Cost-effectiveness Analysis of Intraoperative Cell Salvage for Obstetric Hemorrhage

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ABSTRACT

Background: Cost-effectiveness analyses on cell salvage for cesarean delivery to inform national and societal guidelines on obstetric blood management are lacking. This study examined the cost-effectiveness of cell salvage strategies in obstetric hemorrhage from a societal perspective.

Methods: Markov decision analysis modeling compared the cost-effectiveness of three strategies: use of cell salvage for every cesarean delivery, cell salvage use for high-risk cases, and no cell salvage. A societal perspective and lifetime horizon was assumed for the base case of a 26-yr-old primiparous woman presenting for cesarean delivery. Each strategy integrated probabilities of hemorrhage, hysterectomy, transfusion reactions, emergency procedures, and cell salvage utilization; utilities for quality of life; and costs at the societal level. One-way and Monte Carlo probabilistic sensitivity analyses were performed. A threshold of $100,000 per quality-adjusted life-year gained was used as a cost-effectiveness criterion.

Results: Cell salvage use for cases at high risk for hemorrhage was cost-effective (incremental cost-effectiveness ratio, $34,881 per quality-adjusted life-year gained). Routine cell salvage use for all cesarean deliveries was not cost-effective, costing $415,488 per quality-adjusted life-year gained. Results were not sensitive to individual variation of other model parameters. The probabilistic sensitivity analysis showed that at the $100,000 per quality-adjusted life-year gained threshold, there is more than 85% likelihood that cell salvage use for cases at high risk for hemorrhage is favorable.

Conclusions: The use of cell salvage for cases at high risk for obstetric hemorrhage is economically reasonable; routine cell salvage use for all cesarean deliveries is not. These findings can inform the development of public policies such as guidelines on management of obstetric hemorrhage.

Visual Abstract: An online visual overview is available for this article at http://links.lww.com/ALN/B631. **(ANESTHESIOLOGY 2018; 128:328-37)**

OBSTETRIC hemorrhage is consistently a leading cause of maternal morbidity and mortality worldwide.[1] The use of intraoperative cell salvage as a blood conservation technique is recommended in cases of anticipated extreme blood loss, unavailability of cross-matched compatible blood products, and high average transfusion requirements of a particular procedure in question. It is specifically recommended by several entities including the AABB (formerly known as the American Association of Blood Banks) and the eighth report of "Saving Mothers' Lives" by the United Kingdom's Confidential Enquiries into Maternal Deaths.[2–6]

Intraoperative cell salvage in obstetrics reduces the need for allogeneic blood transfusion and mitigates postpartum anemia after cesarean delivery.[7] These protections may afford women in the peripartum period a number of advantages, including reduced risk for transfusion reactions, administrative errors, alloimmunization, transmission of infectious disease, Rh incompatibility in subsequent pregnancies resulting in hemolytic disease of the newborn, and prevention of anemia, which can in turn enhance postpartum recovery and function.[8–10]

Although the advantages of the implementation and utilization of intraoperative blood salvage are recognized, the process requires an expenditure of resources, including technologist time and the cost of equipment and materials, and its benefits to patient-centered outcomes such as quality of recovery are unknown.[11] In some situations, cell salvage strategies have been found to add cost; in single-level posterior lumbar decompression and fusion surgery, a cell salvage strategy was found to add to total blood product costs, with an incremental cost-effectiveness ratio of $5,555,380 per quality-adjusted life-year gained.[12] On the other hand, cell salvage strategies may add economic value for certain situations. Albright *et al.*[13] performed a cost analysis of the use of cell salvage in obstetrics and concluded that cell salvage is cost-saving in cases of high

What We Already Know about This Topic

- Intraoperative cell salvage in obstetrics reduces the need for allogeneic blood transfusion and mitigates postpartum anemia after cesarean delivery. Overall the implementation and utilization of intraoperative blood salvage has been found to add cost in some situations and may add economic value for other situations.

What This Article Tells Us That Is New

- The use of cell salvage for cases at high risk for obstetric hemorrhage is economically reasonable; routine cell salvage use for all cesarean deliveries is not.

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probability of transfusion or massive transfusion. However, this analysis focused on a healthcare-level perspective and the use of cost-savings as an endpoint. Recommendations from the Panel on Cost-Effectiveness in Health and Medicine[14] suggest that a more useful perspective from the standpoint of informing best practice is a societal perspective, rather than a healthcare-level perspective, and that a more informative endpoint is cost-effectiveness, rather than cost-savings. The terms "cost-saving" and "cost-effective" are not interchangeable; although cost-saving strategies are those that decrease cost irrespective of the benefits, cost-effective strategies are those for which the benefits are sufficiently large compared to the costs, even if it does not save money.[15] A societal perspective provides a basis for decisions that are fair to all parties—individual, health system, payers—and it can better inform global decisions on resource allocation, compared to a healthcare-level perspective or an individual perspective.[16]

Therefore, a cost-effectiveness analysis can be valuable by exposing strategies that may still be beneficial but are possibly overlooked by a cost-savings examination. Although Albright's study examined two main strategies—setting up cell salvage for all cesarean delivery cases *versus* no cell salvage at all—strategies that remain unexamined for cost-effectiveness include using cell salvage for varying degrees of hemorrhagic risk during cesarean delivery, the risk of which changes over the entire reproductive life span. In this context, the goal of this study was to determine under what circumstances the use of cell salvage strategies in obstetric hemorrhage during cesarean delivery is cost-effective, from a societal perspective and over the reproductive life span.

