Preventing Renal Failure in Patients with Rhabdomyolysis: Do Bicarbonate and Mannitol Make a Difference?

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Background: **The combination of bicarbonate and mannitol (BIC/MAN) is commonly used to prevent renal failure (RF) in patients with rhabdomyolysis despite the absence of sufficient evidence validating its use. The purpose of this study was to determine whether BIC/MAN is effective in preventing RF in patients with rhabdomyolysis caused by trauma.**

Methods: **This study was a review of all adult trauma intensive care unit (ICU) admissions over 5 years (January 1997–September 2002). Creatine kinase (CK) levels were checked daily (abnormal, >520 U/L). RF was defined as a creatinine greater than 2.0 mg/dL. Patients received BIC/MAN on the basis of the surgeon's discretion.**

Results: **Among 2,083 trauma ICU admissions, 85% had abnormal CK levels. Overall, RF occurred in 10% of trauma ICU patients. A CK level of 5,000 U/L was the lowest abnormal level associated with RF; 74 of 382 (19%) patients with CK greater than 5,000 U/L developed RF as compared with 143 of 1,701 (8%) patients with CK less than 5,000 U/L ($p < 0.0001$). Among patients with CK greater than 5,000 U/L, there was no difference in the rates of RF, dialysis, or mortality between those who received BIC/MAN and those who did not. Subanalysis of groups with various levels of CK still failed to show any benefit of BIC/MAN.**

Conclusion: **Abnormal CK levels are common among critically injured patients, and a CK level greater than 5,000 U/L is associated with RF. BIC/MAN does not prevent RF, dialysis, or mortality in patients with creatine kinase levels greater than 5,000 U/L. The standard of administering BIC/MAN to patients with posttraumatic rhabdomyolysis should be reevaluated.**

Key Words: **Trauma, Creatine kinase, Rhabdomyolysis, Bicarbonate, Mannitol, Renal failure, Dialysis.**

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Rhabdomyolysis, or the breakdown of striated muscle, has been recognized as a clinical entity for centuries.[1] Among a long list of causes, multisystem trauma, vascular injury, and compartment syndrome are the most common. This muscle damage leads to the release of multiple intracellular components including myoglobin and creatine kinase (CK). Along with hypovolemia, the myoglobin released into circulation is thought to cause renal damage through a variety of mechanisms: direct renal cytotoxicity, renal vasoconstriction, and renal tubular obstruction.[2–5] Although myoglobin causes the renal damage, CK levels are elevated and are most commonly used as an indicator and monitor of rhabdomyolysis.[6]

The level of CK that is associated with an increased risk of renal failure (RF) is unclear, but is reported to be 500 U/L,[7,8] 5,000 U/L,[9] 16,000 U/L,[10] and 75,000 U/L[11] in different studies. To prevent RF in patients with rhabdomyolysis, three treatment strategies are usually instituted: vigorous hydration to maintain renal perfusion and promote dilution of myoglobin; alkalinization of the urine with bicarbonate to prevent myoglobin precipitation in the renal tubules; and administration of mannitol for a variety of effects including osmotic diuresis, vasodilatation of renal vasculature, and free-radical scavenging.[2] Despite the adequate rationale supporting the addition of bicarbonate and mannitol (BIC/MAN) to the therapy of such patients, the clinical evidence is lacking and based only on small studies with sample sizes ranging from 7 to 24 patients.[7,12,13]

In our center, CK levels are monitored routinely on all critically injured patients. This allows us to examine a significant patient sample with evidence of rhabdomyolysis. Our study intends to establish the incidence of rhabdomyolysis in an unselected group of critically injured patients; identify the level of CK associated with an increased rate of RF; and examine the value of BIC/MAN in preventing RF, dialysis, and mortality after posttraumatic rhabdomyolysis.

