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Crush syndrome

Le syndrome de compression

Emily Lovallo [a], **Alex Koyfman** [b], **Mark Foran** [c]

[a] *Department of Emergency Medicine, Alameda County Medical Center and Highland General Hospital, Oakland, CA, USA*
[b] *Department of Emergency Medicine, University of Illinois College of Medicine at Peoria, OSF Saint Francis Medical Center, Peoria, IL, USA*
[c] *Department of Emergency Medicine, New York University School of Medicine, Bellevue Hospital Center, New York, NY, USA*

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KEYWORDS

Crush syndrome;
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Acute kidney injury;
Myoglobinuria;
Compartment syndrome

Abstract The first detailed cases of crush syndrome were described in 1941 in London after victims trapped beneath bombed buildings presented with swollen limbs, hypovolemic shock, dark urine, renal failure, and ultimately perished. The majority of the data and studies on this topic still draw from large databases of earthquake victims. However, in Africa, a continent with little seismic activity, the majority of crush syndrome cases are instead victims of severe beatings rather than earthquake casualties, and clinical suspicion by emergency personnel must be high in this patient group presenting with oliguria or pigmenturia. Damaged skeletal muscle fibres and cell membranes lead to an inflammatory cascade resulting in fluid sequestration in the injured extremity, hypotension, hyperkalemia and hypocalcemia and their complications, and renal injury from multiple sources. Elevations in the serum creatinine, creatine kinase (CK), and potassium levels are frequent findings in these patients, and can help guide critical steps in management. Fluid resuscitation should begin prior to extrication of trapped victims or as early as possible, as this basic intervention has been shown to in large part prevent progression of renal injury to requiring haemodialysis. Alkalinization of the urine and use of mannitol for forced diuresis are recommended therapies under specific circumstances and are supported by studies done in animal models, but have not been shown to change clinical outcomes in human crush victims. In the past 70 years the crush syndrome and

E-mail address: akoyfman8@gmail.com (E. Lovallo)

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its management have been studied more thoroughly, however clinical practice guidelines continue to evolve.

Abstract Les premiers casdétaillés du syndrome de compression ontétédécrits à Londres en 1941 sur des victimesensevelies sous des immeublesbombardés qui présentaient des membresenflés, un choc hypovolémique, une urine foncée, uneinsuffisancerénaleaiguë, et qui finalementdécédaient. La majorité des donnéeset des étudessurcesujetesttoujourstirée des vastes bases de donnéessur des victimes de tremblements de terre. Néanmoins, en Afrique, un continent présentantunefaibleactivitésismique, la majorité des cas de syndrome de compression sontplutôt des victimes de coups violentsque des victimes de tremblements de terre, et la suspicion clinique du personnel des urgencesdoitêtreélevée pour le groupe de patients présentant des oliguriesou des pigmenturies. Des lésions des fibresmusculairessquelettiques et des membranes cellulairessont à l'origined'une cascade inflammatoire qui a pour conséquence la séquestration des fluidesdans les extrémitésblessées, de l'hypotension, de l'hyperkaliémie et de l'hypocalcémie et leurs complications, et des lésionsrénalesd'origines multiples. L'augmentation des taux de créatininesérique, de créatine kinase (CK) et de potassium sont des résultatsfréquents chez ces patients, et peuventvous guider dans les étapesimportantes de la prises en charge. La réanimationliquidiennedevrait commencer avantl'extraction des victimesenseveliesouaussitôtque possible, étantdonnéqu'ilaétéprouvéquecette intervention fondamentaleprévenait en grandepartie la progression des lésionsrénalesavantqu'elles ne nécessitentunehémodyalise. L'alcalinisationurinaire et l'utilisation du mannitol pour unediurèseforcéesont des thérapiesrecommandéesdanscertainescirconstances et s'appuientsur des étudesfaitessur des animaux, maisn'ont pas montré de changementdans les résultatscliniques chez les victimeshumaines du syndrome de compression. Le syndrome de compression etsaprise en charge sontétudiés de manièreapprofondiedepuis 70 ans, cependant les directives relatives à la pratiquecliniquecontinuentd'évoluer.

