

**PERIOPERATIVE CELL SALVAGE BLOOD
TRANSFUSIONS IN ENDONASAL ANGIOFIBROMA
SURGERY AT GROOTE SCHUUR HOSPITAL**

**BY
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Contents

<i>Topic</i>	<i>Page</i>
LIST OF ABBREVIATIONS	3
ABSTRACT	4
PART A: PROTOCOL	5
PART B: STRUCTURED LITERATURE REVIEW	13
PART C: PUBLICATION-READY MANUSCRIPT	33
PART D: APPENDICES	
1. Human Research Ethics Committee approvals	50
2. Departmental Research Committee approval	51
3. Data collection proforma	52
4. Adult Consent form	53
5. Children consent form	56

LIST OF ABBREVIATIONS

PCS	Intra-operative cell salvage
MCS	Microscopy, culture and sensitivity
LDF	Leukocyte depletion filters
JNA	Juvenile Nasopharyngeal Angiofibroma

Abstract

Objective:

Surgical approaches for many tumours are often limited by blood loss, exposure and risk to vital anatomical structures; therefore, the standard of care for certain skull base tumours has become endoscopic transnasal resection. Other surgical disciplines often use cell salvage techniques, but review of the otolaryngology literature reveals very few case reports. General surgery procedures are often carried out in a contaminated field and concerns have been raised about its safety.

This study investigates the value and safety of salvage-type autologous blood transfusion during the endoscopic resection of juvenile nasopharyngeal angiofibromas (JNA).

Methods:

Because JNA is a rare vascular nasal tumour, the study extended over a 3-year period to obtain adequate patient numbers. All patients undergoing endoscopic resection during this period were included in the population sample. Ten patients with JNA were identified and underwent embolization prior to endoscopic resection. In all cases the intraoperative blood salvage apparatus was used. Close post-operative monitoring was performed.

Results:

Homologous blood transfusion could be avoided in all cases and post-operative monitoring revealed no features of severe sepsis. Transient bacteraemia developed in two cases where a leukocyte filter was not used

Conclusion:

Perioperative cell saver utilization and autologous blood transfusion in endonasal JNA surgery is safe and its future use is promising. Homologous blood transfusion can be avoided by using this technique. The use of cell salvage allows for single stage surgery without the need to abandon surgery due to excessive blood loss.

PART A: PROTOCOL

**Perioperative cell salvage blood transfusions in endonasal angiofibroma surgery at
Groote Schuur Hospital**

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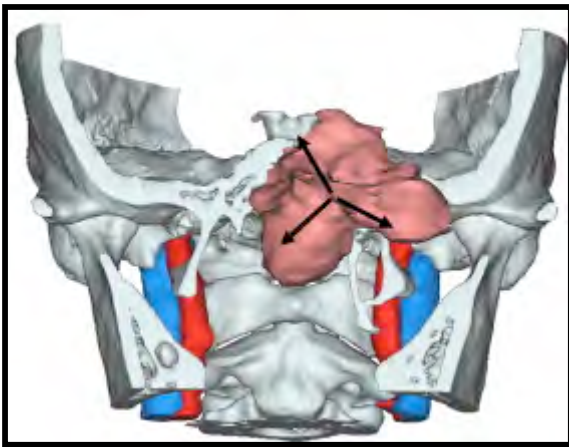
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INTRODUCTION

New technological advances have made the endoscopic resection of skull base tumours possible, with reduced postoperative morbidity without compromising outcomes. The endoscopic resection may be impeded by factors such as blood loss, lack of adequate exposure and tumour proximity to vital anatomical structures. (1, 2, 3)



Angiofibroma extending into nasopharynx & pterygopalatine fossa



Endoscopic transnasal resection of an angiofibroma

There is insufficient data and limited research on the use of cell salvage during the endoscopic resection of benign vascular sinonasal tumours (4). Intraoperative cell salvage (PCS) techniques have however been used for over 25 years in trauma, orthopaedic, urological, liver transplant and cardiac surgery (4).

Cell salvage techniques involve the (4):

- Use of a leukocyte depletion filter (LDF)
- Collection of concentrated red cells that are washed with normal saline prior to infusion
- Use of a centrifuge to separate the components
- Collection of blood intraoperatively

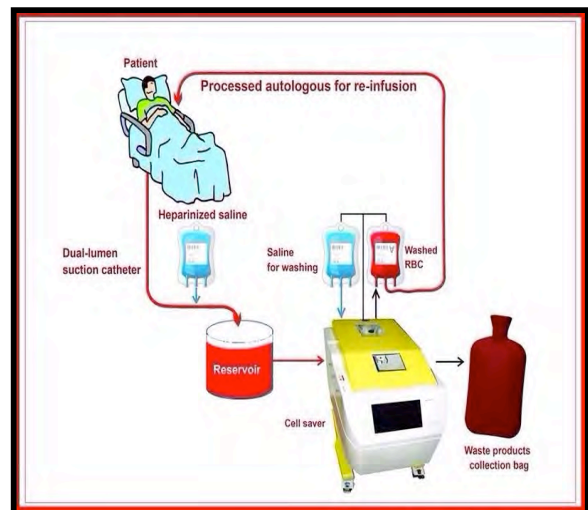
Cell Salvage advantages (5):

- Often acceptable to members of the Jehovah Witness religious group
- Burden on blood donation systems is reduced
- Any blood lost during surgery is proportional to the blood available
- Haemodilution is avoided
- Can be used when significant blood loss is anticipated

Cell salvage machine



Cell salvage technique



The use of intraoperative cell salvage (PCS) overcomes homologous blood transfusion risks that include (6,7)

- Postoperative infection
- End-organ injury
- Immunosuppression
- Volume overload
- Graft versus host disease
- Allergic and febrile reactions

The risk of transfusion-induced HIV and/or Hepatitis B or C during homologous blood transfusion is very low, but some infections occur frequently such as Epstein-Barr virus

(EBV) and cytomegalovirus (CMV). There has been insufficient research into the impact of EBV and CMV infections after homologous blood transfusion.

JUSTIFICATION

The investigation of the benefits of cell salvage during the endoscopic resection of sinonasal angiofibromas (JNA) would be valuable. A prospective study at Groote Schuur Hospital aims to reveal how this technique could:

1. Enable total resection at the first procedure with a reduced need to abandon surgery because of blood loss.
2. Reduce the routine use of homologous blood transfusion during JNA surgery
 - a. With a reduced burden on blood donation systems
 - b. With a reduced risk of transfusion complications
3. Allow for safe surgery for Jehovah Witness patients.

AIM & OBJECTIVES

AIM

This study aims to evaluate the use of cell salvage in endoscopic transnasal surgery for benign vascular tumours, such as JNA. Intraoperative cell salvage (PCS) has been extensively used in other surgical disciplines such as trauma, orthopaedic, urological, liver transplant and cardiac surgery.

OBJECTIVES

- To evaluate how allogeneic blood transfusion could be reduced by examining the evidence with regards to the efficacy of cell salvage
- To examine the evidence on clinical outcomes after using PCS during surgery
- To investigate the presence of bacteria in blood collected from the surgical field for autotransfusion
- To determine if there is an increased risk of bacteremia after using PCS during JNA surgery

RESEARCH DESIGN & METHODS

Study Design

This is a prospective study to investigate the use of intraoperative cell salvage and autologous blood transfusions in endonasal JNA surgery at Groote Schuur Hospital.

