THE ROLE OF ACUTE NORMOVOLAEMIC
HAEMODILUTION IN GASTRO-INTESTINAL SURGERY

G. SANDERS

M. D. 2003
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The Role Of Acute Normovolaemic Haemodilution in Gastro-intestinal Surgery

By

GRANT SANDERS

A thesis submitted to the University of Plymouth in partial fulfilment for the degree of

Doctor of Medicine

Department of Surgery
Derriford Hospital

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Abstract

The Role of Acute Normovolaemic Haemodilution in Gastro-intestinal Surgery

By Grant Sanders

Background:
Allogeneic transfusion confers a risk to the recipient and the recent introduction of leucocyte depleted blood has increased cost pressure on health resources. Colorectal surgery is a high blood usage field with 43% of all patients in our unit being transfused, over a three year period.

Patient perceptions:
Despite the risks associated with transfusion, a majority of patients are willing to have an allogeneic transfusion (85%) and think it is safe (89%), which may have implications in the uptake of alternatives available.

The effect of bowel preparation
Picolax bowel preparation causes significant dehydrating effects which may impair acute normovolaemic haemodilution (ANH). These effects can be minimised by administering intravenous normal saline.

Acute normovolaemic haemodilution (ANH)
ANH significantly reduced allogeneic transfusion rate from 39% to 15% in the pilot study, however the controls were historical. No reduction in transfusion rate was seen (29% and 30%) in the prospective randomised controlled trial (n=160). Pre-operative haemoglobin, blood loss, age, and transfusion protocol were the key factors influencing transfusion.

The effect of ANH on coagulation
ANH causes hypocoagulation, and this may explain why the expected red cell saving, as shown by mathematical modelling, was not seen in patients haemodiluted compared with controls.
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Authors Declaration

At no time during the registration for the degree of Doctor of Medicine has the author been registered for any other University award.

Modules attended included research design and statistics and clinical trials.

Scientific seminars and conferences were regularly attended at which work was often presented and several papers have been prepared for publication.

Publications

Acute Normovolaemic Haemodilution in Colorectal Surgery

G Sanders, AO Coker, NJ Mellor, K Rickards, ARA Rushdon, I Christie, KB Hosie


Randomised clinical trial of intravenous fluid replacement during bowel preparation for surgery.

G Sanders, SJ Mercer, K Saeb-Parsey, MA Akhavani, KB Hosie, AW Lambert

Oral Presentations and Conferences Attended

American Society of Haematology 6-10 December 2002

A prospective randomised controlled trial of acute normovolaemic haemodilution (ANH) in major gastro-intestinal surgery and its effect on coagulation


Blood December 2002; 100 (issue 11): 209

Association of Coloproctology of Great Britain and Ireland, 2-5 July 2002

The effects of surgery and acute normovolaemic haemodilution (ANH) on coagulation

G Sanders, NJ Mellor, PN Robins, ARA Rushton, I Christie, G Nason, JA Copplestone, KB Hosie

Colorectal Disease July 2002; 4 (Suppl 1): Oral 93

Association of Surgeons of Great Britain and Ireland, 22-24 May 2002

Surgery and acute normovolaemic haemodilution (ANH) both impair coagulation

G Sanders, NJ Mellor, PN Robins, AJ Brodribb, ARA Rushton, I Christie, G Nason, JA Copplestone, KB Hosie

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Is intravenous fluid replacement indicated during bowel preparation for colonic surgery?
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Colorectal Disease July 2001; 3 (Suppl 1): A008
Is intravenous fluid replacement indicated during bowel preparation for colonic surgery?

G Sanders, SJ Mercer, K Saeb-Parsey, MA Akhavani, KB Hosie, AW Lambert

British Journal of Surgery April 2001; 88 (Suppl 1): Colorectal 012

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British Journal of Surgery June 2002; 89 (Suppl 1): P51
Patient attitudes towards allogeneic transfusion and the alternatives available

G Sanders, NJ Mellor, K Rickards, D Mason, J Nicholl, JA Copplestone, KB Hosie

British Journal of Haematology May 2002; 117 (Suppl 1): A218

The effects of surgery and acute normovolaemic haemodilution (ANH) on coagulation as measured by the thromboelastogram

G Sanders, NJ Mellor, K Rickards, PN Robins, ARA Rushton, I Christie, G Nason, JA Copplestone, KB Hosie

British Journal of Haematology May 2002; 117 (Suppl 1): A264

Acute Normovolaemic Haemodilution – A Pilot Study

G Sanders, ARA Rushdon, I Christie, AJ Brodribb, KB Hosie

Colorectal Disease July 2001; 3 (Suppl 1): P188
Chapter 1: Introduction and Aims

Blood transfusions are often given to surgical patients and allogeneic transfusion in this setting confers a risk to the recipient in terms of immunomodulation, transmission of disease, allergic reaction, and alloimmunisation. More recently, the introduction of leucodepleted blood has led to an increased cost pressure on health resources. Awareness of the adverse effects of allogeneic blood transfusion has prompted both physicians and patients to search for alternatives to the use of perioperative donor blood.

There are essentially three techniques of autologous transfusion:

a) Predeposit: If surgery is urgent and required within 2 weeks of diagnosis, predonation is impractical. In patients requiring gastrointestinal surgery the ability to absorb nutrients such as iron is often compromised, making preoperative donation of little value.

b) Red cell salvage + reinfusion: This technique is not applicable in abdominal surgery when the bowel is open or in surgery for malignancy.

c) Haemodilution: Acute normovolaemic haemodilution (ANH) entails removal of blood from a patient immediately before or shortly after induction of anaesthesia and simultaneous replacement with cell free fluid. By using this procedure prior to intraoperative blood loss, fresh autologous blood is made available for later transfusion. As a result of haemodilution blood subsequently lost contains proportionally fewer red blood cells per millilitre, thus minimising intraoperative loss of autologous red cells.

Although the indications and exclusion criteria for ANH have been described, the efficacy of ANH is inconclusive and will remain so until well designed trials are
completed. Furthermore, the effect of ANH on coagulation is currently unknown. If ANH proves successful in decreasing the units of allogeneic blood transfused, there would be important psychosocial and health economic consequences.

**Aims of This Study:**

Define the role of haemodilution in gastrointestinal surgery in terms of:

1) reduction in allogeneic blood usage and its potential as a blood saving technique,

2) clinical outcomes and hospital stay,

3) the effect on coagulation,

4) identify patient preferences towards blood transfusion and haemodilution.
Chapter 2: The Risks Of Allogeneic Transfusion

Allogeneic transfusion confers a risk to the recipient in terms of immunomodulation, transmission of disease, allergic reaction, and alloimmunisation. In some regions blood is in short supply. Elective surgery is occasionally cancelled in Canadian cities because of a lack of available blood and a shortfall of four million units of red cells is projected in the United States by 2030 if the present rate of RBC utilization continues. It is likely that blood will become scarcer with increasing population age and the increased number of donors excluded. Every transfusion decision should therefore have a risk/benefit assessment, but what are these risks?

Immunomodulation

In the 1970's the transfusion of allogeneic blood was demonstrated to suppress the immune responses of human hosts to renal allografts. Since then, over 100 observational and clinical studies have examined the immunosuppressive effects occurring with perioperative allogeneic transfusion. The difficulty is that studies comparing outcomes in transfused versus non-transfused neglect confounding factors; largely the reason for transfusion. Even the studies that adjust for the severity of the principal diagnosis often fail to adjust for the presence and severity of co-morbidities (diabetes mellitus, congestive heart disease, lung disease, liver disease or kidney failure), and these may be a more important determinant of post-operative infection. Furthermore, the number of patient days with an indwelling urinary catheter may be the most important determinant of whether a patient develops a postoperative urinary tract infection. It would be unethical to transfuse or not for the purposes of a study. Therefore randomised studies to date have compared the risk of cancer recurrence and/or
post-operative infection between a treatment arm receiving standard or buffy coat reduced red blood cells (RBCs) or whole blood, and a control arm receiving autologous or leucodepleted RBCs or whole blood. The number of leucocytes present in buffy coat depleted packed cells is about 30% of whole blood, compared with 0.1% present in leucocyte depleted blood. These studies are based on the assumption that the transfusion of autologous or leucodepleted RBCs, or whole blood, is immunologically neutral, since transfusion associated immunomodulation (TRIM) has been attributed for the most part to immunologically active white blood cells, although others have proposed allogeneic plasma. Although it is known that allogeneic transfusion impairs T-cell mediated immunoresponse, as measured by a decrease in antigen-driven lymphoblastic transformation and natural killer activity, attributing this as the cause is less certain.

Randomised Controlled Trials

Houbiers et al randomised patients to receive either buffy coat depleted or leucocyte depleted red cells in a study of 697 patients operated on for colorectal cancer. They found no difference between the 2 groups in survival, disease free survival, cancer recurrence rates, or overall infection rates after an average follow up of 36 months. However, those patients who had a curative resection and received a transfusion of any sort had a lower 3 year survival and higher infection rates. They went on to publish two further papers. One illustrated a dose response relationship between units transfused and infection rates: the corrected relative risk was 1.6 for 1-3 units of red cells and 3.6 for more than 3 units. The second looked at 5 year survival and cancer recurrence rates. They again found no difference between groups, but did find a significant reduction in survival between transfused and non-transfused. There was however no difference in cancer
recurrence rates between transfused and non-transfused. They concluded that
transfusion of leucocyte depleted blood in the perioperative period has no effect on
long term survival and/or cancer recurrence.

Two randomised controlled trials have tested this hypothesis using autologous
blood; Busch et al\textsuperscript{15} studied 475 colorectal patients with pre-operative donation
(POD) the autologous technique. 2 units were donated and transfusion could only
take place if >500ml was lost intra-operatively or the haemoglobin fell to <10.5
g/dl. They found no difference in mortality, infectious complications or disease free
survival over a median 2.5 year follow up. However the disease free survival was
significantly greater in patients who received no transfusion. They concluded that it
is the circumstances necessitating transfusion rather than transfusion itself that
are the real determinants. Heiss et al\textsuperscript{16} studied 120 colorectal patients and also
used POD as the autologous technique. Transfusion was recommended if the
haemoglobin fell to <10 g/dl. They found no reduction in cancer recurrence with
autologous transfusion, however a significantly greater percentage of patients in
the allogeneic arm had infectious complications (27% versus 12%). In addition, the
infection rate increased with the number of units transfused. There was however a
design problem with both of these studies. In both studies, as a result of POD
patients presented to the operating theatre with a lower haematocrit than patients
from the allogeneic transfusion arm. In addition, if the POD patients required a
transfusion of more than the 2 units pre-deposited, they were given allogeneic
RBCs. As a result, in the study by Busch et al, 75% of patients in the POD arm
received a transfusion, 28% receiving further allogeneic blood. This compared with
56% of patients in the allogeneic arm being transfused. In the study by Heiss et al,
91% of patients in the POD arm received a transfusion, 35% receiving further
allogeneic blood. This compared with 60% of patients in the allogeneic arm being
transfused.
Tartter et al. studied 221 patients undergoing gastrointestinal surgery randomised to receive packed RBCs or leucocyte depleted cells. They found a significantly greater percentage of patients in the allogeneic arm had infectious complications (44% versus 16%). However there were significantly more patients with ulcerative colitis in the allogeneic group (26 versus 5), which could have affected the results.

The 2 papers with the most dramatic results, illustrating an adverse effect of non-leucocyte depleted blood in colorectal surgery, were by Jensen et al. In the first, they compared patients transfused with whole blood or leucocyte depleted. 53% of patients received a transfusion, with infectious complications occurring in 27% of those transfused with whole blood and 2% of those transfused with leucocyte depleted blood. In the second, they compared patients transfused with buffy coat poor blood or leucocyte depleted blood. 44% of patients received a transfusion of which surgical infectious complications occurred in 18% and 0% respectively. Non-surgical infectious complications (pneumonia, urinary tract infection) occurred in 37% and 14% respectively.

The most stringent study to date was that by Van de Watering et al. who randomised 914 patients scheduled for cardiac surgery to one of 3 treatment arms: buffy coat reduced allogeneic RBCs; WBC reduced allogeneic RBCs filtered before storage; and WBC reduced allogeneic RBCs filtered after storage. They found no significant difference in the incidence of post-operative infection in the 3 arms. However, when the pre and post storage arms were combined, recipients of buffy coat depleted RBCs had a higher incidence of post-operative infection, but the result was not significant (p=0.06). Interestingly, they also detected an unexpected association between WBC-containing allogeneic blood transfusion and mortality from other causes other than post-operative infection (7.8% and 3.6% respectively, p=0.015). When analysed further, they found that this difference was only significant when patients received 4 or more units of blood.
They postulated that their study was more likely than previous randomised controlled trials to detect differences because of the substantially higher transfusion dose in this group of patients (only 5.2% of these cardiac patients received no transfusion). However, this association may have limited applicability because data obtained from patients undergoing cardiac surgery may not be generalizable to other clinical settings. The extracorporeal circuit used in cardiac surgery induces a diffuse inflammatory response that may predispose to postoperative infection or other surgical complications.

The mechanism behind the association between WBC-containing allogeneic transfusion and increased post-operative mortality is unclear. Hebert et al\(^2\), also unexpectedly, reported that a restrictive strategy of allogeneic transfusion may be superior to a liberal transfusion strategy in critically ill patients with normovolaemia. It is clear that more research is needed to elucidate the possible biologic mechanisms that may underlie such other adverse effects of allogeneic transfusion.

Table 2.1, below, was derived from the 7 randomised studies to date and summarises the percentage infection rates in the 3 groups of patients receiving no transfusion, leucocyte depleted or autologous blood (control) or allogeneic / buffy coat reduced blood (treatment). 4 studies show a significant increase in infectious complications in the treatment arm, 1 shows a non-significant increase (p=0.06) and 2 show no increase.
<table>
<thead>
<tr>
<th>Author</th>
<th>Total sample size</th>
<th>Overall % Transfused</th>
<th>Infection %</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Not Transfused</td>
</tr>
<tr>
<td>Jensen^**</td>
<td>197</td>
<td>53</td>
<td>2</td>
</tr>
<tr>
<td>(Colorectal)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Busch'''</td>
<td>475</td>
<td>65</td>
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<tr>
<td>(Colorectal)</td>
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<td>Heiss^16</td>
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<td>75</td>
<td>7</td>
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<td>Jensen^19</td>
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<td>Tartter^17</td>
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<td></td>
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<tr>
<td>Van de Watering^20</td>
<td>914</td>
<td>95</td>
<td>17*</td>
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</table>

Control: *Leucocyte depleted

**Autologous (POD)

Treatment: *Allogeneic whole blood / packed cells

**Buffy coat reduced RBCs

† significant difference between control and treatment arms (p<0.05)

**Table 2.1: Summary of infection rates in published randomised controlled trials**
Meta-analyses

A meta-analysis conducted by Duffy et al\textsuperscript{22} looked at post-operative infection rates in patients receiving autologous and allogeneic blood. They identified 7 suitable studies, 6 using pre-deposit and 1 cell salvage, giving a study population of over 1000. The pooled odds ratio was 2.34 (95\% confidence interval 1.6-3.5), however 5 of these studies were retrospective.

A meta-analysis of 3 randomised trials looking at cancer recurrence\textsuperscript{23} showed no transfusion effect on cancer recurrence; the power however would only detect an effect of greater than 33\% increase.

The largest meta-analysis, published in 1998\textsuperscript{24}, included data from 6 randomised clinical trials with leucocyte depleted or autologous blood in the control arm (5 of which are discussed above) and 2 prospective cohort studies. They found no allogeneic transfusion effect on mortality or cancer recurrence; 3 randomised studies demonstrated an increased risk of post-operative infection in patients receiving allogeneic blood\textsuperscript{16,18,19}, the other 3 did not\textsuperscript{8,15,25}. Two of the randomised studies were by the same author and were felt to be sufficiently different from the others in terms of patient mix and study design to be excluded from the final combined analysis, which revealed no difference between groups. However the power was such that only a 20\% difference would be detected.

Summary of immunomodulation

Observational studies comparing patients with and without transfusion almost uniformly support the hypothesis of an increased risk of post-operative infection in the transfused group. A possible explanation for the disagreement in randomised controlled trials may be the adverse effects of TRIM are small (5-10\%). Vamvakas and Blajchman\textsuperscript{26} illustrated that a study population of 20000 patients would be
required if the overall infection rate in the entire study population was approximately 20% and almost half of the enrolled patients did not receive a transfusion. They concluded that definitive evidence regarding the existence of a deleterious immunomodulatory effect of allogeneic blood transfusion does not exist, but the available data does justify a high degree of suspicion. Similar views were expressed in a publication in the European Journal of Cancer\textsuperscript{27}. Despite this, the signatories of a letter published in Transfusion felt that there was still no evidence to support universal WBC reduction\textsuperscript{28}. These views were echoed at the state of the art conference on TRIM\textsuperscript{29}.

The implementation of universal white cell reduction will preclude the undertaking of further randomised trials investigating TRIM effects mediated by allogeneic WBC's. It has been suggested that a meta-analysis of the raw patient data may be able to explain discrepancies and answer the question\textsuperscript{26}. Until then, the long standing hypothesis of the potentially deleterious immunomodulatory effect of perioperative allogeneic transfusion remains unresolved.

Transmission of Disease

A recent survey has shown that the risks of blood screened by the Australian Red Cross Blood Service being infective for HIV or hepatitis B or C viruses are 0.79, 2.71 and 4.27 respectively per million donations\textsuperscript{30}. Slightly higher rates of HIV transmission have been reported in Canada\textsuperscript{31}. Between 1991 and 1993 in the USA, the risk of blood screened being infectious for HIV or hepatitis B or C were 2.03, 15.87 and 9.71 respectively per million donations. This gave an aggregate risk of 1:34000. Since then, screening tests have been introduced that lessen the risk by 27 to 72\textsuperscript{32}. In a follow up study of recipients of 20,000 units of blood transfused in 22 North London hospitals, no transfusion transmitted infections were identified in blood samples taken 9 months post transfusion\textsuperscript{33}. In the UK, the
risk of transmission of Hep B, Hep C, and HIV is 1 in 100,000 to 400,000, 1 in 3,000,000 and 1 in 4,000,000 respectively (adapted from British Committee for Standards in Haematology 2001). There is no doubt that the risks in developed countries are small; in third world countries they exist to much greater degree. Although there is no evidence of vCJD transmission in humans, concern has been provoked by a study in which one of 10 asymptomatic sheep, 318 days after being given 5g of cow brain infected with BSE in their feed, seemed to transmit BSE to a second sheep via a 400ml blood transfusion. The recent introduction of leucocyte depleted blood has decreased the potential spread of CMV, HTLV 1/11, EBV as well as vCJD.

Allergic Reaction And Wrong Blood To Patient

Non-haemolytic reactions occur in 1-5% of RBC transfusions. They are due to interleukins and antibodies reacting with transfused plasma proteins and allergens. Haemolytic transfusion reactions are rare with current methods of cross matching but continue to occur in the range of 1:24,000. Resultant fatality is in the range of 1 in 250,000 to 1 in a million transfusions.

Analysis of the first 2 annual reports from the SHOT (serious hazards of transfusion) initiative between 1996 and 1998, revealed that 52% (191) of the 366 cases reported were "wrong blood to patient". There were 22 deaths from all causes, 3 from ABO incompatibility. The denominator, however, is not known. In the report 2000-2001 there were a total of 213 incidents of "wrong blood" including 3 deaths, indicating an increase from previous years.
Conclusions

In conclusion, allogeneic transfusion does carry risks. The recent introduction of leucocyte depleted blood has led to an increased cost pressure on health resources. This decision was based on the hypotheses that this practice would 1) prevent the theoretical risk of transmission by transfusion of the agent of variant Creutzfeldt-Jacob disease (vCJD)\(^7,8,40\), 2) enhance overall transfusion safety by reducing the deleterious immunomodulatory effects\(^40\) and prevalence and severity of febrile transfusion reactions\(^7\).

