Erythrocyte Salvage during Cesarean Section

The use of intraoperative erythrocyte salvage has increased substantially during the past decade. Its popularity is likely propelled by a perception of its effectiveness and safety and the desire to avoid potential complications following transfusion of allogeneic blood. However, the risks attendant with the transfusion of allogeneic blood are decreasing. After the current implementation of testing of donor blood with gene amplification techniques, the expected risks of transmission of hepatitis B (1/63,000 units) and hepatitis C (1-3/10^6 units) and the human immunodeficiency virus (1 to 2/10^6 units) should be less than its current historic lowest levels. Other important risks of transfusion are similarly low: fatal hemolytic transfusion reaction (nearly all error induced) of approximately 1 to 2/10^6 units, even more rare fatal septicemia, and an uncertain degree of immunomodulation.

In this issue of Anesthesiology, Waters et al. report the effect of washing and filtering material that is aspirated from the surgical field during cesarean section on the reduction of the concentration of amniotic fluid material in the final processed erythrocyte suspension. In 1994, the National Institutes of Health (Bethesda, Maryland) convened a panel (which included the undersigned) to evaluate autologous transfusion and provide recommendations. This panel endorsed the expanded use of intraoperative erythrocyte salvage but did not recommend this practice during cesarean section. This view was prompted by both a concern that an amniotic fluid embolism might result and a lack of data from prospective randomized studies documenting the safety of this practice.

As with any therapy, the use of intraoperative erythrocyte salvage during cesarean section should be based on considerations of effectiveness and safety compared with the available alternatives. There are two substantial difficulties in assessing the relative safety of intraoperative erythrocyte salvage during cesarean section. First, the pathophysiologic etiology of amniotic fluid embolism is not clear. The inciting components are not known; thus, studies cannot evaluate whether processing salvaged material from the surgical field reduces the specific component or components of amniotic fluid to concentrations below an unknown pathologic threshold. Second, the incidence of amniotic fluid embolism is low: approximately 1/8,000 to 1/80,000. A prospective randomized study with a power of 80% to show that erythrocyte salvage is not likely to increase this incidence by fivefold would require a population of more than 27,000 to approximately 275,000 patients.

In the period since the National Heart, Lung, and Blood Institute report, several reports have evaluated the various aspects of the potential use of erythrocyte salvage and processing during cesarean section. Investigators have evaluated the processed material for potentially detrimental components of amniotic fluid or have transfused patients with the processed erythrocytes that were salvaged during cesarean section, or both. Several devices are available for intraoperative erythrocyte salvage that efficiently remove solute in the supernatant. For example, less than 10% of the heparin and free hemoglobin in the material aspirated from a nonobstetric surgical field appears in the processed erythrocytes suspended in 0.9% NaCl. Therefore, it is reasonable to expect similar elimination rates from aspirated amniotic fluid for solutes or free proteins, such as "tissue factor," free fetal hemoglobin, and α-fetoprotein, but not for cellular components, such as fetal erythrocytes, fetal squamous cells, and cellular debris. Processing devices differ in ability to eliminate lipids from the final erythrocyte suspension.

Therefore, elimination of fetal phospholipids contained in amniotic fluid may also vary.

Investigations examining the product of erythrocyte salvage and processing during cesarean section generally have produced results consistent with these expectations. Tissue factor, free fetal hemoglobin, and α-fetoprotein have been reduced or eliminated from the final erythrocyte suspension, whereas substantial concentrations of fetal erythrocytes and fetal globin in the material aspirated from a nonobstetric surgical field appears in the processed erythrocytes suspended in 0.9% NaCl. Therefore, it is reasonable to expect similar elimination rates from aspirated amniotic fluid for solutes or free proteins, such as "tissue factor," free fetal hemoglobin, and α-fetoprotein, but not for cellular components, such as fetal erythrocytes, fetal squamous cells, and cellular debris. Processing devices differ in ability to eliminate lipids from the final erythrocyte suspension.

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squamous cells\textsuperscript{5,14} and lamellar bodies (composed of phospholipids)\textsuperscript{5} remained.

