Hemosep®
Life changing technology...
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Overview

A number of technologies have evolved to fulfill the haemoconcentration task over the past decades. These include the use of modified dialysis technology and more commonly, the use of centrifuge devices to concentrate cell populations and remove excess water and plasma\textsuperscript{1-3}. These devices are fairly complex in nature and require specialist technical knowledge to operate. In addition, such devices produce both a concentrated blood product and a liquid waste effluent which may represent a contamination risk. These techniques are however considered to be an increasingly important part of modern practice, particularly as blood used during such operations has a significant cost and there remains a risk of transfusion associated infection and reaction if donor rather than autologous blood is utilized.

The object of the Hemosep\textsuperscript{®} development was to design a haemoconcentration technology that produces a blood concentrate in all cell species, maintaining not only the RBC’s but preserving the platelets, WBC’s and clotting residuals and does not require centrifugation and associated blood transfer steps and can be utilized without the need for highly trained technical personnel. In answering this challenge, the Hemosep\textsuperscript{®} concept was developed, based upon the use of a membrane controlled superabsorber driven plasma removal process. This process is carried out entirely in one vessel and requires no additional blood transfer steps or flushing procedures. In essence the Hemosep\textsuperscript{®} device is a one-stop haemoconcentration process for concentrating residual blood from the blood reservoir during surgery. Residual blood is introduced into the device, concentrated using the membrane controlled superabsorber process, and transfused back to the patient using a transfer bag, saving all cell species.

An additional benefit of the Hemosep\textsuperscript{®} technology is that it produces a gelatinous waste product, essentially plasma in a gel matrix, which is safer and easier to dispose of than the large volumes of fluid associated with the more common centrifugation processes.

\textbf{Fig: 1.} The Hemosep\textsuperscript{®} technology: 1. The Hemosep\textsuperscript{®} bag, 2. Hemosep\textsuperscript{®} Shaker, 3. The blood collection bag, 4. Blood reservoir and 5. Suction tool.

**General description of the Hemosep\textsuperscript{®} device**

The Hemosep\textsuperscript{®} device concentrates blood by removing the fluid component of whole blood, the plasma, from a pooled volume of blood salvaged during, or at the end of surgery. The technique for removing the plasma from the blood product, leading to concentration of the cellular components, is fairly simple but involves a number of critical steps and controls.

The Hemosep\textsuperscript{®} system consists of 4 major components (fig. 1):

1. The Hemosep\textsuperscript{®} bag (1)
2. Hemosep\textsuperscript{®} Shaker Unit (2)
3. A blood collection bag for the collection of processed blood (3)
4. Intra operative pump, suction and blood reservoir (4,5)
**Mechanism of action for the Hemosep® device**

The Hemosep® device relies upon two main constituent elements for its primary function of concentrating blood cells from haemodiluted media. These components are the control membrane and the superabsorber; the other elements of the device are designed to simply contain the blood prior to and during processing and to contain plasma removed from the blood product. In use haemodiluted blood is transferred via the suction tool into the blood reservoir and then pumped into the Hemosep® device. The blood is separated from a superabsorber pad by a control membrane with a pore size which prevents the migration of cellular species from the blood into the superabsorber section of the device. Free passage of the plasma however is not restricted and as this fluid passes from the blood through the membrane into the superabsorber, it results in a concentration of the cellular components of the blood held within the bag. Once the appropriate level of haemoconcentration is achieved (normally a packed cell volume in excess of 33%), the blood held in the bag is transferred into a transfer bag for subsequent transfusion to the patient.

**The Hemosep® bag**

The Hemosep® bag element of the system is the active processing section of the device. It consists of a blood bag with a filter membrane bag suspended within it, within which is a sheet of superabsorber material. The filter membrane material employed in the device has a unique size pore structure.

The filter membrane is the control membrane of the system and the unique pore size for this important element of the device has been selected to ensure that no cellular components of the blood product can pass into the superabsorber during use. The unique pore size is small enough to permit efficient fluid transport into the superabsorber but is too restrictively small to permit the passage of cells, even the smallest intact cells, the platelets (fig. 2).
The blood collection bag

The blood collection bag is a simple blood bag which is connected to the outlet of the Hemosep® bag after blood processing and into which the processed blood is drained (fig. 5).

