Intraoperative restrictive versus liberal fluid administration and postoperative outcomes in major abdominal elective surgery
A retrospective study

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Eu, Maria Araújo e Sá Coelho, que abaixo assino, estudante com o número de inscrição 45634 de Medicina da Faculdade de Ciências da Saúde, declaro ter desenvolvido o presente trabalho e elaborado o presente texto em total consonância com o **Código de Integridades da Universidade da Beira Interior**.

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Universidade da Beira Interior, Covilhã 19/04/2023

Dedicatória

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Resumo

Introdução: Apesar da vasta investigação sobre a gestão da fluidoterapia peri-operatória, a falta de consenso sobre a abordagem ideal continua a prevalecer. Embora alguns estudos sugiram que uma abordagem restritiva dos fluidos durante o período peri-operatório pode diminuir a incidência de complicações pós-operatórias, outros demonstram haver uma correlação entre o regime restritivo e o diagnóstico de lesão renal aguda, secundário à hipoperfusão de órgão. A maior parte dos estudos realizados neste âmbito são dirigidos a cirurgia colorretal e os resultados posteriormente extrapolados para a cirurgia pancreática e hepática, que sendo complexas, acarretam desafios cirúrgicos e anestésicos únicos que merecem especial atenção.

Objetivos: O objetivo deste estudo foi comparar o impacto que as abordagens restritiva e liberal de fluidoterapia intra-operatória têm sobre os resultados pós-operatórios em cirurgias eletivas do pâncreas e fígado.

Métodos: Foram avaliados todos os doentes submetidos a cirurgia eletiva pancreática ou hepática entre Agosto de 2017 e Agosto de 2022, num único hospital. Doentes submetidos a cirurgias que registaram complicações cirúrgicas intraoperatórias, doentes submetidos a hemodiálise, cirurgias não eletivas e casos que não requereram internamento na Unidade de Cuidados Intensivos, foram excluídos deste estudo. Foi definido um valor *cut-off* de 2000mL baseado na revisão bibliográfica realizada. Os doentes foram divididos e categorizados em dois grupos distintos, tendo em conta a quantidade de fluido administrada no período intra-operatório: restritivo (<2000mL, n=83) e liberal (≥2000mL, n=34). Os objetivos deste estudo incluíram complicações pós-operatórias major, lesão renal aguda, distúrbios eletrolíticos, necessidade de suporte aminérgico no pós-operatório e registo dos níveis de lactatos séricos.

Resultados: Foram estudados 117 doentes. Não houve diferença estatisticamente significativa na idade, sexo, índice de massa corporal, tipo de cirurgia e sistema de classificação ASA entre os dois grupos. Aos doentes do grupo liberal foi administrado significativamente maior quantidade de fluidos no período intraoperatório (P=0,001). Ambos os grupos tiveram uma administração intraoperatória de vasopressores comparável. O grupo liberal demonstrou ter maior incidência de distúrbios eletrolíticos no período pós-operatório comparativamente com o grupo restritivo (P=0,046). Os níveis séricos de lactato também se mostraram significativamente mais elevados no grupo liberal (P=0,026). Outras complicações como a necessidade de suporte aminérgico no pós-operatório, lesão renal aguda, deiscência da anastomose e edema pulmonar foram semelhantes entre os grupos.

Conclusão: Nos doentes submetidos a cirurgia pancreática ou hepática, a administração liberal de fluidos no período intraoperatório associou-se a um maior aumento do nível de lactato sérico e a uma maior incidência de distúrbios eletrolíticos até 48 horas após o procedimento, em comparação com uma abordagem restritiva de fluidos intraoperatórios.

Palavras-chave

Fluidoterapia;Regimes Liberal versus Restritivo;Complicações pós-operatórias; Anestesiologia Clinica;Cirurgia Abdominal Major.

