



Effect of Calcium Supplement Combined with Carbetocin on Postpartum Hemorrhage in Scarred Uterine Cesarean Section

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ABSTRACT

Cesarean section (CS) in scarred uterus pregnancies (SUPs) is a high-risk obstetric procedure often associated with the risk of postpartum hemorrhage (PH). The objective of this study was to investigate the effect of calcium supplement combined with Carbetocin on PH after CS in SUPs. Data were collected from 112 patients with SUPs who underwent CS in the Ganzhou Fifth People's Hospital from 2020 to 2022. Fifty-six patients received a treatment with calcium agents combined with Carbetocin (Comb group), and another fifty-six patients received a regular treatment (Regu group). The PH outcomes were compared between the groups and statistical analysis was performed. The PH volume in Comb group was substantially inferior to that in Regu group ($P < 0.05$). The incidence of adverse reactions in Comb group was substantially inferior to that in Regu group ($P < 0.05$). Additionally, Comb group had markedly shorter operation time and hospitalization time versus Regu group ($P < 0.05$). Calcium agents combined with Carbetocin markedly reduced the incidence of adverse reactions and the amount of PH after CS in SUPs, and shortened the operation and hospitalization time. Hence, the combined application of calcium agents and Carbetocin in CS was recommended for SUPs to improve the prevention and treatment of PH.

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Authors' Contribution

GL and YD conducted the experiments in this study. GL and YL contributed to the design and interpretation of the current study and wrote the article. All authors read, revised, and approved the final manuscript.

Key words

Carbetocin, Scarred uterus pregnancy, Postpartum hemorrhage, Oxidative stress, Coagulation indicators

INTRODUCTION

Cesarean section (CS) postpartum hemorrhage (PH) often results in serious consequences and poses a threat to the patient's life. The causes of PH are multifactorial, including uterine atony, retained placenta, immunosuppression, poor uterine contractions, and impaired wound healing after CS, with uterine atony being a common contributing factor (Ende *et al.*, 2021). Scarred uterus pregnancy (SUP), an ectopic pregnancy, occurs when a fertilized egg implants at the site of a previous CS scar (Shu *et al.*, 2017). This is a long-term complication of CS, resulting from inadequate healing of the uterine incision, prominent scar formation, or small fissures at the

scar site due to inflammatory factors. When the fertilized egg implants within these fissures in the uterine muscle layer, it leads to SUP. The incidence of SUP is closely associated with the rising rate of CS and approximately 6% of CS patients experience SUPs in subsequent pregnancies (Jiří *et al.*, 2022). Scarred uterus CS is a high-risk obstetric procedure characterized by delivering the baby through the uterine scar. Due to the ischemia, atrophy, and increased fragility of scar tissue, PH after scarred uterus CS is a common and severe complication (Dong *et al.*, 2023), posing great threats to the life and health of the mother.

Scarred uterus is one of the important risk factors for PH after CS. Following CS, the formation of scar tissue at the uterine incision site can affect the elasticity and contractility of the uterine wall. This formation of scar tissue may lead to structural disarray in the uterine smooth muscle layer, resulting in reduced uterine contraction strength and frequency (Doroszevska *et al.*, 2019). Hence, the risk of PH is relatively higher in cases of scarred uterus CS. Numerous studies both nationally and internationally have been conducted to explore effective methodologies for preventing and managing PH in scarred uterus CS. Traditional treatment approaches include surgical repair, blood transfusion, and plasma transfusion (Zheng *et al.*, 2020). Currently,

