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Research Article

Influence of intraoperative fluid administration on creatine kinase, and its effect on kidney function after laparoscopic nephrectomy

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KEYWORDS

Rhabdomyolysis;
Laparoscopic nephrectomy;
Intraoperative fluid

Abstract *Background:* Creatine kinase (CK) is a muscle-specific enzyme, which can be associated with muscle tissue damage. Rhabdomyolysis is a serious postoperative complication following severe muscle destruction. Lengthy procedures, high body mass index and lateral decubitus position are common risk factors.
Objectives: The objective of this study was to investigate the effect of intraoperative fluid administration with two different volumes on CK levels, kidney function and the incidence of rhabdomyolysis after laparoscopic nephrectomy.
Methods: In this prospective randomized study, 100 adult patients, ASA physical status II and III scheduled for laparoscopic nephrectomy were included and, randomized into two equal groups. Patients in Group I received maintenance infusion of Lactated Ringer's solution 4 ml kg^{-1} h^{-1}, while patients in Group II received intraoperative infusion 8 ml kg^{-1} h^{-1} till the end of surgery. Total intraoperative fluid, urine output and, blood loss were all calculated. CK was measured preoperative (T_0), immediately postoperative (T_1), 12 h postoperative (T_2) and at 24, 48, 72 and, 96 h postoperative (T_3–T_6). Serum creatinine was measured preoperative {baseline (T_0)}, 12 h postoperative (T_1) then, daily for 3 days (T_2–T_4). Skin changes as erythema and, induration were monitored.
Results: Insignificant differences were reported between the two groups in terms of patient demographics, operative time, intraoperative blood loss and serum creatinine. Intraoperative fluid intake was significantly higher among patients of Group II {2388 (308.8) vs 1284 (233.3) ml}. CK levels

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were higher in Group I patients in the first 72 h after surgery. Rhabdomyolysis was diagnosed in six patients (6%); only one had elevated serum creatinine and oliguria.

Conclusions: Intraoperative administration of 8 ml kg^{-1} h^{-1} compared with 4 ml kg^{-1} h^{-1} Lactated Ringer's solution led to significant reduction in CK levels as a marker of rhabdomyolysis during laparoscopic nephrectomy.

1. Introduction

Rhabdomyolysis is a destruction of skeletal muscles with extravasation of toxic intracellular contents into the systemic circulation. The severity of rhabdomyolysis ranges from asymptomatic increase in creatine kinase (CK) (a muscle-specific enzyme, which can be associated with muscle tissue damage) to serious conditions with hypovolemia, metabolic acidosis, coagulopathies, respiratory failure and myoglobinuric renal failure [1]. Electrolyte disturbances in the form of hypocalcemia, hyperkalemia, and hyperphosphatemia are associated with severe rhabdomyolysis. Cardiac arrhythmias secondary to severe electrolyte abnormalities occasionally occur. The most serious complication is ARF (as a result of ischemic injury of the nephron), which was reported in about 50% of patients who are usually oliguric, and the mortality rate reaches almost 5% [2–4].

Rhabdomyolysis was recognized initially as a posttraumatic complication. Postoperative rhabdomyolysis occurs secondary to prolonged muscle compression on the operating table due to surgical positioning and patient body mass [4–6]. The lateral flexed decubitus position with the use of the kidney rest may cause prolonged compression of the thigh and gluteal muscles, making rhabdomyolysis a serious complication following nephrectomy [7,8].

Several studies have investigated different types and amounts of fluids for perioperative fluid replacement and the conclusion of the appropriate volume to administer cannot be made [9].

The aim of this prospective randomized study was to investigate and compare the effect of intraoperative fluid administration with two different volumes of Ringer's lactate (LR), 4 ml kg^{-1} h^{-1} vs 8 ml kg^{-1} h^{-1} on CK activity, incidence of rhabdomyolysis and renal function during the postoperative period, after laparoscopic nephrectomy.

2. Methods

In this prospective randomized study, after approval of our local ethics committee and informed written consent from each patient, 100 adult patients American Society of Anesthesiologist (ASA) physical status II and III, scheduled to undergo elective laparoscopic nephrectomy, were included in this study from January 2009 to October 2011 at Kasr Alaini Hospital.

Exclusion criteria includes, age younger than 18 years, patients with left ventricular ejection fraction < 45% (diabetes mellitus), abnormal creatinine, sodium or potassium, conversion from laparoscopic to open surgery, intraoperative hypotension required addition of extra fluid boluses and, history of drug administration {e.g.: cholesterol-lowering drugs (statins)}.

