Acute normovolaemic haemodilution decreases postoperative allogeneic blood transfusion after total knee replacement

D. OLSFANGER, B. FREDMAN, B. GOLDSTEIN, A. SHAPIRO AND R. JEDEIKIN

Summary

We hypothesized that the success of postoperative blood conservation after acute normovolaemic haemodilution (NVHD) is influenced by the extent of intraoperative bleeding and surgical trauma, and the timing of autologous blood transfusion. As total knee replacement is associated with minimal intraoperative but extensive postoperative blood loss, this procedure is ideally suited to acute NVHD. Therefore, to test our hypothesis, 30 patients undergoing elective total knee replacement were enrolled in a prospective, randomized, controlled study. In groups NVHD-2 and NVHD-6, before induction of anaesthesia patients were bled to a target packed cell volume (PCV) of 28–30%, and in the post-anaesthesia care unit autologous blood was transfused over a 2-h period terminating after operation at 2 and 6 h, respectively. In the control group, NVHD was not performed. After operation, platelets, fibrinogen, prothrombin and partial thromboplastin time, and liver function, urea and electrolytes were measured and compared with preoperative baseline values. Significantly (P<0.024) more allogeneic blood was transfused in the control group (21 u.) compared with either group NVHD-2 (7 u.) or group NVHD-6 (5 u.). In the control group, despite the allogeneic blood transfusion, postoperative PCV decreased until day 4 after operation. Coagulation profile, liver function and urea and electrolyte concentrations were unaffected by the method of treatment. We conclude that for total knee replacement, acute NVHD is an effective blood conservation strategy. However, there was no difference in allogeneic blood administration between the two NVHD groups. Coagulation and liver function, and urea and electrolyte concentrations were unaffected by treatment. (Br. J. Anaesth. 1997; 79: 317–321).

Key words

Despite rigorous screening procedures, inadvertent transmission of infectious diseases remains a significant cause of patient morbidity and mortality.1–7 Furthermore, the increase in life expectancy has adversely affected the ratio of recipients to healthy donors and consequently decreased the availability of allogeneic blood.8

In an attempt to conserve natural blood products, curtail financial expenditure, prevent inadvertent transmission of infectious diseases and ensure safe blood transfusion in addition to simplifying the pre-administration process, alternative transfusion methods have been sought. While haemoglobin solutions,9 perfluorocarbons and liposome-encapsulated haemoglobin have been developed, these compounds are expensive, have a limited circulatory half-life and do not replace the immunological or coagulant functions of natural blood products.10 Similarly, preoperative autologous blood donation has been shown to be an expensive blood conservation technique.11 12 Furthermore, because of administrative errors, incompatible blood transfusion may occur.13 14

In the surgical context, acute normovolaemic haemodilution (NVHD) is a potentially useful blood conservation strategy.15 Because autologous blood is ultimately transfused, this simple technique does not require compatibility testing and is not associated with infectious disease transmission. However, as few randomized, prospective, controlled studies have been performed, the efficacy of NVHD in reducing administration of allogeneic blood is the subject of much debate.16–19

In our clinical experience, the extent of intraoperative bleeding and surgical trauma, and the timing of autologous blood transfusion directly influence the success of NVHD as a blood conservation strategy. While we have shown that NVHD for scoliosis surgery decreases allogeneic blood requirements both during and after operation,15 we hypothesize that the extent of intraoperative blood loss during this surgical procedure adversely

Before administering blood to the surgical patient the sample must be collected, stored and screened for infectious disease and donor-recipient compatibility. This complex process requires a costly organizational infrastructure.

DAVID OLSFANGER, MB, CHB, BRIAN FREDMAN, MB, BCH, BERNAUDO GOLDSTEIN, MD, ARIE SHAPIRO, MD, ROBERT JEDEIKIN*, BSC, MB, CHB, FFA(SA), Department of Anesthesiology and Critical Care, Meir Hospital, Kfar Sava, The Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel. Accepted for publication: April 18, 1997.