Abstract

Background: Despite extensive research on perioperative fluid management, there remains a lack of consensus on the optimal approach. While some evidence suggests that a restrictive approach during the perioperative period may decrease the incidence of postoperative complications, other recent studies have demonstrated an association between a restrictive fluid regimen and acute kidney injury due to hypoperfusion. Most studies were done for colorectal surgery and the results extrapolated for pancreatic and hepatic surgery. However, these are complex procedures with unique surgical and anesthestic challenges and therefore deserve special attention.

Objectives: The present study compares the impact of a restrictive versus liberal intraoperative fluid administration on early postoperative outcomes after pancreatic or hepatic surgery.

Methods: We performed a retrospective analysis to all patients who underwent pancreatic or liver surgery in a single centre between august 2017 and august 2022. Exclusion criteria were intraoperative surgical complications, preoperatively dialysed patients, non-elective surgery and patients who were not admitted to the intensive care unit in the postoperative period. A cut-off value of 2000mL was applied based on an exhaustive literature review and the patients were categorized in two groups according to the volume of intraoperative fluid administered: restrictive (<2000mL, n=83) and liberal (≥2000mL, n=34). The postoperative outcomes included major postoperative complications, acute kidney injury, electrolyte disturbances, postoperative vasopressor administered and peak serum lactate levels.

Results: We evaluated 117 patients. There were no statistically significant differences in age, sex, body mass index, type of surgery and ASA physical status between the two groups. Patients in the liberal group received significantly more intraoperative fluid (P=0.001). Both groups had comparable intraoperative vasopressor administration. The liberal group showed a higher incidence of electrolytic disturbances (P=0,046). The median peak lactate level was significantly higher in the liberal group (P=0,026) compared to the restrictive group. The other outcomes such as postoperative vasopressor administration, acute kidney injury, anastomotic dehiscence and pulmonary oedema were similar among the groups.

Conclusion: In patients undergoing pancreatic or liver surgery, a liberal intraoperative fluid administration was associated with higher peak serum lactate level and increased incidence of electrolyte disturbances up to 48 hours after the procedure compared to a restrictive intraoperative fluid administration.

Keywords

Fluid Administration;Liberal versus Restrictive Intraoperative Fluid Regimens;Postoperative Outcomes;Clinical Anaesthesia;Major Abdominal Surgery.

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Abbreviations

AKI	Acute Kidney Injury
ASA	American Society of Anesthesiologists
BMI	Body Mass Index
CDK	Chronic Kidney Disease
CT	Computed Tomography
EIAS	ERAS Interactive Audit System
ERAS	Enhanced Recovery After Surgery
ICU	Intensive Care Unit
IOF	Intraoperative Fluid
IQR	Interquartile Range
KDIGO	Kidney Disease: Improving Global Outcomes
POPF	Postoperative Pancreatic Fistula
RCT	Randomized Controlled Trial
SD	Standard Deviation

Chapter 1

Introduction

Major abdominal surgery remains a significant challenge in the medical field, with high rates of morbidity and mortality despite recent advancements (1). In order to maintain fluid and electrolyte homeostasis, avoid tissue hypoperfusion and fluid overload, and balance oxygen supply and demand (2), the administration of an adequate volume of intravenous fluid is paramount.

While hypovolemia is recognized as the main risk factor when restricting perioperative fluid administration (3), liberal regimens can lead to volume overload and negatively impact cardiopulmonary function (4), delay recovery of gastrointestinal motility (4) cause urinary retention (5), and impair tissue healing (4).

Despite numerous studies on perioperative fluid management, there is still no consensus on the best approach and the results from existing trials are conflicting (5). For many years, the literature suggested that a liberal regimen was more beneficial to maintain adequate intravascular volume (6). However, more recent studies have shown that a restrictive approach in the perioperative period reduces the incidence of postoperative complications (1) (4) (5) (7) . Lately, there has been a focus on goal-directed therapy, in which hemodynamic variables are used to assess blood volume, cardiac function and systemic vascular resistance and therefore optimize the needs of the patient. However, these parameters relate to the macrocirculation and do not always correlate with the microcirculation and tissue perfusion (8).

