A randomised controlled trial and economic evaluation of intraoperative cell salvage during caesarean section in women at risk of haemorrhage: the SALVO (cell SALVage in Obstetrics) trial

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Scientific summary

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Scientific summary

Background

Excessive blood loss (haemorrhage) in childbirth is an important direct cause of maternal death and has a profound impact on survivors. It is responsible for the majority of emergency hysterectomies and maternal critical care admissions. Haemorrhage is more common in women undergoing a caesarean section, particularly in the presence of placental abnormalities (placenta praevia/accreta), pre-eclampsia, antepartum haemorrhage, a history of previous caesarean section(s), or emergency caesarean for any indication. Approximately 166,000 caesarean sections (26% of all deliveries) are performed annually in England, around 60% of which are emergency procedures. It is the most frequent major surgery conducted by the UK NHS. Major haemorrhage can occur without warning during caesarean section with rapid unanticipated deterioration requiring urgent response.

The treatment for major haemorrhage involves donor blood transfusion when the operative loss is life-threatening or when the mother has severe anaemia following arrest of the haemorrhage. Red cell concentrate is a limited resource and is in demand by many clinical services. The high frequency of caesarean sections has a major impact on blood transfusion services (with £7M direct cost for donor blood components alone used in the obstetric setting per year), placing a constant challenge at the delivery of high-quality health care at all points of need simultaneously. There has also been a major shift to more restrictive clinical transfusion practice aligned to the principles of patient blood management, which include using transfusion alternatives when feasible and harnessing the patient's own reserves. Accordingly, donor blood is used sparingly in the healthy obstetric population. This can result in anaemia postnatally, which is potentially associated with longer recovery, increasing hospitalisation costs and wound infection rates.

Intraoperative cell salvage collects the woman's own blood that has been lost during caesarean, processes it and returns it to her circulation. It reduces the infectious and allergenic risks associated with donor blood transfusion. It can be used routinely for moderate blood loss, which is an expected feature of uncomplicated caesarean sections, returning all salvaged blood to minimise postoperative anaemia and its consequences, including reduction in maternal life quality. Cell salvage has been shown to reduce the amount of donor blood given in other operations from a wide spectrum of surgical disciplines, but has hitherto been considered relatively contraindicated for use in obstetrics as a result of theoretical concerns around the risk of contamination of salvaged blood with amniotic fluid, the potential for provoking maternal amniotic fluid embolism (AFE) and the possibility of increasing exposure of the mother to fetal blood. Concerns about AFE have proven unfounded, as research has not only shown that modern equipment effectively removes amniotic fluid from the salvaged blood, but also that transfer of amniotic fluid into the maternal circulation is a common event during birth that does not usually cause any adverse effects. Cell salvage has begun to enter use in caesarean section, but opinion about its value is not yet evidence based.

Objectives

The primary objective of the trial was to determine whether or not the routine use of cell salvage during caesarean section in women at risk of haemorrhage safely reduced the need for donor blood transfusion, in comparison with standard practice when salvage is not routinely used. In addition, we sought to assess the consistency of the effect of cell salvage across subgroups defined by indication for caesarean and to determine the effect of cell salvage on secondary outcomes, including the units of donor blood transfused, fall in perioperative haemoglobin concentration, any resulting morbidity, maternal exposure to fetal blood and the cost-effectiveness of cell salvage.

Methods

The cell SALVage in Obstetrics (SALVO) study was designed as a multicentre individually randomised controlled trial (registered as ISRCTN66118656) with cost-effectiveness analysis. Following the necessary approvals (UK ethics approval number 12/NW/0513), the study was conducted in 26 obstetric units across the UK, aiming to recruit 3050 women to give 80% power to detect a 2% difference in the transfusion rate (control event rate of 5%). Our sample consisted of women who were admitted to the labour ward for delivery by emergency (category 1–3: with an element of maternal or fetal compromise) or elective (category 4: no maternal or fetal compromise) caesarean section, with an identifiable increased risk of haemorrhage, who were at least 16 years old and able to understand written and spoken English. We excluded women undergoing an elective first caesarean owing to either maternal request or known breech presentation, as the risk of severe haemorrhage is very low in these groups. We also excluded women for whom either cell salvage or donor blood transfusion was contraindicated, including those with sickle cell disease or trait, active malignancy (such as abdominal cancer), religious or other beliefs precluding blood transfusion, or significant maternal antibodies making it difficult to find cross-matched blood compatible for transfusion.

