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Comparative Accuracy of Methods for Detecting Postoperative Renal Impairment in Colorectal Surgery Under a Restrictive Fluid Regimen

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Abstract

Objective: Perioperative fluid restriction in major abdominal surgeries carries a potential risk of organ dysfunction such as acute kidney injury. Profound fluid restriction should be applied cautiously. The aim of this study is to compare the accuracy of (serum creatnine, urine output and KDIGO compared to NGAL for detection of postoperative AKI after colorectal surgery.

Methods: Restrictive fluid strategy was applied to all patients with 5 mL/kg/h of lactated ringer (LR) and was administered intraoperatively starting from the induction of general anesthesia till the end of surgery and patient extubation. Data collected included incidence of AKI with three screening tools in addition to intra and postoperative complications.

Results: None of the above tested AKI based criteria has satisfactory both sensitivity and specificity. The sensitivity of urine output for detection of AKI was 72.7 [39.0-94.0] while its specificity was 79.8 [69.9-87.6], for creatinine above 0.3 mg/dl; the sensitivity was 63.6 [30.8-89.1] and specificity was 98.9 [93.9-99.9], and for KDIGO the sensitivity was 81.8 % [95% CI 48.2-97.7] and specificity was 74.2% [95% CI 63.8-82.9].

Conclusion: Despite use CVP for detection of hypovolemia, there is still high incidence of AKI. Creatinine based criteria, urine based criteria or combination of both are inaccurate when volume restriction is applied.

Keywords: Restrictive fluid strategy; Acute kidney injury; KDIGO classifications; Renal biomarkers

Abbreviations: AKI: Acute Kidney Injury; ASA: American Society of Anesthesiologists; CVP: Central Venous Pressure; CKD: Chronic Kidney Disease; DVT: Deep Venous Urombosis; GFR: Glomerular Filtration Rate; HR: Heart Rate; KDIGO: Kidney Disease: Improving Global Outcomes; LR: Lactated Ringer; MAP: Mean Blood Pressure; NGAL: Neutrophil Gelatinase-Associated Lipocalin; PE: Pulmonary Embolism; RBCs: Red Blood Corpuscles; SBP: Systolic Blood Pressure

Introduction

Perioperative fluid restriction in major abdominal surgeries had several advantages which include reduced postoperative morbidity, length of hospital stay aler major abdominal surgery compared to liberal, standard and conventional fluid strategies [1-3]. On the other hand, perioperative fluid restriction carries a potential risk of organ dysfunction such as acute kidney injury [3-7]. So profound fluid restriction should be applied cautiously in surgical patients.

Diagnosis of postoperative AKI depends upon both rise in serum creatinine and/or decrease in urine output. In 2012, Both was incorporated in (the Kidney Disease: Improving Global Outcomes) KDIGO system classification for detection of acute kidney injury [8].

NGAL is one of newly used renal biomarker for early detection of AKI. NGAL belongs to the lipocalin group of proteins and is secreted aler damage of epithelial cells of renal tubules [9,10]. Following kidney injury, accumulation of NGAL in systemic circulation leads to increase in its level in plasma and urine [11].

Ue aim of this study is to compare the accuracy of (serum creatnine, urine output and KDIGO compared to NGAL for detection of postoperative AKI aler open colorectal surgery.

Patients and Methods

Uis is an observational study carried out in Assiut University Hospital and Upper Egypt Cancer Institute, between January 2016 and February 2018 in general surgery operative theatre and post-operative ICU. One hundred consecutive patients undergoing elective colorectal surgery were included in this study. Ue study protocol was approved by local ethics committee of the faculty of medicine, Assiut University and all patients provided written informed consent. Uis research funded by Research Finance Unit, Faculty of Medicine, Assiut University.

One hundred consecutive patients aged between (18 and 80 years), of both sexes, American Society of Anesthesiologists (ASA) grade I-III undergoing elective colorectal surgery with an expected duration of

surgery of more than 3 h. All surgical procedures were done under general anesthesia by senior surgeons.

Patients excluded due to Patient refusal, body mass index greater than 35, renal insufficiency (serum creatinine level more than 180 µmol/l), preexisting neurological or psychological dysfunction, impaired cardiac function, pregnancy and lactation and patients proved to be inoperable during operation. Preoperatively, all patients received mechanical bowel and fasted for 8 h. Antibiotic Cefepime (Maxipime 1 gm) was administered 30 to 60 min before induction of anesthesia.

