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Intraoperative Autologous Blood Transfusion

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INTRODUCTION

Life-saving transfusion using human blood was first described by James Blundell in 1818. He performed ten transfusions, five of which were successful; of these, four were in women suffering postpartum hemorrhage (PPH). He typically used donor blood from the patient's husband, showing that the technique of blood injection with a syringe infusion was safe[1]. In one account, he is credited with the re-infusion of autologous blood[2]. It is entirely appropriate, therefore, that the subject of intraoperative autologous transfusion be described in this textbook on PPH. Blundell's original report described a reasonable outcome considering the crude understanding of blood transfusion techniques in existence almost a century before Landsteiner's identification of the ABO blood groups[3].

Some of the earliest reports of intraoperative blood salvage described the life-saving technique of simply collecting spilt blood from the abdominal cavity, filtering it through a gauze swab, and re-infusing what remained. In the ensuing years, techniques to collect, filter and wash blood lost at the time of surgery have become commonplace, although refinements of the method vary widely and depend not only upon the nature of the surgical procedure, but also the availability of technical resources. As might be expected, expensive apheresis machines are lacking in many, if not most, parts of the world where operative obstetrics are routinely practiced. Nevertheless, the problem of PPH is so common and remains such a clinical challenge that the technique as originally described is still used out of necessity in these circumstances. This chapter describes various methods of autologous blood salvage and, in particular, its evolving use in obstetrics with direct reference to PPH.

DEFINITION

Autologous blood salvage is the collection of spilt blood resulting from surgical or traumatic bleeding that can be undertaken intraoperatively or postoperatively. The collected blood can be filtered and re-infused or filtered, washed and then re-infused.

METHODS

The quality and constitution of re-infused blood vary depending on whether washed or unwashed systems are used. In the absence of automated cell-washing devices, simple collection, filtration and re-infusion during PPH have been described and continue to be used in some areas in the world. However, this technique is not ideal. On the other hand, the use of unwashed blood (particularly for postoperative collection and re-infusion using a sealed postoperative collection unit with a filter) has been used extensively in total knee surgery and appears safe and effective. Interestingly, one report suggested that the use of unwashed blood might have inherent properties that improve the recipient's immune response[4]. The more widely applied intraoperative cell salvage is conducted with apparatus that has the ability to collect spilt blood at the time of the operation and anticoagulate it at the tip of the suction apparatus with citrated solution or heparinized saline (25,000 IU per liter of normal saline) (Figure 1).

Collected blood is then transferred to a centrifugal bowl, where spinning at 5500 revolutions per second moves the heavier red cells to the outer periphery of the bowl. As the bowl fills, the accumulation of red cells forces the plasma, platelets and other cellular debris out of a central exit, discarding waste products of the process. Special sensors identify when the bowl is full of red cells, and the fully automated machine begins to wash the collected and concentrated erythrocytes with normal saline. This process further cleanses the red blood cells. The resultant concentrate is then suspended in normal saline, producing a solution with a hematocrit of 60%. Unfortunately, most of the platelets and clotting factors will have been washed away at this point, and the fluid for re-infusion consists of autologous red cells suspended in normal saline[5]. In the presence of brisk bleeding, any of the commercially available automated cell-washing devices can produce a unit of red cell concentrate in 5–10 min. The volume of lost blood that can be processed is infinite, and reports of cell salvage in major trauma describe its successful use, the process providing approximately 50% of the required red cell transfusion[6]. Of course, in such situations, the use of cell
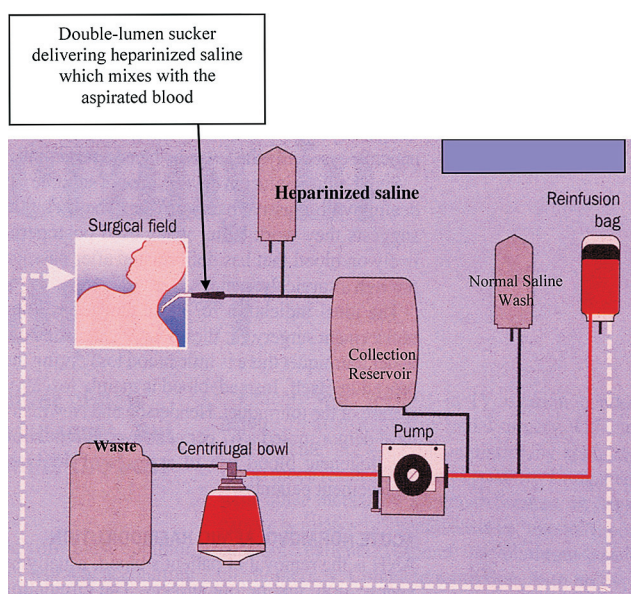
Figure 1 A diagrammatic representation of intraoperative cell salvage. (Adapted from an original drawing with the kind permission of Haemonetics Inc., Baintree). The dotted line represents infusion sent back to the patient. In the case of a Jehovah's Witness, this is primed with saline before starting to complete continuity of the circuit

