Poloxamer 188 Protects against Ischemia-Reperfusion Injury in a Murine Hind-Limb Model

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Background: Ischemia-reperfusion injury can activate pathways generating reactive oxygen species, which can injure cells by creating holes in the cell membranes. Copolymer surfactants such as poloxamer 188 are capable of sealing defects in cell membranes. The authors postulated that a single-dose administration of poloxamer 188 would decrease skeletal myocyte injury and mortality following ischemia-reperfusion injury.

Methods: Mice underwent normothermic hind-limb ischemia for 2 hours. Animals were treated with 150 μl of poloxamer 188 or dextran at three time points: (1) 10 minutes before ischemia; (2) 10 minutes before reperfusion; and (3) 2 or 4 hours after reperfusion. After 24 hours of reperfusion, tissues were analyzed for myocyte injury (histology) and metabolic dysfunction (muscle adenosine 5′-triphosphate). Additional groups of mice were followed for 7 days to assess mortality.

Results: When poloxamer 188 treatment was administered 10 minutes before ischemia, injury was reduced by 84 percent, from 50 percent injury in the dextran group to 8 percent injury in the poloxamer 188 group ($p < 0.001$). When administered 10 minutes before reperfusion, poloxamer 188 animals demonstrated a 60 percent reduction in injury compared with dextran controls (12 percent versus 29 percent). Treatment at 2 hours, but not at 4 hours, postinjury prevented substantial myocyte injury. Preservation of muscle adenosine 5′-triphosphate paralleled the decrease in myocyte injury in poloxamer 188–treated animals. Poloxamer 188 treatment significantly reduced mortality following injury (10 minutes before, 75 percent versus 25 percent survival, $p = 0.0077$; 2 hours after, 50 percent versus 8 percent survival, $p = 0.032$).

Conclusion: Poloxamer 188 administered to animals decreased myocyte injury, preserved tissue adenosine 5′-triphosphate levels, and improved survival following hind-limb ischemia-reperfusion injury. (*Plast. Reconstr. Surg.* 125: 1651, 2010.)

Managing oxygen metabolism is essential for tissue health and successful recovery from disease. Under normal physiologic conditions, many cellular mechanisms exist to regulate oxygen chemistry. However, in disease or following transient disruption of oxygen delivery, oxygen regulatory control is lost, resulting in reperfusion injury. Reperfusion triggers a cascade of acute inflammatory events, leading to cellular death and resulting in tissue dysfunction and necrosis.[1] Ischemia-reperfusion injury is modulated by complex inflammatory and immunologic signaling pathways that have not been fully elucidated. Clinically, ischemia-reperfusion injury is an important factor limiting what can be accomplished in the fields of trauma,[2] vascular,[3,4] transplantation,[5,6] and plastic surgery.[7,8]

There are many pathways activated in ischemia-reperfusion injury. A well-described example, and one of the earliest events in the process, is related to the binding of circulating natural antibodies and the activation of complement.[9]

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First described in myocardial reperfusion by Hill and Ward,[10] complement activation was shown to involve the release of C3a and C5a anaphylatoxins that induce degranulation of mast cells with release of histamine and other chemical mediators. The final common pathway of ischemia-reperfusion injury is edema, attraction of activated leukocytes, and the formation of membrane-attack complexes,[11] all of which lead to disruption of cell membranes and resulting cell death.

The structural integrity of the cell membrane lipid bilayer is critical for cellular viability. To maintain cell membrane integrity, cells possess membrane repair mechanisms that allow recovery from routine day-to-day trauma.[12] Preconditioning up-regulates these paths to allow greater injury tolerance. However, when normal membrane repair mechanisms are exhausted, use of membrane-sealing polymers can be effective in preserving cell viability if administered before extensive molecular degradation has occurred.[13] One class of membrane-sealing polymers are poloxamers [pol(y)ox(y)mers], which are biocompatible, multiblock, surfactant copolymers that have been used as pharmaceutical excipients in blood banking for decades.[14] Poloxamer surfactants have important "surface-active" properties that adsorb to damaged cell membranes, resulting in a shift of water interfacial tension in the direction that favors membrane sealing. One member of this chemical class is poloxamer 188, which is a triblock copolymer of poly(oxyethylene) and poly(oxypropylene) and abbreviated POE-POP-POE. Poloxamer 188 has an average molecular weight of approximately 8400 kDa. The poly(oxyethylene) chains are hydrophilic because of their short carbon unit between oxygen bridges, whereas the poly(oxypropylene) center is hydrophobic because of the larger propylene unit. In addition to their membrane-sealing properties, poloxamers are oxygen free radical scavengers,[12] which adds to their value as a trauma therapeutic. Dextran (10 kDa), a purely hydrophilic polymer, was chosen as a control treatment because its molecular weight is similar to poloxamer 188, it tends to adhere to cell surfaces, and has historically been used as a control for poloxamer 188 effects.[15–17]