*Address for correspondence: Department of Anesthesiology and Critical Care, Meir Hospital, Kfar Sava 44281, Israel.
influences the success of NVHD as a blood conservation strategy. Unlike scoliosis surgery, total knee replacement is performed with an occlusive tourniquet and is associated with minimal intraoperative but expensive postoperative blood loss. As a result, total knee replacement is ideally suited to evaluate the efficacy of acute NVHD on postoperative blood administration. Therefore, we designed a study to determine the effect of NVHD on postoperative allogeneic blood administration after total knee replacement. In addition, we assessed the optimal transfusion time and effect of NVHD on coagulation factors, liver function, and urea and electrolyte concentrations.

Patients and methods
After obtaining Institutional Review Board approval, we studied 30 healthy, ASA I–III patients undergoing elective total knee replacement in a randomized, prospective, controlled, open label design. Patients with a history of ischaemic heart disease, hypertension, chronic renal failure, liver cirrhosis, bleeding disorders or current anticoagulant therapy were excluded.

On arrival in the operating room holding area, the radial artery was cannulated and monitoring equipment attached. Throughout the peroperative period the following variables were recorded at 1–5-min intervals: intra-arterial pressure, electrocardiogram (ECG) and peripheral haemoglobin oxygen saturation (SpO₂). Thereafter, according to a randomization table, patients were allocated to one of three groups: in groups NVHD-2 and NVHD-6, while in the operating room holding area patients were bled via a 16-gauge needle placed in the antecubital fossa to a target packed cell volume (PCV) of 28–30% using standard blood collection sets containing citrate–phosphate–glucose with adenine (CPDA-1; Travenol Laboratories Ltd, Israel). PCV was calculated using a Technicon H2 (Bayer) blood analyser. Blood volume was maintained with lactated Ringer’s solution in a 1:3 (blood:Ringer’s) replacement ratio such that arterial pressure and heart rate remained unchanged. The volume of blood removed was calculated by weighing the collection bag before and after venesection and assuming that 1 mg represented 1 ml of whole blood. All collected autologous blood was stored in the operating room at room temperature. In the control group NVHD was not performed.

On arrival in the operating room, a standardized general anaesthetic technique was used comprising thiopentone 4–6 mg kg⁻¹ and fentanyl 5 μg kg⁻¹ i.v. for induction and 0.5–1.5% isoflurane (end-tidal) and 70% nitrous oxide in oxygen for maintenance of anaesthesia. Tracheal intubation was facilitated with suxamethonium 1.0 mg kg⁻¹ i.v., and surgical relaxation maintained (using a peripheral nerve stimulator) with i.v. pancuronium. After induction of anaesthesia end-tidal carbon dioxide concentration was monitored and the urinary bladder catheterized. Before surgical incision a tourniquet was placed and the operative limb isolated. After placement of the prosthesis, the tourniquet was released and haemostasis performed. Thereafter, the tourniquet was re-inflated until the conclusion of surgery. Intraoperative fluid requirements were administered to maintain heart rate and mean arterial pressure within 20% of baseline values and a urine output of at least 2 ml kg⁻¹ h⁻¹. Intraoperative blood loss was assessed by measuring blood volume in suction containers and by weighing all surgical pads and swobs. No blood was administered during operation.

In the post-anaesthesia care unit (PACU) the operative limb was moved using a continuous passive motion device. Autologous blood was re-infused slowly over a 2-h period terminating 2 and 6 h after operation in the NVHD-2 and NVHD-6 groups, respectively. In the control group allogeneic blood was transfused to maintain PCV > 28%. On arrival in the PACU and for the duration of hospital admission, subcutaneous heparin 3500 u. was administered three times a day. In the orthopaedic department the decision to transfuse allogeneic blood was taken by an orthopaedic surgeon who was blinded as to the method of treatment. Twenty-four hours after operation the volume of blood in the surgical drain was measured. Thereafter, in order to decrease possible infection, the drain was removed. Haemoglobin, PCV, prothrombin time (PT), partial thromboplastin time (PTT), platelet count and fibrinogen were measured on arrival in the operating room, after NVHD but before induction, during operation, in the PACU, daily for 9 days and at 3 months after operation. Similarly, serum glucose, sodium, potassium, calcium, urea and creatinine, cholesterol, albumin and bilirubin concentrations were measured at the same times.