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commonly utilized pharmacological agents for preventing PH in clinical practice include oxytocin and carboprost tromethamine, which are drugs that promote uterine contractions (Gil-Rojas *et al.*, 2018). Studies have found that calcium agents may have a potential role in the prevention and treatment of PH after CS. Calcium agents can enhance the uterine muscle contraction strength by stimulating the contraction of muscle fibers and promoting the formation of intracavitary uterine blood clots, effectively reducing the amount of bleeding (Ansari *et al.*, 2022). This mechanism of action may be related to the critical role of calcium ions in intracellular signaling and muscle contraction processes. Carbetocin, a synthetic analogue of oxytocin, has a longer half-life in the patient's body relative to regular oxytocin and belongs to the category of long-acting oxytocins. Carbetocin can bind to oxytocin receptors, stimulating uterine smooth muscle contractions, increasing uterine contractile force, and frequency, thus further controlling bleeding (Gallos *et al.*, 2019). In a comparative observational study between carbetocin and oxytocin, it was found that carbetocin resulted in a smaller demand for blood transfusion after scarred uterus CS relative to the control group receiving oxytocin. Additionally, carbetocin reduced the need for additional postpartum treatments (uterine contractants and/or anemia management), indicating its more effective role in managing PH after scarred uterus CS (Sotillo *et al.*, 2020). The efficacy of single-factor treatment is not as prominent as that of multi-factor combination therapy. By combining existing disease-modifying therapies or novel formulations, it is possible to enhance potential benefits with an acceptable theoretical basis, good safety profile, and therapeutic efficacy. Attempting to select from different personalized drug combinations, with distinct mechanisms of action, may exhibit synergistic activity, maximizing benefits while minimizing risks (Martinelli, 2006).

Nevertheless, currently, there is no definitive conclusion on the efficacy of calcium agents combined with carbetocin in the prevention and treatment of PH after CS in SUPs. Hence, this work aimed to assess the clinical efficacy of calcium agents combined with carbetocin in preventing and managing PH through the observation of a certain number of patients undergoing CS for scarred uterus pregnancies. The results of this work can provide more accurate treatment guidance for clinical practice, reduce the incidence of PH after CS in SUPs, and improve the safety and quality of life for postpartum mothers.

MATERIALS AND METHODS

Research objects

A total of 112 patients with scarred uterus pregnancies who underwent CS at the Ganzhou Fifth People's Hospital

between 2020 and 2022 were collected as the study subjects. After randomization, there were 56 patients in combination treatment group (Comb group) and 56 patients in the regular group (Regu group).

The inclusion criteria for patients with scarred uterus pregnancies were those who were required CS or had a family request for CS. Patients with pelvic infection, abnormal coagulation function, cardiovascular and cerebrovascular diseases and carbetocin allergy were excluded from the study.

Procedure adopted

Patients who required CS underwent anesthesia with lumbar epidural combined anesthesia (He *et al.*, 2020), which had minimal side effects and was beneficial for postoperative recovery. During surgery the uterine muscle layer was incised, amniotic sac was punctured and the amniotic fluid was darned. The fetus was gently delivered through the incision.

The Regu group received conventional treatment, which included intravenous infusion of 20 units of oxytocin, uterine massage, and blood transfusion. The Comb group, in addition to uterine massage and blood transfusion, received intravenous bolus injection of 100 µg carbetocin, followed by intravenous infusion of 100 mL of 5% glucose injection solution along with 20 mL of calcium gluconate injection solution.

Observation indices

The bleeding volume of the patients during surgery, 2 h, and 24 h after surgery was observed and compared between groups of parturients. Postpartum bleeding and the occurrence of adverse reactions were recorded. The patients bleeding volume was calculated as follows: bleeding volume = (wet weight of wound dressing - dry weight of wound dressing)/ 1.05.

At 24 h post-surgery, 5 mL of venous blood was drawn in anticoagulant tubes, stored at 4°C. Subsequently, plasma was separated which was used for measuring levels of malondialdehyde (MDA), superoxide dismutase (SOD), glutathione peroxidase (GSH-px), and catalase (CAT) Enzyme-linked immunosorbent assay (ELISA) in the serum, comparing the stress indicators in the postpartum CS patients of the two groups. The ELISA procedure strictly followed the instructions provided in the ELISA kit.

Plasma isolated from 5 mL of venous blood of patients collected in anticoagulant tubes before surgery and 24 h postoperatively were processed, for measuring the levels of thrombin time (TT), activated partial thromboplastin time (APTT), and fibrinogen (Fib) before and after surgery in both groups employing Beckman fully automated coagulation analyzers.

The thickness of the uterine myometrium in patients was measured using a color doppler ultrasound diagnostic instrument, including the thickness of the anterior wall, posterior wall, and fundal wall of the uterus. The myometrial thickness in both groups of patients was compared.