Patients were instructed to fast six hours before surgery. On arrival to the operating theater, patients were randomized using a sealed envelope method to one of two groups. Patients in Group I ($n = 50$) received maintenance infusion of Lactated Ringer's solution (LR) 4 ml kg^{-1} h^{-1}, (composition: Na^+ 130 mmol/l, chloride 109 mmol/l, K^+ 4 mmol/l, lactate 28 mmol/l, calcium 1.4 mmol/l), while patients in Group II ($n = 50$) received intraoperative infusion of 8 ml kg^{-1} h^{-1} of the same solution till the end of the procedure. The fluid deficit and blood loss were replaced as indicated.

Routine monitors including, non invasive arterial blood pressure (ABP), heart rate (HR), electrocardiography (ECG), end tidal CO_2 and Oxygen saturation (SpO_2) monitors were applied to all patients (Viralert 2000, North American Drager).

General anesthesia was induced with fentanyl 2 μg/kg, propofol 2 mg/kg and tracheal intubation was facilitated with atracurium 0.5 mg/kg. Anesthesia was maintained with inhaled isoflurane and 50% O_2 in air with atracurium infusion 0.5 mg kg^{-1} h^{-1}. Intermittent bolus doses of fentanyl 1–2 μg /kg were administered to maintain mean arterial blood pressure (MAP) and HR within 20% of base line values. Patients were ventilated with controlled mechanical ventilation adjusted to maintain normocapnea. After tracheal intubation, direct arterial pressure via the radial artery catheter, and central venous pressure (CVP) via the internal jugular vein catheter were monitored.

All patients were positioned in the lateral decubitus position with table flexed at 30° approximately with the kidney rest in an upward position with padding of pressure points.

At the end of surgery reversal of neuromuscular block was achieved with neostigmine 0.04 mg/kg and atropine in a dose of 0.01 mg/kg. After tracheal extubation, patients were transferred to post anesthesia care unit (PACU).

After obtaining a baseline measurement of mean arterial blood pressure (MAP) before induction of anesthesia, MAP was recorded immediately after induction then, every 30 min up to 7 h thereafter. Hypotension, (systolic blood pressure < 90 mm Hg or 20% decrease in the mean arterial pressure from the baseline value) was treated with a fluid bolus of 250 ml of LR solution. Total intraoperative maintenance fluid intake, urine output, blood loss were all calculated. CK, was measured preoperatively baseline (T_0), immediately postoperative (T_1), 12 h postoperative T_2 and after 24, 48, 72 and, 96 h postoperative (T_3–T_6). Serum creatinine was measured preoperatively {baseline (T_0)}, 12 h postoperative (T_1) and, on daily basis for 3 days thereafter (T_2–T_4). Urine myoglobin was also tested in case of high level of CK. Skin changes such as erythema, bruising, induration and, blistering were monitored as well as any change in the urine color. Rhabdomyolysis was diagnosed when serum CK ⩾ 1000 U/L and, the diagnosed patients were managed with vigorous fluid therapy

(500–600 ml/h) and i.v furosemide to maintain urine output > 1.5 ml/kg/h.

3. Statistical analysis

Analysis of data was done using Prism 5.0a (GraphPad Software, Inc.). Data were expressed as mean (SD), ratio or percent as indicated. For comparing data between groups unpaired *t* test was performed. Categorical variables were compared using contingency tables and Fisher's exact test. A p value of < 0.05 was considered statistically significant.

4. Results

Patient demographics are shown in (Table 1).

The mean operative time and the estimated blood loss did not differ between the two study groups. Intraoperative fluid volume administered to patients in Group II and urine output were significantly higher than in Group I (Table 1).

Intraoperative hemodynamics were stable in all patients of both groups throughout the study period. Intraoperative mean arterial blood pressure showed insignificantly higher levels reported in patients of Group II (Fig. 1).

CVP readings during surgery showed, significantly higher levels among patients of Group II (Table 1).

CK rose in all patients of both groups in the first 12 h after surgery, with significantly higher levels recorded in patients of Group I (Table 2). Rhabdomyolysis however, was diagnosed in 6 patients; 5 of them were in Group I and their mean BMI was (31.74 ± 1.4), and operative time was (303 ± 7.58 min), and one patient in Group II his BMI was 33.1 and operative time was 325 min.

Among those patients who developed rhabdomyolysis in Group I, only one had marked CK elevation reaching 4531 U/L in the first 12 h postoperative. This patient had BMI = 33.4 and the operative time was (310 min). Serum creatinine was also increased significantly in this patient reaching 2.6 mg/dl. Fortunately, CK and serum creatinine levels decreased to normal values within the subsequent 3 days after aggressive fluid therapy. Apart from this patient serum creatinine did not significantly increase in any patient of both groups during the study (Table 3).

