

## Prospective randomized controlled trial of acute normovolaemic haemodilution in major gastrointestinal surgery

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**Background.** The efficacy of acute normovolaemic haemodilution (ANH) remains uncertain because of a lack of well-designed prospective randomized controlled trials. The aim of this study was to assess the effects of ANH on allogeneic transfusion, postoperative complications, and duration of stay.

**Methods.** Consecutive patients undergoing major gastrointestinal surgery were randomized to a planned 3-unit ANH, or no ANH. Both groups underwent identical management including adherence to a transfusion protocol after surgery. Outcome measures included the number of patients receiving allogeneic blood, complications, and duration of stay.

**Results.** 380 patients were screened of which 160 were included in the study, median age was 62 yr (range 23–90), 'ANH'  $n=78$ , 'no ANH'  $n=82$ . There was no significant difference between groups in the number of patients receiving allogeneic blood 22/78 (28%) vs 25/82 (30%), the total number of allogeneic units transfused (90 vs 93), complication rate, or duration of stay. Haemodilution significantly increased anaesthetic time, median 55 (range 15–90) vs 40 min (range 17–80) ( $P<0.001$ ). Significantly fewer patients in the ANH group experienced oliguria in the immediate postoperative period 37/78 (47%) vs 55/82 (67%) ( $P=0.012$ ). The most significant factors affecting transfusion were blood loss, starting haemoglobin, and age. When compared with ASA-matched historical controls, the introduction of a transfusion protocol reduced the transfusion rate in colorectal patients from 136/333 (41%) to 37/138 (27%),  $P=0.004$ .

**Conclusions.** In this large pragmatic study, ANH did not affect allogeneic transfusion rate in major gastrointestinal surgery. Preoperative haemoglobin, blood loss, and transfusion protocol are the key factors influencing allogeneic transfusion.

*Br J Anaesth* 2004; **93**: 775–81

**Keywords:** blood, transfusion; surgery

Accepted for publication: August 11, 2004

Blood transfusions are often given to surgical patients and allogeneic transfusion in this setting confers a risk to the recipient because of immunomodulation, transmission of disease, allergic reaction, and alloimmunization. It is likely that blood will become scarcer with increasing population age and the increased number of donors excluded.<sup>1</sup> More recently, the introduction of leucodepleted blood has led to an increased cost pressure on health resources. For these reasons, both physicians and patients have been prompted to search for alternatives to the perioperative use of donor blood.

Acute normovolaemic haemodilution (ANH) is an autologous technique, which has certain advantages over other techniques. There is minimal preoperative preparation for both patient and staff, which makes ANH suitable for both

emergency and elective procedures. Units are collected and stored in the operating theatre incurring no storage or testing costs, and minimizing the chance of a clerical error leading to an incorrect transfusion. All blood collected is returned to the patient thereby eliminating costly blood wastage. As blood is available in theatre, patients can be 'group and saved' allowing a lower cross match:transfusion ratio. The blood is fresh, containing functional platelets and clotting factors and the lowered blood viscosity may have benefits in terms of oxygen delivery.<sup>2</sup> A cardinal benefit, difficult to quantify, is the 'peace of mind' associated with knowing that they are receiving blood free from contamination with variant CJD, HIV, or hepatitis virus.<sup>3</sup> In addition there may also be unknown transfusion transmitted diseases.

Although the technique has been used before, there is still no evidence that ANH is effective in reducing exposure to allogeneic blood.<sup>2,4-11</sup>

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

## Methods

### Eligibility

All patients under the care of the 12 participating surgeons working in one UK district hospital (Derriford Hospital, Plymouth) admitted for major colorectal, gastric or pancreatic surgery were screened for eligibility. These operations were considered high risk (>40%) for allogeneic transfusion. Absolute exclusion criteria were haemoglobin less than 11 g dl<sup>-1</sup>, age less than 18 yr, and had received blood or blood products in the preceding 4 weeks. Exclusion criteria, made at the investigators' and/or anaesthetists' discretion before randomization 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. The study received approval from the Plymouth local research ethics committee.