Anesthetic technique was standardized for all patients. Peripheral venous lines were inserted. Standard monitoring included oxygen saturation and pulse rate, capnography, electrocardiogram, non-invasive blood pressure, core body temperature and urine output. A 3-lumen central venous line was inserted in the internal jugular or subclavian vein just aler induction of general anesthesia.

Induction of anesthesia achieved with slow titration of propofol (2 mg/kg) and fentanyl (2 µg/kg). Muscle relaxation was achieved with cisatracurium (0.15 mg/kg) for tracheal intubation maintained with an infusion titrated to two twitches on neuromuscular monitoring. Anesthesia was maintained with sevoflorane in air and oxygen (1:1) titrated and aiming to maintain intraoperative mean blood pressure (MAP) and heart rate (HR) within 20% of preoperative values.

If the patient systolic blood pressure (SBP) or heart rate raised above 20% of the base line, an additional dose of fentanyl 1 µg/kg, increased in the concentration of inhalational anesthetics were used to deepen the level of anesthesia. Blood transfusion was indicated if hematocrit less than 25% with the aim of keeping the hemoglobin around 8mg/dl. Mechanical ventilation was adjusted to maintain an end-tidal CO_2 between 30 and 35 mmHg throughout the operation. Intraoperative normothermia was maintained by means of warm intravenous fluids and humidifier.

Intraoperative flui6 management and monitoring

Restrictive fluid strategy was applied to all patients with 5 mL/kg/h of lactated ringer (LR) was administered intraoperatively starting from the induction of general anesthesia till the end of surgery and patient extubation.

Detection of hypovolemia and flui6 responsiveness using of flui6 challenge

Central venous cannulation was performed in the right internal jugular or right subclavian vein by the Seldinger technique. Ue depth of insertion of the catheter was 12-15 cm. Baseline CVP was measured. Intraoperative monitoring of CVP was done to guide fluid aiming to maintain it between 10 and 12 mm of Hg.

CVP was measured every 15min. aler induction till the end of the surgery. If CVP at any time was below 10 mmHg, which defines hypovolemia, this hypovolemic state was corrected with a 350 mL bolus of LR as administrated, then CVP was reevaluated aler 10 min following a fluid challenge, if CVP is still lower than 10 mmHg aler bolus infusion of fluid, fluid bolus was then repeated until CVP 10-12 mmHg. If patients CVP was below 10-12 and associated with hypotension defined as MAP below 65 mmHg, 5 mg IV bolus ephedrine was administered as needed to keep MAP over 65 mmHg. CVP reading for each patient was taken before stoppage of mechanical ventilation (final CVP) (Figure 1).

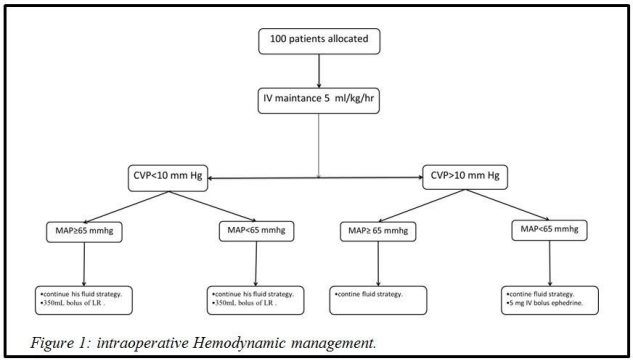

Figure 1: Intraoperative hemodynamic management.

Patients were extubated at the end of the surgery in the operative room aler meeting the extubation criteria according to the institution protocol, then patients were admitted to ICU for 2 days then to their wards alerwards.

Postoperative management

All patients received 4 l of IV fluids as follow: one L of dextrose 5% and three liters LR in the next 48 h. Clear oral fluids were allowed to all patients starting from the third postoperative day. Patients with poor oral intake (<21/day) received additional IV fluids to maintain euvolemia. Blood loss in drains was replaced by same volume of packed RBCs or LR according to Hb concentration. Postoperative multimodal analgesia was achieved with the use of small IV doses of morphine (<5 mg) and acetaminophen (1 gm every 6 h).

Data collection

Patients and surgical data: Uis includes age, weight, height, gender, BMI, operative duration.

Primary outcome: Ue incidence of postoperative acute kidney injury was determined by all of the following criteria separately:

Increase in serum creatinine >0.3 mmol/dL above baseline within 48 h aler the operation. Urine output<0.5 ml/kg/h for 6 h in the next 48 h aler the operation.