Skin changes in the form of erythema and, induration of the dependent thigh and gluteal muscles were noted in one patient who had marked rise in CK. Bruising or blistering was not observed in any of our patients.

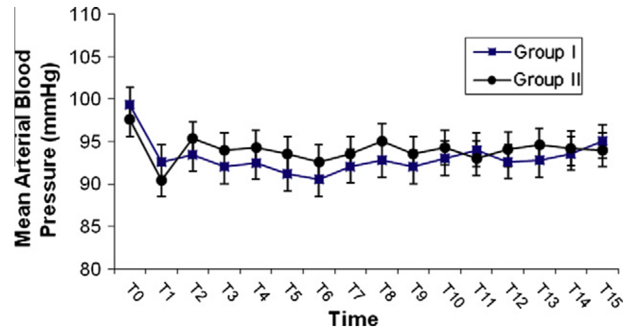

Figure 1 Mean arterial blood pressure (mmHg) at different times of the study T_0 (baseline value, before surgery), T_1 (immediate after induction of anesthesia), T_2–T_{15} (every 30 min thereafter).

5. Discussion

In the current study intraoperative administration of 8 ml $kg^{-1} h^{-1}$ compared with 4 ml $kg^{-1} h^{-1}$ of LR solution was associated with better tissue and renal perfusion as evident by lower levels of CK and higher urine output volumes.

Intraoperative hemodynamic variables were stable with both fluid volumes. Though, patients in Group I had borderline urine output and higher levels of CK with greater chance for development of rhabdomyolysis and deterioration of kidney function.

All patients included in the current study showed significant postoperative rise in CK levels with higher significant levels among patients of Group I. Rhabdomyolysis was diagnosed in five patients in Group I and in one patient in Group II. This could be explained by that, the higher volume of maintenance fluid administered in Group II patients was associated with adequate perfusion of the dependent tissue decreasing the possibility of tissue ischemia, as there were insignificant differences recorded between the two groups in terms of the operative time, BMI and, the body position on the operating table.

The precise incidence of rhabdomyolysis is not well known. The previous reported incidence varies between 0.67% and 4.9% in laparoscopic renal surgeries [10,11]. Harper et al. [12], reported that among 74 patients who underwent hand assisted laparoscopic donor nephrectomy (10.8%) had a CK ⩾ 2500 IU/l and (23%) had a CK ⩾ 1000 IU/l. However, in the present study the incidence of rhabdomyolysis was (6%) which is still within the reported data.

Table 1 Patient demographics and operative data {mean (SD)} or ratio.

	Group I (n = 50)	Group II (n = 50)	P value
Age (yr)	46(5.2)	48(3.7)	0.1264
Sex (M/F)	32/18	34/16	0.8330
BMI (kg/m^2)	28.44(3.47)	29.75(2.38)	0.1287
Operative time (min)	245.2 (24.63)	240.6 (16.69)	0.4493
Intraoperative maintenance fluid (ml)	1284 (233.3)	2388 (308.8)*	< 0.0001
Intraoperative urine output (ml/h)	44.2 (3.82)	73.6 (5.53)*	< 0.0001
Intraoperative blood loss (ml)	285 (54.3)	320 (71.2)	0.0598
Intraoperative CVP (cm H_2O)	9.2 (1.3)	13.7 (3.5)*	< 0.0001

M/F = male/female, BMI = Body mass index, CVP = central venous pressure. P value < 0.05 was considered significant.
* Significantly difference compared to Group I.

Table 2 Changes in serum creatine kinase (CK), in the two groups at different times of the study {mean (SD)}.

Creatine kinase (U/L)	Group I (n = 50)	Group II (n = 50)	P value
T_0	138(16.7)	146(12.3)	0.0616
T_1	405(69.97)	302(46.4)*	< 0.0001
T_2	892.4(803.3)	490.8(50.41)*	0.0161
T_3	684.5(449.3)	386.8(47.41)*	0.0019
T_4	431.9(203.2)	301.8(43.51)*	0.0030
T_5	324.7(123.3)	244.2(26.66)*	0.0025
T_6	151.0(35.37)	153.1(18.62)	0.7948

T_0 (baseline value, before surgery), T_1 (immediate postoperative), T_2 (12 h after surgery), T_3 (24 h after surgery), T_4 (48 h after surgery), T_5 (72 h after surgery), T_6 (96 h after surgery).
* Significantly different compared to Group I. P value < 0.05 was considered significant.

Table 3 Changes in serum creatinine in the two groups at different times of the study {mean (SD)}.