PATIENTS AND METHODS

The medical records of all trauma patients admitted to the surgical intensive care unit (ICU) at our Level I trauma center between January 1997 and September 2002 were reviewed. The trauma registry and ICU database were used to obtain relevant variables. According to existing protocol, CK is monitored daily on all ICU patients. Our laboratory considers CK > 520 U/L as abnormal. BIC/MAN is given at the discretion of the attending surgeon. Patients who receive

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BIC/MAN are treated according to established guidelines,[14] involving a bolus of 0.5 g/kg of mannitol and a bolus of 100 mEq of sodium bicarbonate ($NaHCO_3$) diluted in 1,000 mL of 0.45 normal saline. This is followed by an infusion of mannitol at 0.1 g/kg/h and an infusion of 100 mEq of $NaHCO_3$ diluted in 1,000 mL of 0.45 normal saline at a rate of 2 to 10 mL/kg/h. Further BIC/MAN and fluid therapy are titrated to urine output, urine pH, and serum pH.

Primary outcome was RF, defined as a peak creatinine > 2.0 mg/dL. Secondary outcomes were the need for dialysis, length of stay in the ICU, and mortality. The peak CK level was identified for each patient. The rate of RF was calculated in various groups of patients defined by peak CK levels. The CK value above which patients had a significantly higher rate of RF than the entire population was identified. Patients above and below this value were identified. Data on patient demographics, injury type (blunt or penetrating) and severity (Injury Severity Score [ISS] and Abbreviated Injury Scale [AIS] score), body mass index (BMI, in kilograms per square meter), physiologic variables at admission, therapeutic interventions, and hospital course were collected.

Statistical analysis was performed using the SAS System, version 8.2 (SAS Institute, Inc., Cary, NC) and Microsoft Excel 2002 (Microsoft Corporation, Redmond, WA). Values are reported as mean ± SD, as odds ratio ± 95% confidence interval (CI), or as raw percentages where applicable. Categorical variables were compared using χ^2 or Fisher's exact test, and continuous variables were analyzed using two-tailed *t* test. Dichotomous variables were created out of continuous variables at clinically significant cutoff points (e.g., age > 55, BMI > 30, ISS > 15, extremity AIS score > 3, heart rate > 100 beats/min, systolic blood pressure < 90 mm Hg) and, along with categorical variables, were entered into univariate analysis. Variables with a difference at a value of $p < 0.2$ were included in stepwise logistic regression to identify independent risk factors for developing rhabdomyolysis. Statistical significance was considered at the level of $p < 0.05$ for all comparisons.

Table 1 Comparison between Low-CK Group (<5,000 U/L) and High-CK Group (>5,000 U/L)

	CK < 5,000 U/L (n = 1,701)	CK > 5,000 U/L (n = 382)	*p* Value
Age (yr)	38 ± 18	34 ± 15	0.002
Male gender	79%	88%	<0.0001
BMI (kg/m^2)	27 ± 6	28 ± 5	<0.0001
ISS	20 ± 13	23 ± 13	<0.0001
Peak CK (U/L)	1,737 ± 1,263	15,332 ± 25,876	<0.0001

Table 2 Independent Risk Factors for Developing CK > 5,000 U/L Determined by Stepwise Logistic Regression

Risk Factor	Adjusted Odds Ratio	95% Confidence Interval	*p* Value
Extremity AIS score > 3	5.9	3.2–11.0	<0.0001
Blunt injury	3.0	2.3–3.9	<0.0001
Male gender	2.2	1.6–3.2	<0.0001
Heart rate > 100 beats/min	1.6	1.2–2.0	0.0003
BMI > 30 (kg/m^2)	1.6	1.2–2.0	0.001

RESULTS

There were 2,083 trauma admissions (81% men, 37 ± 17 years old) to the ICU over the study period. The mechanism of injury was 58% blunt, with an ISS of 20 ± 13.

CK Levels

Abnormal CK was found in 1,771 patients (85%), with a mean peak CK of 4,923 U/L (range, 521–258,900 U/L). The population divided into groups by CK level in increments of 5,000 U/L and the rate of renal failure in each group are shown in Figure 1. Patients with a CK from 5,000 to 10,000 U/L had a higher incidence of RF compared with the entire population (15% vs. 10%, $p = 0.03$). Patients were further subdivided by CK increments of 1,000 U/L, and CK from 5,000 to 6,000 U/L was the first group with a higher rate of RF than the entire population (20% vs. 10%, $p = 0.02$). Thus, we determined a peak CK level > 5,000 U/L to be the critical value associated with an increased risk of RF.

