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Postoperative elevation in creatine kinase and its impact on renal function in patients undergoing complex partial nephrectomy

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Abstract

Objective—To identify the risk factors associated with development of postoperative elevation of creatine kinase (CK) and study its effect on renal function in patients who underwent complex multifocal partial nephrectomy (PN).

Methods—Patients who underwent PN at National Cancer Institute between January 2007 and December 2012 were included in the study. Elevated serum CK was defined as >2000U/L. Kidney function was assessed using serum creatinine and eGFR (estimated glomerular filtration rate).

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COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of potential conflicts of interest

Abhinav Sidana has nothing to disclose

Annerleim Walton Diaz has nothing to disclose

Hong Truong has nothing to disclose

M. Minhaj Siddiqui has nothing to disclose

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Adam R. Metwalli has nothing to disclose

Research involving human participants

All patients analyzed in the study were enrolled on various institutional review board-approved protocols. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all the patients at the time of enrollment on various institutional review board-approved protocols. For this retrospective study, a separate consent was not obtained.

Changes were reported as percent change from preoperative values and compared using the Wilcoxon test. Regression analysis was done to identify the predictors of elevation in CK and decline in eGFR.

Results—From 407 total cases, 207 had adequate CK data for analysis. Median number of tumors removed was 3(1-70). Median peak CK was 1458 (82-36788). 42% developed CK elevation>2000U/L. Factors associated with postoperative elevation of CK>2000 were young age ($p=0.009$), high BMI ($p=0.003$) and operating room time ($p<0.001$). Although CK>2000 was associated with significantly greater decline in eGFR (37.4% vs 20.3%, $p<0.001$) in immediate postoperative period, this change largely resolved to a much less clinically relevant (3.3% vs 9.2%, $p=0.040$) change after 3 months. On multivariate analysis, postoperative elevation in CK was not found to be an independent factor determining renal function at 3 months.

Conclusions—In our cohort, a significant proportion of patients developed CK elevations>2000 U/L. While patients with elevated CK had more decline in eGFR in immediate postoperative period, postoperative elevations of CK, did not appear to impact overall long-term renal function in patients undergoing PN.

Keywords

Partial nephrectomy; creatine kinase; rhabdomyolysis; renal cell cancer

INTRODUCTION

Partial nephrectomy (PN) is the preferred method for treating renal masses in hereditary and multifocal renal tumors (1-4). The goal of PN is to preserve renal function and defer or avoid the need for eventual renal replacement therapy. However, PNs, especially in the setting of complex and multiple renal tumors, can be technically challenging, leading to prolonged operative times and subsequent increased risk of postoperative rhabdomyolysis potentially undermining the goal of renal functional preservation.

Although rare, postoperative rhabdomyolysis tends to occur as a consequence of prolonged muscle compression due to surgical positioning (5). Muscle injury causes a cascade of events that lead to leakage of extracellular calcium ions into the intracellular space which leads to muscle destruction and necrosis. As a result, potassium, phosphate, myoglobin, creatine kinase (CK) and urate are released into the circulation. The exact mechanism of how rhabdomyolysis affects glomerular filtration is unclear; myoglobin, is filtered by the kidneys and can precipitate causing obstruction of the renal tubules and may also have directly nephrotoxic effect. In addition, the formation of free radicals from iron and hypoxia due to hypovolemia may also be contributing factors to acute renal failure associated with severe rhabdomyolysis (6,7).

There is no specific value of creatine kinase above which acute renal insufficiency predictably develops, although some publications have described values of concern to be in the order of 1000 and 5000 UI/L (7-9). To our knowledge there is no report in the literature assessing the impact of postoperative elevation of CK in renal function of patients undergoing complex PNs. Herein, we report risk factors associated with development of

postoperative elevation of CK and, also study its effect on renal function in patients who underwent complex multifocal PN.

METHODS

Study sample and design

A retrospective review of our prospectively maintained database to evaluate patients who had undergone PNs on various institutional review board-approved protocols between January 2007 and December 2012 at the National Institutes of Health was done. Four hundred and seven patients who underwent PN by any approach were identified. All patients were positioned in lateral decubitus during the procedure with table flexed and pressure points padded. 207 cases with adequate CK data were included in the study.

