

Hemosep: A New System for Ultrafiltration and Blood Conservation in Cardiac Surgery

Summary

- ✓ **Ultrafiltration (hemoconcentration) is a technology for patient blood management, intended to reduce surgical blood loss and the need for allogeneic (donor) blood transfusion in cardiac and certain other types of surgery.**
- ✓ **With ultrafiltration, beneficial elements of the patient's blood — including red blood cells, platelets, proteins, and clotting factors — are retained, unlike cell saver systems that recover only the red blood cells.**
- ✓ **Ultrafiltration can be used in conjunction with other blood conservation interventions to reduce the risks associated with allogeneic blood transfusions.**
- ✓ **Blood ultrafiltration technologies may provide another option for Jehovah's Witnesses patients whose religious beliefs forbid blood transfusion.**
- ✓ **Although published studies of Hemosep have not reported any adverse events, other ultrafiltration trials have reported an increased need for vasopressor medications to treat low blood pressure in the patients who received ultrafiltration.**
- ✓ **Good quality clinical trials are needed to compare existing blood conservation practices with and without Hemosep, and to identify which patient groups it may benefit.**

The Technology

The risks associated with allogeneic blood transfusion (i.e., donor blood) are now well-known.¹ In Canada, blood transfusions carry small risks for contracting hepatitis and HIV/AIDS, as well as greater risks for immune reactions and bacterial infections.²

Blood transfusion-related costs include the costs of acquiring, processing, storing, and administering donor blood, as well as costs associated with treating adverse effects caused by allogeneic blood transfusions.^{3,4} A recent Ontario study estimated that one unit of blood

(450 mL or slightly less than one pint) costs approximately C\$450 (not including the costs of obtaining and administering the transfusion); sometimes a patient will need several units of blood.⁵ Blood management programs, such as the Ontario Transfusion Coordinators (ONTraC) program, that coordinate interventions to reduce transfusions have achieved impressive cost-savings by minimizing the use of donor blood and, as a result, reducing the rate of transfusion-related adverse events and the length of hospital stays.^{3,5,6}



The Hemosep System

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The supply of donor blood is also a concern. Approximately 40% of Canadians are eligible to donate blood but roughly 4% are blood donors.⁵ Meanwhile, demand for blood products is rising; for use in new, targeted cancer treatments, for example.^{7,8} As well as reducing the risks and costs associated with allogeneic blood transfusion, blood conservation measures may relieve some of the pressures on the donor blood supply.⁹

Cardiac surgery uses a high volume of blood products because of the blood loss both during the surgery and postoperatively.^{3,10,11} In addition, the patient's blood is hemodiluted to allow it to pass through the cardiopulmonary bypass circuit.¹¹ After surgery, these fluids, along with some of the patient's blood, remain in the circuit. The residual blood contains red blood cells (important for oxygen transport and preventing anemia), as well as components that prevent inflammation and promote coagulation.^{12,13} The circuit blood may be either discarded, or processed and re-transfused to the patient using different

techniques to filter out contaminants and remove excess fluid.¹¹

Current guidelines and consensus statements recommend that various blood conservation or “patient blood management” measures be used under the guidance of a multidisciplinary health care team (e.g., nurses, anesthesiologists, perfusionists, surgeons, and laboratory technologists) to minimize the need for allogeneic transfusion in cardiac surgery.¹⁴⁻¹⁶ Blood conservation interventions include:

- restrictive transfusion policies
- preoperative autologous blood donation
- drug therapies to stimulate red blood cell production preoperatively
- minimally invasive surgery to reduce blood loss
- antifibrinolytic drugs to reduce bleeding during the surgery
- intraoperative red blood cell salvage
- ultrafiltration for autotransfusion of blood components back to the patient.^{5,14}