If an alternative could be found, one cardinal benefit not mentioned previously, is the peace of mind associated with receiving blood free from contamination, in particular, with HIV, hepatitis viruses and CJD. Slovic\(^41\) demonstrated that people tend to overestimate "unknown risks" and "dread risks". He defines "unknown risks" as those with delayed effects and new and unfamiliar risks. "Dread risks" are those over which we have no control and those that may have catastrophic consequences. Many patients perceive the risk of HIV in exactly these terms, despite reassuring statistics regarding the transmission of HIV by transfusion. The peace of mind that comes from having control over the risk of HIV and other potentially harmful effects of transfusion is immeasurable, but nonetheless important to the patient undergoing surgery\(^42\).
Chapter 3: Methods of Avoiding Allogeneic Transfusion

A number of methods have been utilised over the years in an attempt to decrease the use of allogeneic blood. These include meticulous surgical technique, transfusion trigger, autologous transfusion (preoperative donation, acute normovolaemic haemodilution, cell salvage, postoperative blood recovery), hypervolaemic haemodilution, controlled hypotension, erythropoietin, aprotonin, and oxygen carrying solutions.

Surgical Technique

The utilisation of good surgical technique which minimises blood loss and recognises the importance of efforts to limit the use of blood to clinical necessity has been emphasised on many occasions.43

Transfusion Trigger

Guidelines from both the Canadian Medical Association and the American Society of Anaesthesiologists suggest that a red cell transfusion is rarely indicated if the Hb is > 10 g/dl and usually indicated if the Hb < 6g/dl in clinically stable patients not at risk of coronary artery disease.44

The recent TRICC study (Transfusion Requirements in Critical Care) demonstrated that a restrictive red blood cell transfusion strategy (maintaining haemoglobin between 7 g/dl and 9 g/dl) appears to be at least as effective and possibly beneficial in certain subgroups. The overall 30 day mortality was lower in the restrictive strategy group (18.7 % versus 23.3%, p=0.11). However, in patients who were less acutely ill (with an Acute Physiology and Chronic Health Evaluation 11 score of ≤20), the 30 day mortality was 8.7% in the restrictive strategy and
16.1% in the liberal strategy arm (p=0.03). Among those less than 55 years of age, the 30 day mortality was 5.7% with the restrictive strategy and 13.0% with the liberal strategy (p=0.02); this did not apply to those with clinically significant cardiac disease. In addition, the mortality rate during hospitalisation was significantly lower in the restrictive strategy group (22.2% versus 28.1%, p=0.05). Jehovah's witness patients\textsuperscript{45} and haemodilution studies have also provided insight into the critical haemoglobin for patients. Conscious healthy adults have been shown to have no evidence of inadequate systemic oxygenation \textit{at} haemoglobin concentrations of 4.5 to 5.0 g/dl\textsuperscript{46}. There is, however, no clear and specific haemoglobin (Hb) below which patients require a transfusion. The decision should be based on age, co-morbidity and vital signs in addition to Hb.

In one study, the mere introduction of transfusion guidelines decreased allogeneic transfusion by 43% in elective surgical patients\textsuperscript{47}.

\textbf{Autologous Transfusion}

Autologous transfusion is a term used to describe any procedure whereby previously donated (or shed) blood is transfused into the patient. In the 1990’s, following substantial improvements in the safety of allogeneic blood, the emphasis has shifted from an effort to eliminate allogeneic transfusion to an objective evaluation of the benefits derived from autologous transfusion. A cardinal benefit difficult to quantify is the "peace of mind" associated with knowing that they are receiving blood free from contamination with HIV or a hepatitis virus\textsuperscript{42}. In addition there may also be unknown transfusion transmitted diseases.

A survey was performed recently looking at the use of alternatives to allogeneic transfusion in Australian hospitals\textsuperscript{48}. POD was most widely used (70% of hospitals), followed by cell salvage (27%) and ANH (24%). In contrast
antifibrinolytic drugs, desmopressin and erythropoietin were used in fewer than 10% of hospitals. The use was greatest in larger hospitals and teaching hospitals, with orthopaedics and cardiothoracic surgery reporting the highest usage. A high proportion of respondents indicated that ANH and POD should be used more often, endorsement for cell salvage being not as high. Interestingly perceptions that the three technologies are cost effective and have few side effects were common reasons for advocating higher use.

Mercuriali et al. have proposed a personalised approach to utilise all the methods available to obtain autologous blood and avoid the use of allogeneic blood. This approach takes into account the predicted blood loss (determined through a constantly updated retrospective analysis) minus the blood loss that patient can tolerate.

Predicted red cell loss = Circulating red cell volume reduction from pre-surgery to post-surgery day 5 + RBC volume transfused:

\[
\text{Red cell loss (ml)} = \text{EBV} \times (Hc_{t0} - Hc_{t5}) + \text{ml of RBC transfused}
\]

The blood loss the patient can tolerate = volume of red cell loss to maintain an accepted minimal haematocrit value:

\[
\text{Tolerated RBC loss (ml)} = (\text{EBV} \times Hc_{\text{baseline}}) - (\text{EBV} \times Hc_{\text{minimum}})
\]

The difference between the predicted and tolerated blood loss is the transfusion requirement of the individual patient expressed in ml of pure RBC (180-200ml RBC/unit, 250ml RBC/unit, or 300ml RBC/unit). This estimate can then be used to determine the transfusion strategy to be adopted, having estimated the net gain of RBC for each strategy.
Pre-Operative Donation

Units of blood are venedected prior to surgery and stored for up to 35 or 42 days depending on the anticoagulant / preservative solution used. POD only applies if the need for blood can be anticipated and a donation plan developed. The last unit is drawn no fewer than 72 hours before surgery, because a 72 hour interval is an estimate of the time needed to compensate for the acute volume and protein deficit caused by a one unit phlebectomy. Iron supplementation should begin as soon as surgery is scheduled, usually 300mg of ferrous sulphate three times a day. The minimal level for autologous donation is 11g/dl, and most patients can make 2 or 3 donations before this level is reached.

The volume of blood a patient can deposit is a function of the total baseline circulating volume of RBC and the rate of recovery of RBC collected at each donation. Each unit of autologous blood collected (350-450ml), decreases haemoglobin by 1g/dl and haematocrit(hct) by 3 points. If insufficient time is given to the patient to compensate for the red cell losses, pre-donation offers very little advantage. Candidates for THR, in optimal clinical and haematological condition (Hb>13.5 g/dl, Hct>40%), donating 3 units over a 10 day period with intravenous iron administration after each donation, took 15 to 22 days to restore the quota of RBC lost with the first collection. Another study demonstrated that collecting a total of 3 units, with collections every 3 days resulted in no greater RBC production than collections every 7 days.

Exclusions / risks – The donation:

The only group of patients who must be excluded from donating according to the American Association of Blood Banks(AABB) Standards are those with significant bacterial infections or any potential for bacteraemia. Some Gram negative bacteria (Yersinia enterocolitica, Pseudomonas species, Citrobacter species ) can multiply
and produce toxins in blood stored in the refrigerator, without causing haemolysis or any usually detectable change in the appearance of the unit.

Candidates are therefore those who are in relatively good health who can tolerate venesection and iron supplementation. A fatality risk of 1 per 101000 units collected would negate all life expectancy benefits attributed to POD\textsuperscript{55}. High risk donors include patients with coronary artery disease, congestive cardiac failure, medication inhibiting the compensatory mechanisms of the cardiovascular system to the withdrawal of blood, aortic stenosis, transient ischaemic attacks and marked hypertension. A study by Popovsky et al\textsuperscript{56} reported that one in 16783 units donated was associated with an adverse event requiring hospitalisation; that is 12 times as high as seen in volunteer blood donors.

Exclusions / risks – The Transfusion:

Transfusion of pre-donated autologous blood is not without risk. In a retrospective review, adverse reactions to autologous blood composed 2.1% of all transfusion reactions reported and involved 0.16% (15/9353) of all POD red cells\textsuperscript{57}, although on further review only 60% were thought to be directly related to the autologous units. Complications include haemolysis of the unit during processing and storage resulting in haemoglobinaemia and haemoglobinuria if transfused, endotoxic shock if contaminated with gram negative bacteria, febrile non haemolytic transfusion reactions due to the release of pro-inflammatory cytokines from white blood cells in the refrigerator if storage is prolonged, and transfusion of the wrong unit. This last error – the administration of autologous blood to an unintended recipient – is of greatest concern. Random misadministration carries a 36% probability that the blood will be ABO incompatible\textsuperscript{58} and 5% of ABO incompatible transfusions have been reported as resulting in fatal acute haemolytic transfusion reactions\textsuperscript{58}. In these situations, the index of suspicion for a haemolytic reaction
may be low as the patient is receiving blood thought to be their own, thus delaying intervention resulting in an even greater risk of adverse outcome. In addition, the misadministration of autologous blood carries with it an increased risk of infectious disease transmission because some hospitals do not test autologous blood donors, and those that do, often accept donors who test positive for one or more markers. A recent report describing POD in Canada found an overall error rate of 1 of 149 units to 1 of 322 units. Most of these were however administrative (late receipt of a unit at hospital or administration of allogeneic blood when POD blood was available). A prospective study by the Belgium SANGUIS group found that 3 of 55 patients with autologous blood available received allogeneic instead. 0.9% of responders to a 1992 College of American Pathologists survey indicated that they had issued autologous blood to the wrong patient on at least one occasion in the previous year. 0.5% reported that units collected from autologous donors had been transfused to the wrong patients on one or more occasions. A 1994 American Association of Blood Banks survey reported that 1.2% of respondents indicated errors involving the transfusion of autologous blood to other patients during the previous year. Although actual error rates are not reported, another study reported an error rate of 1 per 68,000 misadministrations. In the United States 1 of 560,000 autologous units transfused resulted in a fatality due to ABO incompatibility.

Inclusion Criteria:
Eligibility based on blood loss is controversial. Vamvakas et al. say blood loss should exceed 500-1000ml in at least 5-10% of cases. However a British consensus conference on autologous transfusion stated that POD should be considered only if the likelihood of per-operative transfusion exceeds 50%, in view of expense.
Blood losses are however difficult to predict\textsuperscript{61,62} despite attempts to stratify patients pre-operatively\textsuperscript{63-65}.

Efficacy:

In 1992 1 in every 12 units of blood collected in the United States was the result of an autologous donation\textsuperscript{61}. This rate has declined with the re-evaluation of POD. Of 129 patients undergoing elective colorectal cancer surgery over a 2 year period, only 28 were suitable for autologous donation\textsuperscript{66}.

Within the NHS, a current disadvantage is the difficulty of guaranteeing non-cancellation of routine surgery.

POD Induced Anaemia:

The degree of anaemia induced by each unit of POD depends upon the extent of compensatory erythropoiesis and the interval between donations. Three authors reported no compensatory erythropoiesis in patients scheduled for hysterectomy\textsuperscript{67} and radical prostatectomy\textsuperscript{68,69} whereas another reported that 60\% of RBC's lost by weekly donations over a three week period were replenished\textsuperscript{70}. Only with aggressive autologous blood phlebectomy (defined as a goal of 6 units donated over 3 weeks) does the net red cell volume expansion stimulated by the endogenous erythropoietin response to anaemia exceed the equivalent of 1 unit of allogeneic blood\textsuperscript{71}. The use of erythropoietin coupled with iron supplementation may improve this\textsuperscript{72}, although no clinical benefit has been demonstrated\textsuperscript{73,74}. Given that the normal person takes many weeks to regenerate the blood lost in donation and that a lower haemoglobin level at admission is associated with an increased likelihood of transfusion, it is prudent to maximise the time between last donation and date of surgery\textsuperscript{61}.
Mathematical Model:
A mathematical model, with a perioperative threshold haematocrit of 25%, applied to a 70kg patient with a blood volume of 5000ml and initial haematocrit of 45% who had donated 2-4 units of blood pre-operatively, proved that POD could actually be harmful to the patient. This occurs based on the assumption that with each unit donated, compensatory erythropoiesis resulted in replacement of 2/3 of the removed unit thereby dropping the haematocrit by 1%. The threshold haematocrit is therefore reached with a lower intra-operative blood loss than if POD had not taken place. In addition the same patient not pre-donating could lose 2500ml before requiring a transfusion, assuming a transfusion trigger of haematocrit 25%. Since losses of this magnitude are unusual, POD is not only an unnecessary expense for many patients but may actually adversely affect patients. However, for patients with large estimated blood losses, or low starting haematocrits, the use of POD can reduce exposure to allogeneic blood.

Clinical Studies:
In a recent meta-analysis Forgie et al showed that patients who were randomised to receive autologous blood were less likely to receive allogeneic blood, but more likely than control patients to receive any transfusion, a fact also recognised by other authors. There was a direct relationship between transfusion rate in the control group and benefit derived from POD, suggesting that other methods of decreasing blood transfusion, such as transfusion protocol and surgical technique, are important.
A retrospective study looking at POD in prostatectomy showed that 3 unit POD decreased allogeneic exposure compared with controls. However, the study was retrospective, the controls were those who had been excluded from POD and totalled 10, compared with 384 trial patients.
Cost Effectiveness:

Autologous blood donation is a more expensive process than the donation of allogeneic blood and up to half the units are discarded\textsuperscript{77-80}. Furthermore, the addition of erythropoietin has also not been found to be cost effective\textsuperscript{80}. Given the improved safety of allogeneic transfusions today, the increased protection afforded by donating autologous blood is limited and may not justify the increased cost\textsuperscript{78}.

Acute Normovolaemic Haemodilution (ANH)

Acute normovolaemic haemodilution is a technique in which whole blood is removed from a patient, whilst circulating blood volume is maintained with acellular fluid. It is performed shortly before a procedure that is anticipated to result in significant blood loss. By using this procedure prior to intra-operative blood loss, fresh autologous blood is made available for later transfusion. As a result of haemodilution, blood subsequently lost during surgery contains proportionally fewer red blood cells per millimetre, thus minimising intraoperative loss of autologous red cells.

Veneseected blood is collected in standard blood bank bags containing citrate anticoagulant. It is possible to utilise a tilt-rocker with an automatic cut off via volume sensors, thus freeing up staff\textsuperscript{81}. Blood can be stored at room temperature for up to 6-8 hours, or at 4 degrees centigrade for up to 24 hours\textsuperscript{35,81}.

Advantages:

ANH has certain advantages: There is minimal pre-operative preparation for both patient and staff, which makes ANH suitable for both emergency and elective procedures. Units are collected and stored at the bedside incurring no storage or testing costs, and minimising the chance of a clerical error leading to an incorrect
transfusion. All blood collected is returned to the patients thereby eliminating costly blood wastage. Since blood is available in theatre, patients can be “group and saved” allowing a lower cross match ratio. The blood is fresh, containing functional platelets and clotting factors and the lowered blood viscosity may have benefits in terms of oxygen delivery\(^6\).

Eligibility/Safety

Any patient with a haemoglobin level of at least 11g/dl and expected to lose more than 20% of their blood volume intra-operatively can be considered a candidate for ANH\(^3\). These guidelines were echoed again in 1999\(^6\). A 70 kg patient with a starting haematocrit of 45% can have 4 units removed before the haematocrit falls to 30%. Final haematocrits of 20% or 25% are safe because normovolaemia is maintained at all times by the infusion of acellular crystalloid or colloid. The sudden drop in haematocrit is accompanied by a decrease in the arterial oxygen content and is tolerated well by healthy adults due to the significant reserve of the oxygen delivery system: 1000 ml/min of oxygen are delivered to tissues, while only 250ml/min are needed in the resting state. Anaesthesia further reduces oxygen consumption by 20% and cardiac output is also increased in response to the decrease in haematocrit. A shift in the oxygen dissociation curve does not occur during haemodilution.

15% of a heterogeneous population of surgical patients have been found to be at risk for silent ischaemia when extensive preoperative monitoring was applied. 35% of these events occurred in patients not thought to be at high risk for ischaemic heart disease on the basis of preoperative assessment\(^8\). However, the rheological effects of ANH may be beneficial\(^5\). Spahn et al\(^8\), demonstrated that ANH to a haemoglobin of 8.8+/–0.3 g/dl was well tolerated in 20 patients older than 65 years.
The group went on to demonstrate that ANH was well tolerated to a haemoglobin of 9.9\(\pm\)0.2 g/dl in patients with coronary artery disease receiving β blockers\(^{64}\).

**Exclusions:**

Haemodilution is contraindicated in patients with severe myocardial disease of any cause\(^{36}\) (moderate to severe left ventricular impairment, unstable angina, severe aortic stenosis, critical left main stem disease) or cannot raise their cardiac output (previous infarction, calcium channel blockers or β blockers). However, as mentioned previously, Spahn et al\(^{84}\) demonstrated that ANH was well tolerated to an haemoglobin of 9.9\(\pm\)0.2 g/dl in patients with coronary artery disease receiving β blockers.

It is also contraindicated in those who do not have adequate reserve in their oxygen delivery system (restrictive or obstructive pulmonary disease) and may be contraindicated in patients unable to deal with large volume shifts (renal failure) or in patients with a coagulopathy that further dilution of clotting factors exacerbates. Furthermore, the effect of haemodilution on coagulation is still unknown. If haemodilution impairs coagulation, any beneficial effect may be negated by increased blood loss.

**Mathematical Model:**

For any given patient, the total red cell mass saved by ANH, and the extent to which the technique may reduce the need for allogeneic blood transfusion, depends upon three factors: 1) the initial and target haematocrit; 2) the amount of blood venesected; and 3) the amount of surgical blood loss\(^{85}\). Clinical studies of the efficacy of ANH have not examined the relative impact of these factors on red cell mass savings\(^{86}\). Figure 3.1 illustrates the value of ANH. An adult with an estimated blood volume of 5 litres and an initial packed cell volume of 45% could
undergo surgical blood losses of up to 3000ml yet maintain a packed cell volume value that would remain ≥25% after operation. In this model, ANH from an initial packed cell volume of 45% would still allow up to 3500ml of surgical blood loss, and the packed cell volume could be maintained ≥28%.

Feldman et al\textsuperscript{85} designed a model of ANH to understand the conditions where ANH is most likely to be beneficial to the patient and the degree of haemodilution required to achieve that benefit. In this model, patients were venesected to their minimum haematocrit prior to surgical blood loss. The venesected blood was then returned during surgical blood loss at a rate to maintain the minimum haematocrit. In their model, a unit of packed cells was taken as being 250ml with haematocrit of 0.65. They showed that ANH can reduce the need for allogeneic transfusion, if used appropriately. However, the benefits were small (less than 2 units of allogeneic blood saved) unless a significant number of units are venesected (>7). This finding goes against the clinical studies in ANH which demonstrate considerable allogeneic transfusion savings. The authors conclude that well designed prospective studies are still required.

The model designed by Brecher and Rosenfeld\textsuperscript{87} took into account the continual decreasing haematocrit due to blood loss in an isovolaemic patient, largely by using differential equations. Once again, the venesected blood was returned to maintain the minimum haematocrit. In their model, a unit of packed cells was taken as being 350ml with haematocrit of 0.65. They found that for a typical patient with estimated blood volume 5000ml, pre-ANH haematocrit 0.40, minimum haematocrit at which transfusion was begun 0.25, over a range of blood losses (500-2500ml), and 1 to 5 units venesected, the savings never exceeded 0.6 units. In addition, taking into account the continual decreasing haematocrit, for a patient with haematocrit 0.45 who intra-operatively lost 1 litre of blood, the RBC volume would have been 408 ml. If the haematocrit had been reduced to 0.25, the RBC volume
lost would have been 227 ml, a saving of 181 ml. They concluded that published reports documenting substantial savings in allogeneic blood use with ANH were therefore surprising, and carefully controlled, prospective randomised trials were needed.