Poloxamer 188 has been shown to be effective in preserving cell membrane structure and viability following electroporation, high-dose ionizing irradiation, and superoxide injuries.[13,15,18] This protection is thought to be attributable to poloxamer 188 inserting into cell membrane defects and "sealing" the cell, thereby preventing loss of transmembrane ion gradients and intracellular proteins. The physical chemistry of the membrane sealing has been well demonstrated using in vitro lipid monolayer models. Poloxamer 188 was shown to insert into the lipid monolayer when surface tension decreased after membrane poration, and was squeezed out when the membrane integrity was restored.[19]

The purpose of this study was to determine whether a single dose of the nonionic synthetic surfactant poloxamer 188 administered to achieve a maximal subcritical micelle concentration in the extracellular fluid compartment can mitigate skeletal muscle injury caused by 2 hours of ischemia and 24 hours of reperfusion. Parameters of muscle injury include histologic evidence of myocyte fiber damage and depletion of adenosine 5′-triphosphate (an index of metabolic dysfunction). The extent of ischemic skeletal muscle necrosis is known to correlate with the extent of adenosine 5′-triphosphate depletion.[20] In addition, a series of experiments were extended out to 7 days of reperfusion to determine whether administration of poloxamer 188 influenced mortality following hind-limb ischemia reperfusion.

MATERIALS AND METHODS

Animal Care Protocol

Animal care and experimental procedures complied with "Principles of Laboratory Animal Care" (*Guide for the Care and Use of Laboratory Animals*, National Institutes of Health Publication no. 86-23, revised 1996) and were approved by the Institutional Animal Care and Use Committee of the Massachusetts General Hospital. C57BL6 mice (22 to 28 g; Jackson Laboratory, Bar Harbor, Me.) were initially anesthetized by intraperitoneal administration of sodium pentobarbital (60 to 90 mg/kg in a bolus of 0.4 ml normal saline). During the preischemic, ischemic, and initial 3 hours of reperfusion intervals, animals were placed on a heated water blanket to maintain body temperature at 37°C. For the 24-hour reperfusion experiments, mice were returned to their cages in the vivarium and allowed access to water and chow ad libitum. Mice were kept in a 12 hour light-dark cycle, and the room temperature was kept constant between 24° and 26°C.

Poloxamer 188 Treatment

Control mice received 150 μl of normal saline plus dextran (6.0 mM, 8 kDa; Sigma-Aldrich Corp., St. Louis, Mo.). Treated mice received 150 μl of normal saline plus poloxamer 188 (6.0 mM Pluronic F68; Sigma-Aldrich). Both treatments

were administered intravenously by means of tail vein injection. Based on extracellular fluid volume estimated at 24 percent total body weight, the poloxamer 188–treated mice received a dose such that the final concentration of poloxamer 188 in the blood was 0.15 mM, which is below critical micelle concentration. This is equivalent to a dose of 300 mg/kg. For the dose-response experiment, animals received either 150 μl of normal saline plus poloxamer 188, 6.0 mM; 150 μl of normal saline plus poloxamer 188, 12.0 mM; 150 μl of normal saline plus poloxamer 188, 3.0 mM; or 150 μl of normal saline plus poloxamer 188, 0.6 mM; to give final blood concentrations of 0.15, 0.3, 0.075, and 0.015 mM, respectively. Treatment was administered at one of four different time points: 10 minutes before ischemia, 10 minutes before reperfusion, 2 hours after reperfusion beginning, or 4 hours after reperfusion beginning.