salvage only minimizes the demand for allogeneic blood. In cases of massive hemorrhage, cell salvage devices help to recycle transfused allogeneic blood as well as autologous blood. As few platelets and minimal clotting factors are present in these re-infused red cells, careful assessment of coagulation parameters is required, especially in cases of excessive bleeding where massive transfusion is required. Nowadays, this is the case in patients with massive hemorrhage, as the provision of red cells suspended in a mixture of saline, adenine, glucose and mannitol (SAGM) means that only packed allogeneic red cells are being infused, and so similar provisos apply. Under these circumstances, early consideration therefore needs to be given to platelet and fresh frozen plasma administration.

HISTORICAL COMPLICATIONS

Current machines have an extremely good safety record, but it is worthwhile dispelling some misconceptions about the technique that persist. Air embolism is not a problem with modern equipment when it is used correctly. Free hemoglobin is almost completely removed, and the very small amounts that remain have no significant clinical effect. Platelets are activated during salvage, but the majority are removed during the process. Leukocytes, complement and kinins are also activated during salvage, but systemic inflammatory responses have not been reported as clinically relevant.

POTENTIAL CONTRAINDICATIONS

The non-availability of a safe allogeneic blood supply is clearly a situation when the use of cell salvage is justified in an attempt to preserve the patient's own blood and help oxygen carriage. In the UK, current blood conservation recommendations promote the use of cell salvage[7]. The current drive for blood conservation is multifactorial, but the most topical reason is the potential decrease in the availability of donor blood resulting from the introduction of a test for the presence of abnormal prion protein. However, reduced numbers of donors is a problem that had its inception prior to the present testing concerns, as the presence of HIV and other viral pathogens have also restricted the number of potential donors. It is against this backdrop that consideration of cell salvage in PPH was made, and the remainder of this chapter examines the use of intraoperative cell salvage during PPH. Fortunately, the widespread use of such devices has confirmed the safety of this process, providing there is no technical failure and the correct procedure for machine operation is practiced. The use of such devices is endorsed by national guidelines and government directives[8,9].

Following a seminal report[10] supporting this technology, it now is accepted that three areas exist where the process of red cell salvage needs to be used with caution and following a risk–benefit analysis, depending on the clinical urgency of the situation. These involve the use of red cell salvage when spilt operative blood may contain malignant cells, or be heavily contaminated with bowel bacteria. Another area of caution is the use of red cell salvage when contaminated by amniotic fluid. It is accepted that, in the presence of any of these preconditions, cell salvage is not used unless considered necessary.

SAFETY OF CELL SALVAGE IN OBSTETRICS

Two theoretical problems attend the use of cell salvage at the time of cesarean section. First, in an Rh-negative mother, there is a risk of Rh immunization if the fetus is Rh-positive. As the cell saver cannot distinguish fetal from adult red cells, any fetal red cells suctioned from the operative field will be processed and re-infused with the maternal red cells. In practice, studies show that the degree of contamination with fetal red cells during cell salvage at cesarean section is between 1 and 19 ml[11–13]. Applying the standard Kleihauer calculation, this would require between 500 and 2500 units (1–5 ampules) of anti-D to avoid Rh immunization. As all Rh-negative patients require anti-D after cesarean section, patients receiving salvaged blood may simply require an increased dose. Larger doses have been used after mismatched transfusions with no untoward results.