Intended clinical performance

The Hemosep® device is intended to concentrate the residual blood during and after the operative procedure. This blood is highly haemodiluted and if returned to the patient in its raw state, may lead to excessive bleeding and patient haemodilution in the critical post surgical recovery phase. Concentration of this blood product to near-normal cell concentrations (PCV level 33 - 45%) renders it suitable for re-transfusion and diminishes the bleeding risk of unprocessed blood. The transfusion of the processed autologous blood reduces the need for donor blood products and their associated transfusion reactions. The Hemosep® device, under normal clinical conditions, is intended to concentrate residual blood from low PCV's (20% or less) to near-normal levels (at least 33%) without the need for centrifuge technology.

Design calculations

The Hemosep® device is designed to concentrate the residual blood in surgery. The volume of this blood can vary significantly, but is generally in the region of 750ml depending on the amount re-transfused to the patient. The Hemosep® device is therefore designed to meet these requirements and has a capacity of up to 1 litre. The design of the control membrane reflects the need to spare a broad range of cellular species from the smallest platelets to larger white cell species (3-20microns). A unique pore size was selected for this element of the device to meet this need, but it is recognised that some platelets may be lost in processing due to deformation of the cell structure in interaction with the pores.

The amount of superabsorber incorporated into the device was derived from the required performance characteristics to ensure that there is sufficient material for adequate concentration and also to make sure that there is no possibility of superabsorber saturation. This might lead to superabsorber migrations from the inner vessel through the control membrane and into the blood product. With a maximum of 1 litre capacity at a PCV of 20% (extreme clinical conditions), there is 640ml of plasma present in the blood product. Our assessment of superabsorber capacity confirms that the superabsorber is capable of absorbing 234ml of fluid per gram of material. Only in the region of 3g of superabsorber material is required to absorb all of the plasma present. However, to ensure that there is no possibility of the superabsorber transferring from the inner to outer chambers, in other words to ensure unidirectional flow of the fluid, 15g of superabsorber materials is employed in the Hemosep® product. This mass of superabsorber is capable of absorbing up to 3 litres of fluid and represents a considerable margin for safety in the device (fig.5a).

Pre-clinical testing - non clinical performance studies

Early performance tests of the Hemosep® device were performed using fresh heparinised bovine blood with haematocrit adjusted with saline solution to match common clinical values. In addition to testing the performance of the device with bovine blood, tests were carried out using freshly donated human blood to confirm the function of the device under near-clinical conditions.
**Bovine blood tests**

Fresh heparinised bovine blood was diluted using saline to a packed cell volume (PCV) of 20%. A 500ml volume of blood was then injected into the Hemosep® device after the device had been wetted and activated with 200ml of saline. The blood was then left to incubate in the Hemosep® device for a period of 40 minutes. Blood samples were taken from the device at 5 minute intervals and the PCV measured using centrifugation (fig. 6).

**Level of Blood Concentration Achieved in Passive Mode**

![Graph showing the level of blood concentration achieved in passive mode.](image)

**Fig: 6 Effect of passive incubation on packed cell volume (PCV) in fresh heparinised bovine blood haemodiluted to 15%. The clinical target level of PCV (35-40%) was achieved in around 15 minutes.**

In an effort to reduce the processing speed of the device, the addition of an agitation step was introduced. The agitation was provided by placing the blood filled Hemosep® device onto an orbital shaker platform, operating at 120 cycles per minute. This additional process reduced the blood processing time (time to reaching desired clinical values) by up to 30% (fig. 6a).

**Effect of Exposure Time on PCV of Whole Blood with Optimal Device Configuration With Agitation**

![Graph showing the effect of exposure time on PCV with agitation.](image)

**Fig: 6a. Effect of active incubation on packed cell volume (PCV) in fresh heparinised bovine blood haemodiluted to 15%. The clinical target level of PCV (35-40%) was achieved in around 10 minutes. This represents a significant reduction in processing time which may be important in the clinical setting.**

Through these bovine blood studies a number of factors were clarified:

1. The device was shown to function very well in terms of raising the PCV of haemodiluted blood products to acceptable clinical levels.
2. The addition of agitation during the concentration step reduced the processing time, most likely by effectively scouring the control membrane surface with blood during processing, resulting in the maintenance of pore patency.
Studies with human blood

Similar studies to those carried out in bovine blood were performed on fresh heparinised human blood by the National Blood Service, Brentwood, Essex. The focus of these studies was to determine whether the results obtained from the study of the Hemosep® device with bovine blood was reflected in studies with fresh human blood. Although there is little by way of cell size difference between bovine and human blood, there is always a possibility of inter-species differences in terms of testing a novel medical device. These studies utilised a fixed processing time and orbital shaker driven agitation at 120 cycles per minute respectively. The human blood studies went into considerable detail with regard to the overall biocompatibility of the Hemosep® device, however, a summary of the results of the cell processing performance is shown in fig. 7.

