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Research Article

# Goal directed fluid therapy reduces major complications in elective surgery for abdominal aortic aneurysm: liberal versus restrictive strategies

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**KEYWORDS**
Liberal;
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$O_2$ERe;
Abdominal aortic aneurysm

**Abstract** *Background:* Optimal fluid management is crucial for patients undergoing surgical repair of abdominal aortic aneurysm (AAA). Persistent hypovolemia is associated with complications but fluid overload is also harmful.
*Aim:* This study evaluates that perioperative fluid restriction would reduce complications and improve outcome through goal-directed strategies in patients undergoing AAA.
*Methods:* Fifty patients, aged from 60 to 75 years undergoing elective surgical repair of AAA were included in this randomized study. Patients were divided into two groups, 25 for each: liberal group (L) receives 12 ml/kg/h and restrictive group (R) receives 4 ml/kg/h. Goal-directed-therapy approach was concerning assessment of tissue oxygenation. Dobutamine and fluid challenges were used to maintain adequate tissue perfusion during surgery.
*Results:* The patients of the (L) group received a significant greater amount of Lactated Ringer's solution (3586.76 ± 473.21) than the (R) group (1219 ± 140.6). The (R) group had 50% lower rate of major postoperative complications than the (L) group (24% vs 48%) and less hospital stay.
*Conclusion:* A restrictive strategy of fluid maintenance during optimization of oxygen delivery with early treatment directed to maintain oxygen extraction ratio estimate ($O_2$ERe) at < 27% reduces major complications and hospital stay of surgical patients undergo abdominal aortic aneurysm.


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## 1. Introduction

Perioperative fluid requirements were calculated by considering pre-existing deficits, maintenance volumes, and third space loss, depending on the type of surgery. Based on this, the benefits of goal-directed fluid therapy (GDT) "liberal" fluid approach were modulated. On the other hand, a "restrictive" fluid approach has been shown improved postoperative outcomes. Extremes of either approach were shown to induce hyper- or hypovolemia, respectively. Perioperative fluid requirements are well established for different age groups, as avoiding excessive fluid loss or administration provides successful homeostasis [1].

The "liberal" approach aims to optimize total blood volume. To assess the volume status of patients, a wide range of clinical (e.g. capillary refill), physiological (e.g. heart rate, urine output), and biochemical (acid–base deficits, lactate levels) parameters are useful [2].

Restrictive low fluid approach was estimated as 10% less volume than standard [3]. Fluid restriction regimens may increase the likelihood of perioperative hypovolemia and splanchnic ischemia. In patients who underwent major (mainly cardiovascular) surgery, it was shown that low gastric pH measured during the intraoperative period was associated with increased postoperative complications and costs [4]. Gastrointestinal perfusion is often compromised earlier than perfusion in other vascular beds under hypovolemia, stress, and increased metabolic demand [5]. There is a strong association between relative gastric luminal hypercarbia (suggesting relative gastrointestinal hypoperfusion) and postoperative organ dysfunction, including the gastrointestinal tract. Therefore, restoration of oxygen delivery, especially to the splanchnic bed, is of critical importance [6].

The "restrictive" approach actually represented "adequate fluid" substitution, exhibited by hemodynamic stability [7]. This might be true because the extracellular deficit after the usual preoperative fasting proved to be negligible [8] and the basal fluid loss via insensible perspiration or urine production proved not to exceed 1 ml/kg/h during major abdominal surgery [9].

Postoperative organ failures commonly occur after major abdominal surgery, increasing the utilization of resources and costs of care. Tissue hypoxia is a key trigger of organ dysfunction. Tissue hypoxia is diagnosed by an increase in oxygen extraction ($O_2ER$) over a predefined threshold. The development of postoperative organ failures severely affects the prognosis of surgical patients and substantially increases the utilization of resources and cost care. The prevalence of organ failure, length of stays in the ICU and in the hospital as well as postoperative mortality are largely increased in "high risk patients", for whom preoperative risk factors are unavoidable [10].

