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Original study

The effect of intraoperative furosemide administration during minimal invasive oesophageal surgery on the occurrence and prevention of postoperative acute kidney injury - A retrospective observational cohort study

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Abstract

Background: **The decision for volume expansion or fluid removal during surgery is often based on urinary output. The use of intravenous furosemide can reverse oliguria but may harm renal function. The aim of this study is to explore the occurrence of postoperative acute kidney injury (AKI) in patients receiving furosemide compared to patients not receiving furosemide.**
Methods: **Single centre cohort study. Adults scheduled for elective minimal invasive esophagectomy from October 2015 until December 2021 were included. The primary outcome was the occurrence of postoperative AKI in patients. AKI was defined according KDIGO. Secondary outcomes were AKI stages, 90-days mortality, and the occurrence of AKI in patients with intraoperative oliguria.**
Results: **202 patients were included. Furosemide and non-furosemide patients had comparable baseline characteristics. 75% of the patients received <= 5mg furosemide.**
Patients treated with furosemide and without furosemide had similar occurrence rate of AKI (47.2% versus 39.0%, p = 0.45) and severity of AKI (p = 0.40). There was a significant decrease of serum creatinine postoperatively on day 1 and day 2-7, for all patients (p<0.001), furosemide patients (p<0.01 and p<0.01) and non-furosemide patients (p<0.001 and p<0.001).
There was no significance between intraoperative diuresis < 0.5 mL.kg-1.h-1 or < 0.3mL.kg-1.h-1 and the presence of postoperative AKI (p=0.67; p=1.00).
No statistical significance for 90-days mortality was found between AKI and no AKI patients (p=0.70).
Conclusion: **An intravenous dose furosemide to treat intraoperative oliguria during elective minimal invasive esophagectomy in patients that were considered euvolemic, did not prevent AKI nor did it result in AKI.**

Keywords/MESH-terms: **Furosemide, Enhanced Recovery After Surgery, Minimally Invasive Surgical Procedures, Esophageal Neoplasms, Acute Kidney Injury.**

This study was approved by the Ethical Committee of Ghent University Hospital, with registration number database: B670201111232, and amendment number: #ONZ-2022-0018-AM02 (date of amendment: 8 September 2022). Chairman Ethical Committee: Prof. dr. Renaat Peleman.

Introduction

Esophagectomy has evolved to a minimal invasive procedure with a reduction in perioperative blood loss, wound infections, pulmonary complications and length of hospital stay[1,2]. Minimal invasive esophagectomy consists of two distinct phases: the laparoscopic and thoracoscopic phase or the laparoscopic and trans hiatal phase.

In this type of surgery, perioperative fluid management is become more restrictive, targeting 6-7 mL.kg-1.h-1 for open surgery and 3.5 mL.kg-1.h-1 for laparoscopic surgery[3].

Perioperative oliguria is a predictive factor for postoperative acute kidney injury (AKI)[4-7].

AKI occurs in 5% to 18.4% of the patients undergoing major abdominal surgery[8,9]. The occurrence of AKI following thoracic surgery ranges from 4.5% to 14% in patients with respectively a normal and decreased preoperative renal function. 10 All studies demonstrated that AKI is associated with increased use of resources, morbidity and mortality[6,8,11,12].

Furosemide may be the cause of AKI, when it leads to hypovolemia. On the other hand, it may prevent development of AKI by decreasing the metabolic and oxygen demands in the thick ascending limb of Henle's loop by blocking the Na+/K+/2CL- pump in the luminal cell membrane[13,14]. The treatment of perioperative oliguria with a loop diuretic is therefore controversial[15]. A systematic review could not demonstrate benefit nor harm for using furosemide postoperatively in adults who underwent surgery due to the lack of high-quality evidence[16].

An overview of different risk factors of AKI can be seen in figure 1.

