Clinical and Experimental Obstetrics & Gynecology

Clin. Exp. Obstet. Gynecol. **2022**; 49(2): 033
http://doi.org/10.31083/j.ceog4902033

Case Report

Coagulopathy complicating intraoperative blood salvage in patients receiving cesarean section: three case reports and a literature review

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Academic Editor: Michael H. Dahan
Submitted: 11 July 2020 Revised: 10 October 2020 Accepted: 20 October 2020 Published: 26 January 2022

Abstract

Background: Intraoperative cell salvage (ICS) has been used in more than 1100 published obstetrics cases and can reduce the need for allogeneic transfusion effectively. However, ICS could lead to a life-threatening coagulopathy called salvaged blood syndrome (SBS). SBS was reported in several non-obstetric cases but has rarely been reported in obstetric patients. **Cases**: We reviewed all 841 cell savage cases that occurred in our hospital prior to October 2018. Here, we present 3 cases of coagulopathy in patients who received ICS after cesarean section. The rate of obstetrical SBS in our hospital was 0.46%. **Dicussion**: Cesarean section was performed without severe hemorrhage, and we performed the surgical hemostatic procedures as usual. Then, several hours after the surgery and after ICS, bleeding occurred, in which hypofibrinogenemia was more severe than expected based on the amount of postpartum hemorrhage. In addition, other marked changes in coagulation function-related parameters, including a decline in the platelet count and obvious prolongation of the PT and aPTT levels, were also observed. More specific and in-depth studies concerning obstetric SBS are needed.

Keywords: Coagulopathy; Cesarean section; Intraoperative cell salvage; Salvaged-blood syndrome

1. Introduction

Hemorrhage is the leading cause of maternal morbidity and maternal death worldwide [1]. The appropriate use of intraoperative cell salvage (ICS) in obstetrics can reduce the need for allogeneic transfusion and has been used in more than 1100 published cases [2,3]. Amniotic fluid embolism (AFE) has never been reported and remains theoretical [2]. However, ICS could lead to a life-threatening coagulopathy called salvaged-blood syndrome (SBS). SBS has been reported in several nonobstetric cases [4,5]. There has been only one case report of an obstetric patient with reinfusion of more than 2 L of blood cells [6]. We present here 3 cases of coagulopathy in patients who received ICS after cesarean section.

2. Case report

2.1 Patient 1

A 35-year-old pregnant woman with dizygotic twins (through IVF) and GDM (A1) (gestational diabetes mellitus, treated with diet combined with exercise to control the blood glucose level without insulin) received an elective cesarean section at 38 + 1 weeks. She had no history of bleeding disorder and a normal preoperative hematologic profile, including a hemoglobin (Hb) of 105 g/L, hematocrit (Hct) of 33%, platelet (PLT) count of 145 $\times$ 10^9/L, a fibrinogen concentration of 3.7 g/L (normal range 1.8–4.2 g/L), and a normal activated partial thromboplastic time (aPTT) and partial thromboplastin time (PT) of 29 and 11 s, respectively (aPTT normal range 21–37 s, PT normal range 9–12 s).

After successful hemostasis thorough cesarean section, two babies were delivered; a SORIN XTRA System (Sorin Group USA Inc.) with one suction device was used to aspirate the autologous red blood cells for reinfusion. All anesthesiologists who operated the system were trained and familiar with the use of the cell salvage machine in accordance with local established procedures and requirements. The estimated blood loss was approximately 700 mL during the surgery. The collected red blood cells were mixed with heparinized saline in the suction device and washed with 1000 mL of normal saline solution. After a washing and centrifugation cycle, 412 mL of autologous red blood cells (46% HCT) were reinfused by means of filtered blood administration. After surgery, the estimated blood loss was nearly 800 mL, and routine blood tests and coagulation profiles were evaluated. The Hb level was 101 g/L, the Hct was 31.4% and the PLT count was 110 $\times$ 10^9/L. The normal PT, aPTT and fibrinogen concentration were 10 s, 32 s and 2.6 g/L, respectively, there was elevation of D-dimer (45.38 mg/L; normal range 1.3–4.2 mg/L) and fibrinogen degradation product (183.2 mg/L; FDP, normal range 0–13.98 mg/L).