In Vivo Limb Ischemia

Thirty minutes after the induction of anesthesia, a McGivney ligator applicator was used to apply an orthodontic rubber band for 2 hours of hind-limb ischemia followed by reperfusion.[21] The rubber band was placed above the greater trochanter bilaterally. Mice remained anesthetized throughout the duration of ischemia with supplemental anesthesia (sodium pentobarbital) as needed. Animals were allowed to recover from anesthesia after the ischemic period and allowed to live for either 3 hours, 6 hours, 24 hours, or 7 days of total reperfusion, at which time the animals were euthanized and tissues harvested.

Limbs from mice that underwent hind-limb ischemia and reperfusion were fixed in 4% paraformaldehyde for 8 hours. The gastrocnemius muscle from each limb was dissected free from the surrounding tissues, rinsed in Dulbecco's phosphate-buffered saline for 1 hour, and dehydrated serially in graded acetone. Each sample was embedded using JB-4 Embedding Kit (Polysciences, Inc., Warrington, Pa.) under vacuum conditions. The muscles were cut in cross-section at 2-μm thickness using a motorized microtome (Leica Microsystems, Inc., Bannockburn, Ill.), and sections were stained with Masson trichrome.

Stained slides were examined under light microscopy at 200× magnification (Nikon E600 Upright Microscope; Nikon, Tokyo, Japan). Images were acquired using a SPOT Insight Digital Camera (Diagnostic Instruments, Sterling Heights, Mich.) from the entire cross-section of the muscle specimen, and each image was assigned a serial number. Blinded observers then examined the images of each muscle in random order using a random number generator (www.random.org) until a minimum of 600 muscle fibers per section had been scored.

Muscle fibers were scored as uninjured or injured based on the morphology of the individual fibers. Uninjured fibers were characterized as having well-defined borders, uniform texture and colors, easily identifiable satellite cells, and pericellular nuclei. Injured fibers had interrupted or ragged borders, inconsistent texture and color, breaks in the cytoplasm, and nuclei detachment.[22]

Tissue Adenosine 5′-Triphosphate Levels

Samples of frozen muscle (200 mg) were homogenized with a Polytron homogenizer (Brinkmann Instruments, Inc., Westbury, N.Y.) in a test tube containing 10% trichloroacetic acid. Samples were centrifuged for 10 minutes at 10,000 *g*, and supernatants were diluted in Dulbecco's phosphate-buffered saline. The adenosine 5′-triphosphate levels were measured using ATPlite Luminescence Assay according to the manufacturer's protocol (PerkinElmer Life, Waltham, Mass.). Top counts were read using 1450 MicroBeta plate reader (PerkinElmer Life). Concentrations of the unknowns were extrapolated off the standard curve and expressed as nanograms of adenosine 5′-triphosphate per milligram of tissue mass.

Mortality

Animals were allowed to awaken following bilateral in vivo limb ischemia applied as described previously. They were allowed free access to chow and water and were followed for 7 days or until death. Kaplan-Meier survival curves were plotted and curves were compared.

Statistical Analysis

Statistical analysis was performed with Instat (GraphPad Software, Inc., San Diego, Calif.). Data were expressed as means ± SEM. Comparisons were made using analysis of variance and *t* test. A value of $p < 0.05$ was considered significant. Post hoc comparison was performed using Tukey-Kramer parametric analysis. Kaplan-Meier survival curves were compared using the log-rank test. Data are distributed normally as analyzed using the D'Agostino-Pearson omnibus normality test and are suitable for parametric analyses.

RESULTS

Muscle Fiber Injury

Preischemia Treatment

After 24 hours of reperfusion, there was a statistically significant, six-fold decrease in the amount of cell injury in animals treated 10 minutes before ischemia with normal saline plus poloxamer 188 [8 percent ($n = 15$)] compared with control animals [50 percent ($n = 8$); $p < 0.001$] (Fig. 1). Representative photomicrographs of injured and uninjured myocytes are presented in Figure 2.

Prereperfusion Treatment

When administered 10 minutes before the release of the bilateral hind-limb tourniquets and the commencement of the 24-hour reperfusion period, normal saline plus poloxamer 188 [$n = 7$ (12 percent)] provided a significant, more than two-fold difference in percentage myocyte injury as compared with normal saline plus dextran control [$n = 6$ (29 percent); $p < 0.001$] (Fig. 2).

