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ORIGINAL ARTICLE

The effect of anaesthetic management on neutrophil gelatinase associated lipocalin (NGAL) levels after robotic surgical oncology

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Summary

Purpose: *The main objective of this study was to compare the effect of two anaesthetic techniques (general vs combined) on plasma levels of NGAL (Neutrophil Gelatinase Associated Lipocalin) after robotic urogenital oncosurgery. The secondary objective was to correlate NGAL levels with the incidence of acute kidney injury (AKI).*

Methods: *This was a longitudinal prospective study. Forty patients were included and randomized in 2 groups: group C (N=16 cases; combined general-epidural anesthesia) and group G (N=24 cases; control group with general anesthesia). Demographic data, Charlson Comorbidity Index, Apache II, SOFA and ASA scores were similar in both groups. Serum creatinine was determined preoperatively and every 24 hrs for 4 postoperative days to identify AKI according to RIFLE and AKIN criteria. Serum NGAL was determined at 6 and 12 hrs after induction of anesthesia.*

Results: *Serum creatinine increased at 24 hrs postoperatively in both groups as compared to baseline, but significant changes were registered only in the G group (pcontrol = 0.004). Serum NGAL increased significantly in both groups as compared with baseline levels (pcase=0.0034 vs $p_{control}$=0.0001). The incidence of AKI was 12.50% (95% CI 0.4–34) in the C group and 37.50% (95% CI 17–58) in the G group (p=0.0909), respectively.*

Conclusion: *Impaired renal function and AKI occurred in robot-assisted laparoscopic urogenital oncosurgery under both general and combined anaesthesia. The incidence of AKI was lower in patients undergoing combined anesthesia compared to general anaesthesia after robotic urogenital oncosurgery but the difference did not reach statistical significance. However, plasma levels of NGAL were significantly increased at 6 and 12 hrs in the general anaesthesia group as compared with combined anaesthesia. NGAL may be a better marker in detecting postoperative acute kidney injury. Further studies are needed.*

Key words: *acute kidney injury, combined anaesthesia, general anaesthesia, neutrophil gelatinase associated lipocalin, robotic oncosurgery*

Introduction

AKI, previously referred as acute renal failure, is a relatively frequent and serious complication after major surgery [1]. It has been demonstrated that even minor postoperative AKI, defined as a 0.3 mg/dl increase in serum creatinine from baseline, predict a significant increase in short-term

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mortality [2,3]. Risk factors for the development of AKI include impaired renal perfusion, decreased functional renal reserve as well as advanced age, peripheral artery disease, diabetes mellitus, renovascular disease and congestive heart failure [4,5]. Standard parameter for AKI diagnosis is serum creatinine level, which is sometimes an unreliable marker for acute changes in kidney function [6,7]. Several studies have demonstrated that other biomarkers like NGAL [8], become altered before creatinine or oliguria signal a reduction in kidney function. There seems to be a relation between plasma and urinary level of NGAL and the amplitude of kidney deterioration, patient recovery time, length of hospital stay [9] and even increased risk of death [10-12]. As a result, NGAL as well as other markers like IL-18, cystatin C and Kidney Injury Molecule 1 have been considered by some authors to be more accurate in the diagnosis of AKI compared to creatinine and able to distinguish the etiology of AKI [13]. Early identification of AKI is important due to the possibility for early application of preventive therapeutic interventions [14].

Thus NGAL may become important for the diagnosis of postoperative AKI after urogenital robotic oncosurgery which is increasingly used over the past years [15]. During robotic surgery some of the intraoperative conditions may lead to AKI [16].

There are only a few studies focused on the influence of anaesthetic techniques on NGAL levels and on the incidence AKI [17].

The main objective of our study was to evaluate the influence of the anaesthetic technique on plasma NGAL levels after robotic urogenital oncosurgery. The secondary objective was to correlate NGAL levels with the incidence of AKI evaluated by using the postoperative creatinine levels.

Methods

Study design

This prospective longitudinal interventional study was approved by the Ethics Committee of the "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca and registered retrospectively in the National Clinical Trial Database NCT018988897.