Study variables

Serum creatinine and CK levels were assessed preoperatively, daily postoperatively and at 3 month postop follow up. Kidney function was evaluated using estimated Glomerular Filtration Rate (eGFR) based on the CKD–EPI– Creatinine 2009 formula (10). The assessment of change in kidney function was reported as percent change in eGFR from preoperative values. Acute renal failure was classified using the RIFLE (Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function and End-stage kidney disease) classification proposed by the Acute Dialysis Quality Initiative group (11,12). Risk of acute kidney injury is defined as a decrease from baseline in eGFR >25%, whereas renal injury is a drop of >50% and renal failure is >75% lower than baseline. To categorize renal functional outcomes, the Kidney Disease Outcomes Quality Initiative stages of chronic kidney disease (CKD) were used. Elevated serum CK consistent with rhabdomyolysis was defined as a peak postoperative CK value >2000 U/L. This value was selected based on sample distribution and previous reports in the literature (8,9,13,14). Urine myoglobin was not routinely checked and was not analyzed in this study. Patients with elevated CK were managed with aggressive hydration with or without urinary alkalinization (15).

Statistical methods

Statistical analysis was done using statistical software R. Proportions were compared using ChiSqaures and Wilcoxon test were run to compare continuous variables. Univariate and multivariate logistic regression analysis was done to identify the risk factors associated with elevation of CK in our patient cohort. Univariate and multivariate linear regression analysis was subsequently used to assess the role of CK elevation in 3 month follow-up renal functional outcomes. Statistical significance was considered with a p value 0.05.

RESULTS

Four hundred and seven patients underwent PN at our Institution between January 2007 and December 2012. 207 cases with adequate CK data were reviewed retrospectively. Patient characteristics, perioperative variables and renal function data of the studied cohort are summarized in table 1. Mean age was 48.0 years. Majority of the procedures were done

through open approach (58.5% of cases). Median number of tumors resected was 3 (range 1-70). No patients had preoperative eGFR <15 (Stage V CKD). The majority of patients, 80.2% (166/207), were either stage I or II CKD at baseline.

Risk factors associated with elevated CK

42% (87/207) of our patients who underwent PN had a peak CK > 2000 U/L. Young age, male gender, high body mass index (BMI), operating time, number of kidney tumors resected and estimated blood loss were significantly correlated with elevated CK in our patient cohort. Table 2 presents the mean values of these variables for patients with CK 2000 (120/207 patients) versus > 2000 U/L (87/207 patients) during hospital stay. A multivariate logistic regression was done to identify factors which could predict elevated CK >2000. Age (Odds ratio 0.959, 95% CI 0.929 to 0.99, p=0.009), BMI (Odds ratio 1.096, 95% CI 1.0131 to 1.166, p=0.003) and operating room time (in hours, Odds ratio 2.286, 95% CI 1.668 to 3.133, p<0.0001) were the only factors independently predicting elevated CK >2000 in our cohort (table 3).

Renal function outcomes

53.1% (110/207) of our patients had > 25% decline in eGFR postoperatively. However, this degree of renal dysfunction was transient because mean eGFR at 3 month follow-up was 74.8 which was a mere 4.8% lower than baseline. Table 4 summarizes the renal function outcomes by dichotomized elevated serum CK in our cohort. Patients with CK levels > 2000 had significantly greater percent decrease in eGFR during both the postoperative course and at 3 month follow up, though the actual difference in mean change in eGFR was smaller at the follow up visit. Similar associations of CK levels were found with percent increase in creatinine in postoperative and follow up period. A higher proportion of patients with elevated CK developed renal injury per RIFLE classification (27.6% vs 5.8%, p<0.001). Of note, only 2 patients developed >75% decline in eGFR corresponding to renal failure per RIFLE classification. Patients who underwent a multiplex PN, defined as 3 or more tumors removed from a single renal unit during one operation (16/17) had significantly more decline in their eGFR (33.1% vs 19.6%, p < 0.001) during the hospital stay compared to patients with less than 3 tumors. However, at 3 month follow up there was no difference in percent change in eGFR between the two groups (p= 0.866).

Since age, gender, BMI, operating time, number of kidney tumors resected and estimated blood loss were significantly correlated with elevated CK in our patient cohort, we performed multivariate linear regression analysis to determine if elevated CK independently predicts impaired renal function outcomes at 3 month follow up. The coefficients of the regression analysis are shown in table 5. While peak postoperative CK level was significant on univariate analysis, it was not found to be an independent predictor for decline in eGFR on multivariate analysis. Use of renal ischemia was the only factor which was found to be significant on multivariate analysis (p=0.006).

Seventy six percent (157/207) of our patients had kidney function return to baseline at three month follow-up. Only 24% (50/207) migrated to a higher CKD stage, one to stage 4 (GFR of 15-29) and none to stage 5 (GFR<15 or patient on dialysis). Of those who migrated to a

higher CKD stage, more than half (26/50) had CK > 2000 U/L during the postoperative period.