Postreperfusion Treatment

When animals were treated 2 hours after the release of the bilateral hind-limb tourniquets, the histologic injury score was 15 percent in the normal saline plus poloxamer 188 group ($n = 14$) compared with 40 percent in the normal saline plus dextran group ($n = 10$; $p < 0.05$) (Fig. 1). In contrast, when poloxamer 188 was administered 4 hours after reperfusion ($n = 6$), myocyte injury at 24 hours of reperfusion was identical to that of dextran controls ($n = 7$).

Dose Response to Poloxamer 188 Administration

Normal saline plus poloxamer 188 given before the initiation of reperfusion demonstrated a classic sigmoidal dose-response curve, with the optimal minimum dose seen to be 300 mg/kg (Fig. 3) ($n = 8$ for each group).

Effect of Poloxamer 188 on Skeletal Muscle Adenosine 5′-Triphosphate

When treated 10 minutes before reperfusion, animals that received both normal saline plus poloxamer 188 ($n = 8$) and normal saline plus dextran ($n = 9$) showed a significant decrease in cellular adenosine 5′-triphosphate levels compared with sham animals ($n = 9$). After 3, 6, and 24 hours of reperfusion, animals treated with normal saline plus poloxamer 188 had significantly greater levels of adenosine 5′-triphosphate than those treated with normal saline plus dextran (6.23 ng/mg versus 2.53 ng/mg at 3 hours, 6.15 ng/mg versus 2.83 ng/mg at 6 hours, and 5.55 ng/mg versus 2.41 ng/mg at 24 hours; $p < 0.05$) (Fig. 4).

When treated 2 hours after reperfusion, animals that received normal saline plus poloxamer 188 ($n = 8$) had significantly greater levels of adenosine 5′-triphosphate than control animals

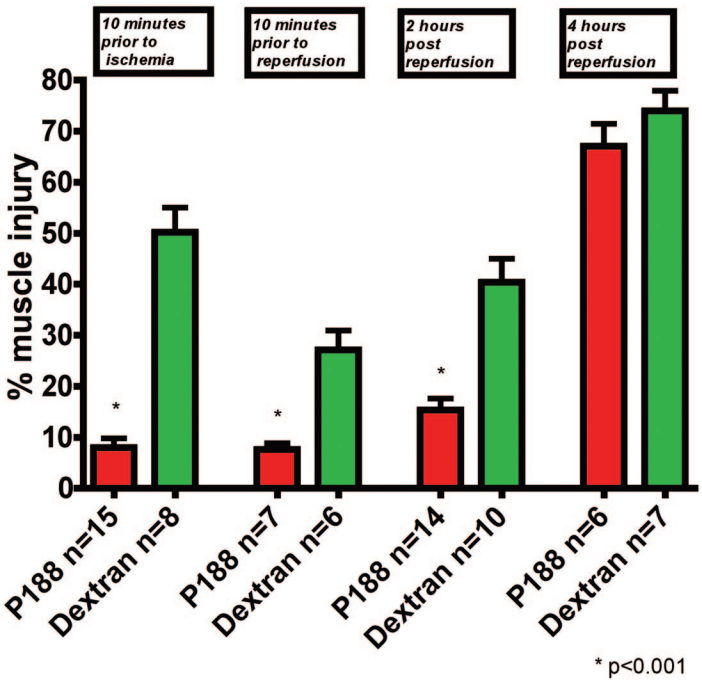

Fig. 1. Histologic injury following treatment at various time points. *P188*, poloxamer 188.