For all women undergoing elective caesarean section, information about the study was provided at least 1 day before the surgery, usually at the time of booking the caesarean section; written informed consent for the study was then obtained before the surgery. For women undergoing emergency caesarean section, either written informed consent was obtained before the surgery, if there was sufficient time for discussion and reflection, or otherwise verbal consent was taken immediately before the surgery with written consent obtained after the operation, usually on the postnatal ward. In either case, in order for consent to be properly informed, the woman either (1) had to have received information antenatally before the onset of labour and previously stated her willingness to take part in the study or (2) following a substantial amendment to the protocol, had sufficient time and was not too distressed to receive study information after admission to the labour ward (this was deemed to be the case if the woman was comfortable with effective epidural analgesia in situ, or not yet in established first stage of labour, and had at least 1 hour to come to a decision after receiving the information and prior to giving verbal consent). Participating women were randomised by entry into an online system to either caesarean section with cell salvage, with cell-saver set-up and collection of shed blood from the outset of surgery and return of any processed blood obtained (intervention group), or to caesarean section without cell salvage, with transfusion of donor blood according to local guidelines (control group).

The primary outcome was the proportion of women receiving donor blood transfusion due to haemorrhage. Trial groups were compared according to this outcome on an intention-to-treat basis, estimating the effect using odds ratios (ORs) and 95% confidence intervals (CI). Two prespecified subgroup analyses were planned, including analysis of treatment effect by indication for caesarean section (elective or emergency) and by treatment centre. The first of these was analysed by statistically testing for an interaction between indication for caesarean section and treatment. The second was analysed by testing for a random regression coefficient for the effect of treatment at different centres, in addition to a random intercept. In order to account for women in the control group who received cell salvage due to a clinical decision, an additional sensitivity analysis was planned that would assume that all instances of return of salvaged blood in the control group would have been instances of donor blood transfusion had the cell salvage machine not been present. Analyses were adjusted for a random effect of treatment centre and fixed effects of stratification variables and other baseline characteristics believed to be associated with the outcome measure of haemorrhage a priori.

Secondary outcomes included units of blood transfused, time to first mobilisation, length of hospital stay, pre and postoperative serum haemoglobin, maternal exposure to fetal blood as measured by a Kleihauer–Betke test, maternal fatigue, adverse events (including transfusion reactions), resources used intraoperatively and postoperatively, costs of staff training, and process outcomes (including volume of salvaged blood returned and technical failure of cell salvage).

A cost-effectiveness analysis was carried out from the NHS perspective based on the principal clinical outcome of the trial with the results expressed as cost to avoid donor blood transfusion. A decision tree model was used, which collated all the relevant resource use, cost and outcome data collected prospectively during the trial to compare the overall cost-effectiveness of cell salvage with standard care. The resource use for both groups of the trial was estimated by evaluating the individual components of these procedures (bottom-up costing). Unit cost data were then attached to the resource use. A probabilistic sensitivity analysis was carried out to explore the effects of the inherent uncertainty in parameter estimates on model results.

Results

Between June 2013 and April 2016, 3054 participants requiring caesarean section from 26 participating hospitals were initially recruited for randomisation. After 26 exclusions for eligibility and consent issues, 3028 participants were randomly allocated to either control ($n = 1511$) or intervention ($n = 1517$). Of these 3028 participants, 1672 were scheduled for emergency and 1356 for elective caesarean section. A further 35 participants had to be excluded after randomisation owing to vaginal delivery or transfer to another site. We analysed data from 1492 participants in the control group and 1498 participants in the cell salvage group, after these exclusions for eligibility and loss to follow-up. Adherence to assigned intervention was 95.6% in the cell salvage group and 96.1% in the control group. Among the women treated with cell salvage in the intervention group, 50.8% had salvaged blood returned, with an average volume of 259.9 ml.