Recently, an attempt to remove fetal squamous cells and debris by filtration of the final processed erythrocyte suspension was not successful.\textsuperscript{14} As reported in this issue of \textit{Anesthesiology}, Waters \textit{et al.},\textsuperscript{5} by using a different filter (intended to remove leukocytes from donated blood), nearly eliminated fetal squamous cells from the filtered erythrocyte suspension. The authors' attribution of their improved results (compared with a previous study\textsuperscript{14}) to the use of a different filter appears reasonable because before filtration their product contained substantial numbers of fetal squamous cells.

Other differences among studies may have resulted from differences among erythrocyte salvage devices, sizes of processing bowls, amounts of saline wash, and degree of technical expertise in device operation. Use of erythrocyte salvage devices using technologies other than a centrifugation-type bowl during cesarean section has not been studied. Many of the reports do not contain sufficient information to evaluate these differences. This is not unexpected because intraoperative erythrocyte salvage in the United States has been a largely unregulated cottage industry. Although devices marketed for the purpose require approval of the US Food and Drug Administration (FDA), their use, the training of the operators, and quality assurance of the product do not. The American Association of Blood Banks is developing "Standards" and "guidance" applicable to intraoperative erythrocyte salvage to ensure the quality of erythrocytes salvaged and processed for transfusion.

The literature contains four reports of 174 patients who were underwent transfusion with erythrocytes after salvage during cesarean section and washing.\textsuperscript{12,16-18} With the exception of one case of heparin overdose,\textsuperscript{17} those reports contain no other occurrence of adverse events. Although some may regard these results as reassuring, only one of the reports\textsuperscript{12} was of a prospective randomized study in which a mean ± SD of 363 ± 153 ml (range, 125-800 ml) blood was salvaged, washed, and transfused in 34 patients. The absence of symptoms in 34 patients allows one to state with 95% assurance that those symptoms would not likely occur in more than 8% of a similar population that was given this relatively small amount of salvaged and processed erythrocytes. The value of "lack of symptoms" emanating from a retrospective chart review is less clear. Even if all 174 patients (including those from retrospective chart reviews) truly had no adverse events, the 95% confidence level is approximately 2% for this limited amount of transfused erythrocytes (i.e., up to 2% of the population might have an adverse event). Neither figure approaches the reported incidence for amniotic fluid embolism of 0.01 to 0.001%. In addition, there is a single case report of fatal amniotic fluid embolism after transfusion of erythrocytes salvaged during cesarean section.\textsuperscript{19} Therefore, it cannot be stated that use of this technique during cesarean section does not add risk of amniotic fluid embolism.

A second safety concern for the use of salvaged and washed cells during cesarean section involves the transfusion of fetal erythrocytes to the mother. There is no reason to believe that the devices used for washing salvaged erythrocytes can distinguish between maternal and fetal erythrocytes. Studies that have evaluated the washed cells have found substantial concentrations of fetal cells mixed with the maternal cells in the final product.\textsuperscript{5,12,14,15} Waters \textit{et al.}\textsuperscript{5} confirm these previous findings and note a concentration of fetal hemoglobin approximately four times that measured in maternal blood. Transfusion of erythrocytes salvaged during cesarean section could result in the administration of a substantial additional load of fetal erythrocytes not present in other allogeneic blood. Antigens present on fetal erythrocytes but absent on maternal erythrocytes can result in alloimmunization. Therefore, erythrocytes salvaged during cesarean section must be regarded as allogeneic. In the report by Rainaldi \textit{et al.},\textsuperscript{12} material processed from half the patients was incompatible with the maternal blood. The suggestion of Waters \textit{et al.},\textsuperscript{5} that the quantity of fetal hemoglobin in maternal blood should be measured after the transfusion of salvaged erythrocytes and that immune globulin should be administered as necessary, is appropriate.

How are we to determine whether it is safe to use erythrocytes salvaged during cesarean section? The Food and Drug Administration has had to face a similar problem in attempting to assess the "safety" of artificial oxygen carriers (hemoglobin solutions and fluorocarbon emulsions). The approach of the Food and Drug Administration has been to require a prospective, randomized study of 600 patients: 300 each per treatment and control groups. The required number of treated patients was doubled after one study was halted because of an increased incidence of death in the treated group. The absence of an amniotic fluid embolism in a study of this size would indicate, with 95% confidence, that the adverse event probably would not occur in more than 1% of the population, but could not approach that degree of
assurance for the far lesser frequency of amniotic fluid embolism, approximately 0.005%.