This study aims to investigate whether an intraoperative intravenous bolus of furosemide, even low dose (<= 5mg), can prevent postoperative AKI in patients undergoing minimally invasive esophagectomy. As secondary outcomes: the occurrence of the different AKI severity stages (1 to 3), in patients with and without intravenous furosemide bolus intraoperatively; 90-days mortality (mortality at day 90 postoperatively); the evolution of serum creatinine measured preoperatively, postoperatively on day 1, and the maximum value on postoperative day 2-7; and the association of intraoperative oliguria (using three different definitions) and postoperative AKI. This is of interest because of the intention of optimizing perioperative kidney functioning during a minimal invasive esophagectomy without the side effects of normal dosage of furosemide administration nor the disturbance of the fluid balance. It can give us the information needed for further research on this topic.

Materials and methods

Study design and patient selection

This study comprises a single-centre, retrospective cohort analysis, based on a large scale, existing and previously approved registry of the department of gastro-intestinal surgery. The study wasn't

Modifiable	Non-Modifiable
• Anemia/Blood transfusion	• Chronic kidney disease
• Hypertension	• Chronic liver disease
• Hypercholesterolemia	• Congestive heart failure
• Hypoalbuminemia	• Diabetes mellitus
• Infection/Sepsis	• Older age
• Mechanical ventilator	• Peripheral vascular disease
• Nephrotoxic agents	
• Use of vasopressors/inotropes	
• High risk surgery	
• Emergency surgery	
• Hemodynamic instability	
• Use of intra-aortic balloon pump	
• Longer time in cardiopulmonary bypass pump	

Fig. 1 — Risk factors of AKI.
The different risk factors of AKI which has been summarized by Thongprayoon et al.
Thongprayoon C, Hansrivijit P, Kovvuru K, Kanduri SR, Torres-Ortiz A, Acharya P, Gonzalez-Suarez ML, Kaewput W, Bathini T, Cheungpasitporn W. Diagnostics, Risk Factors, Treatment and Outcomes of Acute Kidney Injury in a New Paradigm. J Clin Med. 2020 Apr 13;9(4):1104. doi: 10.3390/jcm9041104. PMID: 32294894; PMCID: PMC7230860.

registered on a platform. All consecutive adult patients (≥ 18 years) who underwent minimal invasive oesophageal surgery at the Ghent University Hospital from 8th October 2015 until 23rd December 2021 were included. Patients with CKD (chronic kidney disease) without diuretic treatment were not excluded from the study. Patients already on diuretics preoperatively or who underwent kidney surgery, e.g. nephrectomy, or -transplantation were excluded from this study. These patients were excluded due to the possible influence on the preoperative kidney function and serum creatinine or a possible interaction with furosemide.

The minimal invasive approach is based on the recommendations described in the ERAS (enhanced recovery after surgery) protocol. 2,17

This manuscript adheres to the applicable STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

The research was performed by dr. Van Speybroeck, under supervision of prof. dr. De Baerdemaeker, prof. dr. Hoste en dr. Schaubroeck. This was performed in a period ranging between October 2021 and December 2023 (26 months).

This study was approved by the Ethical Committee of the University Hospital, with registration number database: B670201111232, and amendment number: #ONZ-2022-0018-AM02 (date of amendment: 8 September 2022).

Fluid management protocol

Intraoperative fluid management was based on a central venous pressure (CVP) goal set between 5 – 10 mmHg, maintenance of urine output above 0.5 mL.kg-1.h-1, and a baseline fluid administration of ± 3.5 mL.kg-1.h-1 for laparoscopic surgery to maintain left ventricular end diastolic volume index (LVEDI) and cardiac index (CI), as suggested by Concha et al. 3 LVEDI and CI were not routinely measured perioperatively. Fluid losses on top of baseline fluid administration were compensated with crystalloids or colloids (gelatines or starches) at the anaesthetist discretion. Low dose intravenous furosemide bolus (2.5 – 5 mg) was considered in case of oliguria despite of abovementioned fluid management.

