Randomized controlled trial of goal-directed haemodynamic treatment in patients with proximal femoral fracture

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Editor’s key points
- This trial compared goal-directed haemodynamic therapy and conventional management in elderly patients undergoing femoral fracture surgery.
- This is the largest single study in this patient group, but the trial was stopped early with no significant differences in primary outcomes.
- The number of patients achieving haemodynamic goals was similar in both groups.
- These results may reflect other differences in patient management in this study compared with previous data.

Background. Patients with proximal femoral fracture (PFF) are at high risk of postoperative complications. Goal-directed haemodynamic treatment (GDHT) in other high-risk surgical patients reduces postoperative complications. We aimed to compare effects of GDHT and routine fluid treatment (RFT) on postoperative outcomes after PFF surgery.

Methods. PFF patients (≥70 yr) were enrolled in this single-centre, open, randomized, controlled, parallel-group superiority trial with concealed allocation using computer-generated randomization. Treatments: (i) GDHT to attain oxygen delivery index \( \geq 600 \text{ ml min}^{-1} \text{ m}^{-2} \) using fluids and dobutamine and (ii) a protocol-guided RFT. After 150 enrolled patients, the trial was stopped due to slow recruitment. The short-term primary outcome measure was the relative risk (RR) of postoperative complications; secondary measures were (i) administered fluid levels, (ii) vasopressor requirements, and (iii) haemodynamic responses.

Results. For the GDHT group, 74 and for the RFT group 75 patients were designated. The RR of postoperative complications (GDHT vs RFT) was 0.79 (95% confidence interval 0.54–1.16); the volumes of i.v. fluids decreased (1078 vs 1440 ml, \( P = 0.01 \)); fewer patients required treatment of hypotension (18.5% vs 75%, \( P < 0.005 \)); there were more patients with increased oxygen delivery at the end of operation (28% vs 8%, \( P = 0.04 \)), but the haemodynamic goal was achieved in only 27% of patients in the GDHT group.

Conclusions. The magnitude of risk reduction of postoperative complications is clinically relevant, but the trial was underpowered and the null hypothesis cannot be rejected.

Keywords: complications; elderly; fluid therapy; haemodynamics; hip fractures
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registered at the registration site of the US National Institute of Health (ClinicalTrials.gov; ref. NCT01141894).

The trial is a single-centre, open, randomized (1:1), and controlled parallel-group superiority clinical trial. Trial follow-up extends to 12 months and continues. The trial was run at Karolinska University Hospital, a primary teaching hospital in Huddinge, Sweden (south of Stockholm); this region has a population of 310,000; about 17,600 persons are >75 yr and 5600 are >85 yr.

**Trial population**

The trial population consisted of patients aged ≥70 yr and weight ≥40 kg who were undergoing PFF surgery during regular operating hours. Exclusion criteria were: (i) patients who could be harmed due to the treatment (ongoing myocardial infarction, chronic dialysis), (ii) concomitant medication with lithium, (iii) known allergy to lithium or medical device components, (iv) weight ≤40 kg, (v) life expectancy <6 months, (vi) pathological fractures and conditions, (vii) inability to give informed consent, (viii) anticipated difficulties obtaining data during the first postoperative year (as judged by a research team member), and (ix) operations scheduled during hours when research team was unavailable. (Patients with pathological fractures had a presumed survival of <12 months. Given the planned follow-up of 12 months, these patients were not included).

One research team member (anaesthetist) evaluated patients’ eligibility. Eligible patients were enrolled if a signed informed consent was obtained after they received information about trial-specific procedures.

**Randomization and allocation**

The Karolinska Trial Alliance (www.randomization.com) produced a computer-generated list of random numbers that were used for treatment-group allocation. The allocated treatment was obtained via telephone after acquisition of informed consent forms. The allocation sequence was not available to the research team. After the allocation sequence was acquired, a research nurse assigned patients to one of the treatment groups. After assignment to a group, the treatment was not blinded to patients or operating theatre caregivers. The assigned treatment was coded in the data set for primary and secondary outcome analyses.