Statistical analysis

The data from preoperative and postoperative indicators of the parturients were compiled, and SPSS 26.0 was employed for data analysis. Indicated as mean $\pm$ standard deviation ($\bar{x} \pm s$), continuous data were compared using t-tests. Presented as percentages (%), categorical data were compared using chi-square tests. $P < 0.05$ was considered statistically significant.

RESULTS

In Comb group, the average age of parturients was 29.36 ± 4.83 years, the average gestational age was 38.2 ± 2.4 weeks, and the mean parity was 1.6 ± 0.5 . In Regu group, the average age of parturients was 28.95 ± 4.64 years, the average gestational age was 37.7 ± 2.6 weeks, and the mean parity was 1.7 ± 0.4 . The analysis results revealed inconsiderable differences in the age, gestational age, and parity of the two groups of parturients ($P > 0.05$) (Table I).

Table I. Comparison of general information of two groups of parturients.

Index	Regu group (n=56)	Comb group (n=56)	P value
Age (years old)	28.95 ± 4.64	29.36 ± 4.83	0.264
Pregnancy cycle (week)	37.7 ± 2.6	38.2 ± 2.4	0.118
Deliveries frequency/times	1.7 ± 0.40	1.6 ± 0.50	0.342

Table II. Comparison of intraoperative and postoperative bleeding (ml).

Time	Regu group	Comb group	P value
Intraoperative	252.46 ± 38.11	174.23 ± 26.75	0.012
Postoperative 2h	374.13 ± 28.25	198.22 ± 25.12	0.036
Postoperative 24h	443.64 ± 36.14	279.16 ± 29.11	0.001

The analysis results for the comparison of bleeding volume between two the groups showed that the amount of maternal bleeding in Comb group was substantially inferior to that in Regu group ($P < 0.05$) (Table II).

Through observation as shown in Table III, in Regu group, there were 5 cases (8.9%) of tachycardia, 3 cases (5.4%) of fever, 7 cases (12.5%) of nausea and vomiting,

5 cases (8.9%) of chills, and 3 cases (5.4%) of elevated blood pressure. In Comb group, there were 2 cases (3.6%) of tachycardia, 1 case (1.8%) of fever, 1 case (1.8%) of nausea and vomiting, 2 cases (3.6%) of chills, and 1 case (1.8%) of elevated blood pressure. The results presented in Table III reveal that the incidence of adverse reactions in Comb group (41.07%) was substantially inferior to that in Regu group (12.50%) ($P < 0.05$).

Table III. Comparison of study indicators between two groups after operation.

Indicators	Regu group (n=56)	Comb group (n=56)	P value
Number of adverse reactions (n, %)			
Increased heart rate	5(8.9%)	2(3.6%)	0.041
Heating	3(5.4%)	1(1.8%)	0.022
Nausea and Vomiting	7(12.5%)	1(1.8%)	0.003
Chills	5(8.9%)	2(3.6%)	0.031
Hypertension	3(5.4%)	1(1.8%)	0.001
Oxidative stress			
MDA ($\mu\text{mol} \cdot \text{L}^{-1}$)	8.71 ± 1.46	6 ± 1.11	0.035
SOD (u/L)	328 ± 28.12	417 ± 22.16	0.002
GSH-px ($\text{nmol}/(\text{min} \cdot \text{ml})$)	382 ± 31.41	457 ± 24.52	0.021
CAT (u/L)	319 ± 18.25	389 ± 25.23	0.004
Coagulation			
Fib ($\text{g} \cdot \text{ml}^{-1}$)	0.65 ± 0.23	1.33 ± 0.25	0.018
TT (s)	9.15 ± 3.14	14 ± 4.13	0.027
APTT (s)	12.5 ± 4.02	22.5 ± 4.24	0.004
Thickness of myometrium (mm)			
Anterior uterine wall	6.6 ± 1.46	8.43 ± 1.29	0.014
Posterior wall of uterus	7 ± 1.52	8.54 ± 1.21	0.027
Uterine fundus wall	7.4 ± 1.61	8.64 ± 1.18	0.002
Adverse reaction rate (%)	12.50	41.70	0.026
Operative time (time)	62.16 ± 12.2	53.44 ± 13.1	0.033
Hospital stay (d)	57.5 ± 11.1	40.01 ± 10.5	0.004

Following ELISA testing, the results presented in Table III indicates that the postoperative serum MDA levels in Comb group are substantially inferior to those in Regu group ($P < 0.05$). Conversely, the levels of antioxidant substances, such as SOD, GSH-px, and CAT, in Comb group were greatly superior than those in Regu group ($P < 0.05$).