There were 1,701 patients (82%) with CK < 5,000 U/L (Low-CK group) and 382 patients (18%) with CK > 5,000 U/L (High-CK group). Patients in the High-CK group were younger, more severely injured, more often male, had a higher BMI, and had higher peak CK levels (Table 1). Stepwise logistic regression revealed five risk factors to be independently associated with a peak CK > 5,000 U/L: extremity AIS score, blunt injury, male gender, admission heart rate > 100 beats/min, and BMI > 30 kg/m^2 (Table 2).

Renal Failure

Overall, 217 patients (10%) developed RF and 97 patients (5%) required dialysis. During the study period, 331 of 2,083 patients (16%) died. The mortality among patients with RF (85 of 217 [39%]) and those receiving dialysis (31 of 97 [32%]) was higher than the mortality of patients with neither renal failure nor dialysis (241 of 1,822 [13%], $p < 0.0001$).

Table 3 Independent Risk Factors for RF Determined by Stepwise Logistic Regression

Risk Factor	Adjusted Odds Ratio for Renal Failure	95% Confidence Interval	*p* Value
Age > 55 yr	3.2	2.2–4.8	<0.0001
ISS > 16	2.7	1.8–3.9	<0.0001
CK > 5,000 U/L	2.4	1.7–3.4	<0.0001
Male gender	2.2	1.4–3.6	0.001
BMI > 30 kg/m^2	1.5	1.1–2.1	0.008

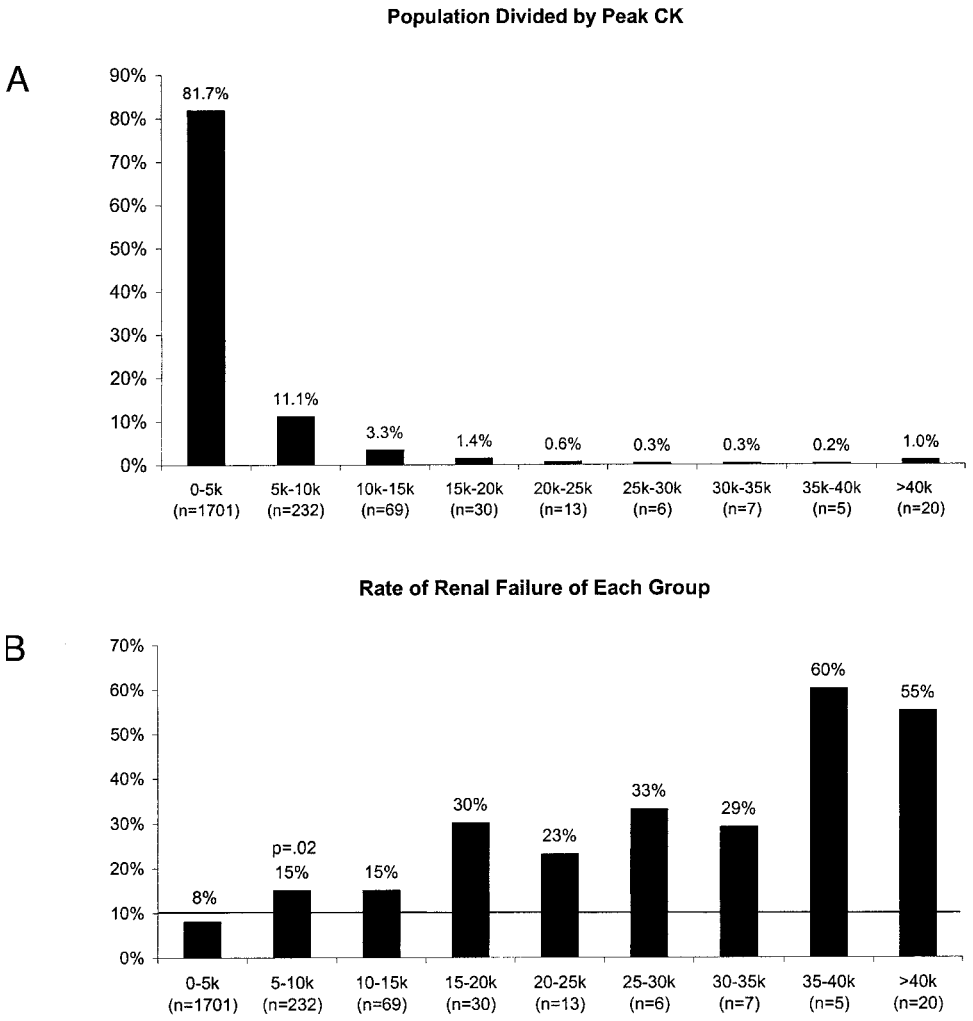

Fig. 1. A, *Population divided by peak CK in increments of 5,000 U/L (shown as a percentage).* B, *Rate of RF for each group (shown as a percentage).* Solid line *represents 10% rate of RF for the entire population.*