Vamvakas et al noted that based on the above model, an adult with an initial haematocrit of at least 45% could, without ANH, maintain a post-operative haematocrit of at least 25% and avoid an allogeneic transfusion, if there was an intra-operative blood loss of up to 3939 ml.

Singbartl et al commented that the mean volume of blood collected during ANH did not differ from the mean blood loss, concluding that the most cost effective method is no ANH. They further commented that they knew of no PRCT comparing the efficacy of ANH with no ANH using the same transfusion trigger.

Figure 3.1: Maximal allowable blood loss in a patient with a blood volume of 5000 ml and an initial packed cell volume value of 45% (solid line) or 40% (broken line), with and without ANH
Efficacy Of ANH:

Controlled Trials

Wong et al\(^{90}\) looked at 145 patients, undergoing elective infra-renal aortic surgery, randomised to receive allogeneic transfusion or a combination of cell salvage and ANH. They demonstrated a significant reduction in the number of units transfused, but not the number of patients transfused. However, only a mean of 1.66 450ml units of blood were venesected for ANH, and since two variables were studied, it is impossible to know the relative effect of either one.

In a three arm study, McGill et al\(^{91}\) randomised patients undergoing cardiac surgery to cell salvage, ANH plus cell salvage and control. They demonstrated a significant reduction in the number of patients and units transfused in the cell salvage group compared with control, but no additional benefit with ANH. However, only 10ml/kg blood was venesected during ANH.

Boldt et al\(^{92}\) looked at 60 patients undergoing retropubic prostatectomy divided into 3 groups, ANH, controlled hypotension, and a control. They venesected a mean (SEM) 1278 (150) ml and replaced this with gelofusine at a ratio of 1:1. In the hypotensive group, they aimed to maintain MAP at 50mmHg using sodium nitroprusside. They found significantly fewer units of blood were transfused in the study groups, the hypotensive group having the least (21, 14, and 28 respectively). The number of patients transfused in the 3 groups were 9, 5, and 12 respectively. However only a mean of 710ml extra fluid was administered to the ANH group compared with controls, implying that the ANH group were bled rather than haemodiluted.

Goodnough et al\(^{91}\) proposed that ANH should replace POD. They argued that POD has the same effect as ANH: the haematocrit level reductions from POD (42 to 36%) simply represent minimal chronic haemodilution, as shown in the section entitled "POD induced anaemia". These views were echoed by Rottman et al\(^{93}\) and
Monk et al. The net result of this is an increased likelihood of perisurgical transfusions and patients discharged with haematocrits lower than if they had not undergone POD. The above is only the case if the POD units are not all transfused, which assumes that POD transfusion carries the same risk as allogeneic transfusion.

Two studies from the same author, appear to report the same accumulating cohort of patients. All patients were haemodiluted to a haematocrit of 28% and the outcome compared with the additional effects of POD. Because 60% of POD units were wasted, there was a net loss of RBC in 80% of patients. There was a mean saving of 112±38ml of RBC attributed to ANH. Although they claimed that ANH can achieve an equivalent clinical outcome compared with POD, they compared their 21% transfusion rate in the ANH alone group with other studies reporting transfusion rates with POD.

Herregods et al demonstrated no difference in ST segment depression in patients undergoing ANH to a haematocrit of 34% compared with controls during coronary artery bypass grafting. Although they demonstrated a significant decrease in allogeneic blood exposure with ANH, the control group had significantly greater blood loss.

Olfsanger et al found significantly greater number of units transfused in controls compared with patients haemodiluted to a target PCV of 28-30% (mean 1000ml collected) undergoing total knee replacement. However, only 30 patients were studied, randomised into 3 groups; 2 receiving ANH and 1 control. The control group had higher ASA grades and significantly greater postoperative blood losses.

Oishi et al prospectively studied patients undergoing total hip replacement using ANH in combination with POD and cell salvage. Only 33 patients were studied and the strategies were too impractical and expensive.
Earlier studies were mostly flawed and the deficiencies have been well reviewed\textsuperscript{100,101} (inadequate numbers, differing populations of patients compared, wide variations in the volume of autologous blood withdrawn, no transfusion protocol, and most importantly, the use of historical controls).

**Meta-Analysis**

An integration of the results of 5 randomised controlled trials by meta-analysis looking at the odds ratio of allogeneic transfusion in patients having ANH compared with POD revealed no significant difference\textsuperscript{53,61}. They were selected randomised controlled trials. Two of the five were in press; one was foreign, one an abstract, and one from 1992.

Bryson et al\textsuperscript{52} demonstrated that trials without a transfusion protocol showed marked reductions in both the likelihood of exposure to allogeneic blood and the units transfused. In contrast, however, studies with a transfusion protocol failed to show statistical significant reductions in either. They concluded that larger trials with carefully defined indications for the transfusion of allogeneic blood are required to establish efficacy.

**Consensus Conferences**

The Royal College of Physicians of Edinburgh in 1995\textsuperscript{43,51} and 1998\textsuperscript{74,98} noted that there was still no evidence that ANH was effective in reducing exposure to allogeneic RBC, and although serious hazards had not been reported, the physiological effects of the procedure remained uncertain. The panel concluded that randomised controlled trials were required before ANH could be widely recommended. This view was echoed by the British Committee for Standards in Haematology\textsuperscript{36}.

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Others
Some critics have pointed to the modest conservation benefit of moderate ANH, and attribute any reduced allogeneic exposure to a more conservative transfusion practice.
Faust et al. found that the additional crystalloid and colloid given during ANH can falsely dilute the intravascular haemoglobin level in the early postoperative period, making anaemia and allogeneic transfusion more likely. They also commented on the difficulty predicting which patients are likely to benefit in view of varied blood losses.

Cost Effectiveness:
ANH is undoubtedly the cheapest form of autologous transfusion, however since the efficacy is unknown, it is impossible to comment on its cost effectiveness. Monk et al. showed that transfusion costs were 73% higher for patients who had pre-donated 3 units of blood compared with those patients treated with ANH. ANH has been suggested as an inexpensive and effective means of reducing allogeneic blood exposure in a report of the American Society of Anaesthesiologists Task Force on blood component therapy.

Cell Salvage
Blood salvage involves the collection of shed blood from the operative field or surgical drains and the return of that blood to the patient. Shed blood is suctioned, mixed with citrate anticoagulant, filtered, collected into a reservoir, washed with saline, concentrated and returned to the patient.
Unprocessed salvaged blood differs from circulating blood because it has high levels of free haemoglobin and fibrin degradation products (FDP), free red cell stroma and procoagulant phospholipids, reduced and dysfunctional platelets,
decreased levels of coagulation factors, and various amounts of surgical field debris. Transfusion of these products may result in nephrotoxicity, DIC, thrombocytopenia, coagulopathy and microemboli. Washing removes free haemoglobin, FDP, red cell stroma and procoagulant phospholipids, fat and fibrin emboli, cellular microaggregates, bone fragments, etc.

Cell salvage is contraindicated in the presence of potential contamination of the operative field by bacteria, malignant cells, amniotic or ascitic fluid, although recent published work suggests that the risk of dissemination of malignant disease is minimal.

In one study, adverse reactions to transfusion of salvaged red cells occurred at a rate of 0.027% (5/18,506) units during a 6 year period. One death, due to air embolism during cell salvage, was reported to the New York State Department of Health between 1990 and 1995, out of 32,000 transfusions.

**Efficacy of cell salvage:**

The amount of RBC conserved depends on the rate of haemorrhage, the willingness of the surgeon to use an aspirator and not gauzes, the pressure of aspiration and the limitation of formation of bubbles during aspiration. In addition, it has the potential to be used in emergency cases.

**For:**

The Royal College of Physicians of Edinburgh Consensus Conference concluded in 1995 that an increasing body of evidence indicated that cell salvage could substantially reduce the need for allogeneic blood. The case had strengthened by 1998 as evidence had accumulated that cell salvage was practical, safe, relatively inexpensive, and potentially even cost saving. A meta analysis of the effectiveness of cell salvage from ISPOT (International Study of Peri-operative
Transfusion) group showed that cell salvage in orthopaedic surgery decreased the proportion of patients requiring allogeneic transfusion\textsuperscript{103}. In a three arm study, McGill et al\textsuperscript{91} demonstrated a significant reduction in the number of patients and units transfused in patients undergoing cardiac surgery.

**Against:**

However in 3 prospective randomised controlled trials, cell salvage did not result in fewer allogeneic transfusions\textsuperscript{90,104,105}. Bell et al\textsuperscript{104} showed a significant reduction in the number of units transfused from a median of 4 in controls to 3 in the cell salvage group, but not in the number of patients transfused in cardiac surgery. Wong et al\textsuperscript{90} also showed a significant reduction in the number of units transfused, but not the number of patients transfused in infra-renal aortic surgery, using a combination of cell salvage and ANH. Clagett et al\textsuperscript{105} however, showed no benefit in cell salvage in elective infra renal aortic surgery. Goodnough et al\textsuperscript{61} found that intra-operative cell salvage was not cost effective unless the blood loss exceeded 1000ml. Most patients requiring transfusion clinically will generally require more blood than is available by salvage. Therefore, it may be of value, not because it reduces the requirements for transfusion, but because it provides blood that is less costly to obtain and is immediately available in the event of rapid blood loss. However, cost effectiveness has not been addressed in any large prospective controlled trial looking at outcomes\textsuperscript{102}.

**Post operative blood recovery (PBR)**

PBR is used most commonly in cardiovascular and joint replacement surgery. Studies looking at efficacy have reached disparate conclusions; at least 3 have shown lack of benefit whereas at least 2 have shown benefit\textsuperscript{61}.
Hypervolaemic Haemodilution

Hypervolaemic haemodilution may provide the benefits of extreme haemodilution with a greater margin of safety\textsuperscript{106-108}.

Controlled Hypotension

The concept of induced hypotension is to produce a reduction in peripheral vascular resistance and thus hydrostatic pressure while maintaining cardiac output\textsuperscript{109}. Some haemodilution is likely to occur and may induce a state of hypervolaemia. The study by Boldt et al\textsuperscript{92} showed that controlled hypotension with sodium nitroprusside resulted in the greatest reduction in number of units and patients transfused when compared with ANH or control in patients undergoing retropubic prostatectomy.

Erythropoietin

Recombinant human erythropoietin (epoetin alfa) is a glycoprotein that stimulates red blood cell production. Early data suggests that EPO alone decreases the exposure to allogeneic blood\textsuperscript{110-112} and the benefit is greatest in anaemic patients. Recombinant human EPO and iron, administered to anaemic patients in a three centre ITU trial, decreased the number of transfusions\textsuperscript{113}. Further evidence was gained from Mercuriali et al, who randomised 50 female patients undergoing total hip replacement into 3 groups; placebo and 2 different doses of EPO. They demonstrated that EPO decreased exposure to allogeneic blood in patients who were anaemic (haematocrit<39%). On this occasion supplemental iron was given intravenously as well as orally. EPO given with proper iron support can produce a mean increase of 1 g/dl\textsuperscript{72}. 
EPO has been approved in the United States and Canada to increase the RBC mass of patients before elective surgery. EPO and ANH have been used in combination in patients undergoing radical prostatectomy. In that study, preoperative EPO was effective in minimising the perioperative anaemia associated with ANH and surgical blood loss, and the transfusion of allogeneic blood compared to patients undergoing either ANH alone or POD for blood conservation. Another study by the same group demonstrated that EPO increased the haematocrit level in patients undergoing ANH and these levels remained significantly greater than a control group, undergoing ANH alone, at every measurement after baseline, including discharge. They also demonstrated a relationship between baseline haematocrit and transfusion rate. They further suggested that baseline haematocrit could be used to make an informed decision about EPO. This conclusion was also supported by Sowade et al in patients undergoing elective open heart surgery.

The role of EPO in POD (pre-operative donation) is much more limited than initially expected. This is because no clinical benefit has been demonstrated in EPO treated donors, despite increased RBC production and collection in iron deficient donors. In a study comparing EPO with POD in 47 non-anaemic patients (haematocrit>39% at the time of first donation) undergoing orthopaedic procedures, EPO did not reduce exposure to allogeneic blood, but did allow a greater number of units to be donated. Price et al also showed that EPO can prevent anaemia and increase the number of blood units collected during POD. The Royal College of Physicians of Edinburgh Consensus Conference concluded that the evidence of the value and safety of EPO in POD is unclear, and that any benefits from the use of EPO in this setting remain unproven.
Side Effects:
Most clinical experience using EPO is in patients with chronic renal failure undergoing long-term administration. In this setting, well documented side effects include arterial hypertension, cerebral convulsions, and an influenza-like syndrome. Some studies have shown an increase in thromboembolic events. The frequency and type of side effects from short term use are not well established. The results from an orthopaedic study have suggested the increased possibility of deep vein thrombosis with EPO, especially if the baseline haemoglobin is greater than 13 g/dl\textsuperscript{116}.

Aprotonin
Aprotonin has been shown in several systematic reviews of trials in cardiothoracic surgery to reduce the need for allogeneic blood and for re-operation because of continued bleeding\textsuperscript{117,118}. However its efficacy has to be set against its high cost.

Oxygen Carrying Solutions
At the present time the two types of oxygen carrying fluids being developed are haemoglobin (Hb) solutions and perfluorochemical emulsions (PFC)\textsuperscript{1,119}. Oxygen carrying solutions have short effective lives (3-48 hours) and are plasma and platelet free. They include the cell free haemoglobin moieties derived from humans (10% diaspurin crosslinked haemoglobin -DCLHb), xenobiotic products (bovine or pig based), recombinant human haemoglobin and synthetic perfluorocarbons. All of the Hb solutions appear to possess a vasoconstrictive effect which may be related to the binding of nitric oxide by the free haemoglobin solutions\textsuperscript{1,119}. Concerns about endotoxin contamination and immunogenicity also exist with several Hb solutions.
The only oxygen carrying solution approved for clinical use is a PFC emulsion. Its use is restricted to the perfusion of coronary arteries after percutaneous transluminal coronary angioplasty\(^1,119\). Problems however include short intravascular half life, low oxygen carrying capacity, poor shelf life and temperature instability. Until further studies are performed, these fluids remain experimental.

**Conclusion**

Meticulous surgical technique and the use of a transfusion protocol represent good practice. Pre-operative donation requires careful donor selection, venesection, adequate storage of blood and correct re-transfusion on a tightly defined time scale, often not practical in cancer surgery. Its efficacy remains questionable. Cell salvage and post operative blood recovery are currently not applicable in the presence of malignancy or when the bowel is open. Controlled hypotension and the use of EPO have had varying degrees of success, but have not been widely adopted. In the future, EPO may be used alongside other techniques, especially in the presence of anaemia. Aprotonin's efficacy has to be set against its high cost. Oxygen carrying solutions remain largely experimental at present. Acute normovolaemic haemodilution, however, is a relatively inexpensive, simple, and safe technique which appears to be ideally suited to gastrointestinal surgery, however its efficacy is unproven.
Chapter 4: Current Blood Usage

Aim

The aim of this study was to ascertain the current departmental allogeneic transfusion requirements.

Methods

All patients undergoing colectomy surgery performed between 1997 and 1999 were identified retrospectively from our colorectal cancer database. Subsequently the data collected was cross referenced with our haematology computers to identify which patients had been transfused, the timing of transfusion (perioperative indicating on the day of surgery), and the number of units transfused. Pre-operative transfusions were excluded from the final analysis. Patients were grouped by ASA grade, as our target population for ANH were those of ASA 1 or 2.

Results

43% of the 470 identified patients were transfused a total of 532 units, 64 perioperatively and 468 postoperatively (table 4.1). In the ASA 1 and 2 patients, 41% of 333 were transfused a total of 357 units, 10 perioperatively and 347 postoperatively (table 4.2).
<table>
<thead>
<tr>
<th>PROCEDURE</th>
<th>NO. PATIENTS</th>
<th>NUMBER (%) TRANSFUSED</th>
<th>Units</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Peri</td>
<td>Post</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Right Hemicolecotomy</td>
<td>107</td>
<td>43 (40)</td>
<td>22</td>
<td>84</td>
<td>106</td>
<td></td>
</tr>
<tr>
<td>Extended Right Hemicolecotomy</td>
<td>39</td>
<td>18 (46)</td>
<td>9</td>
<td>35</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Transverse Colectomy</td>
<td>12</td>
<td>6 (50)</td>
<td>2</td>
<td>8</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Left Hemicolecotomy</td>
<td>42</td>
<td>13 (31)</td>
<td>3</td>
<td>23</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Sigmoid Colectomy</td>
<td>38</td>
<td>8 (21)</td>
<td>6</td>
<td>21</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Hartmann’s Procedure</td>
<td>22</td>
<td>15 (68)</td>
<td>2</td>
<td>31</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Anterior Resection</td>
<td>158</td>
<td>57 (36)</td>
<td>9</td>
<td>157</td>
<td>166</td>
<td></td>
</tr>
<tr>
<td>AP Resection</td>
<td>41</td>
<td>33 (80)</td>
<td>8</td>
<td>87</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Subtotal Colectomy</td>
<td>6</td>
<td>5 (83)</td>
<td>3</td>
<td>9</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Panproctocolectomy</td>
<td>5</td>
<td>5 (100)</td>
<td>0</td>
<td>13</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>470</td>
<td>203 (43)</td>
<td>64</td>
<td>468</td>
<td>532</td>
<td></td>
</tr>
</tbody>
</table>

Table 4.1: Transfusion rates for all ASA grades

<table>
<thead>
<tr>
<th>PROCEDURE</th>
<th>NO. PATIENTS</th>
<th>NUMBER (%) TRANSFUSED</th>
<th>Units</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Peri</td>
<td>Post</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Right Hemicolecotomy</td>
<td>78</td>
<td>28 (36)</td>
<td>9</td>
<td>13</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Extended Right Hemicolecotomy</td>
<td>24</td>
<td>10 (42)</td>
<td>18</td>
<td>51</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Transverse Colectomy</td>
<td>8</td>
<td>4 (50)</td>
<td>0</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Left Hemicolecotomy</td>
<td>30</td>
<td>8 (27)</td>
<td>1</td>
<td>16</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Sigmoid Colectomy</td>
<td>23</td>
<td>5 (22)</td>
<td>3</td>
<td>12</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Hartmann’s Procedure</td>
<td>11</td>
<td>8 (73)</td>
<td>0</td>
<td>16</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Anterior Resection</td>
<td>119</td>
<td>41 (34)</td>
<td>5</td>
<td>118</td>
<td>123</td>
<td></td>
</tr>
<tr>
<td>AP Resection</td>
<td>31</td>
<td>24 (77)</td>
<td>8</td>
<td>61</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Subtotal Colectomy</td>
<td>4</td>
<td>3 (75)</td>
<td>3</td>
<td>4</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Panproctocolectomy</td>
<td>5</td>
<td>5 (100)</td>
<td>0</td>
<td>13</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>333</td>
<td>136 (41)</td>
<td>47</td>
<td>310</td>
<td>357</td>
<td></td>
</tr>
</tbody>
</table>

Table 4.2: Transfusion rates for ASA grades 1 and 2
Discussion

The departmental transfusion rate identified is similar to other published data (table 4.3). In view of the fact colorectal surgery is a high allogeneic blood usage field, any technique capable of reducing transfusion rates would therefore have a significant impact.