All enrolled patients were analysed for the primary outcome measure. The secondary outcome measures were not analysed when (i) arterial catheter insertion was unsuccessful, (ii) LiDCO monitor technical errors prevented monitoring, or (iii) unexpected operating list changes (logistics-related) postponed the operation outside the scope of regular operating hours.

**Treatments**

Figure 1 shows the treatment algorithm. Before the trial, a written multidisciplinary programme of standard care was introduced to standardize (i) pre-, intra-, and postoperative supplementation of fluids and nutrition, (ii) time between admission and operation, and (iii) preoperative pain treatment (femoral nerve block at admission).

**Treatment given in both groups**

Between the admission to the hospital and operation, all patients received infusion of crystalloids based on individual assessment by the geriatricians. If no contraindication existed, then spinal anaesthesia was used for both groups: heavy bupivacaine 5 mg ml⁻¹, 1.5–2 ml (the lower limit of the dose recommendation for spinal anaesthesia was based on a Swedish trial done by Olofsson. The upper limit was used when surgery delay was presumed for various reasons), and 1 ml sufentanil 5 µg ml⁻¹. After anaesthesia, all patients received a background infusion of buffered glucose 25 mg ml⁻¹, at a rate of 1 ml kg⁻¹ h⁻¹ and Ringer’s acetate, at a rate of 2 ml kg⁻¹ h⁻¹. The infusion was discontinued at the end of surgery. All patients were monitored with a lithium dilution cardiac output (CO) monitor (LiDCO, LiDCO Ltd, Sawston, Cambridge, UK), which was calibrated twice with i.v. lithium chloride (0.15 mmol ml⁻¹, 2 ml).

These objectives were set for both groups (i) mean arterial pressure between 70 and 110 mm Hg and vasopressor support by phenylephrine or ephedrine, if the systolic arterial pressure declined by more than 30% from initial values, and (ii) haemoglobin concentration at or more than 100 g litre⁻¹. Haemodynamic data were saved on the LiDCO monitor. A research nurse documented all intra- and postoperative data (e.g. administered fluids, blood units, anaesthetics, and vasopressor support) in a case report form. All electronic data (e.g. haemodynamic data and blood-gases analyses) were collected and saved by intensive care unit pilot (Dipylon Medical AB, Solna, Sweden).

**Goal-directed haemodynamic treatment**

Fluid challenge (3 ml kg⁻¹) with colloid was administered and repeated if a 10% increase in stroke volume (SV) was achieved. If no increase occurred, and if oxygen delivery (DO₂) was <600 ml min⁻¹ m⁻², then a dobutamine infusion was started at 0.2–10 µg kg⁻¹ min⁻¹. The infusion was stopped if tachycardia (>100 beats min⁻¹) occurred. Further fluid challenges were given if the SV decreased by 10%. The research team administered GDHT, which was discontinued at the end of the operation.

**Routine fluid treatment**

The RFT was identical to a previously introduced clinical programme. The attending anaesthesia team managed the RFT. The research team assured adherence to the clinical programme. Ringer’s acetate (300–500 ml) or colloids were administered before spinal anaesthesia. It was followed by the background infusion of buffered glucose and Ringer's acetate according to the treatment algorithm (Fig. 1). Other fluids or vasopressor treatment (e.g. phenylephrine and ephedrine) for correction of decreasing arterial pressure were administered at the attending anaesthetist’s discretion.
Glucose 50 mg ml⁻¹ at 40–80 ml h⁻¹

Randomization

Routine fluid treatment

Fluid bolus 3–500 ml

Fluid challenge 3 ml kg⁻¹ repeated if SV increased by 10%

If no increase of SV and $\text{DO}_2 \text{I} < 600 \text{ ml min}^{-1} \text{ m}^{-2}$

start of dobutamine

Anaesthesia

Buffered glucose 25 mg ml⁻¹ at 1 ml kg⁻¹ h⁻¹ and Ringer's acetate at 2 ml kg⁻¹ h⁻¹

Vasoactive support if systolic blood pressure decreases by more than 30% from the pre-anaesthesia value

Vasoactive support if systolic blood pressure decreases by more than 30% from the pre-anaesthesia value

Repeated fluid challenges 3 ml kg⁻¹ when the SV decreases by 10%

Vasoactive support if no effect of vasactive support increased fluid infusion rate

If no increase of SV and $\text{DO}_2 \text{I} < 600 \text{ ml min}^{-1} \text{ m}^{-2}$

titration of dobutamine

Fig 1 Intervention algorithm.
The LiDCO monitor was covered for the attending anaesthesia team.