### Interventions

Standard preoperative preparation included full blood count, urea and electrolytes, cross match according to procedure, ECG and chest X-ray. Picolax<sup>®</sup> (Ferring Pharmaceuticals Ltd, Middlesex, UK) bowel preparation, if required, was administered the day before surgery. The resulting dehydration was minimized by administering 2 litres of N saline with 20 mmol potassium chloride intravenously over 12 h, commencing the evening before surgery.<sup>12</sup>

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.

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 8 g dl<sup>-1</sup>, was calculated using a formula described by Gross.<sup>13</sup> 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 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 solution 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, and used at the anaesthetist's discretion.

The patient was monitored during the operation using standard equipment for the operation concerned. Minimum monitoring included continuous ECG, heart 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 a patient required a transfusion before the completion of surgery, autologous blood was used before any allogeneic. We did not feel protocol-driven intra-operative haematocrit alone would be an accurate indicator of need for transfusion in view of the large fluid shifts present during surgery with significant blood loss. Therefore, although intra-operative transfusion usually followed protocol (Table 1), this was at the anaesthetist's discretion. After surgery patients underwent standard care including adherence to a standard transfusion protocol (Table 1).<sup>14</sup>

Oropharyngeal temperature was measured at knife to skin and again at the end of the operation. Blood loss was estimated in graduations of 250 ml by swab weight, suction volumes, and surgeon/anaesthetist estimates. Anaesthesia time was the duration from arrival in the anaesthetic room until knife to skin. Duration of operation commenced at knife to skin.

### Outcomes

Primary outcome measures were the proportion of patients transfused with allogeneic red blood cells and the number of units transfused in the first 3 days after surgery. Secondary outcome measures were time taken to venesection, complications, and duration of stay.

Urine output was measured hourly for at least 24 h after surgery. Oliguria was defined as urine output less than 30 ml h<sup>-1</sup>. Full blood count and urea and electrolytes were measured at 24 and 48 h with the former measured

**Table 1** Transfusion protocol

Haemoglobin >10 g dl <sup>-1</sup>	No transfusion
Haemoglobin 8–10 g dl <sup>-1</sup>	Transfuse if: Abnormal ECG or ischaemic heart disease or obstructive lung disease or consultant's discretion or unable to absorb oral iron
Haemoglobin <8 g dl <sup>-1</sup>	Transfuse

again at discharge and 30 days. Patients were followed up at 30 days by telephone.

### Complications

Definitions used were standard for our unit. Pyrexia of unknown origin was defined as a temperature greater than 37.5°C over a period of 48 h 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 i.p. 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 more than 1000 organisms ml<sup>-1</sup> with associated pyrexia. Deep vein thrombosis and pulmonary embolus were diagnosed clinically and confirmed by above-knee duplex scanning and CTPA (CT pulmonary angiography) or V/Q scanning, respectively. Anastomotic leak was present if diagnosed clinically and confirmed radiologically.

### Randomization and blinding

Randomization was in variable sized blocks and allocation obtained by telephone to Sheffield Medical Care Research Unit. The patients were blinded to treatment allocation throughout the study period.

### Sample size

A sample size of  $n=78$  in each arm was calculated based on reducing allogeneic blood exposure from 41% (transfusion rate in our unit for all ASA I and II patients ( $n=333$ ) undergoing colectomy surgery from 1997 to 1999 inclusive, identified from our colorectal database) to 20%, with a power of 80% and two-tailed significance level of 0.05.

### Analysis

Continuous data were analysed using the Student's *t*-test or Mann-Whitney *U*-test depending on the distribution of the data. Proportional data were analysed using the  $\chi^2$  test or Fisher's exact test. All analysis was performed on an intention-to-treat basis with  $P<0.05$  taken as being significant, using SPSS version 9. Logistic regression was used to identify factors associated with having a transfusion. The model was built in stages and factors significant at the 10% level were retained. Interactions among variables were examined.

### Results

During an 18-month period, 380 consecutive patients were screened of whom 224 (59%) were eligible. A majority were

excluded because of co-existing medical disease (110) or a preoperative haemoglobin less than 11 g dl<sup>-1</sup> (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 randomize (7). 160 gave consent and were randomized, ANH  $n=78$ , no ANH  $n=82$  (Fig. 1), none of whom had significant co-morbid disease.