Anesthesia management

Most of the patients received a thoracic epidural before induction unless they refused or there was a presence of absolute contra-indications. The anaesthesist was free in chosing induction agents, but at our centre, most of the time, induction is done with sufentanil, propofol and rocuronium. The anaesthesist is free to choose a multimodal approach with the usage of dexmedetomidine and ketamine. As a volatile anaesthetic, sevoflurane was used during the entire procedure. A bolus of ropivacaine was given on the epidural before incision. Intraoperatively, extra boluses could have been given. Also, boluses of sufentanil are a possible approach, which depended on the decision of the anaesthesist. A PCEA (or PCIA) pump was started as postoperative pain management. Intraoperative monitoring was the ASA standard of care with inclusion of an arterial and central line. If vasopressors were needed, noradrenaline was started.

Outcomes

The primary outcome is defined as the occurrence of postoperative AKI. According to the Kidney Disease: Improving Global Outcomes (KDIGO) definition of AKI, postoperative AKI was calculated until seven days postoperatively based on urine output and/or serum creatinine. 18 Recording of AKI was stopped when patients were discharged from the ICU or up to a maximum of 7 days. The administration of a furosemide bolus, high- or low-dose, was per protocol based on the intraoperative urine production and was exclusively given to patients with oliguria, defined by a urine output of <0.5 mL.kg-1.h-1. The separate analysis for low-dose furosemide administration is added in supplement.

Secondary outcomes were the occurrence of the different AKI severity stages (1 to 3), in patients with and without intravenous furosemide bolus intraoperatively, 90-d mortality (mortality at day 90 postoperatively), the evolution of serum creatinine measured preoperatively, postoperatively on day 1, and the maximum value on postoperative day 2-7, and the association of intraoperative oliguria and postoperative AKI. For this last endpoint we explored several definitions of oliguria: a) the KDIGO criterion of <0.5 mL.kg-1.h-1 18, b) by Mizota et al. of <0.3 mL.kg-1.h-1 5 and c) the definition by Puckett et al. of <0.2 mL.kg-1.h-1. 19

Definitions

AKI is defined following the KDIGO guidelines by an increase of serum creatinine or a period of oliguria (Table I). The increase in serum creatinine (Scr) with more than 0.3 mg/dL should occur within 48 hours, and the increase in serum creatinine to ≥1.5 times baseline should occur within 7 days and baseline serum creatinine was defined in this study as the preoperative value. 18 The different KDIGO stages are listed in Table I.

KDIGO stages based on urinary output, serum creatinine levels and the combination of both, were calculated by a dedicated excel-formula. This

Table I. — KDIGO stages.

Stage	Serum creatinine	Urine output
1	1.5 – 1.9 times baseline OR >= 0.3 $mg.dL^{-1}$ increase	< 0.5 $mL.kg^{-1}.h^{-1}$ for 6-12 hours
2	2.0 – 2.9 times baseline	< 0.5 $mL.kg^{-1}.h^{-1}$ for >= 12 hours
3	3.0 times baseline OR increase in serum creatinine to >= 4.0 $mg.dL^{-1}$ OR initiation of renal replacement therapy	< 0.3 $mL.kg^{-1}.h^{-1}$ for >= 24 hours OR anuria for >= 12 hours
Definition of the three different KDIGO stages using serum creatinine and urine output.		

methodology has been used previously in two large studies concerning AKI[20,21].

Statistical analysis

A sample size calculation showed a total of 139 patients is required when an allocation ratio of ¼ is used with one patient in the low-dose furosemide group for four patients in the non-furosemide group, to detect a clinical size-effect of a 0.3mg/dL increase of creatinine with alfa set at 0.05, a power of 80%, and a standard deviation of 0.5.

Statistics used for categorical variables were the chi-square test, or fisher exact test in case of small expected frequencies. Normal distribution was assessed by inspecting the graphical visualizations (QQ-plot, box-plot, histogram) and by analysing the Shapiro-Wilk test for normality. Based on these results, the non-parametrical Mann-Whitney U test was used for continuous variables. Multiple dependent variables were compared with the Friedmann test and subsequent the Wilcoxon signed-rank test, and independent with the Kruskall-Wallis test. A Bonferonni correction was applied for multiple comparisons.