Data are expressed as mean (±SD or ±SEM). Descriptive variables were analysed using chi-square tests. Continuous variables were analysed using analysis of variance (with Bonferroni’s correction for multiple comparisons). In all cases P<0.05 was considered statistically significant.

Results
Patient data (table 1) and duration of anaesthesia and surgery (table 2) were comparable in the three groups. To achieve the target PCV, 1003 (228) and 985 (197) ml of blood were removed over a period of 43 (6) and 41 (4) min in the NVHD-2 and NVHD-6 groups, respectively (table 2). Perioperative crystalloid administration and urine output are presented in table 2. Mean intraoperative surgical blood loss was 370 (78), 353 (63) and 360 (91) ml in the NVHD-2, NVHD-6 and control groups, respectively. In the control group allogeneic blood was transfused to maintain PCV > 28%. On arrival in the PACU and for the duration of hospital admission, subcutaneous heparin 3500 u. was administered three times a day. In the orthopaedic department the decision to transfuse allogeneic blood was taken by an orthopaedic surgeon who was blinded as to the method of treatment. Twenty-four hours after operation the volume of blood in the surgical drain was measured. Thereafter, in order to decrease possible infection, the drain was removed. Haemoglobin, PCV, prothrombin time (PT), partial thromboplastin time (PTT), platelet count and fibrinogen were measured on arrival in the operating room, after NVHD but before induction, during operation, in the PACU, daily for 9 days and at 3 months after operation. Similarly, serum glucose, sodium, potassium, calcium, urea and creatinine, cholesterol, albumin and bilirubin concentrations were measured at the same times.

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| Table 1 Patient characteristics for the three groups (mean (SD or range) or number) |
|---------------------------------|------------------|------------------|
| NVHD-2                          | NVHD-6           | Control          |
| n                               | 10               | 10               | 10               |
| Age (yr)                        | 71 (61–87)       | 65 (54–71)       | 72 (60–82)       |
| Sex (M/F)                       | 2/8              | 1/9              | 2/8              |
| Weight (kg)                     | 71 (10)          | 78 (15)          | 72 (11)          |
| Height (cm)                     | 155 (5.6)        | 159 (8.1)        | 154 (5.7)        |
| ASA (I/II/III)                  | 6/4/0            | 7/3/0            | 5/3/2            |
Normovolaemic haemodilution

319

Twenty-four hours after operation, the volume of blood collected from the surgical drains was 409 (94), 495 (122) and 575 (193) ml in the NVHD-2, NVHD-6 and control groups, respectively.

As a result of the study design, before induction of anaesthesia PCV values in the two NVHD groups were significantly lower than those in the control group. Similarly, on arrival in the PACU a significantly higher PCV was recorded in the control group. During the postoperative period, PCV in the control group decreased, reaching its lowest point on day 4 after operation. However, because of allogeneic blood transfusion, statistical significance was not reached (fig. 1).

In the control group, significantly (P<0.024) more allogeneic blood was transfused after operation (table 3). All control patients received allogeneic blood transfusions. A total of 21 u. of packed cells were transfused, with each patient receiving at least 2 u. of blood (table 3). Between days 3 and 6 days after operation, 17 u. of allogeneic blood were transfused. In the NVHD-2 group, six patients received allogeneic blood transfusions and a total of 7 u. of packed cells were administered. Five patients received 1 and one patient received 2 u. of blood. In the NVHD-6 group, five patients received 1 u. of allogeneic blood.