The High-CK group had a worse outcome compared with the Low-CK group, with higher peak serum blood urea nitrogen levels (27.4 mg/dL vs. 20.4 mg/dL, $p < 0.0001$), peak serum creatinine levels (1.8 mg/dL vs. 1.3 mg/dL, $p < 0.0001$), and rate of RF (19% vs. 8%, $p < 0.0001$), and longer ICU stay (13.1 days vs. 8.7 days, $p < 0.0001$). There was a trend in the need for dialysis (6% vs. 4%, $p = 0.10$) and no difference in mortality (17% vs. 16%, $p = 0.51$).

Variables found to be independently associated with RF, through stepwise logistic regression, include age > 55 years, ISS > 16, peak CK > 5,000 U/L, male gender, and BMI > 30 kg/m^2 (Table 3). To allow easier bedside calculation, only the three most significant risk factors were used to create a probability model of RF on the basis of the presence or absence of each risk factor (Table 4). The risk of RF increased with each incremental increase in CK by 5,000 U/L, as shown by the adjusted odds ratio for developing RF at each CK level (Fig. 2).

Bicarbonate and Mannitol

Of the 382 patients in the High-CK group, 154 patients (40%) received BIC/MAN therapy (BIC/MAN group), whereas 228 patients (60%) did not (No-BIC/MAN group). The two groups were similar; there was no difference in RF (22% vs. 18%, $p = 0.27$), dialysis (7% vs. 6%, $p = 0.57$), or mortality (15% vs. 18%, $p = 0.37$). Forcing BIC/MAN as a variable in the stepwise logistic regression to identify independent risk factors of RF (Table 3), CK > 5,000 persisted as an independent risk factor (Table 5). In fact, BIC/MAN was an independent risk factor for RF as well. The BIC/MAN and No-BIC/MAN groups were similar, with the exception of peak CK levels (Table 6). For this reason, the two groups were further compared at similar CK levels. The subgroups were organized by peak CK levels, which allowed an adequate sample of patients at each level: 5,000 to 15,000 U/L (n = 301; 100 BIC/MAN and 201 No-BIC/MAN), 15,000 to 30,000 U/L (n = 49; 30 BIC/MAN and 19 No-BIC/MAN),

Table 4 Probability Model of RF Including Three Most Significant Risk Factors Determined by Stepwise Logistic Regression

Age > 55 yr	CK > 5,000 U/L	ISS > 16	Probability of RF
+	+	+	0.41
–	+	+	0.21
+	+	–	0.21
+	–	+	0.20
–	+	–	0.09
–	–	+	0.09
+	–	–	0.09
–	–	–	0.03

and > 30,000 U/L (n = 32; 24 BIC/MAN and 8 No-BIC/MAN). Even at similar CK levels, there was no difference in RF, dialysis, or mortality (Fig. 3).

DISCUSSION

Although posttraumatic rhabdomyolysis has been written about extensively for decades,[15] multiple issues remain unresolved, including the following: How common is posttraumatic rhabdomyolysis? What CK value places patients at risk for RF? Does therapy with BIC/MAN prevent RF in patients with rhabdomyolysis? Our study attempts to address several of these issues.

Our long-standing liberal screening policy of measuring serum CK levels on all trauma ICU admissions allows us to identify accurately the incidence of rhabdomyolysis after severe trauma. Our study reveals that rhabdomyolysis is much more common than previously described. In this series of consecutive trauma ICU admissions, 85% (1,771 of 2,083) had elevated CK levels. This represents the largest sample of trauma patients with elevated CK reported to date.