After obtaining written informed consent, 40 American Society of Anasthesiology (ASA) physical status I-III patients scheduled for robot-assisted laparoscopic urogenital oncosurgery between May 2010 and February 2012 were randomly allocated into 2 study groups using a computer generated sequence: group G (control group, N=24) included patients assigned to general anaesthesia and group C (case group, N=16) included patients assigned to combined general-epidural anaesthesia. All patients were operated by the same surgical team.

Inclusion/exclusion criteria

Inclusion criteria were the absence of preexisting chronic renal disease defined by RIFLE criteria and AKIN classification [18].

Exclusion criteria were patient refusal to participate, preexisting renal disease, and emergency surgery.

Anaesthesia methodology

All patients were premedicated with alprazolam 0.5 mg per os.

Induction of anaesthesia was the same in both groups: sufentanil 2 μg/kg, propofol 1.5 mg/kg and rocuronium 0.5 mg/kg. Anaesthesia was maintained in both study groups with sevoflurane 1-1.5 MAC. All patients were ventilated with 50% oxygen in air using pressure- controlled mode of ventilation with end-tidal carbon dioxide partial pressure maintained at 35-45 mmHg. Rocuronium 10 mg i.v. was administered when needed to maintain adequate muscle relaxation.

Sevoflurane was stopped at the last stitch and neostigmine and atropine were administered for antagonizing muscle block.

In group C, epidural catheter was placed before induction of anesthesia through a Touchy needle (BRAUN Perifix Epidural Anasthesia Catheter), at thoracic level (T10-T12) using the loss of resistance technique and 4 cm of catheter was left in space. The efficacy of sympathetic block was tested with 15 mg plain bupivacaine 0.5%. Continuous 0.125% bupivacaine was administered afterwards during surgery with a rate of 6-8 ml per hour according to analgesic needs (heart rate and blood pressure increased by 15% as compared with baseline, tears, mydriasis or sweating).

In group G intraoperative analgesia was achieved using sufentanil boluses of 10μg when necessary (heart rate and blood pressure increased by 15% as compared with baseline levels, tears, mydriasis or sweating).

Postoperative analgesia was achieved with a multimodal regime in group G: continuous background infusion of i.v. morphine 2 mg/ h, i.v. morphine boluses of 2 mg, and oral acetaminophen 1000 mg at 8 hrs.

In the case group postoperative analgesia was achieved by administering epidural 0.125% plain bupivacaine with sufentanil 0.1μg/ml at 6-8 ml/h rate that was increased (1ml/h steps) when needed to get a VAS≤ 3 and oral acetaminophen 1000 mg at 8 hrs.

Intraoperatively routine ASA basic monitoring was used: electrocardiogram (ECG), heart rate (HR), non invasive arterial blood pressure (BP), pulse oximetry (SpO_2), end-tidal CO_2 ($Et\ CO_2$) and sevoflurane (Et Sevo), minimum alveolar concentration (MAC) of sevoflurane, and core temperature (Dräger Infinity patient monitor nasopharyngeal thermocouple probe, Dräger Fabius

Plus produced in Lubeck, Germany). Hypotension was defined as a decrease over 20% from baseline values and was promptly treated with ephedrine i.v. boluses 5-10 mg and increase of fluid administration.

Preoperative renal function was assessed by using RIFLE criteria and AKIN classification. Plasma levels of NGAL were determined at 6 and 12 hrs after induction of anaesthesia. AKI was defined as an absolute increase of serum creatinine by 0.3 mg/dl (26.4 mmol/l) as compared with baseline levels within 48 hrs post-operatively, in accordance with the AKIN classification [19].

The 2013 update of the Spanish Consensus Statement on alternatives to allogenic blood transfusion recommends (grade 1A) restrictive transfusion therapy, maintaining haemoglobin concentrations ≥ 9 g/dL [20].

Robotic interventions

Robotic interventions were performed using Da Vinci surgical robot. This system consists in an ergonomic surgeon console, a patient cart with four interactive robotic arms, a 3D high resolution visualization interface and specific EndoWrist articulated tools [21]. This system is designed to transform, filter and transmit the surgeon's hand movements into precise movements of the instruments. The main advantages of this surgical technique are: 3D visualization, reduced bleeding and complications, less postoperative pain, rapid resumption of intestinal transit, smaller scars, and reduced hospitalization combined with quick recovery [22].