The second theoretical problem is contamination with amniotic fluid, raising the specter of iatrogenic amniotic fluid embolus (AFE). This theoretical complication has been investigated by several workers, and has not been found to be a problem in practice[12–16]. The difficulty is that the precise elements of amniotic fluid which cause the rare and unpredictable 'anaphylactoid syndrome of pregnancy' (as AFE is more correctly called) remain unknown. To conduct a

prospective, randomized, controlled trial with an 80% power to demonstrate that cell salvage does not increase the incidence of AFE by five-fold would require up to 275,000 patients, a number so large that the effort is unlikely ever to be undertaken. To demonstrate the absolute safety of a technique without randomized, controlled trials requires careful clinical audit of a large number of cases, supported by robust *in vitro* evidence.

IN VITRO STUDIES OF AMNIOTIC FLUID CLEARANCE

In vitro studies have examined the clearance of α-fetoprotein[14], tissue factor[15], trophoblastic tissue[12], fetal squames and lamellar bodies[13] from maternal blood by the cell salvage process. Small molecules are removed in the plasma fraction by the centrifuge and wash process, whereas particulate material is removed by the use of specialized leukodepletion filters. Using the combination of cell salvage and these specialized filters, every element of amniotic fluid that has been studied so far has been effectively removed from salvaged blood prior to re-transfusion[12–16].

CLINICAL CASES

Prior to 1999, approximately 300 cases in which cell-salvaged blood was administered to patients had been reported worldwide[16]. No obstetric clinical or physiological problems were encountered, despite the fact that filters were not used at this time. This means that each of these patients had some exposure to amniotic fluid, and with no ill effects. Waters and colleagues[13] described not only the complete clearance of squamous cells and phospholipid lamellar bodies from filtered, cell-salvaged blood, but also clearly demonstrated the presence of both these amniotic fluid markers circulating in the maternal central venous blood at the time of placental separation. In 100% of patients in this trial, amniotic fluid was demonstrated in the circulation of healthy parturients undergoing elective cesarean section. It is therefore probable that amniotic fluid routinely enters the maternal circulation and does no harm in the vast majority of cases. This exposure may trigger the syndrome of AFE due to an anaphylactoid reaction to an as-yet unidentified endogenous mediator in a very small number of women, the incidence of which varies between 1 in 8000 and 1 in 80,000 patients[17]. *[Editor's note: As it has never been studied, there is no evidence to state that entry does not occur in an unknown number of cases of vaginal parturition. L.G.K.]* Clearly, reinfusion of cell-salvaged blood, even if contaminated with traces of amniotic fluid, presents no extra risk to the woman from whom that blood has come, as she has already been exposed to it.

In 1999, a single report appeared describing a seriously ill Jehovah's Witness with severe pre-eclampsia complicated by HELLP syndrome who died in Holland after having received cell-salvaged blood[18]. In an oral presentation in London sometime afterward,

one of the speakers referred to this case as a 'death due to obstetric cell salvage'[19]. It should be noted, however, that a patient who is seriously ill with HELLP syndrome and who refuses platelet and coagulation factor transfusion is unlikely to survive. Under such circumstances, it is a mischaracterization to suggest that her death was related to the use of cell salvage rather than to ascribe it to her refusal to accept blood component therapy.