We used the statistical program IBM SPSS Statistics for Windows, Version 28.0 (Armonk, NY: IBM Corp, USA). The results were assumed to be statistically significant when double-sided $p < 0.05$.

Results

A total of 221 patients were screened for this study. Of these, 19 were excluded due to preoperative diuretic use. Four missing values for the intraoperative furosemide dosage are noted. Of 198 patients, 36 (17.8%) received furosemide intraoperatively (figure 2). The baseline characteristics of the patient cohort are in Table II. Median age of patients was 68 y, and 81.7% were male.

Baseline characteristics

A total of 36 patients were administered furosemide during surgery, in 27 patients (75%) this was at a dose of 5 mg or less (Table III, supplement).

The patients who were administered furosemide had comparable baseline characteristics compared

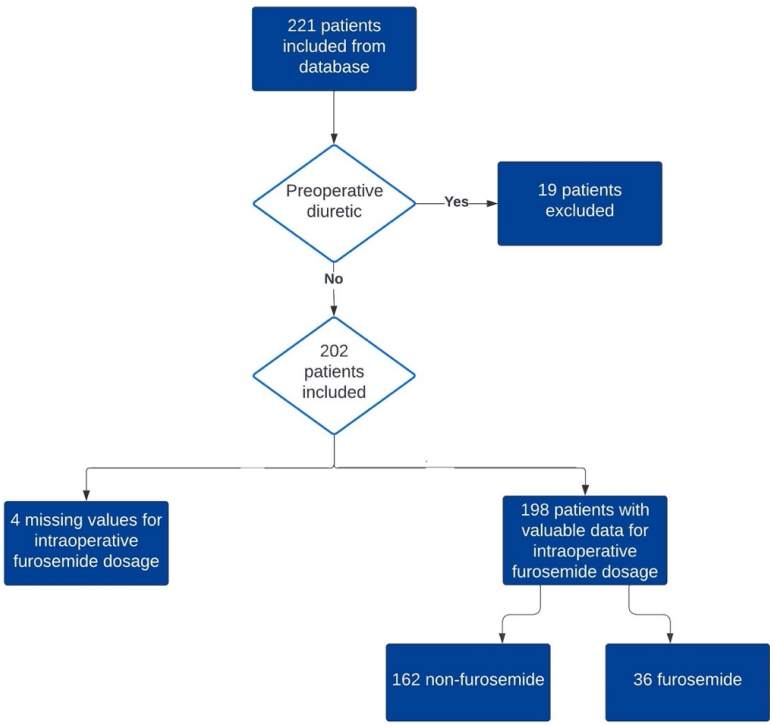

Fig. 2 — Flowchart of patient inclusion.

Table II. — Patients baseline characteristics.

	All patients (n = 202)	Furosemide (n = 36)	Non-furosemide (n = 162)	P-value
Age (y)	68 (59.0 – 74.0)	69 (59.0 – 74.8)	67 (59.0 – 73.0)	0.29
Gender Female Male	 37 (18.3%) 165 (81.7%)	 4 (11.1%) 32 (88.9%)	 33 (20.4%) 129 (79.6%)	0.20
Weight (kg)	77 (59.0 – 74.0)	76.5 (67.8 – 91.0)	77 (64.0 – 87.0)	0.36
BMI ($kg.m^{-2}$)	25.2 (22.5 – 28.4)	26.2 (23.8 – 29.5)	25.0 (22.3 – 28.0)	0.21
Comorbidities				
Arterial hypertension	75 (37.1%)	13 (36.1%)	61 (37.7%)	0.86
COPD	25 (12.4%)	8 (22.2%)	17 (10.5%)	0.09
Liver disease	7 (3.5%)	1 (2.8%)	6 (3,7%)	1.00
Diabetes type 1 or 2	28 (13.9%)	4 (11.1%)	24 (14.8%)	0.56
Ischemic heart disease	30 (14.9%)	8 (22.2%)	21 (13%)	0.16
Perioperative data				
Duration of surgery (min)	503 (447.5 – 562.5)	512 (455 – 570)	495 (443.8 – 556.3)	0.23
Urine output ($mL.kg^{-1}.hr^{-1}$)	0.89 (0.64 – 1 .29)	0.98 (0.56 – 1.36)	0.89 (0.65 – 1.27)	0.80
Preoperative serum creatinine ($mg.dL^{-1}$)	0.86 (0.72 – 1.02)	0.93 (0.78 – 1.04)	0.84 (0.71 – 1.00)	0.05
Outcome data				
Postoperative day 1 serum creatinine ($mg.dL^{-1}$)	0.76 (0.65 – 0.88)	0.82 (0.70 – 1.00)	0.73 (0.63 – 0.84)	<0.01
Maximum serum creatinine postoperative day 2-7 ($mg.dL^{-1}$)	0.71 (0.62 – 0.82)	0.78 (0.67 – 0.96)	0.71 (0.61 – 0.80)	0.02
Length of ICU stay (days)	1.0 (1.0 – 2.0)	1.0 (1.0 – 2.8)	1.0 (1.0 – 2.0)	0.31
Length of hospital stay (days)	14.0 (11.0 – 14.0)	14.0 (11.0 – 21.0)	14.0 (11.0 – 20.0)	0.79