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Number Patients</th>
<th>Transfused (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>Jensen\textsuperscript{18}</td>
<td>197</td>
<td>104 (53)</td>
</tr>
<tr>
<td>1994</td>
<td>Houbiers\textsuperscript{5}</td>
<td>697</td>
<td>446 (64)</td>
</tr>
<tr>
<td>1995</td>
<td>Vignal\textsuperscript{120}</td>
<td>161</td>
<td>86 (53)</td>
</tr>
<tr>
<td>1996</td>
<td>Jensen\textsuperscript{19}</td>
<td>589</td>
<td>260 (44)</td>
</tr>
<tr>
<td>1998</td>
<td>Edna\textsuperscript{121}</td>
<td>446</td>
<td>290 (65)</td>
</tr>
<tr>
<td>2000</td>
<td>Mynster\textsuperscript{122}</td>
<td>740</td>
<td>452 (61)</td>
</tr>
<tr>
<td>2002</td>
<td>Present Study</td>
<td>470</td>
<td>203 (43)</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>3300</td>
<td>1841 (56)</td>
</tr>
</tbody>
</table>

Table 4.3: Published transfusion rates in resections for colorectal cancer
Chapter 5: Patient Attitudes Towards An Allogeneic Transfusion

Introduction

Public opinion is a strong driving force. Although cost effectiveness is important in health science terms, a new technique is more likely to be adopted if there is positive public opinion. Likewise, if patient attitudes towards an allogeneic transfusion are largely negative, available alternatives are more likely to be favoured.

Aims

To assess patient's attitudes towards allogeneic transfusion and the alternative autologous techniques available.

Methods

Ethical approval was obtained from the Plymouth local research ethics committee. A questionnaire (figure 5.1) was administered to patients undergoing major gastrointestinal surgery, eligible for acute normovolaemic haemodilution (group 1). Verbal information was subsequently given regarding the risks of an allogeneic transfusion (transfusion reaction, increased infectious complications, transmission of disease, alloimmunisation) and the technique of ANH. The questionnaire was re-administered by telephone at 30 days post-operatively and again at 3 months. The same questionnaire was administered to an age and sex matched control group of patients (group 2), having operations highly unlikely to require an allogeneic transfusion. The same information regarding the risks of an allogeneic
transfusion and ANH was supplied and the questionnaire re-administered at 30 days.
Figure 5.1: PATIENT PREFERENCE SURVEY

In Derriford Hospital we are looking at patients' attitudes to blood transfusions. Please complete the following questionnaire.

1. Are you:-
   - Male ☐
   - Female ☐

2. Age:-
   - 18-25 ☐
   - 26-40 ☐
   - 41-60 ☐
   - 61-80 ☐
   - over 80 ☐

3. Occupation: ____________________________

4. Highest Educational Qualification: ____________________________

5. Have you had an operation before as an adult which meant an overnight stay in hospital?
   - Yes ☐
   - No ☐
   In which year? ____________

6. Have you ever been a blood donor?
   - Yes ☐
   - No ☐

7. Have you ever had a blood transfusion before?
   - Yes ☐
   - No ☐
   In which year? ____________

8. Would you refuse a blood transfusion on religious/moral/ethical grounds?
   - Yes ☐
   - No ☐
   If yes go to question 10

9. How willing would you be to accept a blood transfusion? (Tick one box)
   - Very willing ☐
   - Somewhat willing ☐
   - Not sure ☐
   - Not very willing ☐
   - Very Unwilling ☐

10. How safe do you think a blood transfusion is? (Tick one box)
    - Very safe ☐
    - Somewhat safe ☐
    - Not sure ☐
    - Not very safe ☐
    - Very unsafe ☐

11. Are you aware that there are Medical techniques, which may allow you to avoid a blood transfusion from another person.
    - Yes ☐
    - No ☐
12. Are you aware of any of the following techniques?
   - Pre op donation
   - Cell Saver
   - Haemodilution

Thank you for your time.
Results

165 patients were recruited, group 1 n=127, group 2 n=38. There were no significant differences between groups in baseline demographics/characteristics (table 5.1/5.2).

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (%)</th>
<th>Group 2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>77 (61)</td>
<td>22 (58)</td>
</tr>
<tr>
<td>female</td>
<td>50 (39)</td>
<td>16 (42)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-25</td>
<td>4 (3)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>26-40</td>
<td>2 (8)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>41-60</td>
<td>37 (29)</td>
<td>17 (44)</td>
</tr>
<tr>
<td>61-80</td>
<td>72 (57)</td>
<td>15 (40)</td>
</tr>
<tr>
<td>&gt;80</td>
<td>4 (3)</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>

Table 5.1: Baseline demographics

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>127</td>
<td>38</td>
</tr>
<tr>
<td>Previous surgery as adult %</td>
<td>84</td>
<td>72</td>
</tr>
<tr>
<td>Previous blood donation %</td>
<td>37</td>
<td>24</td>
</tr>
<tr>
<td>Previous transfusion %</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>Aware autologous alternatives %</td>
<td>17</td>
<td>16</td>
</tr>
</tbody>
</table>

Table 5.2: Baseline characteristics
The graphs below (figure 5.2) illustrate the percent of patients answering very or somewhat safe/willing in the 2 groups over the study period.

**Study Group**

- **Willing to Have Transfusion**
- **Safe to Have Transfusion**

<table>
<thead>
<tr>
<th>Questionnaire Intervals</th>
<th>% Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0</td>
<td></td>
</tr>
<tr>
<td>Day 30</td>
<td></td>
</tr>
<tr>
<td>3 Months</td>
<td></td>
</tr>
</tbody>
</table>

- **Study Group**
  - Day 0 to Day 30: \( p < 0.001 \)
  - Day 0 to 3 months: \( p < 0.001 \)
  - Day 30 to 3 months (willing): \( p = 0.003 \)

**Control Group**

- **Willing to Have Transfusion**
- **Safe to Have Transfusion**

<table>
<thead>
<tr>
<th>Questionnaire Intervals</th>
<th>% Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0</td>
<td></td>
</tr>
<tr>
<td>Day 30</td>
<td></td>
</tr>
</tbody>
</table>

- **Control Group**
  - Day 0 to day 30: \( p < 0.001 \)

**Figure 5.2:** Percent of patients answering very or somewhat safe/willing in the 2 groups
Figure 5.2: Percent of participants assigned to each study arm at the end.

- 0.001: Day 0 to Day 1
- 0.002: Day 1 to Day 3
- 0.003: Day 3 to Day 6
- 0.004: Day 6 to Day 9
- 0.005: Day 9 to Day 12

Control Group

*Note: Additional details or labels that are not fully visible or legible in the image.*
Conclusion

A majority of patients are willing to have an allogeneic transfusion (85%) and think it is safe (89%). Both education and undergoing major surgery coupled with a blood saving technique significantly effect attitudes, although the effect lessens with time. The lack of patient awareness of the risks of allogeneic transfusion has implications in terms of uptake of alternatives available.
Chapter 6: A Prospective Randomised Controlled Trial Of Intravenous Fluid Replacement During Bowel Preparation For Surgery

Introduction

Two sachets of Picolax® (Ferring Pharmaceuticals Limited, Middlesex, UK) are administered to patients for bowel preparation prior to colonic surgery in our Unit. Sodium picosulphate is hydrolysed in the colon to reduce water and electrolyte absorption while the magnesium citrate acts as an osmotic laxative. It had been our impression that a large number of patients receiving bowel preparation were dehydrated when they came to surgery. One of the principles of acute normovolaemic haemodilution, is that the patient is normovolaemic at all times.

This prospective randomised controlled study was designed to assess the effects of administering intravenous fluid during bowel preparation.

Methods

Patients receiving bowel preparation for colonic procedures were recruited. Group 1 was randomised by sealed envelope to receive no intravenous fluid while group 2 received a calculated volume of intravenous normal saline during bowel preparation, which commenced at the same time as taking Picolax (i.v. infusion rate per hr = 4mls/kg for the first 10kg + 2mls/kg for the second 10kgs + 1ml/kg for each subsequent kg). Both groups received two sachets of Picolax® six hours apart starting eighteen hours before their procedure and were encouraged to drink unlimited clear fluids until six hours before that time. The study received approval from the Plymouth local research ethics committee and patients were required to give informed consent for their inclusion.
Physiological (weight, pulse, supine and erect blood pressure) haematological (haemoglobin, haematocrit) and biochemical (sodium, potassium, urea, creatinine, urine osmolality) variables were measured immediately before administering bowel preparation and repeated one hour prior to their procedure or immediately before premedication. A sample size of twenty in each group was estimated based on finding a difference in weight between groups of 0.5kg with a standard deviation of 0.55\(^2\), power of 80% and significance level of 0.05. Weight was measured to the nearest half kg using a single Seca (Hamburg, Germany) analogue scale, which was checked annually by the Bristol Scales Company (Bristol, UK). Care was taken to ensure the same clothing was worn at both weighings. Blood pressure and heart rate were measured with the Dinamap Compact TS (Johnson & Johnson Medical Inc, Tampa, Florida, USA). Supine readings were taken after lying undisturbed for 30 minutes. Subsequent erect readings were taken two minutes after sitting or standing. In addition, total fluid intake and output, American Society of Anaesthetists (ASA) grade\(^2\), and weight of faeces were recorded. Fluid intake included oral and intravenous fluids.

Data was assessed for normality using the Shapiro Wilk test and subsequently analysed within groups and between groups using paired and unpaired t-tests as appropriate. A p<0.05 was taken as being significant.

**Results**

Forty-one patients were recruited with a median age 69 years (range 29-86), group 1 n=22, group 2 n=19. There were twenty six males and fifteen females. There was no difference between groups in baseline variables, age, sex, ASA grade, or diagnosis prior to bowel preparation and no evidence of non-normality in any of the variables studied (tables 6.1-6.3). On completion (table 6.2 and 6.3), there was a significant difference between groups in mean weight loss (p=0.01),
postural change in systolic pressure (p=0.015) and serum creatinine (p=0.008). In addition there was a significant difference within group 1 in weight loss (p<0.001), fall in erect systolic pressure (p=0.011) (graph 1), fall in erect diastolic pressure (p=0.023), and fall in supine diastolic pressure (p=0.005). Serum potassium concentration decreased significantly in groups 1 and 2, p=0.019 and p<0.001 respectively and supine pulse rate increased significantly in both groups p=0.046 and p=0.047 respectively. The mean difference in fluid input in the two groups was 2078ml. The mean urine output in group 1 was 982ml and group 2 1808ml (p=0.004) but the faeces weight was not significantly different (p=0.93) between groups (table 6.4).

<table>
<thead>
<tr>
<th>Group 1 (22)</th>
<th>Group 2 (19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>69 (29-86)</td>
<td>69 (34-85)</td>
</tr>
<tr>
<td>ASA</td>
<td></td>
</tr>
<tr>
<td>2 (1-3)</td>
<td>2 (1-2)</td>
</tr>
</tbody>
</table>

**Table 6.1:** Patient demographics (median and range)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Initial</th>
<th>Change</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>1</td>
<td>77.8 (3.9)</td>
<td>-1.6 (0.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>75.1 (3.1)</td>
<td>-0.5 (0.3)</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>0.72</td>
<td>0.011</td>
<td></td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>1</td>
<td>96.5 (6.0)</td>
<td>+1.8 (1.5)</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>91.6 (4.8)</td>
<td>-3.8 (1.3)</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>0.53</td>
<td>0.008</td>
<td></td>
</tr>
</tbody>
</table>

**Table 6.2:** Mean (SEM) change in variable before and after picolax
<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Initial</th>
<th>Final</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postural Pressure Drop* (mmHg)</td>
<td>1</td>
<td>-1.6 (3.4)</td>
<td>7.2 (4.0)</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>-2.9 (2.9)</td>
<td>-5.7 (3.1)</td>
<td>0.47</td>
</tr>
<tr>
<td>Erect Systolic Pressure (mmHg)</td>
<td>1</td>
<td>145 (3.8)</td>
<td>132 (6.5)</td>
<td>0.011</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>142 (4.5)</td>
<td>137 (5.2)</td>
<td>0.40</td>
</tr>
<tr>
<td>Erect Diastolic Pressure (mmHg)</td>
<td>1</td>
<td>84 (2.5)</td>
<td>77 (2.8)</td>
<td>0.023</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>84 (2.4)</td>
<td>80 (3.5)</td>
<td>0.30</td>
</tr>
<tr>
<td>Supine Diastolic pressure (mmHg)</td>
<td>1</td>
<td>81 (1.7)</td>
<td>75 (2.1)</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>79 (2.5)</td>
<td>79 (2.0)</td>
<td>0.95</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>1</td>
<td>4.4 (0.10)</td>
<td>4.1 (0.10)</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>4.4 (0.07)</td>
<td>4.1 (0.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Supine Pulse (bpm)</td>
<td>1</td>
<td>77 (2.8)</td>
<td>82 (2.5)</td>
<td>0.046</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>76 (2.6)</td>
<td>82 (3.4)</td>
<td>0.047</td>
</tr>
</tbody>
</table>

*Significant difference between groups after picolax p=0.015

**Table 6.3:** Mean (SEM) variable before and after picolax

<table>
<thead>
<tr>
<th></th>
<th>Total Fluids In (ml)</th>
<th>Urine Output (ml)</th>
<th>Faeces Weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>1669 (254)</td>
<td>982 (129)</td>
<td>1203 (182)</td>
</tr>
<tr>
<td>Group 2</td>
<td>3747 (359)*</td>
<td>1808 (253)</td>
<td>1183 (139)</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.001 (1269-2886)</td>
<td>0.004 (275-1377)</td>
<td>0.93</td>
</tr>
</tbody>
</table>

Total fluids includes oral and intravenous

*Mean IV input 2 litres; mean oral intake 1.7 litres

**Table 6.4:** Mean (SEM) fluid input, urine / faeces output
Discussion

Picolax bowel preparation has previously been shown to cause a significantly greater weight loss and increased haemoglobin concentration compared with a group of matched patients undergoing body surface surgery. Patients of ASA grade 3 were noted to feel faint on standing, after bowel preparation. Kutt et al also demonstrated an increase in haemoglobin concentration prior to barium enema examination. In addition there was a correlation between patients with a raised haemoglobin and those experiencing headache. In a retrospective study, Lee et al looked at peri and post-operative fluid requirements in patients undergoing in-patient versus outpatient bowel preparation. The in-patient group were given IV fluids overnight whereas the outpatient group commenced IV fluids one to two hours prior to surgery. Although there was a shorter length of stay in the outpatient group, they also had increased peri and post-operative fluid requirements.

Lawrance et al in a prospective randomised study looked at five different oral fluid regimens in 197 patients and found no difference in any of the groups with regard to adverse events. Hill et al demonstrated that patients with cellular potassium depletion were at risk of hypokalaemia after bowel preparation with sodium phosphate.

The current study confirms the dehydrating effect of Picolax® bowel preparation as measured by the decrease in weight, erect systolic, erect diastolic and supine diastolic pressures in group 1, and the significant difference in postural pressure change between groups. None of these variables changed significantly in group 2, signifying that the dehydrating effect was negated with the administration of intravenous saline. Interestingly, although both groups were encouraged to drink unlimited clear fluids during preparation, their oral intake was not significantly different (table 6.4). In both groups the serum potassium concentration decreased...
significantly. The supine pulse rate increased significantly in both groups implying a cause other than hypovolaemia.

In conclusion, Picolax® bowel preparation has significant clinical effects, which may be particularly detrimental in elderly or cardiovascularly compromised patients. Furthermore, the use of an epidural results in vascular dilatation amplifying any pre-existing hypovolaemia. It is therefore extremely important to correct these dehydrating effects prior to any venesection for haemodilution. This can be achieved by administering a simultaneous volume of intravenous fluid (mean 2 litres in this study). Consideration should also be given to potassium replacement.
Chapter 7: Acute Normovolaemic Haemodilution in Colorectal Surgery – A Pilot Study

Introduction

The aim of this pilot study was to assess whether ANH reduced exposure to allogeneic blood, affected clinical outcome and hospital stay, and is feasible in colorectal surgery.

Methods

The study received approval from the Plymouth local research ethics committee. All patients admitted for major colorectal surgery were screened for haemodilution eligibility (Hb>11g/dl, ASA 1 or 11) and informed consent obtained.

Standard pre-operative preparation included FBC, U&E, cross match according to procedure, ECG and CXR. Picolax® (Ferring Pharmaceuticals Ltd, Middlesex, UK) bowel preparation, if required, was administered the day before surgery. The resulting dehydration was minimised by administering two litres of N/Saline with 20mmol potassium intravenously over 12 hours, commencing in the evening, prior to surgery.

Haemodilution commenced in the anaesthetic room and continued in the operating theatre if needed. The volume of blood to be withdrawn (maximum 3 units), whilst maintaining the haemoglobin above 8g/dl, was calculated using a formula described by Gross (figure 7.1). A 14 gauge cannula was sited in either the external jugular vein or a large forearm vein. Extension tubing with a three way tap and rubber bung was connected which allowed access away from the surgical drapes. Standard blood bags containing anticoagulant citrate-phosphate-dextrose (CPD) were used to passively collect the blood. The bags were placed on scales on the floor and oscillated by hand during venesection to allow adequate mixing of
anticoagulant. Once filled, the blood bag tubing was clamped, the bag labelled and stored with the patient at room temperature in the operating theatre.

Warmed cell free fluid was administered via a second cannula during blood withdrawal to maintain normovolaemia. The first litre of blood withdrawn was replaced with 1 litre of gelofusine. Subsequent blood withdrawal was replaced with Hartmann’s at a ratio of 3 or 4:1. A Hemocue B-Haemoglobin photometer (Hemocue Ltd, Sheffield, UK) undergoing regular quality control checks was present in theatre to allow near patient haemoglobin testing.

The patient was monitored during the operation using standard equipment for the operation concerned. Minimum monitoring included continuous ECG, pulse rate and oxygen saturation. Radial artery catheters and central venous lines were used at the anaesthetist’s discretion. At the end of the operation, all the autologous blood was re-transfused. If, at the anaesthetist’s discretion, a patient required a transfusion prior to the completion of surgery, autologous blood was used prior to any allogeneic.

Haemoglobin, haematocrit, and clotting (APTT, INR) were measured before and after haemodilution, hourly through the procedure, and before and after re-transfusion.

Patients in the haemodilution group underwent standard postoperative care including adherence to a transfusion protocol (figure 7.1). Primary outcome measures included the number of patients transfused and the number of units transfused. Secondary outcome measures included time taken to venesect, complications and length of stay.
\[ V = EBV \times (H_O - H_F) \div H_{AV} \]

- \( H_O \) = initial haematocrit or Hb concentration
- \( H_F \) = target haematocrit or Hb concentration
- \( H_{AV} \) = average of haematocrits or Hb concentration
- \( EBV \) = estimated blood volume (70 ml/kg man, 65 ml/Kg woman)

**Figure 7.1**: Formula for Volume of Blood Withdrawn

<table>
<thead>
<tr>
<th>Haemoglobin</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10 g/dL</td>
<td>No Transfusion</td>
</tr>
<tr>
<td>8 – 10 g/dL</td>
<td>Transfuse if: Abnormal ECG or, Ischaemic Heart Disease or, Obstructive Lung Disease or, Consultant's Discretion or, Unable to absorb oral iron</td>
</tr>
<tr>
<td>&lt; 8 g/dL</td>
<td>Transfuse</td>
</tr>
</tbody>
</table>

**Figure 7.2**: Transfusion Protocol
Results

123 of 317 (39%) ASA 1 and 2 patients operated on between 1997 and 1999, and matched for type of operation, were transfused a total of 328 allogeneic units (median 2, range 1-7) (table 7.1).