Materials and Methods

Perspective, Assumptions, Model Cohort, and Model Structure

Review by the University of Pittsburgh Institutional Review Board was not required for this activity, which utilized existing data from published research or otherwise available in the public domain. Data from the National Vital Statistics Reports on births (2013) was used as the foundation of our base case and cohort.[17] Our base case was a 26-yr-old primiparous woman presenting for a scheduled cesarean delivery. A societal perspective and a lifetime time horizon were assumed. Decision analysis with Markov state processing formed the basis of the model structure; with this approach, individuals in the cohort cycle through the model through various states of postcesarean, interval pregnancy, and posttransfusion with or without cell salvage (fig. 1). Markov models allow the evaluation of events that can occur multiple times over a life span, such as childbirth and its attendant risks for hemorrhage. We modeled three primary strategies: using cell salvage for all cesarean deliveries (IOCS-ALL), using cell salvage only for deliveries at high risk for hemorrhage (IOCS-HR, defined under Rates, Costs, and Probabilities section), and no utilization of cell salvage (IOCS-NO). Our cohort was comprised of women requiring cesarean delivery, with average age at first pregnancy of 26 yr and reproductive life span is 19 yr.[17] Birth rates were adjusted by age based on data available from the Centers for Disease Control National Vital Statistics Reports.[6] A cycle length of 1 yr was applied to each Markov state. A discount rate of 3% was applied to future costs and benefits. Lifetime medical costs were included. Cell salvage was assumed to have been used throughout the entire cesarean delivery. Because of the rarity of adverse events associated with cell salvage,[18] the model assumed no risks associated with the use of cell salvage. Other key assumptions are shown in table 1. Digital files of the full model and details on model structure are completely available upon request. All analyses were performed using TreeAge Pro Suite 2015 software (TreeAge Software, USA).

Rates, Costs, and Probabilities

To every strategy, mean hospital costs for "Pregnancy, Childbirth, and the Puerperium," as coded by Major Diagnostic Category ($4,414) and assessed in 2012 dollars, were added.[19] We added physician and technician costs to every strategy; hospital, physician, and technician costs were added and ranges were set at ±25% to capture regional variations in cost plus possible uncertainty based on the relationship of reimbursement *versus* true cost.[20] Costs for transfusion reactions were aggregated by International Classification of Diseases, Ninth Revision, Clinical Modification code according to available 2012 data.[19] Severe transfusion reactions for which cost data were available and included in the model encompassed transfusion-associated circulatory overload, transfusion-related acute lung injury, transfusion-related infections, delayed hemolytic transfusion reactions, infusion reactions not otherwise specified, and transfusion reactions not otherwise specified. Mild transfusion reactions for which cost data were available encompassed febrile transfusion reactions.

Women in the model were defined as being at high risk for hemorrhage based on known risks for hemorrhage including placenta previa, placenta accreta, repeat cesarean delivery or multiparity, chorioamnionitis, placental abruption, hypertensive disorders during pregnancy, and trial of labor after cesarean with subsequent uterine rupture.[13,21,22] Other hemorrhage risks that were not modeled, to minimize model complexity, included risk for hemorrhage due to macrosomia, multiple pregnancies, obesity, prolonged labor, intrauterine infections, or instrumental vaginal delivery. Probabilities on death from hemorrhage were based on data available from the Centers for Disease Control Pregnancy Mortality Surveillance System,[17] which notably included not only intraoperative mortality, but also deaths after stillbirths, abortions, and ectopic pregnancies. Probability of death from transfusion was based on the leading cause of mortality after allogeneic transfusion, transfusion-associated lung injury, with an assumed incidence of transfusion-associated