Therefore, the use of early and efficient therapeutic strategies was able to detect and to treat potential triggers of organ failures, such as tissue hypoperfusion. If hypoperfusion is not adequately managed, tissue hypoxia could occur, resulting from an impairment of the adaptive mechanisms of myocardial contractile function, under the influence of inflammatory mediators, and the peripheral tissues will then increase their oxygen extraction ($O_2ER$) [11].

When $O_2ER$ increases over a threshold value, venous oxygen saturation will decrease and lactic acidosis can occur. Hence, the use of $O_2ER$ calculated from arterial and mixed venous oxygen saturation as a therapeutic goal, is appropriate to monitor goal-directed hemodynamic strategies because it reflects the balance between oxygen delivery and consumption [12].

The interpretation of venous oxygen saturation is eventually similar when mixed venous blood drawn from a pulmonary artery catheter is replaced by venous blood drawn from a central venous line (CVL) [13]. Goal-directed therapy, including fluid challenge, blood transfusion, and inotropes titrated to keep central venous oxygen saturation higher than a predetermined threshold of 70%, was associated with decreased mortality and rate of organ failures [14].

In this study, our primary outcome was to compare the number of patients who had major postoperative complications between liberal and restrictive fluid therapy groups in patients undergoing AAA. Major complications were defined as any untoward medical events that prolonged hospitalization, were life-threatening or caused death (e.g. 1-cardiovascular complications; arrhythmias (e.g. atrial fibrillation with hemodynamic disturbance and the need for antiarrhythmic drugs) and hypertensive crisis that required vasodilators for control and/or prolonged ICU stay. 2-Renal dysfunction was defined as an increase in serum creatinine level by more than twice the baseline level during the post-operative period in patients with previously normal renal function. 3-Gastrointestinal dysfunction was defined as feeding intolerance for more than 5 days postoperatively or the need for parenteral nutrition. 4-Extubation failure was failure to extubate the patient within the first 24 h after the operation or the need for reintubation within 72 h after extubation. 5-Anastomotic leakage was considered complication of tissue healing. 6-Infectious complications were detected as peritonitis and wound abscess).

And our secondary outcome was to compare between liberal and restrictive fluid therapies in patients undergoing AAA as regards the mean dose of dobutamine administered, number of fluid challenges received, number of transfused RBCs units and the length of ICU and hospital stays.

## 2. Methods

This study was conducted in a single blinded manner in which the patients were blinded to the study group allocation. Randomization was done using computer-generated number table of random numbers in a 1:1 ratio and conducted using sequentially numbered, opaque and sealed envelope (SNOSE). The drugs were prepared by the hospital pharmacy and were covered in foil and handled to the anesthesia resident caring for the patient. The anesthesia resident was not involved in any other part of the study. Intraoperative and postoperative data collections were achieved by the same anesthesia resident. The study was performed in Nasr City Insurance Hospital, Cairo, Egypt. The study protocol was approved from the institutional ethical committee and written informed consent was obtained from all the patients.

Fifty patients scheduled for surgical repair of abdominal aortic aneurysm were randomized in two groups:

***Group (L)*** twenty-five patients subjected to "liberal" approach of 12 ml/kg/h of Ringer lactate starting from induction of anesthesia.

***Group (R)*** twenty-five patients subjected to "restrictive" approach of 4 ml/kg/h starting from induction of anesthesia.

Exclusion criteria were refusal of consent, unplanned surgery, congestive heart failure, chronic renal failure, acute myocardial ischemia prior to enrollment, or severe ventricular or supraventricular arrhythmia.

Clinical predictors are clinical findings that can help identifying patients who require treatment, hospitalization and expecting outcome of the patient. Clinical predictors in this study included arterial hypertension, chronic obstructive pulmonary disease (COPD), diabetes, previous myocardial infarction (MI) and previous cerebrovascular accident (CVA).