Between October and December 1999, 26 of 55 (47%) patients screened for eligibility were recruited for ANH. 18 male and 8 female patients with a median age of 58 years (range 34-75) underwent operations (table 7.1). Five patients were venesected 3 units, twenty 2 units, and one had one unit. Four of the twenty six patients (15%) were transfused a total of thirteen allogeneic units (median 3, range 2-5). The reduction in the number of patients transfused from 123/317 (39%) to 4/26 (15%) was statistically significant p=0.017 (Chi square). Haemodilution increased anaesthetic time by a median of 19 minutes (range 9-40). There were no post operative complications in the ANH group and no significant alterations in clotting during haemodilution. The median length of stay was 9 days (range 6-13).

| Procedure | Non-haemodiluted | | | Haemodiluted | | | |
|-----------|-----------------|----------------|----------------|-----------------|----------------|----------------|
| No. Patients | No. T* (%) | Total Units | No. Patients | No. T* (%) | Total Units | |
| Right / Ext Right Hemicolecotmy | 110 | 42 (38) | 97 | 1 | 0 | 0 |
| Left Hemicolecotmy | 53 | 13 (25) | 32 | 6 | 0 | 0 |
| Anterior Resection | 119 | 41 (34) | 123 | 13 | 3 (23) | 11 |
| AP Resection | 31 | 24 (77) | 69 | 4 | 1 (25) | 2 |
| Subtotal Colectomy | 4 | 3 (75) | 7 | 2 | 0 | 0 |
| TOTAL | 317 | 123 (39) | 328 | 28 | 4 (15) | 13 |

* Number patients transfused (%)

Table 7.1: Allogeneic blood usage in non-haemodiluted and haemodiluted patients
Discussion

47% of patients screened were eligible for ANH. The majority were excluded because of anaemia and co-morbid disease. However, in this pilot study of selected patients ANH is a feasible and effective method of reducing allogeneic blood exposure in major colorectal surgery. Although the control group was matched for ASA grade and operation, it remains historical. A prospective randomised controlled trial is now urgently required.
Chapter 8: Acute Normovolaemic Haemodilution in Gastrointestinal Surgery – A Prospective Randomised Controlled Trial

Aim

The aim of this study was to define the role of acute normovolaemic haemodilution in gastrointestinal surgery in terms of its potential as a blood saving technique, and the effects on clinical outcomes and hospital stay.

Methods

The study received approval from the Plymouth local research ethics committee. All patients under the care of the twelve participating surgeons admitted for major colorectal, gastric or pancreatic surgery were screened for eligibility. Absolute exclusion criteria included Hb<11g/dl, age<18 years, and blood or blood products in the preceding four weeks. Exclusion criteria at the investigators’ and/or anaesthetists’ discretion included abnormal ECG, ischaemic heart disease, obstructive lung disease, renal disease, hypertension, abnormal liver function and coagulation abnormality. Informed consent was obtained and the patient remained blinded to treatment allocation throughout the study period. Refer to chapter 7, page 66 for further method details.

Oropharyngeal temperature was measured at knife to skin and again at the end of the operation. Blood loss was estimated by swab weight, suction volumes and surgeon / anaesthetists estimates. Patients underwent standard postoperative care including adherence to a standard transfusion protocol105 (figure 8.1). Urine output was measured hourly for at least 24 hours. Oliguria was defined as urine output < 30ml/hr. Full blood count and urea and electrolytes were measured at 24
and 48 hours with the former measured again at discharge and 30 days. Patients were followed up at 30 days, 3 months and 6 months by telephone.

Primary outcome measures included the number of patients transfused and the number of units transfused. Secondary outcome measures included time taken to venessect, complications and length of stay.

A sample size of \( n=80 \) was calculated based on reducing allogeneic blood exposure from 41% (transfusion rate for ASA 1 and 11 patients undergoing colectomy surgery from 1997 to 1999 inclusive) to half, 20.5%, with a two tailed power of 80% and significance level of 0.05. Randomisation was by medium sized variable blocks and obtained by telephone to a distant centre.

Continuous data was analysed using the Student t test or Mann Whitney U depending on the distribution of the data. Proportional data was analysed using the chi-squared and Fishers exact test. All analysis was performed on an intention to treat basis with a \( p<0.05 \) taken as being significant. Logistic regression was used to identify factors associated with the need for a transfusion. The model was built in stages and factors significant at the 10% level were retained. Interactions among variables were examined.

Pyrexia was defined as a temperature of greater than 37.5 °C over a period of 48 hours on two or more occasions, with negative urine, wound, sputum and blood cultures and requiring antibiotics. Wound infection was defined as an accumulation of pus with spontaneous discharge or requiring surgical drainage and was graded as minor or major. Cellulitis with associated pyrexia and raised white cell count was regarded as minor. Deep infection was defined as pelvic or intraperitoneal infection as diagnosed by imaging or laparotomy. Septicaemia was defined as positive blood cultures in association with swinging high pyrexia. Chest infection was defined as productive cough, pyrexia and abnormal CXR. Urinary tract
infection was defined as a positive culture > 1000 organisms / ml with associated pyrexia.

<table>
<thead>
<tr>
<th>Haemoglobin</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10g/dL</td>
<td>No Transfusion</td>
</tr>
<tr>
<td>8 – 10 g/dL</td>
<td>Transfuse if: Abnormal ECG or, Ischaemic Heart Disease or, Obstructive Lung Disease or, Consultant’s Discretion or, Unable to absorb oral iron</td>
</tr>
<tr>
<td>&lt; 8g/dL</td>
<td>Transfuse</td>
</tr>
</tbody>
</table>

Figure 8.1: Transfusion Protocol

Results

During an eighteen month period, 316 consecutive patients were screened of which 160 (51%) were eligible, ANH n=78, no ANH n =82. The median age was 62 years (range 23-90) and 84 were male, 76 female. There was no difference between groups in age, sex, weight, starting haemoglobin, type of operation, duration of operation and blood loss. There was a statistically significant difference between the groups in both pre-operative and post-operative temperature (p<0.01) (table 8.1), however the difference in median temperatures was 0.1 °C and 0.3° C respectively.

There was no significant difference between groups in the number of patients receiving allogeneic blood 23/78 (29%) versus 25/82 (30%), or the total number of allogeneic units transfused (92 versus 93). The number of patients transfused
perioperatively or in recovery in the two groups were 15/78 and 20/82. Postoperatively, days 1-3, 9/78 and 8/82 were transfused (table 8.2). The type of operation performed and transfusion rates are shown in table 8.3.

The most significant factors affecting transfusion were blood loss, starting haemoglobin and age (table 8.4, figure 8.2-8.4). In the ANH group, the allogeneic transfusion rate was lower in those patients with an estimated blood loss of >750ml (16/42 versus 24/46, p=0.185), but higher in those patients with an estimated blood loss of <750ml (7/36 versus 1/36, p=0.055) (table 8.2). A test for interaction as to whether there was a difference in effect between high and low blood loss groups was marginally significant (Chi square p=0.007).

When compared with ASA matched historical controls, the introduction of a transfusion protocol reduced the transfusion rate in the colorectal patients from 136/333 (41%) to 38/138 (28%), p=0.006.

There was no significant difference in the transfusion triggers in each group (table 8.5). However, in 6 patients, 3 in each group, the transfusion protocol was violated and transfusion occurred postoperatively with a haemoglobin > 8d/l.

There was no significant difference in haemoglobin levels between groups throughout the study period (table 8.6). In addition, there was no significant difference in pre-operative and day 2 calculated (figure 8.5) RBC loss (ANH 614ml SD 427, no ANH 616ml SD 451). The median lowest intra-operative pre autologous transfusion haemoglobin in patient's haemodiluted was 7.7 g/dl (4.8-11).

Venesection lasted a median of 30 minutes (10-70), and significantly increased anaesthetic time, median 55 minutes (range 15-90) versus 40 minutes (range 17-80) (p<0.001). Significantly fewer patients in the ANH group experienced oliguria in the immediate post-operative period 37/78 (47%) versus 55/82 (67%) (p=0.012).
There was no significant difference in complication rate in the 2 groups (table 8.7), however the complication rate was significantly greater in patients who received allogeneic blood compared with those who did not, 16/48 (33%) versus 20/112 (18%) (p=0.03).

There was no significant difference in the number of postoperative days stay in the 2 groups, median 8 (5-110) versus 10 (5-92), ANH and no ANH respectively.
<table>
<thead>
<tr>
<th></th>
<th>ANH (78)</th>
<th>Control (82)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
<td>43</td>
<td>35</td>
</tr>
<tr>
<td>Female</td>
<td>74 (14)</td>
<td>73 (15)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62 (23-85)</td>
<td>62.5 (24-90)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74 (14)</td>
<td>73 (15)</td>
</tr>
<tr>
<td>Starting Hb (g/dl)</td>
<td>13.5 (1.2)</td>
<td>13.5 (1.3)</td>
</tr>
<tr>
<td>Duration operation (hr:min)</td>
<td>1:53 (0:45-5:20)</td>
<td>1:55 (0:15-5:08)</td>
</tr>
<tr>
<td>Blood Loss (ml)</td>
<td>750-1000 (100-4500)</td>
<td>750-1000 (100-4368)</td>
</tr>
<tr>
<td>*Temp start (°C)</td>
<td>35.7 (34.7-36.8)</td>
<td>35.8 (35.0-36.7)</td>
</tr>
<tr>
<td>*Temp end (°C)</td>
<td>35.5 (33.9-37.1)</td>
<td>35.8 (34.5-36.9)</td>
</tr>
<tr>
<td>**Fluid Input (ml)</td>
<td>4500 (2000-11000)</td>
<td>3500 (1100-9000)</td>
</tr>
<tr>
<td>**GA Time (min)</td>
<td>55 (15-90)</td>
<td>40 (17-80)</td>
</tr>
<tr>
<td>Venesection Volume (ml)</td>
<td>1350 (0-1454)</td>
<td></td>
</tr>
</tbody>
</table>

Results in median (range) except weight and starting Hb mean (sd)
*p<0.01
**p<0.001

Table 8.1: Patient demographics and baseline measures

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Blood loss &lt; 750ml</th>
<th>Blood loss &gt; 750</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Day 0</td>
<td>Day 1-3</td>
</tr>
<tr>
<td>ANH Patients %</td>
<td>23/78</td>
<td>15/78</td>
<td>9/78</td>
</tr>
<tr>
<td>Units</td>
<td>92</td>
<td>52</td>
<td>26</td>
</tr>
<tr>
<td>Median (range)</td>
<td>3 (2-14)</td>
<td>3 (2-8)</td>
<td>3 (2-4)</td>
</tr>
<tr>
<td>CORT Patients %</td>
<td>25/82</td>
<td>20/82</td>
<td>8/82</td>
</tr>
<tr>
<td>Units</td>
<td>93</td>
<td>56</td>
<td>22</td>
</tr>
<tr>
<td>Median (range)</td>
<td>3 (1-16)</td>
<td>2 (1-5)</td>
<td>3 (2-4)</td>
</tr>
</tbody>
</table>

Table 8.2: Transfusion rates by timing of transfusion and blood loss
<table>
<thead>
<tr>
<th></th>
<th>ANH (78)</th>
<th>Control (82)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Transfused</td>
</tr>
<tr>
<td></td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>Right hemicolectomy</td>
<td>8</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td>Left hemicolectomy</td>
<td>23</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Rectum</td>
<td>33</td>
<td>16 (48)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>4</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Panproctocolectomy</td>
<td>0</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Whipples</td>
<td>3</td>
<td>2 (67)</td>
</tr>
<tr>
<td>Gastrectomy</td>
<td>3</td>
<td>2 (67)</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>2 (50)</td>
</tr>
</tbody>
</table>

Others: 2 gastroenterostomies, 2 division adhesions, 1 biopsy pancreas, 1 stricturoplasty, 1 excision sarcoma (left abdomen)

Table 8.3: Type of operation and transfusion rate:

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin / g/dl increase</td>
<td>160</td>
<td>0.43</td>
<td>0.28 – 0.65</td>
</tr>
<tr>
<td>Blood loss</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤500</td>
<td>45</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>501-1000</td>
<td>39</td>
<td>4.17</td>
<td>0.91 – 18.91</td>
</tr>
<tr>
<td>1001-1500</td>
<td>43</td>
<td>13.37</td>
<td>3.22 – 55.54</td>
</tr>
<tr>
<td>&gt;1500</td>
<td>33</td>
<td>54.76</td>
<td>11.54 – 259.82</td>
</tr>
<tr>
<td>Age / year increase</td>
<td>160</td>
<td>1.03</td>
<td>1.00 – 1.07</td>
</tr>
</tbody>
</table>

Table 8.4: Multivariate logistic regression model for transfusion

Figure 8.2: Graph showing the estimated relationship between pre-operative haemoglobin and the probability of transfusion by blood loss for a patient aged 82 (median)
Figure 8.3: Graph showing the estimated relationship between pre-operative haemoglobin and the probability of transfusion by blood loss for a patient aged 53 (lower quartile of age distribution)

Figure 8.4: Graph showing the estimated relationship between pre-operative haemoglobin and the probability of transfusion by blood loss for a patient aged 70 (upper quartile of age distribution)
Table 8.5: Allogeneic transfusion triggers

<table>
<thead>
<tr>
<th></th>
<th>ANH</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb Trigger Day 0 (g/dl)</td>
<td>7.1 (4.8-8.6) n=14/15</td>
<td>7.4 (5.2-12.2) n=9/9*</td>
</tr>
<tr>
<td>Hb Trigger Day 1-3 (g/dl)</td>
<td>7.5 (4.7-8.0) n=9/20</td>
<td>7.7 (7.2-9.8) n=8/8**</td>
</tr>
</tbody>
</table>

*3 out of 9 patients transfused with trigger > 8 (9.8, 9.9, 12.2)
**3 out of 8 patients transfused with trigger > 8 (8.3, 8.5, 9.8)

Table 8.6: Haemoglobin variation during study period

<table>
<thead>
<tr>
<th></th>
<th>ANH</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb Day 1 (g/dl)</td>
<td>10.5 (6.0-15.4) 74</td>
<td>10.8 (7.2-15.0) 76</td>
</tr>
<tr>
<td>Hb Day 2 (g/dl)</td>
<td>10.8 (6.9-14.9) 67</td>
<td>10.4 (7.5-15.0) 69</td>
</tr>
<tr>
<td>Hb Discharge (g/dl)</td>
<td>11.8 (8.4-14.7) 75</td>
<td>11.7 (8.7-14.9) 73</td>
</tr>
<tr>
<td>Hb Day 30 (g/dl)</td>
<td>12.4 (9.2-16.0) 64</td>
<td>12.3 (7.5-14.8) 65</td>
</tr>
</tbody>
</table>

RBC loss = (EBV * (Hct₀-Hct₂)) + (250 * number units transfused by day 2)

EBV = estimated blood volume (70 ml/kg man, 65 ml/Kg woman)

Figure 8.5: RBC Loss$^{49,61}$
### Complications by transfusion:

1) **Number complications**
   - **Transfused (24/48)**
   - Not transfused (21/112)
   - \( p = 0.049 \) (Chi square)

2) **Number of patients with complications:**
   - **Transfused** \( 12*1, 1*2, 2*3, 1*4 = 16 \) patients/48
   - **Not Transfused** \( 19*1, 1*2 = 20 \) patients/112
   - \( p = 0.032 \) (Chi square)

### Complications by Group:

1) **Number of complications**
   - ANH 19/78
   - No ANH 26/82

2) **Number of patients with complications:**
   - **ANH**: \( 11*1, 2*2, 1*4 = 14 \) patients/78
   - **Control**: \( 20*1, 2*3 = 22 \) patients/82
   - \( p = 0.179 \)

**Table 8.7**: Complications by group and by presence of transfusion
Discussion

51% of 316 patients screened were eligible for ANH. A majority were excluded because of co-existing medical disease or a pre-operative haemoglobin <11g/dl (44). Two patients were excluded because of HIV. A further 64 were eligible, but excluded because of lack of trial staff (48), refusal to enter the study (9), and no access/time to randomise (7). Therefore true eligibility, if the technique were to be adopted, would be 59% (224/380).

The number of patients receiving allogeneic blood and number of units transfused in the 2 groups were virtually identical (29% and 30%, 92 and 93 units). It is interesting to observe the transfusion rates in the 2 groups, broken down by blood loss (table 8.2), as mathematical modelling has shown that it is procedures with significant blood loss that are likely to benefit. In those patients with a blood loss of > 750ml, fewer were transfused in the ANH group (16/42 compared with 24/46), compared to greater number of patients transfused in the ANH group when the blood loss < 750ml (7/36 compared with 1/36). The dilutional effect can result in "falsely" diluted haemoglobin levels thereby triggering transfusion when it is not required. This point has been realised by other authors. If the ANH group were significantly over transfused when the blood loss was < 750ml, one would expect the haemoglobin levels postoperatively to have reflected this. However, the haemoglobin levels in each group on days 1, 2, discharge and 30 (table 8.6) were also virtually identical as was the calculated RBC loss. It remains possible that in high blood loss groups, haemodilution does marginally reduce allogeneic transfusion, and our subgroup is underpowered to show this.

Logistic regression identified 3 factors which affect transfusion; starting haemoglobin, blood loss and age, which concurs with previous studies. 29% of the 154 patients excluded were so because of a starting haemoglobin of <11g/dl. Looking at the entire study population (380 patients), 29% had a starting
haemoglobin <12g/dl and 47% <13g/dl. These figures imply that pre-operative boosting of haemoglobin level may be of use in decreasing allogeneic transfusion.

The introduction of a transfusion protocol significantly reduced our unit's transfusion rate from 41% to 28%, illustrating that the presence of a transfusion protocol will reduce transfusion rates, thereby explaining the large allogeneic savings seen in studies with historical controls.

The median volume of blood venesected was 1350ml (0-1454). 11 patients had less than 800ml venesected; 5 had no blood venesected, 4 due to failed IV access and the other due to consultants decision in theatre (listed for major operation, minor performed). In total 56/78 (72%) patients had the desired > 1000ml venesection. The main reasons for failure included poor venous access resulting in low flow or clot formation in the tubing, and anaesthetist discretion preventing further venesection. Excluding those patients with < 1000ml venesection from analysis, again resulted in no significant difference in transfusion rates 14/56 (25%) versus 25/82 (30%).

Haemodilution increased anaesthetic time by a median of 15 minutes, despite haemodiluting during insertion of epidurals, urinary catheters and draping the patient. This delay would have cost implications, if the technique were to be adopted.

Although there was no significant difference in complication rate between groups, there was a significantly increased complication rate in those patients who received allogeneic blood. This occurred despite the use of leucocyte depleted allogeneic blood. It is still unclear whether it is the events necessitating transfusion, rather than transfusion itself exerting an effect.

The Haemocue may have had an effect on transfusion rate, as demonstrated in other studies.
In conclusion, in this, the largest study performed in the past 25 years, ANH did not affect allogeneic transfusion rate, complication rate or length of stay in major gastro-intestinal surgery. Pre-operative haemoglobin, blood loss and transfusion protocol are the key factors influencing allogeneic transfusion.
Chapter 9: The Effects of Surgery And Acute Normovolaemic Haemodilution On Coagulation As Measured By The Thromboelastogram

Introduction

Replacement of a proportion of blood volume with crystalloid or colloid may have an effect on haemostasis. However, what this effect is and the degree of haemodilution at which it occurs is unknown. Furthermore, surgery in conjunction with blood loss, may also affect coagulation, by activation of coagulation and fibrinolysis with concomitant consumption of coagulation factors.

There are a number of methods to quantify the hypothesised effect. The most important effect on haemostasis (the one which will affect the adoption of ANH as a technique) is clinical. If haemostasis is suppressed then total blood loss (at operation and ongoing) would be increased, blood requirement increased and relative Hb may be lower. If ANH resulted in a hypercoagulable state, the incidence of DVT’s would be increased. Other tests of coagulation that could indicate an effect include PT (prothrombin time), APTT (activated partial thromboplastin time), platelet count, fibrinogen, antithrombin, the activation markers for coagulation F(1+2) and TAT (specific markers for intravascular thrombin formation), and the markers of fibrinolysis (D Dimer - specific marker for reactive degradation of cross linked fibrin), PAP (plasmin alpha2 antiplasmin – reflects the amount of generated plasmin in the circulation) and the thromboelastogram (TEG).