Even though a considerable amount of research has been conducted to determine the optimal approach for major abdominal surgery, the majority has focused on colorectal procedures, rather than pancreatic and hepatic surgeries which themselves pose significant technical challenges and are associated with high morbidity and postoperative complications. (6) (9)

The Enhanced Recovery After Surgery (ERAS) society guidelines for pancreatoduodenectomy and liver surgery recommend a restrictive regimen and the use of a goal-directed fluid therapy algorithm (10) (11).

The aim of this study was to compare the impact of a restrictive versus liberal intraoperative fluid regimen on early postoperative outcomes after pancreatic or hepatic surgery in a Portuguese hospital.

Chapter 2

Materials and Methods

This retrospective study was approved by the Ethics Committee of Hospital Beatriz Ângelo.

2.1 Patient Population Selection

This study included adult patients, who underwent elective pancreatic or liver surgery from august 2017 to august 2022 in Hospital Beatriz Ângelo in Loures, Portugal.

A total amount of 143 patients underwent pancreatic or hepatic surgery. Exclusion criteria were intraoperative surgical complications (n=2), preoperatively dialysed patients (n=0), non-elective surgery (n=17) and patients who were not admitted to the intensive care unit (ICU) in the postoperative period (ICU) (n=7).

In total, 117 patients were considered eligible for data collection and were accordingly selected as the patient population for this study. The study flow chart is showed in Figure 1.

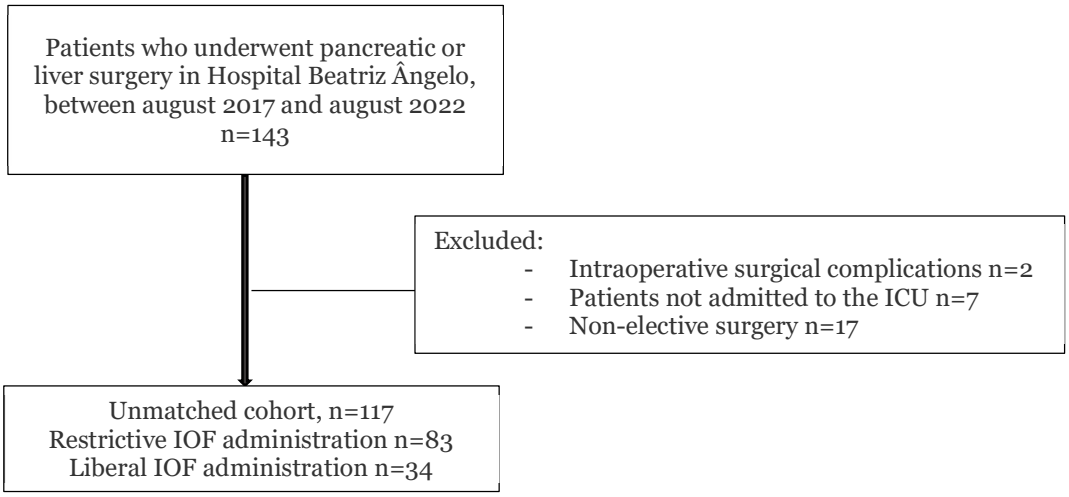
2.2 Intraoperative Fluid Management

Intraoperative fluid (IOF) was administered according to the institution's fluid therapy protocols and responsible anaesthesiologist's choice. Following an exhaustive literature review, we established a cut-off value of 2000mL, considering there is no consensus and the existing studies adopted varying cutoffs in their classification of restrictive and liberal approaches (2) (3) (4) (5) (12). All the patients who underwent elective pancreatic or liver surgery were categorized into two groups according to intraoperative fluid volume administrated: restrictive (<2000ml) and liberal (≥2000ml).

