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ERCİYES UNIVERSITY FACULTY OF MEDICINE
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KAYSERİ

REPERFUSION EFFECTS AFTER CRUSH SYNDROME

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Lecture Outline

- Causes
- Definitions
- Pathophysiology
- Clinical aspects
- Management

Causes of Mass Casualties with Crush Syndrome

- Building collapse
  - **Earthquakes**
  - Landslides
  - Bombings
  - Construction accidents
  - Heavy snow on roof
- Mine or trench collapse

1999 Marmara earthquake: -Death toll: 17,480

-Injured: 43,953

Major Mass Casualty Events with Reports of Crush Syndrome

- **Earthquakes:**
  - Tangshan, China 1976
  - Armenia 1988
  - Iran 1990 and 2003
  - Northridge, California 1994
  - Kobe, Japan 1995 ("Hanshin-Awaji")
  - Izmit, "Marmara" 1999)
  - Van, Turkey 2011
- **Terrorist bombings:**
  - Israel
  - Lebanon
  - Saudi Arabia

Crush Syndrome
Official Definitions

- From recent consensus meeting:
  - "A crush injury is a direct injury resulting from crush. Crush syndrome is the systemic manifestation of muscle cell damage resulting from pressure or crushing."
- Another:
  - Crush syndrome is the clinical condition caused by compression of muscle with subsequent rhabdomyolysis which can then cause the complications of electrolyte disturbances, fluid sequestration, & myoglobinuria.

Incidence of Crush Syndrome in Mass Casualty Events

- 10 to 60% of survivors extricated from collapsed buildings.
  - Up to half may develop renal failure
    - At least half of these require dialysis
- Typically about 20% of injured are hospitalized, and 5 to 20% of these have crush injury, and 0.5 to 1% end up needing dialysis.

Pathogenesis of Traumatic Rhabdomyolysis

- Pressure-induced increase in capillary permeability
  ⇒ muscle cell edema (compartment syndrome)

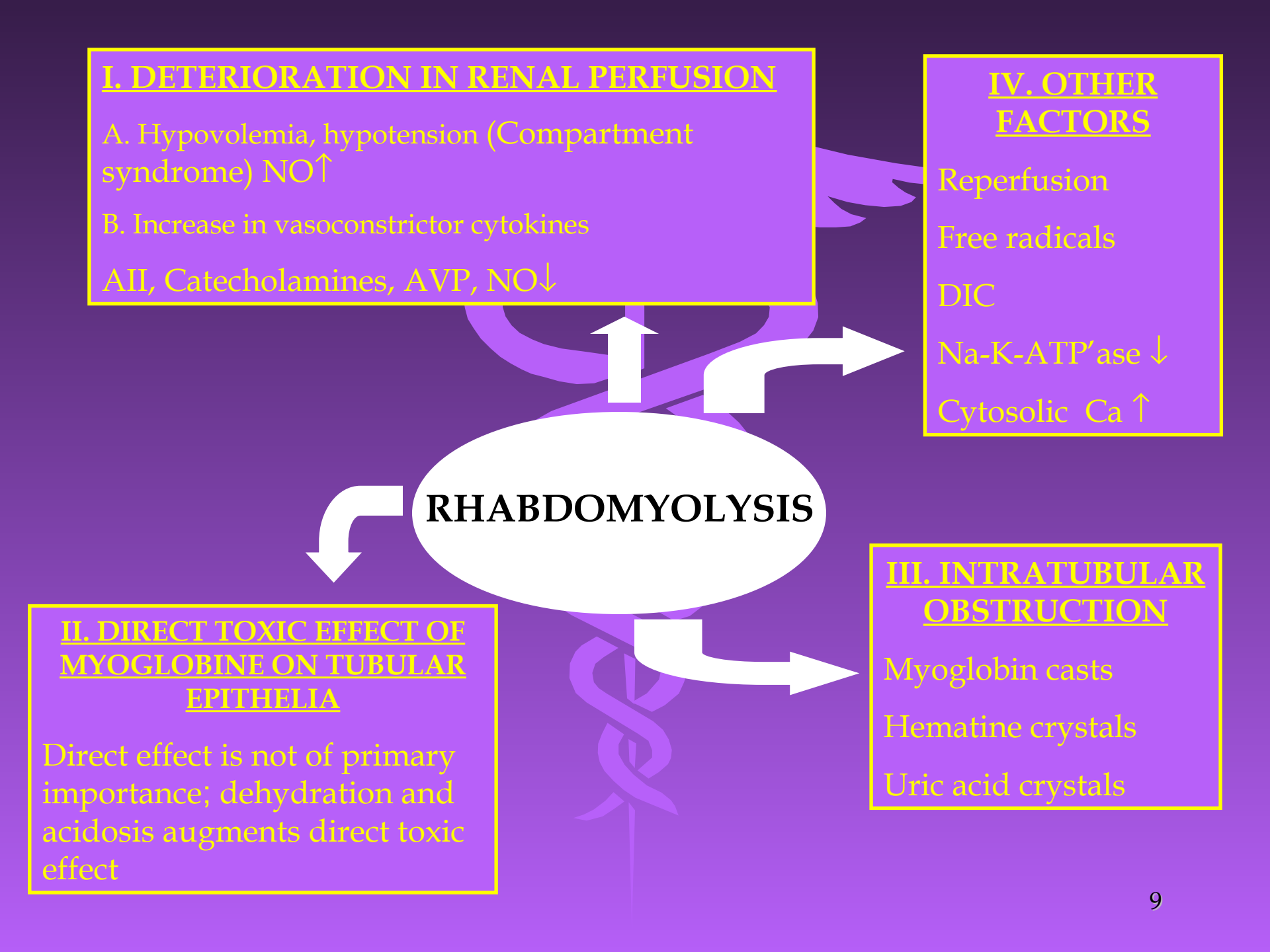
- Impaired muscle perfusion / reperfusion injury

