688.4 ± 229.5 versus 544.45 ± 177.4 with p-value 0.092) and complications [2 (1.9%) versus 0 (0%) with p-value 0.999] (Table 2 & figures 1, 2 & 3).

Table (2): Comparison between study groups according to operative data (n=214)

<table>
<thead>
<tr>
<th>Operative data</th>
<th>Group A (n=107)</th>
<th>Group B (n=107)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complications</td>
<td>2 (1.9%)</td>
<td>0 (0%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Estimated Blood Loss (ml)</td>
<td>688.4 ±229.5</td>
<td>544.45 ± 177.4</td>
<td>0.092</td>
</tr>
<tr>
<td>Major Obs. Hge. ≥ 1000 ml</td>
<td>17 (15%)</td>
<td>6 (5.7%)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

The use of additional uterotonic was statistically significant higher in group (A) than in group (B) [26 (24.3%) versus 14 (12.1%) with p-value 0.035]. There were no significant differences between studied groups regarding PPH [13 (12.1%) versus 5 (4.7%) with p-value 0.111], conservative management of PPH [5 (4.7%) versus 2 (1.9%) with p-value 0.908], BL.

Transfusion [5 (4.7%) versus 1 (0.9%) with p-value 0.953], ICU admission, [3 (2.8%) versus 1(0.9%) with p-value 0.972], side effects [6 (5.6%) versus 8 (7.5%) with p-value 0.38] and hospital stay [1.24 ± 0.638 versus 1.065 ± 0.315 with p-value 0.235]. Also, there were no significant differences between studied groups regarding re-exploration, hysterectomy, DIC and maternal mortality there (No reported cases) (Table 3 & figures 4 & 5).
Table (3): comparison between study groups according to treatment outcome (n=214)

<table>
<thead>
<tr>
<th>Treatment Outcomes</th>
<th>Group A (n=107)</th>
<th>Group B (n=107)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPH</td>
<td>13 (12.1%)</td>
<td>5 (4.7%)</td>
<td>0.111</td>
</tr>
<tr>
<td>Conservative</td>
<td>5 (4.7%)</td>
<td>2 (1.9%)</td>
<td>0.908</td>
</tr>
<tr>
<td>Add uterotonics</td>
<td>26 (24.3%)</td>
<td>14 (13.1%)</td>
<td>0.035</td>
</tr>
<tr>
<td>BL. Transfusion</td>
<td>5 (4.7%)</td>
<td>1 (0.9%)</td>
<td>0.953</td>
</tr>
<tr>
<td>Exploration</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>ICU admission</td>
<td>3 (2.8%)</td>
<td>1 (0.9%)</td>
<td>0.972</td>
</tr>
<tr>
<td>DIC</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Maternal Mortality</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Hospital stay (Days)</td>
<td>1.24 ± 0.638</td>
<td>1.065 ± 0.315</td>
<td>0.235</td>
</tr>
<tr>
<td>Side effects</td>
<td>6 (5.6%)</td>
<td>8 (7.5%)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Figure (4): Bar chart between study groups according to operative outcome.

Figure (5): Bar chart between study groups according to post-operative hospital stay
There were no significant differences between studied groups regarding pre-operative HCT (36.15 ± 2.99 versus 36.83 ± 2.2 with p-value 0.060) and post-operative HCT (33.86 ± 2.85 versus 34.17±2.30 with p-value 0.378). Also, there was no significant differences between studied groups regarding pre-operative Hb (11.24 ± 0.822 versus 11.24 ± 0.67 with p-value 0.17) and post-operative Hb (10.18 ± 1.21 versus 10.47 ± 0.833 with p-value 0.122) (Table 4 and figure 6).