2.3 Surgical Procedures

Data were collected from the patients who underwent pancreatoduodenectomy, distal pancreatectomy and splenectomy, total pancreatectomy, hepatic lobectomy, liver metastasectomy and other hepatic surgeries. Only 4 hepatic procedures were laparoscopic.

Figure 1 Study Flow Chart



Abbreviations: ICU-Intensive Care Unit; IOF-Intraoperative Fluid

2.4 Data Collection

All data were collected from the hospital's clinical software (Soarian Clinicals and Innovian®) and from EIAS (ERAS Interactive Audit System), including age, sex, Body Mass Index (BMI) and ASA (American Society of Anaesthesiologists) physical status of each patient. Type of surgery, intraoperative fluid volume and administered vasopressor were obtained from the anaesthesia records. ICU data were used to obtain postoperative vasopressor, peak serum lactate levels, sodium and potassium levels and specific postoperative complications including pulmonary oedema and anastomotic dehiscence. Creatinine levels up to 7 days after the procedure were also collected.

2.5 Definitions

Acute Kidney Injury (AKI) was defined according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria as an increase in serum creatinine concentration by 0.3mg/dl within 48 hours or a 1.5 time increase from the baseline value within 7 days or urinary output less than 0.5 ml/kg/h for 6-12 hours. Urinary output data was not possible to collect due to lack of consistent records and therefore was not used as a diagnostic marker of AKI.

Electrolyte disturbances included hypernatremia (Na>145mmol/L) or hyponatremia (Na <135 mmol/L) or hyperkalaemia (K >5.0mmol/L) or hypokalaemia (K <3.5 mmol/L).

Normal serum lactate level was defined as less than 1.6 mmol/L.

Pulmonary oedema was diagnosed through pulmonary auscultation and thoracic ultrasound.

All these outcomes were evaluated in the first 48 hours after surgery.

Anastomotic dehiscence was identified through both patient's clinical status and abdominal computed tomography (CT), during the first 5 days after surgery.

2.6 Statistical Analysis

Statistical analysis was performed using SPSS software version 23 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive data were reported as mean ± standard deviation (SD), median (interquartile range - IQR) or number of patients (percentage) as appropriate. Categorical variables were compared using the Pearson's Chi-square test or Fisher's exact test. For continuous variables, differences between groups were tested using Student's t test for normally distributed data or the Mann-Whitney U test for non-normally distributed data (based on Kolmogorov-Smirnov test). A p-value < 0.05 was considered statistically significant.

Chapter 3

Results

3.1 Demographic Characteristics:

The final patient population for the study included 117 patients. The clinical data of the study's population is showed in Table 1.

Amongst 117 patients (73 males, 44 females), 83 (70,9%) and 34 (29,1%) patients were included in the restrictive and liberal groups, respectively. The mean age was 65,6 years (SD = 11,7) and the mean BMI was 25,6 kg/m² (SD=4,3).

There were 5 patients (4,3%) classified as ASA I physical status, 60 (51,3%) as ASA II, 49 (41,9%) as ASA III and 3 (2,6%) as ASA IV.

The surgeries included pancreatoduodenectomy (n=53, 45,3%), distal pancreatectomy and splenectomy (n=16, 13,7%), total pancreatectomy (n=2, 1,7%), hepatic lobectomy (n=14, 12%), hepatic segmentectomy (n=22, 18,8%), hepatic metastasectomy (n=8, 6,8%) and other hepatic surgeries (n=2, 1,7%).

There were no statistically significant differences in age, sex, BMI, ASA physical status and type of surgery between the two groups (P>0.05, Table 1).

3.2 Intraoperative Variables:

As expected, there was a statistically significant difference in the median IOF administrated between the restrictive and the liberal groups, 1300 mL (IQR=500) and 2500 mL (IQR=925), respectively (P =0,001, table 1).