Patient baseline characteristics, including comorbidities, perioperative data and outcome date. Data are reported as n (%) or median (25% quartile- 75% quartile). The p-values for the multiple variables were measured between the furosemide and the non-furosemide group. N = number; ICU = intensive care unit.

to the patients without furosemide administration (Table II), except for a higher preoperative serum creatinine in the furosemide group.

Primary outcome: Occurrence of AKI

AKI occurred in 82 of all patients (40.6%). Based on urine output criteria, 82 patients had AKI (40.6%), compared to 2 patients with AKI (1%) when assessed by serum creatinine criteria only. Patients treated with furosemide and without furosemide had similar occurrence rate of AKI (47.2% versus 39.0%, p = 0.45) (supplemental Table IV).

Secondary outcomes

1. Severity of AKI by KDIGO stages

A cross-table of the calculated KDIGO-stages is shown below (Table V).

2. Change in serum creatinine

There was a significant decrease of serum creatinine concentration from preoperatively to postoperative day 1 and to the maximum concentration in the postoperative period day 2-7 (Table VI). This was similar in the furosemide and non-furosemide cohorts.

3. Oliguria

Intra-operative oliguria (< 0.5 mL.kg-1.h-1) occurred in 12.3% of patients. There was no statistical significance between intraoperative diuresis less than 0.5 mL.kg-1.h-1 and the presence of postoperative AKI, regardless the KDIGO staging, with a p-value of 0.667 (Table VII).

4. Mortality

No statistical significance for mortality was found between AKI and no AKI patients (Table VIII).

Table V. — Occurrence rate of KDIGO stages between furosemide and non-furosemide exposed patients.

	All patients (n=202)	Furosemide (n=36)	Non-furosemide (n=162)	P-value
AKI KDIGO combined No AKI Stage 1 Stage 2 Stage 3	 116 (57.4%) 40 (19.8%) 40 (19.8%) 1 (0.5%)	 19 (52.8%) 6 (16.7%) 11 (30.6%) 0 (0%)	 97 (59.9%) 33 (20.4%) 28 (17.3%) 1 (0,6%)	0.395
AKI KDIGO UO No AKI Stage 1 Stage 2 Stage 3	 120 (59.4%) 40 (19.8%) 41 (20.3%) 1 (0.5%)	 19 (52.8%) 6 (16,7%) 11 (30.6%) 0 (0%)	 99 (61.1%) 33 (20.4%) 29 (17.9%) 1 (0.6%)	0.393
AKI KDIGO Scr No AKI Stage 1 Stage 2 Stage 3	 195 (96.5%) 2 (1.0%) 0 (0%) 0 (0%)	 36 (100%) 0 (0%) 0 (0%) 0 (0%)	 157 (96.9%) 2 (1.2%) 0 (0%) 0 (0%)	1.000
AKI KDIGO UO is presence and staging of AKI based on the urine output criteria only of the KDIGO definition AKI KDIGO Scr is presence and staging of AKI based on the serum creatinine criteria only of the KDIGO definition.				