Normal Haemostasis (figure 9.1)

The physiological initiation of coagulation is the complex of TF (tissue factor) with factor VIIa. Minute concentrations of TF.VIIa complex initiate explosive thrombin...
Chapter 6. The Effect of Summary and Scenario Interaction on The Perception of Comprehension of the Reader by the Author.
generation after a lag phase. During the lag phase, low amounts of Xa are generated by direct activation. This Xa activates a small amount of V, allowing the formation of the prothrombinase complex Xa.Va and generating low amounts of thrombin. This thrombin then feeds back to activate all the V to Va and all the VIII to VIIIa. Note that activation releases factor VIII from its inactive complex with vWF. Meanwhile, small amounts of IX have been activated to IXa by TF.VIIa. At this point, maximal amounts of tenase complex VIIIa.IXa and prothrombinase complex Xa.Va have formed and prothrombin conversion proceeds explosively.

Solid arrows = change of state; Dotted arrows = proteolytic activation / deactivation; Bold = complexes

Figure 9.1: The network of haemostasis

85
Thromboelastogram (TEG)

The TEG is a graphic method of displaying the stages in the formation of a whole blood clot and therefore provides a visual pattern of functional clotting status. It was first developed by Hartert in 1948, but remained largely a research tool until recently, when the search for a quick useful bedside test of coagulation coupled with improved computer systems, rediscovered the value of TEG.

The TEG has as its core two mechanical parts (fig 9.2): a cuvette and a piston. Blood is placed in the cuvette which oscillates through 4°45′ at 37° C. The piston is suspended in the blood sample by a torsion wire which is transduced to a chart recorder. When no clot exists, the motion of the pipette does not affect the piston, and the chart records a straight line. As strands of fibrin form they attach to the piston which becomes coupled to the motion of the cuvette. The transduced image therefore represents the shearing elasticity of the evolving blood clot.

The TEG pattern is divided into component variables (fig 9.3). Reaction time (r) is the interval between the start of recording and the time at which the amplitude of the trace is 2mm. It reflects the function of the intrinsic clotting pathway and initial fibrin formation. Coagulation time (r and k) is the time required for the amplitude to reach 20mm; this provides information on not only the intrinsic factors but also platelets and fibrinogen. The clot formation rate is represented by the alpha angle. The maximum amplitude (MA) is the greatest amplitude achieved on the TEG and is a measure of clot strength and elasticity.

Whole blood samples can be analysed immediately (within 4 minutes of sampling to prevent missing the onset of coagulation) or stored in citrate at room temperature and analysed between 30 and 90 minutes after reconstitution with calcium. Activation with celite speeds up the coagulation process.
Fig 9.2: Thrombelastograph® Coagulation Analyser (TEG®)

Coagulation Index: +2.52
Normal Range: -3.0 to +3.0

Fig 9.3: TEG Trace
Literature Review

A number of studies have been performed looking at the effect of haemodilution. The difficulty is extrapolating the results from an in vitro setting, to in vivo, to surgery itself and surgery in the presence haemodilution. It is this final situation which is clinically relevant, although the steps along the way provide valuable insight into the processes occurring.

In vitro studies

Ruttmann et al\(^{135}\) (no celite activation) showed a decrease in r time and k time, and increase in alpha angle, with in-vitro dilution of blood using N/Saline or Haemaccel as compared with control. The MA increased in the saline treated group but remained unchanged in the Haemaccel group. They concluded that the changes of hypercoagulability are induced by haemodilution itself rather than the properties of the diluent, although saline haemodilution has a more marked effect on final clot strength.

Mardel et al\(^{136-138}\) demonstrated a decrease in in-vitro clot weight and strength (MA) with increasing dilutions of both Haemaccel and Gelofusine, compared with the same dilutions with saline or Ringer’s. Scanning electron microscopy showed a reduction in cross linkage with the colloids compared with dilution with saline, or controls from undiluted blood. They hypothesised that this effect could be due to gelatin binding to fibronectin, as demonstrated by other authors\(^{139,140}\). They therefore endorsed Ruttmann et al’s\(^{135}\) suggestion that in vivo studies need to take place. Unfortunately, at this stage Mardel and colleagues did not know that saline led to hypercoagulation which was therefore not a true control. It is possible that
the changes they observed were an increase in clot weight and strength with saline. Their findings will therefore not be included in the final summary.

Egli et al.\textsuperscript{141} looked at the effects in vitro of hydroxyethyl starch 200 000/0.5 (HES), succinylated gelatin (Physiogel 4%), and 5% human albumin solution on coagulation. Blood samples from 96 patients were allocated randomly to one of six groups, to be haemodiluted to 30% or 60% by each of the 3 volume expanders. Blood coagulation was simultaneously assessed in native blood, after haemodilution with one of the above, and also after haemodilution to the same degree with N/Saline, with celite activation. Compared with native blood progressive haemodilution with any of the plasma expanders did not affect $t$ time, but did increase $k$ and decrease the alpha angle. This was significant at 30% haemodilution with HES, but only at 60% with the other 2. The clot strength was decreased in all plasma expander groups at 30% and 60% haemodilution as measured by a decrease in MA. Saline haemodilution resulted in a decrease in $r$ and $k$, and increase in alpha angle at 30% haemodilution. At 60% all 3 variables recovered. MA decreased significantly at 60% haemodilution. They concluded that blood coagulation is compromised by in vitro haemodilution with all 3 plasma expanders. In addition, moderate haemodilution with crystalloids appeared to augment in vitro coagulation, in keeping with other studies\textsuperscript{135,142}. The study by Ruttman et al.\textsuperscript{135} showing a hypercoagulable state at 20% haemodilution with gelatin, was not observed in this study at 30% haemodilution; on the contrary, at 60% haemodilution coagulation was impaired (prolonged $r$ and $k$ time, increase in alpha angle, decrease in MA), indicating that the degree of haemodilution may be crucial.
Petroianu et al\textsuperscript{143} looked at dilutions of blood 10:2, 10:4, and 10:10 in vitro with varying types of gelatin solutions, dextrans and hydroxyethyl starch (HES) preparations. Samples were citrated and analysed within 4 hours of sampling after activation with celite. They found that coagulation was compromised when the dilution ratio of blood volume to colloid solution $>10:4$. Gelatin solutions had less effect on blood coagulation than either HES or dextran.

Nielsen et al\textsuperscript{144} tested the hypothesis that haemodilution (ANH to 75\%) and the fluid administered would adversely alter the TEG in Rabbits. Fluids used included 6\% hetastarch in 0.9\% NaCl, 5\% HAS in 0.9\% NaCl, balanced electrolyte solution containing either 6\% pentastarch or 6\% hetastarch. In vitro ANH resulted in a significant decrease in haemostatic function (increase in $r$ time, decrease in alpha angle and MA), largest after ANH with albumin. The in vivo effects, in rabbits anaesthetised but not undergoing surgery, were that of a decrease in $r$ time, increase in alpha angle and decrease in MA (accelerated clot formation with reduced strength) there were no significant fluid dependent effects. They concluded that the effects of ANH and the fluid used were markedly different between in vitro and in vivo ANH studies, with only the in vitro study demonstrating fluid specific effects.

In vitro studies summary

The crystalloids appear to result in hypercoagulation: N/Saline causes hypercoagulation (decrease in $r$ and $k$, increase in alpha angle, increase in MA)\textsuperscript{135}. N/Saline causes a hypercoagulable state at 30\% dilution with a decrease in $r$, decrease in $k$, and increase in alpha angle\textsuperscript{141}. However, at 60\% dilution, these figures revert to normal and the MA decreases\textsuperscript{141}.
The colloids tend to result in hypocoagulation, except for this first study: Haemaccel causes hypercoagulation (decrease in r and k, increase in alpha angle). Gelatin, HES and 5% human albumin solution cause a hypocoagulable state with an increase in k, decrease in alpha angle and decrease in MA at 60% dilution with all three, and 30% dilution with HES. Gelatin, dextrans and HES result in compromised coagulation when the dilution > 10:4. Hetastarch and HAS result in a significant decrease in haemostatic function.

An interesting finding by Nielsen et al. was the lack of correlation between the in vivo and in vitro dilutional effects. In vivo they found accelerated clot formation with a reduced strength, drawing into question the validity of a number of the studies performed in vitro.

In Vivo studies

Ruttman et al. administered 1000ml of either N/Saline or HES intravenously over 30 minutes to healthy volunteers, using the native TEG for analysis. They found a significant reduction in fibrinogen and AT111 in both groups. In the saline group there was significant shortening of the r and k times, increase in alpha angle and MA. HES decreased the MA but did not otherwise affect the TEG. They concluded that haemodilution exerted a procoagulant effect. The effect with HES was offset by its antiplatelet action as shown by platelet aggregometry.

The in-vivo study did not involve surgery or anaesthesia therefore lending good support to the argument that it is the IV fluid itself which causes the effect. They confirmed that the effect was not due to acid-base or electrolyte composition of the diluent fluid.

Ng et al. studied 20 patients undergoing major hepatobiliary surgery randomised into 2 groups; ANH (30% blood volume replacement with saline) and control. ANH
began after induction of anaesthesia and all samples were taken prior to the start of surgery. Samples were processed as whole blood (no citrate) and not activated with celite. The haemodiluted group showed significant shortening of r time and k time, and widening of alpha angle when compared with control. AT 111 and other natural procoagulants and anticoagulants closely followed the haematocrit with the exception of TAT, indicating that a disproportionate reduction in anticoagulants is not the mechanism. They concluded that in vivo haemodilution with saline can cause a hypercoagulable state.

In vivo studies summary
The crystalloids again appear to result in hypercoagulation. N/Saline causes a decrease in r, decrease in k, increase in alpha angle, increase in MA\textsuperscript{145}. N/Saline results in a decrease in r and k times, and increase in alpha angle\textsuperscript{147}. The colloids again appear to cause a hypocoagulable state, although only one has been studied: HES causes a decrease in MA, although this decrease may be due to its antiplatelet action\textsuperscript{145}.

Surgery studies
Tuman et al\textsuperscript{148} looked at the effect of progressive blood loss on coagulation in 87 adults, undergoing a variety of operations, using the TEG (whole, uncitrated blood). Patients were given crystalloid solution as replacement for ongoing blood loss, with packed red cells administered if blood loss exceeded 35% estimated blood volume (EBV). With blood losses up to 15% EBV, TEG parameters revealed a hypercoagulable state (decrease in r and k, increase in alpha angle and MA). 8 patients had blood losses of >50% EBV. Of these, 6 showed signs of progressive hypercoagulability. The remaining 2 showed a marked reduction in MA by the time 10 units of packed cells had been given, implying a probable deficit in platelet
function. Subsequent platelet transfusion resulted in dramatic improvement in the MA.

Ng et al. studied 21 Chinese patients undergoing a wide variety of "general surgery" with an anticipated blood loss of up to 20% blood volume. Blood loss was replaced with N/Saline. They took samples immediately after induction and then every hour until the end of surgery, analysing them with the TEG without celite activation. They showed the progressive development of a hypercoagulable blood state with increasing amounts of surgical blood loss and replacement with N/Saline as demonstrated by shortening of the r and k times, increase in the alpha angle. Splitting their patients into 2 groups based on degree of blood loss, showed that the group with greater blood loss (therefore greater haemodilution) had significantly shortened r and k times and increased alpha angle. The correlation with blood loss and subsequent haemodilution with saline decreases the possibility that it is the surgical stress causing the effect. In addition, there was no further change in coagulation when Hb fell from 90% to 85% of pre-operative level which might suggest a dilutional hypocoagulable state was evolving.

Karoutsos et al. randomised patients undergoing total hip or knee replacement to receive one of 3 plasma expanders to replace surgical blood loss; 3.5% modified gelatin solution (molecular weight 35 000 DA), 6% low molecular weight hydroxyethyl starch or 5% albumin solution. They showed that IV gelatin plasma expanders resulted in a hypercoagulable state as measured immediately post surgery with the native TEG. They demonstrated a decrease in r, decrease in r+k, and increase in alpha angle. Interestingly, the MA (maximum amplitude) was normal, indicating normal clot strength. Despite these changes in the TEG, no clinically significant change in standard tests of haemostasis was observed. All
patients, however, were also involved in pre-op donation, and, cell salvage was used in some.

Huttner et al\textsuperscript{150} assessed the effects of perioperative volume replacement with different colloids (4% gelatine, low and medium molecular weight HES) on haemostasis in 60 patients undergoing major abdominal surgery. Ringer lactate was given to all three groups. Measurements included APTT, platelet count, fibrinogen, F1+2 (marker of thrombin generation), TAT 111 (marker of thrombin neutralisation), D-Dimer (marker of fibrin formation and degradation), vWF (marker of endothelial injury), platelet function. Intraoperative blood loss was approximately 910ml to 960ml in the 3 groups. Colloid infusion volumes varied from 1880ml to 2250ml by the time surgery was completed. They found no significant difference in blood loss between groups. F1+2, TAT 111, D-Dimer all increased significantly during and after surgery, with no difference between groups. vWF also increased in all groups, showing the significantly highest increase in the gelatine treated group. Platelet function remained within normal range and without group difference. They went on to comment that in vitro studies neglect the surgical effect of activating coagulation, hence the discrepancies.

**Surgery studies summary**

Crystalloids lead to a hypercoagulable state\textsuperscript{148}. N/Saline leads to a decrease in r and k times and increase in alpha angle, the changes correlating with the degree of blood loss. However no further change was seen when the Hb fell from 90\% to 85\% of preoperative level\textsuperscript{142}.

Gelatin results in a hypercoagulable state with a decrease in r, decrease in r+k, and increase in alpha angle, with no changes seen with HES or HAS\textsuperscript{149}.

Surgery activates coagulation factors\textsuperscript{150}.
ANH studies

Kramer et al.\textsuperscript{151} performed ANH in 30 patients to a mean haematocrit of 25% for major vascular reconstruction. Venesected blood was replaced with 1.5 volumes of colloid and crystalloid. They noted an increase in PT from a mean of 12 to 15.5 seconds, APTT from a mean of 30 to 60 seconds, a decrease in platelets from 250 to $175\times10^9/L$, and decrease in fibrinogen from $4g/L$ to $2g/L$. All values returned to normal by the first post-operative day.

Mcloughlin et al.\textsuperscript{152} demonstrated a considerable disturbance of coagulation parameters (PT, APTT, FIB, PLT, coagulation factor levels) in 8 profoundly haemodiluted adolescents (initial target Hb 7g/dl with 5% albumin in 0.9%Saline as replacement; ultimately up to 75% volume exchange) undergoing surgical correction of scoliosis, and 29 swine undergoing stepwise ANH until death. They explained the coagulopathy developing during ANH by a combined deficiency of coagulation factors. Interestingly platelet count was relatively spared, possibly due to release of platelets sequestered in the spleen.

Olfsanger et al.\textsuperscript{197} showed no differences in PT and APTT with ANH using ringers lactate in patients undergoing elective TKR.

Fukusaki et al.\textsuperscript{153} looked at 40 patients undergoing THR, randomised into control, induced hypotension, ANH, ANH plus hypotension. The first 2 groups also underwent pre-deposit. The 1 litre of venesected blood in the ANH group was replaced with HES at a ratio of 1:1. They found that ANH caused a significant decrease in platelet count, fibrinogen, AT111, and significant increase in APTT during surgery, although the changes did not appear to be clinically important. There were however no significant alterations in coagulation parameters in the
control group undergoing surgery. It is already known that HES affects coagulation.

Boldt et al\textsuperscript{92} found no perioperative alteration in platelet count, APTT, fibrinogen, AT111, or D Dimer in patients haemodiluted with gelatin (15ml/kg venesection) undergoing retropubic prostatectomy.

Hobisch-Hagen et al\textsuperscript{154} looked at 40 patients undergoing orthopaedic surgery, randomised to ANH or control. They used gelofusine at a ratio of 1:1 to replace the blood venesected, whilst intra-operative blood loss was replaced with a combination of gelofusine and Ringer’s lactate. The control group underwent between 1 and 3 unit POD, and in both groups cell salvage was used. A mean (SEM) of 855 (60) ml of blood was venesected at haemodilution. In the ANH group, there was a significant increase in APTT immediately prior to transfusion, when compared with a sample taken immediately after induction of anaesthesia (baseline). Fibrinogen decreased significantly during surgery in both groups, when compared with baseline. Platelet count decreased significantly with surgery in both groups. AT111 decreased significantly in both groups until transfusion, when compared with baseline. There was an increase in activation markers for coagulation (F1+2, TAT) and fibrinolysis (DD, PAP) in both groups, with no difference between groups. However, all the changes shown were small. In addition, the control group were not a true control as POD is known to cause a decrease in haematocrit, essentially acting like pre-operative haemodilution. The addition of cell salvaged blood may have resulted in activation of coagulation not normally seen, although this effect would only have been seen after transfusion of salvaged blood. They concluded that ANH does not cause additional perioperative disturbances in haemostasis.
ANH studies summary

Colloid and crystalloid combined results in an increase in PT, increase in APTT, and reduction in platelets and fibrinogen. The use of HAS and saline results in a considerable disturbance of coagulation parameters, although this was with profound haemodilution. Ringers lactate results in no alteration in PT or APTT. Gelatin results in no alteration in platelet count, APTT, or fibrinogen. Although gelatin resulted in a significant increase in APTT, decrease in fibrinogen and platelet count (although these changes were seen in the control group not haemodiluted). HES leads to a decrease in platelet count and fibrinogen, with an increase in APTT.

Conclusion

So where are we left? All the changes seen are small, except for those profoundly haemodiluted (75%) and clinical impact is uncertain. Because of the presence of so many confounding factors, what is needed is a study that uses fluids in quantities that most readily reflect current practice. For the further understanding of the coagulation system, it is interesting to show that N/Saline causes a hypercoagulable state in vitro, however is it important? The best strategy is to perform a study looking at one parameter and conducting it in a prospective randomised fashion in order to test the hypothesis. For example, surgical patients could be randomised to receive only saline / Hartmann's or crystalloid / colloid and samples taken regularly throughout the procedure. It would answer the question "is it the fluid or the dilution that matters", a point commented on by Roche and Ruttman. It would of course be difficult to standardise transfusion, and in some the anaesthetists may not be willing to avoid plasma expanders when needed. Some would argue that it is actual practice that matters, which is the basis for most of the above studies, and the rationale behind our study.
<table>
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<th>In vivo</th>
<th>Surgery</th>
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↑ hypercoagulation effect
↓ hypocoagulation effect
↔ no effect
↓ small hypocoagulation effect

**Table 9.1**: The overall effects on coagulation of intravenous fluids administered in vitro, in vivo, as replacement for surgical blood loss, and during surgery with ANH
Study Performed

Aim

This study was designed to assess the effect of ANH on haemostasis in patients undergoing surgery.

Methods

The study received approval from the Plymouth local regional ethics committee. Patients were recruited from a large (n=160) randomised controlled trial of ANH in major gastrointestinal surgery in which all patients under the care of the twelve participating surgeons admitted for major colorectal, gastric or pancreatic surgery were screened for eligibility. Recruitment commenced half way through the ANH study and was based on availability of the thromboelastogram. Absolute exclusion criteria included Hb<11g/dl, age<18 years, and blood or blood products in the preceding four weeks. Exclusion criteria at the investigators and/or anaesthetists discretion included abnormal ECG, ischaemic heart disease, obstructive lung disease, renal disease, hypertension, abnormal liver function and coagulation abnormality. Informed consent was obtained and the patient remained blinded to treatment allocation throughout the study period.

All patients received a standard anaesthetic comprising propofol induction, isoflurane maintenance and muscle relaxation with atracurium or rocuronium. Antibiotic prophylaxis with cefuroxime and metronidazole was given shortly after induction. Epidural catheters were sited either awake or asleep depending upon the anaesthetist's preference.
Patients in the ANH group who received bowel preparation were given 2 litres of N/Saline, which commenced on the day prior to surgery. The volume of blood to be withdrawn (maximum 3 units), whilst maintaining the haemoglobin above 8g/dl, was calculated using a formula described by Gross (figure 1). The first litre of venesected blood (maximum 3 units) was replaced with warmed gelofusine at a ratio of 1:1; the remainder replaced with warmed Hartmann's, ratio 3 or 4:1.