Upon the arrival of the patients to the operating room, i.v. line was inserted. Standard monitoring was placed including pulse oximetry, ECG. Invasive monitoring was inserted under local anesthesia, an arterial line was inserted in the radial artery and central venous catheter was inserted in the internal jugular vein (CVL). Urinary catheter and temperature probe were applied after induction of anesthesia. An epidural catheter was inserted before surgery and 10 ml of bupivacaine hydrochloride 0.25% was injected as adjuvant for general anesthesia and for postoperative pain relief.

Induction of anesthesia was obtained by midazolam 0.05–0.07 mg/kg, fentanyl 3 ug/kg, propofol 2 mg/kg and atracurium besylate 0.5 mg/kg. Endotracheal intubation was followed by maintenance of balanced technique involving isoflurane and oxygen, incremental doses of fentanyl and atracurium besylate hourly. Volume controlled mode was used for ventilation, tidal volume was maintained at 8–10 ml/kg, and the respiratory rate was maintained at 10–12/min to maintain the end-tidal carbon dioxide pressure at 35–40 mmHg monitored by capnography (General Electric, Datex-Ohmeda Aespire).

Blood gas levels measured on arterial and central venous samples, arterial pH, arterial lactate (by RADIOMETER ABL800 BASIC) and oxygen extraction ratio estimate ($O_2$ERe) ($SaO_2$-$ScVO_2$/$SaO_2$) were recorded after induction of anesthesia, hourly throughout surgery, half an hour after the end of anesthesia, and hourly during the first 6 h of the postoperative period.

In both groups, the patients were managed to achieve predefined standard goals: MAP > 80 mmHg, urinary output > 0.5 ml/kg/h, and CVP from 8 to 12 cm$H_2O$ until the first postoperative day. The management protocol was to keep $O_2$ERe < 27% and checked hourly; if exceeded 27% check for CVP; if < 10 cm$H_2O$ and hematocrit > 30%, fluid challenge was done by infusion of colloids, and each challenge was 250 ml (Tetraspan 60 mg/ml, B BRAUN Melsungen AG Germany), or RBCs transfusion when hematocrit < 30%. If $O_2$ERe still > 27%, dobutamine infusion of 3 ug/kg/min up to 15 ug/kg/min started. But if CVP > 10cm$H_2O$, dobutamine infusion started without fluid challenge (Fig. 1).

Fluid responsiveness was tested after induction of anesthesia and whenever serum lactate increased to > 2 mEq/l for two consecutive measurements or diuresis declined to < 0.5 ml/kg/h for 2 h. Anesthesia was discontinued when the operation was completed. Patients were extubated in the operating room when they fulfilled the standard criteria (adequate protective reflexes, adequate oxygenation, and stable hemodynamics). Once the patients were sent to ICU, both groups received 1.5 ml/kg/h of lactated Ringer's solution as fluid maintenance. The therapeutic goals in the ICU were the same as in the operating room. Follow-up was done for 24 h postoperatively.

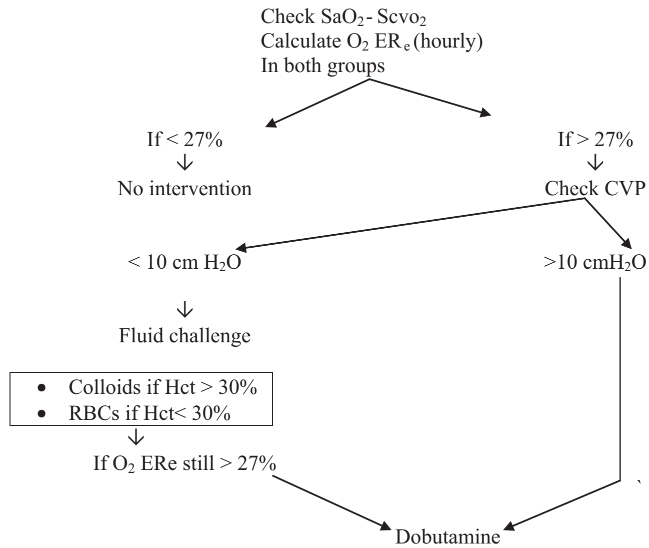



**Figure 1** Protocol for management of patients included in the study.

The study drugs were prepared by the anesthesia resident not involved in any other part of the study. Intraoperative and postoperative data collections were achieved by the same anesthesia resident.

