The Impact of Restrictive Versus Conservative Intraoperative Fluid Strategies upon the Renal Outcome in Colorectal Surgeries. A Randomized Controlled Trial

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Abstract

Background: intraoperative fluid handling has a lot of concerns upon the postoperative organ function. One of the most sensitive organs which could be affected is the kidney.

Objectives: We conducted this trial to address the impact of restrictive vs. conservative fluid approaches on postoperative renal complications, hemodynamics and hospital stay.

Patients and methods: Prospective, randomized, double-blind placebo-controlled trial at Assiut University Hospitals. The study included 60 adult patients with American Society of Anesthesiologists (ASA) grade II-III undergoing elective colorectal surgery with an expected operative duration of at least two hours. Grouping was based upon the intraoperative fluid management Group (R): 6 mL/kg/h. of lactated ringer (LR), Group (C): 12 mL/kg/h. of LR. The preoperative serum Neutrophil gelatinase-associated lipocalin (NGAL) level (basal value) then by the 2nd and 24th postoperative hours, KDIGO (Kidney Disease: Improving Global Outcomes), serum urea and creatinine were documented by the end of 1st and 2nd postoperative days. Intraoperative hypovolemia events were noted as well.

Results: serum NGAL has increased >149 ng/ml in three patients within group C, and two patients within group R; however, the difference was statistically insignificant p= 0.5. KDIGO showed significant difference between the two groups, with higher number of patients in the group R with p= 0.043. Serum urea and creatinine, intraoperative hypovolemic episodes showed insignificant differences between groups.

Conclusion: no evident difference between restrictive and conservative intraoperative fluid strategies was noticed upon the early postoperative serum NGAL and other systems complications in patients undergoing major colorectal surgeries.

Keywords: Intraoperative; Fluid strategies; Renal outcome

DOI: 10. 21608/svuijm.2023.178375.1462

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Received: 3 November,2022.

Revised: 8 December, 2022.

Accepted: 20 December, 2022.

Published: 16 April, 2023

Cite this article as: Khaled Abdelbaky Abdelrahman, Jehan A Sayed, Mohamed I. Seddik, Amr M. Thabet, Mohamed Abdallah Abdelnaser. (2023). The Impact of Restrictive Versus Conservative Intraoperative Fluid Strategies upon the Renal Outcome in Colorectal Surgeries. A Randomized Controlled Trial. *SVU-International Journal of Medical Sciences*. Vol.6, Issue 2, pp: 169-180.

Introduction

Intraoperative fluid administration is one of the topics that has been controversial for years **(Holte et al., 2007)**. Liberal fluid strategy during abdominal surgery results in a significant reduction in stress response and hospital stay, this could be accompanied by many harms as tissue edema, weight gain and postoperative hypoxemia **(Holte et al., 2007)**. On the other hand, the restrictive strategy has resulted in fewer postoperative complications and shorter hospital stays **(De Aguilar-Nascimento et al., 2009)**. This strategy has some concerns related to insufficient intravascular volume, tissue perfusion, cellular oxygenation and risk of organ dysfunction **(Gobindram and Gowrie-Mohan, 2007)** resulting in delayed restoration of bowel function and wound healing due to inadequate oxygen delivery **(Futier et al ., 2010)**.

One of the sensitive organs to perioperative fluid management is the kidney; however, studies of perioperative AKI lack agreement on uniform definitions and diagnostic tools. There were few studies focused upon AKI after abdominal surgery **(Gameiro et al., 2016)**. The incidence of postoperative AKI was about 22.4% in major abdominal surgeries, 28.1% in colorectal surgery **(Teixeira et al., 2014)**. Different criteria were introduced to detect acute kidney injury as RIFLE **(Bellomo et al., 2004)**, AKIN **(Mehta et al., 2007)**, KDIGO (*Kidney Disease: Improving Global Outcomes)* **(Kellum et al., 2012)**. The physiological response to stress, pain and tissue trauma following surgery may affect the ability of these criteria to detect the actual incidence of acute kidney injury **(Lehner et al., 2016).**

Our hypothesis is that fluid handling in colorectal surgeries might affect the renal outcome.

Primary outcome: the incidence of AKI as reflected upon Neutrophil Gelatinase-associated Lipocalin (NGAL). Secondary outcome: Acute kidney injury using (KDIGO classification), intraoperative hypovolemia events, and hospital stay.