Autologous transfusion (autotransfusion) technologies salvage and re-transfuse the patient’s blood. These have been used for many years to reduce both surgical blood loss and the need for allogeneic blood transfusion.^{17,18} Many autotransfusion technologies were originally pieced together using existing hospital equipment, such as electric blood pumps, and blood filtering and storage devices.¹⁸ Blood concentration (hemoconcentration) was achieved using modified dialysis or centrifuge devices to remove some of the water and plasma, but these in-house systems were relatively complicated to use.¹⁹

Ultrafiltration (hemofiltration) uses filtration, rather than centrifugation, to separate out red blood cells and other blood components for re-transfusion to the patient.⁹ Unlike cell salvage technologies that “wash” and separate out the red blood cells, ultrafiltration technologies filter and remove fluids (to minimize adverse events due to hemodilution) and contaminants, while preserving red blood cells and other beneficial components (e.g., platelets, proteins, and clotting factors) for re-transfusion.^{11,14}

Recent blood conservation guidelines from The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists summarized the evidence on three types of ultrafiltration used in cardiac surgery, as follows:¹⁴

- **conventional ultrafiltration** (used during cardiopulmonary bypass) — no benefit regarding red blood cell use or reduced blood loss
- **modified ultrafiltration** (used after cardiopulmonary bypass) — significant reductions in blood loss and fewer requirements for transfusions of red blood cells or platelets, which suggests a benefit through reduced hemodilution and the need for blood transfusion
- **zero balance ultrafiltration** (replacing the ultrafiltrate fluid with an electrolyte solution) — no reduction in blood loss or transfusion.

Modified ultrafiltration was introduced in the 1990s, and several different systems have been developed since then.²⁰ The Hemosep system is a recent commercial system for modified ultrafiltration and hemoconcentration. Hemosep is intended to reduce blood loss in cardiac and other types of “clean site” surgery, including pediatric surgery [personal communication: Margaret Hanlon-Bell, BHC Medical, Mississauga (ON), 18 Nov 2014]. The system has four main parts: a Hemosep bag, which contains the “chemical sponge” filter; an agitator to keep the blood from coagulating and increase the rate of filtration; a blood collection bag; and a cell concentrator bag. Hemosep removes plasma fluid and contaminants from blood salvaged from the cardiopulmonary bypass machine (either during or after surgery), allowing the concentrated blood product to be re-transfused to the patient.^{19,21}

Regulatory Status

The Hemosep system (Advancis Surgical/Brightwake Ltd., Nottinghamshire, UK) was first licensed by Health Canada as a Class II medical device in November 2012; additional system components were licensed in January 2014.²² The Canadian distributor is BHC Medical Inc. (Mississauga, Ontario).

Another commercial device specifically for blood ultrafiltration in cardiac surgery is the Hemobag system (Global Blood Resources LLC, Somers, Connecticut), which received Health Canada licensing in 2009.

Patient Group

While allogeneic blood transfusion carries risks, anemia is also a risk factor for surgical patients.¹⁶ Certain heart surgery patients are known to be at higher risk for bleeding and requiring blood transfusion, including older patients, those with lower levels of red blood cell

volume (due to preoperative anemia or smaller body size), and those undergoing complex cardiac procedures.^{13,14}

As blood ultrafiltration can be used within a closed loop system, it may also offer an option for Jehovah's Witnesses patients whose religious beliefs forbid blood transfusions.^{20,23,24}

Current Practice

Approximately 50,000 cardiac surgeries are performed in Canada each year.³ One recent commentary notes that blood conservation in cardiac surgery is a "multimodal and multidisciplinary process, with increasing numbers of successful blood management programs."³ Ontario's ONTraC program is one example, but at least 35 blood conservation programs are in place at hospitals across Canada.^{3,25}

Methods

Literature Search Strategy

The peer-reviewed literature search included the following bibliographic databases: PubMed, Embase, The Cochrane Library (2014, Issue 8), and the University of York Centre for Reviews and Dissemination (DARE, NHS EED, and HTA) databases. Grey literature was identified by searching relevant sections of the CADTH *Grey Matters* checklist (<http://www.cadth.ca/resources/grey-matters>) and manufacturers' websites. No methodological filters were applied to limit retrieval by publication type. The search was restricted to English language documents published within the last five years (August 2009 to August 2014), with monthly PubMed updates to January 2015.