Population and Sampling

Population:

The sample population will include patients with JNA who are undergoing endoscopic surgical resection and require cell saver blood transfusion.

Sampling:

1. The technician will collect blood from the cell saver unit and send it to the *National Health Laboratory Service (NHLS)* for microscopy, culture and sensitivities (MCS)
2. Blood will be collected from each patient, who will then receive autologous blood rather than allogeneic blood
3. Patients will be monitored for signs of infection postoperatively by routine methods such as pulse rate and temperature
4. Patients' medical records accessed for the following data:
 - Blood loss and volume of autologous blood transfused
 - Culture results
 - Any adverse reaction to the transfusion, such as fever or allergic reactions

Sample size:

The study will include all patients who undergo endoscopic resection of JNA. Because JNA is a rare vascular nasal tumour with only a few patients presenting to our unit per year. this study encompasses a 3 - 4 year period. We aim to include at least 10 patients.

ETHICS AND COMMUNICATION

Ethical consideration

Confidentiality:

Only hospital folder numbers will be used during the collection, analysis and reporting of data to protect the identity of patients.

Beneficence:

Valuable information might be gleaned regarding the benefits of using PCS during the endoscopic resection of JNA. Cell salvage techniques could make surgery possible for Jehovah Witness patients and could avoid allogeneic blood transfusions.

By examining the evidence of the efficacy of cell salvage, certain benefits may be determined. The need for allogeneic blood transfusion may be reduced and clinical outcome may be improved.

Non-maleficence:

No patients will be subjected to harm from the procedures performed in this study. Most patients require blood transfusion during the resection of JNA (whether endoscopic or open techniques are used). By using cell saver techniques there is less risk of disease transmission and adverse reactions.

Process of Obtaining Informed Consent and Assent:

JNA is a vascular tumour only occurring in young adolescent males, usually before the age of 18 years. Consent will be obtained from every adolescent patient involved in this study, as well as from their parents.

Stakeholder and reporting

The results of the study will be reported back to the Division of Otolaryngology at Grootte Schuur Hospital as a formal report.

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PART B: LITERATURE REVIEW

A review of the English literature reveals few studies relating to the control of blood loss through the use of cell salvage during endoscopic sinonasal surgery. The role of cell salvage techniques within the contaminated surgical field is controversial as this was considered to be a contraindication during the early teaching of this subject. This has now been challenged. Due to safety concerns related to transfused blood products, surgeons have used allogeneic blood. There is a belief that there is very little risk from using allogeneic blood because a specialist laboratory screens the blood. Therefore, the risks of Hepatitis C and Human Immunodeficiency Virus (HIV) contamination of allogeneic blood are considered to be very low (1). However, these infections are prevalent in many developing countries and are a significant concern as health care services often do not meet the highest international standards and are often inadequately equipped.

It is expensive to provide blood products that are safe and reliable and this influences costs related to using allogeneic blood (2). There have been more recent concerns relating to variant Creutzfeldt-Jakob disease, which have had a negative impact on blood transfusion services and the availability of blood and blood products. The criteria applied to donors that might have been exposed to this disease have become stricter.

Within clinical practice, using allogeneic blood raises many issues, but specifically in Sub-Saharan Africa where infections such as malaria, syphilis, Hepatitis C, Hepatitis B and HIV are prevalent. There are many studies that have proven that blood products can transmit infection. Healthcare professionals also need to restrict the use of allogeneic blood as this is a limited resource despite effective screening in some areas. There are various factors in Sub-Saharan Africa that influence the supply of donated blood, such as financial constraints, lack of education, misconceptions, cultural issues and social issues.

The following table summarises how allogeneic blood received from a blood bank often causes complications that are commonly exposed (10) (SHOT report 2012).

Reaction	% of total adverse events
Acute transfusion reactions	29
Incorrect blood component transfused	25
Handling and storage errors	13
Anti-D events	13
Inappropriate and unnecessary transfusion	7
Haemolytic transfusion reactions	5
Autologous transfusion reactions	3
Transfusion-related acute lung injury (TRALI)	2
Transfusion-associated circulatory overload	2
ABO incompatibility	1
Mortality	0.9
Transfusion transmitted infections	0.6
Post-transfusion purpura	0.1
Transfusion-associated dyspnoea	0.1

Table 1: SHOT report 2012

Medical research has encouraged health professionals to reduce the use of allogeneic blood transfusions to overcome the problems associated with its high costs, blood shortages and blood safety by using new medical technologies. The surgical field has now widely adopted cell salvage as one of these new techniques. In the United Kingdom,

surgical patients receive around half of the blood transfused, which justifies the need to adopt techniques that reduce perioperative allogeneic red cell transfusion (3).

In 1881, Blundell was the first health professional to use autologous transfusion for patients with post-partum haemorrhage by using swabs soaked in blood that were then washed in saline. This mixture was re-infused into the patient, but high mortality often resulted. It was not until 1931 that this technology advanced when blood was re-infused directly to the patient from a haemothorax. The first cell salvage device was developed in 1943 and collected blood by suction into a reservoir that removed the clots and subsequently passed the blood through a cloth. This technique forms the basis for later cell saver machines; devices were first available commercially in the 1960s.

Intraoperative cell salvage blood transfusion has three stages: The surgical field is used to collect blood; a double-lumen suction device is used to suction the blood; and heparinised saline is added. A filter is used when the mixture is pumped to a collection reservoir and then red blood cells are separated by centrifugation in a spinning container.

Discarded components are transferred to the waste bag and the container retains the separated red blood cell component. The spinning centrifuge system has normal saline pumped inside and through the heavier red blood cell component. The residual waste products pass into the waste line. Waste products include plasma, free haemoglobin, cell debris and anticoagulant. Saline is then added to the remaining blood cells to achieve a haematocrit between 50% and 60% and after pumping it to a bag, the product is ready for transfusion (4). The surgical team decides whether to adopt cell salvage for patients intra-operatively. Specific clinical situations could require adaptations if there is a possibility of significant unexpected bleeding (5).

Previous studies found that, when compared to blood from a blood bank, the function and morphology of red cells collected from cell salvage was of higher quality and retained normal membrane stability (6). Other studies have revealed that after re-transfusion, patients have a good survival rate, as stores of adenosine triphosphate and 2, 3-diphosphoglycerate are higher in collected blood when compared with allogeneic blood (7).

In 2009, guidelines were issued by the *Association of Anaesthetists of Great Britain and Ireland*, which highlighted issues for intraoperative cell salvage use. It included patients who decline transfusion of allogeneic blood, patients with unusual antibodies and blood types, patients that are at risk for bleeding, low initial haemoglobin, or estimated loss of blood of more than 20% of the patient's blood volume, or more than 1000 ml (8).

Findings from previous studies did not recommend using the cell saver in contaminated surgery, but more recent research has investigated microbiological contamination of salvaged blood to evaluate clinical effects. Microbiological contamination of salvaged blood during sterile procedures has an incidence of between 12.7% (9) and 33.3% (10) in previous studies, but no studies could be found on reviewing the literature on endonasal surgery (11).

Kudo et al. carried out a survey of cell saver use in neurosurgical procedures, and the processed blood was subjected to microbiological analysis. The cell saver specimens were sent for MCS and both staphylococci and streptococci were cultured. The blood that was collected was not transfused (12).