In all patients skin discolouration and swelling caused by subcutaneous haematoma were noted in the ipsilateral dependent thigh and flank.

Preoperative platelet count, PT and PTT were similar in the three groups, and after haemodilution no significant changes were recorded in the NVDH-2 and NVDH-6 groups. Postoperative evaluation of these variables revealed no significant difference between the three groups. Compared with baseline, blood fibrinogen increased significantly in all three groups. While these values remained high until discharge, maximal concentrations were recorded 4 days after operation.

NVDH had no effect on perioperative glucose, calcium, creatinine, urea and electrolytes, cholesterol or bilirubin concentrations. A similar decrease in serum albumin concentration was noted in all groups.

On day 4 after operation, one patient in group NVHD-2 complained of sudden, intense right-sided chest pain which was followed by both circulatory and respiratory arrest. Despite extensive resuscitation the patient died. Because of family preference no post mortem was performed.

Patient follow-up 3 months after operation revealed a PCV of 36.8%, 36.3% and 35.1% in the NVHD-2, NVHD-6 and control groups, respectively. Fibrinogen concentrations measured at this time were similar to preoperative values.

**Discussion**

The results of this study demonstrated that acute NVHD was an effective blood conservation strategy when performed for total knee replacement. Patients who underwent acute haemodilution required

<table>
<thead>
<tr>
<th>Anaesthetic data (mean (SD))</th>
<th>NVHD-2</th>
<th>NVHD-6</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venesection (ml)</td>
<td>1003 (228)</td>
<td>985 (197)</td>
<td></td>
</tr>
<tr>
<td>Venesection (min)</td>
<td>43 (6)</td>
<td>41 (4)</td>
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<tr>
<td>Ringer’s lactate (ml)</td>
<td>4310 (633)</td>
<td>4370 (334)</td>
<td>1890 (375)</td>
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<tr>
<td>Blood loss (ml)</td>
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<tr>
<td>24-h drain</td>
<td>370 (78)</td>
<td>353 (63)</td>
<td>360 (91)</td>
</tr>
<tr>
<td>Urine output (ml)</td>
<td>1775 (103)</td>
<td>1165 (176)</td>
<td>658 (346)</td>
</tr>
<tr>
<td>Anaesthesia time (min)</td>
<td>241 (25)</td>
<td>229 (33)</td>
<td>227 (21)</td>
</tr>
<tr>
<td>Surgery time (min)</td>
<td>201 (23)</td>
<td>188 (35)</td>
<td>183 (19)</td>
</tr>
</tbody>
</table>

**Figure 1** Mean (SEM) perioperative packed cell volume (PCV) in groups NVHD-2 (▲), NVHD-6 (●) and in the control group (▲) before and after normovolaemic haemodilution (NVHD), in the post-anaesthesia care unit (PACU) and up to 3 months after operation. *P<0.05 compared with groups NVHD-2 and NVHD-6, respectively.

<table>
<thead>
<tr>
<th>Postoperative days</th>
<th>NVHD-2</th>
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<th>Control</th>
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<tr>
<td>n</td>
<td>1 2 3 4 5 6 7 8 9</td>
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<td>1</td>
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**Table 3** Postoperative allogeneic blood administration in the three treatment groups. n = patient per group. Numbers in table represent number of units administered to patient per postoperative day.
significantly less postoperative allogeneic blood. In contrast, between days 3 and 6 after operation, nine patients in the control group received allogeneic blood, most receiving at least 2 u.

Analysis of the postoperative PCV data suggests that NVHD directly influenced transfusion requirements and may have affected postoperative blood loss (Fig. 1). As expected from the study design, in the immediate postoperative period PCV in the control group was significantly higher compared with groups NVHD-2 and NVHD-6, respectively. After autologous blood transfusion there was no significant difference in postoperative PCV between the three groups. Therefore, as PCV was stable and the allogeneic transfusion greater in the control group, it appears that NVHD may reduce postoperative blood loss.