KDIGO classification using both the above criteria (Appendix 1)

AKI diagnosed by serum NGAL level >149 ng/ml in the 24 h aler the operation [12-15]. Serum NGAL levels was done by enzyme-linked immunosorbent assay (ELISA). Uree blood samples were withdrawn: one sample before induction for determination of baseline value, second sample taken 2 h aler the end of the surgery, and lastly the third sample withdrawn 24 h aler the surgery.

Secondary outcomes:

Intraoperative and postoperative fluid balance in first and 2 sec day. Fluid balance was measured as intake (intravenous fluids plus transfused packed RBCs) minus output (urine, blood loss).

Incidence of intraoperative complications as hypovolemia detected by CVP, hypotension and bradycardia.

Postoperative complication as anastomotic leak, hypotension, DVT/PE and sepsis.

Statistical analyses

Data were presented as mean ± SD, median, range or percentage as appropriate. Paired t-test was used to compare between pre- and post-operative data, sensitivity and specificity was calculated for AKI using urine, creatinine, and KDIGO based criteria compared to NGAL. P-value <0.05 is statistically significant, otherwise is non-significant.

Results

One hundred and thirty three consecutive patients were screened for eligibility. Ten patients were excluded due to impaired renal function, eleven patients due to impaired cardiac function, three patients refused to participate and seven patients were with history of cerebrovascular stroke and two patients were lactating.

In our cohort the mean age of patients was 49.3 ± 16.7 years and the median (range) was 50 (21-83) years. Male patients represented 55 (55%) of cases and female patients represented 45 (45%) of cases. Ue mean weight of the patients was 74.3 ± 14.5 kg and the median (range) was 74 (47-108) kg. Ue mean height of the patients was 168.8 ± 7.8 cm and the median (range) was 169.5 (150-192) cm. Ue mean body mass index of the patients was 26.0 ± 4.5 (kg/m^2) and the median (range) was 26.5 (15.8-34.9) (kg/m^2). ASA grade, 48 (48%) patient were ASA grade I, 34 (34%) were ASA grade II and 18 (18%) were ASA grade III. Ue mean surgical duration was 4.2 ± 1.2 hours and the median (range) was 4 (2-7). Ue mean duration for hospital stay was 6.9 ± 3.9 day. Ue median (range) was 6 (2-30) day (Table 1).

	Mean ± SD	**Median (range)**
Age (years)	49.3 ± 16.7	50 (21-83)
Gender (male/female)	55/45	
Weight (kg)	74.3 ± 14.5	74 (47-108)
Height (cm)	168.8 ± 7.8	169.5 (150-192)
Body mass index (BMI)(Kg/m2)	26.0 ± 4.5	26.5 (15.8-34.9)
ASA; (I/II/III)	48/34/18	
Surgical duration (hours)	4.2 ± 1.2	4 (2-7)
Hospital stay (days)	6.9 ± 3.9	6 (2-30)

Table 1: Demographic and surgical data (Data are presented as mean ± standard deviation, median and range, ASA status presented as numbers, P-value<0.05 is considered statistically significant).

Post-operative serum creatinine, and urea level showed no significant differences compared to pre-operative values. On the other hand, serum NGAL level increased significantly form baseline value of 96.1 ± 28.6 ng/ml; mean ± SD to 101.7 ± 39.2 ng/ml; mean ± SD aler 24 hours of operation (Table 2).

		Pre-operative	**2 hours post-operative**	**24 hours post-operative**
Serum creatinine (umol/L)	Mean ± SD	73.5 ± 21	-	79 ± 35.8
	Median (range)	69 (19.1-115)	-	70 (36-243)
	p-value	-	-	0.132
Urea (mmol/L)	Mean ± SD	3.9 ± 1.7	-	4 ± 2.1
	Median (range)	3.8 (0.7-10.7)	-	3.7 (0.6-10)
	p-value	-	-	0.591
NGAL (ng/ml)	Mean ± SD	96.1 ± 28.6	94.8 ± 29.3	101.7 ± 39.2
	Median (range)	97 (0-149.4)	95.5 (36.3-170)	102.8 (6.9-183.2)
	p-value	-	0.491	0.038

Table 2: Laboratory data (data are presented as mean ± standard deviation, median and range, p-value<0.05 is considered statistically significant).