There is insufficient evidence of the effectiveness of using cell saver systems with patients for endonasal surgery from reviewing the English ENT literature, although this topic has been studied for maxillofacial surgery. *Rohling et al.* used a sample population of nine patients for their study, and found that bacteria grew on all cell saver red blood cell concentrates, which were mostly staphylococcus aureus and streptococcus viridans. However, the researchers did not document the degree of contamination. The findings revealed that patients had autologous blood transfused, which resulted in a rise in

cytokine levels and a transient bacteraemia. Correlation with clinical features did not suggest sepsis. Intraoperative antibiotics were given to all patients (13). There is general agreement that around the nasal and oral cavities, the quantity and species of bacteria varies, but research regarding PCS use in maxillofacial surgery provides practical insights into likely consequences of its use (14).

Waters et al. used *Bacillus fragilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Escherichia coli* to inoculate expired packed erythrocytes. They demonstrated that bacterial colony-forming units could be cleared by between 97.6% and 100%, when blood is subjected to a leukocyte filtration system and is washed (15).

Cardiac surgery is the main field that has been studied. One study used a large sample population of 401 patients and routinely cultured samples of cell saver blood. The blood cultures were positive in 12.7% of cases. Most of these cases resulted in cultures that produced coagulase-negative staphylococci, meaning that contaminated blood was transfused back into the patient. It was however not associated with significant morbidity or mortality (16).

Studies have examined the use of perioperative cell salvage in relatively contaminated areas. *Yamada et al.* (17) used PCS in 33 total abdominal hysterectomies that were contaminated with vaginal flora; 75% of the transfused units revealed contamination, but the findings indicated that the blood transfusions did not result in negative effects for patients (17). Another study of hollow viscous injury and trauma produced similar results (17).

Antibiotic prophylaxis is mandatory for all surgery in contaminated fields, and cases mentioned earlier had all had prophylactic antibiotics (14). Forty patients formed a randomised control trial in a study by *Wollinsky et al.* (18) that were undergoing primary hip arthroplasty. These findings revealed that although the treatment arm showed no bacterial contamination, the sample population showed a 40% contamination rate (18).

General guidelines for the use of cell salvage during surgery would include the following:

1. A patient with significant red blood cell antibodies
2. A Jehovah's Witnesses patient requiring surgery where significant blood loss is anticipated
3. When significant blood loss of more than 1000 mL is anticipated (19)

The National Institute for Health and Clinical Excellence (NICE) issued a recommendation in April 2008 to endorse using autologous blood transfusion for cancer surgery, and particularly for cystectomy and prostatectomy (20). A Cochrane review recently showed that cell salvage did not result in adverse outcomes, and that when used it reduced transfusion rates.

Recent findings by *Catling et al.* (21) suggested adding a leukocyte filter to the cell saver in gynaecologic malignancies, based on a sample of 50 patients with intraoperative presence of tumour cells that were undergoing surgery for ovarian, endometrial or cervical cancer. Samples of blood were taken from the cell saver re-transfusion bag before and after leukocyte filtration, the cell saver reservoir, the efferent tumour vein and the central venous line (21). Immunohistochemistry was used to identify tumour cells by using anti-cytokeratin antibodies against epithelial cells, and the findings revealed no tumour cells in the post-leukocyte filtration or effluent tumour vein samples, 34 of 50 cell saver reservoir samples and 2 of 50 central line samples.

The American Association of Blood Banks (AABB) published 'Standards for Perioperative Collection and Transfusion' to create guidelines for carrying out intraoperative cell salvage that should establish a safe standard of care (22). When blood is subjected to a leukocyte filtration system and washed, *Waters et al.* found that 97.6% to 100 % of bacterial colony-forming units could be cleared (22).

Researchers have continued to question the significance of transfused cell saver blood causing bacteraemia, and whether this could be more significant than when surgery

causes a transient bacteraemia. Cardiac surgery provides the most evidence relating to humans, as this discipline deals with more surgical cases requiring the use of cell saver blood. Samples of cell saver blood were routinely cultured in a large study of 401 patients, and in 12.7% of this population sample, blood cultures were positive, where most cultures grew coagulase-negative staphylococci. Patients had received contaminated blood in these cases, because culture results were received after transfusion, but the findings reported that no significant mortality or morbidity was linked to the transfusion, even though bacteria was observed in over 90% of contaminated bags (23).

The mechanism of leukocyte reduction by LDF is inadequately understood. It is widely accepted that centrifugal effects are the mechanisms to eliminate bacteria with cell saver methods. Erythrocytes have a thickness of 2 μm and a diameter of 8 μm , but the size of bacteria could vary from 1 – 2 μm in length and 0.5 – 1 μm in diameter. These measurements suggest that bacterial removal mechanisms cannot depend on size alone, but would be more dependent on adhesive characteristics of the filter, such as the surface structure of the material used in the filter, wettability and surface charge (24, 25).

The use of leukodepletion filters to remove bacteria has revealed four potential mechanisms (24–25)

1. Filtration enhanced by complement-mediated bacterial killing
2. The filter retains bacteria by adherence to leukocyte surfaces
3. The disintegration of cells and deformability of infected cells in the filter
4. The filter media removes the bacteria directly

In research that examined the capacity of LDFs to extract tumour cells from salvaged blood, 50 gynaecology surgery patients formed an observational study, and samples of blood were collected after passing through an LDF, from the cell saver before and after processing and before the operation. The results revealed viable tumour cells that were observed in 62% of samples after processing, in 68% of cell saver reservoirs before processing and in 4% of preoperative samples. No tumour cells were found when

salvaged blood had been passed through an LDF, although tumour cell fragments were revealed, but these were not able to cause metastases.

A study in the USA of a large teaching hospital to analyse associated costs of cell salvage and allogeneic blood transfusion used a comparison of average costs of a unit of cell salvage blood and allogeneic blood, and discovered that an average saving of \$110.54 per unit could be achieved by using cell salvage (24, 25).

JUVENILE NASOPHARYNGEAL ANGIOFIBROMA (JNA)

JNA is a rare, benign, vascular head and neck tumour (0.5%) found in adolescent males (26,27). It originates in the posterior nasal cavity / nasopharynx. JNA are noted for their progressive and locally invasive spread and they often result in degrees of morbidity that are significant, and usually related to massive haemorrhage or intracranial extension. Hippocrates first described JNA in the 5th Century BC in conjunction with nasal polyps (28).

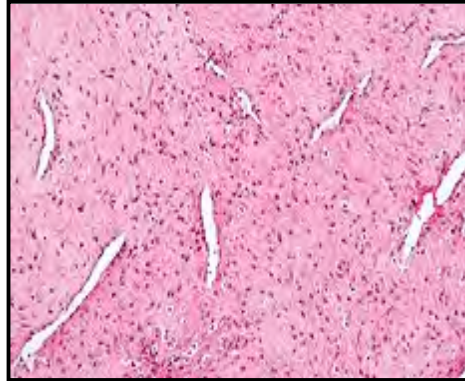
Demographics

JNA occurs in teenage males between 10 and 25 years of age but most cases are identified between 14 and 15 years of age (29). It demonstrates a very slow rate of growth (are indolent), and patients are often symptomatic for at least 6 to 12 months before diagnosis. When diagnosed, around 70% of these young male patients have already reached stage II presentation (29).

Origins and pathophysiology

JNA normally originates from the internal maxillary artery, although this tumour can also originate from the internal, external and common carotid arteries, as well as the ascending pharyngeal artery. The exact original site of JNA lack widespread agreement, but most findings support the view that JNA is involved at the posterolateral nasal wall at the sphenopalatine foramen.