Patients and methods

This is a double-blinded randomized controlled clinical trial, which was first approved by the local ethics committee of the Faculty of Medicine, Assiut University then registered in the clinical trial (NCT03070080). The study was adhered to the declaration of Helsinki and all patients have given informed consent, and involved 60 adult patients with American Society of Anesthesiologists (ASA) grade II-III undergoing elective colorectal surgery with an expected operative duration of at least two hours. All procedures were performed under general anesthesia by the same surgery and anesthesia teams. Exclusion criteria included body mass index > 35 Kg/m^2, pregnancy and lactation, inflammatory bowel disease, coronary artery disease with impaired cardiac function, renal insufficiency (serum creatinine level > 180 μmol/l), hypertension, diabetes and chronic NSAIDS use.

Randomization was done using computer-generated random number tables, and the patients were equally

allocated into one of the two study groups according to the strategy of intraoperative fluid management as following; restrictive fluid strategy (group R) or conservative fluid strategy (group C), (6). Lactated ringer (LR) was administered intraoperatively starting with the induction of anesthesia till the patient extubation as following: Group (R): 6 mL/kg/h. of lactated ringer (LR), Group (C): 12 mL/kg/h. of LR. The participants and outcome assessing physicians were kept blind to the grouping process (**Fig.1**).