This data, taken from the study of human blood match very well with that derived from bovine studies. A similar outcome was apparent in the analysis of platelet survival rates when the Hemosep® device was employed with human blood (fig. 8a & 8b).

Overall the results derived from the human blood trials mimicked those obtained from the study of bovine blood. Both studies show that the Hemosep® device:

* Concentrates haemodiluted blood, raising PCV from sub-normal levels to normal clinical levels.
* The use of the device, incorporating the unique control membrane, results in concentration of platelets from sub-normal levels to normal clinical levels.

In addition to these findings with regards to the basic function of the Hemosep® device, the National Blood Service report confirmed that the device was not associated with haemolysis and increased white cell populations to normal clinical values.
The Hemosep® bag is the active processing section of the device and consists of three parts:

1. **The blood bag** - This houses the technology (the filter membrane and the super absorbent pad) and blood whilst it is filtered.

2. **Filter membrane** - This has a unique pore structure to control what is able to pass through during filtration so that no cellular components can pass into the super absorbent pad.

3. **Super absorbent pad** - This absorbs all unwanted blood product during the filtration in the filter membrane and turns them into a gel like substance for easy disposal once complete.
**Clinical outcome of transfusion processed by ultrafiltration in patients undergoing coronary bypass**

**Abstract**
Terence Gourlay- Bioengineering Unit, University of Strathclyde-UK
Serdar Gunaydin- University of K. Kale, Turkey

**Objective**
Following termination of cardiopulmonary bypass (CPB), the circuit contains a significant volume of diluted blood and various methods have been used to salvage this blood including direct transfusion or centrifugation/washing of the circuit volume. We designed a prospective clinical trial to determine the clinical outcomes of transfusion of autologous blood processed by a novel ultrafiltration device (Hemosep® Advancis Surgical, Nottingham, UK) in high risk patients undergoing coronary re-vascularization.

**Patients & Methods**
Over a 6-month period, 40 high risk patients (Euroscore 6+) undergoing CABG with full heparin dose strategy were prospectively randomised into 2 equal groups (N=20). In group 1, following the cessation of CPB, salvaged blood in the venous reservoir was pumped into the Hemosep® bag until the desired volume has been introduced and processed for re-transfusion back to the patients. Group 2 patients were controlled and this technology was not employed. Blood samples were collected at baseline (T1); at the end of the CPB (T2) and 24 h (T3), postoperatively.

**Comparison with patient’s pre-operative blood**

<table>
<thead>
<tr>
<th></th>
<th>Pre Surgery</th>
<th>Post Hemosep®</th>
<th>%Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>White Cell Count</strong></td>
<td>6.71 +/- 0.63</td>
<td>13.8 +/- 1.9</td>
<td>105.6</td>
</tr>
<tr>
<td><strong>Platelet Count</strong></td>
<td>198636 +/- 31101</td>
<td>192650 +/- 34906</td>
<td>-3.4</td>
</tr>
<tr>
<td><strong>Haematocrit</strong></td>
<td>43.5 +/- 1.9</td>
<td>39.45 +/- 2.1</td>
<td>-9.3</td>
</tr>
<tr>
<td><strong>Haemoglobin</strong></td>
<td>12.14 +/-1.51</td>
<td>12.83 +/- 0.85</td>
<td>5.6</td>
</tr>
</tbody>
</table>

**Effect of Hemosep® device on cell populations and haemoglobin. Comparison of pre-surgery and post-Hemosep® blood samples.** All factors were within 10% of “normal” pre-surgical levels with the exception of white cell counts which were almost double the baseline levels in these patients. This is probably the result of well documented white cell dynamics associated with the deployment of cardiopulmonary bypass.