The postoperative differences in coagulation indicators were observed in both groups of patients. In Comb group, the differences in preoperative and postoperative values of TT, APTT, and Fib were greatly superior than those in Regu group ($P < 0.05$).

The postoperative uterine myometrial thickness of the two groups of parturients was observed. The recovery of myometrial thickness in the anterior wall, posterior wall, and fundal wall of the uterus in Comb group was markedly better than that in Regu group ($P < 0.05$). The results also indicate that Comb group had markedly shorter operation time and hospital stay versus Regu group ($P < 0.05$).

DISCUSSION

Studies have revealed that calcium-dependent mechanisms can promote the activation of regulatory myosin light chain, leading to increased cell cytoskeletal tension and favoring cell shortening, resulting in vasoconstriction (Ribeiro-Silva *et al.*, 2021). In a study of intracellular free calcium in pulmonary arterial smooth muscle cells from patients with idiopathic pulmonary arterial hypertension, the activation of Piezo1 (Piezo-type mechanosensitive ion channel component 1) by Yoda1 (GlyT2-IN-1) induces intracellular calcium release from internal calcium stores by targeting intracellular (intra-) Piezo1 localized to subcellular organelles, including the endoplasmic reticulum/sarcoplasmic reticulum, mitochondria, and nucleus. This leads to an increase in $[Ca^{2+}]_i$, as well as a mechanism that positions Piezo1 at the plasma membrane for calcium influx independent of storage operation. Moreover, the Piezo1-mediated increase in $[Ca^{2+}]_i$ is associated with enhanced contraction and proliferation of pulmonary arterial smooth muscle cells (PASMCs), and Yoda1 induces dose-dependent vasoconstriction in rat pulmonary arteries with endothelium denudation. When comparing PASMCs from patients with idiopathic pulmonary arterial hypertension (PAH) to donor PASMCs, a notable upregulation and increased activity of Piezo1 were observed in idiopathic PAH PASMCs, leading to elevated intracellular calcium levels ($[Ca^{2+}]_i$) and excessive proliferation (Liao *et al.*, 2021). This suggests that smooth muscle contraction is related to the content of calcium ions. The entry of calcium ions into smooth muscle cells can bind to actin and myosin, thereby enhancing ATPase activity (Wang *et al.*, 2022). It has been reported in the literature that calcium sparks are caused by the cooperative opening of a cluster of arginine-sensitive Ca^{2+} release channels in the sarcoplasmic reticulum of smooth muscle cells. Calcium enters through dihydropyridine-sensitive voltage-gated Ca^{2+} channels, activating calcium sparks, which then elevate the global cytosolic Ca^{2+} concentration. This, in turn, indirectly increases Ca^{2+} entry through membrane depolarization, thus enhancing smooth muscle contraction force (Jaggard *et al.*, 2000). This highlights that calcium agents can increase the contractile force of uterine muscles, promote