Two hours after the operation, the condition of the patient was stable, but ten hours after the operation, a marked increase in vaginal bleeding was noted, and the estimated blood loss was up to 1060 mL. Blood tests showed a sharp decrease in the fibrinogen concentration of 1 g/L, and Hb was 86 g/L, Hct was 27%, and the PLT count was 110 $\times$

10^9/L; there were slightly elevated PT and normal aPTT values of 13 s and 34 s, respectively, and D-dimer was >80.00 mg/L and FDP was 332.8 mg/L. Then, to correct the coagulation function and anemia, 4 U of blood cell suspension, 400 mL of fresh frozen plasma and 4 U of cryoprecipitate were administered intravenously, and a Bakri intrauterine balloon tamponade was applied immediately.

Eleven hours after surgery, hemoglobinuria was detected, and 10 mg dexamethasone and 10 mg furosemide were intravenously injected. Thirteen hours after surgery, the total urine output was up to 700 mL. Coomb's test was negative. Since there was no elevation in white blood cells and the temperature was normal before and after surgery, there was no evidence of infection. Normal coagulation tests performed over the next 24 hours showed a fibrinogen concentration of 4 g/L, an Hb of 78 g/L and a PLT count of 124 $\times$ 10^9/L. Two days after the surgery, the Bakri intrauterine balloon was removed, and the patient was discharged 4 days after surgery.

2.2 Patient 2

A 30-year-old pregnant woman with suspected macrosomia had an elective cesarean section at 40 weeks. She had no history of bleeding disorder and a normal preoperative hematologic profile, including an Hb of 115 g/L, Hct of 36.1%, PLT count of 162 $\times$ 10^9/L, and a PT, aPTT and fibrinogen concentration of 11 s, 27 s and 3.9 g/L, respectively.

After successful hemostasis thorough cesarean section, the patient delivered a son who weighed 3960 g via the SORIN XTRA System (Sorin Group USA Inc.), and anesthesiologists began to perform procedures as described above. The estimated blood loss was approximately 800 mL during the surgery. Red blood cells were collected and washed by following the same procedure used in case one. A total of 396 mL of autologous red blood cells (52% HCT) was reinfused. The hemodynamic status was stable with stable vital signs, and the urine output was approximately 100 mL.

Four hours after surgery, a marked increase in vaginal bleeding was noted, and the estimated blood loss was up to 1160 mL. A Bakri intrauterine balloon tamponade was applied immediately, and the hematologic profile also showed a sharp decrease in the fibrinogen concentration of 0.8 g/L; the Hb was 115 g/L, the Hct was 36.5%, the PLT count was 118 $\times$ 10^9/L, and the abnormal PT and aPTT values were 14 s and 38 s, respectively. Then, 400 mL of fresh frozen plasma, 8 U of cryoprecipitate and 8 g of fibrinogen were infused immediately to improve coagulation function. After that, a small amount of constant blood loss still existed, and red blood cell suspension (2 U), fresh frozen plasma (200 mL), and cryoprecipitate (4 U) were infused to correct coagulation function and anemia. The hematologic profile showed an elevated fibrinogen concentration of 2.4 g/L, an Hb of 90 g/L, an Hct of 28.1%, a PLT count of 95 $\times$ 10^9/L, and abnormal PT and aPTT values of 13 s and 32 s, respectively. Bilateral uterine artery embolization was carried out. Twelve hours after surgery, an abnormal PT of 18 s and an INR of 1.56 (normal range 0.85–1.15) were observed, and 900 U thrombin complex was administered intravenously to reverse the possible coagulation disorder.

Sixteen hours after surgery, the hematologic profile showed a fibrinogen concentration of 3.6 g/L, an Hb of 86 g/L, an Hct of 25.8%, a PLT count of 93 $\times$ 10^9/L, and PT and aPTT values of 12 s and 40 s, respectively. On the first day after surgery, the coagulation tests became normal, with a hematologic profile showing a fibrinogen concentration of 4.1 g/L, an Hb of 83 g/L, an Hct of 25%, a PLT count of 101 $\times$ 10^9/L, and normal PT and aPTT values of 11 and 27 s, respectively. Since there was no elevation of white blood cells and the temperature was normal before and after surgery, there was no evidence of infection. The Bakri intrauterine balloon was removed. This patient was discharged 9 days after surgery.

2.3 Patient 3

A 30-year-old pregnant woman was diagnosed with gestational thrombocytopenia during pregnancy. The lowest platelet count was 66 $\times$ 10^9/L at 38 + 4 weeks throughout her pregnancy, and the platelet count was 77 $\times$ 10^9/L when she was admitted at 38 + 6 weeks because of breech position. Other preoperative hematologic levels were within the normal range, including a fibrinogen concentration of 3.5 g/L, an Hb of 128 g/L, an Hct of 37.8%, and normal PT and aPTT values of 10 s and 30 s, respectively.