Triggering event: Increase in cytosolic Ca^{++}

Activation of intracellular proteolytic enzymes

Rhabdomyolysis

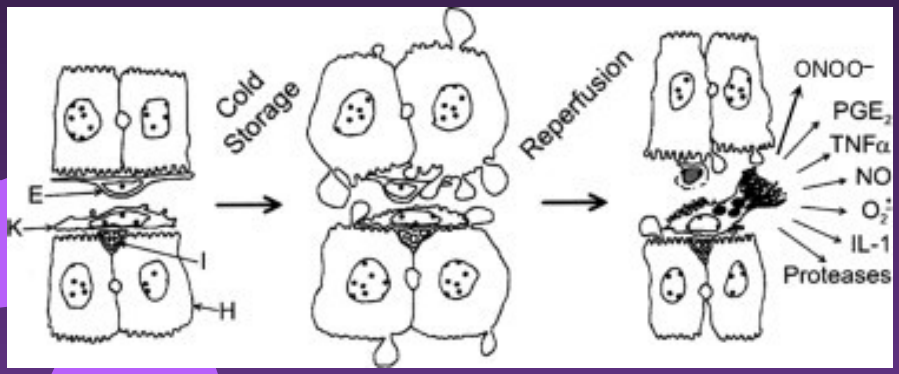
Better OS, Stein JH. NEJM, 1990; Zager Kidney Int, 1996


I. DETERIORATION IN RENAL PERFUSION
A. Hypovolemia, hypotension (Compartment syndrome) NO↑
B. Increase in vasoconstrictor cytokines
AII, Catecholamines, AVP, NO↓
IV. OTHER FACTORS
Reperfusion
Free radicals
DIC
Na-K-ATP'ase ↓
Cytosolic Ca ↑
RHABDOMYOLYSIS
II. DIRECT TOXIC EFFECT OF MYOGLOBINE ON TUBULAR EPITHELIA
Direct effect is not of primary importance; dehydration and acidosis augments direct toxic effect
III. INTRATUBULAR OBSTRUCTION
Myoglobin casts
Hematine crystals
Uric acid crystals