The exact level of CK above which the risk of RF becomes significant is unknown. Although often arbitrary, CK levels ranging from 500 to 75,000 U/L have been suggested.[7–11] By dividing our population by peak CK and comparing groups to the entire population, we found a CK level > 5,000 U/L to be associated with an increased risk of RF. This High-CK group had a higher rate of renal failure (19% vs. 8%, $p < 0.0001$) and a trend toward the need for dialysis (6% vs. 4%, $p = 0.10$). In addition, through stepwise logistic regression, CK > 5,000 U/L was found to be an independent risk factor for developing RF. The combination of age > 55, ISS > 16, and CK > 5,000 U/L is associated with a probability of RF of 41%, compared with a 3% probability of RF in the absence of these three risk factors. Also, as the level of peak CK rises from 5,000 U/L to > 30,000 U/L, the adjusted odds ratio of developing RF rises from 2.4 (95% CI, 1.7–3.4) to 8.0 (95% CI, 3.6–17.8).

When examining the high-risk population of patients with CK > 5,000 U/L, BIC/MAN therapy made no difference in preventing RF, dialysis, or mortality. Also, when BIC/MAN was forced into the logistic regression for independent risk factors of RF, CK > 5,000 U/L remained as an independent risk factor for RF. In fact, BIC/MAN also appeared as an independent risk factor for RF. This may be because patients that receive BIC/MAN are already at high risk for RF, or because BIC/MAN therapy may be contributing to developing RF.

With the population further subdivided into groups with similar CK levels, it is more difficult to draw conclusions. In

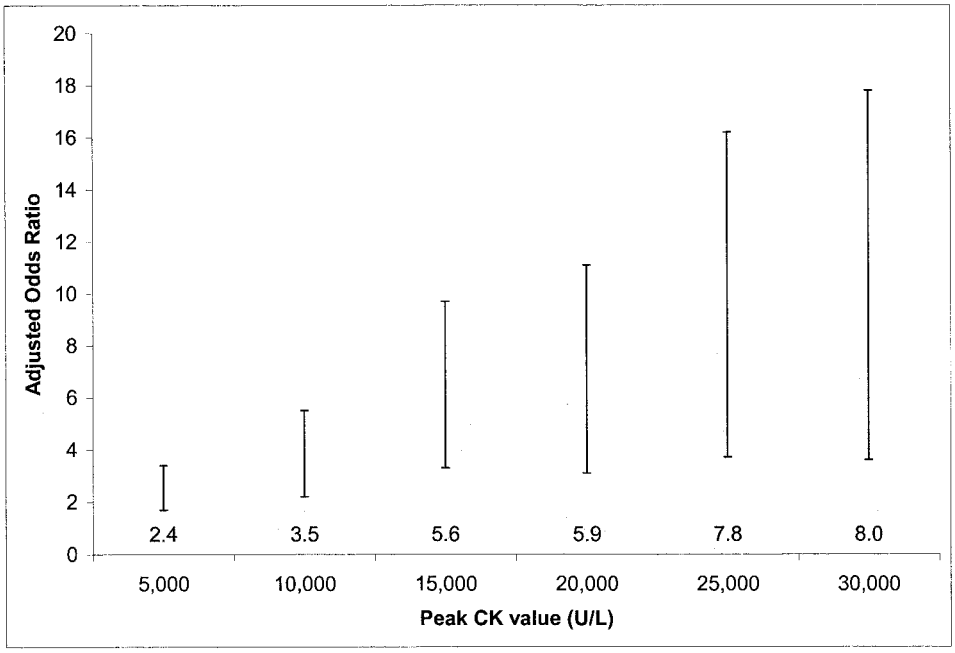

Fig. 2. *Adjusted odds ratio for RF at each increment of CK (error bar represents 95% confidence interval).*

Table 5 **Independent Risk Factors for Renal Failure Determined by Stepwise Logistic Regression, with BIC/MAN Forced in as a Variable**

	Adjusted Odds Ratio for Renal Failure	95% Confidence Interval	*p* Value
Age > 55 yr	3.1	2.1–4.4	<0.0001
ISS > 16	2.6	1.8–3.7	<0.0001
Male gender	2.1	1.4–3.4	0.002
BIC/MAN therapy	2.1	1.3–3.2	0.0009
CK > 5,000 U/L	1.9	1.3–2.8	0.0008