The median age was 62 yr (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 preoperative and postoperative temperature ( $P<0.01$ ) (Table 2); however, the difference in median temperatures was 0.1 and 0.3°C, respectively.

There was no significant difference between groups in the proportion of patients receiving allogeneic blood 22/78 (28%) vs 25/82 (30%), or the total number of allogeneic units transfused (90 vs 93) (Table 3). The number of patients transfused allogeneic blood intra-operatively or in recovery in the two groups was 15/78 and 20/82. Post surgery on days 1–3, 9/78 and 8/82 were transfused (Table 3). The type of operation performed and transfusion rates are shown in Table 4.

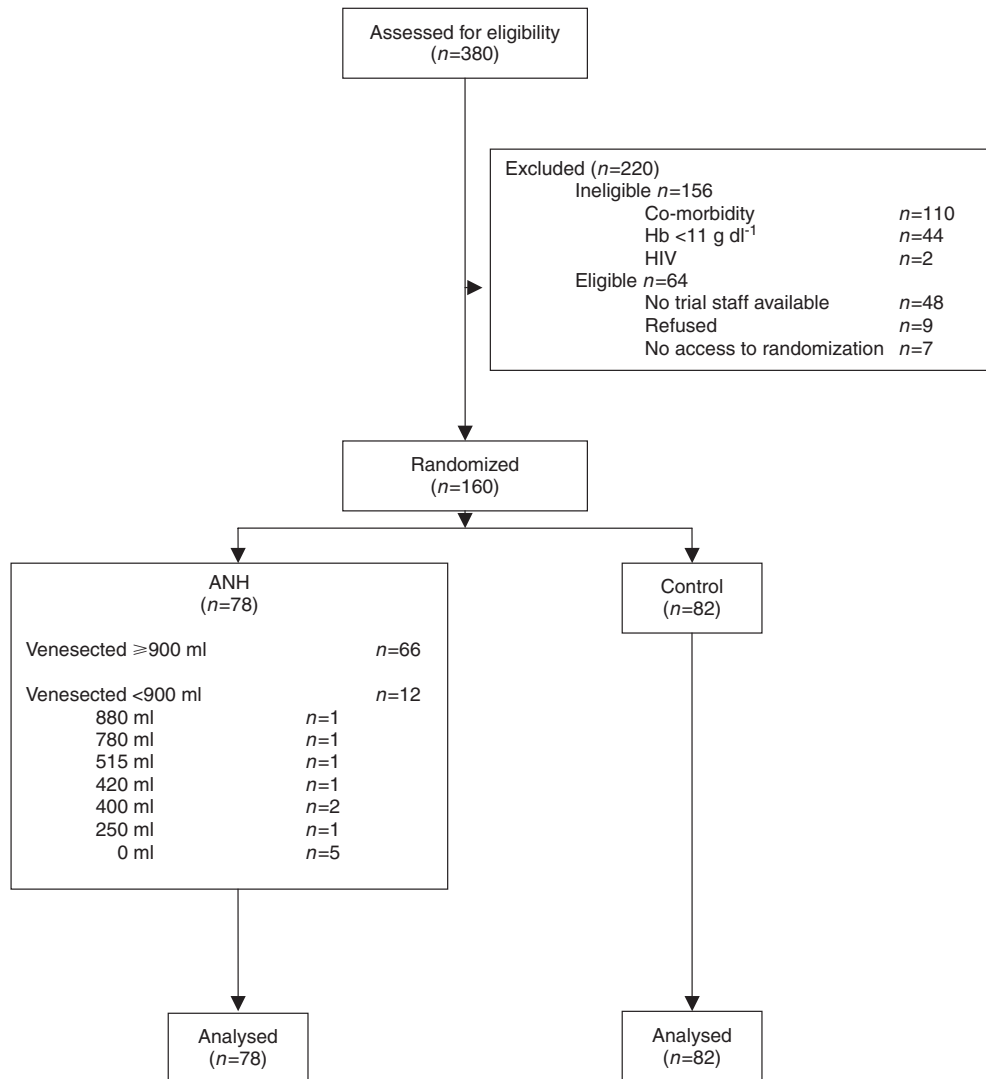
The most significant factors affecting transfusion were blood loss, starting haemoglobin, and age (Table 5).