Pathophysiology of Crush Syndrome

- Not usually directly due to ischemia
- Main cause is stretch of the muscle sarcolemma
  - Sarcolemma permeability increases
  - Influx of sodium, water, & extracellular calcium into the sarcoplasm
    - Results in cellular swelling, increased intracellular calcium, disrupted cellular function & respiration, decreased ATP production, & subsequent myocyte death
- Lysed cells release inflammatory mediators; vasoconstriction and muscle swelling can then cause early or even days delayed compartment syndrome

Systemic Sequelae of Crush Injury



- Result from death of muscle cells and leak of intracellular metabolites into the systemic circulation ("**reperfusion injury**").
  - Superoxide anions (free radicals) then cause further membrane injury.
- May not manifest until just after entrapped part of body is extricated.

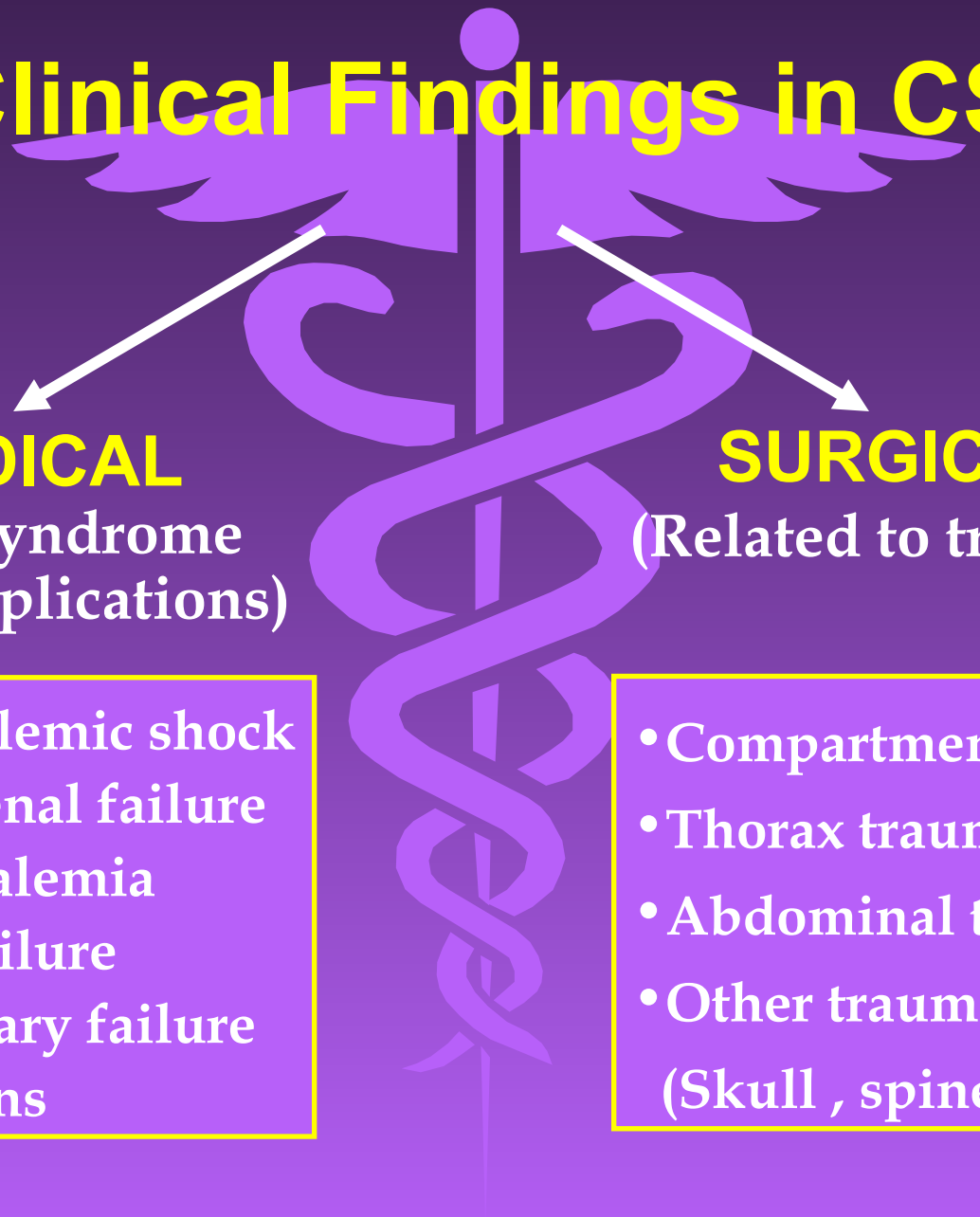
Metabolic Derangements from Crush Syndrome