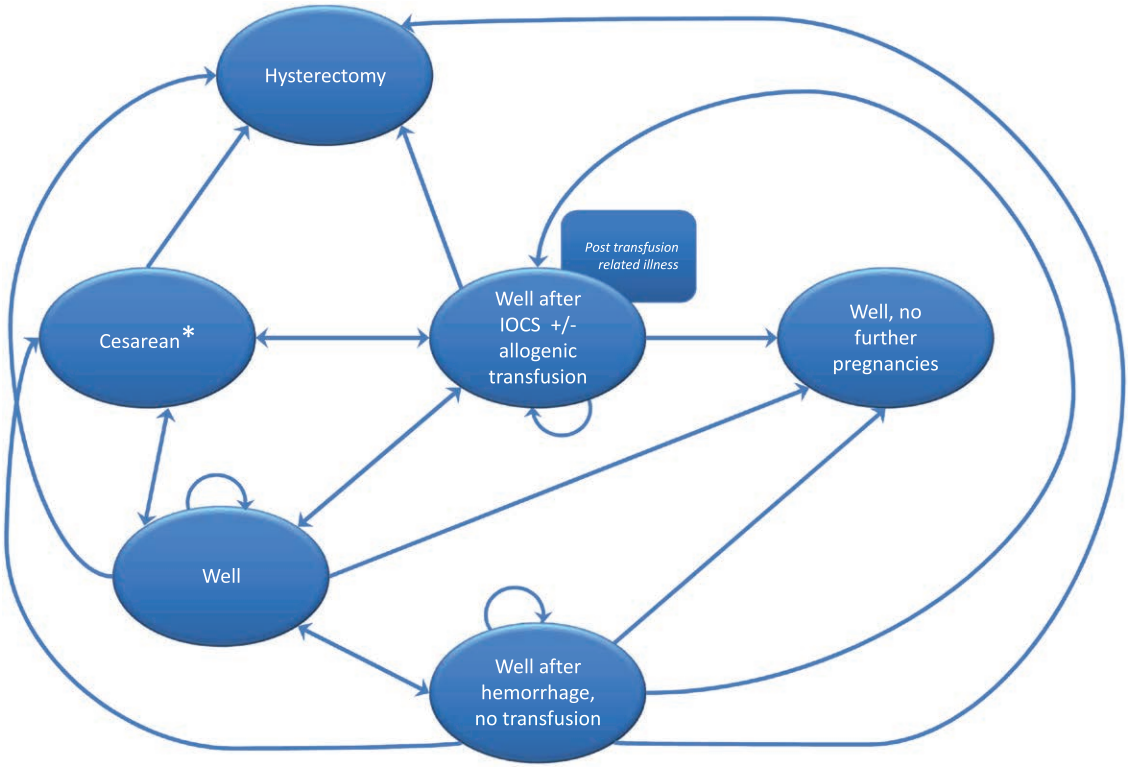

Fig. 1. Markov state transition diagram. Each *oval* represents a health state, and *arrows* in between the *ovals* demonstrate potential directions of transition that each patient can make with each cycle of the model. *Curved arrows* pointing back toward the same health state indicates a return to the same health state in the next cycle (cycle length = 1 yr). Posttransfusion-related illness was modeled as a health state associated only with the receipt of intraoperative cell salvage (IOCS) and allogeneic transfusion. All women in the cohort eventually transition to a "die" health state, not pictured. *Model start point.

Table 1. Key Assumptions for the Decision Analysis Model

The base case is a pregnant, 26-yr-old gravida 1 para 0 presenting for cesarean delivery.
The reproductive life span is 19 yr, from ages 26 to 45 yr.
Given its cumulative rarity, women who get transfusion-related illnesses are not at risk for future transfusion-related illnesses upon subsequent transfusions.
Women who die from hemorrhage will have received both allogeneic transfusion as well as emergent hysterectomy.
Women who undergo hysterectomy will have also received allogeneic transfusion with or without cell salvage, depending on the strategy being examined.
No significant risks are associated with the use of cell salvage.

lung injury at 1:5,000 and a range quoted at 5 to 10%.[23] The probability of vaginal birth after cesarean was calculated as a pooled chance of success associated with trial of labor after cesarean both after one prior cesarean delivery (probability 0.67, range 0.20 to 1.0), as well as successful vaginal birth after cesarean after a history of successful vaginal birth after cesarean (probability 0.89, range 0.20 to 1.0).[6,24] Other probabilities modeled included that of hemorrhage in primary cesarean delivery, hysterectomy, emergent hysterectomy, severe transfusion-related illness, requiring transfusion, and pooled risk for contracting transfusion-related illness.[25–33] In the model, separate from the risk of dying from hemorrhage, we also modeled the risk of dying from all causes, and we used life tables to account for age- and sex-specific death rates from other causes. All upper- and lower-limit ranges were defined by values published in the literature (table 2). To assess whether the ranges were a reasonable test of a parameter's importance, distributions around all variables were varied widely in the sensitivity analyses, with upper and lower limits defined by values published in the literature.

Utilities

Utilities of health states were determined based on available data in the literature and are reported as measurements of quality-adjusted life-years. The utility of the health state associated with the receipt of cell salvage was not available and was therefore imputed based on its rate of expected benefits in reducing allogeneic transfusion.[34] Based on this information, the use of cell salvage results in an average saving of 0.68 units of allogeneic packed erythrocytes per patient (95% CI, 0.49 to 0.88), translating to a 32% reduction in the use of allogeneic packed erythrocytes. We therefore assumed a 32% improvement in the utility of the health state associated with transfusion alone to define the utility of the health state associated with receipt of salvaged blood. To account for this assumption in utility, the