There was no significant difference in the most recent median (range) haemoglobin level before transfusion in each group; day 1–3, 7.4 (5.2–12.2) and 7.7 g dl<sup>-1</sup> (7.2–9.8), ANH and control, respectively. However, in six patients, three in each group, the transfusion protocol was violated and transfusion occurred after the operation with haemoglobin greater than 8 g dl<sup>-1</sup>.

There was no significant difference in median (range) haemoglobin levels between groups throughout the postoperative study period (day 1, 10.5 (6.0–15.4) and 10.8 g dl<sup>-1</sup> (7.2–15.0); day 2, 10.8 (6.9–14.9) and 10.4 g dl<sup>-1</sup> (7.5–15.0); discharge, 11.8 (8.4–14.7) and 11.7 g dl<sup>-1</sup> (8.7–14.9); day 30, 12.4 (9.2–16.0) and 12.3 g dl<sup>-1</sup> (7.5–14.8); ANH and control, respectively). In addition, there was no significant difference in preoperative and day 2 calculated red blood cell (RBC) loss (ANH mean 614 ml (SD 427), control mean 616 (SD 451)).<sup>2,15</sup> The median lowest intra-operative preautologous transfusion haemoglobin in patients who were haemodiluted was 7.7 g dl<sup>-1</sup> (4.8–11).

Venesection lasted a median of 30 min (10–70), and significantly increased anaesthetic time (Table 2), median 55 (range 15–90) vs 40 min (range 17–80) ( $P<0.001$ ). Significantly fewer patients in the ANH group experienced oliguria in the immediate postoperative period 37/78 (47%) vs 55/82 (67%) ( $P=0.012$ ).

There was no significant difference in complication rate in the two groups (Table 6) 14/78 (18%) vs 22/82 (27%)  $P=0.179$ ; however, the complication rate was significantly greater in patients who received allogeneic blood compared



**Fig 1** Progress through the phases of the randomized controlled trial.

**Table 2** Patient characteristics, baseline measures and operative details. Baseline measures in median (range) except weight and starting haemoglobin mean (SD). \*Difference between groups significant at  $P<0.01$ . †Difference between groups significant at  $P<0.001$

Baseline measures (Units)	ANH (78)		Control (82)	
	Male	Female	Male	Female
Sex	43	35	41	41
Age (yr)	62 (23–85)		62.5 (24–90)	
Weight (kg)	74 (14)		73 (15)	
Starting haemoglobin (g dl <sup>-1</sup> )	13.5 (1.2)		13.5 (1.3)	
Duration operation (h:min)	1:53 (0:45–5:20)		1:55 (0:15–5:08)	
Blood loss (ml)	750–1000 (100–4500)		750–1000 (100–4368)	
Temp. start (°C)*	35.7 (34.7–36.8)		35.8 (35.0–36.7)	
Temp. end (°C)*	35.5 (33.9–37.1)		35.8 (34.5–36.9)	
Fluid input (ml)†	4500 (2000–11000)		3500 (1100–9000)	
Anaesthetic time (min)†	55 (15–90)		40 (17–80)	
Venesection volume (ml)	1350 (0–1454)			

with those who did not, 16/48 (33%) vs 20/112 (18%) ( $P=0.03$ ). There were no specific complications as a result of ANH.

There was no significant difference in the number of days stay in the two groups, median 8 (5–110) vs 10 (5–92), ANH and no ANH, respectively.

## Discussion

The number of patients receiving allogeneic blood and number of units transfused in the two groups were virtually identical (28 and 30%, 90 and 93 units). It is interesting to observe the transfusion rates in the two groups, broken down by estimated blood loss (Table 3), as mathematical modelling has shown that it is procedures with significant blood loss that are likely to benefit.<sup>4,8</sup> In those patients with a blood loss of more than 750 ml (post-hoc analysis), fewer were transfused in the ANH group (16/42 compared with 24/46), whilst a greater number of patients were transfused in

**Table 3** Transfusion rates in ANH and control by timing of transfusion (entire study period, day 0, days 1–3) and blood loss (all patients, patients with blood loss less than 750 ml, patients with blood loss more than 750 ml). Figures in bold represent the total number of patients receiving a transfusion after or during surgery