- Hypovolemia (fluid sequestration in damaged muscle)
- Hyperkalemia
- Hypocalcemia (due to calcium deposition in muscle)
- Hyperphosphatemia
- Metabolic acidosis
- Myoglobinemia / Myoglobinuria

Effects of Myoglobinuria in Crush Syndrome

- Bywaters' studies showed that acidic urine is required for myoglobin to cause renal injury.
- At pH <5.6, myoglobin dissociates into its 2 components:
  - Globin (shown nontoxic if infused)
  - Ferrihemate (probably the toxic component)
- Myoglobin can precipitate (particularly with hypovolemia and acidosis) and directly obstructs renal tubular flow.
- Myoglobin is also directly toxic to the renal tubular cells.

Clinical Findings in CS



MEDICAL
(Crush syndrome and complications)

- Hypovolemic shock
- Acute renal failure
- Hyperkalemia
- Heart failure
- Pulmonary failure
- Infections

SURGICAL
(Related to trauma)

- Compartment syndrome
- Thorax trauma
- Abdominal trauma
- Other traumas (Skull , spine, pelvis)

Clinical Manifestations

- Range from asymptomatic to acute renal failure and DIC
- Triad: Muscle pain, weakness, dark urine
- Musculoskeletal signs
- General manifestations: Malaise, fever, tachycardia, nausea, vomiting
- Complications
  - -Early
  - -Late

Complications

Early

- Hypovolaemia
- Hyperkalaemia
- Hypocalcaemia
- Cardiac arrhythmias
- Cardiac arrest
- Compartment syndrome

Late (12-72 hrs)

- Acute renal failure
- DIC
- ARDS
- Sepsis

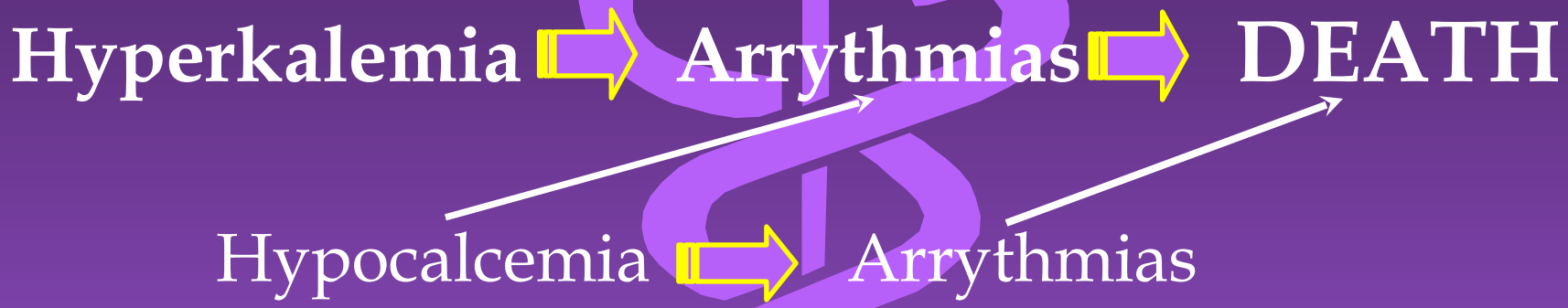
Most Important Rule in Renal Triage

Even mildly injured victims carry the risk of crush syndrome. Rescued patients should be checked for their urinary output with or without using “Foley catheters”, cases with dark and low volume of urine pose a greater risk for developing acute renal failure and should be transferred to larger medical centers with nephrology departments.