Table VI. — Evolution of the serum creatinine between furosemide and non-furosemide group.

Serum creatinine (mg. dL^{-1})	Preoperative value: median (IQR)	Postoperative day 1: median (IQR)	Max Postoperative d 2-7: median (IQR)	P
All patients (n=202)	0.86 (0.71 – 1.02)	0.76 (0.65 – 0.88)	0.71 (0.62 – 0.82)	
All patients	0.86 (0.71 – 1.02)	0.76 (0.65 – 0.88)		< 0.001
All patients	0.86 (0.71 – 1.02)		0.71 (0.62 – 0.82)	< 0.001
Furosemide (n=36)	0.93 (0.78 – 1.04)	0.82 (0.70 – 1.00)	0.78 (0.67 – 0.96)	
Furosemide	0.93 (0.78 – 1.04)	0.82 (0.70 – 1.00)		0.035
Furosemide	0.93 (0.78 – 1.04)		0.78 (0.67 – 0.96)	0.002
Non-furosemide (n=162)	0.84 (0.71 – 1.00)	0.73 (0.63 – 0.73)	0.71 (0.61 – 0.80)	
Non-furosemide	0.84 (0.71 – 1.00)	0.73 (0.63 – 0.73)		< 0.001
Non-furosemide	0.84 (0.71 – 1.00)		0.71 (0.61 – 0.80)	< 0.001

Table VII. — Oliguria according to AKI.

	Oliguria (<0.5 mL.kg-1.min-1)	No oliguria	Total	P-value
AKI	9 (36%)	69 (41.2%)	78	0.667
No AKI	16 (64%)	97 (58.4%)	113	
	Oliguria (<0.3 $mL.kg^{-1}.min^{-1}$)	No oliguria	Total	P-value
AKI	1 (50%)	77 (40.7%)	78	1.00
No AKI	1 (50%)	112 (59.3%)	113	
	Oliguria (<0.2 $mL.kg^{-1}.min^{-1}$)	No oliguria	Total	P-value
AKI	0	78	78	No p-value calculated
No AKI	0	113	113	

Table VIII. — Mortality at day 90 according to AKI status.

Mortality at 90-d	No AKI (n = 115)	AKI (n = 80)	P-value
No	110 (95.7%)	75 (93.8%)	0.743
yes	5 (4.3%)	5 (6.3%)	

Table IX. — Mortality at day 90 according to KDIGO.

KDIGO	1	2	3	P-value
Mortality within 90 days	3 (3.8%)	2 (2.5%)	0 (0%)	0.695
No mortality	36 (45%)	38 (47.5%)	1 (1.3%)	

We found no association between AKI severity stage and mortality at 90-d (Table IX).

Sensitivity analysis

All results were reproduced when the outlier with stable CKD was excluded from the analysis. No significant difference in results was found.

Discussion

In patients undergoing elective minimal invasive esophagectomy with or without intra-operative administration of furosemide, postoperative AKI occurred in 40%, mainly based on urine output criteria. There was no difference in occurrence of postoperative AKI or AKI severity between the furosemide and non-furosemide group or between groups who received high- or low-dose furosemide. Intraoperative oliguria (< 0.5 mL.kg-1.h-1) occurred in 12.3% of patients and was not associated with postoperative AKI. Intraoperative diuresis of less than 0.2 mL.kg-1.h-1 did not occur in this cohort. An association between AKI and 90-day mortality could not be demonstrated in this study.

AKI was present in 40% of patients, mainly based on urine output. This could imply a functional AKI rather than a 'structural' change in kidney function, which is also reflected by the low mortality rates in the AKI group.