A vasopressor was administered in 75,9% of the surgeries in the restrictive group and in 85,3% in the liberal group. The difference between the two groups was not statistically significant (P>0.05, table 1).

Table 1 Demographic characteristics and intraoperative variables

Parameter	Total (n=117, 100%)	Restricted group (n=83, 70,9%)	Liberal group (n=34, 29,1%)	P-value
Age (years) - mean ± SD	65,6 ±11,7	66,2 ± 11,6	64,2 ± 11,9	*0,408*
Sex - n (%)				
Male	73 (62,4 %)	51 (61,4%)	22 (64,7%)	*0,741*
Female	44 (37,6%)	32 (38,6%)	12 (35,3%)	
BMI (kg/m²) - mean ± SD	25,6 ± 4,3	25,8 ± 4,6	25,3 ± 3,3	*0,572*
ASA - n (%)				
I	5 (4,3%)	3 (3,6%)	2 (5,9%)	*0,671*
II	60 (51,3%)	42 (50,6%)	18 (52,9%)	
III	49 (41,9%)	35 (42,2%)	14 (41,2%)	
IV	3 (2,6%)	3 (3,6%)	0 (0%)	
Type of surgery - n (%)				
Pancreatoduodenectomy	53 (45,3%)	34 (41%)	19 (55,9%)	*0,333*
Distal Pancreatectomy + Splenectomy	16 (13,7%)	13 (15,7%)	3 (8,8%)	
Total Pancreatectomy	2 (1,7%)	2 (2,4%)	0 (0%)	
Hepatic Lobectomy	14 (12%)	8 (9,6%)	6 (17,6%)	
Hepatic Segmentectomy	22 (18,8%)	18 (18,8%)	4 (11,8%)	
Hepatic Metastasectomy	8 (6,8%)	7 (8,4%)	1 (2,9%)	
Other Hepatic Surgeries	2 (1,7%)	1 (1,2%)	1 (2,9%)	
Total IOF volume (mL) - median (IQR)	1500 (950)	1300 (500)	2500 (925)	***0,001***
Intraoperative Vasopressor -n (%)	92 (78,6%)	63 (75,9%)	29 (85,3%)	*0,261*

Abbreviations: ASA-American Society of Anesthesiologists, BMI-Body Mass Index, IOF-intraoperative fluid, IQR-Interquartile range, SD-Standard Deviation.
The ASA criteria for physical status include classification for normal health (I), mild systemic disease (II), severe systemic disease (III) and severe systemic disease that is a constant threat to life (IV).

3.3 Postoperative Outcomes in ICU

Postoperative outcomes based on IOF volume are summarized in Table 2.

Comparing patients who had an intraoperative restrictive and liberal approach, we observed that the median peak lactate level was significantly higher in the liberal group (2,8 mmol/L versus 3,7 mmol/L, *P*=0,026). Additionally, the liberal group showed a higher incidence of electrolytic disturbances (22,9% versus 41,2%, *P*=0,046), namely hyponatremia and hyperkalaemia.

There were no statistically significant differences between the two groups regarding the postoperative vasopressor administration (75,9% versus 85,3%, *P*=0,261), AKI (16,9% versus 26,9%, *P*=0,235) and anastomotic dehiscence (12% versus 11,8%, *P*=0,966).

None of the patients included in this study were diagnosed with pulmonary oedema.