As postoperative PCV and allogeneic blood requirements were similar in the NVHD-2 and NVHD-6 groups, it appears that the timing of the autologous blood administration did not affect postoperative allogeneic blood requirements. This may be explained by the relatively short time interval between autologous blood transfusion (2 and 6 h after operation). However, autologous blood was kept at the patient’s bedside and stored at room temperature. A longer transfusion time interval between groups would have required more elaborate storage and safety facilities and consequently reduced the attractiveness of NVHD as a blood conservation strategy.

In previous studies the use of acute NVHD has been associated with variable results. In a retrospective analysis of patient records Goodnough and colleagues16 demonstrated only modest blood conservation after acute preoperative NVHD in patients undergoing radical prostatectomy. Furthermore, during surgical correction of scoliosis, retrospective uncontrolled studies demonstrated that 42–66% of patients who underwent NVHD required postoperative allogeneic blood transfusion.13,20,21 These studies differ from our investigation in both study design and timing of autologous blood transfusion. In previous investigations prospective studies were not performed and the efficacy of NVHD was determined by comparison with historical controls. Furthermore, as both scoliosis surgery and radical prostatectomy are traumatic procedures associated with significant intraoperative blood loss, autologous blood was transfused either during or on completion of the operative procedure. Thus the potential allogeneic blood transfusion-sparing effects of NVHD may have been lost.

We postulate that the postoperative allogeneic blood-sparing effect demonstrated in this study was likely multifactorial. First, Milam and colleagues22 suggested that in polycythaemic children undergoing cardiac surgery, NVHD results in improved blood flow in the microcirculation and thus decreases coagulopathies and consequent postoperative bleeding. Second, fresh autologous blood is rich in platelets and clotting factors. This together with improved microcirculation may result in decreased postoperative bleeding.23–26 It is of interest that in our study perioperative PT, PTT, platelets and fibrinogen concentrations were unaffected by the treatment. However, we measured quantitative rather than qualitative function. Furthermore, NVHD may modify the activity of components of the clotting cascade which were not measured. Third, as NVHD decreases PCV, blood with a low red blood cell mass may have been lost into the extravascular compartment. This is supported by the fact that an ipsilateral thigh and flank haematoma was noted in all patients. As intraoperative and 24-h blood loss were similar in the three groups, we suggest that “diluted” blood formed the haematoma in the two haemodilution groups. However, the time of onset and extent of this haematoma were difficult to compare.

In our opinion the sudden death reported in our study was a consequence of the surgical procedure rather than the anaesthetic technique. As the fatal event occurred 4 days after operation and the patient complained of acute right chest pain before cardiorespiratory collapse, we conclude that a massive pulmonary embolism was the likely cause of the patient’s death. This theory is supported by the fact that the incidence of deep vein thrombosis and pulmonary embolism after total knee replacement is 40–84% and 1.7%, respectively.27–29 Unfortunately, a post mortem was not performed.

This study design may be criticized as the trigger to transfuse after discharge from the PACU was based on the orthopaedic surgeon’s “transfusion culture” rather than predefined criteria. It is for this reason that the majority of patients in the two NVHD groups received only 1 u. of allogeneic blood. In our opinion patients who required only 1 u. of allogeneic blood were probably transfused inappropriately. If this subset of patients were excluded from statistical analysis the effect of NVHD on postoperative blood requirements would have been even more significant.

We conclude that the efficacy of acute NVHD is likely to be improved in procedures associated with minimal intraoperative but significant postoperative blood loss. Therefore, for total knee replacement, acute haemodilution is a convenient and effective blood conservation strategy. While the exact mechanism of this blood conservation is unclear, to maximize allogeneic blood conservation strict postoperative transfusion criteria must be defined.

References