Diagnostic Testing in Patients with Crush Injury

- ECG should be seen as early as possible to look for signs of hyperkalemia
- Handheld fingerstick blood analyzer may be useful in the field to identify hyperkalemia early
- Routine labwork to obtain:
  - CBC, platelets, type and screen, electrolyte panel, BUN, creatinine, CPK, liver panel, urinalysis
- Optional labwork: ABG, myoglobin, PT, PTT
- Chest X-ray
- Other radiographs, computed tomography, etc. to evaluate for other injuries

Hyperkalemia-Death Relationship in Earthquake-Related Death Cases



- **"Most frequent cause of earthquake related deaths is direct effect of trauma."**
- **On the other hand most rescued patients die because of hyperkalemia.**

Collins, 1991; Better, 1993; Noji, 1992; Oda, 1997

Medical Interventions at the Disaster Field

- Rescued victims who are seemingly well, can get worse or even die as soon as extrication

RESCUE DEATH

- Severe metabolic acidosis
- Fatal hyperkalemia

- Rescue teams must include health care providers

Noji. Crit Care Clin 1992

Medical Interventions at the Disaster Field

-Apply facemask to protect from dust inhalation

-Oxygen (if no risk of fire at the scene)

-Check the amount of urine (Urination, Foley).

-Fluid administration in case of hypovolemia; follow urinary output.

-If no urinary output, fluid output + 1000 -1500 mL.

-Never use potassium containing fluids empirically

Emergent Treatment of Hyperkalemia from Crush Syndrome

- Normal saline IV fluid bolus
- IV $NaHCO_3$ 50 to 100 meq
- Aerosolized albuterol (2.5 mg in 3 cc)
- Less effective or practical:
  - IV dextrose (25 grams) & insulin (5 units IV)
  - PO or PR kayexalate
- Note that IV calcium is controversial (as it may just worsen intramuscular hypercalcemia)
- Emergent hemodialysis may be needed

Medical Interventions at the Disaster Field

Early Fluid Administration is of Vital Importance !

(1 L / hr saline)

Better and Stein. NEJM 1990

Main Treatment for Crush Syndrome: IV Fluid Resuscitation

- Normal saline (0.9%) preferred
  - (Lactated Ringers contains 4 meq/L of potassium, & so may worsen hyperkalemia, & also has calcium)
- If started early, may prevent later development of renal failure
- Best if IV fluids can be started even prior to extrication

Recommended IV Fluid Infusion Rates for Crush Syndrome

- 1 to 1.5 liters per hour for young adults
- 20 cc per kg per hour for children
- 10 cc per kg per hour for elderly
- Insert foley catheter as early as possible:
  - Target urine output should be >50 cc per hour for adults, and >2 cc per kg per hour for children
  - Some references advocate 150 to 200 cc per hour target in early phase

Use of IV Bicarbonate for Crush Syndrome

- Goal is to have alkaline urine (check with pH paper)
- Can bolus supplement the normal saline with 50 meq (1 amp) doses
  - Up to 300 meq per 24 hours may be needed
- Or add 3 ampuls (150 meq) to one liter D5W and infuse as first or second IV bolus

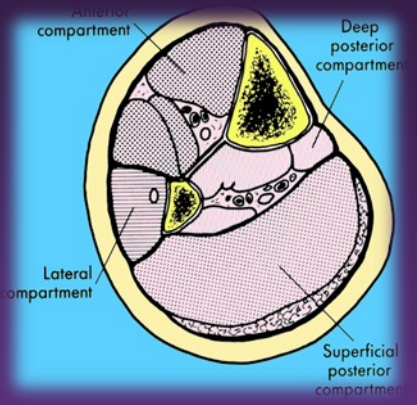
Use of Mannitol for Crush Syndrome

- May help eliminate myoglobin from the kidney & prevent renal failure
- May be useful to initiate diuresis in a patient who has adequate normal saline on board but whose urine output is still <2 cc per kg per hour, or if adequate urine output is still not achieved 4 hours after treatment started
- Mannitol 20% solution 0.25 grams per kg IV over 10 to 30 minutes
- Maximum dose: 2 grams per kg per day (or 200 grams per day)