Table 2. Parameter Values for Base Case and Sensitivity Analyses

Description	Base Case	Parameter Range		Source†
		Low	High	
Average age of first pregnancy*	26	--	--	6
Birth rate*				
Ages 25–29 yr	0.11	--	--	6
Ages 30–34 yr	0.10	--	--	6
Ages 35–39 yr	0.05	--	--	6
Ages 40–44 yr	0.01	--	--	6
Cost IOCS use (setup + utilization costs)	$22,154.00	$16,615.50	$27,692.50	19
Cost IOCS setup	$64.45	$48.34	$80.56	11
Cost cesarean, routine	$9,777.00	$7,332.75	$12,221.25	19
Cost of cesarean due to uterine rupture	$11,602.00	$8,701.50	$14,502.50	19
Cost of hemorrhage	$9,394.00	$7,045.50	$11,742.50	19
Cost, emergent hysterectomy	$16,410.00	$12,307.50	$20,512.50	19
Cost, hysterectomy, nonemergent	$16,410.00	$12,307.50	$20,512.50	19
Cost of mild transfusion reaction	$10,976.00	$8,232.00	$13,720.00	19
Cost of pregnancy loss due to Rh	$8,972.00	$6,729.00	$11,215.00	19
Cost of repeat cesarean delivery, nonemergent/scheduled	$9,777.00	$7,332.75	$12,221.25	19
Cost of treatment for severe transfusion-related illness	$15,887.18	$11,915.38	$19,858.97	19
Cost of TOLAC	$17,514.00	$13,135.50	$21,892.50	24
Cost, transfusion alone	$25,190.43	$18,892.82	$31,488.04	19
Cost of allogenic transfusion + IOCS	$29,730.38	$22,297.78	$37,162.97	19
Cost of treatment for uterine rupture	$18,314.00	$13,735.50	$22,892.50	24
Cost of VBAC	$12,514.00	$9,385.50	$15,642.50	24
Probability of setting up IOCS	0.87	0.65	1.00	11
Probability of use of IOCS alone	0.82	0.62	1.00	13
Probability of IOCS used at all	0.21	0.16	0.26	11
Probability of death from hemorrhage	0.000018	0.00	0.00	17
Probability of dying	0.00001	0.00001	0.00002	23
Probability of actually hemorrhaging in cases of high risk for hemorrhage	0.22	0.17	0.28	21
Probability of actually hemorrhaging in cases of low risk for hemorrhage	0.01	0.01	0.01	21
Probability of emergent hemorrhage	0.01	0.01	0.01	21
Probability of hemorrhage (primary cesarean delivery)	0.048	0.04	0.06	31
Probability of having high risk for hemorrhage	0.004	0.00	0.00	21
Probability of hysterectomy	0.0047	0.00	0.01	33
Probability of emergent hysterectomy	0.003	0.00	0.00	33
Probability of needing either transfusion or IOCS	0.13	0.10	0.16	11
Probability of pregnancy loss due to Rh sensitization	0.0001	0.00	0.00	19
Probability of severe transfusion-related illness	0.032	0.02	0.04	32
Probability of TOLAC	0.196	0.15	0.25	6
Probability of transfusion alone	0.02	0.02	0.03	25
Probability of allogenic transfusion + IOCS	0.016	0.01	0.02	7
Probability of contracting transfusion-related illness (pooled risk)	0.006	0.00	0.01	23,26-30
Probability of uterine rupture associated with TOLAC	0.007	0.01	0.008	24
Probability of VBAC	0.78	0.20	1.0	6,24
Utility of cesarean due to uterine rupture	0.51	0.32	0.74	36,37
Utility of hemorrhage	0.87	0.65	0.91	47
Utility of hemorrhage, received IOCS only	0.96	0.72	0.91	39
Utility of hemorrhage, received allogeneic transfusion	0.59	0.44	0.74	36,39
Utility of hysterectomy (chronic utility)	0.88	0.75	0.95	46
Utility of hysterectomy (acute utility)	0.57	0.30	0.93	36-39,43,46
Utility of pregnancy loss due to Rh sensitization	0.90	0.50	1.00	40,42
Utility of repeat cesarean (acute)	0.42	0.32	0.53	36
Utility of TOLAC	0.84	0.63	0.91	36

(Continued)

Table 2. (Continued)

Description	Base Case	Parameter Range		Source†
		Low	High	
Utility of transfusion-related illness	0.75	0.56	0.91	
Utility of mild transfusion reaction	0.90	0.68	0.91	41
Utility of severe transfusion-related illness	0.60	0.45	0.75	41
Utility of uterine rupture	0.51	0.38	0.64	38
Utility of VBAC	0.62	0.47	0.78	36,38
Utility of well state, no further pregnancies	0.91	0.50	0.99	37
Utility of well state after cesarean	0.59	0.31	0.96	48
Utility of well state, after hemorrhage	1.00	0.97	0.99	37
Utility of well state, after allogeneic transfusion and IOCS	0.86	0.82	0.90	34
Utility of well state, after allogeneic transfusion alone	0.80	0.60	0.91	35
Utility of well state, after cesarean (chronic)	0.91	0.50	0.10	37,44,45,48

*Data used in birth tables to model probability of pregnancy after base case throughout the reproductive life span. No ranges applied because these values were not varied in sensitivity analyses. †Sources refer to the reference list.