**Fig 9A - Haematocrit Levels**

**Fig 9B - WBC**

**Fig 9C - Platelet Count**

**Results**
Mean processed blood was 775±125mL80% (N=16) patients in group 1 and 30% (N=6) in control group did not receive any bank blood (p<0.05). Postoperative bleeding was 545±180 cc in group 1 versus 725±200 cc in control (p<0.05). IL-6 levels (pg/ml) were significantly lower in group 1 versus control at T3 (11±4 versus 32±8; p<0.05). CD11b/CD18 levels (%) were significantly lower in group 1 (14±4) versus control (23±8) at T3 (p<0.05).
Effect of Hemosep® device on cell populations and haemoglobin. Comparison of pre- and post- Hemosep® blood samples

<table>
<thead>
<tr>
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<th>Post Hemosep®</th>
<th>%Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>White Cell Count</strong></td>
<td>10.97 +/- 0.98</td>
<td>15.78 +/- 1.5</td>
<td>43.6</td>
</tr>
<tr>
<td><strong>Platelet Count</strong></td>
<td>148800 +/- 23841</td>
<td>173272 +/- 79786</td>
<td>16.4</td>
</tr>
<tr>
<td><strong>Haematocrit</strong></td>
<td>22.5 +/- 1.6</td>
<td>38.45 +/- 2.7</td>
<td>70.9</td>
</tr>
<tr>
<td><strong>Haemoglobin</strong></td>
<td>7.78 +/- 1.02</td>
<td>11.45 +/- 1.05</td>
<td>47.2</td>
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</tbody>
</table>

Results clinical follow up

<table>
<thead>
<tr>
<th></th>
<th>Hemosep® (N=52)</th>
<th>Control (N=50)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td><strong>Postoperative Bleeding</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(24 h) (cc)</td>
<td>545±180</td>
<td>725±200</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td><strong>RBC Transfusion (Unit)</strong></td>
<td>1±0.8</td>
<td>2.4±1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>FFP Transfusion (Unit)</strong></td>
<td>0.95±1.2</td>
<td>2.4±3</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td><strong>Patients with no Transfusion</strong></td>
<td>73% (38 pts)</td>
<td>38% (19 pts)</td>
<td>&lt;0.05</td>
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</table>

Conclusions

Use of the Hemosep® device for salvaging blood is associated with significant decrease in post-CPB inflammatory response, postoperative bleeding and the need of transfusion with prevention of exposure to expensive and precarious allogeneic blood products.

Residual ECC blood was also analysed with respect to:

![Serum Albumin Levels](image1)

![Factor V11 Levels](image2)

![Serum Fibrinogen Levels](image3)

![IL-6 Levels](image4)
Cardiac application

For some decades now, clinicians have employed Haemoconcentration, either during the operative procedure, or more commonly on the residual blood left in the CPB system at termination of CPB to concentrate the blood cells prior to re-administration to the patient. These include the use of modified dialysis technology and more commonly, the use of centrifuge devices to concentrate cell populations and remove excess water and plasma.

The Hemosep® device can be utilised to ultra-filtrate this residual blood following termination of the CPB system. This approach reduces the need for donor blood and blood associated products therefore reducing the risks associated with it.

To collect the blood left in the heart lung machine, simply connect the concentrator bag with the leur lock connection to the tubing below the reservoir for gravity fill applications, or connect to the tubing above the reservoir and pump the blood into the concentrator bag, as shown in the diagram to the right.

Patient Features and Benefits

- Patient’s own blood is transfused, reducing the risk of contamination and reaction
- Decreased need for donor blood and associated transfusion products, leading to a reduction in donor dependency
- Assists in the reduction of post-operative bleeding, resulting in improved patient recovery
- Maintenance of platelet population means there is preservation of normal clotting function
- Reduction in inflammatory molecules, resulting in a reduction in post-operative complications
Intra operative application

Further developments of the Hemosep® device has resulted in an intra operative option with the addition of a heparin infused suction tool. The device is capable of aspirating blood from the surgical site directly into a blood reservoir; this can be filled up to a volume of 1000ml and then pumped directly into the Hemosep® concentrator bag for processing of the blood. It is still possible to continue with the suction of fluid from the surgical site while the concentrator bay is being shaken on the device.

The use of the Hemosep® intra operative device presents a wealth of application possibilities, with the inclusion of the Intra Operative suction tool and blood reservoir the device could be used during most blood loss procedures.