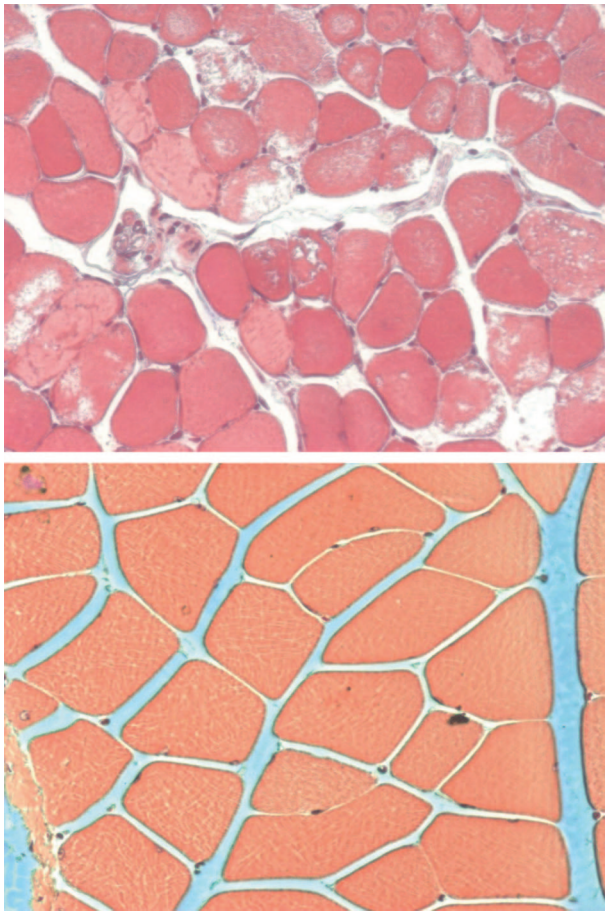

Fig. 2. Microscopic skeletal muscle morphology. (*Above*) Mix of injured and uninjured muscle fibers in a control animal. (*Below*) Uninjured fibers in a poloxamer 188–treated animal.

($n = 6$) after 24 hours of reperfusion (2.2 ng/mg versus 0.49 ng/mg) (Fig. 4).

Effect of Poloxamer 188 on Survival

When poloxamer 188 was administered 10 minutes before reperfusion, 75 percent of the mice survived 7 days ($n = 12$) compared with only 25 percent of the dextran control mice ($n = 12$; $p = 0.007$) (Fig. 5). Poloxamer 188 treatment ($n = 12$) 2 hours after reperfusion continued to provide a significant survival advantage over dextran control ($n = 12$) (poloxamer 188, 50 percent; control, 8 percent; $p = 0.032$) (Fig. 6).

DISCUSSION

Previous studies have established poloxamer 188 as a membrane-sealing polymer that interacts directly with monolayers[23] and damaged membranes.[19] Poloxamer 188 is effective in stabilizing membranes and improves survival and recovery of a variety of cell types from an array of injuries, including radiation injury, electroporation, and mechanical trauma.[24–27] Poloxamer 188 has not, however, been previously used in skeletal muscle ischemia-reperfusion injury. Various reports[15,16,19,23] have described the essential conditions for poloxamer 188–mediated membrane sealing in various types of cells. It has been shown that the surfactant monomer is the active agent, not the surfactant micelle. For membrane-sealing purposes, poloxamer 188 is typically administrated at concentrations well below the critical micelle concentration of 0.1 to 1.0 mM at physiologic temperatures. These experiments demonstrate that a single dose of the nonionic surfactant poloxamer 188 given before or after the onset of ischemia or reperfusion modulates murine skeletal muscle injury and survival following bilateral lower extremity ischemia reperfusion.

Poloxamer 188 has been shown to remain primarily in extracellular fluid in rodents, canines, and humans after intravenous administration with little or no intracellular uptake.[28] Renal clearance by means of glomerular filtration accounts for over 90 percent of poloxamer 188 clearance.[29] Mean renal clearance of purified poloxamer 188 is estimated at 5.21 liters/hour, and elimination half-life is estimated to be 7.65 hours.[29] As myocyte injury begins almost immediately following initiation of reperfusion and is irreversible within 4 hours of reperfusion, administration of a single dose of poloxamer 188 either before or during the ischemic period or in the early reperfusion period should ensure an adequate therapeutic plasma level during the period when the myocytes are still salvageable.

The potential therapeutic benefits of poloxamer 188 for treatment of ischemia-reperfusion injury has been previously recognized and investigated.[27,28] However, in previous studies, the therapeutic rationale for poloxamer 188 therapy was mostly directed toward the well-established effect of poloxamer 188 on blood rheology. Poloxamer 188 has the effect of reducing the effective viscosity of blood, making it easier to perfuse through stenotic arteries. In previous human trials investigating poloxamer 188 as an adjunct to coronary artery transluminal angioplasty, treatment was administered by continuous intravenous infusion for several days. However, this therapeutic approach was found to be associated with renal dysfunction. Increases in serum creatinine levels were seen in 2.3 to 8.8 percent of patients treated with poloxamer 188. Greater creatinine rises were observed with increased poloxamer 188 doses. Poloxamer 188 in these studies was administered at doses of 300 mg/kg/hour and upward for 48 hours.[30,31] These