Overall, the transfusion rate was 2.5% in the group assigned to cell salvage and 3.5% in the control group (adjusted OR 0.65, 95% CI 0.42 to 1.01; $p = 0.056$). In the planned subgroup analysis, the transfusion rate was 3.0% in women assigned to salvage and 4.6% in the control group among emergency caesareans (adjusted OR 0.58, 95% CI 0.34 to 0.99), whereas it was 1.8% in the intervention group versus 2.2% in the control group among elective caesareans (adjusted OR 0.83, 95% CI 0.38 to 1.83) (interaction $p = 0.46$, suggesting that the difference in effect between subgroups was not statistically significant). In an additional, exploratory, subgroup analysis, the transfusion rate was 1.9% in women assigned to the salvage group and 2.9% in the control group among caesareans with normal placentation (adjusted OR 0.56, 95% CI 0.34 to 0.94), whereas it was 9.6% versus 8.9% among caesareans with abnormal placentation (adjusted OR 0.83, 95% CI 0.38 to 1.83) (interaction $p = 0.28$). A sensitivity analysis assuming that donor blood transfusion would have been required had cell salvage not been deployed in the control group showed a reduction in the proportion of participants requiring donor blood transfusion (5.6% vs. 2.5%, adjusted OR 0.39, 95% CI 0.26 to 0.59; $p < 0.001$).

There were small differences between groups for time to mobilisation [median 0.74 vs. 0.72 days, adjusted hazard ratio (HR) 1.11, 95% CI 1.03 to 1.19; $p = 0.006$] and length of hospital stay (2.131 vs. 2.126 days, adjusted HR 1.08, 95% CI 1.00 to 1.16; $p = 0.050$). Mothers assigned to cell salvage had greater exposure to fetal blood than those in the control group (25.6% vs. 10.5%, adjusted OR 5.63, 95% CI 1.43 to 22.14; $p = 0.013$). There were no differences between groups in other secondary outcomes. There was no case of AFE observed in any instances of cell salvage use.

The results of the economic evaluation suggested that routine cell salvage is more costly than standard care with the average cost per patient estimated at £1327 compared with £1244. The incremental cost-effectiveness ratio representing the average additional cost of routine cell salvage during caesarean section in women at risk of haemorrhage compared with standard care was estimated to be approximately £8110 to avoid a donor blood transfusion. This estimate was shown to be robust in sensitivity analyses.

Conclusions

There was modest evidence for an effect of routine use of cell salvage during caesarean section on the need for donor blood transfusion, particularly among emergency procedures. In women with rhesus D (RhD)-negative blood groups who gave birth to RhD-positive babies, cell salvage was associated with increased maternal exposure to fetal blood, which needs to be matched with higher doses of anti-D if cell salvage is to be deployed during caesarean sections among RhD-negative mothers. Our finding highlights the need to adhere to guidelines on anti-D prophylaxis and the need for vigilance also with respect to the potential sensitisation to other, more rare antibodies. The health economic analysis could not demonstrate that cell salvage was more cost-effective than standard care. Recommendations for future research include:

1. Investigate the impact of non-rhesus antibody sensitisation with long-term follow-up of mothers exposed to cell salvage during caesarean section.
2. Investigate the need for greater amounts of routine anti-D administration when cell salvage has been used.
3. Investigate factors, for example swab washing or number of suckers used, that increase the likelihood of returning blood during use of cell salvage.
4. Investigate the effectiveness of cell salvage in specific subgroups, for example placenta accreta.
5. Investigate the role of cell salvage in low- to middle-income countries where caesarean rates are rising and blood transfusion services are not well developed.
6. If new, cheaper or more efficient cell salvage technology becomes available, the conclusions of the SALVO trial may need to be revisited. The same is true if donor blood shortages should become extreme and acute.

Trial registration

This trial is registered as ISRCTN66118656.

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