There is insufficient clarity regarding the pathophysiology of JNA origin. The tumours are normally located at the superior margin of the sphenopalatine foramen. Some argue that the underlying mechanism of JNA is associated with the embryologic chondrocartilage of the skull bones (30). The development of JNA could also be associated with the pituitary androgen-oestrogen axis (30), because on some JNA cells, androgen and oestrogen receptors have been observed (31). Other studies have indicated that insulin-like growth-factor-2, transforming growth-factor beta-1 or vascular endothelial growth-factor receptor-2 could have a role (32). Research studies have also proposed that JNA could be a vascular hamartoma or inflammatory reaction (33).



Histopathology

From a histological perspective, the JNA cells are observed to be of myofibroblast origin and are surrounded by a fibrous pseudocapsule. Within the neoplasm there is a distribution of multiple vascular channels of abundant endothelial cells that are embedded within a collagenous tissue network. The characteristics of JNA reveal an absence of a muscular layer, so that a lack of vasoconstriction ability could explain its tendency for haemorrhage (34).

Presentation

Diagnosis of JNA could be based on a patient presenting with the following symptoms:

- A nasal mass of reddish or purplish colour that is smooth and lobulated
- A large tumour burden linked to massive haemorrhage
- Facial swelling or proptosis that could indicate progression of tumour
- Dacryocystitis when anterior extension could obstruct the nasolacrimal duct in advanced tumours
- Recurrent nasal bleeding or epistaxis in adolescent males

- Unilateral nasal obstruction
- Atypical symptoms such as anosmia, hyposmia, palatal deformity, rhinolalia, and blockage of the eustachian tubes with middle ear effusions and conductive hearing loss

Submucosal extension is characteristic of JNA and the tumour can spread towards the superior orbital fissure, infratemporal fossa or the pterygomaxillary fossa (35), and in 20% to 36% of cases intracranial extension occurs within the pituitary parasellar region or the anterior or middle cranial fossae region (36).

Successful treatment requires complete surgical excision; 46% of incomplete resections will result in recurrence of the tumour (37). There is a high risk of tumour extension to the clivus, pterygoid base and sphenoid sinus. A review of the literature reveals patients over the age of 25years can demonstrate spontaneous regression, which could be explained by pubertal hormonal changes (38).

Differential diagnosis

- Rhabdomyosarcoma
- Olfactory neuroblastoma
- Nasopharyngeal carcinoma
- Chondrosarcoma,
- Chordoma
- Craniopharyngioma
- Nasal polyps
- Hemangiopericytoma
- Pyogenic granuloma

Staging

In 1981, Sessions first classified JNA, but since that time, various modifications have been included by Andrews (1989), Chandler (1984) and Fisch (1983). Radkowski most

recently introduced and adapted the staging system based on the degree of skull base erosion and the tendency of JNA to extend posteriorly to the pterygoid plates (39). However, classifications of Sessions and Fisch are the two most commonly adopted:

Classification (Sessions):

Stage	Features
1A	Tumour only identified in posterior nares and/or nasopharyngeal vault
1B	Tumour identified in posterior nares and/or nasopharyngeal vault with at least 1 paranasal sinus involved
2A	Minimal lateral extension into pterygomaxillary fossa
2B	Pterygomaxillary fossa fully occupied with or without superior erosion of orbital bones
3A	Skull base erosion Minimal intracranial extension
3B	Extensive intracranial extension with or without extension into cavernous sinus

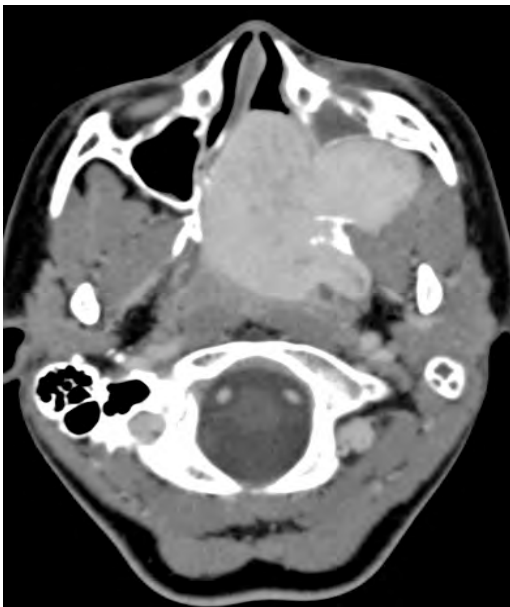
Classification (Fisch):

Stage	Features
I.	Tumours only identified in nasal cavity, nasopharynx with no bony destruction
II.	Tumours have invaded pterygomaxillary fossa, paranasal sinuses with bony destruction
III.	Tumours have invaded infratemporal fossa, orbit and/or parasellar region remaining lateral to cavernous sinus.
IV.	Tumours have invaded cavernous sinus, optic chiasmal region, and/or pituitary fossa

Imaging studies

A computed tomography (CT) scan can reveal the characteristic features of JNA, and diagnosis of JNA is supported by the lack of regional or distant metastasis. JNA exhibits characteristic features on CT scan as the presence of bony modelling with tumour growth, and the presence of a vascular mass with an epicentre at the posterior nasal cavity.

CT imaging is superior when compared to magnetic resonance imaging (MRI) in terms of evaluating bony details. JNA is normally associated with anterior bowing of the posterior maxillary sinus wall, known as the Holman-Miller sign. CT scans can also reveal widening of the sphenopalatine foramen, but the degree of intracranial extension is better assessed by MRI scans. To identify the source vessels, and for preoperative embolization, angiography is critical. Embolization is considered effective to reduce intraoperative blood loss and should be done 24 to 72 hours prior to surgical resection (40, 41, 42).



CT showed an intensely enhancing mass in sphenopalatine region

Surgery for JNA

Surgical excision is the main treatment modality (43) and endoscopic resection of JNA has attracted significant interest. To gain adequate exposure and to dissect around the tumour, a middle turbinectomy, posterior septectomy and wide middle meatal antrostomy is often required. The sphenopalatine artery is often within the tumour bulk but removing the posterior maxillary sinus wall can expose this area. Denker's approach can enable access laterally to lesions involving the infratemporal fossa. A diode handheld laser is useful to perform extracapsular tumour dissection, especially from the pterygopalatine and infratemporal fossas.

Transnasal endoscopic approaches offer various benefits, such as better postoperative surgical morbidity without outcome being compromised. Endoscopic approaches do present important limitations, such as bleeding, with exposure often being difficult due to tumour bulk. Blood loss can be managed by applying two methods during endoscopic JNA surgery, such as preoperative embolization and intraoperative cell saver blood transfusion.



JNA visible on nasal endoscopy



En-bloc resection of JNA

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PART C: ARTICLE MANUSCRIPT

Perioperative cell salvage blood transfusions in endonasal angiofibroma surgery at Groote Schuur Hospital

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Abstract

Objective

Surgical approaches for many tumours are often limited by blood loss, exposure and risk to vital anatomical structures; therefore, the standard of care for certain skull base tumours has become endoscopic transnasal resection. Other surgical fields often use cell salvage techniques, but review of the otolaryngology literature to discover the benefits of these techniques, reveal very few case reports. In general surgery, cell salvage is carried out in a contaminated field and concerns have been raised about its safety.

This study investigated the value and safety of salvage-type autologous blood transfusion during the endoscopic resection of juvenile nasopharyngeal angiofibromas (JNA).