IOCS = intraoperative cell salvage; TOLAC = trial of labor after cesarean; VBAC = vaginal birth after cesarean.

distribution of the utility of this health state was varied widely in probabilistic sensitivity analyses so that the relative impact of this variable on the model conclusions could be assessed. Ranges were based on ranges in the published literature with base-case values based on means or medians as appropriate. A similar approach was taken to the utility of the health state associated with transfusion, because this information is not available.[35] The utility of the health state after cesarean due to uterine rupture included the health state associated with emergency cesarean, which included uterine rupture as well as other emergencies, and the health state associated with cesarean due to uterine rupture alone.[36,37] Other utilities modeled included utilities associated with hemorrhage, transfusion, hysterectomy (acute and chronic health states), pregnancy loss, mild transfusion reactions, severe transfusion-related illness, uterine rupture, vaginal birth after cesarean, and cesarean delivery (acute and chronic health states).[38–48] Table 2 shows rates, costs, probabilities, and utilities with corresponding distributions that were used in the model; the table also lists corresponding literature from which base-case and upper- and lower-limit range values were derived.

Analyses

Treatment strategies were compared based on incremental cost-effectiveness ratio. The incremental cost-effectiveness ratio is defined as the ratio of the incremental cost of one strategy compared to another, over the improvement measured in quality-adjusted life-years. Cost-effectiveness was defined as a strategy that costs less than $100,000 per quality-adjusted life-year gained, based on suggestions that the common cited benchmark for willingness to pay of $50,000 per quality-adjusted life-year gained may be outdated and that standards greater than $100,000 per quality-adjusted life-year gained may be excessive.[49,50]

One-way and probabilistic sensitivity analyses were conducted around all cost, utility, and probability variables to address the uncertainty around these parameters and to account for the extrapolation of some of these values from nonobstetric literature. One-way sensitivity analysis is performed to examine the effect of changing one or more variable in the model, to determine which variables are most influential to the model results. In the one-way sensitivity analysis, we varied all parameters individually to detect the effect of these variations on model results. A Monte Carlo probabilistic sensitivity analysis is performed to produce a distribution of possible incremental cost-effectiveness ratio outcomes. In the Monte Carlo probabilistic sensitivity analysis, the exact value of a variable is replaced with a distribution, and the incremental cost-effectiveness ratios are calculated based on the set of values drawn from their respective distributions. By this analysis, simultaneous variation of all parameters is achieved. In our analysis, distributions of each parameter were randomly sampled over 1,000 trials to determine the proportion of the time in which each strategy is cost-effective at a willingness-to-pay threshold of $100,000. Cost distributions were varied by γ functions, and probability and utility distributions were varied by triangular functions over all sampling trials.

Results

Base-case Analysis

The use of cell salvage for cases at high risk for hemorrhage was cost-effective, with an incremental cost-effectiveness ratio of $34,881 per quality-adjusted life-year gained. The routine use of cell salvage for all cesarean deliveries was not cost-effective, with an incremental cost-effectiveness ratio of $415,488 per quality-adjusted life-year gained (table 3).

One-way Sensitivity Analyses

Results of the one-way sensitivity analyses are shown in figure 2. There were six variables that influenced the results

Table 3. Cost-effectiveness Rankings for Base Case

Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	ICER
No IOCS	$11,431.74	NA	23.97	NA	NA
IOCS high risk only	$11,432.40	$0.67	23.97	0.000019	$34,881.69
IOCS all	$11,509.63	$77.23	23.97	0.000186	$415,488.39

ICER = incremental cost-effectiveness ratio; IOCS = intraoperative cell salvage; NA = not applicable.

of the cost-effectiveness analysis by more than 10%. In order of most to least influential, these variables were the utility of the health state associated with transfusion (estimate, 0.6 to 0.91), the cost of allogeneic transfusion alone (estimate, $18,892 to 31,448), the cost of cell salvage (estimate, $16,615 to 27,692), the cost of hemorrhage (estimate, $7,045 to 11,742), the cost of allogeneic transfusion in addition to cell salvage (estimate, $22,297 to 37,162), and the probability of receiving salvaged blood alone (estimate, 0.615 to 1.0). The probability of transfusion-related illness was varied and did not significantly affect the results; the incremental cost-effectiveness ratio was not substantially changed by the risk for transfusion-related illness (probability estimate, 0.0 to 0.0111). For the health state associated with wellness after transfusion, at a utility of 0.902 or greater, the IOCS-HR strategy exceeds the $100,000 per quality-adjusted life-year threshold ($115,887 per quality-adjusted life-year). The results of the model were least sensitive to the probability of using cell salvage (estimate, 0.0 to 0.8) and the disutility of hysterectomy (estimate, 0.0 to 0.01).

Probabilistic Sensitivity Analysis

The results of the probabilistic sensitivity analysis showed that at the $100,000 per quality-adjusted life-year gained threshold, there is a greater than 85% likelihood that a strategy employing cell salvage for cesarean deliveries at high risk for hemorrhage is favorable. At willingness-to-pay thresholds between $0 to about $35,000 per quality-adjusted life-year gained, a strategy of no cell salvage for any cesarean delivery is favored, and cell salvage for cesarean deliveries at high risk for hemorrhage is not favored (range iterations that no cell salvage strategy is cost-effective at this willingness to pay threshold, 50 to 90%). A strategy of using cell salvage for all cesarean deliveries was not favored if the willingness to pay threshold was $200,000 per quality-adjusted life-year gained or less (maximum percent iterations that cell salvage for all cesarean deliveries is cost-effective, 5%; fig. 3).