Table (4): Comparison between study groups according to blood indices  (n=214)

<table>
<thead>
<tr>
<th>Blood Indices</th>
<th>Group A (n=107)</th>
<th>Group B (n=107)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-operative HB (gm/dl)</td>
<td>11.24±0.822</td>
<td>11.24±0.67</td>
<td>0.17</td>
</tr>
<tr>
<td>Post-operative HB (gm/dl)</td>
<td>10.18±1.21</td>
<td>10.47±0.833</td>
<td>0.122</td>
</tr>
<tr>
<td>Pre-operative HCT (%)</td>
<td>36.15±2.99</td>
<td>36.83±2.2</td>
<td>0.060</td>
</tr>
<tr>
<td>Post-operative HCT (%)</td>
<td>33.86±2.85</td>
<td>34.17±2.3</td>
<td>0.378</td>
</tr>
</tbody>
</table>

Figure (6): Bar chart between study groups according to blood indices.

DISCUSSION

Nowadays, worldwide, Cesarean sections are the most common type of surgery conducted. According to a recent study, Egypt has a calculated 51.8% estimated Cesarean section rate, placing it third among all countries in the globe (10). Considering that intravenous (IV) oxytocin has the criterion of a short half-life (4–10 minutes), it may be advantageous to maintain uterine contractions during Cesarean section operation and the first few hours after delivery through which the majority of primary bleeding happens (7).

The primary goal of this research was to gauge the influence of two different oxytocin regimens; intravenous slow oxytocin boluses (5 IU) and oxytocin infusions (40 IU in 500 ml 0.9% saline over 4 hours) on the body. After a great deal of debate, we selected two primary outcomes, both of which represented uterine atony. Given that severe obstetrical bleeding is the leading cause of maternal fatalities globally, it is the most relevant clinical outcome. In cases of uterine atony, however, medical professionals step in and give an extra uterotonic medication. This intervention would be a significant result in and of itself.

In the interest of objectivity, we evaluated the total blood loss during Cesarean section and right after surgery; however, we opted to use a calculation-based estimate derived from preoperative and postoperative packed cell volume (PCV). In resource-poor environments where blood tests are not frequently conducted, the measured blood loss would have greater significance.

The findings of our research demonstrated that, while there was no significant difference between the studied groups regarding estimated blood loss (EBL) (688.4 ± 229.5 versus 544.45 ± 177.4. Major obstetric hemorrhage (EBL ≥ 1000 ml) was statistically significantly higher in group (A) [17 (15%) versus 6 (5.7%)]. Similar to our trial, Selim and colleagues (11) looked at 180 women scheduled for elective CS and contrasted the outcomes of a 10-IU oxytocin bolus vs. a 10-IU oxytocin bolus & infusion of 30-IU oxytocin over a 4-hour period. With a p-value of 0.07, they discovered that there is no discernible difference between the two groups' mean blood loss (436.9 ± 51 versus 461.3 ± 50.7).
Conversely, Kajendran and associates (12) carried out a study analyzing oxytocin bolus (5 IU) versus oxytocin bolus (5 IU) and infusion of 20 IU oxytocin over 4 hours, they examined 92 pregnant women scheduled for an elective CS. Their findings, in contrast to ours, showed that oxytocin bolus and infusion group (intervention group) had significantly diminished mean computed blood loss and declined surgeon visual evaluation of blood losses (476.9 vs. 552.1) (p=0.01), but there was no significant difference in the incidence of major obstetric hemorrhage (p=0.153).

In terms of the results of the treatment, our research showed that group (A) used more uterotonics than group (B) [(26 (24.3%) versus 14 (12.1%)] with a p-value of 0.035. This aligns with the conclusions of Gungorduk et al. (13) where statistically significant difference was observed between the oxytocin bolus and infusion groups and the bolus group, with more women in the former group requiring extra uterotonic medications than in the latter [69 (19.2%) vs. 28 (7.8%), P < 0.001]. In contrast, there was no discernible difference in the extra uterotonics required or therapies after blood loss when compared to Kajendran and colleagues (P=0.216) (13).

In our study, PPH occurred in 13 (12.1%) versus 5 (4.7%) with p-value 0.111 where cases were conservatively managed in 5 (4.7%) bolus group versus 2 (1.9%) bolus & infusion group with p-value 0.908 using bimanual compression, bilateral uterine artery ligation and B-lynch sutures. Fortunately, there were no reported cases that underwent re-exploration, Hysterectomy and DIC or maternal mortality.