Methods

JNA is a rare vascular nasal tumour and the study extended over a 3-year period to obtain adequate patient numbers. All patients undergoing endoscopic resection during this period were included in the population sample. Ten patients with JNA were identified and underwent embolization prior to the endoscopic resection. In all cases the intraoperative blood salvage apparatus was used. Close post-operative monitoring was performed.

Results

Homologous blood transfusion could be avoided in all cases. Postoperative monitoring revealed transient bacteraemia in two cases where the leukocyte filter was not used, but no evidence of septicaemia.

Conclusions

Perioperative cell saver and autologous blood transfusion in endonasal JNA surgery is safe. Homologous blood transfusion can be avoided by using this technique. The use of cell salvage allows for single stage surgery without the need to abandon surgery due to excessive blood loss and its future use is promising.

INTRODUCTION

For more than 25 years, trauma, orthopaedic, urological, liver transplant and cardiac surgery have used intraoperative cell salvage (PCS) techniques (1). However, in contaminated surgical fields the role of cell salvage techniques has been contentious. Contaminated surgical fields have been previously considered as a relative or absolute contraindication for intraoperative cell salvage. A review of the literature reveals no research about the utilisation of cell salvage techniques in endonasal surgery.

Tumour surgery often results in the need for intraoperative allogeneic blood transfusion due to heavy blood loss. Many reports have focused on allogeneic transfusion risks, such as immunomodulation and infection. During juvenile nasopharyngeal angiofibroma (JNA) surgery, severe intraoperative bleeding can occur and preoperative embolization is useful to keep bleeding to a minimum. Intraoperative cell salvage blood transfusion can be used to avoid the use of allogeneic blood transfusion, thereby minimising the risk of developing transfusion complications.

The autologous red cell recovery system, also known as the “cell saver”, has a double lumen tube that mixes the aspirated blood with a heparin solution and collects it in a reservoir (*Figure 1*). A centrifuge is then used to separate erythrocytes from the blood and cell stroma, free haemoglobin and plasma flow to the waste bag. The leukocyte filter is used to provide further protection, and blood is then re-infused into the patient (*figure1*). The mechanisms of leukocyte reduction by leukocyte depletion filter (LDF) are insufficiently understood, but it is widely accepted that centrifugal effects are the mechanisms to eliminate bacteria with cell saver methods. Bacterial removal mechanisms of the leukocyte depletion filter (LDF) cannot depend on the size of bacteria alone, but would be more dependent on adhesive characteristics of the filter, such as the surface structure of the material used in the filter, wettability, surface charge, the disintegration of cells and deformability of infected cells in the filter (2,3).

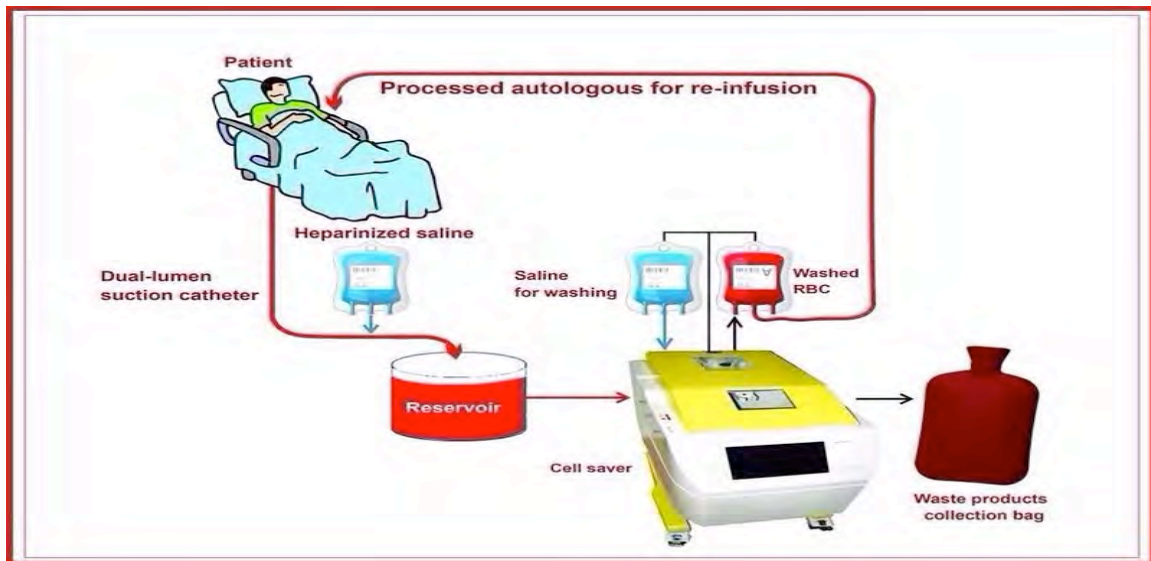


Figure 1: Cell salvage techniques

Centrifugal effects are used to eliminate bacteria with cell saver techniques, but there is insufficient understanding of the precise mechanisms of leukocyte elimination by leukocyte depletion filter (LDF). Reports indicate that 97.6% to 100% of bacterial colony-forming units could be cleared when blood is subjected to a leukocyte filtration system and is washed.

Cell salvage can eliminate or reduce the need for allogeneic blood transfusions and avoid the infectious and non-infectious complications that occur after transfusions. A review of the literature shows that cell salvage is effective in reducing allogeneic blood transfusion requirements during adult elective surgery. Based on evidence gleaned from cardiac and orthopaedic surgery, it is safe and effective. Recent reports indicate that cell salvage is increasingly used during trauma surgery even though the surgical field is often deemed contaminated. All reports relating to trauma surgery have found cell salvage to be a safe technique that avoids allogeneic blood transfusion.

According to our reading, there has been no research done with regards to the role of red cell salvage in endoscopic JNA surgery. This research forms a preliminary study into the role of cell salvage during JNA surgery.

MATERIAL AND METHODS

The *Human Research Ethics Committee* of the *University of Cape Town* approved the prospective study. The study included all patients undergoing endoscopic resection of JNA at *Groote Schuur Hospital* and *Panorama Mediclinic*. Ten patients were included; they all underwent pre-operative embolization, had intra-operative cell salvage and close postoperative monitoring.

Patients scheduled for elective endoscopic transnasal resection of a JNA were included in the population sample if the estimated blood loss was more than 500ml and they would qualify for intraoperative blood transfusion. Exclusion criteria included patients who bled minimally intraoperative and did not require blood transfusion.

Patients were all male and aged between 12 and 20 years (Figure 2). One patient was a Jehovah's Witness and allogeneic blood transfusion was therefore not allowed. Autologous blood transfusion via a salvage system was acceptable to the Jehovah's Witness group if intraoperative blood transfusion was required.

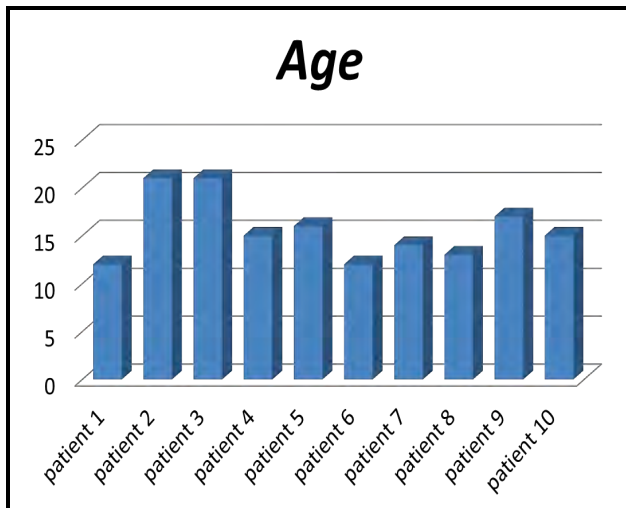


Figure 2: Age distribution

Based on the Fisch staging system for JNA, 6 patients had stage 2 tumours and 4 had stage 3 tumours (Table 1, Figures 3 & 4). Two patients had staged procedures with initial

incomplete resection and the rest of the sample population had successful complete resection of the tumour at the first surgery.