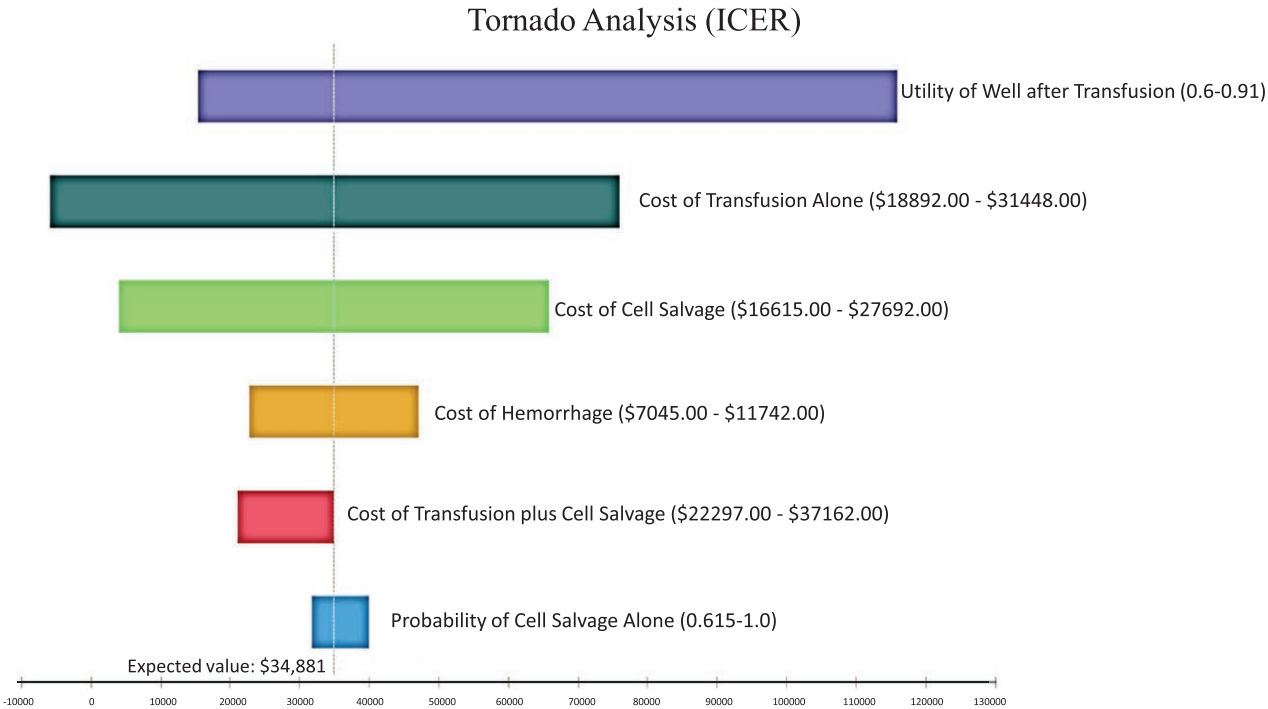

Fig. 2. Incremental cost-effectiveness ratio (ICER) tornado diagram for one-way sensitivity analysis for the strategies intraoperative cell salvage high risk only *versus* no intraoperative cell salvage. The *vertical line* denotes the base-case expected value ($34,881). Variation around the variables listed induces a variation of 10% or greater from the base-case ICER. The utility of the well state after transfusion is the most sensitive parameter. The probability of using cell salvage and the disutility of hysterectomy are least influential to the results of the model (not shown).