the formation of intracavity clotting, and consequently reduce the amount of bleeding. Carbetocin, a synthetic oxytocin analogue, stimulates uterine smooth muscle contraction. In a randomized, double-blind, non-inferiority trial, immediate postpartum intramuscular injection of heat-stable Carbetocin (100 μ g dose) was relative to oxytocin (10 IU dose) following vaginal delivery, and it was found that Carbetocin markedly reduced postpartum bleeding in patients (Widmer *et al.*, 2018). This finding aligns with the results of the current study, where the combination of calcium agents and Carbetocin in Comb group resulted in a greatly inferior incidence of PH versus Regu group. Carbetocin has a longer duration of action relative to oxytocin, reducing the need for additional uterine supplements. Furthermore, its heat stability allows for storage at room temperature (Day *et al.*, 2022). In the study by Albazee *et al.* (2022), Carbetocin markedly reduced intraoperative blood loss, hemoglobin/hematocrit levels, blood transfusion requirements, and additional surgical interventions, suggesting that Carbetocin can bind to uterine smooth muscle-specific receptors, inducing rhythmic contractions, and accelerating the existing contraction frequency. This effectively increases uterine tension and further reduces the risk of bleeding. Thus, the present study explored the synergistic effect of combining calcium agents with Carbetocin, revealing improved preventive and therapeutic outcomes for PH in scarred CSs.

PH following CS in scarred pregnancies can lead to oxidative stress in the body, resulting in the production of harmful metabolites that affect the coagulation function. Oxidative stress indicators, including MDA, SOD, GSH-px, and CAT, play crucial roles in this process. MDA is a metabolic product of oxidative stress and is associated with the amount of postpartum bleeding. SOD, GSH-px, and CAT are factors involved in counteracting oxidative stress (Yin *et al.*, 2022). When pregnant women experience abundant bleeding, it triggers an inflammatory response, leading to oxidative stress and excessive production of oxidative metabolites, thereby causing the body to consume large quantities of antioxidant factors (Ndrepepa, 2019). In this work, the levels of MDA in the postoperative period were greatly inferior in Comb group versus Regu group, while the levels of SOD, GSH-px, and CAT were higher in Comb group than in Regu group. These findings suggest that the combination of calcium agents and Carbetocin effectively reduces the amount of PH in scarred uterine CSs and alleviates postpartum oxidative stress reactions. Regarding the control of postpartum coagulation indicators, both groups of patients showed a decrease in coagulation indicators after surgery. Nevertheless, the Carbetocin group exhibited a greatly superior degree of reduction

in coagulation indicators before and after the operation versus Regu group. This suggests that the combination of calcium agents and Carbetocin accelerates platelet aggregation and improves the postoperative coagulation ability of parturients. In terms of observing the thickness of the uterine myometrium, postoperative measurements revealed that the anterior wall, posterior wall, and fundal wall of the uterus in Comb group were thicker than those in Regu group. This indicates that the combination of calcium agents and Carbetocin can increase the thickness of the uterine myometrium, making it a more effective treatment approach for scarred uterine CS relative to conventional treatment methodologies.

The findings indicated that the incidence of PH in the group treated with the combination of calcium agents and Carbetocin was greatly inferior versus Regu group. Moreover, the average amount of bleeding in Comb group was also markedly reduced. Additionally, Comb group exhibited markedly shorter surgical and hospitalization durations versus Regu group. These results suggest that the use of calcium agents in combination with Carbetocin has favorable clinical efficacy in preventing PH in scarred CSs.

Nevertheless, it is essential to note that this work has certain limitations. The sample size of the study is relatively small, which may lead to statistical constraints. Further large-scale randomized controlled trials are still necessary to validate these observational findings. Nevertheless, the results of this work still hold significant clinical implications. The combined application of calcium agents and Carbetocin demonstrates certain advantages in preventing PH in scarred CSs. This provides clinicians with an effective treatment strategy to reduce the risk of PH and improve maternal health outcomes.

CONCLUSION

The combination of calcium agents and Carbetocin demonstrates promising clinical efficacy in preventing PH in scarred CS. Nevertheless, further investigations are still warranted to validate these observational findings, and clinicians should make individualized treatment decisions based on patients specific conditions and needs. We hope this work will offer valuable insights for clinical practice and contribute to the development of more effective strategies for the prevention and treatment of PH in scarred CSs.

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IRB approval

This study was approved by the Advanced Studies Research Board of Ganzhou Fifth People's Hospital, Jiangxi Province, China.

Ethical approval

The study was carried out in compliance with guidelines issued by ethical review board committee of Ganzhou Fifth People's Hospital, China. The official letter would be available on fair request to corresponding author.

Statement of conflict of interest

The authors have declared no conflict of interest.

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