**Outcome measures**

The primary postoperative outcome measure was the difference between the absolute risks of postoperative complications in survivors at hospital discharge, expressed by RR. Postoperative complications were prospectively assessed as per predefined criteria of Copeland and colleagues

(Supplementary Appendix). Secondary outcomes were volume of administered fluids, proportion of patients with intraoperative hypotension, intraoperative haemodynamic responses, mortality (within 30 days of surgery), aggregated healthcare costs, use of social services, and postoperative quality of life at 12 months. (The long-term data collection and the detailed analysis of haemodynamic responses are still ongoing.)

In the GDHT group, a patient was defined as fluid challenge responder if SV increased more than 10% of fluid challenge; in the RFT group, if the SV increased more than 10% of pre-anesthesia fluid loading. In both groups, a patient was defined as (i) an achiever if the DO2I was 600 ml·min⁻¹·m⁻² (±10%) during at least one time point while in treatment and (ii) a treatment responder if the DO2I exceeded the preoperative values by 10% at the end of treatment.

**Statistical analyses**

Sample size was based on data from a Swedish trial on patients undergoing PFF surgery (61%). Based on the expected absolute risk (0.61) and RR (0.63) for postoperative complications (GDHT vs RFT) on other high-risk surgical patients, a sample size was calculated (80% power, \( P<0.05 \) at two-sided error), and the calculation accounted for that age and co-morbidity influence only 57% of the complications. Consequently, a sample size of 660 patients was required.

For the statistical analyses, the Stata statistical software (version 12.1) and SAS version 9.3 (SAS Campus Drive, Cary, NC, USA) were used. Data were specified as median and range. The difference between absolute risks of complications in survivors was expressed by RR using a 95% confidence interval (CI) on the intention-to-treat basis. To test for differences between the groups, we used the Mann–Whitney U-test for continuous variables and Fisher’s exact test for categorical variables. Analysis of variance was used for repeated measures. For multiple testing, we used a procedure MULITEST in SAS. A value of \( P<0.05 \) was considered statistically significant.

**Results**

A total of 282 patients were screened for eligibility between March 2009 and September 2011; 150 patients were enrolled. One patient was enrolled twice (excluded for logistical reasons and enrolled again the next day) and so 74 patients were designated for GDHT and 75 for RFT; these patients were analysed for the expected primary outcome (i.e. on intention-to-treat basis). Seven patients did not receive the intended treatment (one due to technical error, two due to unsuccessful arterial cannulation, and four due to changes in the operation list). Therefore, 70 received GDHT and 72 received RFT (Fig. 2).

An interim analysis on efficacy and safety was run (as planned) after 100 patients (October 2010). At this point, no statistical difference was observed in the primary outcome, and no safety issues were detected. Despite attempts to accelerate it, patient recruitment was slower than expected. So 1 yr later (September 2011), when 150 patients were enrolled, the trial was stopped.

Table 1 displays patient characteristic data, risk scoring, and co-morbidities. Patient characteristics, risk scores, and co-morbidities were similar in the two groups (Table 1). The number of diabetic patients was 18 in the GDHT group and nine in the RFT group, but this was not significantly different \( (P=0.51) \).

**Primary outcome measure**

The absolute risk of postoperative complications for survivors was 0.36 in the GDHT group and 0.45 in the RFT group. The RR of postoperative complications, based on intention to treat, was 0.79 (95% CI 0.54 – 1.16), \( P=0.38 \) (Table 2), and the RR for mortality was 0.80 (95% CI 0.56 – 1.14) \( P=0.38 \).

