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Letter to the Editor

Poloxamer-188 may be Helpful in Ischemic Stroke in Animal Models, but not in Humans

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Letter to the Editor

We read with interest the article by Xu *et al*. on the effect of poloxamer-188, a nonionic, linear triblock copolymer, in alleviating cerebral ischemia/reperfusion injury in mice [1]. It was found that intravenous administration of poloxamer-188 reduced infarct size, improved neurological deficits, and decreased water content in the brains of mice after ischemia/reperfusion injury [1]. Poloxamer-188 also suppressed reactive oxygen species (ROS), nuclear factor light chain enhancer, interleukin-6, and tumor necrosis factor-alpha, and inhibited the release of cytochrome C and lysosomal protease into the cytoplasm [1]. The study is interesting, but some points need to be discussed.

The first issue is that ischemic stroke damages not only mitochondrial and lysosomal membranes, but all membranes of neurons, glial cells, endothelial cells, smooth muscle cells, and fibrocytes. Furthermore, ischemic stroke can affect not only organelle or cell membranes, but also the entire metabolism, signal transmission, and reproduction of cells. For this reason, it is unlikely that a molecule that seals cell membranes can be of any real benefit to cells that are damaged by ischemia and become necrotic.

The second issue is that poloxamer-188 has been tested in several other diseases besides ischemic stroke, but has not shown any lasting, long-term positive effects in these diseases. For example, poloxamer-188 was used in Duchenne muscular dystrophy, but was unable to cure the disease [2]. Poloxamer-188 has also been used in sickle cell anemia, Parkinson's disease, and amyotrophic lateral sclerosis [3, 4]. In all of these diseases, poloxamer-188 only showed a positive effect in cell cultures or animal models of the disease, but these results could never be translated into clinical application. Another strong argument against the efficacy of poloxamer-188 as a drug is that it is approved as a therapeutic agent and ingredient in other approved biological drugs, but not as a standalone drug for a specific disease. Clinical trials as a therapeutic agent for sickle cell anemia have shown mixed results. Poloxamer-188 may also have potential in the treatment of burn wounds and traumatic brain injuries, but these applications are still in the preclinical research phase.

The third issue is that the side effects of poloxamer-188 were not taken into account when the molecule was investigated for clinical use. Potential side effects known from animal studies include diarrhea, delayed liver growth, eye irritation, skin irritation, and itching. Poloxamer-188 may also have harmful effects on skeletal muscle [5].

The fourth point is that compensatory mechanisms to prevent cerebral ischemia were not sufficiently taken into account. Clinical manifestation and stroke volume depend on collateralization of the cerebral blood supply. In the best case, the blood supply via the other three cerebral arteries is sufficient to prevent the development of an ischemic lesion. In the worst case, there is no cross-flow from the contralateral side or the ipsilateral posterior circulation to the medial and anterior cerebral arteries, resulting in a stroke. Since the capacity of the collateral blood supply may vary among the animals studied, different stroke volumes may not be a treatment effect of polaxomer-188, but rather due to individual blood supply.

In summary, stroke destroys more than just membranes, which is why poloxamer-188 may have limited efficacy in clinical use.

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