Venous samples were taken at fixed points (shown below) and analysed using standard laboratory tests (INR APTT, fibrinogen, platelets) and the thromboelastogram. Blood loss during surgery was replaced with a combination of gelofusine, Hartmann's and N/Saline. The patient was monitored during the operation using standard equipment for the operation concerned. To maintain normothermia during surgery, a rewarming system (Bair Hugger), and fluid warmers were used. At the end of the operation, all the autologous blood was re-transfused. If a patient required a transfusion prior to the completion of surgery, autologous blood was used prior to any allogeneic. At all times during the operation, transfusion was at the anaesthetist's discretion.

Oropharyngeal temperature was measured at knife to skin and again at the end of the operation. Blood loss was estimated by swab weight, suction volumes and surgeon / anaesthetists estimates.

Chemical peri-operative deep venous thrombosis prophylaxis, using 5000iu heparin subcutaneously, was administered after haemodilution. No patients were taking antiplatelet therapy.

Blood Sample Analysis

Samples were taken through a free flowing 14 gauge cannula, without the use of a tourniquet. The first 6ml were discarded, to avoid sampling activated blood. Platelet count, APTT, PT and derived fibrinogen were measured using a standard
autoanalyser. TEG samples were collected in standard citrated tubes (3 mls of blood mixed with 0.3 mls of citrate) and stored at room temperature, a technique validated by Bowbrick et al. Samples were analysed between 30 and 90 minutes from collection. 1ml of citrated blood was placed in a pot containing celite and inverted 5 times. 340 microlitres were transferred to the TEG cup using reverse pipetting, and mixed with 20 microlitres of 0.2 Molar Calcium chloride at 37° Centigrade. The TEG trace was run until the maximum amplitude (MA) was recorded.

Statistical Analysis
Data was analysed within groups using the Wilcoxon signed rank test and between groups using Mann-Whitney. However, the measurements on the patients were taken through time and as such constitute a longitudinal data set. In particular, observations on a measurement for a given patient are likely to be correlated and often require special statistical models such as those describe in Diggle et al. We used the OSWALD package to fit and verify several models, to broadly confirm the results of the previous two tests.
### Sample Timing and Intervention

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<td>ANH</td>
</tr>
<tr>
<td>Post ANH (prior to knife to skin)</td>
<td>1 Hour into surgery</td>
<td>1 Hour</td>
</tr>
<tr>
<td>1 Hour</td>
<td>1 Hour</td>
<td>Further surgery</td>
</tr>
<tr>
<td>Pre re-transfusion</td>
<td>Re-transfusion of autologous blood</td>
<td></td>
</tr>
<tr>
<td>Post re-transfusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>End Op</td>
<td>End Op</td>
<td></td>
</tr>
</tbody>
</table>


Results

33 patients were recruited, ANH n=17, no ANH n=16. The groups were matched for age, sex, weight, starting haemoglobin, duration of operation, and intra-operative temperature (table 9.2). 3 of the 17 patients haemodiluted had less than 3 units venedected.

<table>
<thead>
<tr>
<th></th>
<th>ANH (17)</th>
<th>No ANH (16)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Female</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>63 (23-80)</td>
<td>66 (32-81)</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>72 (14)</td>
<td>76 (11)</td>
</tr>
<tr>
<td><strong>Starting Hb (g/dl)</strong></td>
<td>13.5 (1.3)</td>
<td>13.5 (1.3)</td>
</tr>
<tr>
<td><strong>Duration operation (min)</strong></td>
<td>117 (77-295)</td>
<td>124 (50-308)</td>
</tr>
<tr>
<td><strong>Blood Loss (ml)</strong></td>
<td>1250-1500 (500-3750)</td>
<td>1000-1250 (100-3000)</td>
</tr>
<tr>
<td><strong>Temp start (°C)</strong></td>
<td>35.6 (34.9-36.0)</td>
<td>35.8 (35.3-36.7)</td>
</tr>
<tr>
<td><strong>Temp end (°C)</strong></td>
<td>35.3 (34.2-36.0)</td>
<td>35.6 (34.9-36.2)</td>
</tr>
<tr>
<td>*<strong>Fluid Input (ml)</strong></td>
<td>5000 (3000-9500)</td>
<td>4250 (2500-7000)</td>
</tr>
<tr>
<td><strong>Venesection Volume (ml)</strong></td>
<td>1359 (780-1454)</td>
<td></td>
</tr>
<tr>
<td><strong>Patients Transfused</strong></td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td><strong>Peri-operative</strong></td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td><strong>Transfusion</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p=0.05

**Allogeneic transfusion

Table 9.2: Illustrating groups matched

103
As operation progressed (table 9.3) there was a decrease in platelet count (p<0.001) and fibrinogen (p=0.001), and increase in APTTR (p=0.002) and INR (p=0.001). The TEG confirmed this with a decrease in alpha angle (p=0.008), MA (p=0.003) and G (p=0.001), and increase in K (p=0.008).

<table>
<thead>
<tr>
<th></th>
<th>Pre GA</th>
<th>Post GA</th>
<th>1 Hour</th>
<th>End Op</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angle deg</td>
<td></td>
<td>71.8 (57-80)</td>
<td></td>
<td>68.8 (39.5-78.5)** ‡</td>
</tr>
<tr>
<td>R min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K min</td>
<td></td>
<td>1.3 (0.8-3.8)</td>
<td></td>
<td>1.8 (0.8-5.8)** ‡</td>
</tr>
<tr>
<td>MA mm</td>
<td></td>
<td>66 (47.5-76.5)</td>
<td></td>
<td>59.3 (42-66.5)** ‡</td>
</tr>
<tr>
<td>G d/sc</td>
<td></td>
<td>9709 (4524-16277)</td>
<td></td>
<td>7271 (3621-9825)†† ‡</td>
</tr>
<tr>
<td>Platelets 10⁹ /L</td>
<td>291 (201-546)</td>
<td>258 (178-493)**</td>
<td>225 (164-377)**</td>
<td>186 (122-344)†† ‡</td>
</tr>
<tr>
<td>APTTR</td>
<td>0.9 (0.8-1)</td>
<td>0.9 (0.7-1.2)*</td>
<td>1.1 (1-1.4)**</td>
<td>1.3 (1-1.8)** ‡</td>
</tr>
<tr>
<td>INR</td>
<td>1.1 (1-1.3)</td>
<td>1.2 (1-1.4)**</td>
<td></td>
<td>1.3 (1.1-1.8)** ‡</td>
</tr>
<tr>
<td>Fibrinogen g/L</td>
<td>3.6 (2-7)</td>
<td>2.7 (1.7-6)**</td>
<td>2.1 (1.3-3.3)*</td>
<td>1.8 (0.9-2.2)†† ‡</td>
</tr>
</tbody>
</table>

P value is for comparison with previous value except for ‡=post GA to End Op

*p<0.05

**p<0.01

†p=0.001

††p<0.001

Table 9.3: No ANH (only results showing a significant difference included)
ANH (table 9.4) reduced platelet count ($p=0.003$) and fibrinogen ($p=0.001$), and increased APTT ($0.003$) and INR ($p=0.001$). R time was shortened ($p=0.001$) but there was also a decrease in MA ($p=0.001$) and G ($p<0.001$). Re-transfusion of autologous blood increased platelet count ($p=0.03$) and fibrinogen ($p=0.004$), decreased APTT ($p=0.017$) and INR ($p=0.002$), without affecting the TEG.
<table>
<thead>
<tr>
<th></th>
<th>Pre GA</th>
<th>Post GA</th>
<th>Post ANH</th>
<th>1 Hour</th>
<th>Pre re-transfusion</th>
<th>Post re-transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angle deg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>71</td>
<td>67.5</td>
<td>69.3 (50-78)*</td>
<td>†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(56.5-80)</td>
<td>(56.5-76.5)**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R min</td>
<td>3.9</td>
<td>2.4</td>
<td>67.5</td>
<td>69.3</td>
<td>69.3 (50-78)*</td>
<td>†</td>
</tr>
<tr>
<td></td>
<td>(2.4-5.3)</td>
<td>(1.4-4.5)†</td>
<td>(56.5-76.5)**</td>
<td>3.5 (2.2-6.8)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.4</td>
<td>1.7</td>
<td>1.7 (0.9-2.7)**</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.8-3.9)</td>
<td>(0.9-2.7)**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MA mm</td>
<td>67.8</td>
<td>60</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(58-78)</td>
<td>(22.5-72)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G d/sc</td>
<td>10505</td>
<td>7500</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(6905-17727)</td>
<td>(1451-12857)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets 10⁹ /L</td>
<td>215</td>
<td>154</td>
<td></td>
<td>154</td>
<td>164 (87-333)*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(114-477)</td>
<td>(111-372)**</td>
<td></td>
<td>(86-299)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APTTR</td>
<td>0.9</td>
<td>1</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3 (1.1-2.1)*</td>
<td>†</td>
</tr>
<tr>
<td></td>
<td>(0.7-1)</td>
<td>(0.8-1.3)*</td>
<td>(1.1-1.5)*</td>
<td>(1.1-1.5)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>1.1</td>
<td>1.2</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5 (1.3-1.9)</td>
<td>††</td>
</tr>
<tr>
<td></td>
<td>(1.0-1.5)</td>
<td>(1.1-1.6)††</td>
<td>(1.2-1.6)*</td>
<td>(1.3-1.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen g/L</td>
<td>3.3</td>
<td>2.1</td>
<td>1.4</td>
<td>1.6</td>
<td>1.7 (0.8-3.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1.9-5.6)</td>
<td>(1.2-3.7)††</td>
<td>(1.1-2.8)**</td>
<td>(0.7-3.5)*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P value is for comparison with previous value except for †=post ANH to pre-retransfusion

*p<0.05; **p<0.01; †p=0.001; ††p<0.001

Table 9.4: ANH (only results showing a significant difference included)
Between the groups (table 9.5) there was no difference in any of the variables measured immediately before or after the induction of anaesthesia. At the time of knife to skin, the ANH group had a lower platelet count ($p<0.001$), increased INR ($p=0.006$), reduced MA ($p=0.010$) and G ($p=0.011$), but shortened R time ($p=0.004$). At 1 hour into operation, the platelet count remained lower ($p=0.002$) and the INR ($p=0.005$) and APTTR ($p=0.008$) significantly prolonged. Immediately prior to re-transfusion the only difference was a prolonged INR ($p=0.023$). By the end of the operation there was no difference between groups. In addition there was no difference in estimated blood loss (table 1).
<table>
<thead>
<tr>
<th></th>
<th>No ANH Post GA</th>
<th>ANH Post ANH</th>
<th>No ANH 1 Hour</th>
<th>ANH 1 Hour</th>
<th>No ANH End Op</th>
<th>ANH Pre re-transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angle deg</td>
<td></td>
<td></td>
<td>72.5 (39.5-80.5)</td>
<td>67.5 (56.5-76.5)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R min</td>
<td>4.2 (0.8-5.3)</td>
<td>2.4 (1.4-4.5)**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MA mm</td>
<td>66 (47.5-76.5)</td>
<td>60 (22.5-72)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G d/sc</td>
<td>9709 (4524-16277)</td>
<td>7500 (1451-12857)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets 10⁹ /L</td>
<td>258 (178-493)</td>
<td>154 (111-372) ††</td>
<td>225 (164-377)</td>
<td>149 (101-283)**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APTTTR</td>
<td>0.9 (0.7-1.2)</td>
<td>1.1 (0.8-1.5)*</td>
<td>1.1 (1-1.4)</td>
<td>1.3 (1.1-1.5)**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>1.1 (1-1.3)</td>
<td>1.2 (1.1-1.6)**</td>
<td>1.2 (1-1.4)</td>
<td>1.5 (1.2-1.6)**</td>
<td>1.3 (1.1-1.8)</td>
<td>1.5 (1.3-1.9)*</td>
</tr>
<tr>
<td>Fibrinogen g/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p≤0.05

**p<0.01

†p=0.001

††p<0.001

Table 9.5: Comparison between groups ANH vs. No ANH (only results showing a significant difference included)
Conclusion

Coagulation is significantly impaired as operation progresses. Acute normovolaemic haemodilution impairs coagulation. The re-transfusion of fresh autologous blood improves coagulation to a similar state as patients not undergoing ANH. During operation, coagulation remains significantly impaired by ANH.

These highly significant results suggest detailed study is now required. The fact the ANH study (chapter 7) showed no saving of RBC's may be due to the fact more were lost because of hypocoagulation.
Chapter 10: Thesis Summary and Conclusion

Allogeneic transfusion does confer risk to the recipient, although these risks are small. The presence of an immunomodulatory effect is largely supported by observational studies although this is not uniform across randomised controlled trials. A possible explanation for the disagreement may be the effects of immunomodulation are small, and the studies are underpowered. The implementation of universal white cell reduction will preclude the undertaking of further randomised controlled trials investigating the immunomodulatory effects mediated by allogeneic white blood cells. The risk of disease transmission is no doubt extremely small in developed countries; in the third world, this risk is much greater. The potential for transmission of vCJD remains unknown. The greatest real risk to the recipient remains the transfusion of “wrong blood to patient”, although the percentage risk of transfused units is unknown. Allogeneic blood is likely to become scarcer with increasing population age and the increased number of donors excluded. Furthermore the introduction of leucocyte depleted blood has led to an increased cost pressure on health resources.

Patients admitted to hospital for surgical procedures appear to understand that the risks of transfusion are relatively small (85% willing to have an allogeneic transfusion), but are largely unaware of autologous alternatives (19%). Gastrointestinal surgery is a high blood usage field. In our colorectal unit the transfusion rate between 1997 and 1999 was 43%, which correlates with other published data (overall transfusion rate of 56%). A personalised approach, as proposed by Mercuriali et al (page 29), may be of use when planning which, if any, blood saving technique to employ.
There are many methods of decreasing allogeneic transfusion, however most are not applicable to gastrointestinal surgery for malignancy (chapter 3). Meticulous surgical technique and the use of a transfusion protocol, however, represent good practice. The introduction of a transfusion protocol significantly decreased transfusion rate in our unit from 41% to 28% (page 75). Logistic regression (page 82) demonstrated that operative blood loss was one of the three factors significantly affecting transfusion, the others being starting haemoglobin and age. Looking at our entire study population (380 patients), 29% had a starting haemoglobin < 12g/dl and 47% < 13g/dl. These figures imply that pre-operative boosting of haemoglobin may be of use in decreasing allogeneic transfusion. A study has subsequently been set up looking at the effect of supplemental oral ferrous sulphate administered at the time of diagnosis of colorectal cancer until admission. Erythropoietin may also be of value in this setting.

The use of Picolax® bowel preparation causes a significant dehydrating effect which can be minimised by administering intravenous fluids. This is an important finding as ANH involves large fluid shifts and relies on the patient being normovolaemic at all times. The additional use of an epidural, which amplifies the dehydration by expanding the intra-vascular space, may lead to increased instability whilst surgery is in progress, thereby triggering a transfusion when it is possibly not required.

Acute normovolaemic haemodilution, so ideally suited to gastrointestinal surgery (page 35), does not appear to reduce transfusion rate. When compared with a matched historical control group, ANH significantly reduced allogeneic transfusion rate in our unit from 39% to 15%. However, when prospectively studied, and randomised, there was no reduction in transfusion rate (29% and 30%), or the number of units transfused (92 and 93), illustrating the problem with historical controls and the importance of well controlled randomised trials. The dilutional
effect of ANH may result in "falsely" diluted haemoglobin levels thereby triggering transfusion when it is not required (page 82). It remains possible that in high blood loss groups, haemodilution does marginally reduce allogeneic transfusion. The administration of intravenous fluid affects coagulation; the result being dependant on the type of fluid and degree of dilution. Although the effects are statistically significant, the clinical implication is questionable. Why N/Saline causes hypercoagulation is unknown. In view of this finding, it may be prudent to use N/Saline rather than Hartmann's or colloid solution during resuscitation, and further study into this area is certainly justified. The fact that the prospective randomised study of ANH showed no red blood cell saving in the ANH group may be due to the fact more were lost in this group because of the hypocoagulation effect of ANH. The TEG provides valuable information about the stages in formation of a whole blood clot. The recent improvement in the technology to process the information means that the TEG is gradually gaining approval, especially in its use differentiating between surgical bleeding and coagulopathy.

Overall Conclusion
This work has provided level one evidence of an absence of beneficial effect of acute normovolaemic haemodilution in major gastro-intestinal surgery. Methods to minimise allogeneic transfusion should be targeted at increasing pre-operative haemoglobin, possibly with the use of ferrous sulphate with/without erythropoietin, and decreasing blood loss with good surgical technique. Transfusion education alongside the introduction of a transfusion protocol has been shown to be beneficial and remains the basis of good practice.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANH</td>
<td>Acute normovolaemic haemodilution</td>
</tr>
<tr>
<td>APTT</td>
<td>Activated partial thromboplastin time</td>
</tr>
<tr>
<td>APTTR</td>
<td>Activated partial thromboplastin time ratio</td>
</tr>
<tr>
<td>ASA</td>
<td>American society anaesthesiologist’s</td>
</tr>
<tr>
<td>AT111</td>
<td>Antithrombin 111</td>
</tr>
<tr>
<td>EBV</td>
<td>Estimated blood volume</td>
</tr>
<tr>
<td>EPO</td>
<td>Erythropoietin</td>
</tr>
<tr>
<td>F(1+2)</td>
<td>Fragments 1 and 2</td>
</tr>
<tr>
<td>INR</td>
<td>International normalised ratio</td>
</tr>
<tr>
<td>PAP</td>
<td>Plasmin alpha2 antiplasmin</td>
</tr>
<tr>
<td>PCV</td>
<td>Packed cell volume</td>
</tr>
<tr>
<td>POD</td>
<td>Pre-operative donation</td>
</tr>
<tr>
<td>PT</td>
<td>Prothrombin time</td>
</tr>
<tr>
<td>RBC</td>
<td>Red blood cell</td>
</tr>
<tr>
<td>TAT</td>
<td>Thrombin anti-thrombin</td>
</tr>
<tr>
<td>TEG</td>
<td>Thromboelastogram</td>
</tr>
<tr>
<td>R</td>
<td>Interval between start of recording and time at which amplitude of trace 2mm</td>
</tr>
<tr>
<td>K</td>
<td>Time taken from R for amplitude to reach 20mm</td>
</tr>
<tr>
<td>α</td>
<td>Angle formed by slope of TEG trace from R to K value</td>
</tr>
<tr>
<td>MA</td>
<td>Maximum amplitude</td>
</tr>
<tr>
<td>G</td>
<td>Derived value from MA</td>
</tr>
<tr>
<td>TF</td>
<td>Tissue factor</td>
</tr>
<tr>
<td>TRIM</td>
<td>Transfusion associated immunomodulation</td>
</tr>
<tr>
<td>WBC</td>
<td>White blood cell</td>
</tr>
</tbody>
</table>
Reference List


46. Lieberman JA et al. Critical oxygen delivery in conscious humans is less than 7.3 ml O2 x kg(-1) x min(-1). *Anesthesiology* 2000; **92**: 407-13.


57. Domen RE. Adverse reactions associated with autologous blood transfusion: evaluation and incidence at a large academic hospital. *Transfusion* 1998; **38**: 296-300.


72. Mercuriali F et al. Use of erythropoietin to increase the volume of autologous blood donated by orthopedic patients. Transfusion 1993; 33: 55-60.