**Secondary outcome measures**

Table 3 lists intra- and postoperative data (based on patients who received the treatment).

The GDHT group received less fluid per minute, less crystalloids but more colloids and more red blood cells (Table 3). Fewer GDHT patients needed vasopressors for correction of intraoperative hypotension: \( 18.5\% \) vs \( 75\% \) \( (P<0.005) \). Patients in both groups, who needed vasopressors (\( n=67 \)), were treated with phenylephrine, although in four patients, it did not provide an adequate effect and in these patients, epinephrine was used. In the GDHT group, 47 patients received dobutamine (dose range \( 0.2 – 9.5 \mu g \cdot kg^{-1} \cdot min^{-1} \)); in 23 patients, dobutamine could not be titrated because (i) of time limitation (12 patients), (ii) of heart rate \( >100 \) beats \( min^{-1} \) (four patients), (iii) they were spontaneous achievers (six patients), and (iv) of suspected aortic valve stenosis (one patient). In seven patients, titration was terminated due to heart rate \( >100 \) beats \( min^{-1} \). One patient received dobutamine in the RFT group. On the group level (irrespective of whether or not dobutamine was administered), no difference was achieved between the temporal changes of the DO2I (Fig. 3). The number of first fluid challenge responders was 27 (38.5%) in the GDHT group; in the RFT group, 10 (13.8%) patients responded with increased SVI to the pre-anesthesia fluid loading \( (P=0.02) \). The number of treatment responder (i.e. the DO2I exceeded the preoperative values by 10% at the end of treatment) was 20 (28%) in the GDHT group and 6 (8%) in the RFT group \( (P=0.04) \). No difference was found in the number of achievers \( [DO2I=600 \text{ ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2} (10\%) \text{ during at least } 5 \text{ min}] : 27\% \text{ vs } 19\% \text{ (GDHT vs RFT). No differences were found regarding intraoperative blood losses, urinary output, use of medication to achieve...
sedation, amount of fluids given after operation, length of stay on the postoperative care unit, and length of hospital stay.

**Discussion**

This trial report describes short-term primary and secondary outcomes (i.e. risk reduction of postoperative complications, volume of administered fluids, and main haemodynamic effects) when GDHT is compared with RFT. The long-term outcomes of the treatment are pending. Although a clinically relevant risk reduction of postoperative complications was achieved in the survivors, the null hypothesis could not be rejected. These factors favoured GDHT: number of patients with improved oxygen delivery during treatment, and fewer required vasopressors for the correction of the intraoperative hypotension.

**Comparisons with previous findings**

The present trial was stopped earlier than planned but is still larger (n=150) than the previously reported two GDHT trials on patients with PFF,\(^{19, 20}\) in which the pooled number of
Table 1 Patient characteristics. Categorical variables are given as number; continuous variables, as median and range. There were no differences between the groups. P-POSSUM, Portsmouth Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity

<table>
<thead>
<tr>
<th>Complication</th>
<th>Routine (n = 75)</th>
<th>GDHT (n = 74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>85 (70–101)</td>
<td>86 (71–101)</td>
</tr>
<tr>
<td>Female/male</td>
<td>75/25</td>
<td>71/29</td>
</tr>
<tr>
<td>ASA I/II/III/IV</td>
<td>2/20/43/7</td>
<td>1/19/43/7</td>
</tr>
<tr>
<td>P-POSSUM physiology score</td>
<td>20 (19–21)</td>
<td>20 (18–22)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>23 (22–24)</td>
<td>23 (22–24)</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>43</td>
<td>42</td>
</tr>
<tr>
<td>Respiratory diseases</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Hypertension</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>Kidney diseases</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Disease of central nervous system</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Dementia</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>Other diseases</td>
<td>10</td>
<td>9</td>
</tr>
</tbody>
</table>

Table 2 Number of complications, the absolute, and RR of postoperative complications. There were no significant differences between the groups.