The second issue for consideration of the appropriate use of erythrocytes salvaged during Cesarean section is that of efficacy. Several components of efficacy necessitate consideration. First, what are the circumstances during cesarean section that necessitate the transfusion of the mother with cells from any source? Average maternal blood loss is approximately 600 ml during vaginal delivery, and is approximately 1000 ml during cesarean section, a difference of only approximately 400 ml. At term pregnancy, maternal blood volume is increased by approximately 30-40% with return to normal values within 1 week. Loss of 1,000 ml blood during cesarean section in an average mother, while maintaining isovolemia with an adequate quantity of asanguinous fluid, would decrease maternal hemoglobin concentration from the usual value of approximately 12 g/dl to 10 g/dl immediately after surgery. Thereafter, the hemoglobin concentration would increase as maternal blood volume decreased during the ensuing week to the non-pregnant normal state by reduction of plasma volume. In reports that evaluated erythrocyte salvage during cesarean section, material sufficient for analysis could be collected in only 10 of 27 patients. In those 10 patients, the average volume of material produced for transfusion was 186 ml at a hematocrit value of 49% or 91 ml erythrocytes, the amount contained in approximately one half of 1 unit of erythrocytes. Thus, during cesarean section erythrocyte recovery is ordinarily low.

More than a decade ago, the National Institutes of Health Consensus Conference on Red Cell Transfusion recommended that erythrocytes not be transfused when the recipient’s hemoglobin concentration is greater than 7 g/dl. More recently, the American Society of Anesthesiologists (ASA) approved an ASA Task Force recommendation that for a healthy patient, intraoperative erythrocyte transfusion is not usually needed for hemoglobin concentrations of greater than 6 g/dl. Furthermore, a hemoglobin concentration of 5 g/dl does not produce evidence of inadequate systemic oxygen delivery. Thus, the usual low blood loss (and erythrocyte recovery) during cesarean section, together with the increased blood volume during pregnancy and the ability of healthy humans to tolerate low hemoglobin concentrations, indicate that it should be very unusual for transfusion to be necessary during cesarean section. This conclusion is supported by the data of Sherman et al. Older reports of a greater incidence of transfusion during cesarean section probably resulted from the clinical application of transfusion thresholds that were higher than those that are currently recommended and are physiologically acceptable. Therefore, the routine use of a technology of uncertain safety during cesarean section is not warranted.

Nevertheless, for unusual occasions, cesarean section may result in blood loss that is sufficient to necessitate erythrocyte transfusion. Although banked blood might not be available immediately, a similar limitation may exist for salvaged and washed erythrocytes. Several minutes are necessary to set up washing devices. The device, if available, is likely to be stored in a location other than the obstetric suite because the need, and presumably the use, of these expensive devices is unusual in obstetric surgery. Transport of the device and the arrival of a dedicated, trained person to operate the device (as is strongly recommended and may become required) may cause further delay. These delays may be longer than the time to obtain type O or type-specific erythrocytes from the blood bank. Furthermore, if elimination of fetal tissue is an important concern (it may not be), the use of a leukodepletion filter of the type described by Waters et al. substantially decreases the flow rate at which the processed cells can be administered to a rate (approximately 30 ml/min) that is insufficient to maintain isovolemia or to provide substantial augmentation of oxygen-carrying capacity during substantial hemorrhage.

The reports published during the past several years have begun the process of evaluating the safety of the use of erythrocyte salvage and processing during cesarean section. However, larger prospective randomized studies are necessary to document the safety of this technique for the occasional obstetric patient for whom it may be efficacious and needed. Until then, the use of this technique during cesarean section should be limited to those times when it is the only way to augment the patient’s oxygen-carrying capacity, when it is necessary to preserve function or life. The need may become more frequent if the predicted shortage of blood in the United States becomes a reality.

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