Our study showed a higher detection of AKI making use of the urine output criteria. This can be explained by a late increase in serum creatinine compared to a quicker urine output decrease[22]. Including urine output in the AKI definition detects AKI hours earlier than when only using serum creatinine, allowing early prevention of AKI[23]. Vanmassenhove et al. found a significant increase in AKI incidence, twelve hours after ICU admission, almost exclusively based on UO criterium, which would have been missed by Scr criterium only[24]. Similarly, we found in a large cohort of critical COVID-19 patients that majority of AKI was defined by urine output criteria only[21]. This underlines the importance of analysing both Scr and UO in detecting AKI. It needs to be highlighted that in critically ill patients who underwent major surgery a rise in serum creatinine may be masked by decreased creatinine production predominantly due to muscle wasting, and a postoperative positive fluid balance. Kellum et al. concluded that short- and long-term risk of AKI are highest when both serum creatinine and urine output criteria are fulfilled[25].

Measuring urine output intra-operatively is one of the most widely used indicators to make clinical decisions for volume expansion and maintenance of euvolemia[26]. It is important to note that different mechanisms lie at the basis of perioperative oliguria. The pneumoperitoneum and surgical stress response are fluid unresponsive, with the risk of fluid overload when repeated boluses are given[27]. Hypervolemia causes an increased intravascular hydrostatic pressure, damaging the endothelial barrier with fluid accumulation in the interstitial space[28] and may lead to anastomosis insufficiencies[29]. A pneumoperitoneum can cause a reduction in urine output and possibly an increase in serum creatinine. Therefore, European guidelines promote low-pressure laparoscopy (5-7 mmHg)[30]. In our centre an abdominal pressure of 14 mmHg and thoracal pressure of 8 mmHg is used. However, in our cohort, intra-operative oliguria was not frequently observed.

The predictive value of perioperative oliguria for developing postoperative AKI is low[4,11]. There are different strategies to follow when intraoperative oliguria occurs.

The RELIEF trial showed a reduction in postoperative AKI risk when oliguric patients were randomized to a moderately liberal fluid protocol compared to restrictive fluid regimen[31,32]. A meta-analysis found a decrease in 30-days mortality using a goal-directed fluid therapy (GDFT)[33]. The renal clearance of infused crystalloid fluid in an anesthetized patient undergoing surgery is diminished compared to a conscious, spontaneous breathing person[2,3]. This can be attributed to the anaesthesia induced hypotension, the stress response, the pneumoperitoneum during laparoscopic surgery and the hemodynamic

effects of positive pressure ventilation on the venous return and stressed volume. Consequently, urinary excretion increases little despite additional intravascular fluid[4,5]. Despite the disadvantages of fluid overload and the risk associated with fluid administration, 'true' hypovolemic patients, who are at risk for development of AKI, are still in need of fluid boluses in combination with vasopressors. The need of fluid boluses must be recognized on time[34-36], which makes a proper peri-operative diagnostic tool mandatory.

In non-hypovolemic patients, permissive oliguria can be applied. A meta-analysis showed insufficient evidence to associate a restrictive fluid therapy with oliguria and the risk of acute renal failure[37], which makes it possible to handle the watchful waiting strategy.

Another possible medical approach to persistent oliguria despite adequate fluid therapy is the administration of a diuretic to optimize the urine output. This was not beneficial nor causing harm in our study population. A single, lower dose of furosemide can be used instead of a higher dose ≥ 10mg. A retrospective cohort study identified a reduced incidence of AKI after correction of the intraoperative oliguria with furosemide administration[38]. Awareness should be raised for the fact that diuretics are seen as risk factors for AKI[39-41], which has a correlation with high dosage[40]. In our study the dosage of furosemide is so low, that the risk of a diuretic induced AKI or other side effects on the renal functioning is probably lower compared to standard or high doses. When furosemide is used and urine output is augmented, special attention is needed to maintain an euvolemic state and to correct electrolyte disturbances.

Patients with known chronic kidney dysfunction undergoing a minimal invasive esophagectomy procedure are additionally vulnerable for AKI[42]. Preoperative optimalisation of the kidney function is being advised with a perioperative vigilance for deterioration and with thoughtful consideration if use of diuretics is appropriate. Since, there was only 1 patient with chronic kidney disease (defined as an estimated glomerular filtration rate <60 mL/min), our data cannot be used to explore this further.