Laboratory determinations assays

Six ml of blood were collected at 6 and 12 hrs after induction of anaesthesia. Each sample was divided into three Eppendorf tubes, frozen and stored at -80°C (SNIJDERS Scientific Freezer, Holland). Serum NGAL was determined by ELISA method, performed in wells loaded with a monoclonal antibody against human NGAL (Rapid Human ELISA Kit /KIT 037/, BioPorto Diagnostics, Copenhagen, Denmark). NGAL was detected with monoclonal antibody conjugated with horseradish peroxidase and the reaction was developed with the color reagent. Calibrators, controls and diluted samples were incubated with the conjugate (peroxidase-conjugated antiNGAL antibody).

Substrate containing tetramethylbenzidine (TMB) was added to each well, and peroxidase-linked anti-NGAL antibodies developed a color reaction. Chemical and enzymatic reaction was stopped and the color intensity was read at 450 nm in an ELISA reader. Color intensity depended on the concentration of NGAL in the sample. The results of the calibrators were used to perform a calibration curve of the NGAL concentration to be read in evidence.

Serum creatinine was determined by the spectrophotometric (enzymatic colorimetric) method.

Normal values of plasma NGAL as given by the literature are 70-105 ng/ml and the cut-off value for NGAL plasma level suggestive for AKI was considered 150 ng/ml [23].

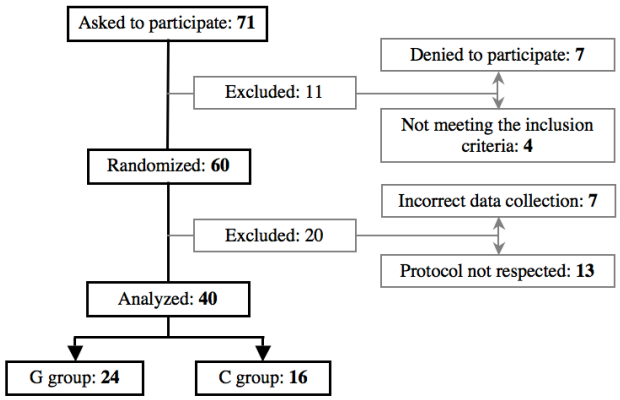

Figure 1. Patients' flow chart.

Statistics

Statistical analyses were performed using Statistica (v.8; Stat. Soft. Inc., USA). The sample size was calculated from a pilot study (N=5 patients from each group). Calculated differences for creatinine showed a 0.1460 mg/dL mean difference between the two groups. A type one error rate (α) of 0.05 and a power goal of 0.8000 led to a sample size of 12 patients per group, with an actual power for required sample size equal to 0.8223. The calculation of sample size was done with Power and Sample Size program (v.3).

Qualitative variables were described by frequency and percentage, with 95% confidence intervals (95% CI). Kolmogorov-Smirnov test was used to test the normality of quantitative data. Quantitative variables were described by mean and standard deviation for normally distributed data.

Student's t-test was used to compare quantitative normally distributed data, while Mann-Whitney test was used to compare groups whenever variables were not normally distributed. Differences between within-group repetitive measurements were investigated using Wilcoxon's test whenever data were not normally distributed. The frequencies of qualitative data between two groups were compared with Z-test.

A significance level of 5% for univariate analysis and a p-value <0.05 were considered significant. The threshold of significance level for Wilcoxon's test was 0.01. Sensitivity and specificity and associated 95% CI of the markers in identification of AKI were calculated.