Study Selection Criteria

Published studies that assessed the use of the Hemosep device were selected for review of the clinical evidence. Studies of alternative devices or methods for ultrafiltration, unpublished data, older publications, and information from clinical experts were also included, where appropriate, to place this technology in context.

The Evidence

The current evidence on Hemosep consists of one randomized, single centre clinical trial and feasibility study of its use in 102 patients undergoing cardiac bypass surgery.¹⁹ The patients in the Hemosep group received re-transfusion of their salvaged blood,

processed through Hemosep, following their bypass surgery, while patients in the control group did not receive re-transfusion of their salvaged blood.¹⁹ Significantly more patients in the Hemosep group did not receive any allogeneic blood transfusions (38 from a total of 52 patients) in comparison to those in the control group (19 from a total of 50 patients).¹⁹ Of those who did require allogeneic transfusions, patients in the Hemosep group required fewer units of blood (1 ± 0.8 units of red blood cells in the Hemosep group versus 2.4 ± 1 in the control group; $P = 0.032$). There were no technical failures with the Hemosep device, and clinical staff were reportedly "pleased with its ease of use and overall performance."¹⁹ A conference report of preliminary results from this study also noted a decrease in both postcardiac bypass inflammatory response and postoperative bleeding in the Hemosep patients.²⁶

A small, randomized controlled trial ($n = 47$) compared hematocrit levels of patients who received salvaged blood processed by Hemosep with patients who received similar quantities of unfiltered salvaged blood. The latter is not the standard of practice at most Canadian cardiac surgery centres [personal communication: John Miller, Mazankowski Alberta Heart Institute, Edmonton (AB), 19 Nov 2014]. This study, reported only in a conference abstract, found no significant difference in hematocrit levels between the two groups.²⁷

Trials of other (non-Hemosep) ultrafiltration technologies include a randomized controlled trial of 197 patients at one Canadian hospital, the Processed Residual Blood in Cardiac Surgery trial, which assessed the use of blood ultrafiltration in adult patients undergoing uncomplicated heart bypass surgery.¹² This trial used a hemoconcentrator and ultrafiltration but not the Hemosep device. The trial's primary outcome was the number of patients requiring allogeneic red blood cell transfusions. There was no difference in the proportion of patients who received allogeneic blood transfusions (39% of patients in both groups received transfusions). For secondary study outcomes, ultrafiltration did not significantly decrease the quantity of red blood cells transfused; rates of postoperative hemorrhage were similar, as were patients' hemoglobin levels at discharge.¹² However, the investigators caution that their study did not use continuous ultrafiltration during the bypass surgery and did not include patients undergoing complex cardiac surgeries who are at greater risk for needing blood transfusions. Results

using continuous ultrafiltration and in high-risk patients may differ.¹²

Another small Canadian study investigated the methodological feasibility of conducting a blinded, randomized controlled trial of ultrafiltration in cardiac bypass surgery. This study used a Terumo hemofilter rather than the Hemosep system. The study found no difference in the units of red blood cells transfused between the ultrafiltration and the control groups, although the ultrafiltration group patients had higher hematocrit values (levels of red blood cells). Note that this study was underpowered to detect significant differences. Patients in the ultrafiltration group received more frequent and higher doses of vasopressor drugs for the treatment of low blood pressure.¹⁰

Adverse Effects

The trial of Hemosep included measurement of acrylate levels from the ultrafiltration membrane in the processed hemoconcentrated blood. No measurable levels of acrylate were detected.¹⁹ The trial report cites clinical and laboratory studies of Hemosep that confirmed that levels of plasma-free hemoglobin in the processed blood were not elevated post-processing (which would indicate a higher risk for adverse effects post-transfusion).^{19,28} After processing with Hemosep, the resulting blood product had a higher white cell count (believed to be part of the cellular response to the cardiopulmonary bypass) but was otherwise similar to the pre-operative blood.¹⁹ No adverse events in patients were reported.