	All patients			Patients with blood loss <750 ml			Patients with blood loss >750 ml		
	All	Day 0	Days 1–3	All	Day 0	Days 1–3	All	Day 0	Days 1–3
<b>ANH</b>									
Patients (%)	<b>22/78 (28)</b>	15/78 (19)	9/78 (12)	<b>6/36 (17)</b>	5/36 (14)	1/36 (3)	<b>16/42 (38)</b>	10/42 (24)	8/42 (19)
Units	90	52	26	21	18	3	69	34	23
<b>CONTROL</b>									
Patients (%)	<b>25/82 (30)</b>	20/82 (24)	8/82 (10)	<b>1/36 (3)</b>	1/36 (3)	0/36 (0)	<b>24/46 (52)</b>	19/46 (41)	8/46 (17)
Units	93	56	22	1	1	0	92	55	22

**Table 4** Transfusion rate in ANH and control by type of operation. Others: two gastroenterostomies, two division adhesions, one biopsy pancreas, one stricturoplasty, one excision intra-abdominal sarcoma

	ANH (78)		Control (82)	
	Number	Transfused (%)	Number	Transfused (%)
Right hemi-colectomy	8	1 (12.5)	8	0 (0)
Left hemi-colectomy	23	1 (4)	22	2 (9)
Anterior/AP resection	33	15 (45)	39	16 (41)
Subtotal colectomy	4	1 (25)	2	1 (50)
Panproctocolectomy	0	0 (0)	1	1 (100)
Whipples	3	2 (67)	5	4 (80)
Gastrectomy	3	0 (0)	2	0 (0)
Other	4	2 (50)	3	1 (33)

**Table 5** Multivariate logistic regression model for transfusion

Variable	n	Odds ratio	95% CI
Haemoglobin/1 g dl <sup>-1</sup> increase	160	0.43	0.28–0.65
Blood loss			
≤500	45	1.00	–
501–1000	39	4.17	0.91–18.91
1001–1500	43	13.37	3.22–55.54
>1500	33	54.76	11.54–259.82
Age/yr increase	160	1.03	1.00–1.07

**Table 6** Number of complications by group and by presence of allogeneic transfusion. UTI, urinary tract infection; RTI, respiratory tract infection

Complications	ANH (78)	Control (82)	Allogeneic transfusion	
			Yes (48)	No (112)
Pyrexia	0	3	1	2
UTI				
Discharge	5	4	7	2
Day 30	3	3	0	6
RTI				
Discharge	1	1	2	0
Day 30	1	0	0	1
Wound infection				
Discharge	1	5	3	3
Day 30	2	1	2	1
Deep infection	1	0	1	0
Septicaemia	1	1	2	0
DVT	2	2	2	2
PE	0	2	0	2
Anastomotic leak	0	3	2	1
Death	2	1	2	1
Total	19	26	24	21

the ANH group when there was a blood loss of less than 750 ml (6/36 compared with 1/36), although neither of these results were significant. The dilutional effect can result in 'falsely' diluted haemoglobin levels thereby triggering transfusion when it is not required. This point has been realized by other authors.<sup>16</sup> If the ANH group were over transfused when the blood loss was less than 750 ml, one would expect the haemoglobin levels after surgery to reflect this. However, the haemoglobin levels in each group on days 1, 2, discharge, and 30 were also virtually identical, as was the calculated RBC loss. It remains possible that in high blood loss groups, haemodilution marginally reduces allogeneic transfusion rate, and our subgroup is underpowered to show this. However, once blood loss was greater than 2500 ml all patients received allogeneic blood (7/7 and 5/5 ANH and control, respectively).

Logistic regression identified three factors, which affect transfusion; starting haemoglobin, blood loss, and age, which concurs with previous studies.<sup>17</sup> Twenty-nine per cent of the 154 patients excluded were so because of a starting haemoglobin of less than 11 g dl<sup>-1</sup>. Looking at the entire study population (380 patients), 29% had a starting haemoglobin level of less than 12 g dl<sup>-1</sup> and 47% of more than 13 g dl<sup>-1</sup>. These figures imply that preoperative boosting of haemoglobin level may be of use in decreasing allogeneic transfusion.