Results

From 2010 to 2012, 71 patients were asked to participate in the study. Seven patients declined

Table 1. Demographic data of the study groups

Characteristics		*G group (N = 24)*	*C group (N = 16)*	*p value*§
Age, years*		62.5 (56–65)	60.5 (51.5–67.25)	0.91
Gender (M/F)		20/4	13/3	0.13
BMI (kg/m^2)		27.10 ± 2.46	27.58 ± 5.35	0.29
ASA Patients, N (%;95%CI)	I	4 (16.66;4.34-37.33)	7 (43.7;19.14-68.36)	0.06
	II	17 (70.83;50.17-87.33)	7 (43.7;19.14-68.36)	0.08
	III	3 (12.5;4.34-33.16)	2 (12.5;0.39-37.11)	1.0
Charlson Comorbidity Index		3.625 ± 1.928	3.625 ± 2.203	1.0
Apache score		4.373 ± 2.335	5.875 ± 2.740	0.08

BMI: body mass index, ASA: American Society of Anesthesiology, §Student's t-test, *median (range)

Table 2. Perioperative data of the study group

Characteristics	*G group (N=24)*	*C group (N=16)*	*p value*§
Surgical procedure, N (%; 95% CI)			0.68
Radical prostatectomy*	18 (75; 54–91)	11 (69;44–87)	
Other oncological interventions*	6 (25; 9-46)	5 (31;13-56)	
Duration of intervention (min)**	5.19 ± 1.01	4.39 ± 0.90	0.01
Length of hospital stay (days)**	22.60 ± 1.95	16.82 ± 7.19	0.09
Lenght of ICU stay (days) **	2.20 ± 0.45	2.06 ± 1.44	0.79

*N (%;95% CI), **mean±standard deviation, §Student's t-test

Table 3. Fluid balance in the study groups

Fluids	*G group*	*C group*	*p value*§
Intraoperative fluids (ml)*	1500.00 ± 500.00	1323.53 ± 498.16	0.49
Postoperative fluid balance (ml)*	248.00 ± 474.63	190.59 ± 683.08	0.86
Intraoperative blood loss (ml) **	250 (200–300)	250 (200–300)	0.97

* mean ± standard deviation, ** median and interquartile range, §Student's t-test

Table 4. Creatinine levels in the study groups

Creatinine (mg/dL)	*Parameter*	*C group N=16*	*G group N=24*	*p value*§
Baseline	mean	0.925	0.980	0.3546
Postoperative day 1	mean	1.006	1.234	0.1805
Postoperative day 2	mean	0.927	1.068	0.1033
Postoperative day 3	mean	0.903	1.007	0.3623
Postoperative day 4	mean	0.866	0.958	0.1386

§Student's t-test

participation, 4 patients did not meet the inclusion criteria while 60 were randomized and allocated to intervention (30 patients in 2 groups). Forty patients completed the study; 20 patients were excluded for study protocol violation or for incorrect data collection (Figure 1). Data from 24 patients in G group and 16 patients in C group were analyzed.

There were no significant differences in demographic data between the study groups.

No patient developed significant hypotension as defined in Methods section for more than 5 min during the operation, and no patient developed hypothermia.

There was no need for blood transfusion in any patient; blood transfusion was indicated at Hb

Table 5. Within-groups comparison of serum creatinine levels in the study groups

Serum creatinine	*p value*§	
	C group	*G group*
Creat 1-Creat 0	0.232	0.004
Creat 2-Creat 0	1.000	0.254
Creat 3-Creat 0	0.485	0.637
Creat 4- Creat 0	0.177	0.488

Creat 0=basal value; Creat 1=1 postoperative day; Creat 2= postoperative day 2; Creat 3= postoperative day 3; Creat 4= postoperative day 4.
§Student's t-test

Table 6. Incidence of AKI in the study groups

	G group N=24	*C group N=16*	*p value*§
AKI+*	9 (37.5;17-58)	2 (12.5;0.4-34)	0.0909

*patient numbers (%; 95% CI), §Student's t-test

Table 7. Plasma levels of NGAL in the study groups

NGAL ng/ml	*C group (N=16)**	*G group (N=24)**	*p value*§
6 hrs	142.0 (122.5-164.5)	230.0 (139.5-450.0)	0.011088
12 hrs	93.0 (117.0-117.0)	225.0 (133.0-385.0)	0.000504

§Mann-Whitney U test, *median and interquartile range

levels below 9 g/dl, as seen in Tables 1, 2 and 3.