Table 1: Tumour profiles according to Fisch staging system

6 patients	Stage 2 Tumours invading pterygomaxillary fossa, paranasal sinuses with bony destruction
4 patients	Stage 3 Tumours invading infratemporal fossa, orbit and/or parasellar region remaining lateral to cavernous sinus



Figure 3: CT showing stage 3 JNA

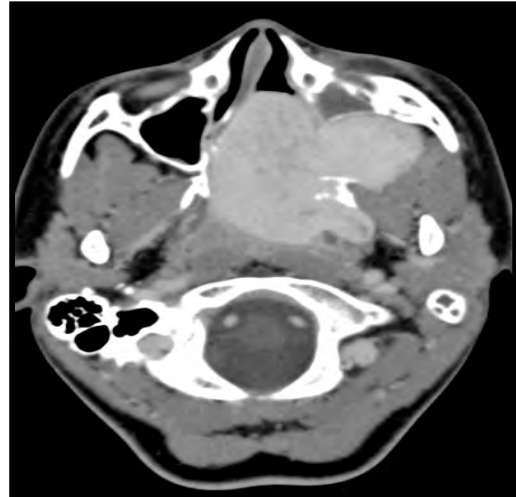


Figure 4: Tumour invading infra-temporal fossa

An intra-operative nasal swab was taken to determine the presence of bacteria and to obtain sensitivities in the event that antibiotics were required postoperatively. The cell saver system was used to salvage autologous blood. A second specimen for MCS was taken from the cell saver system to detect the presence of organisms in the autologous blood that was to be transfused back to the patient.

The anaesthetist and surgeon based decisions to transfuse each patient on their haematocrit and clinical stability. Blood was collected from the cell saver unit by the technician and all patients received autologous blood instead of allogeneic blood.

Washed, concentrated red blood cells (RBC) were returned to the patients. All patients received prophylactic intraoperative antibiotics and a post-operative course of broad spectrum antibiotics. Patients were monitored for signs of infection / septicaemia by routine methods such as temperature and pulse rate. A blood culture was performed one day following surgery to exclude a bacteraemia or septicaemia.

RESULTS

The study included 10 patients scheduled for elective endoscopic transnasal resection of a JNA, whose estimated intraoperative blood loss was more than 500 mL and required blood transfusion. All patients had cell saver blood transfusions based on their intraoperative clinical stability and blood investigations. The volume of blood re-infused as a percentage of the volume lost is an underestimate because the blood lost is diluted and the re-infused blood has a high haematocrit, usually more than 50%, therefore allowing adequate transfusion. The mean volume of blood lost from the 10 patients was 1530 mL (500ml-4000ml). The mean volume of re-infused blood was 875 mL (200 ml-2600 ml) (Figure 5).

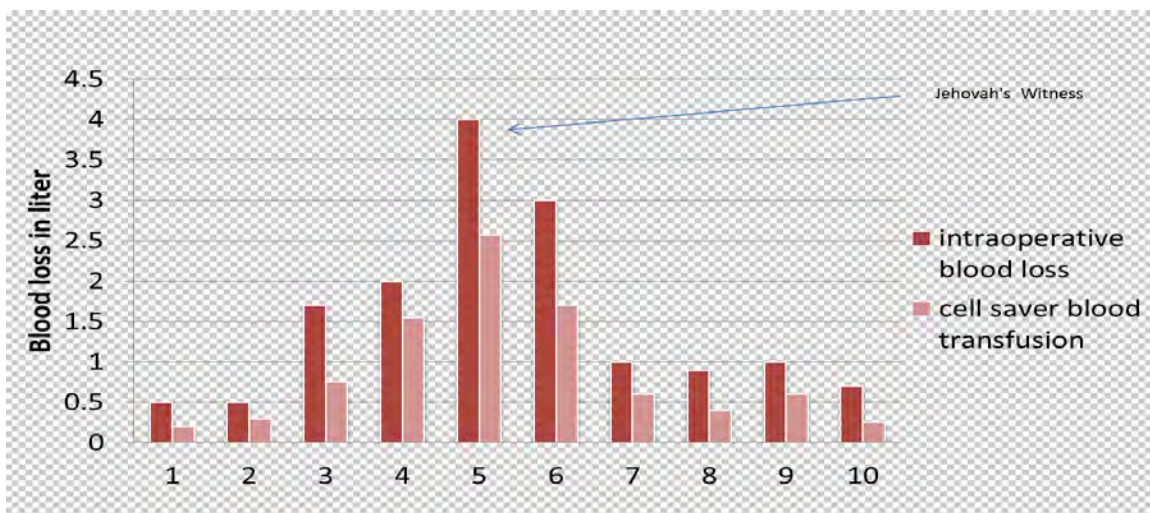


Figure 5: Intraoperative blood loss and perioperative cell salvage blood transfusions

In order to evaluate whether the operative field was contaminated or not, nasal swabs were taken from the prepared surgical field just before the resection of the tumour. Bacterial growth was detected in all specimens. Organisms that were cultured included: *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus viridans*, and *Moraxella catarrhalis* (Table 3).

<i>Bacteria</i>	<i>Nasal cavity</i>
<i>Staphylococcus aureus</i>	5 (50%)
Methicillin resistant <i>Staphylococcus aureus</i> (MRSA)	1
<i>Staphylococcus epidermidis</i>	1
<i>Streptococcus viridans</i>	2
<i>Moraxella catarrhalis</i>	1

Table 3: Microbiologic results of swabs of the nasal cavity

All patients received intraoperative antibiotics and an intravenous postoperative course of broad spectrum antibiotics. Routine methods were adopted to monitor patients postoperatively for any sign of infection, such as temperature and pulse rate. A blood culture was performed on the day following the operation.

The leukocyte filter was not used in two cases, as it was not available in the state hospital at that time. In both of them, the same organism that was isolated from the nasal cavity was also cultured from the cell saver washed blood. Postoperatively they developed a transient bacteraemia with a raised temperature and pulse rate and a positive blood culture. In both cases the same organism was cultured from the operative field and post-operative blood culture (Table 4). Both were treated with the appropriate IV antibiotics according to sensitivities and both recovered completely.