When compared with ASA matched historical controls (used for sample size calculation), the introduction of a transfusion protocol reduced the transfusion rate in the colorectal patients from 136/333 (41%) to 37/138 (27%), *P*=0.004. This may be study- and/or transfusion-protocol related, but explains the large allogeneic savings seen in studies with historical controls.

The median volume of blood venesected was 1350 ml (0–1454). Twelve patients had less than 900 ml venesected (Fig. 1); five had no blood venesected, four because of failed i.v. access and the other because of consultant's decision in theatre (listed for major operation, minor performed). In total 66/78 (85%) patients had the desired greater than/equal to 900 ml venesection. The main reasons for failure included poor venous access resulting in low flow or clot formation in the tubing, and anaesthetist's discretion preventing further venesection. Excluding those patients



with less than 900 ml venesection from analysis, again resulted in no significant difference in transfusion rates 20/66 (30%) vs 25/82 (30%). This illustrates that the technique is not as simple in practice as it appears to be in theory.

Haemodilution increased anaesthetic time by a median of 15 min, 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. Epidural local anaesthetic block may have resulted in hypervolaemic haemodilution, as i.v. fluids were administered to compensate for the vasodilation. Although this affected both groups equally, as all patients had epidurals, the results cannot necessarily be extrapolated to patients not receiving an intra-operative epidural.

It was not felt possible to blind the clinicians, investigators, or anaesthetists. It would have been possible to involve a separate clinician to decide upon appropriateness of allogeneic transfusion after surgery, however, this was not felt necessary in view of the transfusion protocol, which was adhered to in all but three patients in each group.

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.

In this study, the largest performed in the past 25 yr, ANH did not affect allogeneic transfusion rate, complication rate, or duration of stay in major gastrointestinal surgery. The study was designed to be pragmatic and applicable widely.

In the recent study performed by Matot and colleagues,<sup>18</sup> in patients undergoing liver resection, the median blood loss was 750 and 890 ml in the ANH and control groups, respectively. This was despite attempting to select patients with an anticipated blood loss of 70% or more of the patient's blood volume and illustrates that blood loss prediction remains difficult. They did show a reduction in allogeneic transfusion rate from 36 to 10% in patients haemodiluted, with a median venesection volume of 2020 ml and 39 patients in each arm. However, the safety of ANH, in particular to extreme levels, remains unknown. Carvalho and colleagues<sup>19</sup> reported a case of myocardial ischaemia in a patient undergoing ANH before abdominal aortic aneurysm repair. Some other studies have also shown a reduction in transfusion rate with ANH. Wong and co-workers<sup>20</sup> studied 145 patients, undergoing elective infra-renal aortic surgery, randomized 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 units (450 ml) of blood were venesected for ANH, and as two interventions were studied, it is impossible to know the relative effect of either one.

Boldt and colleagues<sup>21</sup> looked at 60 patients undergoing retropubic prostatectomy allocated to three 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 50 mm Hg 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 three groups were 9, 5, and 12, respectively. However, only a mean of 710 ml extra fluid was administered to the ANH group compared with controls, implying that patients in the ANH group were bled rather than haemodiluted.

Herregods and co-workers<sup>22</sup> 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.

Olsfanger and colleagues<sup>23</sup> found a significantly greater number of units transfused in controls compared with patients who were haemodiluted to a target packed cell volume (PCV) of 28–30% (mean 1000 ml collected) undergoing total knee replacement. However, only 30 patients were studied, randomized into three groups; two receiving ANH and one control. The control group had higher ASA grades and significantly greater postoperative blood losses.<sup>11</sup>

In a three-arm study, McGill and colleagues<sup>24</sup> randomized 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, although only 10 ml kg<sup>-1</sup> blood was venesected during ANH.

Earlier studies were mostly flawed and the deficiencies have been well reviewed<sup>25,26</sup> (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).

Our study demonstrates that the widespread use of 3-unit ANH is not justified in major gastrointestinal surgery. The efficacy of extreme ANH, in cases with massive blood loss remains unknown, but the safety in these situations is questionable.

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