Table 3 displays results of the comparison of the three screening tests for AKI in terms of accuracy measures. Comparison of accuracy measures showed that the highest sensitivity was for 81.8% [95% CI 48.2-97.7] for KDIGO based criteria, followed by urine and then creatinine base criteria. Ue highest sensitivity for KDIGO based criteria was on expense of low specificity 74.2% [95% CI 63.8-82.9] which is the lowest between the study tests. Positive predictive values were highest for creatinine based criteria almost triple the value in the other two criteria. On the other hand negative predictive values were comparable in the three AKI based criteria. Creatinine based criteria showed the highest overall accuracy 95% [95%CI 88.7-98.4] followed by urine based criteria 79% [95% CI 69.7-86.5] and lastly KDIGO based criteria 75% [95% CI 65.3-83.1] (Table 3).

Ue intraoperative fluid balance was 876.6 ± 308.1ml; mean ± SD and the median (range) was 835 (120-1940) ml. Ue fluid balance in the 2nd and 3rd postoperative day was significantly lower than in the 1st post-operative day (Table 4).

	Creatinine based AKI	**Urine base AKI**	**KDIGO based AKI**

	Abnormal NGAL level	Normal NGAL level	Total	Abnormal NGAL level	Normal NGAL level	Total	Abnormal NGAL level	Normal NGAL level	Total
Abnormal test	7	1	8	8	18	26	9	23	32
Normal test	4	88	92	3	71	74	2	66	68
Total	11	89	100	11	89	100	11	89	100
Sensitivity	63.6 [30.8-89.1]			72.7 [39.0-94.0]			81.8 [48.2-97.7]		
Specificity	98.9 [93.9-99.9]			79.8 [69.9-87.6]			74.2 [63.8-82.9]		
Positive predictive value	87.5 [48.7-98.1]			30.8 [20.4-43.5]			28.1 [20.0-38.00]		
Negative predictive value	95.7 [90.9-97.9]			95.9 [89.9-98.4]			97.1 [90.4-99.2]		
Accuracy	95.0 [88.7-98.4]			79.0 [69.7-86.5]			75.0 [65.3-83.1]		

Table 3: Results of 2 x 2 tables and accuracy measures. All accuracy measures are displayed as percentage [95% confidence interval].

	Mean ± SD	Median (range)	p-value
Intraoperative fluid balance (ml)	876.6 ± 308.1	835 (120-1940)	-
Fluid balance in the 1st postoperative day (ml)	3016.7 ± 585.4	3170 (1250-3730)	-
Fluid balance in the 2nd postoperative day (ml)	2113.1 ± 963.3	1860 (460-3730)	0.001
Fluid balance in the 3rd postoperative day (ml)	2502 ± 1731.7	1695 (540-6340)	0.003

Table 4: Fluid balance (Data are presented as mean ± standard deviation, median and range. p-value<0.05 is considered statistically significant).

Intra-operative complications	
• Bradycardia	5 (5%)
• Hypotension	15 (15%)
• Hypovolemia	14 (14%)
Post-operative complications	
• Anastomotic leak	4 (4%)
• Hypotension	7 (7%)
• DVT/PE	1 (1%)
• Sepsis	3 (3%)
• Mortality	2 (2%)
DVT: Deep venous thrombosis; **PE:** Pulmonary embolism	

Table 5: Intra- and post-operative complications (data are presented as number (percentage).

Bradycardia occurred in 5 (5%) patients, hypotension occurred more frequently as 15 patients suffered from hypotension, and again hypovolemia measured by CVP<10 was noticed in 14 (14%) patients out of 100 patients. Anastomotic leak occurred in 4 (4%) patients in the early postoperative period. Seven patients developed hypotension. DVT/PE occurred in one (1%) patient postoperatively. Postoperative sepsis developed in 3 (3%) patients postoperative. Two (2%) patients died in the early postoperative period the first one (1%) died in day 3 because of DVT/PE and the other (1%) patient died 15 days aler operation due to anastomotic leak and secondary sepsis (Table 5).

Discussion

In our study we measured the incidence of post-operative AKI with restrictive fluid management with three different tools. Ue incidence of AKI using urine based criteria (less than 0.5 mg/kg/h) was 26%, while it was 8% using a rise in serum creatintine more than 0.3 mg/dl in the first 48 h, and finally using KDIGO classification for AKI which depends on both urine output and/or serum creatinine it was 32%. We compared the incidence of the above criteria with a rise in serum NGAL level as more accurate reference test for early detection of AKI. Ue results of our study showed that none of the above tested AKI based criteria has satisfactory both sensitivity and specificity. Ue sensitivity of urine output for detection of AKI was 72.7 [39.0-94.0] while its specificity was 79.8 [69.9-87.6], for creatinine above 0.3 mg/dl; the sensitivity was 63.6 [30.8-89.1] and specificity was 98.9 [93.9-99.9], and for KDIGO the sensitivity was 81.8 % [95% CI 48.2-97.7] and specificity was 74.2% [95% CI 63.8-82.9].

