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Mini Review

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Can Glucose-Insulin-Potassium Prevent Skeletal Muscle Ischemia-Reperfusion Injury?

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Extremity injuries cost an estimated $80 billion a year [1] and exsanguination is a key factor in fatalities following both civilian and military trauma [2,3]. Tourniquets, the primary prevention against extremity exsanguination, and an often used tool in emergent and elective surgeries, are not benign [4]-skeletal muscle apoptosis and necrosis following tourniquet use are common and can lead to limb paralysis, amputation, and even death if rhabdomyolysis and kidney failure occur [5-7]. While muscle does not respond well to ischemia, reperfusion is what causes the most significant damage following tourniquet use in what has been termed the ischemia-reperfusion injury [8,9].

Globally, the deadliest ischemia-reperfusion injury is a myocardial infarctio [10]. Preventing muscle damage from myocardial infarctions, through preventing the consequences of the ischemia-reperfusion injury, has been an active area of research in cardiology since heart attacks were described in 1912 [11]. In orthopedics, the prevention of ischemia-reperfusion injury in skeletal muscle has not been as well studied, and to date, no definitive treatments exist [8,9].

One unique treatment in the prevention of myocardial ischemia-reperfusion injury following myocardial infarction is glucose-insulin-potassium (GIK). Since first being tested in the 1960s [12-16], several studies have shown that GIK may reduce myocardial Ischemia-reperfusion injury by stabilizing cell membranes [17,18] increasing glycogen content and adenosine triphosphate (ATP) [19,20] reducing free fatty acids (FFA) and reactive oxygen species (ROS) [21,22], and increasing growth hormone/factor production [23-26].

Although several clinical studies have been performed on GIK for cardiac muscle, the recommendations on its use remain mixed. Most large analyses report that it reduces mortality [27-33], while one found no effect [34], and another found higher mortality with its use [35]. Despite the generally positive results in the cardiac literature, only one study has looked at GIK in skeletal muscle, finding that it reduces glycogen depletion during fasting. However, these authors did not comment on its effect on skeletal muscle ischemia-reperfusion injury [36].

Similar to cardiac muscle, skeletal muscle ischemia-reperfusion injury occurs through ischemic ATP depletion and reperfusion-mediated ROS production [37]. ATP depletion destabilizes the electrochemical gradient of the sarcolemma, leading to increased intracellular proteolytic enzymes. Excess ROS increases sarcolemma permeability, and similarly increases intracellular proteolytic enzymes [38]. These enzymes degrade the muscle cell, releasing large quantities of muscle breakdown products including myoglobin, CK, and lactate dehydrogenase that can be nephrotoxic [37]. Since GIK can mitigate these processes in cardiac muscle [19-22], it may have some utility in reducing skeletal muscle ischemia-reperfusion injury.

Skeletal muscle ischemia-reperfusion injury occurs secondary to several pathologic processes. Traumatic causes, both blunt and sharp, can lead to compartment syndrome, vascular injury, and may require tourniquet use for bleeding control. Iatrogenic causes such as the elective use of tourniquets in upper and lower extremity surgery, vessel re-anastomosis or bypass causing reperfusion, and anticoagulation-related compartment syndrome are also relevant. While these causes differ in frequency and severity, they share a similar pathophysiological pathway that may potentially benefit from GIK. Thus, GIK may play a role in reducing traumatic and

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iatrogenic morbidity and mortality following musculoskeletal injury.

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