Contraindications to Mannitol

- Established anuric renal failure
- Severe congestive heart failure
  - These patients may require pressors such as dopamine in order to tolerate the fluid load required for treatment, or may need early dialysis

Compartment Syndrome in Crush Injury



- Normal muscle compartment pressure is <15 mmHg
- Pressure >30 mmHg produces muscle ischemia, so fasciotomy indicated if pressure is persistent above this
- Irreversible muscle damage occurs after 6 hours, & irreversible nerve damage may occur after 4 hours of ischemia
- If the patient is hypotensive, they can have significant ischemia at lower compartment pressures

Additional Treatments for Crush Injury

- Don't forget **oxygen** suplementation (even if the patient is not hypoxemic, O_2 may help ischemic muscle)
- Don't forget **pain medications**
- Address **tetanus immunization** status
- **Acetazolamide** (250 mg PO tid) may help excrete bicarbonate in the urine
- **Furosemide** may initiate diuresis but not favored since it makes acid urine

Free Radical Scavengers and Antioxidants

- The magnitude of muscle necrosis caused by ischemia-reperfusion injury has been reduced in experimental models by the administration of free-radical scavengers.
- Pentoxyphylline is a xanthine derivative used to improve microvascular blood flow. In addition, it acts to decrease neutrophil adhesion and cytokine release.
- Vitamin E, vitamin C, lazaroids (21-aminosteroids) and minerals such as zinc, manganese and selenium all have antioxidant activity and may have a role in the treatment of the patient with rhabdomyolysis.

Hori et al. BMC Musculoskeletal Disorders 2013, 14:113
http://www.biomedcentral.com/1471-2474/14/113

BMC Musculoskeletal Disorders

RESEARCH ARTICLE Open Access

Protective effect of edaravone for tourniquet-induced ischemia-reperfusion injury on skeletal muscle in murine hindlimb

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Abstract

Background: Studies have shown that ischemia-reperfusion (I/R) produces free radicals leading to lipid peroxidation and damage to skeletal muscle. The purposes of this study were 1) to assess the histological findings of gastrocnemius muscle (GC) and tibialis anterior muscle (TA) in I/R injury model mice, 2) to histologically analyze whether a single pretreatment of edaravone inhibits I/R injury to skeletal muscle in murine models and 3) to evaluate the effect of oxidative stress on these muscles.

Methods: C57BL6 mice were divided in two groups, with one group receiving 3 mg/kg intraperitoneal injections of edaravone (I/R + Ed group) and the other group receiving an identical amount of saline (I/R group) 30 minutes before ischemia. Edaravone (3-methy-1-pheny1-2-pyrazolin-5-one) is a potent and novel synthetic scavenger of free radicals. This drug inhibits both nonenzymatic lipid peroxidation and the lipoxygenase pathway, in addition to having potent antioxidant effects against ischemia reperfusion. The duration of the ischemia was 1.5 hours, with reperfusion at either 24 or 72 hours (3 days). Specimens of gastrocnemius (GC) and anterior tibialis (TA) were removed for histological evaluation and biochemical analysis.

Results: This model of I/R injury was highly reproducible in histologic muscle damage. In the histologic damage score, the mean muscle fibers and inflammatory cell infiltration in the I/R + Ed group were significantly less than the corresponding values of observed in the I/R group. Thus, pretreatment with edaravone was observed to have a protective effect on muscle damage after a period of I/R in mice. In addition, the mean muscle injury score in the I/R + Ed group was also significantly less than the I/R group. In the I/R + Ed group, the mean malondialdehyde (MDA) level was lower than in the I/R group and western-blotting revealed that edaravone pretreatment decreased the level of inducible nitric oxide synthase (iNOS) expression.

