Poloxamer-188 Reduces Electroporation-Induced Skeletal Muscle Edema

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Introduction

Electric fields of the magnitude and duration likely to occur in electrical injury result in skeletal muscle electroporation and subsequent tissue necrosis. MRI may be useful for noninvasive assessment of electrical shock effects on living tissue and on the response of tissue to therapy. It has been reported that Poloxamer 188 (P188) is able to seal damaged cell membranes [1]. Using a previously described rat hind limb model of electrical injury [2], in this study we employ MRI to demonstrate that intravenously administered P188 arrests muscle tissue edema caused by electrical shock.

Methods

Fully anesthetized and medically stabilized female Sprague-Dawley rats (300 ± 20 g) were subjected to 12 electrical rectangular pulses of 2kV and ~2A amplitude with duration of 4 ms. There was a 10-second separation period between consecutive shocks to allow thermal relaxation. Animals received either P188 or Lactated Ringer's Injection (control) intravenously at approximately 60 minutes after electrical shock (after the first series of images were collected).

Proton magnetic resonance images were recorded using a 4.7-Tesla Bruker scanner (200 MHz). A Multi Slice Multi Echo (MSME) spin echo sequence was used to obtain T_2-weighted images (Fig. 1). Ten slices were prescribed, 2mm thick, and separated by 2mm, over the entire mid-thigh region of the leg. For each slice, images at 10 different TEs ranging from 10ms to 100ms, and with a TR = 2000ms, were collected. Images with resolutions of 128x128 pixels were obtained on a field of view 5cm x 5cm. Imaging began at approximately 60 minutes after electrical shock and continued until 3 hours post-shock.

The signal intensities at different TE times were used to fit an exponential decay and measure the T_2 value in each voxel. Voxels with T_2 values > 80 ms were considered edematous. The volume of edema was measured for each of the 10 slices through the entire leg of the rat. This was done at two separate times corresponding to approximately 60 minutes post shock (t1) and approximately 180 minutes post shock (t2) for each rat. The volume of edema for each of the 10 slices was summed at each time t1 and t2 to estimate the *total volume of edema* for each rat at the two time-points. These two values were used to determine the percent increase of total volume of edema between the two time-points:

(Total volume of edema $_{t2}$ - Total volume of edema $_{t1}$) / Total volume of edema $_{t1}$ = % Increase in total volume of edema from time t1 to time t2.

Results

There were noticeable increases of the volume of edema with time for electrically injured limbs (Fig. 1). Control-treated rats averaged a 58.0% (± 6.59% S.D.) increase in total volume of edema from time-point t1 to t2. The total volume of edema for P188-treated rats increased by 46.6% (± 2.96% S.D.) between t1 and t2 (Fig. 2). In legs where no electroporation occurred, no change in T_2 occurred (data not shown).

Discussion

Disruption of the plasma membrane due to electrical current leads to the release of intracellular contents into the outer environment and an osmotic water inflow. These effects trigger edema, which raises the local hydration level over its physiological value. We used MRI to monitor the change of the hydration level in the muscle tissue. We treated the injured muscles with P188 and observed that it helped to arrest edema. The method used was shown to be effective not only in characterizing the degree of injury resulting from electrical shock, but also in monitoring the effects that treatments may have on the injury.

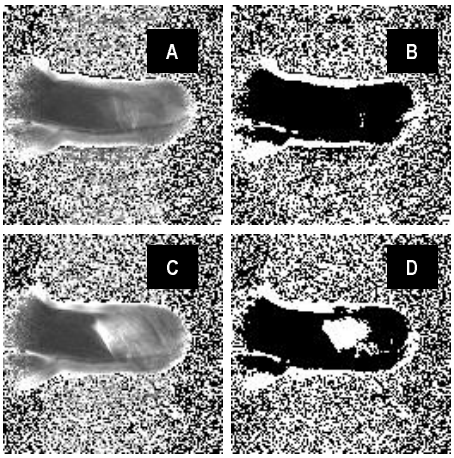

Figure 1: T_2-weighted images corresponding to time-points t1 (A) and t2 (C). T_2-weighted images were used to determine T_2 values in the leg at t1 and t2. Voxels with T_2 values > 80 ms were considered injured, and are shown with high intensities in (B) and (D), for time-points t1 and t2 respectively.

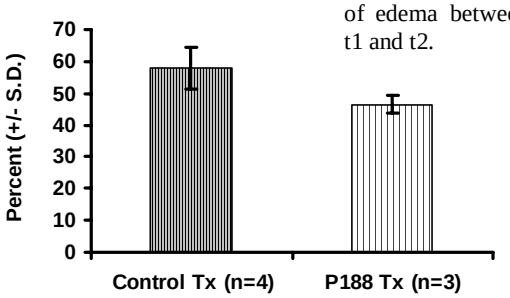

Figure 2: Mean % increase in total volume of edema between times t1 and t2.

References

1. Lee RC, et al. Ann N Y Acad Sci. 888:266-73, 1999.
2. Block TA, et al. J Burn Care Rehabil. 16(6): 581-8.

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