Contents

African Relevance

- Crush syndrome may present after severe beatings, the most common presentation in Africa, not only as a result of entrapment
- Crush syndrome, when discovered early, can usually be managed conservatively and haemodialysis, a much more costly and high risk procedure, can be avoided
- Emergency personnel must consider it in the differential diagnosis of victims of severe beatings with pigmenturia or tense compartments

What's new?

- Discusses the epidemiology of crush syndrome in a historical as well as present day, Africa-relevant context
- Provides a thorough but simplified overview of the complicated pathophysiology of crush syndrome
- Provides an approach to the management of crush victims at each stage of injury

Introduction

Crush syndrome (CS) is defined as traumatic compression of muscle tissue with resulting acute kidney injury (AKI). The syndrome was first described in a case series of 5 patients who were trapped beneath rubble in London during World War II, resulting in injury to their extremities, followed by swollen limbs, hypovolemic shock, dark urine, renal failure, and death.[1] The syndrome has been more thoroughly studied since the setting of large-scale natural disasters such as earthquakes. In Africa, where the incidence of earthquakes is small,[2] there are limited data, though an increasing number of cases of crush syndrome are resulting from interpersonal violence.[4–8] Regardless of aetiology, the diagnosis and management of this syndrome is important for emergency personnel.

Rhabdomyolysis alone, when significant, can lead to AKI, and can be caused by numerous traumatic and non-traumatic events, including prolonged seizure activity, muscle compression in the setting of severe intoxication or stroke, medication side effects, certain rheumatologic diseases, building collapse, traffic accidents, and beatings. This review will discuss specifically rhabdomyolysis and AKI in the setting of crush injury with limb compression and ischaemia.

Epidemiology

Crush syndrome develops in an estimated 2–5% in all earthquake victims[3] and in up to 50% of victims of traumatic rhabdomyolysis[32] and 10.5% in victims of severe beatings.[4] The estimated proportion of patients who require haemodialysis varies widely from 0% to 75%,[8,11] and several studies have attempted to analyse the many variables that may play a role in the outcome of CS victims. For example, when comparing the Kashmir, Pakistan earthquake in 2005 to the Marmara, Turkey earthquake in 1999, both of which occurred in densely populated regions, there was a statistically significant higher number of CS patients in general, a higher number of which required haemodialysis, and a higher number of which died in Marmara despite there being more total deaths and more total injured survivors in Kashmir, with similar intensities of quakes. The principal theory for these outcomes being that the Kashmir disaster occurred during the day, whereas the Marmara quake occurred in the middle of the night, while most people were supine. Hence, the increased prevalence of crushed extremities instead of fractured extremities.[9] Other relevant variables include quality of infrastructure, with regard to buildings and roads, which accounts for both ease of extrication from rubble, as well as arrival of rescue crews, and season, as dehydration plays a major role in the pathophysiology of CS.

With regard to outcomes from non-disaster settings but specifically trauma-related crush syndrome, 10–20% of patients develop renal dysfunction, with 1.5–2% of patients requiring dialysis for oliguric renal failure.[4,10] High-risk variables significantly associated with rates of renal impairment include delay to admission >12 h, severe metabolic acidosis with bicarbonate level less than 17, low initial haemoglobin, heavy pigmenturia, body surface area affected $>18\%$, and high serum creatine kinase (CK) levels.[4,6,10]

Pathophysiology

The pathophysiology of crush syndrome is best understood when considered as a two-part process. First, there is traumatic rhabdomyolysis, or skeletal muscle breakdown, followed by the cascade of events resulting from release of muscle cell contents, including hypotension secondary to intravascular hypovolemia, hyperkalaemia, and renal failure.