As can be seen in Table 4, no significant difference in serum creatinine levels was noticed between the study groups in any of the 4 postoperative days.

Within-groups comparison of creatinine levels are shown in Table 5.

As can be seen in Table 4, the trends of serum creatinine were similar in both groups: an increase in the 1st postoperative day followed by a decrease in days 2, 3, and 4. Serum creatinine was significantly increased as compared with baseline on the first postoperative day in both groups, but significant changes were observed only in the G group (general anesthesia) (p=0.004) (Table 5).

Two patients from the C group had criteria for AKI+ (12.50%, 95% CI 0.4–34) while in the G group 9 patients had criteria for AKI+ (37.50%, 95% CI 17–58) (p=0.0909)) (Table 6).

Plasma levels of NGAL in study groups at 6 and 12 hrs postoperatively are shown in Table 7. As can be seen in this Table, NGAL plasma levels were significantly increased at 6 and 12 hrs after induction of anaesthesia in the G group as compared with the C group.

Tables 8 and 9 show the correlation between the number of patients having positive criteria for AKI (AKI+) according to AKIN classification and plasma level of NGAL in the study groups at 6 and 12 hrs postoperatively.

As can be seen in these Tables, the sensitivity of serum NGAL to detect AKI was greater at 6 hrs than at 12 hrs.

When we included AKI+ and NGAL above the cut-off of 150 ng/dl, the sensitivity of NGAL in both groups was 81.82% (95% CI 52.30-94.86) at 6 hrs and 72.73% (95% CI 43.44-90.25) at 12 hrs. Specificity of NGAL as a diagnostic tool was 55.17% (95% CI 37.55-71.59) at 6 hrs and 62.07% (95% CI 44-77.31) at 12 hrs.

Discussion

AKI is a pathologic condition produced by decreased kidney perfusion, inflammation, and toxins and facilitated by comorbid states like: insulin-requiring diabetes, peripheral vascular disease, congestive heart failure, and chronic obstructive pulmonary disease (COPD); female gender and age are also predisposing factors for AKI [24,25]. Major surgery and especially renal and urogenital surgery also predispose to AKI due to decreased renal perfusion and surgical trauma and inflammation [26]. AKI is diagnosed using RIFLE and AKIN criteria, based on serum creatinine determination and urinary output.

There is evidence that regional anaesthesia improves renal function when added to general anaesthesia for major surgery [27]. The beneficial effects of regional anesthesia on renal function consist in anti-inflammatory effects, blockage of sympathetic activity, and reduced cytokine production and specific renal effects like improved microcirculation and function [28]. A positive effect of regional anesthesia on prostate cancer was also demonstrated [29]. There are few data in literature on the influence of regional anesthesia on AKI incidence in major surgery.

In our study the incidence of AKI as defined by RIFLE and AKIN criteria after urogenital robotic oncosurgery was 37.5% in patients with general anesthesia and 12.5% in combined anaesthesia group, incidence that is similar with those in major surgeries: as reported by Haase-Fielitz et al, in cardiac surgery, 39% of the patients associated AKI [30]. There are few studies on AKI in urologic robotic oncosurgery. Robotic surgery was devel-

Table 8. Correlation between NGAL plasma levels at 6 hrs and AKI+criteria. Specificity and efficacy of NGAL plasma levels in detecting AKI

	Plasma NGAL (ng/ml) at 6 hrs	*AKI+ Patients, N*	*AKI- Patients, N*	*Sensitivity % (95% CI)*	*Specificity % (95% CI)*
C group (N=16)	>150	1	4	50 (9.45-90.55)	71.43 (45.35-88.28)
	<150	1	10		
G group (N=24)	>150	8	9	88.89 (56.5-98)	40 (19.82-64.25)
	<150	1	6		

Table 9. Correlation between NGAL plasma levels at 12 hrs and AKI+criteria. Specificity and efficacy in detecting AKI

	Serum NGAL at 12 hrs (ng/ml)	*AKI+ Patients, N*	*AKI- Patients, N*	*Sensitivity % (95% CI)*	*Specificity % (95% CI)*
C group (N=16)	>150	0	2	0 (0-65.76)	85.71 (60.06-95.99)
	<150	2	12		
G group (N=24)	>150	8	9	88.89 (56.5-98.01)	40 (19.82-64.25)
	<150	1	6		

oped in the last years and our study was the first to investigate the effects of 2 different anaesthetic regimens on AKI incidence after robotic surgery.