Cell salvage in obstetrics was introduced in the UK in 1999, and its use has grown rapidly, with most major obstetric units now advocating the technique in selected circumstances. The Confidential Enquiry into Maternal and Child Health 2000–2002 (CEMACH)[20] stated that '. . . (cell salvage) may be used in any case of obstetric haemorrhage, not just women who refuse blood transfusion' and described the technique as 'a new development which will prove helpful in the future'. It further stated that 'the risk of causing coagulopathy by returning amniotic fluid to the circulation is thought to be small'. Subsequent to this, the 2005 revised Guidelines for Obstetric Anaesthetic Services were published jointly by the UK Obstetric Anaesthetists Association (OAA) and the Association of Anaesthetists of Great Britain and Ireland (AAGBI)[21], stating that 'an increasing shortage of blood and blood products and growing anxiety about the use of donor blood are leading to an increasing interest in the use of cell salvage in obstetrics. Staff will have to be suitably trained, and equipment obtained and maintained. . .'

In November 2005, the UK National Institute for Clinical Excellence (NICE) reported on Cell Salvage in Obstetrics[22], describing cell salvage as 'an efficacious technique for blood replacement, well established in other areas of medicine' and pointing out the *theoretical* concerns when used in obstetrics. NICE goes on to recommend that clinicians using it in the UK should report any side-effects to the UK Department of Health Regulatory Authority (MHRA), that patients should be fully informed prior to its use, and that cell salvage in obstetrics should be performed by multi-disciplinary teams that have developed regular experience in its use.

PRACTICAL USE OF CELL SALVAGE IN OBSTETRICS

The present experience with the use of cell salvage in obstetrics in the UK is substantial; cases include major hemorrhage due to placenta previa, placenta accreta, ruptured uterus, extrauterine placentation, massive fibroids and placental abruption, as well as more routine use in Jehovah's Witnesses to avoid postoperative anemia[14].

The following guidelines used for cell salvage in obstetric use in the Swansea NHS Trust Hospitals, UK are an example:

(1) It may be used for any situation in which allogeneic blood is used, but to date has been confined to cesarean sections and uterine

re-exploration or laparotomy following PPH. In reality, vaginal blood loss can be collected and cell salvaged, as fears about infection have proved unfounded as long as the patients are on antibiotics. The technical problem with physically collecting vaginal blood loss can be addressed with the planned use of the BRASSS drape described in Chapter 11.

(2) The machine is prepared and operated according to standard operating procedure, with an 'in-continuity' set-up for Jehovah's Witnesses (the whole circuit is run through with saline and the re-transfusion bag connected to the intravenous cannula before starting the salvage suction, thereby establishing a continuous circuit between the blood lost and the recipient vein).

(3) In cases where there is doubt about the extent of expected blood loss, it is economical to set up the aspiration and reservoir kit only – the decision to process and re-transfuse can be made when the degree of hemorrhage becomes clear (e.g. 'expected' bleeding from placenta previa).

(4) Where practicable, amniotic fluid should be removed by separate suction prior to starting cell salvage. However, some authors suggest that this is not necessary and that the quality of the washing procedure is sufficient to remove fetal contaminants[23].

(5) Suction should be via the wide-bore suction nozzle already supplied in the kit, and the surgeon should try to suction blood from 'pools' rather than 'dabbing' tissue surfaces with the suction tip, as this minimizes erythrocyte damage.

(6) Blood from swabs can be gently washed with saline and salvaged from a sterile bowl into the main reservoir.

(7) Suction pressure should be kept as low as practicable (less than 300 mmHg) to avoid red cell damage, although higher vacuum can be safely used if necessary with only a minimum increase in red cell damage.

(8) It is advisable to use a leukocyte depletion filter (Leukoguard® RS Pall) in the retransfusion circuit if there is any risk of amniotic fluid contamination. This is currently the only filter that removes all particulate elements of amniotic fluid (fetal squames, lamellar bodies). Such a filtration process will necessarily slow down the rate at which blood can be infused, but it is permissible to pressurize the bag of salvaged red cells up to 200 mmHg after having ensured there is no air in the bag (otherwise it may burst!). In situations when hemorrhage is rapid, it is possible to connect more than one suction nozzle to the reservoir, and two filters and a dual line to the re-infusion bag.