DISCUSSION

Rhabdomyolysis is a rare but worrisome complication of prolonged surgical procedures, particularly following complex nephron-sparing surgery due to prolonged positioning in lateral decubitus. The potential negative impact of rhabdomyolysis on renal function can further compound the impact caused by renal ischemia and loss of normal renal parenchyma during PN. The exact incidence of rhabdomyolysis in a complex PN series has not been previously described. In a review of 600 laparoscopic radical nephrectomies, Glassman DT *et al* reported a postoperative incidence of 0.67% (18). All the affected patients in their series had clinical signs of rhabdomyolysis with CK levels much higher than 10,000. In this study, we have used a cut off CK>2000 based on similar cut offs used in trauma and emergency department literature to define significant rhabdomyolysis (9,14). This cut off yielded a higher incidence of significant rhabdomyolysis in our study. Still, a 42% incidence of CK levels >2000 in our cohort reflects the increased technical challenges and prolonged operative time required for complex multifocal PN which comprised the majority of our cases.

Male sex, increased body mass index, prolonged operative times and lateral decubitus position are few of the main risk factors previously reported to be associated with the development of rhabdomyolysis (18-20). In our series, patients with elevated CK had a higher number of tumors removed and had prolonged operating times and more blood loss, representing increased complexity of these cases. While increased BMI was found to be significantly associated with elevated CK, male sex was not found to be an independent factor in regression analysis. Younger patients had greater elevation of CK, probably due to higher muscle mass in these patients. The most important modifiable factor in our analysis was operating room time with doubling of the odds of developing elevated CK >2000 with every hour increase in time. Recently, two studies using national inpatient and hospital discharge databases have demonstrated male sex, obesity, prolonged surgery and perioperative bleeding to be associated with increased incidence of rhabdomyolysis in patients undergoing urologic procedures for malignancy (21,22). While the risk factors reported in these studies are similar to our study, the reported incidence of rhabdomyolysis (0.1% in one study and 0.001% in another study) was much lower. In both studies, cases were identified using ICD-9 code of rhabdomyolysis in patient's chart; an approach that may suffer from undercoding and might result in underreporting, as noted by one of the study authors. The higher incidence in our study can also be attributed to using a CK cut off instead of clinical symptoms of rhabdomyolysis and a higher complexity of cases in our study.

Acute renal failure, described by need of renal replacement therapy, as a result of rhabdomyolysis has been described in up to 50% of the cases in the literature (23-25). While the etiology of acute renal failure in rhabdomyolysis is multifactorial, myoglobin toxicity seems to play a major role. Myoglobin toxicity is related to mechanical "plugging" of the renal tubules, direct toxic effects, and alterations in renal blood flow. In majority of the

studies, rhabdomyolysis has been reported in patients with extensive trauma and crush injury. Hypovolemia, due to hemorrhage or fluid sequestration, and acidosis are accompaniments in these cases and can potentiate renal injury due to myoglobin. In our cohort with CK levels >2000, while 69% of patients had a transient decline in eGFR by more than 25%, only 2.3% had decline more than 75% and met RIFLE criteria for failure. The less significant impact on renal function in our cohort could be due to generally adequate hydration of surgical patients in perioperative period and aggressive postoperative management of elevated CK at our center. The proportion of our patients with a >25% decline in eGFR, is higher than 13.3% reported by Jeldres C *et al* in their series of 166 PNs (26). This is most likely explained by the highly complex nature of the surgeries performed at our institution as the mean number of tumors resected per kidney in our series was 8 whereas Jeldres series does not report any multiple tumor resections. Furthermore, in addition to multiple tumor resections for each surgery, many patients in our series had undergone multiple ipsilateral surgeries; the complexity and morbidity of reoperative renal surgery is well documented, accounting for the increased operative times and blood loss seen in our series and likely the increased incidence of elevated CK levels postoperatively (1:27:28).