Table 2 Postoperative Outcomes in ICU

Outcomes	Total (n=117, 100%)	Restricted group (n=83, 70,9%)	Liberal group (n=34, 29,1%)	P-value
AKI - n (%)	23 (19,7%)	14 (16,9%)	9 (26,5%)	*0,235*
Peak Serum Lactate Level (mmol/L) - median (IQR)	2,9 (1,8)	2,8 (1,7)	3,7 (2,2)	***0,026***
Electrolyte Disturbances - n (%)	33 (28,2%)	19 (22,9%)	14 (41,2%)	***0,046***
Postoperative Vasopressor - n (%)	50 (42,7%)	31 (37,3%)	19 (55,9%)	*0,066*
Major Postoperative Complications				
Pulmonary oedema - n (%)	0 (0%)	0 (0%)	0 (0%)	
Anastomotic Dehiscence - n (%)	14 (12%)	10 (12%)	4 (11,8%)	*0,966*

Abbreviations: AKI- Acute Kidney Injury, IQR-Interquartile range

Chapter 4

Discussion

Despite numerous studies regarding the impact of IOF volume administration on postoperative outcomes, the available evidence remains limited. While several studies concluded that a restrictive IOF regimen can effectively lower the incidence of postoperative complications, such as infections, respiratory complications and Postoperative Pancreatic Fistula (POPF) in the case of pancreatic surgeries (1) (4) (5) (7), other studies have not found any significant difference between the two fluid regimens (2) (6) (13). In 2018, a large Randomized Controlled Trial (RCT) demonstrated that disability-free survival at one year did not differ when comparing the two IOF approaches. However, the study concluded that a restrictive strategy was associated with higher rates of AKI. (12)

Hepatic and pancreatic surgeries are complex procedures characterized by inherent physiological stress due to the lack of distensibility of the organs, their specific anatomical location, the superior number of anastomoses and the longer operative time, which can lead to significant evaporative fluid losses. (6). Given these factors, it is still unclear whether the existing guidelines for IOF can be extrapolated and applied to liver and pancreatic surgeries. (11)

Unlike other studies, we collected the peak serum lactate levels as well as the levels of sodium and potassium up to 48 hours after the procedure. Our results in patients undergoing pancreatic and liver surgeries showed that patients who received a liberal IOF administration had a higher postoperative median peak serum lactate level and more incidence of electrolytic disturbances.

Lactate is an endogenous non-toxic metabolically active molecule that is a product of anaerobic glycolysis and is used as energetic substrate for gluconeogenesis mainly in the liver. Although an increase in serum lactate level is often associated with hypoperfusion and hence restrictive fluid regimens, our results showed the opposite. The peak median serum lactate level was significantly higher in the liberal group when compared to the restrictive one. On one hand, excessive fluids may induce oedema and impair tissue perfusion, increasing lactates in circulation (1). In recent years, some studies found that a liberal IOF administration during pancreatoduodenectomy was associated with higher incidence of POPF, which can lead to intraabdominal infection followed by an increase in serum lactate (1) (7). Additionally, a liberal approach regarding fluids administrated in the early postoperative care has been demonstrated to elevate the infection rate (14). On the other hand, hyperlactatemia following elective abdominal surgery, namely pancreatic and extensive liver surgery, may be related to the procedure itself which causes activation of coagulation and inflammatory pathways (15) as well as induces microcirculatory disturbances. These will damage the intestinal epithelial cells promoting the translocation of bacteria and

exudation of their metabolic products which will increase lactate levels (16). In liver surgery, clamping during parenchymal resection causes ischemia of the hepatic cells which decreases the ability of the liver to metabolize lactate (17). The underlying liver disease and its extension can also affect lactate metabolism (17).