Administration and Cost

Hemosep is used in conjunction with existing blood conservation practices; consequently, it will be an additional cost. For example, at the Mazankowski Alberta Heart Institute, current patient blood management includes multi-pass hemoconcentration of the entire volume of the cardiopulmonary bypass circuit, as well as hemofiltration. In addition, cell saving and/or autotransfusion is frequently used during cardiac surgery procedures [personal communication: John Miller, Mazankowski Alberta Heart Institute, Edmonton (AB), 19 Nov 2014].

The price of the Hemosep system ranges from C\$5,000 to C\$7,000, with disposables costing anywhere from \$450 to \$600 per surgery [personal communication: Margaret Hanlon-Bell, BHC Medical, Mississauga (ON), 16 Oct 2014]. As an example, if this technology

was used on all cardiac surgery patients at the Mazankowski Alberta Heart Institute, the incremental cost would be approximately \$1 million per year [personal communication: Dr. David B. Ross, Mazankowski Alberta Heart Institute, Edmonton (AB), 11 Nov 2014].

The potential cost-savings of blood conservation interventions depends on the volume of blood salvaged.²⁹ Some studies suggest that at least 1.5 to 2 units of blood must be recovered to ensure cost-effectiveness; but, depending on the cost of the blood conservation technology, savings could be achieved with even lower volumes of salvaged blood if this avoids the cost of treating adverse effects from allogeneic blood transfusions.^{9,29}

Ultrafiltration and hemoconcentration may also reduce the amount of contaminated surgical waste by-products by removing the fluid from the bypass circuit residues.¹⁹ The waste by-product from the Hemosep process is basically a plasma gel, which may be easier to dispose of than the fluid wastes produced by cell saver centrifuge systems.¹⁹

Concurrent Developments

Advancis Surgical is developing the Hemosep system for use in other types of surgery, including trauma and orthopedic surgery.²¹

Rate of Technology Diffusion

According to the Canadian distributor, small trials of Hemosep in both cardiac and orthopedic surgeries are expected to begin soon in several Ontario centres. Other than in these planned trials, no Canadian hospitals are currently using the Hemosep system [personal communication: Margaret Hanlon-Bell, BHC Medical, Mississauga (ON), 29 Aug 2014].

The Hemobag system is being used at Royal University Hospital and at the University of Saskatchewan, and has also been used at the University of Ottawa Heart Institute [personal communication: Keith A. Samolyk, Global Blood Resources, Somers (CT), 17 Oct 2014].

Implementation Issues

Patients at higher risk for requiring blood transfusion when undergoing cardiac surgery may benefit most from blood conservation measures. However, evidence

of the value of stratifying high-risk patients to receive blood conservation interventions is lacking.^{13,14}

Previous work by ONTraC has shown a marked reduction in length of hospital stay and rate of postoperative infection in cardiac bypass patients who received perioperative blood management interventions.^{5,16} (Note that the ONTraC study reports did not mention the use of ultrafiltration.)

A recent consensus statement on technologies for blood management in cardiothoracic surgery concluded that there is moderate evidence to recommend that ultrafiltration (either continuous or modified) be used for blood conservation but that further research is needed.¹⁵ An important consideration is that most studies of ultrafiltration and of other blood conservation interventions have focused on outcomes such as the volume of blood transfused rather than more important clinically relevant outcomes, such as death, stroke, myocardial infarction, and kidney failure.¹⁵ There is also a need for more evidence to determine whether ultrafiltration offers an additional benefit beyond that obtained with cell savers and antifibrinolytics, and which type of ultrafiltration — continuous or modified — is superior.¹⁵

Preliminary evidence indicates that the use of ultrafiltration may be effective, but further evidence is needed to compare ultrafiltration systems and to determine their role within existing interventions for patient blood management.

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