Currently, a defined CK value that can reliably be associated with the subsequent development of ARF has not been established (29:30). Harper JD *et al*, described the incidence of elevated CK and its effect on kidney function in hand assisted laparoscopic donors and recipients. They found that a peak postoperative CK >2500 U/L was associated with an increased percent change in creatinine compared to the group with CK <2500 U/L (8). In our study, when comparing the effect of CK elevation >2000 on kidney function, there were absolute differences in percent change in eGFR between the two groups both in the immediate postoperative period and at 3 month follow up, though the difference at 3 month was less clinically relevant on the order of 5%. Furthermore, loss and damage of normal renal parenchyma and renal ischemia also contributes to worsening of renal function in PN patients in postoperative period and can confound the impact of elevation in CK in our cohort. Though most of the PNs in our center involved enucleation of tumors, loss of some amount of renal parenchyma cannot be entirely ruled out. The more complex cases (prolonged operating times, more tumors removed), with elevated CK, in our cohort were also more prone to potential damage to surrounding renal parenchyma. While our data does not provide quantification of renal parenchymal loss, renal ischemia was studied and was found to determine renal function outcome. This was reflected in multivariable analysis, when controlling for age, number of tumors resected, EBL and BMI, renal ischemia but not CK elevation was found to be an independent predictor of decline in eGFR at 3 month follow up. Most multifocal PN at our center are done without the use of renal ischemia as multiple renal tumors are enucleated and would require prolonged period of clamping with potential detrimental effects on kidney. Since only 30% of our cases required renal hilar occlusion, use of renal ischemia is probably a surrogate for the most complex lesions in this series. It is likely that much of the absolute difference in decline of eGFR between the groups is a byproduct of the increased complexity of cases as suggested by the higher number of tumors removed, longer operating room times and more blood loss in patients with elevated CK. With respect to non-renal sequelae of rhabdomyolysis, Malinoski DJ *et al*

reported that irreversible changes occur in the skeletal muscle at 2-4 hours of ischemia and necrosis occurs after 6 hours (31). In addition, accumulation of fluid in a third space in severely edematous muscles reduces intravascular volume which may lead to pre-renal RAKI. No patients in our series required intervention such as fasciotomy for local symptoms of muscle injury.

To the best of our knowledge, this is the first study evaluating the risk factors and impact of elevated CK in already vulnerable population of patients undergoing complex partial nephrectomies. This analysis has shed light onto factors which can be modified to decrease the chances of this complication in setting of PNs. A high index of suspicion should be maintained for the patients with risk factors of CK elevation such as young age, high BMI and prolonged surgery accompanied with excessive perioperative blood loss; and anyone with significantly elevated CK should be managed aggressively to prevent renal injury. In postoperative PN patients with elevated CK at our institution, the goals of the management are to correct volume depletion if present and to prevent renal injury by intratubular cast formation. Patients with elevated CK are hydrated aggressively with isotonic fluids to maintain urine output in range of 200-300 ml/hr (15). CK levels are monitored periodically. Sodium bicarbonate is added to fluid if there is evidence of systemic acidosis. The decision to consult nephrology service for further recommendations is individualized based on CK levels and degree of renal impairment.

This study is limited by its retrospective nature and the inherent biases associated with that approach. Since, all the patients who underwent PN did not have CK information; a selection bias might have been introduced in our study, as the more complicated cases could have been more likely to have CK tests ordered. Also, while presence or absence of renal ischemia was studied as a predictive factor, details of ischemia time were not readily available in our database and were not considered in analysis. Another limitation of this study is its possible applicability given the unique patient population. Nevertheless, these findings provide important information regarding the impact of postoperative elevations in CK and its effect on renal function in patients who undergo complex PN.

CONCLUSION

In complex PN patients, a significant proportion of patient develops significantly elevated CK levels consistent with rhabdomyolysis. While elevation of CK is associated with postoperative worsening of renal function, it is not an independent predictor of a permanent impairment of renal function. A high index of suspicion should be maintained for the patients with risk factors of CK elevation such as young age, high BMI and prolonged surgery accompanied with excessive perioperative blood loss; and anyone with significantly elevated CK should be managed aggressively to prevent renal injury. Overall, complex PN, using tumor enucleation, for multifocal renal cell carcinoma provides excellent renal functional preservation despite prolonged surgical times and relatively frequent incidence of postoperative rhabdomyolysis.

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Table 1

Patient characteristics, perioperative variables and renal function data of the studied cohort (n=207)

Median Age in years (min,max)	49.0 (19.0,83.0)
Gender	
Male (percentage)	60.4
Median BMI (min,max)	28.7 (17.2,79.5)
Solitary kidney (percentage)	14.5
Surgical approach (percentage of cases)	
Open	58.5
Robotic	34.8
Laparoscopic	6.7
Median number of tumors removed (min,max)	3 (1,70)
Renal ischemia (percentage of cases)	
No ischemia	70.0
Warm ischemia	25.1
Cold ischemia	4.8
Median estimated blood loss in ml (min,max)	1200 (50,11000)
Median operating room time in mins (min,max)	435 (199,838)
Median preoperative serum CK (min,max)	99 (21,8047)
Median highest postoperative serum CK (min,max)	1458 (82,36788)
Median preoperative serum creatinine (min,max)	1.0 (0.4,3.1)
Median highest postoperative creatinine (min,max)	1.3 (0.6, 7.3)
Median creatinine at 3 months follow-up (min,max)	1.1 (0.5,4.1)
Median preoperative eGFR (min,max)	77.2 (25.8,140.5)
Median lowest postoperative eGFR (min,max)	55.7 (7.5,129.4)
Median eGFR at 3 months follow-up (min,max)	74.4 (16.4,138.9)