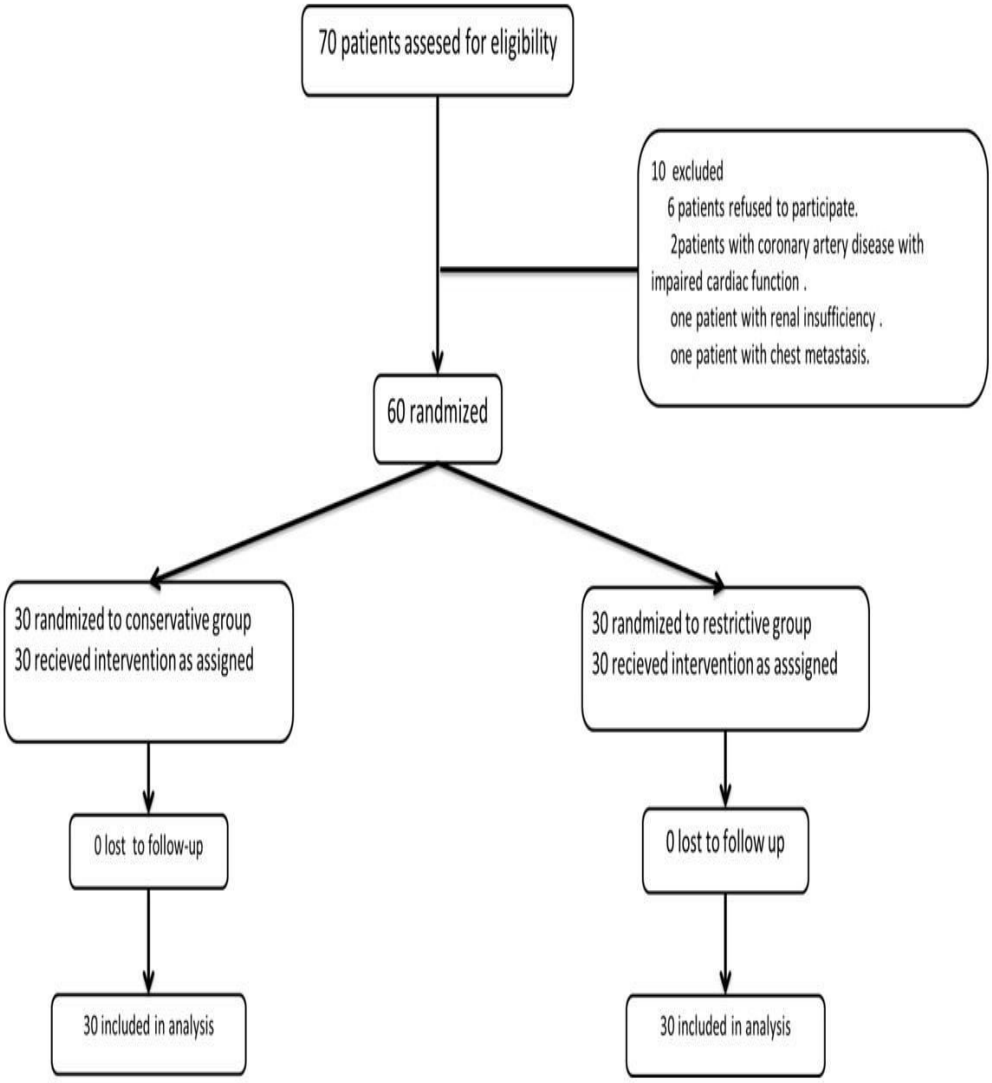

Fig.1. CONSORT flow chart

Preoperatively, all patients fasted for six hours and underwent mechanical bowel preparation. Antibiotic prophylaxis (Cefepime 1g plus metronidazole 15 mg/kg) for all patients was administered 30 to 60 minutes before surgical incision. Two peripheral intravenous cannulas were inserted. Anesthesia was induced with propofol (2 mg/kg) and fentanyl

(3µg/kg), and muscle relaxation with cisatracurium (0.15mg/kg) for tracheal intubation. Maintenance of anesthesia was attained under sevoflurane 2-3% in air/oxygen (1:1), with the depth targeted intraoperative mean blood pressure (MAP) and heart rate (HR) within 20% of preoperative values. Mechanical ventilation parameters included tidal volume of 8 mL/kg at a rate of 8-12 cycles/minute (to maintain an end-tidal CO_2 between 35 and 40 mm Hg) and positive end-expiratory pressure of 5 cm H_2O. Intraoperative normothermia was maintained by the means of a warmed blanket, humidifier, and warm intravenous fluids. A 3-lumen central venous catheter was inserted after the induction of anesthesia through the right internal jugular vein.

Monitoring: Standard monitoring included peripheral O2 saturation (SpO2) and heart rate through pulse oximetry, capnography, electrocardiogram, non-invasive blood pressure, core body temperature and urine output. **Detection of hypovolemia and fluid responsiveness** were attained through the Pleth variability index (PVI) (Mindray monitor, model: iPM 12) which is a non-invasive monitoring modality reflecting the response to fluid handling in a numerical pattern has been used in this study **(Sandroni et al., 2012)**. According to this formula ([($P_I$max - $P_I$min)/$P_I$max] X 100), where P_I max and P_I min represent the maximal and the minimal values respectively, of the plethysmographic perfusion index (P_I) over one respiratory cycle) PVI was calculated **(Zimmermann et al., 2010)**. A PVI value of >13% before fluid infusion differentiated between fluid responders and non-responders **(Yu et al., 2015)**. Accordingly, fluid responders were managed by infusion of 250 ml bolus of LR over 15 min and the same volume repeated if PVI remained > 13%. If PVI of 13% value and associated with hypotension (MAP < 65 mmHg), in spite of fluid expansion, 5 mg intravenous (IV) bolus of ephedrine was given. Bradycardia (HR <50 beats/minute) was treated with IV 0.5 mg atropine.

Packed RBCs transfusion was allowed whenever hematocrit < 25% or blood loss (assessed by suction volume and weighing used gauzes) >1500 ml. After the end of surgery, patients were transferred to the postoperative ICU and received routine fluid management consisted of 2-3 ml/kg/hour iv dextrose 5% and LR over the next two days until oral fluids were allowed. Multimodal analgesia was applied to all patients in the form of paracetamol (1 gm every 6 hours) and 2-3 nalbuphine shots was given on demand.

Assay of Neutrophil Gelatinase-associated Lipocalin (NGAL): Five millilitres of venous blood were obtained in a plain vial from the patients. Collected blood samples were stored at 4°C, and centrifugation was done at 6000 rpm. Samples were frozen at -20°C until assayed. Quantitative measurement of serum NGAL levels was done by enzyme-linked immunosorbent assay (ELISA) reader: BioTek model: ELX800.

Data collection included the preoperative serum NGAL level (basal

value) then by the 2nd and 24th postoperative hours. Acute kidney injury using KDIGO guidelines based on serum creatinine and urine output were documented by the end of 1st and 2nd postoperative days. Intraoperative hypovolemia events and their fluid management, hospital stay and other non-kidney related complications were noted as well.

KDIGO has developed a catalog of clinical practice guidelines informing the care of patients with, or at risk of developing, kidney diseases. The KDIGO definition of Acute Kidney Injury (AKI) relies on three diagnostic criteria: a rise in serum creatinine (sCr), a decrease in urine output (UO), and administration of renal replacement therapy (RRT).