Muscle compression causes both stretch of fibres and ischaemia, resulting in calcium ion influx, decreased ATP production secondary to anaerobic metabolism, and increased neutrophil chemo-attractants, all of which ultimately lead to rhabdomyolysis. After extrication in the case of entrapped victims, reperfusion of ischaemic muscle generates free oxygen radicals and delivers neutrophils to the area, further promoting a cascade of damage via release of proteolytic enzymes, hypochlorous acid production, and increasing microvascular resistance. Ultimately, destruction of the cell membrane results in the failure of electrolyte regulation and balance between the intracellular and extracellular environments and cellular oedema, followed by cell lysis. When this process occurs throughout a muscle within a space confined by fascial planes, as in the forearm or calf, compartment syndrome can result. Findings often include a tense swollen muscle compartment, paraesthesia or anaesthesia, pain with passive stretch, weakness or paralysis, and eventually loss of or diminished distal pulses, though intra-compartmental pressures can be markedly elevated with preservation of pulses.[17]

As in compartment syndrome, cellular membrane damage causes leaky capillary beds, resulting in intravascular volume loss in the damaged extremity. In the case of crush syndrome, the sequestration of large volumes of fluid can lead to hypotension and hypovolemic shock, the latter being the most common cause of death in the first 4 days after crush injury.[12] For this reason, a pre-existing state of dehydration places the patient at an increased risk of early death if not fluid resuscitated appropriately. With cell lysis, the body faces a significant toxin load from the ischaemic tissue causing acidaemia, as well as electrolyte abnormalities including most importantly hyperkalaemia, hyperphosphataemia, and hypocalcaemia. Cardiotoxicity from hyperkalaemia is the second most common cause of death immediately after extrication or reperfusion in crush syndrome.

In addition to hypovolemia and rhabdomyolysis, renal injury comprises the third major component of crush syndrome. The aetiology of renal damage is three-fold. First, the hypovolemia that results from the previously described mechanisms results in hypoperfusion of the kidneys and stimulation of the renin–angiotensin–aldosterone axis, which causes efferent arteriole vasoconstriction in an attempt to

preserve glomerular filtration rate (GFR). However, in the presence of myoglobin, plasma endothelin-1 and platelet activating factor[17] cause afferent vasoconstriction, ultimately reducing total renal perfusion and GFR. Additionally, myoglobin is a direct inhibitor of nitric oxide, again promoting vasoconstriction and kidney ischaemia. Second, myoglobin release from damaged skeletal muscle in the process of rhabdomyolysis floods the plasma, over-saturating the haptoglobin molecules that normally bind it and resulting in increased myoglobin filtration load to the renal tubules. Because the molecule is too large to be reabsorbed, myoglobinuria results, which can be picked up by simple urine dipstick as ''blood'' in the setting of dark tea-coloured urine, with the absence of red blood cells on urine microscopy. In the renal tubules, high concentrations of myoglobin react with Tamm–Horsfall protein and precipitate, forming casts. This process is enhanced in acidic urine conditions, and some data show decreased cast formation when sodium bicarbonate is given to alkalinize the urine.[17] A large volume of myoglobin casts then obstructs the tubules, causing leakage of the glomerular filtrate, and further renal injury. Third and most importantly, the myoglobin itself is directly nephrotoxic. As myoglobin separates into protein and a haeme-iron molecule in the acidic urine, lipid peroxidation and free radical formation ensues, damaging the renal tubules.

Diagnosis

Since aggressive early management of renal injury is essential in reducing morbidity and mortality associated with crush syndrome, having a high suspicion in the setting of significant trauma to the extremities or torso is necessary. Key components of the history include both duration and severity of the crush injury or assault, oral and intravenous fluid intake prior to arrival, and urine output.[11] Signs of crush syndrome include frequently a painful and swollen extremity or other significant soft tissue injury with dark or red appearing urine, and poor urinary output. With regard to laboratory tests, the inexpensive urine dipstick showing blood, with absence of red blood cells on microscopic review is highly suggestive and specific for myoglobinuria and thus rhabdomyolysis. A serum CK level can be helpful, and serial levels as well as urine output should be monitored as levels over 8500 U/L have been correlated to acute renal failure and the need for dialysis,[10,12,20] though how strong that correlation is appears to still vary between studies.[11,12,18,19,21]

Simple calculation of the estimated body surface area affected may help predict outcomes.[10] Recent studies have also validated use of the Risk, Injury, Failure, Loss and End-stage renal failure (RIFLE) classification system for crush victims in the disaster setting to predict to what degree more advanced interventions such as haemodialysis may be needed, using the parameters of the serum creatinine level to measure glomerular filtration rate and urine output.[14,15] In recent earthquakes in Haiti and Chile, a point-of-care (iSTAT®, Abbott, USA) device was used in the field to check serum creatinine levels and triage patients[16] and may be considered for similar disaster situations in the future in which a functioning laboratory is an unrealistic amenity.