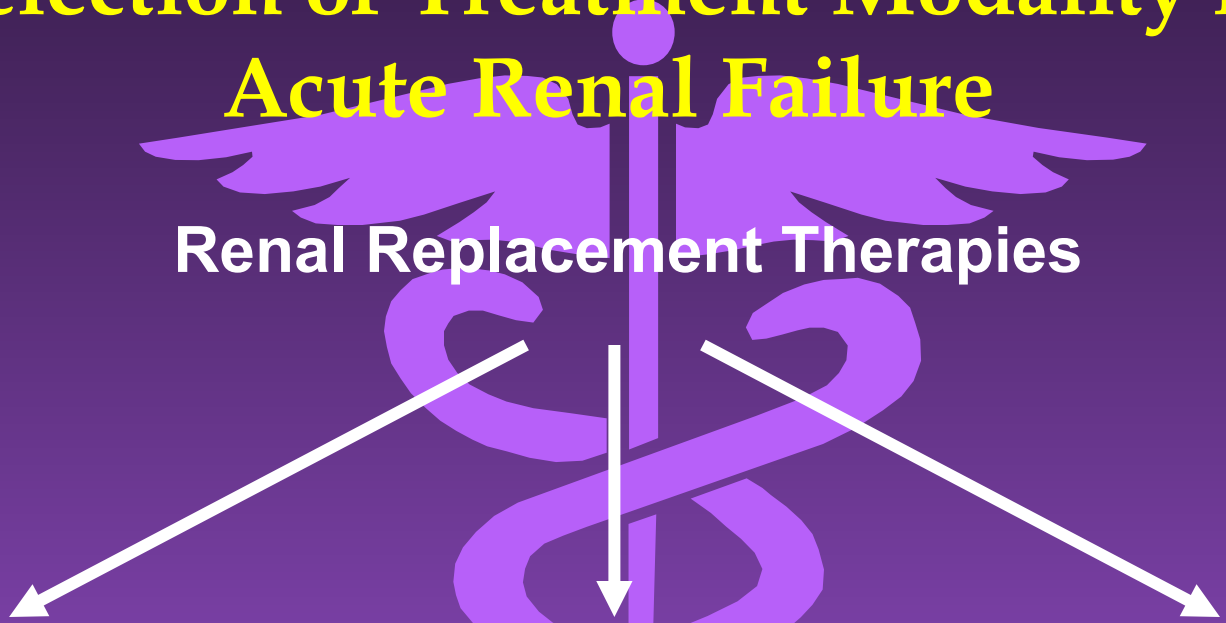
Conclusions: Edaravone was found to have a protective effect against I/R injury by directly inhibiting lipid peroxidation of the myocyte by free radicals in skeletal muscles and may also reduce the secondary edema and inflammatory infiltration incidence of oxidative stress on tissue.

Keywords: Ischemia-reperfusion injury, Skeletal muscle, Free radical scavenger, Edaravone, iNOS

Indications for Dialysis

- BUN >100 mg/dL, Creatinine >8 mg/dL
- Potassium >7 mEq/L
- Hyponatremia
- Blood pH < 7.1, $sHCO_3$ <10 mEq/L
- Oliguria, anuria
- Hypervolemia
- Uremic symptoms: Pericarditis, uremic lethargy, nausea, vomiting
- Clinical judgement is the most important criterium

Selection of Treatment Modality in Acute Renal Failure



Peritoneal Dialysis

- Rarely used
- e.c. If no vascular access
- May be used more oftenly in selected cases

Intermittent Dialysis

- Hemodialysis mostly
- Isolated ARF

Continious Hemodialysis

- Hemofiltration mostly.
- Complicated case, multiorgan failure

Conclusion–I

- Rescue operation should continue for 5 days
- Even the slightly injured are prone to developing crush syndrome
- Empirical antihyperkalemic treatment
- ECG is the “first thing to do” on admission

Conclusion–II

- CVP measurement is reliable in the beginning and also during the maintenance fluid treatment

- Fasciotomy is a risk factor for septicemia, should be done only if necessary

- Patients from nearest location should be seen first!

- Continuous "Disaster medicine training" for medical personel

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THANK YOU……

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