According to our study findings, there exists also a statistically significant difference between the restrictive and the liberal group regarding the occurrence of electrolyte disturbances. One of the main roles of electrolytes and their homeostasis is the distribution of fluids throughout the human body (18). Hence, one of the goals of IOF administration is to maintain correct plasma constitution (19). In surgical patients, a balanced crystalloid solution should be preferred over 0.9% saline (11) to avoid complications such as hyperchloremic acidosis and increased risk of renal failure, which can contribute to higher mortality rates (20). Our study indicates that a liberal IOF administration is associated with a higher incidence of electrolyte imbalances when compared to a more restrictive approach, namely hyponatremia and hyperkalemia. Excessive fluid volume can contribute to a dilution of electrolytes leading to the development of hyponatremia. However, postoperative hyponatremia is complex and can result from a combination of factors, including not only fluid administration but also the physiological stress of surgery, which can trigger neuroendocrine changes such as the release of catecholamines, vasopressin and aldosterone ultimately leading to water and sodium retention, potassium loss and reduced urinary output (20). Furthermore, in other studies, hyponatremia has been recognized as an indicator of intraabdominal sepsis having a high specificity profile for anastomotic leak (21). In our study, hyperkalemia also emerged as one of the prominent electrolyte disturbances in the postoperative period. The causes of this condition may be diverse, including underlying medical conditions like Chronic Kidney Disease (CKD), as well as medication usage during the perioperative period, which may interfere with potassium excretion (Angiotensin Converting Enzyme-inhibitors, Angiotensin Receptor Blockers, Beta Blockers, Potassium-sparing diuretics, Heparin and some antibiotics). Additionally, extensive tissue dissection during surgery can cause tissue injury, leading to the leakage of potassium from intracellular compartments. Metabolic acidosis is another postoperative complication that can contribute to hyperkalemia (22). Although hyperkalemia is typically associated with AKI and hypovolemia, it is worth noting that this electrolyte disturbance can also be related to fluid overload which can contribute to edema and impair tissue healing. This leads to a reduction in effective plasma volume, ultimately resulting in hyperkalemia. (23) It is important to acknowledge that the data regarding the sodium and potassium levels data were collected up to 48h after major abdominal surgery, during the period that includes postoperative fluid administration. Additionally, we did not collect information regarding the type of fluids administered. These factors could potentially introduce some bias into the results, which make it challenging to draw definitive conclusions from our results.

Although we did not show a causal relationship between the IOF volume and postoperative AKI, it is necessary to conduct larger studies to determine any possible relationship. In our study, it

was not possible to collect urinary output values due to insufficient hospital records. However, the perioperative period has shown to be associated with some diagnostic challenges as the urinary output is frequently decreased due to the release of aldosterone and vasopressin from stress or even anaesthesia. (24) We identified patients with AKI applying the KDIGO classification system for serum creatinine levels. It should be noted that serum creatinine can also be altered by other factors commonly altered in the perioperative period, namely muscle injury, volume overload, nutrition and steroids (24), which can lead to a potentially inaccurate diagnosis of AKI, if only KDIGO criteria are applied. Furthermore, whether a diagnosis of postoperative AKI based on creatinine levels alone is clinically significant is a subject of discussion, since patients might still have proper urinary output and acid-base and water-salt balance, though some evidence shows a higher risk of decreased renal function in patients who had postoperative AKI (25).

We found no difference regarding the need for vasopressor therapy, which is surprising, considering that the administration of fluids is often a first-line therapy for hypotension and therefore one could hypothesize that restrictive fluid regimens would be associated with an increased use of vasopressors.

Pulmonary oedema and anastomotic dehiscence, two complications often linked to fluid overload related to liberal fluid regimens, also did not show any difference between the two groups. This might be explained by the reduced sample size of our study.

To the best of our knowledge, our study is the first one in Portugal to compare the postoperative outcomes in restrictive versus liberal IOF administration. The study has several limitations: first, this was a single-centre study with a relatively small sample size. Therefore, larger studies are necessary to confirm our results. Second, IOF administration is only one aspect of perioperative fluid management and postoperative fluid administration may also have an impact on the patient outcomes. Lastly, although we studied both pancreatic and liver surgery, future studies should aim to separate them for a more thorough investigation and to be able to specify each outcome based on the type of surgery performed.

Chapter 5

Conclusions

In conclusion, our results suggest that in pancreatic and liver surgery, the liberal IOF administration is associated with a significantly higher median peak serum lactate level and increased incidence of electrolytic disturbances in the postoperative period.
Further studies comparing different fluid regimens are needed to validate our results.

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