This study has several limitations. First, this is a single centre cohort study, which may have a lack of generalizability of the results.

Despite the efforts made to assemble an accurate database, missing data are still present.

The preoperative creatinine was used as baseline, in most of the cases the creatinine the day before surgery. In a few cases the blood sample was older, up to a month. When the creatinine value was a month old, previous blood samples were assessed to establish if the values were steady state. We assumed that patients who fulfilled the criteria of AKI during their preoperative screening were excluded for surgery as surgery would have been postponed to a later date after diagnostic workout and pre-operative optimization of this risk factor. Most of the patients receive neoadjuvant chemotherapy with regular blood samples. Therefore, AKI would have been detected and corrected early during this therapy stage.

The postoperative creatinine levels were on postoperative day 1 and the highest creatinine between postoperative day 2 and 7. The latter was chosen because of an inconsequence in timing of the blood samples on the non-ICU wards, especially on day 5-6-7. In future prospective studies, we advise a daily measurement of serum creatinine making it possible to determine AKI based on serum creatinine more accurately.

In 2018, the ERAS protocol was initiated at our hospital. It is possible that this could have influenced our results.

To minimize the influence of different operation strategies, we only selected the minimal invasive esophagectomy procedures. Our conclusions cannot be extrapolated to patients undergoing non-laparoscopic esophagectomy due to a high difference in physiology between open and laparoscopic procedures.

Furosemide was administered in the presence of oliguria, which could have biased our results, hypothezing that patients with oliguria intra-operatively have a higher risk of AKI. This was not confirmed in our study.

Due to time restraints, we weren't able to calculate a propensity score.

Conclusion

Our study of retrospective character and within his limitations, concludes that a furosemide administration, even low dose, to treat intraoperative oliguria during elective minimal invasive esophagectomy in euvolemic patients did not prevent AKI nor did it result in AKI. Intra-operative oliguria was not associated with postoperative AKI. Furosemide use was not associated with higher mortality in minimal invasive esophagectomy. To confirm these results, randomized controlled trials with larger sample sizes or multicentre collaborations are necessary.

Acknowledgements: The KDIGO-stages have been calculated making use of a pre-existing excel-file developed by doctor Vandenberghe W. of the intensive care department Ghent University Hospital. This is based on previously mentioned definition of AKI;

KDIGO stages based on urinary output, serum creatinine levels and the combination of both, were calculated by a dedicated excel-formula.

The authors report there are no competing interests to declare.

Data availability statement: Data are available with the corresponding authors.

Supplement

Low-dose furosemide administration vs non-furosemide, high-dose vs low-dose and high-dose vs non-furosemide

Baseline characteristics

A total of 36 patients were administered furosemide during surgery, in 27 patients (75%) this was at a dose of 5 mg or less (supplemental Table III).
The patients who were administered a low-dose furosemide had comparable baseline characteristics compared to the patients without furosemide administration (Table X), except for a higher serum creatinine on postoperative day 1.

Primary outcome : Occurrence of AKI

The occurrence rate of AKI between low-dose furosemide and non-furosemide are listed in supplemental Table XI. Both cohorts had similar occurrence rate of AKI.

Secondary outcomes

1. Severity of AKI by KDIGO stages

A cross-table of the calculated KDIGO-stages for the low-dose furosemide and non-furosemide group is shown below (supplemental Table XII). There are 3 missing values (1.6%) for the combined KDIGO stages.

A second comparison of the KDIGO stages between the non-furosemide group with the higher dose furosemide group (>5mg furosemide) was made and a third comparison was performed between the low-dose furosemide group and the higher dose furosemide group (>5mg furosemide). The p-value are respectively 0.13 and 0.50 with no statistical significance between the two groups.

2. Change in serum creatinine

There was a significant decrease of serum creatinine concentration from preoperatively to the maximum concentration in the postoperative period day 2-7 (supplemental Table XIII). No statistical significance was found between the serum creatinine preoperative and the serum creatinine postoperative day 1 ($p = 0.04$) after a Bonferonni correction with p-values being significant < 0.02.

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