She underwent an emergency cesarean section on the day of admission, and the cesarean section was successful. The hemostasis was thorough, and a daughter was delivered that weighed 3420 g via the SORIN XTRA System (Sorin Group USA Inc.); the anesthesiologists started to perform procedures as described above. The estimated blood loss during the operation was 800 mL during the surgery. After a routine washing and centrifugation cycle, 203 mL of autologous red blood cells (60% HCT) were reinfused. The urine output was 100 mL at the end of the operation. Routine blood tests and coagulation profiles were performed during the operation. The fibrinogen concentration was 2.6 g/L, the Hb was 96 g/L, the Hct was 29.1%, and the PLT count was 58 $\times$ 10^9/L. The hematologic file also showed elevated PT and normal aPTT values of 17 s and 33 s, respectively.

Fresh frozen plasma (400 mL) and 8 U cryoprecipitate were administered intravenously to improve coagulation function. Two hundred milligrams of hydrocortisone via intravenous drip was given after the operation for thrombocytopenia. During plasma transfusion, anaphylaxis emerged, so the intravenous drip of hydrocortisone was continued, and 1/3 subcutaneous injections of antiallergic epinephrine hydrochloride were used. Forty milligrams of methylprednisolone via intravenous drip was used for thrombocytopenia. During that time, the coagulation test showed sharp

decreases in Fbg to 0.6 g/L, PT to 11 s, aPTT to 31 s, TT to 24 s, Hb to 123 g/L, the PLT count to 11 $\times$ 10^9/L, and Hct to 36.2%. Single-donor apheresis of 2 U platelets, 6 g fibrinogen and tranexamic acid were used for treatment of thrombocytopenia and as a pro-coagulant. Then, 4 g fibrinogen and furosemide were used once again.

Eventually, hemostasis was achieved. At 7 hours after surgery, the urine output was 250 mL, and a coagulation test was performed. Other parameters were as follows: Fbg 4 g/L, PT 11 s, aPTT 32 s, TT 19 s, INR 0.97, Hb 103 g/L, PLT count 94 $\times$ 10^9/L, and Hct 30.6%. Repeated blood tests during the 3-day hospital stay were normal, with an Hb of 96 g/L, a PLT count of 134 $\times$ 10^9/L, and an Hct 30%; on postoperative day 7, the patient was discharged from the hospital. Since there was no increase in white blood cells and the temperature was normal before and after surgery, there was no evidence of infection. This patient was lost to follow-up, and we could not measure the PLT count later. Based on the elevated PLT count detected 4 days after delivery (134 $\times$ 10^9/L), gestational thrombocytopenia was a possible diagnosis.

3. Discussion

These three abbreviated case reports might illustrate the features of SBS after cesarean section. Cesarean section was performed without severe hemorrhage, and we performed surgical hemostatic procedures as usual. Then, several hours after surgery and ICS, bleeding occurred, in which hypofibrinogenemia was more severe than expected based on the amount of postpartum hemorrhage. In these three cases, large changes in fibrinogen levels were obvious before and after the correction of coagulation function. The change in fibrinogen levels may have been subtler than that in other coagulation or thrombotic factors, including thrombocytes, in our cases.

In 1998, Rebarber A *et al.* [7] showed that there was no demonstrably increased risk of intravascular coagulation in patients receiving autologous blood collection autotransfusion during cesarean section through a multicenter historical cohort study including 139 cases. With the increasing use of ICS during surgery, this rare complication has attracted attention. Recently, an RCT (Randomized controlled trial) study showed that among the adverse events, three cases of thrombocytopenia among 1498 women who underwent intraoperative cell salvage during cesarean section occurred, and the rate was 0.2% [3]. We reviewed all 841 cell savage cases that occurred in our hospital until October 2018 and found the three cases described here, and the rate of SBS in the obstetrical unit in our hospital was 0.46%, which was similar to that observed in the abovementioned study.

Early in 1992, David *et al.* [4] reported two cases of SBS in nonobstetrics surgeries, and they were confused by the difference in dilutional coagulopathy and disseminated coagulopathy in situations of major blood loss without *in vitro* hemostatic test results. Upon obtaining a more in-depth understanding of SBS, dilutional coagulopathy was considered the main reason for SBS.