Ue 2nd and 3rd day postoperative fluid balance was significantly lower compared to the first postoperative day this may due to decrease urine output in the first postoperative day as a result of intraoperative fluid restriction when compared to urine output in the 2nd and 3rd postoperative day.

Different definitions for fluid restriction were used in different studies in colorectal surgeries. Brandstrup et al. used 500 ml dextrose intraoperatively and 500 ml of HAES 6% to replace losses in perioperative mangment in restrictive group [1]. Nisanevich et al. used 4 ml/kg/h of lactated ringer intraoperatively [3]. Holt et al. used 7 ml/kg/h of ringer lactate intraoperatively [4]. de Aguilar-Nascimento used less than 30 ml/kg/day of crystalloid for four days postoperative [2]. Futier et al. used 6 ml/kg/h of LR intraoperatively [6]. Abraham-

Nordling et al. used glucose 2.5% i.v. and infused at rate 2 ml/kg /h. Myles et al., 5 ml/kg/h administered intraoperative.

Incidence of AKI with fluid restriction varies in different studied with different diagnostic measures. Holte et al. found that the incidence was 12.5% of restrictive group and was secondary due to sepsis [4]. Futier et al. found that incidence of AKI was 11.1% in restrictive group and diagnosed by (urine output<500 ml/day, increase in the creatinine level of >30% from the preoperative value) [6]. Abraham-Nordeling et al. found that incidence was 2.5% in restrictive fast tract colorectal surgery diagnosed by serum creatinine level more than 180 µmol/l [16]. Myles et al found that incidence of AKI was 8.6% in restrictive group using KDIGO criteria.

Ue use of serum creatinine as a marker of renal function is limited for several factors as it requires relatively longer half-life to rise [17]. Serum creatinine not truly represents the drop in GFR especially in critically ill patient's e.g. sepsis. Drugs such as cimetidine compete with creatinine secretion through renal tubules [17-19]. Ue patients' volume status affects serum concentration of creatinine. Uis may result in late detection of AKI in patients with volume overload [20,21]. Ue use of serum creatinine for detection of AKI depends upon its baseline value which represents kidney steady state before onset of AKI. Ue preoperative kidney function is not always available so that various surrogate estimates are frequently used [17]. Uese methods may increase or decrease the actual incidence of AKI [22]. It doesn't give idea about the renal reserve. In healthy patients, the rise of serum creatinine >0.3 mg/dl as a result decrease in the GFR while in patient with CKD, such rise in serum creatinine may be accepted as daily variation [23]. Finally, the only use of serum creatinine cannot give detailed information about the actual stage of AKI or the deterioration and improvement of kidney function.

Aler surgery, and following stress, pain or trauma, the physiological response of functioning kidneys may result in oliguria. On the contrary, Urinary output may continue until kidney function almost stops [15-17]. As result of the above factors the diagnosis of AKI may delayed or missed or over-diagnosed. Ue urine output depends upon weight which may be misleading especially in obese patients. So, the European Renal Best Practice Guidelines (2012) recommend using the ideal weight to avoid over diagnosis of AKI [24].

KDIGO depends upon both serum creatinine and urine output as sign of excretory function and also for diagnosis and staging of AKI but they are not specific and should be explained according to clinical conditions. Some patients fulfill the AKI criteria but they don't have AKI while others patients with renal injury but do not meet the criteria for AKI [17-25].

As a result of drawbacks of serum creatinine and urine output, new renal biomarkers were developed as adjunctive for diagnosis of AKI and to substitute or complement serum creatinine [23-26]. Uey vary in the time and origin of release aler onset of AKI so, identification of the etiology and various pathophysiological process in AKI and differentiate it from recovery process is allowed [27].

Ue current study has three major limitations that worth mentioning, first, the present study used lactated ringer solution for restrictive fluid regimen, the use of other crystalloids or colloids may alter the incidence of AKI. Second limitation is the use of CVP as goal directed therapy. Uird limitation is the short follow up period.

Conclusion

Despite use CVP for detection of hypovolemia, there is still high incidence of AKI. creatinine based criteria, urine based criteria or combination of both are inaccurate when volume restriction is applied.

We recommend the use of newer, more accurate renal biomarkers for early detection of AKI when volume restriction is used.

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