Patient	Intraoperative blood loss (ml)	Cell Saver blood transfusion	Nasal Swab	Cell Saver blood culture	Postoperative blood culture
Patient 1	500 ml	200 ml	Staphylococcus Aureus	No Growth	No Growth
Patient 2	500 ml	300 ml	Staphylococcus Aureus	No Growth	No Growth
Patient 3	1700 ml	700 ml	Staphylococcus Aureus	No growth	No Growth
Patient 4 No LDF	2000 ml	1500 ml	Staphylococcus Aureus	Staphylococcus Aureus	Staphylococcus Aureus
Patient 5 Johavah's Witness	4000 ml	2500 ml	Streptococcus Viridans	No Growth	No Growth
Patient 6	3000 ml	1700 ml	Methicillinresistant Staphylococcus Aureus (MRSA)	No Growth	No Growth
Patient 7	1000 ml	600 ml	Staphylococcus Epidermidis	No Growth	No Growth
Patient 8	900 ml	400 ml	Streptococcus Viridans	No Growth	No Growth
Patient 9	1000 ml	600 ml	Moraxella Catarrhalis	No Growth	No Growth
Patient 10 No LDF	700 ml	250 ml	Staphylococcus Aureus	Staphylococcus Aureus	Staphylococcus Aureus

Table 4: Summary of results

Postoperatively, all patients in this study were admitted to the intensive care unit for one day for monitoring. Laboratory coagulation tests were taken on arrival in the ICU, and the mean INR (international normalised ratio) in the control group was 1.1. None of the patients had postoperative epistaxis or any evidence of coagulopathy.

Routine postoperative monitoring revealed that haemoglobin and coagulation levels were within the normal range for all patients, with no evidence of major complications such as haemoglobinuria, coagulopathy, cardiopulmonary issues and major sepsis (Figure 6). None of the patients required any allogeneic blood products. Regular follow up after discharge showed no adverse events.

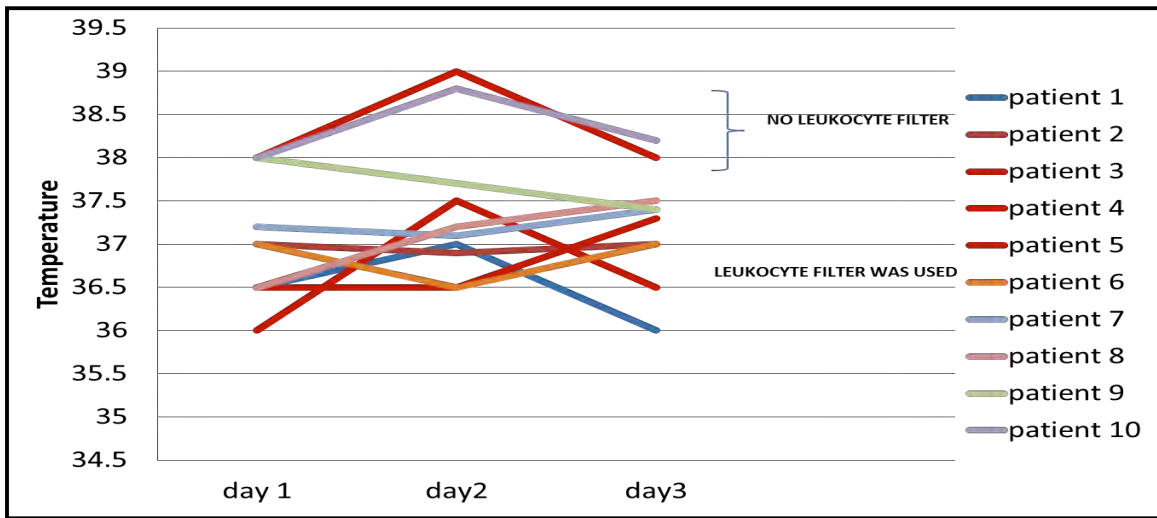


Figure 6: Routine post-operative temperature monitoring

The mean hospital stay for all patients was 3 days. Nasal packs were removed on the second day after surgery and no patients were required to return to the theatre for haemostasis. All patients were seen in the clinic 7 days after surgery for routine endoscopic examination and nasal debridement. Yearly follow up was planned for all patients.

DISCUSSION AND CONCLUSIONS

Earlier literature did not recommend the use of cell saver techniques in contaminated surgery. There has been insufficient research regarding the use of cell salvage during transnasal endoscopic surgery for benign vascular tumours (1). However, for the past 25 years, intraoperative cell salvage techniques have been used in trauma, orthopaedic, urological, liver transplant and cardiac surgery (1).

The most common benign vascular neoplasm of the nasopharynx is juvenile angiofibroma (JNA) (2). It has locally destructive growth features and cause bony erosion despite its benign histology. JNA can extend intracranially and cause complications that are potentially life threatening, such as intraoperative massive blood loss and fatal epistaxis (2). There are fibrotic and vascular elements within these tumours, but as the vessels lack elastic lamina and elastic fibres, they are unable to contract which may result in significant blood loss during surgical resection (3, 4). The management of JNA can be challenging because of its aggressive growth pattern, complex adjacent anatomical vital structures and rich vascular supply.

Our institute uses two methods to control blood loss during JNA surgery: the first method is preoperative embolization which was performed in all our patients. The second method is intraoperative cell salvage technique.

A review of the literature indicates that cell salvage techniques could be used in routine surgery when the patient has significant red blood cell antibodies, is a member of the Jehovah's Witness religious group or when significant blood loss is anticipated (over 1000 mL) (5). There are many advantages when using intraoperative cell salvage techniques, such as for Jehovah Witness patients who usually accept this form of blood transfusion, reduced burdens on blood donation systems, the blood available is proportional to the blood lost during surgery, haemodilution is not caused, and it can be used when significant blood loss is anticipated (6). Salvaged red cells also have a better oxygen delivery profile, and the system is cost-effective.

Intraoperative cell salvage autologous transfusion can avoid complications such as end organ injury, immunosuppression, volume overload, graft versus host disease and allergic and febrile reactions. Findings from previous studies indicate that allogeneic blood transfusion can be associated with increased mortality, myocardial infarction and increased risk of tumour recurrence (7).

It is widely accepted that the use of the leukocyte depletion filter and centrifugal effects in cell saver techniques removes bacteria, and previous reports indicate that 97.6% to 100% of bacterial colony-forming units can be cleared when blood is subjected to the leukocyte filtration system and is washed.

Timberlake and McSwan (1988) studied cell saver techniques and suggested that for gastrointestinal perforation patients, cell saver blood could be used when no banked blood is available as long as broad spectrum antibiotic prophylaxis is given. The findings from this study explained that from 11 patients with enteric contaminated blood, 3 of these had an infectious wound complication. It most likely included a nosocomial complication from the intensive care unit, but this study reported no deaths (8).

Kang et al. (1991) studied 14 patients undergoing liver transplant surgery and found positive cultures in the re-transfusion bag in 8 of 28 samples. Infections were not observed in this study, and after 1 week the cultures taken from patients had remained sterile (9).

Other surgical fields have also demonstrated the successful use of culture-positive cell saver blood. A Japanese study looked at cell salvage autologous transfusions over a 2-year period. Samples of salvaged blood were taken before re-infusion and findings revealed one third of all samples were culture positive (10). *Ezzedine et al.* (11) discovered an infection incidence of 12.7% from cultured samples of salvaged blood from every case that required autologous transfusion. *Locher and Sailer* (12) studied salvage autologous transfusion in maxillofacial surgery and revealed that most patients had received between 1 and 10 million organisms in each blood volume re-transfused. All these previous studies reported that no adverse clinical consequences occurred when the contaminated blood was given.

Another concern associated with cell salvage blood is the promotion of coagulopathy, but no evidence of coagulopathy was revealed in all patients, and all laboratory parameters were normal.

The use of cell salvage autologous blood transfusion has clearly indicated its cost effectiveness, as allogeneic blood products were avoided for all patients. However, the cost of leukocyte filters should be a consideration when comparing allogeneic blood products, although these filters are not expensive. The issue of cell salvage costs is important, and most research studies have found that the financial benefits of autologous transfusion are significant, such as shorter hospital stay, reduced blood transfusion reactions, reduced postoperative infection rates, and reduction in allogeneic blood transfusion. However, there is a need to compare the comparative costs of cell salvage blood transfusion and allogeneic blood transfusion in a randomised controlled study.