In our clinical trial, there were no significant differences between studied groups regarding post-operative HCT (33.86 ± 2.85 versus 34.17 ± 2.30 with p-value 0.378) and post-operative Hb (10.18 ± 1.21 versus 10.47 ± 0.833 with p-value 0.122). This agrees with Sheehan et al. (14) where about 2000 women assigned for elective CS were evaluated. Comparing oxytocin bolus (5 IU) versus oxytocin bolus (5 IU) & infusion of 40 IU oxytocin over 4 hours. They found no significant difference as regards hemoglobin drop and mean fall in hematocrit.

Similarly, Kajendran and colleagues (12) found no significant difference in postoperative haemoglobin drop (1.37 (1.1 – 1.6) vs. 1.40 (1.1 – 1.7) P=0.92) or postoperative packed cell volume (3.28 (2.7 – 3.9) vs. 4.08 (3.4 – 4.7) P=0.07). However, unlike our results Gungorduk and colleagues (13) declared that mean estimated loss of blood was statistically significant higher in bolus only group than in bolus & infusion group (866.89 ± 232.28 versus 609.63 ± 208.52 with P < 0.001). Postoperative Hct was statistically significant higher in bolus & infusion group than in bolus only (29.93 ± 1.06 versus 29.38 ± 1.00 with P < 0.001). Also, postoperative Hb was statistically significantly higher in group bolus & infusion group than in bolus only (9.56 ± 0.69 versus 9.46 ± 0.73 with P < 0.001).

Hemodynamic instability, nausea, vomiting, and headaches are among the adverse reactions of oxytocin, according to a number of investigations and observational research (15). In our study, side effects occurred in 6 (5.6 %) in bolus group versus 8 (7.5%) in bolus & infusion group, with p-value 0.38. This agrees with Kajendran and colleagues (12) where occurrence of side effects in bolus & infusion group was 208/1033 (20.1%) compared to 185/1025 (18.0%) in bolus only (p=0.21).

Again, Gungorduk and colleagues (13) found that there were statistically insignificant differences between both groups regarding side effects [15 (4.2%) vs 21 (5.8%), P = 0.31].

Our study, however, was restricted to women having elective CS; non-elective deliveries should be the focus of future research. From a scientific standpoint, we need to add a third comparison group that represents applying an injection of oxytocin (infusion only) combined with a placebo bolus in contemporary clinical practice. To accommodate this extra group would mean deviation from the hospital policy in accordance with guidelines issued by the Royal College of Gynecologists and Obstetricians. However, we concluded that this strategy may not be permitted in any of our enrollment facilities where oxytocin bolus is the routine standard practice.

Further investigation aimed at minimizing significant maternal hemorrhage and hemorrhagic consequences is crucial, even as the frequency of CS continue to rise. Research from the past has demonstrated that an emergency CS carries a higher risk of serious obstetric hemorrhage than an elective one. Future research should focus on non-elective deliveries as our study was restricted to women awaiting elective CS.

CONCLUSION AND RECOMMENDATIONS

Ultimately, this randomized study revealed that following a 5 ml IV oxytocin slow bolus during an elective CS, an additional infusion of 40 IU oxytocin in 500 ml of saline solution over the following four hours reduced the risk of major obstetric hemorrhage and lessens the need for additional uterotonics. One strategy would be to suggest that all women having an elective CS get an oxytocin infusion after a gradual IV bolus. This strategy would lessen the objective clinical judgment on when to administer a further uterotonic drug and decrease maternal hemorrhage during and 24 hours following birth, when most PPH occur.

The manuscript's authors declare that:
1) The work is not being considered by anybody else.
2) None of the material has been previously published.
3) This manuscript has been revised and approved by all writers.

- **Conflict of Interest:** No conflict of interest.
- **Acknowledgment:** None.
- **Funding Source:** This study was self-funded.

**REFERENCES**