<table>
<thead>
<tr>
<th>Complications</th>
<th>Routine (n = 75)</th>
<th>GDHT (n = 74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Respiratory</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Acute kidney failure</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Confusion</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Sepsis</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Deep-vein thrombosis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Wound infection</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Delayed healing</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Decubitus</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Wound haematoma</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Other complications</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Fatality/survivors</td>
<td>4/71</td>
<td>3/71</td>
</tr>
<tr>
<td>Total number of complications</td>
<td>43</td>
<td>44</td>
</tr>
<tr>
<td>Number of survivors with complications (absolute risk)</td>
<td>34 (0.45)</td>
<td>27 (0.36)</td>
</tr>
<tr>
<td>Relative risk per intention-to-treat (95% CI)</td>
<td>0.79 (0.54–1.16)</td>
<td></td>
</tr>
<tr>
<td>Number of complications and fatality (absolute risk)</td>
<td>38 (0.51)</td>
<td>30 (0.41)</td>
</tr>
<tr>
<td>Relative risk including mortality (95% CI)</td>
<td>0.8 (0.56–1.14)</td>
<td></td>
</tr>
</tbody>
</table>

In the present trial, we developed a cost-effectiveness model aligned with guidelines for health technologies assessments and found in this pre-trial analysis that RR of postoperative complications (but not mortality) heavily influences cost-effectiveness of GDHT. Consequently, the present trial was designed to assess the risk of postoperative complications and their influence on health-related quality of life, because such factors are required for cost-effectiveness analysis.

The present trial confirmed previously reported reduced frequency of intraoperative hypotension but not reduced length of hospital stay. (Hospital stay length is not included as an outcome measure in the present trial, but we report it for comparison with the previous GDHT trials on patients with PFF trials.) It must be emphasized that length of hospital stay was shorter in both groups compared with the previous trials, probably due to the applied multidisciplinary programme of standard care. This finding does not imply that GDHT is less beneficial than previously suggested, because the potential influence of GDHT on length of hospital stay may be overshadowed by the powerful effect of the applied multidisciplinary programme of standard care.

The lower frequency of intraoperative hypotension in the GDHT group might be due to the use of dobutamine, because the GDHT group received less fluids (15 vs 21 ml min⁻¹) compared with the RFT group in the present trial. In comparison with other trials: 22 vs 15.5 ml min⁻¹ were administered (treatment vs routine) in the Sinclair trial. In the Venn trial, the CVP group received 26 ml min⁻¹, the Doppler group received 34.7 ml min⁻¹, and the routine care group received 19.8 ml min⁻¹. These differences indicate that patients in the previous trials were dehydrated, but the present population was not. It seems that in the previous trials, the fluid deficit was underestimated by routine treatment, and it was overestimated in the present trial when RFT is compared with the GDHT.

In the RFT group, the proportion between the mean levels of administered crystalloids, colloids, and blood is 1:0.12:0.12. In the GDHT group, the proportion is 1:0.78:0.52. These proportions are comparable with previous trials (Table 4). The RFT group received more crystalloids because in line with the multidisciplinary clinical programme, crystalloids were
administered at the discretion of the attending anaesthetist before spinal anaesthesia and for replacement of estimated fluid losses.

Criteria for postoperative complications in the present trial were similar to those used in one of the previous GDHT trials on PFF, where cardiopulmonary and renal complications dominated—an observation not confirmed in the present trial. RR for postoperative complication was 0.5 (95% CI 0.24–1.04) in Venn’s trial (using the published data) and 0.79 (95% CI 0.54–1.16) in the present population. Both trials indicated that a clinically relevant risk reduction of postoperative complications may be achieved, but due to the limited number of observations, the null hypothesis could not be rejected.

Based on the mean value of RR, the number needed to treat (NNT) in Venn’s trial was 3; in the present trial, the NNT was 8. This difference may be due to the higher age of our patients and to the multidisciplinary clinical programme. In order of the number of affected patients in total (GDHT and RFT groups), these complications occurred: urinary tract infection (28), respiration (12), cardiovascular (11), other (10), confusion (9), and decubitus (7). Most likely, no GDHT strategy could influence all these complications.