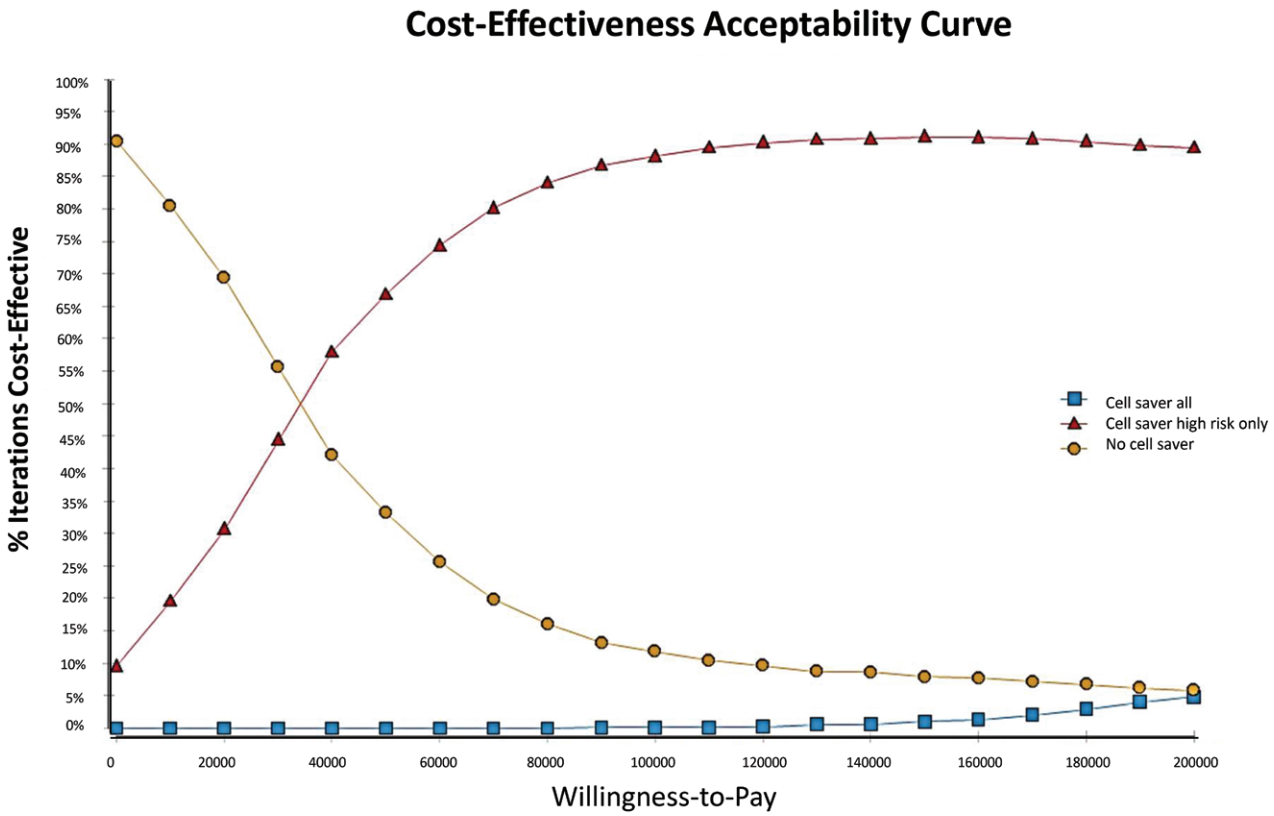

Fig. 3. Monte Carlo probabilistic sensitivity analysis. At the $100,000 per quality-adjusted life-year gained threshold, there is greater than 85% likelihood that cell salvage for cesarean deliveries at high risk for hemorrhage is a favorable strategy. At willingness-to-pay thresholds below $35,000 per quality-adjusted life-year gained, a strategy of no cell salvage for any cesarean delivery is favored. Below a willingness to pay threshold of $200,000 per quality-adjusted life-year gained, using cell salvage for all cesarean deliveries is not a favorable strategy. CE = cost-effectiveness.

Discussion

This study assesses the cost-effectiveness of cell salvage for cesarean deliveries from a societal perspective, over the reproductive life span. Our results support that it is economically reasonable to use intraoperative cell salvage in cases of cesarean delivery that are at high risk for hemorrhage. The societal perspective and lifetime horizon of our analysis can inform broader applications in the development of public policy, such as national guidelines on management of obstetric hemorrhage. At the same time, the analysis is limited in terms of its ability to guide hospital-level considerations that would drive individual institutional decisions to purchase and implement cell salvage strategies in obstetrics.

If the utility of the health state associated with transfusion is equal to or greater than 0.902, the IOCS-HR strategy exceeds the $100,000 per quality-adjusted life-year threshold ($115,887 per quality-adjusted life-year). The one-way sensitivity analysis shows that other variables vary the results of the cost-effectiveness analysis, but not at $100,000. Therefore, the only variable that will make the IOCS-HR strategy unfavorable is this utility value; other variables do not meaningfully fluctuate the results. Although it is interesting that the utility of the health state associated with transfusion is the most sensitive variable, it is unlikely to be realistically influential, in that when considered in the context of varying all parameters by the Monte Carlo sensitivity analysis, at a willingness-to-pay level of $100,000, there is a greater than 85% likelihood that IOCS-HR would still be favored.

Several other investigations have evaluated the economic ramifications of using cell salvage in obstetrics from a hospital-level perspective.[13,51–54] Brearton *et al.*[54] published the results of their institutional experience with cell salvage for obstetric hemorrhage over time. Their findings were consistent with ours in that the rate of return of salvaged shed blood was higher for emergency and high-risk cases. The investigators also detected a decreased rate of return of salvaged shed blood over time, which was associated with the increased utilization of cell salvage for routine cases. Despite these findings, the authors felt that the rate of return of salvaged blood offset the costs of cell salvage setup compared to the cost of using allogeneic blood.[54] Our findings challenge this latter conclusion, because the results of our Monte Carlo probabilistic sensitivity analysis show that a strategy of using cell salvage for all cesarean deliveries irrespective of risk for hemorrhage is never cost-effective, at the $200,000 per quality-adjusted life-year threshold or below. Waters *et al.*[53] took a hospital-level economic examination of implementation

and maintaining cell salvage as part of a blood management program and found that cell salvage can be significantly less expensive than allogeneic blood, although institutional level costs are still dependent upon case volume, expected levels of blood loss per case, and initial investment costs.