Management

Because the complications of crush syndrome are life-threatening, the key to management is prevention. Whenever possible, aggressive fluid resuscitation should begin in all crush victims prior to their extrication.[22] Studies have found that patients often remain hemodynamically stable while entrapped, but it is after extrication that hypotension and renal injury begins,[23] secondary to the inflammatory cascade that is part of limb crushing and ischaemia-reperfusion discussed above. Intravenous fluids help to prevent renal ischaemia by increasing perfusion and force diuresis, with the goal to avoid myoglobin cast obstruction of the tubules, though its efficacy appears to fall after the first 6–12 h.[22,25–27] The International Society of Nephrology Renal Disaster Relief Task Force (RDRTF) recommends the use of isotonic saline at a rate of 10–15 mL/kg/h for 2 L total, and then the rate should be decreased to 500 mL/h to avoid fluid overload. Other factors to be taken into consideration in initial fluid resuscitation prior to extrication include climate and on-going blood loss, number of limbs affected, other medical problems (congestive heart failure), and age (more cautious resuscitation in the elderly).[26] There is no role for bicarbonate therapy or lactated Ringer's solution in this phase. Lactated Ringers in particular are contraindicated due to the high risk at baseline in these patients of developing severe hyperkalaemia.

Baseline serum electrolyte levels, including calcium, and a CK would be helpful to obtain, but would be likely impossible in the early stages of a disaster setting. Because of the potential for mortality secondary to hyperkalaemia, if a level cannot be obtained, an electrocardiogram could substitute as a screening test if available. Some have advocated for administration of a preventive dose of oral sodium polystyrene sulfonate with 33 percent sorbitol in a 1:3 ratio to remove potassium via excretion in the faeces,[26] but given the lack of evidence and potential risks associated with this treatment in any setting, it cannot be recommended for treatment of crush injury at this time. If neither laboratory testing nor electrocardiogram analysis is available, empiric treatment for the possibility of hyperkalaemia should consist of intravenous normal saline alone.

Following extrication or after a patient presents with assault-related crush injury, some have argued that the resuscitation fluid should be changed to an isotonic saline-bicarbonate mixture to achieve a urine pH above 6.5 to encourage an alkaline diuresis and prevent further haeme-protein precipitation, tubular cast formation, and decrease the release of free iron from myoglobin, slowing the lipid peroxidation-free radical formation cascade.[23,28] Although there is theoretical benefit to this alkalinization of the urine, there is no evidence of improved clinical outcomes in direct comparison to saline-only diuresis.[20,22,29] Similarly, there is no evidence for one particular rate or formulation of fluid administration, however the two reviewed below here are based on the experiences of the RDRTF, and is varied based on the clinical condition of the patient and laboratory work-up. It is important to keep in mind the role that high volume normal saline infusion may play in furthering metabolic acidosis- by diluting the serum bicarbonate as well as by contributing negative chloride ions, thus generating a hyperchloraemic metabolic acidosis.[34] Should that arise, more bicarbonate may be added and less iso-

tonic saline can be infused, via switching the base fluid to half normal saline (0.45% normal saline) if the pH trends towards significant acidosis.

- One litre of isotonic saline, alternating with 1 L half isotonic saline with 50 mEq sodium bicarbonate or
- Two litres of isotonic saline, followed by 1 L half isotonic saline with 50 mEq sodium bicarbonate[31,32]

The risks associated with alkalinization deal primarily with calcium regulation. Hypocalcaemia may occur and patients can develop tetany, seizures, and/or arrhythmias.[28] Another beneficial side effect of alkalinization includes intracellular shift of potassium ions, which could help counteract hyperkalaemia, one of the most fatal and common components of crush syndrome.[11,32,33] For this reason, in addition to frequent monitoring of potassium levels, arterial pH should be followed and not exceed 7.5, and calcium and bicarbonate levels should guide continued therapy. Hypocalcaemia should be treated only if severe or if the patient is symptomatic, as deposited calcium in damaged muscles may mobilize later, resulting in hypercalcaemia. If bicarbonate levels reach over 31 mEq/litre,[32] or the urine pH does not increase after 4 to 6 h of infusion[34] the alkaline solutions should be discontinued, and infusion with isotonic or half isotonic saline should be continued.