Table 6 **Comparison between the BIC/MAN Group and the No-BIC/MAN Group**

	BIC/MAN (n = 154)	No-BIC/MAN (n = 228)	*p* Value
Age (yr)	35 ± 16	34 ± 14	NS
Male gender	86%	90%	NS
BMI (kg/m^2)	29 ± 6	28 ± 5	NS
ISS	23 ± 13	23 ± 13	NS
Peak CK (U/L)	23,492 ± 38,336	9,819 ± 7,586	<0.0001

NS, not significant.

patients with CK levels from 5,000 to 30,000 U/L, BIC/MAN made no difference. However, in patients with CK > 30,000 U/L, there was a trend toward improved outcome for the BIC/MAN group in terms of preventing RF, dialysis, and mortality. The lack of statistical significance may be attributable to beta error from a small sample size.

The majority of evidence in support of BIC/MAN therapy is rooted in animal studies. Zager[16] evaluated the beneficial effects of bicarbonate in a rat model directly infused with myoglobin. He concluded that bicarbonate protected the kidneys by increasing urinary myoglobin solubility and facilitating its excretion. The same group went on to investigate the effects of mannitol on a rat model of glycerol-induced renal injury.[17] They found that mannitol confers a functional protection, but is not cytoprotective. Also, they concluded that the protective effects of mannitol appear to be attributable to its osmotic diuretic action rather than the other postulated mechanisms. Human studies have been flawed by methodological design and small sample sizes.

In 1979, Eneas et al.[12] reported 20 patients with evidence of myoglobinuria who were all treated with intravenous infusions of BIC/MAN. Eleven did not respond to therapy and required dialysis. The group that did not respond to BIC/MAN had a higher peak CK level than the "responders" (54,000 U/L vs. 16,000 U/L, $p < 0.001$). They vaguely concluded that some patients with myoglobinuria will respond to infusion of BIC/MAN. In 1984, Ron et al.[13] evaluated seven patients who sustained rhabdomyolysis after the collapse of a building. All patients received crystalloid resuscitation along with BIC/MAN therapy, and there was no control group. None of the patients developed RF, and the authors attributed this success to the early institution of appropriate therapy, despite the absence of a control group. Both of these studies were flawed by the lack of a control group.

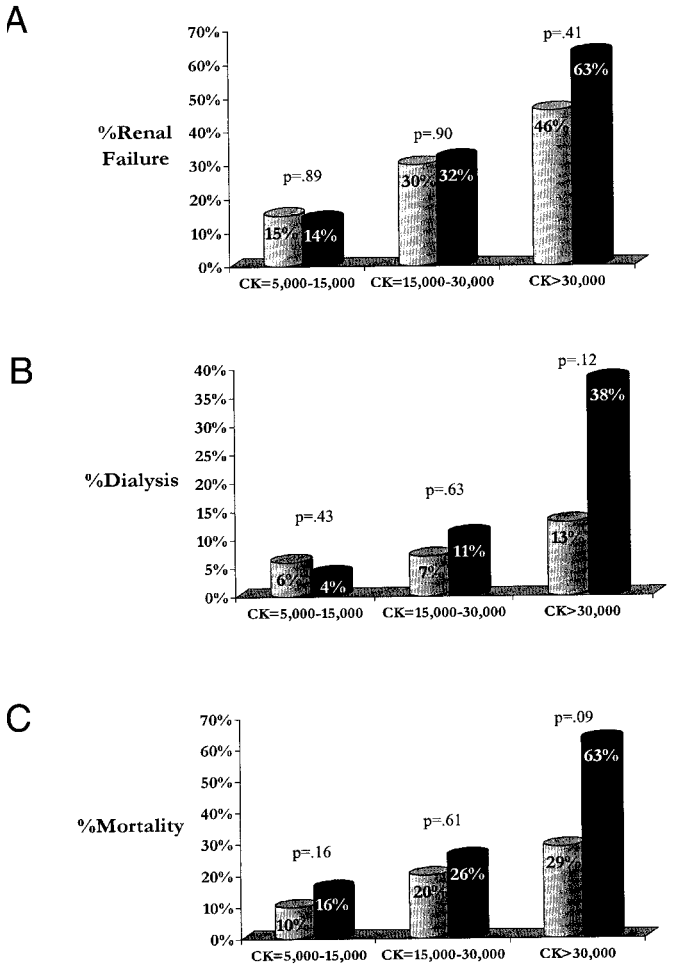

Fig. 3. *Outcomes in BIC/MAN group (*gray bar*) and No-BIC/MAN group (*black bar*) for population divided by increments of CK: 5,000 to 15,000 U/L, 15,000 to 30,000 U/L, and > 30,000 U/L.* A, *Rate of renal failure (shown as a percentage).* B, *Rate of dialysis (shown as a percentage).* C, *Rate of mortality (shown as a percentage).*