(9) As with any transfusion, the patient should be carefully monitored, preferably in an obstetric 'critical care' facility for 24 h. Coagulation tests should be obtained post-transfusion, and repeated if abnormal or if clinically indicated. If the patient is Rh-negative, a Kleihauer–Braun–Betke test should be performed and appropriate quantities of anti–D administered within 72 h.

Obstetric units that use cell salvage should keep a careful records for audit reporting in due course – with any problems also being reported to SHOT (Serious Hazards of Transfusion) (UK) as per NICE guidelines. Since the original edition of this textbook was published in 2006, no instances of AFE have been reported as a result of cell salvage use in the area of obstetrics. However, there have been reports of adverse events when leukodepletion filters (LDF) are used to improve the quality of the returned red cells.

LEUKOCYTE DEPLETION FILTERS: PAST AND CURRENT ISSUES

Concern regarding AFE led to the introduction of LDFs (Pall Medical, Pall Europe Ltd, Portsmouth, England). These filters have two mechanisms of action. First, they act as a passive sieve when blood passes through a microfiber web and there is active adhesion to a negative surface charge[24]. The original *in vitro* studies all used an LDF of some kind[12,13], and therefore, the use of an LDF was advocated in composing guidelines. Such filters are not without their own problems. In May 1999, the US FDA reported that in the preceding 5 years significant hypotensive events had occurred in over 80 patients receiving blood products transfused through a bedside LDF[25]. During the same time period, however, it was estimated that approximately 20 million bedside LDFs had been used. Given the rarity of this reaction, a recommendation was made that should a patient develop signs of an 'LDF reaction', the transfusion should be stopped immediately and the symptoms should resolve rapidly. Of interest, this reaction occurred only with bedside leukodepletion, and not with blood that had been stored after filtration, suggesting that the act of leukodepletion pre-storage altered the quality of the blood being returned.

In January 2011 the FDA repeated its concerns regarding LDFs stating that 'bedside filtration has been associated with precipitous hypotension in the transfusion recipient, an infrequent yet serious adverse effect not associated with pre-storage leukocyte reduction. Patients on ACE [angiotensin converting enzyme] inhibitors appeared to be particularly susceptible'[26]. It is possible that there is something present in filtered blood following the passage through an LDF that is transient and is removed or disappears following a period of storage at 4°C.

All blood in the UK has been LD filtered prior to storage since 1999. Following the NICE recommendations that cell salvage with LDFs for obstetrics and malignancy seemed a safe process to manage troublesome hemorrhage and provide a source of autologous

blood, 13 reports of hypotension have been made to SHOT. Reporting of adverse events related to autologous techniques was commenced with a pilot scheme in 2007[27–29]. The 2007 report does not state whether a filter was used, but the other 12 cases from 2008 to 2010 all have LDF and acid–citrate–dextrose (ACD) anticoagulant use as common factors. Two case reports were published in 2010 describing severe hypotension occurring in relation to cell salvaged blood transfusion in obstetrics[30,31]. In both instances, the hypotension resolved on cessation of the infusion. As discussed in the accompanying editorial, it could not be determined with absolute certainty that the LDF was responsible as in neither case was transfusion attempted without filtration[32]. SHOT have analysed these reactions in detail and have not identified any other drug or agent as a precipitant (personal communication – Sue Catling).

These rare events have been studied by SHOT and by the UK Cell Salvage Action Group (Better Blood Transfusion – NHS Blood and Transfusion (NHSBT)) who are also aware of other cases that have been informally discussed and do not yet appear in the SHOT statistics. One case reported the use of heparin as anticoagulant compared with all others that had used ACD. Some cases are complex and multifactorial with massive hemorrhage in sick individuals, where it is difficult to ascertain the precise cause of the hypotension; in others there is a clear time relationship between the onset of sudden hypotension and infusion of cell salvaged, LD filtered blood. The other common factor is the use of ACD anticoagulant, rather than heparin. At present there is no UK national database on cell salvage, so it is not known how many patients received cell salvaged blood during these years, nor how many times the LDF was used.