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95. Monk TG, Goodnough LT, Birkmeyer JD, Brecher ME, Catalona WJ. Acute normovolemic hemodilution is a cost-effective alternative to preoperative autologous blood donation by patients undergoing radical retropubic prostatectomy. *Transfusion* 1995; 35: 559-65.


Acute normovolaemic haemodilution in colorectal surgery


*Colorectal Unit, Department of Surgery, Derriford Hospital, Plymouth, UK and †Department of Anaesthetics, Derriford Hospital, Plymouth, UK

Aims: Blood transfusions are often given to surgical patients. This study was designed to assess whether acute normovolaemic haemodilution (ANH) reduces exposure to allogeneic blood, affects clinical outcome and hospital stay, and is feasible in colorectal surgery.

Methods: All ASA I and II patients undergoing colectomies performed between 1997 and 1999 were identified retrospectively from our colorectal cancer database to ascertain our current peri and postoperative transfusion practice. Twenty-six selected patients subsequently underwent ANH during colectomy surgery. The number of patients and units transfused were identified.

Results: One hundred and twenty-three of 317 (39%) patients identified from our colorectal cancer database were transfused a total of 328 units (median 2, range 1-7). Of the 26 patients undergoing ANH, 4 (15%) were transfused a total of 13 units (median 3, range 2-5). The reduction in number of patients transfused was statistically significant (P = 0.017). ANH increased anaesthetic time by a median of 19 min. There were no complications associated with ANH and the median hospital stay was 9 days (range 6-13).

Conclusions: In this pilot study of selected patients, ANH is a feasible and effective method of reducing allogeneic blood exposure in major colorectal surgery. A prospective randomised controlled trial is now urgently required.

INTRODUCTION

Blood transfusions are often given to surgical patients. Allogeneic blood in this setting confers a risk to the recipient in terms of allergic reaction, increased infectious complications, transmission of disease, alloimmunisation and possibly increased cancer recurrence. More recently, the introduction of leucocyte depleted blood has led to an increased cost pressure on health resources.

Acute normovolaemic haemodilution (ANH) is an autologous transfusion technique. Blood is venesected from a patient immediately before or shortly after the induction of anaesthesia and simultaneously replaced with cell free fluid. By using this procedure prior to intraoperative blood loss, fresh autologous blood is made available for later transfusion. As a result of haemodilution blood subsequently lost contains proportionally fewer red blood cells per millilitre, thereby minimising loss of autologous cells.

Although the technique has been used in other fields of surgery including cardiac, orthopaedic, urological, hepatic and vascular, it has not been reported in colorectal surgery.

The aim of this pilot study is to assess whether ANH reduces exposure to allogeneic blood, affects clinical outcome and hospital stay, and is feasible in colorectal surgery.

PATIENTS AND METHODS

The study received approval from the Plymouth local regional ethics committee. We identified all ASA II colorectal cancer patients operated on between 1997 and 1999 from our database to ascertain our current peri and postoperative transfusion practice. All patients subsequently admitted for major colorectal surgery were screened for haemodilution eligibility (Hb > 11 g/dl, ASA I or II) and informed consent was obtained.

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0748-7983(02)0035.00 © 2002 Elsevier Science Ltd. All rights reserved.
cOHR OF PRIMARY COLORECTAL TUMOURS USING THE PULSE
LABELLING TECHNIQUE, AS REVIEWED ELSEWHERE. DUKES' 
STAGE AND PATIENT AGE AND GENDER WERE FOUND TO BE 
STATISTICALLY SIGNIFICANT PREDICTORS OF PATIENT OUTCOME IN A 
multi-variable analysis. The lack of association in this study between proliferation parameters including 
dynamic indices, and survival is consistent with the 
findings in a smaller cohort of breast cancers studied in a 
similar fashion with in vivo pulse labeling, and is 
consistent with an earlier analysis from this cohort. In 
vivo dynamic proliferation indices are a research tool with no immediate clinical applications. Apoptosis, 
cell loss and exfoliation play a significant role in the 
volume growth of tumours in vivo. Proliferation data do 
not describe this important feature of tumour growth, 
nor of other components of the biological aggressiveness 
of colorectal carcinoma including metastatic potential and invasive characteristics. Nevertheless the 
BrdUrd/flow cytometry labelling technique has provided 
valuable and unique information about tumour behavio
from the quantitative study of time vectored cell 
proliferation parameters of clinical tumours in vivo in a 
safe and simple way.

ACKNOWLEDGEMENTS

We thank Dr G D Wilson and the late Dr N McNally 
of The Gray Laboratory, Northwood, Middlesex, for 
technical help in the primary study Mr M R Thompson, 
Professor I. Taylor and Mr P C. Weaver and 
Mr C D Johnson for permission to study patients 
under their care, and the patients who kindly agreed to 
participate in the study. DAR was funded between 1989 
and 1991 by the Cancer Research Campaign and by the 
Wessex Regional Health Authority. R I Cutress is 
funded by a Robertson Trust Training Fellowship from 
the Royal College of Surgeons of Edinburgh.

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bromodeoxyuridine-derived proliferation indices in 75 invasive 
obtained. Standard pre-operative preparation included FBC, U&E, cross match of 2 units, ECG and CXR. Picolax\textsuperscript{R} (Ferring Pharmaceuticals Ltd, Middlesex, UK) bowel preparation was administered the day before surgery. Two litres of n/saline with 20 mmol potassium were administered over 12h, commencing in the evening, prior to surgery.

The volume of blood to be withdrawn (maximum 3 units), whilst maintaining the haemoglobin above 8 g/dl, was calculated using a formula described by Gross\textsuperscript{12} (Fig. 1). After induction of anaesthesia, a 14 gauge cannula was sited in either the external jugular vein or a large forearm vein. Extension tubing with a three way tap and rubber bung was connected which allowed access away from the surgical drapes. Standard blood bags containing anticoagulant citrate-phosphate-dextrose (CPD) were used to passively collect the blood. The bags were placed on scales on the floor and oscillated by hand during venesection to allow adequate mixing of anticoagulant. Once filled, the blood bag tubing was clamped, the bag labeled and stored with the patient at room temperature in the operating theatre.

Warmed cell free fluid was administered via a second cannula during blood withdrawal to maintain normovolaemia. The first litre of blood withdrawn was replaced with 1 L of gelofusine. Subsequent blood withdrawal was replaced with Hartmann’s at a ratio of 3 or 4:1. A Hemocue B-Haemoglobin photometer (Hemocue Ltd, Sheffield, UK) was present in theatre to allow near patient haemoglobin testing.

The patient was monitored during the operation using standard equipment for the operation concerned. At the end of the operation, all the autologous blood was re-transfused. If, at the anaesthetist’s discretion, a patient required a transfusion prior to the completion of surgery, autologous blood was used prior to any allogeneic.

Haemoglobin, haematocrit, and clotting (aPTT, INR) were measured before and after haemodilution, hourly through the procedure, and before and after retransfusion.

Patients in the haemodilution group underwent standard postoperative care including adherence to a transfusion protocol (Table I). Primary outcome measures included the number of patients transfused and the number of units transfused. Secondary outcome measures included time taken to venesect, complications and length of stay.

**RESULTS**

One hundred and twenty-three of 317 (39%) ASA I and 11 patients operated on between 1997 and 1999 were transfused a total of 328 allogeneic units (median 2, range 1–7) (Table 2). Between October and December 1999, 26 of 55 (47%) patients screened for eligibility were recruited for ANH. 18 male and 8 female patients with a median age of 58 years (range 34–75) underwent operations (Table 2). Five patients were venesected 3 units, twenty had 2 units, and one had one unit. Four of the 26 patients (15%) were transfused a total of 13 allogeneic units (median 3, range 2–5). The reduction in

\[ V = EBV \times (H_0 - H_f)/H_{AV} \]

where

- \( V \) = volume of blood withdrawn
- \( EBV \) = estimated blood volume (70 ml/kg man, 65 ml/Kg woman)
- \( H_0 \) = initial haematocrit or Hb concentration
- \( H_f \) = target haematocrit or Hb concentration
- \( H_{AV} \) = average of haematocrits or Hb concentration

Table I Transfusion protocol

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Non-HAEMODILUTED</th>
<th>HAEMODILUTED</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>No. T* (%)</td>
<td>Total units</td>
</tr>
<tr>
<td>Right/exit right hemicolectomy</td>
<td>110</td>
<td>42 (38) 97</td>
</tr>
<tr>
<td>Left hemicolectomy</td>
<td>53</td>
<td>13 (25) 32</td>
</tr>
<tr>
<td>Anterior resection</td>
<td>119</td>
<td>41 (34) 123</td>
</tr>
<tr>
<td>AP resection</td>
<td>31</td>
<td>24 (77) 69</td>
</tr>
<tr>
<td>Subtotal colectomy</td>
<td>4</td>
<td>3 (75) 7</td>
</tr>
<tr>
<td>Total</td>
<td>317</td>
<td>123 (39) 328</td>
</tr>
</tbody>
</table>

* Number patients transfused (%)

Table 2 Allogeneic blood usage in non-haemodiluted and haemodiluted patients

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Non-HAEMODILUTED</th>
<th>HAEMODILUTED</th>
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<tr>
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</tr>
<tr>
<td>Total</td>
<td>317</td>
<td>123 (39) 328</td>
</tr>
</tbody>
</table>

* Number patients transfused (%).
the number of patients transfused from 123/317 (39%) to 4/26 (15%) was statistically significant, \( P = 0.017 \) (\( \chi^2 \)).

Haemodilution increased anaesthetic time by a median of 19 min (range 9–40). There were no post-operative complications in the ANH group and no significant alterations in clotting during haemodilution. The median length of stay was 9 days (range 6–13).

**DISCUSSION**

Strategies for blood conservation include meticulous surgical technique, transfusion protocol,\(^{13}\) erythropoietin,\(^{14}\) hypotensive anaesthesia,\(^{8}\) pre-operative donation,\(^{15}\) cell salvage\(^{16}\) and ANH. The first two represent good practice. Both erythropoietin and hypotensive anaesthesia have been used with varying degrees of success but have not been widely adopted. Pre-operative donation (POD) requires careful donor selection, venesection, adequate storage of blood and correct re-transfusion on a tightly defined time scale, often not practical in cancer surgery.\(^{17}\) Although POD has been shown to reduce allogeneic exposure, the total transfusion rate is increased,\(^{18}\) thereby increasing the probability of an incorrect transfusion.\(^{19}\) In addition, POD has not been found to be cost effective.\(^{20}\) Cell salvage is currently not applicable in the presence of malignancy or when the bowel is open.

ANH has certain advantages. There is minimal pre-operative preparation for both patient and staff. Units are collected and stored at the bedside incurring no storage and testing costs, and eliminating the chance of an incorrect transfusion. All units collected are re-transfused in the patient, preventing wastage. Since blood is available in theatre, patients can be ‘group and saved’ allowing a lower cross match ratio.

However, only 47% of patients screened were eligible for ANH. The majority were excluded because of anaemia and co-morbid disease. Despite the use of ANH in other fields of surgery, its benefits remain inconclusive.\(^{21,22}\) Colorectal surgery is unique in that it is a high blood usage field and the other autologous techniques are less applicable.

In this pilot study of selected patients, ANH is a feasible and effective method of reducing allogeneic blood exposure in major colorectal surgery. Although the control group was matched for ASA grade and operation, it remains historical. A prospective randomised controlled trial is now urgently required.

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Randomized clinical trial of intravenous fluid replacement during bowel preparation for surgery

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Background: Bowel preparation using purgatives has previously been shown significantly to increase haemoglobin concentration and decrease weight. This prospective randomized study assessed the effects of administering intravenous fluid during bowel preparation.

Methods: Patients having bowel preparation with Picolax® for colonic procedures were randomized prospectively to receive no intravenous fluid (group 1) or calculated intravenous crystalloid based on body-weight (group 2) during preparation. Physiological, haematological and biochemical variables were measured before and after bowel preparation.

Results: Forty-one patients were recruited with a median age of 69 (range 29-86) years, 22 in group 1 and 19 in group 2. There was no difference between groups in any of the variables measured before bowel preparation. On completion, there was a significant difference between groups in mean weight loss (P = 0.01), postural change in systolic pressure (P = 0.015) and serum creatinine concentration (P = 0.008). In addition there was a significant fall in erect blood pressure after bowel preparation in group 1 (P = 0.02). The mean urine output in group 1 was 982 ml and in group 2 was 1808 ml (P = 0.004). The faeces weight between groups was not significantly different.

Conclusion: Picolax® bowel preparation has a significant dehydrating effect, which can be minimized by administering a simultaneous volume of intravenous fluid (mean 2 litres in this study).

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Introduction

Two sachets of Picolax® (Ferring Pharmaceuticals, Langley, UK) are administered to patients for bowel preparation before colonic surgery in our unit. Sodium picosulphate is hydrolysed in the colon to reduce water and electrolyte absorption, while magnesium citrate acts as an osmotic laxative. It was our impression that a large number of patients receiving bowel preparation were dehydrated when they came to surgery. This prospective randomized controlled study assessed the effects of administering intravenous fluid during bowel preparation.

Patients and methods

Patients receiving bowel preparation for colonic procedures were recruited. Patients in group 1 were randomized by sealed envelope to receive no intravenous fluid while those in group 2 received a calculated volume of intravenous normal saline during bowel preparation, starting at the same time as Picolax® administration (intravenous infusion rate per h 4 ml per kg for the first 10 kg, 2 ml per kg for the second 10 kg then 1 ml per kg for each subsequent kilogram). Both groups received two sachets of Picolax® 6 h apart, starting 18 h before operation, and were encouraged to drink unlimited clear fluids until 6 h before that time. The study received approval from the Plymouth local research ethics committee and patients were required to give informed consent for inclusion.

Physiological (weight, pulse, supine and erect blood pressure), haematological (haemoglobin, haematocrit) and biochemical (sodium, potassium, urea, creatinine, urine osmolality) variables were measured immediately before starting bowel preparation and repeated 1 h before starting bowel preparation and repeated 1 h before procedure or immediately before premedication. Weight was measured to the nearest 0.5 kg using a single Sca (Hamburg, Germany) analogue scale, which was checked annually by the Bristol Scales Company (Bristol, UK). Care was taken to ensure that the same clothing was worn at both weighings. Blood pressure and heart rate were measured
Intravenous fluid replacement during bowel preparation (or surgery • G. Sanders, S. J. Mercer, K. Saeb-Parscy et al.

with a Dinamap Compact TS (Johnson and Johnson Medical, Tampa, Florida, USA). Supine readings were taken after lying undisturbed for 30 min. Subsequent erect readings were taken 2 min after sitting or standing. In addition, total fluid intake and output, American Society of Anesthesiologists (ASA) grade\(^2\), and weight of faeces were recorded. Fluid intake included oral and intravenous fluids.

A sample size of 20 in each group was calculated, based on finding a difference in weight between groups of 0.5 kg with a standard deviation of 0.55\(^3\), power of 80 per cent and significance level of 0.05. Data were assessed for normality using the Shapiro Wilk test and subsequently analysed within groups and between groups using paired and impaired \(t\) tests as appropriate. \(P < 0.05\) was taken as significant.

**Results**

Forty-one patients were recruited with a median age of 69 (range 29-86) years; there were 22 in group 1 and 19 in group 2. There were 26 men and 15 women. There was no difference between groups in baseline variables, age, sex, ASA grade or diagnosis before bowel preparation, and no evidence of non-normality in any of the variables studied. On completion (Tables 1 and 2), there was a significant difference between groups in mean weight loss (\(P = 0.01\)), postural change in systolic pressure (\(P = 0.015\)) and serum creatinine level (\(P = 0.008\)). In addition there was a significant change in weight within group 1 (\(P < 0.001\)), fall in erect systolic pressure (\(P = 0.011\)), fall in erect diastolic pressure (\(P = 0.023\)) and fall in supine diastolic pressure (\(P = 0.005\)). Serum potassium concentration decreased significantly in groups 1 and 2 (\(P = 0.019\) and \(P < 0.001\) respectively) and supine pulse rate increased significantly in both groups (\(P = 0.046\) and \(P = 0.047\) respectively). The mean difference in fluid input in the two groups was 2078 ml. The mean urine output in group 1 was 982 ml and that in group 2 was 1808 ml (\(P = 0.004\)) but the faeces weight was not significantly different between groups (Table 3).

**Discussion**
Picolax\(^\circ\) bowel preparation has previously been shown to cause a significantly greater weight loss and increased

### Table 1 Change in body-weight and serum creatinine level with Picolax\(^\circ\) bowel preparation

<table>
<thead>
<tr>
<th>Group</th>
<th>Initial</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>2.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Creatinine (mmol/l)</td>
<td>965</td>
<td>65</td>
</tr>
</tbody>
</table>

Values are mean(s.e.m.). \(*P < 0.001, \#P = 0.009\) versus initial (paired \(t\) test); \(\#P = 0.01, \&P = 0.008\) versus group 1 (independent samples \(t\) test).

### Table 2 Blood pressure, pulse and serum potassium concentration before and after Picolax\(^\circ\)

<table>
<thead>
<tr>
<th>Group</th>
<th>Initial</th>
<th>Final</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postural pressure drop (mmHg)</td>
<td>1</td>
<td>18 (3-4); 4 (2-9)</td>
</tr>
<tr>
<td>Erect systolic pressure (mmHg)</td>
<td>1</td>
<td>145 (4)</td>
</tr>
<tr>
<td>Erect diastolic pressure (mmHg)</td>
<td>1</td>
<td>84 (2); 77 (3)</td>
</tr>
<tr>
<td>Supine diastolic pressure (mmHg)</td>
<td>1</td>
<td>81 (2); 79 (3)</td>
</tr>
<tr>
<td>Potassium (mmol/l)</td>
<td>1</td>
<td>4.4 (0.1); 4.1 (0.1)</td>
</tr>
<tr>
<td>Supine pulse (beats/min)</td>
<td>1</td>
<td>76 (3); 85 (3)</td>
</tr>
</tbody>
</table>

Values are mean(s.e.m.). There was a significant difference in postural pressure drop between groups after Picolax\(^\circ\) (\(P = 0.015\), independent samples \(t\) test). n.s., Not significant. *paired \(t\) test.

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haemoglobin concentration compared with a group of matched patients undergoing body surface surgery. Patients of ASA grade 3 were noted to feel faint on standing, after bowel preparation. Kutt et al. also demonstrated an increase in haemoglobin concentration before barium enema examination. In addition there was a correlation between patients with a raised haemoglobin level and those experiencing headache. In a retrospective study, Lee et al. examined perioperative and postoperative fluid requirements in patients undergoing inpatient versus outpatient bowel preparation. The inpatient group was given intravenous fluids overnight whereas the outpatient group commenced intravenous fluids 1–2 h before surgery. Although there was a shorter length of stay in the outpatient group, these patients also had increased perioperative and postoperative fluid requirements. In a prospective randomized study Lawrance et al. studied five different oral fluid regimens in 197 patients and found no difference in any of the groups with regard to adverse events. Hill et al. demonstrated that patients with cellular potassium depletion were at risk of hypokalaemia after bowel preparation with sodium phosphate.

The present study confirms the dehydrating effect of Picolax® bowel preparation as measured by the decrease in weight, erect systolic, erect diastolic and supine diastolic pressures in group 1, and the significant difference in postural pressure change between groups. None of these variables changed significantly in group 2, indicating that the dehydrating effect was negated with the administration of intravenous saline. Interestingly, although both groups were encouraged to drink unlimited clear fluids during preparation, their oral intake was not significantly different (Table 3). In both groups the serum potassium concentration decreased significantly. The supine pulse rate increased significantly in both groups, implying a cause other than hypovolaemia.

In conclusion, Picolax® bowel preparation has significant clinical effects, which may be particularly detrimental in elderly or cardiovascularly compromised patients. The dehydrating effects can be minimized by administering a simultaneous volume of intravenous fluid (mean 2 litres in this study). Consideration should also be given to potassium replacement.

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