Statistical analysis

In this study, we have used an 80% power to detect a real 20 % change in the primary outcome (NGAL) and alpha error of 0.05, accordingly, sample size was calculated to be 56 patients for both groups, and 60 participants were recruited to compensate for any drop out. Normality of the data was firstly tested by Shapiro Wilk test. Comparison of results of between the two groups was attained as following Chi-square test for categorical data, unpaired t-test for parametric continuous numerical data and Mann Whitney test was used for non-parametric data. A P-value <0.05 was considered as statistically significant. Statistical analysis was conducted with IBM SPSS. Statistics for Windows, software version 23.0. IBM Corp. (2015).

Results

Sixty adult patients were randomized and completed the study according to the protocol as shown in figure 1, and all of them were comparable as regards to the demographic, surgical and clinical data with non-significant differences in between (**Table 1**).

Table 1: Patients' characteristics and surgical data

Variables	Group C	Group R	P-value
Age (years)	52.4 ± 11.8	48.8 ± 15	0.306
Sex (male/female)	15/15	17/13	0.398
Weight (kg)	74.4 ± 12.8	70.1 ± 14.6	0.226
Height (cm)	166.2 ± 7.4	168.6 ± 8.4	0.231
BMI (kg/m^2)	27 ± 4.9	24.7 ± 5.0	0.071
Duration of anesthesia (minutes)	312.1 ± 78.5	308.1 ± 61.8	0.827
Length of hospital stay (day)	5.6±1.35	5.7±1.55	0.76

Data are presented as mean± standard deviation or number (ratio). P< 0.05 is considered statistically significant.

Serum NGAL has increased >149 ng/ml in three patients within group C, and two patients within group R; however, the difference was statistically insignificant. As regards to the KDIGO evaluation of the renal status, there was a significant difference between the two groups, with the number of patients who have renal affection during the postoperative period was higher in the group R. Urine output was significantly lower in the restrictive fluid group within the intraoperative period (**Table 2**).

Intraoperative hypovolemic episodes have occurred in three patients in the R group, but still with the insignificant difference in comparison to the other study group. Intra operative perfused fluid and its balance was significantly higher in group C; however, the postoperative fluid balance got significantly higher in the group R in the 1st and 2nd postoperative days (**Table 2**).

Table 2: Renal outcome variables

Variables	Group C n = (30)	Group R n = (30)	P-value
Baseline NGAL level	84.6 ± 6.4	96.9 ± 4.6	0.124
NGAL level after 2 hours	82.8 ± 6.4	95.4 ± 5	0.126
NGAL level after 24 hours	92.2 ± 6.7	105.4 ± 5.7	0.140
NGAL > 149 ng/ml (number of patients)	3(10%)	2 (6.6%)	0.5
Acute kidney injury according to *KDIGO* classification (number of patients)			
● **Normal**	28 (93.3%)	20 (66.6%)	0.043
● **AKI stage 1**	0 (0%)	5 (16.6%)	
● **AKI stage 2**	1 (3.3%)	4 (13.3%)	
● **AKI stage 3**	1 (3.3%)	1 (3.3%)	
Intraoperative urine output (ml)	636±611	299±249	0.007

Data are presented as number (percentage), and mean± standard deviation. P<0.05 is considered statistically significant.

There were insignificant differences between the two groups as regards to blood transfusion, and hemodynamic events (blood pressure, heart rate) during the operative time (**Table 3, Fig.2&3**).

Table 3: Hypovolemic episodes and Fluid management

Variables	Group C n=30	Group R n=30	P-value
Hypovolemia episodes / patient	**0**	**3**	**0.119**
Blood transfusion; **Number of patients** **Packed RBCs units**	**7 (23%)** **0 (0-3)**	**3 (10%)** **0(0-2)**	**0.149** **0.141**

Volume of crystalloid perfused (ml)	**3869±296**	**1765±120**	**0.001**
Intraoperative fluid balance (ml)	**2665±218**	**1307±157**	**0.001**
Postoperative fluid balance (ml)			
• **First postoperative day**	**2670±106**	**3328±58**	**0.001**
• **Second postoperative day**	**1351±137**	**1705±84**	**0.031**
• **Third postoperative day**	**1173±118**	**1362±95**	**0.185**

Data are presented as number, ratio, median (range) or mean ± standard error. P-value <0.05 is considered statistically significant.