Table 2Patient characteristics and perioperative variables by peak CK value (Mean ($\pm$ SD))

	Peak CK (n= 120)	2000 Peak CK> 2000 (n= 87)	<i>P value</i>
Age	50.4 $\pm$ 13.4	44.9 $\pm$ 11.7	0.002
%Males/%Females	53.3% / 46.7%	70.1% / 29.9%	0.02
BMI	28.6 $\pm$ 7.1	32.5 $\pm$ 7.0	< 0.0001
# of Tumors	4.7 $\pm$ 6.4	12.2 $\pm$ 14.0	< 0.0001
EBL	1014.5 $\pm$ 938.7	2463.2 $\pm$ 2229.3	< 0.0001
OR Time (min)	383.84 $\pm$ 92.0	524.1 $\pm$ 98.8	< 0.0001

Table 3

Univariate and multivariate logistic regression to identify predictors of peak postoperative CK >2000

	Univariate			Multivariate		
	Odds Ratio	95% CI	P-value	Odds Ratio	95% CI	P-value
Age	0.967	(0.945 , 0.989)	0.003 *	0.959	(0.929 , 0.990)	0.009 *
Gender (Male)	2.053	(1.146 , 3.676)	0.016 *	1.349	(0.595 , 3.058)	0.474
BMI	1.09	(1.041 , 1.141)	<0.001 *	1.096	(1.031 , 1.166)	0.003 *
Number of tumors	1.085	(1.044 , 1.128)	<0.0001 *	1.009	(0.965 , 1.056)	0.688
Estimated blood flow (per 100ml)	1.079	(1.048 , 1.112)	<0.0001 *	1.034	(0.998 , 1.071)	0.061
OR time (hours)	2.636	(1.995 , 3.482)	<0.0001 *	2.286	(1.668 , 3.133)	<0.0001 *
Use of renal ischemia	0.905	(0.494 , 1.656)	0.745			
Solitary kidney	0.544	(0.236 , 1.254)	0.153			

* denotes significant p value

Table 4

Change in serum creatinine and eGFR by dichotomized elevated serum CK

	Peak CK 2000	Peak CK>2000	p-value
Percent change in serum creatinine from preoperative value			
Post-op day 1	19.4	51.4	<0.001
Peak Post-op Creatinine	29.4	68.7	<0.001
Creatinine at 3-month follow-up	7.4	14.5	0.041
Percent change in eGFR from preoperative value			
Post-op day 1	-13.0	-30.0	<0.001
Lowest eGFR post-op	-20.3	-37.4	<0.001
eGFR at 3-month follow-up	-3.3	-9.2	0.040
Percentage of patients with			
>25-50% decline in eGFR (Risk)	35.8	39.1	0.664
>50-75% decline in eGFR (Injury)	5.8	27.6	<0.001
>75% decline in eGFR (Failure)	0	2.3	0.175

Table 5

Univariate and multivariate linear regression analysis of factors associated with percent change in eGFR at 3 mon follow up

	Univariate			Multivariate		
	Coefficient	95% CI	P-value	Coefficient	95% CI	P-value
Age	-0.10	(-0.305 , 0.103)	0.332			
Gender (Male)	-2.87	(-8.255 , 2.522)	0.298			
BMI	-0.41	(-0.768 , -0.05)	0.027 *	-0.35	(-0.712 , 0.022)	0.067
Number of tumors	-0.23	(-0.463 , 0.012)	0.065	-0.18	(-0.445 , 0.091)	0.198
Estimated blood flow (per 100ml)	-0.11	(-0.258 , 0.046)	0.172			
OR time (hr)	-1.77	(-3.103 , -0.437)	0.010 *	-1.03	(-2.736 , 0.685)	0.241
Peak CK (> 2000 vs. 2000)	-5.90	(-11.202 , -0.602)	0.030 *	-1.34	(-8.043 , 5.353)	0.694
Use of renal ischemia	-6.31	(-12.077 , -0.546)	0.033 *	-8.17	(-13.928 , -2.409)	0.006 *
Solitary kidney	-2.07	(-9.636 , 5.494)	0.592			

* denotes significant p value