Bradykinin has been suggested as one possible cause of the LDF related hypotension. It is a potent vasodilator with a short plasma half-life of 15 seconds due to its breakdown by ACE in the lungs. Evidence already exists in the dialysis population that filter membranes can cause hypotension as a result of bradykinin release[33,34]. Iwama investigated the effect of these negatively charged membranes on whole autologous blood *in vitro*[35]. He showed that passing whole blood through a negatively charged membrane at room temperature caused massive release of bradykinin, the concentration of which increased 4000 fold from 13 pg/ml to 55,933 pg/ml. These levels are capable of causing significant hypotension on re-infusion, and Iwama confirmed this point by giving such blood to six patients which resulted in a greater than 20% reduction in blood pressure. The proposed mechanism is that the negatively charged non-biologic filter surface activates coagulation factor XII. This activation process then triggers formation of the enzyme kallikrein from pre-kallikrein, resulting in cleavage of bradykinin from its high molecular weight precursor kininogen. The role of bradykinin is also supported by the clinical reports that patients on ACE inhibitors appear to be particularly susceptible[26].

Nevertheless, some uncertainty still exists as to whether bradykinin is responsible. To date, only whole blood has been studied, and cell salvaged blood consists of red cells suspended in saline with minimal plasma remaining; as such, it lacks a plasma source of bradykinin. Other potential mechanisms are that bradykinin is generated on the negative membrane from a non-plasma source, such as the white cells themselves, or that an entirely different mediator is involved. Cysteinyl leukotrienes can cause bronchoconstriction via the leukotriene (LT)1 receptor and can increase vascular permeability and inflammation via receptor pathway LT2. However, currently these substances have no identified role in acute vasodilation.

Further doubts exist in relation to LDFs being responsible for the observed hypotension. For example, if exposure to a negative membrane consistently causes vasoactive mediator release, then why is this reaction not seen consistently with every cell salvaged transfusion that uses a LDF? Potentially such reactions may only be occurring in individuals who are either constitutionally or therapeutically ACE deficient. Studies to investigate the bradykinin and leukotriene concentration in cell salvaged blood before and after passage across the LDF in normal clinical conditions are about to start in the UK, and the results should help to answer these questions.

In the meantime, the MHRA[36], the AAGBI[37] and SHOT[29] have issued statements warning clinicians to be aware of this possible adverse reaction, which has in every case been rapidly and effectively treated by stopping the transfusion and the appropriate use of fluids and vasopressors. In some cases, the cell salvage transfusion has then been completed without the LDF[38]. This raises the issue as to the necessity of the LDF in obstetric practice.

Before the introduction of LDFs, unfiltered cell salvaged blood was re-infused in almost 400 cases without the development of AFE or any other adverse effect[39–41]. Indeed, parturients who were completely well have been shown to have unequivocal evidence of amniotic fluid in their circulation[13]. In addition, very early studies from Peru suggested that deliberate infusion of amniotic fluid is not harmful[42], and this is consistent with the animal studies that have failed to replicate human AFE[43–46].

A technical problem with using an LDF is that it significantly reduces the rate at which salvaged blood can be given. This should not be circumvented by pressurizing the blood, and thus it severely restricts transfusion in a torrential hemorrhage. In practice, where rapid transfusion is required, or hypotension due to the filter is suspected, it can be removed and transfusion continued without it. As highlighted in the introduction to this chapter, anecdotal reporting from many countries where LDFs are not available describes the life-saving use of red cell salvage often undertaken with the most rudimentary equipment. The use of citrate as an anticoagulant and simple gauze filtration has been reported as a useful source of red cells for transfusion in the emergency situation.

SUMMARY

The use of intraoperative cell salvage is a safe method of conserving operative blood loss and minimizing the need for allogeneic transfusion. In an environment where allogeneic blood is in limited supply or the demands for blood transfusion are great, as in the case of massive PPH, the use of intraoperative cell salvage may be life-saving. Its use in this area continues to gain clinical acceptance.

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