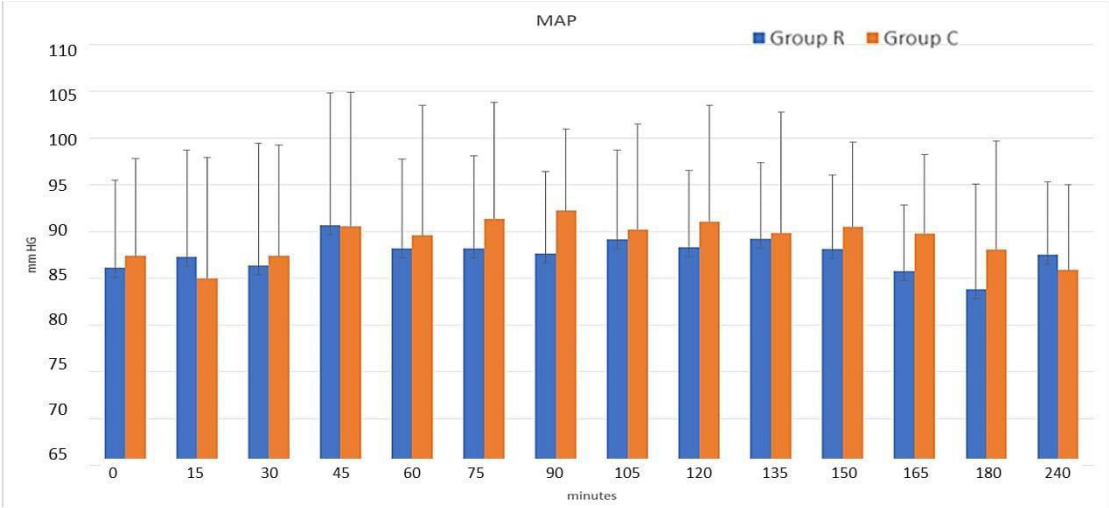

Fig. 2. Mean arterial blood pressure in both groups

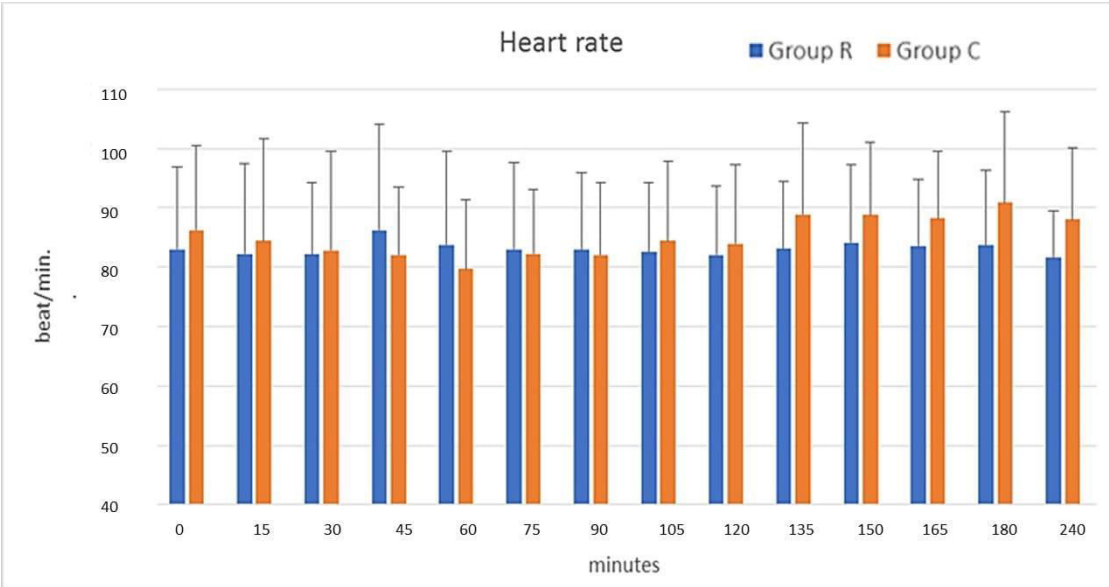

Fig.3. Heart rate in both groups

The early postoperative complication showed insignificant differences between groups. They included wound infection (1/0), fistula (1/3) and pulmonary embolism (1/0) in group C versus group R in consequences. The hospital stay showed insignificant difference between the two groups (**Table 1**).