Our findings highlight the importance of considering the value of the $100,000 per quality-adjusted life-year threshold. We used the $100,000 per quality-adjusted life-year threshold based on modern recommendations grounded on the notion that the historical $50,000 per quality-adjusted life-year threshold is too low.[34] However, the World Health Organization has suggested that thresholds of $110,000 to 160,000 per quality-adjusted life-year are more appropriate, based on global assumptions about values, attitudes toward risk, and information on per capita annual income. Other economists have gone so far as to suggest that $200,000 to 300,000 per quality-adjusted life-year thresholds should be the standard, based on increases in healthcare expenditures over time, improvements in health associated with those expenditures, and willingness-to-pay attitudes.[49,50] In this analysis, if we liberalize the threshold to $150,000 to 200,000 per quality-adjusted life-year, the utility of the health state associated with transfusion is no longer sensitive nor influential on the results of this analysis. Thus, at thresholds greater than $150,000 per quality-adjusted life-year, there is even more confidence in the conclusion that IOCS-HR is a cost-effective strategy compared to IOCS-NO or ICOS-ALL.

Historically, implementation of cell salvage in obstetrics has been limited by concerns regarding maternal alloimmunization requiring additional Rho(D) immune globulin administration in Rh-negative mothers and a concern for amniotic fluid embolism, although there has only been one case report suggesting a potential link between amniotic fluid embolism after cell salvage.[2] Other concerns have included dilutional coagulopathy and hypotension, which have been reported after reinfusion of shed blood through a leukocyte depletion filter. Although technical errors are extremely rare, there have been reports of hemolysis progressing to disseminated intravascular coagulation and heparin toxicity associated with incorrect or inadequate washing. However, the overall potential risks of cell salvage in obstetrics are generally aligned with the risks in the general population.[2,4] A 2016 retrospective cohort study reported two adverse events associated with intraoperative cell salvage, both in obstetric patients, and the investigators quoted an overall rate of patient-related adverse events related to intraoperative cell salvage of between 0 and 2 per 33,351 (0 to 0.006%).[18]

There are limitations to this study. There are few probabilities and health state utilities that have been explicitly examined in the obstetrical and perinatal patient population, and therefore it was necessary to extrapolate some of these values and vary them over wide ranges in sensitivity analyses to generate a meaningful model. However, as evidenced by the results of our one-way sensitivity analysis, the impact of the extrapolations over these values on the overall conclusions of this study are likely to be minimal. Second, the probability of death from hemorrhage was based upon available Centers for Disease Control data, which included not only intraoperative mortality, but also stillbirths, abortions, and ectopic pregnancies, which are not specific to our cohort but may have led to an overestimation of our results. Third, we only compared three strategies: no cell salvage at all, cell salvage for cesarean deliveries at high risk for hemorrhage, and cell salvage for all cesarean deliveries. There may be other operative strategies in obstetrics worth modeling in terms of cost-effectiveness of cell salvage, including risk stratification based on each specific risk factor or accounting for unanticipated postpartum hemorrhage that occurs in women who have no risk factors, as occurs with traumatic causes of hemorrhage (*e.g.*, operative injuries, uterine rupture, uterine inversion). We did not undertake analyses of this latter nature because clinical decisions to set up cell salvage ahead of time are made based upon known risk factors at the time of cesarean delivery. We cannot comment on the cost-effectiveness of implementing cell salvage later during a case of unexpected postpartum hemorrhage after cesarean delivery in a woman with no apparent risk factors. Future studies could investigate this important question by undertaking a hospital-level perspective based on institutional rates of unexpected postpartum hemorrhage and gauging uncertainty in parameter estimates by varying distributions in one-way and probabilistic sensitivity analyses based on means and variances of variable probabilities, costs, and utilities of that particular hospital. The lifetime time horizon assumed in this analysis can be limiting in that longer time horizons make it more challenging to estimate costs and quality-adjusted life-year values, although the use of tunnel states enabled us to vary some disease-specific hazards over time. Another limitation is that we assumed no risk of complications related to cell salvage, although more precisely the risk is extremely low (0.006%). Our rationale in this assumption was that the risk of adverse events was rare, and we expect that the quality-adjusted life-year loss per event would be minimal; however, the true impact of this minimal risk on dollars per quality-adjusted life-year gained is not known by this analysis. Finally, our analyses included costs in the year 2012 because this is the most recent available medical cost information. However, our sensitivity analyses varied these values widely and should not significantly impact the results of our study.

Although the current analysis provides economic information that supports the general use of cell salvage for cesarean deliveries at high risk for hemorrhage, individual hospitals still need to evaluate the feasibility and local cost ramifications of adopting cell salvage technology at their institutions. Costs to the hospital will depend on case volume, estimated volume of blood shed per case, and initial equipment and training costs. Modification to our model or use of an alternative model such as that provided by Waters

et al.[53] can assist in hospitals considering implementation of cell salvage technology for cesarean delivery.

In summary, cell salvage for cases at high risk for hemorrhage is economically reasonable compared to strategies of cell salvage use for all cesarean deliveries or no cell salvage use at all. Elucidating the utility of the health state associated with allogeneic transfusion in obstetric patients will be useful in assessing the robustness of these results. Obstetric blood management guidelines may be informed by these findings.

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Competing Interests

The authors declare no competing interests.

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