Again, the rate and total volume administered is varied based on the fluid status of the patient, taking pulmonary oedema and urinary output into strong consideration, however in general the recommended rate is 500 mL/h for the first 24 h. After the first day of hospitalization, the rate can be titrated back, but should still amount to total infusion greater than the total urinary output, as large volumes may still be sequestered in damaged muscles. In well-supervised settings, up to 10–20 L of fluid has been given per day[22,25] however, a more conservative 6 L total per day is recommended in resource-limited settings such as natural disasters, in which close monitoring to ensure there is no development of fluid overload is often unavailable.[35]

A trial addition of 50 mL of 20% mannitol to each litre of fluids at a rate of 5 g per hour has been suggested if urinary flow is greater than 20 mL/h.[34] In theory, mannitol protects against tubular necrosis by encouraging an osmotic diuresis, decreasing the likelihood of obstructive cast formation and haeme-pigment induced damaged.[36] It may also act as a free radical scavenger[23,36] and extract sequestered water from injured extremities, preventing compartment syndrome.[34,37,38] However, no randomized controlled studies have been done to date to study the effects of mannitol in the clinical setting controlling for other variables in treatment, and the studies that have been done have mixed results.[20,22,27,30] At best, only a trend towards improved outcomes was found in patients with very high CK levels over 30,000.[27,39] Mannitol is contraindicated if after a trial period of its use to encourage a forced diuresis urine output of 200 mL/h or greater still cannot be established.[34,51] Of note, mannitol can be directly nephrotoxic on its own, particularly in the oliguric or anuric patient, in which it can lead to hyperosmolality secondary to loss of free water, hyperkalaemia, renal vasoconstriction and tubular toxicity if the dose exceeds 200 g per day or accumulates to more than 800 g, known as osmotic nephrosis.[34,37] Plasma osmolality should be measured during treatment with mannitol.

Target urine output is based on the urine volume needed to prohibit tubular cast obstruction, and is estimated to be between 200 and 300 mL/h.[32,34,52] If this is achieved, the aforementioned fluid regimens should be followed until myoglobinuria is gone, which can be followed by urine dipstick or visual inspection. In the case of oliguria or anuria, forced diuresis should be abandoned if signs of fluid overload exist, and instead 500–1000 mL of fluid in excess of the previous day's urine output can be administered. Although some sources recommend placement of central venous pressure (CVP) catheter to monitor CVP continuously as another marker for fluid overload, there is concern that CVP is an unreliable marker for intravascular fluid status and perhaps arterial pulse pressure variation can be monitored instead, if possible given available resources. [40,41]

Although loop diuretics have been used to encourage diuresis,[43] they have no proven role, do not improve outcomes,[43–46] and are not currently recommended. There has only been one study that found decreased progression to dialysis in the setting of oliguria and AKI in the setting of rhabdomyolysis secondary to crush syndrome.[46]

Once a patient has developed AKI and progressive oliguria or anuria, or other complications of crush syndrome discussed previously, the standard indications for initiation of haemodialysis apply, including hyperkalaemia, acidaemia, fluid overload, and uraemia. The many challenges to initiating dialysis in a disaster setting have been discussed at length elsewhere.[9,11,29,47,48]

Compartment syndrome is a known complication of crush syndrome when the extremities are involved, though it can be easily missed when occurring in the buttocks, as in a severe beating situation.[4] It is important to remember that cases rarely present with the typical paraesthesia, paralysis, pain out of proportion, pulselessness, and pallor, and index of suspicion must be high. Although a compartment pressure persistently over 30 mmHg confirms the diagnosis, the diagnosis is primarily a clinical one. Historically, fasciotomy has been performed routinely after the diagnosis was made, and should still be performed if in a controlled hospital setting and if discovered early. However, in disaster or resource-limited settings the risks and complications can outweigh benefits. In such situations, immediate and long-term outcomes are worse among patients in whom fasciotomy is performed, including wound infection, sepsis, and increased progression to amputation.[49,50] Conservative management is now recommended when compartment syndrome is encountered outside of the hospital setting, and fasciotomy should be avoided except when there is loss of the distal pulse and absence of direct arterial injury or hypotension has been excluded.[50]

Conflict of interest

The authors have no potential conflicts of interest to report.