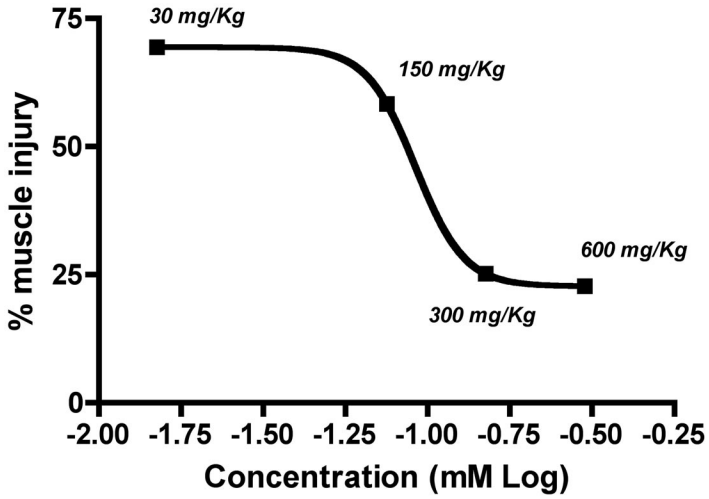

Fig. 3. Dose-response curve to poloxamer 188 treatment. Increased doses of poloxamer 188 decreased the amount of skeletal muscle injury.

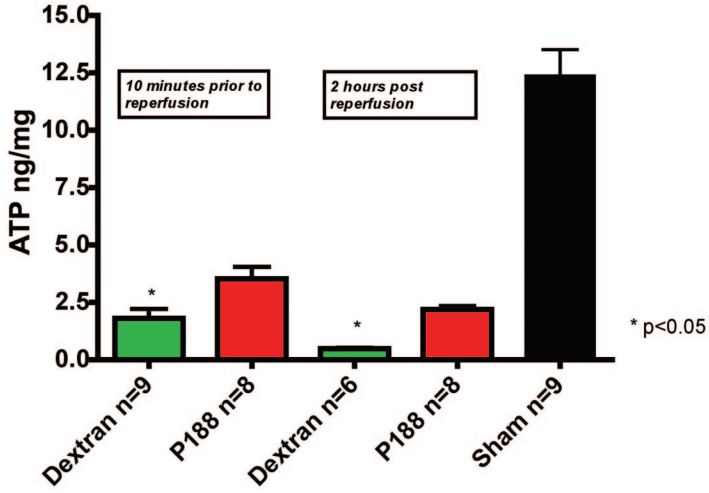

Fig. 4. Skeletal muscle adenosine 5′-triphosphate (*ATP*) levels after ischemia-reperfusion. Poloxamer 188 (*P188*) treatment administered 10 minutes before reperfusion or 2 hours after reperfusion decreased depletion of adenosine 5′-triphosphate ($p < 0.05$ versus dextran); however, adenosine 5′-triphosphate remained significantly less than sham levels at 24 hours of reperfusion ($p < 0.001$).

investigators later demonstrated reduced renal injury by reducing the polydispersity of commercially available poloxamer 188.

In our studies, a different approach was taken. The therapeutic strategy was to augment the natural membrane repair process to render the ischemic tissue more injury tolerant. Copolymer surfactant sealing of disrupted cell membranes occurs within the time frame of seconds after surfactant membrane contact. Thus, we hypothesized that a substantial therapeutic benefit to ischemia-reperfusion–injured tissue could be derived from a single-bolus administration of poloxamer 188 that would avoid prolonged renal exposure to high concentrations. This report is particularly significant for showing therapeutic benefit from a single-dose administration of poloxamer 188 for ischemia-reperfusion injury.