Serum creatinine (mg/dl)	Group I (n = 50)	Group II (n = 50)	P value
T_0	1.05(0.20)	0.96(0.27)	0.1928
T_1	1.129(0.36)	0.99(0.15)	0.1006
T_2	1.17(0.34)	1.028(0.13)	0.0615
T_3	1.146(0.24)	1.08(0.14)	0.3226
T_4	1.11(0.17)	1.06(0.13)	0.2079

T_0 (baseline value, before surgery), T_1 (12 h after surgery), T_2–T_4 (subsequent 3 days postoperative), P value < 0.05 was considered significant.

Our results are in agreement with the previous results of Wolf et al. [13] who reported that among patients who underwent urological laparoscopic surgery those who developed rhabdomyolysis, had longer operative time (mean 379 vs 300 min) and higher body weight (mean 91 vs 80 kg). The mean operative time recorded in those patients who developed rhabdomyolysis in the current study was (306.7 vs 235.3 min) and, their mean body weight was (91.7 vs 79.2 kg).

Glassman et al. [11] suggested that high perfusion pressures or permissive hypertension during surgery could improve perfusion to the dependent soft-tissue and prevent the development of rhabdomyolysis. On the other hand, Concha et al. [14] demonstrated that, crystalloid administration in a rate of $3.4 \pm 0.8\ \text{ml kg}^{-1}\ \text{h}^{-1}$ for laparoscopic colorectal surgery compared to $5.9 \pm 2\ \text{ml kg}^{-1}\ \text{h}^{-1}$ for open surgery was sufficient to maintain baseline left ventricular end diastolic volume index (LVEDVI) and cardiac index. However, renal function and perfusion during their study were not evaluated to exclude the possibility hypoperfusion.

Among those patients who developed rhabdomyolysis in our study, only one had elevated serum creatinine and oliguria, CK level in this patient at 12 h postoperative was 4531 U/L. Aggressive fluid hydration successfully increased urine output and reduced CK and serum creatinine to baseline values within 3 days postoperative.

Myoglobinuria appears in 50% of the severe cases; a level > 1000 ng/ml is directly related to ARF [15]. Urine myoglobin was negative in all patients who developed rhabdomyolysis in the present study.

From the previous reported cases, several factors can be identified as being potentially the cause in the development of rhabdomyolysis. Obesity has been recognized as a common predisposing factor [16,17].

Long operative time is another factor that predisposes to rhabdomyolysis. Long periods of direct muscle compression can compromise the compartment pressure in the buttock and start compartment syndrome. The pressure level at which ischemia occurs varies from one patient to another due to differences in cardiac output, blood pressure, hemoglobin level and, hemoglobin saturation. When tissue pressures are within 10–30 mm Hg of the diastolic blood pressure, muscle ischemia occurs [18].

Hypotension can significantly increase the risk of myonecrosis. Ischemia for more than 3 h leads to increased capillary permeability, after 4 h of ischemia myonecrosis and myoglobinuria can occur. Rhabdomyolysis is often evident in the immediate postoperative period when the ischemic muscle is reperfused [16,17,19,20]. Proper padding of pressure areas may be helpful, but it decreases pressures in dependent parts by only 16% [21].

Yokoyama et al. [10] showed that, lateral decubitus position reduces tissue perfusion significantly due to decrease cardiac output and mean arterial pressure as a result of decreased venous return with table flexion and elevation of the kidney-bridge.

Treatment of rhabdomyolysis requires aggressive fluid administration to ensure urine output $> 1.5\ \text{ml kg}^{-1}\ \text{h}^{-1}$. Loop diuretics and, mannitol are also used. Sodium bicarbonate and acetazolamide are used to produce alkaline urine [11,22]. Dialysis is indicated if the kidneys do not respond to the previous supportive measures and severe renal dysfunction occurs [23].

Patients with cardiac problems that potentially cause inadequate tissue perfusion and, patients with high BMI undergoing laparoscopic procedures in positions that may lead to increase compartment pressure for a prolonged period are at higher risk for development of rhabdomyolysis. Proper perioperative hydration and, avoidance of hypotension during anesthesia, all are factors that may prevent this complication. Routine measurement of CK in the immediate postoperative period for high risk patients helps in the early diagnosis and prevention of this morbid condition.

6. Conclusion

This study highlights a possible postoperative complication that could be seen with the frequent laparoscopic urological surgeries. Proper intraoperative hydration with administration of 8 ml kg^{-1} h^{-1} of Lactated Ringer's solution may help prevent this complication. Further studies with a larger number of patients particularly those who at high risk for development of rhabdomyolysis are still needed to find out the proper intraoperative fluid management protocol.

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