### *2.1. Analysis of data*

PASS 11 was used for sample size calculation, where a sample size of 22 patients per group will achieve 80% power to detect a difference of 50% in proportion of postoperative complications. The reference group proportion is 0.5000. The calculations assume that two, one-sided $Z$ tests are used. Although the significance level is targeted at 0.0500, the level actually achieved is 0.0561. 25 patients per group were included to replace any missing data. The statistical analysis was performed using SPSS software package version 17 (Chicago, IL). Data were expressed as mean values ± SD, median (IQR) and numbers (%). Student's $t$-test was used to analyze the parametric data, and Mann–Whitney test for nonparametric data and categorical variables were analyzed using the $\chi^2$ test, with $p$ values < 0.05 considered statistically significant.

## 3. Results

A total of 50 patients were evaluated for the inclusion in this study between January 2012 and June 2013. Patients were randomized to 25 patients for each group.

Demographic data for both groups were shown in Table 1 and no significant differences between groups were found. The mean age of the patients of both groups (L) and (R) was 65.8 ± 2.4 and 66.8 ± 3 respectively.

Table 2 showed that (L) group received a significantly greater amount of lactated Ringer's solution (3586.76

**Table 1** Baseline patients' data.

| Variables | Group L $n = 25$ | Group R $n = 25$ | $P$ |
|---|---|---|---|
| Age (years) | 65.8 ± 2.4 | 66.8 ± 3 | 0.48 |
| Operative time (h) | 4.03 ± 0.43 | 4.06 ± 0.34 | 0.72 |
| Blood loss | 439.44 ± 92.2 | 462.2 ± 93 | 0.39 |
| *Clinical predictors* | | | |
| Arterial hypertension | 16 | 18 | 0.46 |
| COPD | 3 | 4 | |
| Diabetes | 10 | 9 | |
| Previous MI | 2 | 3 | |
| Previous CVA | 3 | 0 | |

Data are presented as mean ± SD.
$P > 0.05$ is considered statistically non-significant.
COPD: chronic obstructive pulmonary disease.
MI: myocardial infarction.
CVA: cerebro-vascular accident.

± 473.21 ml) during surgery than the (R) group (1219 ± 140.6 ml) (mean ± SD) ($P < 0.001$). However, the (R) group received a significantly greater amount of colloid (1219.04 ± 268.27 ml) than the (L) group (920 ± 206.7) ($P < 0.001$).

The mean dose of dobutamine administered to the (L) and (R) groups, respectively, was 3.78 ± 3 ug/kg/min vs 6.12 ± 3.47 ug/kg/min ($P$ 0.014) (Table 2).

All patients in each group except 3 patients in (L) group and 2 patients in (R) group received at least one fluid challenge. In the (L) group 49 fluid challenges were performed while in the (R) group 65 fluid challenges were performed ($P = 0.007$). Patients showed positive fluid challenge: 13 patients (59%) in group (L) and 12 patients (52%) in group (R) ($P = 1$) Table 2. Patients in group (R) received fluid challenges earlier than group (L).

Eight patients in group (L) vs 9 patients in group (R) received PRBCs. Transfused RBCs units are 15 and 17 units in (L) and (R) groups (1.8 ± 0.4) unit per patient vs (1.9 ± 0.9) unit per patient respectively ($P = 1$) (Table 2). Achievers of GDT are 73% in (L) group and 63% in (R) group ($P$ 0.39) (Table 2).