In an experimental protocol where poloxamer 188 was administered 10 minutes before the onset of ischemia, there was a marked decrease in skeletal muscle injury. This preischemic treatment protocol mimics clinical conditions where arterial occlusion occurs in a planned fashion, such as

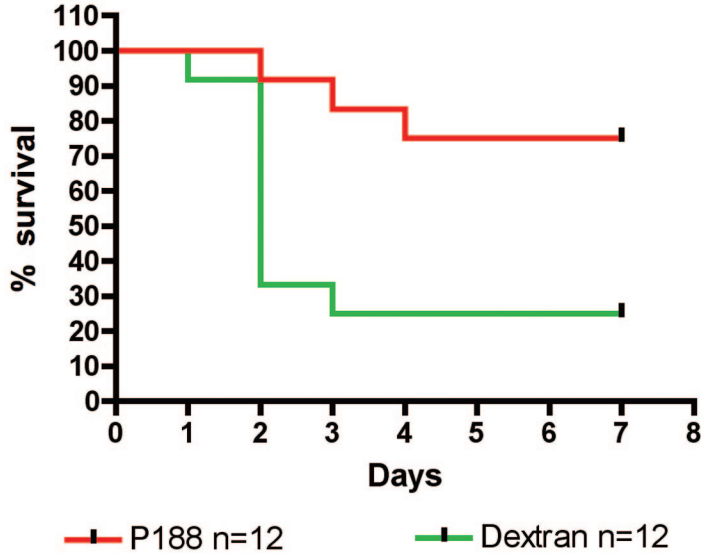

Fig. 5. Kaplan-Meier survival curve when treatment was given 10 minutes before the start of reperfusion: 75 percent of animals treated with poloxamer 188 survived for 7 days compared with 25 percent of control animals ($p = 0.0077$).

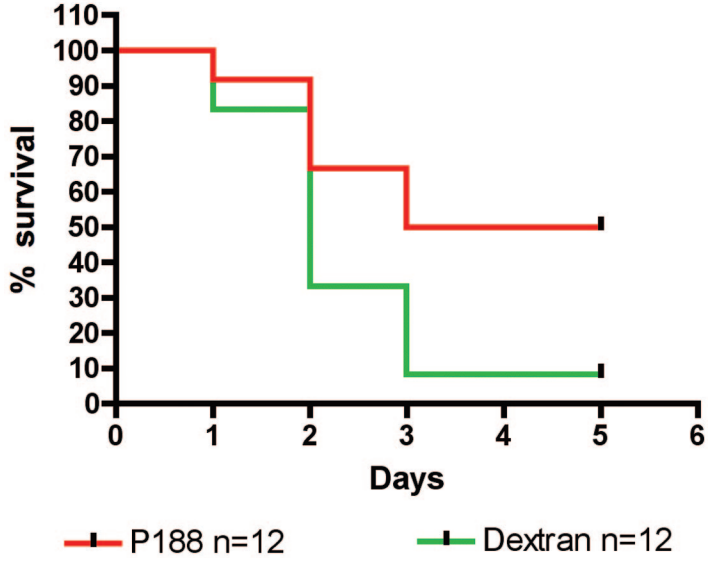

Fig. 6. Kaplan-Meier survival curve when treatment was given 2 hours after the start of reperfusion: 50 percent of poloxamer 188–treated animals survived for 7 days compared with 8.3 percent of control animals ($p = 0.032$).

aortic cross-clamp during arterial reconstructions or skeletal muscle tissue free flaps (Fig. 1). Systemic and local complications associated with planned vascular occlusions are usually manageable with fluid resuscitation and close management of patients' hemodynamic profile in an intensive care setting. In contrast, treatment of patients with acute arterial occlusions (i.e., popliteal embolus or a thrombosed free flap), therapeutic interventions are more difficult because of the development of the no-reflow phenomenon. In these clinical scenarios, therapeutic intervention can only effectively begin immediately before reperfusion. To mimic this clinical situation, poloxamer 188 was administered immediately before reperfusion. Even when poloxamer 188 was

administered during ischemia, before reperfusion, it effectively decreased skeletal muscle injury to an equivalent level observed when this single dose was administered before ischemia (Fig. 1).