**Response to dobutamine**

GDHT use was supported by the number of patients who increased on the DO2I during treatment. These patients had a slight dobutamine-induced heart rate increase and SV index increase (values not demonstrated). The preoperative cardiac index found in our patients (2.7 litre min⁻¹ m⁻²) could be compared with another population of patients.
with PFF (mean age 86 yr) in a descriptive trial with symptomatic heart failure. These researchers reported a cardiac index of 2.4 litre min$^{-1}$ m$^{-2}$ and a left ventricular ejection fraction of <35%. This indicates that patients in our trial had poor cardiovascular condition. The dobutamine infusion was started when the patients did not respond to further fluid challenges, and the DO$_2$I was below the goal. In 12 patients, the operation was almost completed at this stage of the algorithm, and these patients were not treated with dobutamine. Only 27% of the patients achieved the haemodynamic goal—compared with what is reported on a younger population (40–80%). Dobutamine was discontinued due to tachycardia in 14% of the patients, which is comparable with what is described for younger patients. Our finding does not indicate that dobutamine should be avoided in this population.

Implications on future research

We found lower absolute risk of postoperative morbidity in the control group (0.45) than expected (0.61). Given the expected RR found by the present trial (0.79), a sample size of 1000 patients should be required (80% power, $P<0.05$ at two-sided error).

When the trial was commissioned, one of the prerequisites was to start the operation within regular operating hours (daytime, Monday to Friday), while the research team was available. The recruitment of 150 patients took more than 2 yr; further recruitment of the remaining 850 patients would take 5–6 yr. Such a large trial may need a multicentre design to assure adequate recruitment.

Conclusions

The GDHT algorithm proposed by Shoemaker and colleagues may reduce the risk of postoperative complications in elderly PFF patients, but due to the reduced sample size and to the fewer complications than expected, we have failed to reject the null hypothesis. Some observed postoperative complications probably may not be influenced by GDHT algorithm. When GDHT is compared with RFT, fewer intraoperative fluids were administered, fewer patients required vasopressors for correction of intraoperative hypotension, and more patients increased on the DO$_2$I by 10% at the end of treatment.

Supplementary material

Supplementary material is available at British Journal of Anaesthesia online.

Declaration of interest

None declared.

Table 4 Volume median and (mean) and proportion of median and mean values (ml) of administered crystalloids, colloids, and blood using the present trial’s and previous trials’ published data. The Sinclair trial reported medians. The Venn trial reported mean values.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>GDHT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystalloid median</td>
<td>1197(1288)</td>
<td>493 (663)</td>
</tr>
<tr>
<td>Colloids median</td>
<td>0 (167)</td>
<td>430 (519)</td>
</tr>
<tr>
<td>Blood median</td>
<td>0 (162)</td>
<td>387 (345)</td>
</tr>
<tr>
<td>Crystalloid/colloid</td>
<td>1:0</td>
<td>1:0.88:0.78</td>
</tr>
<tr>
<td>Blood mean</td>
<td>1:0.12:0.12</td>
<td>1:0.78:0.52</td>
</tr>
<tr>
<td>Crystalloid/colloid</td>
<td>1:0</td>
<td>1:0.97:0.37</td>
</tr>
</tbody>
</table>

Vertical bars denote 0.95 confidence intervals

Figure 3 Temporal changes of oxygen delivery index. Values are compared at calibration (before intervention) and at the end of the operation. In the RFT group, 72 patients; in the GDHT group, all of 70 patients are included in the comparison regardless of whether or not they have received dobutamine.
Box 2. Main findings from observational studies (n = 42). Median duration of follow-up was 2.3 years (range 1.1 – 3.8).

- **Efficacy**:
  - Pain relief
  - Function improvement
  - Reduced incidence of complications
  - Improved long-term outcomes

- **Safety**:
  - No significant adverse events reported

- **Economic benefits**:
  - Cost savings associated with decreased hospital stay and reoperations

- **Indicators of efficacy**:
  - **Pain relief**
  - **Function improvement**
  - **Reduced complications**

- **Indicators of safety**:
  - **No adverse events**

- **Economic indicators**:
  - **Cost savings**

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