A significant increase in serum creatinine in the first postoperative day in general anaesthesia group was detected in our study as compared with the other postoperative days. Similar results have been reported by Lassnigg et al. [31].

In the last years other markers were described by the literature as specific for early and accurate detection of AKI, like CystatinC, Kidney Injury Molecule1, Interleukin18 [13].

NGAL is a sensitive, specific and highly predictive early biomarker of AKI [29]. NGAL is expressed in acute tubular injury and was identified using functional genomics, transcriptomic and proteomic techniques. NGAL precedes an increase in serum creatinine with more than 24 hours [32]. NGAL has been investigated in experimental and clinical studies, and seems to be one of the most promising biomarkers for AKI.

Previous studies reported a sensitivity of 84% and a specificity of 94% and ROC AUC 98% in detecting AKI for a cut-off ≥ 150 ng/ml of plasma NGAL [31].

Measurement of plasma levels of NGAL may predict AKI after major surgery, and is an independent predictor of AKI duration and severity, length of ICU stay, renal replacement therapy and hospital death [29]. NGAL was also investigated during robotic surgery, especially the effect of deep Trendelenburg position on renal function [33].

In our study we determined plasma levels of NGAL after robotic urogenital oncosurgery at 6 and 12 hrs. Our results showed a significant increase in plasma levels of NGAL at both 6 and 12 hrs in general anaesthesia group as compared with combined general-regional anaesthesia group (p=0.011 at 6 hrs and p=0.0005 at 12 hrs).

In the literature there are different protocols for determining postoperative levels of NGAL from 2 hrs to 5 days postoperatively and at the moment there is no consensus on the best time interval for these evaluations. We have chosen these intervals taking in consideration that at the beginning of the learning curve, surgical time for robotic procedures was approximately 6 hrs and that the epidural analgesia was maintain for 12 hrs postoperatively, so we determined plasma levels of NGAL before removing epidural catheter.

In our study, the sensibility of plasma NGAL as a diagnostic tool for AKI diagnosis was higher at 6 hrs as compared with levels at 12 hrs (0.8182 vs 0.7273).The overall sensibility of NGAL, at 6 hrs, in detecting AKI was high 81.82%. Similar sensibility of plasma NGAL in diagnosis of AKI after cardiopulmonary by-pass has been reported

by Lima et al [34].

Our study has a few limitations. One of the limitations is the relatively small sample size, even if this was calculated based on differences in creatinine levels in our pilot study.

Another limitation is the significant difference in the length of surgical procedure in study groups. This can be at least partially explained by the fact that robotic procedures at the beginning of the learning curve were randomized to be performed under general anaesthesia. However this difference was overcome by maintaining adequate volume status and cardiovascular stability and by the similarities in the other perioperative data. We also do not have a baseline determination of plasma level of NGAL that would have been useful for comparison with postoperative levels. We assumed that by having normal plasma levels of preoperative creatinine in all patients and by excluding patients with preexisting renal problems, kidney function was normal in preoperative period. Similar protocols for postoperative determinations of plasma NGAL to detect postoperative AKI have also been reported [23]. In the same time, an extended time interval for NGAL evaluation would have been probably useful for a more accurate picture of AKI extension and influence on patients' outcome.

In conclusion, in our study impaired renal function and AKI occurred in robot-assisted laparoscopic uro-genital oncosurgery under both, general and combined anaesthesia.

The incidence of AKI was lower in patients undergoing combined anesthesia compared to general anesthesia after robotic urogenital oncosurgery but the difference did not reached statistical significance. However plasma levels of NGAL were significantly increased at 6 and 12 h in general anaesthesia group as compared with combined anaesthesia. Thus NGAL may be a better marker in detecting postoperative acute kidney injury. Further studies are needed.

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