Regarding variables used for assessment for tissue perfusion, pH and serum lactate didn't differ between groups at baseline, intraoperative or postoperative. Central venous oxygen saturation values ($Scvo_2$) were similar in both groups at preoperative period ($P$ 0.046) and intraoperative time ($P$ 0.9) and at ICU admission ($P$ 0.7). Similarly $O_2ERe$ were maintained to achieve GDT in both groups all over the surgery at preoperative, intraoperative, and postoperative (($P$ 0.66), ($P$ 0.28), and (P 0.183) respectively) (Fig. 2).

The rate of major postoperative complications was 50% less in the (R) group than in the (L) group and 24% in (R) group vs 48% in (L) group ($P = 0.03$). Difference in ICU days was 4.04 ± 1.3 in (L) group vs 2.36 ± 0.34 in (R) group ($P = 0.3$), while the difference in the length of hospital stay was 9.9 ± 1.5 in (L) group and 6.56 ± 0.92 in (R) group ($P = 0.001$) (Table 3).

## 4. Discussion

This study confirms the effect of restrictive fluid therapy in the setting of GDT for optimization of tissue perfusion and reduction of major complications in open AAA repair. Infusion of 4 ml/kg/h compared to 12 ml/kg/h of lactated Ringer's solution as maintenance fluid during GDT with $O_2ERe$ and serum lactate reduced the incidence of major complications by 50%.

Administration of large amount of crystalloids during prolonged surgery results in weight increase 3–6 kg [15]. There is a dose–response relationship between complications and increasing body weight on the day of surgery. Positive fluid balance has been associated with more complications and increased mortality in surgical patients admitted to ICU [16–18].

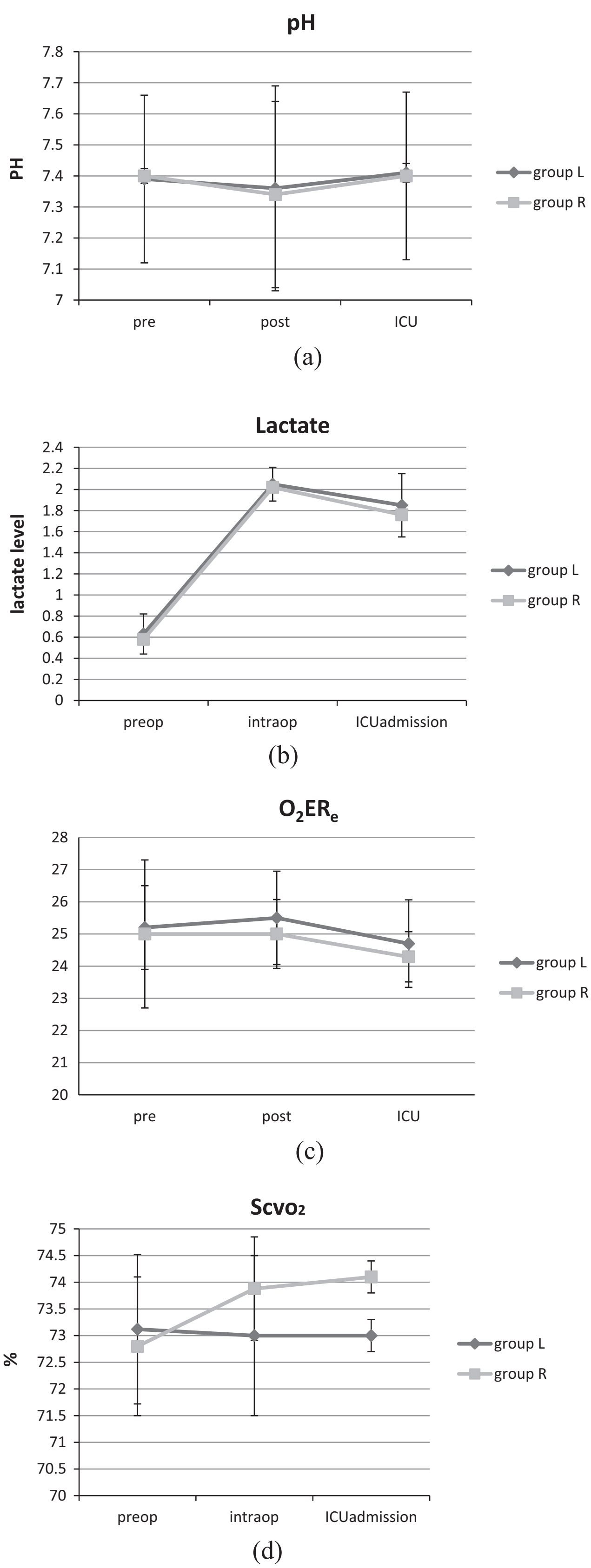
Nisanevich et al. [7] compared 4 ml/kg/h with 12 ml/kg/h of fluid maintenance during gastrointestinal surgery and reported significant decrease in postoperative morbidity. In another study, fluid administration of a median of 3000 ml compared to 6300 ml, reduced complications and length of hospital stay after colorectal surgery [19].