African relevance

Most data on crush syndrome have been collected in the setting of large-scale natural disasters, where crushed extremities can be common, but other causes such as severe beatings are more common in Africa. Although data are limited, crush

syndrome should be considered in all cases of severe beating, in addition to traumatic crush injuries secondary to industrial or agricultural accident, road traffic accidents, or building collapse.

Summary and recommendations

- Crush syndrome should be considered in patients presenting with crush injury and oliguria.
- The combination of circulating myoglobin, its toxic side effects, and hypovolemia secondary to sequestering of fluid in injured extremities leads to acute tubular necrosis and acute kidney injury.
- In entrapped patients at high risk for crush injuries, aggressive intravenous fluid administration with isotonic saline at the rate of 10–15 mL/kg/h for 2 L total followed by a rate of 500 mL/h is recommended while patients are being extricated.
- Following extrication, initial rate of urine output should be documented and serum potassium, bicarbonate, phosphate, calcium, creatinine, and CK levels should be monitored. Because of the significant risk of hyperkalaemia, potassium and calcium should be monitored more frequently, and if impossible, consider obtaining an electrocardiogram to assess cardiac toxicity and empirically treating with potassium-binding substrate.
- Once hospitalized, hydration may be switched to an alkaline and 0.45% normal saline solution at a rate of 500 mL/h, though the benefit of this intervention is primarily theoretical and more randomized controlled trials need to be done to establish clinical efficacy.
- In patients with a minimal urine output > 20 mL/h, addition of a 20% mannitol solution to each litre of fluid at a rate of 5 g/h can be considered to encourage an osmotic diuresis. If after a trial period urine output has not improved to 200 mL/h, mannitol should be discontinued. The benefit of mannitol is primarily theoretical and more randomized controlled trials need to be done to establish true clinical efficacy over hydration with normal saline alone.
- No goal urine output has been definitively established, but 200–300 mL/h is the accepted target, as this rate has been shown to discourage cast obstruction of renal tubules.
- Caution should be taken to avoid fluid overload and pulmonary oedema, and CVP and arterial pulse pressure may be monitored to assess fluid status.
- Haemodialysis should be initiated for the usual indications.
- Fasciotomy for compartment syndrome in a disaster setting should be avoided except in the absence of a distal pulse, but is otherwise indicated when there is high clinical suspicion.

Appendix A. Short answer questions

1. In which of the following scenarios should crush syndrome be suspected?
   a. In a victim of a severe beating, with Creatine Kinase (CK) level of 10,000 U/L at triage
   b. In a victim of a severe beating, with affected body surface area (BSA) of 25%
   c. In a rural traffic accident victim whose leg was stuck beneath a truck for 4 h
   d. All of the above
   e. None of the above

2. When should fluid resuscitation of an entrapped victim begin, and with what kind of fluid?
   a. After extrication, with normal saline
   b. After extrication, with normal saline with sodium bicarbonate added
   c. Before extrication, with normal saline
   d. Before extrication, with normal saline with sodium bicarbonate added
   e. Before extrication, with lactated ringers solution

3. What are the major causes of death in crush syndrome patients?
   a. Cardiotoxicity from hyperkalaemia, hypovolemic shock, severe sepsis
   b. Cardiotoxicity from hypercalcaemia, hypovolemic shock, severe sepsis
   c. Cardiotoxicity from hypocalcaemia, hypovolemic shock, DIC
   d. Cardiotoxicity from hyperkalaemia, pulmonary oedema, severe sepsis
   e. Cardiotoxicity from hypocalcaemia, pulmonary oedema, DIC

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