In our series, 154 of the 382 patients with CK > 5,000 U/L received BIC/MAN, allowing a control group for comparison. The only other study with a control group[16] showed results similar to ours. Homsi et al.[7] reported on 24 ICU patients with rhabdomyolysis. Fifteen patients received saline resuscitation plus BIC/MAN, whereas nine patients received only saline resuscitation. The authors reported that RF could be prevented with early saline resuscitation and that the addition of BIC/MAN seemed to be unnecessary. There has never been a prospective, controlled trial evaluating the efficacy of BIC/MAN therapy in preventing rhabdomyolysis-induced RF.

There are several limitations to the current study. Like all previous studies on the topic, this study is inherently flawed by its retrospective design. Also, despite a large sample size

of trauma ICU patients and an aggressive screening of CK levels, this study suffers from a relatively small sample of patients with markedly elevated CK levels. In addition, we rely on CK as a surrogate marker for myoglobin, which is actually causing the renal damage. Both CK and myoglobin have been proposed as markers for the severity of rhabdomyolysis. CK has been proposed to be a more reliable marker than myoglobin in assessing the presence and severity of damage to muscles, because of its longer and more consistent elevations.[6] Others have advocated serum myoglobin levels as more accurate, because of faster elimination kinetics than CK.[9] No consensus in the literature exists as to which marker best identifies rhabdomyolysis and can be used to follow these patients. We use CK as a marker for rhabdomyolysis because it is an easily obtainable laboratory test, and urine myoglobin results are not available for several days at our institution.

An additional flaw may be our definition of RF. The difficulty in defining RF is reflected in one review, which found 26 different definitions in studies looking at postoperative RF.[18] Although dialysis is a "hard" measure of RF, only 5% of our population required dialysis, making it too infrequent to use as the definition for RF. A serum creatinine higher than 2 mg/dL has been used extensively to define RF in a broader sense, indicating dysfunction of the renal cell rather than necrosis and inability for recovery. One study showed a creatinine of 2 mg/dL or higher increased the odds ratio for mortality sevenfold.[19] We found similar results in our population, with patients who developed RF having a higher mortality than those patients who did not develop RF (39% vs. 13%, $p < 0.0001$).

Finally, this study lacks stringent criteria for the initiation and maintenance of BIC/MAN therapy. Although a protocol is in place for administering BIC/MAN,[14] therapy is started at the discretion of the attending surgeon. Also, ongoing treatment with BIC/MAN is not guided by protocol but rather by surgeon interpretation of serum pH, urine pH, and urine output. Despite these limitations, this is the largest series with a control group examining the benefit of BIC/MAN in patients with traumatic rhabdomyolysis.

CONCLUSION

This is the largest series of posttraumatic rhabdomyolysis patients studied. Rhabdomyolysis after trauma is more common (85%) than previously reported. Trauma patients admitted to the ICU, especially those with significant risk factors, should be aggressively screened with serum CK levels. Approximately 20% of trauma patients develop significant rhabdomyolysis (CK $>$ 5,000 U/L). Independent risk factors for developing significant rhabdomyolysis are extremity injury, blunt mechanism, male gender, tachycardia, and BMI $>$ 30 kg/m^2. Patients with a CK level $<$ 5,000 U/L are not at risk for RF after rhabdomyolysis, whereas CK $>$ 5,000 U/L is an independent risk factor for RF. BIC/MAN therapy does not prevent RF, the need for dialysis, or mortality in patients with CK $<$ 30,000 U/L. There is some indication that BIC/MAN therapy may be beneficial in patients who develop CK levels $>$ 30,000 U/L. The standard of routinely administering BIC/MAN to patients with mildly elevated CK levels should be reconsidered. A prospective, controlled, multicenter trial is necessary to determine whether BIC/MAN therapy is beneficial at higher CK levels.

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