Contrary to our results, Bennett-Guerrero et al. [18] compared two regimens of fluid maintenance, 6 ml/kg/h of crystalloid in the restrictive group and 12 ml/kg/h of crystalloid in the conventional group integrated with GDT in patients undergoing major surgery. The incidence of postoperative complica-

**Table 2** Therapeutic interventions in both groups.

| Variables | Group L | Group R | $P$ |
|---|---|---|---|
| Crystalloids (ml) | 3586.76 ± 473.21 | 1219 ± 140.6 | < 0.001 |
| Colloids (ml) | 920 ± 206.7 | 1219.04 ± 268.27 | < 0.001 |
| Fluid challenge | 22 | 23 | 1 |
| *No. of fluid challenge* | | | |
| 1 | 3 | 0 | 0.007 |
| 2 | 11 | 7 | |
| 3 | 8 | 13 | |
| 4 | 0 | 3 | |
| Positive fluid challenge | 13 | 12 | 1 |
| Patients received RBCs | 8(32%) | 9(36%) | 1 |
| Number of RBCs units received | 15(1.8 ± 0.4) | 17(1.9 ± 0.9) | 1 |
| Dobutamine dose | 3.78 ± 3 | 6.12 ± 3.47 | 0.014 |
| GDT achievers | 73% | 63% | 0.39 |

Data are presented as mean ± SD or number of patients.
$P > 0.05$ is considered statistically non-significant.



Lines are mean values and error bars are SD

**Figure 2** Time course of (a) pH, (b) lactate, (c) $Scvo_2$ and (d) $O_2ERe$.

tions, especially anastomotic leak and sepsis, was higher in the restrictive group than in the conventional group. Although these investigators used fluid GDT based on maximization of a flow-related parameter, DO2 was not a target, making direct comparison with our study difficult.

In this study, we used two indices for assessment of tissue oxygenation: $Scvo_2/O_2ERe$ and arterial lactate. Lactate rose later than $Scvo_2$ and $O_2ERe$. Major complications were observed more in patients with at least single elevated lactate level (15 complications in 11 patients) than in patients with no elevation of lactate (6 complications in 5 patients) (*P* 0.03). The increase in lactate lasted for long time, while the change in $Scvo_2$ and $O_2ERe$ was transient. These findings were mirrored with tissue hypoperfusion that caused hypoxia, decreased oxygen consumption with production of lactate, cell injury and organ failure.

This study manages a goal-directed to $O_2ER$ calculated from central venous sample ($O_2ERe$) value lower than a threshold of 27% reduces the incidence of postoperative complications and length of hospital stay. The critical value of 27% for $O_2ERe$, represents the hypoxic threshold and was reported by investigators [20] as a predictor of survival in high-risk patients.