Using the unique ultrafiltration technique the device is able to effectively produce a high quality blood product in order to aid the patient recovery time and dramatically reduce the need for donor blood and associated products.

Hemosep® intra operative can give health care professionals flexibility of use by utilising the suction capabilities of the device and assessing the appropriate direction to either filter the blood or disregard the fluid and take other action. This flexible approach is achieved by packing the Hemosep® consumables in separately sterilized packaging and making them available via different ordering codes. By designing the device in this way Advancis Surgical are able to increase your flexibility and help control surgical costs.

The Hemosep® consumables consists of:

1. The concentrator and blood bag
2. The suction tool and wand
3. The blood reservoir and internal pump

Aspirate directly from the surgical site and pump from the reservoir into the concentrator bag.
**Frequently asked questions**

**How is leukocyte activation managed?**
Leukocyte activation is not a real problem post-CPB. The leukocyte dynamics associated with CPB result in a high leukocyte population, but these are largely in an inactivated state. If health care professionals are concerned about the leukocyte population of the concentrate, they may choose to leukocyte filter the material. Some clinical groups leukocyte filter all blood products as a matter of course. The view of many health care professionals is that this should not be necessary.

**Will the Hemosep® device aid in the reduction of post-operative bleeding?**
Post-operative bleeding is a major factor in any major surgery, there are several factors surrounding the cause of this. One factor is the reduction in clotting factors associated with the current practice of only giving a patient back the red blood cells, therefore reducing the clotting agents in the blood and the Hemosep® device. The Hemosep® device recycles the blood in all cell species, retaining the residual clotting factors in the concentrate; this in turn will aid in the reduction of post-operative bleeding and potential help in the reduction of surgery.

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**Are there any other areas the device can be used in?**
Advancis Surgical will be developing additions to the device for use in the Orthopaedic, Paediatric and Neonatal practices.

**I currently have a contract for cell salvage devices, how can I justify the purchase of this product for my trust?**
Due to the way Hemosep® recycles the cell species, it saves money by reducing the need to add platelets to a patient (the cost of platelets are £209.30 per bag with an average 1.2 bags being used per patient transfusion). Hemosep® can save around £150 per patient, making it economical even if current cell salvage techniques are still in place.

**Will Hemosep® remove any damaged RBC, WBC cells as with the Cell Saver device?**
The Hemosep® device will remove fragmented cells and fragments below the pore size.

**What is the overall quality of blood returned to the patient post CPB?**
The blood product returned after concentration is very similar to that of the pre-surgical blood.

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**Do you have details of the effect of the activated platelet levels and any potential issues surrounding it?**
There is no suggestion at the present time that platelets are activated by the process.

**How much heparin is left in the processed blood?**
The levels of heparin left in the processed blood are negligible, when transfused back to the patient the systemic levels are within the same scope as levels needing to be achieved when heparin is administered; it is therefore not necessary to increase the protamine levels, in cases where several bags of blood are transfused back to the patient it is advised to monitor the A.C.T. and take appropriate action.

**In which surgical procedure is Hemosep® best suited?**
Hemosep® is best suited to elective producers where a steady blood loss occurs; in cases of massive trauma many centres will adopt the practice of returning the whole blood to the patient in order to give the blood back as quickly as possible. Standard cell saver devices can be used to accomplish this, however in the case of massive trauma there is little evidence to suggest there is any clinical benefit to the patient.

**What are the benefits of returning the white blood cells (WBC)?**
The WBC are in a nonactivated state therefore classed as fresh WBC’s, these are essential to fighting infections in the body and should therefore aid in the overall recovery period.

**Assessment of platelet activation and overall quality**
This is yet to be investigated fully but there is no reason to assume that platelet function will be impacted by the use of the technology. There is no high shear during the process and surface contact is minimal. Small platelets and platelet fragments are removed by the system, resulting in a loss of around 30% of platelet numbers. These studies are underway, however our clinical studies suggest that there is a reduction in the need for platelets post-surgery.
References
5. Blood transfusion and the Anaesthetist Blood Compartment Therapy 2005
7. Prices for blood, blood components and diagnostic services for 2004/2005, Prof. Lindsey Davies, Regional Director of Public Health at the Department of Health and Social Care