The exact cause of the three cases described here has still not been completely demonstrated to be postpartum hemorrhage-induced disseminated coagulopathy, since there was blood loss of no more than 1000 mL (800 mL) in 2 cases and of 1160 mL in another case when an obviously abnormal fibrinogen concentration, platelet level, and PT and aPTT levels were observed. It seemed that the amount of blood loss was not in line with the rapid declines in the fibrinogen concentration and platelet level. On the other hand, we also know that the amount of PPH (postpartum hemorrhage) is usually estimated to be less than the actual amount, and there is also a possibility that we made an inadequate estimation of bleeding volume; however, the vital signs were stable in these 3 cases after surgery, and the urine output in these three cases was appropriate. There may be another explanation for the fact that the estimated blood loss seems inadequate; during the ICS, blood cells might be damaged, the loss of blood cells might exist, and the total amount of blood collected may be less than expected [8]. We are inclined to consider the possible cause of these three cases to be dilutional coagulopathy. However, we admit it may be difficult or impossible to clarify the cause-effect relationship between ICS and the subsequent coagulopathy.

As an anticoagulant, heparin could also be a possible reason for SBS, but according to the evaluation of the ICS device, the heparin elimination rate ranged from 98% to 100% [9,10]. The presence of heparin in salvaged blood has been well studied. Heparin washout is routinely used as a quality measure. In general, one can expect less than 10 units of blood per 225 mL bolus, which is a clinically insignificant amount of heparin. Based on the ICS routine of our hospital, the total amount and the transfusion speed of normal saline containing heparin followed strict standards, and heparin might therefore rank lower as one of the possible reasons.

Another possible main cause of SBS may be the activation of coagulation by damaged erythrocytes or by mediators released by platelets or leukocytes, which was proposed in the 1990s [4]. However, this is less likely because of the use of leucocyte depletion filters (LDFs) in ICS devices. Platelets and leucocytes could be activated during the cell-concentration phase of blood salvage if there existed excessive hemodilution of the salvaged blood with saline, and reinfusion of such blood can result in intravascular damage and inflammation and thereby induce coagulopathy [6]. In addition, red blood cell damage was presumed to be one possible reason, and hemoglobinuria might indicate the existence of damaged red blood cells among reinfused red blood cells that could act as thromboplastin-like substances and initiate disseminated coagulation [4]. One patient involved in our cases showed hemoglobinuria, which was presumed to be a sign of hemolysis, but Coomb's

test was negative. The reason for the damage of red blood cells might have been vacuum aspiration of blood that was collected during surgery. Control of the aspiration pressure might be necessary to reduce the risk of SBS. In our three cases, our surgical procedure followed the established routine in that the baseline aspiration pressure was set between 100 mmHg and 150 mmHg.

Amniotic fluid embolus (AFE) was mentioned in ICS-related studies but has remained theoretical because of the use of LDFs, which can remove all elements of amniotic fluid effectively [2,10]. In our three cases, there was no AFE-related evidence, as the SPO_2 was in the normal range, and there was stable arterial blood pressure and no relative complaints from patients during the whole rescue process in these three cases.

The amount of autologous blood that is appropriate for reinfusion after standard treatment is uncertain. According to the guidelines for autologous blood transfusion in China in 2019, the timing of ICS application was determined according to the bleeding condition and the presurgery Hb level. This can be used for autotransfusion to meet certain standards, but there is no clear standard to define the term "certain". According to the routine procedure used for autologous blood transfusion after years of practical experience, when the presurgery Hb level is over 100 g/L and when the total amount of autologous red blood cells after a series of processes is 60 mL, as calculated according to the amount of blood multiplied by the Hct, the collected autologous blood can be returned to the patients. The total amount of autologous red blood cells needed can change depending on the presurgery Hb level. However, there are also restrictions; when the Hct of autologous blood was lower than 20%, reinfusion was not applied, and when constant bleeding occurred, Hct was not taken into consideration, and autotransfusion was unconditionally executed.

4. Conclusions

Our case report revealed that the rate of SBS in obstetrics was 0.46%. Additional specific and in-depth studies concerning the characteristics and mechanism of obstetric SBS are necessary for further understanding of this special syndrome.

Author contributions

WRG and XRX designed the research study. YZ performed the research, collected data and wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This research was approved by ethics committee of Obstetrics and Gynecology Hospital of Fudan University (2020-08). All participants signed informed consent.

Acknowledgements

We would like to express our gratitude to all those who helped us during the writing of this manuscript and to all the peer reviewers for their opinions and suggestions.

Funding

This work was partly supported by National Natural Science Foundation of China (81871183); National Natural Science Foundation for Young Scholars of China (81701470); the Shanghai Committee of Science and Technology (18411963400); Shanghai Medical Center of Key Programs for Female Reproductive Diseases (2017ZZ01016); and the Shanghai Key Program of Clinical Science and Technology Innovation (17411950500; 17411950501).

Conflict of interest

The authors declare no conflict of interest.

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