Discussion

In this study, it has been noticed the serum NGAL as a renal biomarker for early detection of acute renal injury shown insignificant difference between both groups; however, the intraoperative fluid restriction policy has demonstrated a significantly higher incidence of postoperative AKI according to KDIGO classification compared to the conservative group. Interestingly, the intraoperative urine output was significantly higher in the conservative group than the restrictive group. The fluid balance got significantly higher in the restrictive group in the 1st and 2nd postoperative days.

Serum NGAL is already known to be more accurate, sensitive and early detector of AKI **(Mishra et al., 2005)**, so that why we have relied upon for such purpose, and to our knowledge, this is the first work which correlates the intraoperative fluid handling with the postoperative NGAL. Serum NGAL as a renal protein biomarker was discovered in 2003 following experimental renal ischemia in a mouse model, and its expression was detected predominantly in the proliferating proximal tubule cells **(Mishra et al., 2003)**. Any decrease in GFR resulting from AKI would be expected to decrease the renal clearance of NGAL and its accumulation in the systemic circulation **(Grigoryev et al., 2008)**. The NGAL increase is a common and sensitive response to tubular injury, and the onset of its rise occurs after two hrs and can be detected up to 24 hours after injury depending on AKI severity**(Fadel et al ., 2012)**.

The use of different classifications for the detection of AKI as RIFLE, AKIN, KDIGO has two main concerns, which are related to creatinine and urine output. However, the utilization of creatinine as a guide to renal function is limited, because the glomerular filtration rate (GFR) needs up to 24 hours of decrease to be reflected upon creatinine. As such, 24-36 hours are required for the serum creatinine concentration to rise after a definite renal insult **(Moran and Myers, 1985).**oliguria could be a normal physiologic response during periods of prolonged fasting, hypovolemia, postoperative times, stress, pain and or trauma, on the other hand, urine output may continue until kidney function almost stops **(Guay and Lortie ,2004).**

Parallel to our results, the findings of **Myles et al.(2018)** who conducted their study upon 1490 Patients undergoing major abdominal surgery and received restrictive fluid strategy, they found that such fluid strategy was associated with a significant increase in the acute kidney injury using KDIGO; however, they did not use any renal biomarker for detection of renal injury. On the contrary, some studies found a non-significant increase in the incidence of AKI in restrictive fluid

strategy, all of them used criteria depended upon serum creatinine and urine output. For example, **De Aguilar-Nascimento et al. (2009)** utilized a fluid volume of < 30 ml/kg/ d in 28 adult patients underwent major abdominal operations without specific intravascular volume monitoring, while we have applied the restrictive fluid protocol intraoperatively with meticulous monitoring of hypovolemic events through PVI.

Futier et al. (2010) utilized goal-directed variation in peak aortic flow velocity as a guide for fluid infusion in two groups, where fluid handling was either 6 ml /kg /hr. or 12 ml/ kg/hr. (restrictive versus conservative fluid management) in 70 adult patients underwent major abdominal surgeries. They recommended not to utilize excessive fluid restriction in such group of patients to avoid post-operative complications; however, they were not included renal dysfunction **(Futier et al. 2010)**. Hypovolemia was detected (through PVI) in three patients only in the restrictive fluid group and successfully managed with fluid bolus. Our results are in agreement with **Cohn et al. 2010** who mentioned that restricted fluid strategy had only rare episodes of hypovolemia, while some studies found that restrictive fluid strategy can be associated with higher incidence of hypovolemia with an increase the need for vasopressor **(Nisanevich et al ., 2005)**.

As regards to post-operative complications and hospital stay, we found no significant differences between the two study groups. Some studies documented that restrictive fluid strategy can be associated with decreased postoperative complications, as well as, hospital stay **(Brandstrup et al., 2003)**. On the other hand, studies found that restrictive fluid strategy could be associated with higher incidence of postoperative complications e.g. anastomotic leak and/or perianastomotic abscess, sepsis, acute lung injury and acute kidney injury **(Myles et al ., 2018)**. We assume that this conflict can arise from the difference between such studies and our work as regards to the surgical details (duration, type), the number of participants, as well as the variations within the fluid strategies used.

Conclusion

No evident difference between restrictive and conservative intraoperative fluid strategies was noticed upon the early postoperative serum NGAL and other systems complications in patients undergoing major colorectal surgeries.

Study's limitations

The sample size could be insufficient to detect statistically significant differences as regards to NGAL, and other systems complications. The other issue is that the possibility of late complications was undetected due to lack of follow up after hospital discharge.

Financial support: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Support was provided solely from departmental resources.

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