Pearse and colleagues [21] found that early goal directed therapy was effective to decrease complications after major surgery. This study speculated that the prevention of tissue hypoxia as soon as a warning signal was detected (i.e. an increase in $O_2ERe$) in high-risk surgical patient, helped to avoid postoperative organ failure [22–24].

Optimization of oxygen delivery by correcting hypovolemia and/or an inadequately low cardiac output is the only possibility to reverse tissue hypoxia. The timing of therapeutic intervention is a definite key, as shown in this study, when the same amount of fluid challenges and PRBCs was administered earlier in (R) group than in (L) group.

The dobutamine dose was significantly higher in group (R) than in group (L) (Table 2). However, the dose was much lower than in previous studies [25–27], where the hemodynamic target was achieved with 20–25 ug/kg/min of dobutamine. Data of the study suggested that $O_2ER$ could be optimized with low doses of dobutamine in conjunction with appropriate fluid loading. Dobutamine was preferred over other tested agents such as adrenaline or dopexamine, because we hypothesized that a transient myocardial depression was the causative factor of tissue hypoxia unresponsive to fluid loading [28].

The efficacy of GDT to reach a hemodynamic target was usually confirmed in conditions of tissue hypoperfusion and early reversible tissue hypoxia such as the initial phase of trauma, severe sepsis, and surgery [10,14,24,28–31]. The success of studied approach was explained by the rapid prevention of tissue hypoxia as soon as a warning signal was noticed.

In another prospective randomized study in patients undergoing open AAA repair, standard fluid management resulted in a cumulative fluid balance of 8.2 L on postoperative day vs 2.6 L for restricted management. Total and postoperative length of stay in hospital was reduced by 50% in the restricted group [32].

Guidelines indicate a need for 10–15 ml/kg/h of crystalloids as maintenance fluid in addition to the replacement of blood loss during major and prolonged surgery. The basis for this

**Table 3** Major complications in liberal and restrictive groups.

| Variables | Group L | Group R | *P* |
|---|---|---|---|
| Total numbers of complications | 22 | 8 | 0.0023 |
| C.V. complications | | | |
| AF | 2 | 1 | 0.0023 |
| Hypertensive crisis | 4 | 2 | |
| Anastmosis leak | 2 | 0 | |
| Peritonitis | 2 | 1 | |
| Wound abscess | 2 | 0 | |
| Renal dysfunction | 5 | 2 | |
| GI dysfunction | 3 | 1 | |
| Extubation failure | 2 | 1 | |
| Number of patients with complications | 12(48%) | 6(24%) | 0.03 |
| ICU (days) | 4.04 ± 1.3 | 2.36 ± 0.34 | 0.03 |
| Hospital stay (days) | 9.9 ± 1.5 | 6.56 ± 0.92 | 0.001 |

Data are presented as absolute number of patients, (%) or mean ± SD.

standard recommendation is an assumed large intravascular volume deficit caused by evaporation, fasting, and third spacing, all to be replaced by crystalloids. More recent studies have shown that extracellular volume expands rather than contract with fluid balance [33].

### *4.1. Strengths and limitations*

These encouraging results had been simply achieved by an earlier and more aggressive hemodynamic management, which didn't not require any additional invasive or expensive equipment or procedures. The issue of whether the therapeutic approach tested here may decrease postoperative mortality would require a much larger sample of patients.

## 5. Conclusion

In conclusion, during surgical repair of AAA, close monitoring of $O_2$ER was calculated from central venous blood sample and GDT. Intraoperative hemodynamic GDT with restrictive fluid maintenance and inotropic therapy to achieve the AAA could be easily performed with the use of minimally invasive hemodynamic monitoring and got better patient outcomes.

## Recommendations

A study comparing the postoperative complications between liberal and restrictive fluid therapy in patients undergoing AAA with a much larger sample of patients is planned as follow-up research to this study.

## Conflict of interest

None.

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