This institute reduces the costs of cell salvage by using this standby technique in every JNA case, which includes collecting blood from the operative field. Heparin is added to the collected blood, and only processed if a sufficient volume is recovered, or if the patient requires blood transfusion. The disposables and the leukocyte filter need only be set up when a decision to process the blood is made. We found that using the standby technique reduced the costs of cell salvage by 90% if no blood was processed.

Our study has shown that cell saver techniques are beneficial in JNA surgery, as the surgery can be completed in one stage and there is a decreased need for allogeneic blood transfusion, and is often acceptable to Jehovah's Witness patients, as an alternative to allogeneic blood transfusion. This study has also demonstrated that intraoperative cell salvage is a safe technique in endoscopic JNA surgery. It is however important to use leucocyte depletion filters and intraoperative and postoperative broad spectrum antibiotics. These findings indicate that when bacteria are introduced with the re-transfused blood, the intact immunological system adapts to protect patients against a number of commensal micro-organisms. This explains the good tolerance to the iatrogenic bacteraemia that was caused.

The combination of washing blood cells and using a leucocyte filter significantly reduced the bacterial load in processed blood that could then be safely re-transfused to the patient.

Leukocyte depletion filters have been widely used during the processing of donated blood to remove white blood cells and their use is now acknowledged to improve cell salvage safety and to reduce the incidence of any cell salvage adverse effects (13). Various findings have revealed that leukocyte depletion filters are effective in removing white blood cells, tumour cells, (14, 15, 16) amniotic fluid, (17) and bacteria (18).

In conclusion, cell salvage autologous blood transfusion is safe and effective in reducing allogeneic blood transfusion requirements in endoscopic JNA surgery. Cell salvage should be considered in all cases of JNA surgery as significant blood loss is usually anticipated. This can also be used in situations when patients refuse allogeneic blood products. The standby technique allows cell salvage to be used in cases where blood transfusion is not required, but significant bleeding is a possibility, which contributes to greater reduction in allogeneic blood transfusion requirements. Leukocyte depletion filters are recommended to provide an additional element of safety, and should be used in all cell salvage autologous blood transfusions. In addition, a contaminated surgical field is not a contraindication for the use of cell salvage blood as long as adequate precautions are taken. Recent evidence has shown that cell salvage may be used in malignancy surgery, and that the only contraindication to using cell salvage blood, is the patient's refusal to accept autologous blood.

Although the use of intraoperative cell salvage in combination with a leukocyte depletion filter appears to be safe in endoscopic JNA surgery, further research is needed with a larger population sample to define the efficacy of this technique in saving allogeneic blood and its impact on several outcome variables.

CONSENT

Written informed consent was obtained from the patients and their parents for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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11 March 2013

HREC REF: 415/2012

Dr H Wasi
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NGSH

Dear Dr Wasi

PROJECT TITLE: PERIOPERATIVE CELL SALVAGE BLOOD TRANSFUSIONS IN ENDONASAL ANGIOFIBROMA SURGERY AT GROOTE SCHUUR HOSPITAL

Thank you for addressing the issues raised Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has formally approved the above mentioned study.

Approval is granted for one year till the 15 March 2014.

Please submit a progress form, using the standardised Annual Report Form, if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

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Department of Surgery

Departmental Research Committee

Professor Anwar Suleman Mall

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27th June 2012

Dr H Wasi
Department of Surgery
Division of Otolaryngology
Grootte Schuur Hospital
University of Cape Town

Dear Dr Wasi,

RE: PROJECT 2012/064

**PROJECT TITLE: Perioperative cell salvage blood transfusions in endonasal
angiofibroma surgery at Grootte Schuur Hospital**

The above proposal was reviewed by the Department of Surgery Research Committee and I am pleased to inform you that the committee approved the study.

Please use the above project number in all future correspondence.

Yours sincerely

**PROFESSOR ANWAR S MALL
CHAIRMAN: RESEARCH COMMITTEE**

Perioperative cell salvage blood transfusions in endonasal angiofibroma surgery at Groote Schuur Hospital

Patient's hospital sticker

1- Preoperative:

Fisch staging

Basic blood investigation which include

FBC, Hb, Platelet, and INR

2- Intraoperative :

Nasal swab for MCS

Blood will be collected from the cell-saver unit by the technician and sent for MCS

Intraoperative blood Loss (ml)

Perioperative cell salvage blood transfusions(ml)

3- Post op

Post op temperature monitoring

Basic blood investigation: FBC, Hb, platelet, and INR

Blood culture

4- Other information will be collected from patient's record

Study title

Perioperative cell salvage blood transfusions in endonasal angiofibroma surgery at Grootte Schuur Hospital

What is the purpose of the study?

Cell saver blood is widely used in major surgery around the World. Cell saving is used in cardiac/heart, transplant, trauma and other surgery. It is a way to give you your own blood back instead of giving other peoples blood to you if you need it. We are looking at the possibility of reducing the amount of blood transfusion needed by giving you your own blood back.

Why have I been chosen?

We are asking you to take part in this study as you are having an operation that is likely to require being given blood.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

This study does not include any additional testing or investigations. All the preoperative, postoperative investigation and postoperative clinical monitoring are performed routinely as part of medical care at GSH for every patient who undergo this procedure and who receive intraoperative cell salvage blood transfusion. In this study we will only collect and analyse data that will be collected from those investigations and clinical observation. This will help us monitor you and how the cell saver works during your operation at the same time it will not affect the standard of care you receive. Cell saver blood is used in angiofibroma surgery at GSH without any remarkable complications thus far. All patients who had cell saver blood transfusion for angiofibroma surgery at GSH were discharged from hospital without major complications .

What are the risks and benefits?

There are no additional risks or additional benefits to you

Are there costs and payments?

There be no additional costs to you or your family

Confidentiality

The information obtained from this study will be published in the future such that your identity will remain anonymous. Medical records related to this study are confidential, but may be examined by researchers from this institution

Right to withdraw

You have the right to refuse to participate in, or withdraw from, this study at any time, and your decision will not adversely affect your care at this institution.

Who has reviewed the study?

The Human Research Ethics Committee, Faculty of Health Sciences, University of Cape Town have reviewed this study

Investigators

Dr H.Wasl, Dr D.Lubbe

Contact for Further Information

Division of otolaryngology, H53, OLD Main building, Groote schuur Hospital, observatory, Cape Town, 7925

Human Research Ethics Committee
Faculty of Health Sciences
University of Cape Town
Room: E52.23
Old Main Building, GSH
Tel: 021 406 6338
Fax: 021 406 6411

Patient sticker

Please initial box

- 1. I confirm that I have read the above information for the above study and have had the opportunity to ask questions.
- 2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
- 3. I understand that sections of any of my medical notes may be looked at by responsible individuals from the University of Cape Town or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.
- 4. I agree to take part in the above study.

Name of Patient(or Child) Date Signature

Name of Parent / Guardian (if required) Date Signature

Name of Person taking consent (if different from researcher) Date Signature

Researcher Date Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes

Study title

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Name of Parent / Guardian
(if required)

Date

Signature

Name of Person taking consent
(if different from researcher)

Date

Signature

Researcher

Date

Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes

DECLARATION

I, ...*HISHAM WASL*....., hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signed by candidate

Date: ...26/5/2015.....