The restoration of blood flow (i.e., reperfusion of an acutely ischemic limb or flap) triggers a complex cascade of biochemical, immunologic, and cellular events that results in muscle edema, myocyte necrosis, apoptosis, and impaired muscle function.[32,33] One of the earliest events involved in the process of reperfusion injury is the binding of circulating natural antibody (immunoglobulin M) and the subsequent activation of complement. Previous findings in hind-limb, intestinal, myocardial, and burn models have found that injury is mediated by a local effect of specific natural immunoglobulin M with subsequent complement activation.[34,35] Many inflammatory pathways, including the generation of reactive metabolites of molecular oxygen, are activated during ischemia-reperfusion injury.[36] The formation of reactive oxygen metabolites contributes to the formation of chemotactic stimuli and the expression and/or activation of adhesion molecules, and reduces the concentration of the antiadhesive agent nitric oxide. These events lead to neutrophil infiltration and adhesion to postcapillary venules. Plugging of capillary venules during reperfusion is the basis of the no-reflow phenomenon and plays a crucial role in the genesis of ischemia-reperfusion injury. Therapeutic interventions that begin a few hours after the onset of reperfusion have to overcome a well-established pathologic process. These experiments demonstrate that after 2 but not 4 hours of reperfusion, poloxamer 188 significantly reduces skeletal muscle injury (Fig. 1). The observed temporal effect of poloxamer 188 on limiting skeletal muscle injury even when administered during reperfusion lends credence to the concept that poloxamer 188 reduces injury by membrane sealing.

Immunoglobulin M binding to affected tissues begins during the ischemic injury and continues for up to 6 hours following initiation of reperfusion. Complement activation, as indicated by C3 deposition on endothelial and muscle cells, is seen within minutes of reperfusion.[37] Similarly, mast cell activation and degranulation is seen within 1 hour of the initiation of reperfusion.[38] Neutrophil depletion has been shown to protect against ischemia-reperfusion injury, but only when carried out immediately after initiation of reperfusion.[39] As these pathways have already been activated before our administration of poloxamer 188, it is unlikely to exert its major effect through direct interaction or interference with these pathways. Thus, as a therapeutic agent, poloxamer 188 appears to be effective in the most relevant emergent clinical conditions (i.e., after the onset of established ischemia).

In addition to experiments that confirmed a temporal relationship between poloxamer 188 administration and effective protection against ischemia-reperfusion–induced skeletal muscle necrosis, a dose-response relationship was demonstrated between calculated poloxamer 188 concentration and the extent of muscle necrosis. Maximal protection against skeletal muscle injury was observed at a dosage of 300 to 600 mg/kg (Fig. 3). The direct relationship between the concentration of poloxamer 188 and limiting muscle injury suggests a specific mechanism whereby this drug has beneficial effects.

Based on the observations obtained from the dose-response curve, experiments were designed to determine whether poloxamer 188 therapy resulted in preservation of skeletal muscle adenosine 5′-triphosphate levels. Poloxamer 188 administered 10 minutes before reperfusion and 2 hours after reperfusion effectively preserved levels of skeletal muscle adenosine 5′-triphosphate levels (Fig. 4). Although adenosine 5′-triphosphate levels did not return to preischemic baseline after treatment with poloxamer 188, these results are consistent with previous studies with canine gracilis muscle where recovery of energy stores was incomplete even after 2 days of reperfusion.[40]

In a series of mice where poloxamer 188 was administered 10 minutes before reperfusion, overall survival at 7 days was 80 percent, significantly better than mice treated with normal saline and dextran (Fig. 5). This protective effect on mortality was also observed when poloxamer 188 was administered 2 hours after beginning reperfusion (Fig. 6). Although treatment with poloxamer 188 is clearly effective from a histologic and biochemical perspective when given up to 2 hours of reperfusion, the most important factor in recovery from limb ischemia (i.e., survival) appears to be related to early treatment, if possible before reperfusion.

Previous work on skeletal muscle ischemia-reperfusion injury has focused on the effects of pretreatment or preconditioning with a variety of agents.[41–43] In the clinical setting, pretreatment is often not a viable option, as the onset of ischemia can be a sudden, unpredictable event. Limited protection has been demonstrated with therapies given at the initiation of reperfusion. Ischemic postconditioning,[44] levosimendan,[45] and acetylcholine[46] have been shown to reduce infarct size in myocardial ischemia reperfusion models when given at the time of reperfusion. However,

no effective late therapies have yet been developed. Our results suggest that poloxamer 188, which has been approved by the U.S. Food and Drug Administration for other uses, could become a beneficial clinical option, as it provides a late, salvage therapy and effective prereperfusion protection.

CONCLUSIONS

Our study demonstrates that administration of poloxamer 188 attenuates skeletal muscle ischemia-reperfusion injury and reduces mortality in a murine model. We feel that this drug, given as a single dose, may be a potential therapeutic intervention for skeletal muscle ischemia-reperfusion injury in the clinical setting.

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