Long-Term Effects of Ivermectin on Neutrophil Extracellular Traps after Cerebral Ischemia -Reperfusion in Rats

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ABSTRACT

Introduction: Stroke is the second cause of death worldwide; the vast majority of strokes are ischemic type. A chain of events occurs during ischemic stroke, such as neutrophil infiltration, a double-edged sword. Neutrophil activation triggers the formation of neutrophil extracellular traps (NETs). NETs comprise decondensed chromatin decorated with citrullinated histone H3 (H3cit) and the enzyme myeloperoxidase (MPO). Recently, the detrimental effects of NETs on cerebral ischemia-reperfusion were reported. Ivermectin, as an antiparasitic drug, has recently shown other different therapeutic effects. Our research team showed that administering three doses of ivermectin has neuroprotective effects. We aim to determine whether this protective effect is still present in long-term use in the recovery phase and the effect of ivermectin treatment on NETs.

Methods and **Materials:** In this study, 24 male Wistar rats were randomly divided into four groups: Control, ivermectin (IVM), cerebral ischemia/reperfusion (IR), and IVM + IR. For induction of ischemic stroke, the common carotid arteries were clamped for 20 minutes, and then the clamps were removed after deep anesthesia. Ivermectin was administered intraperitoneally at 2mg/kg/day for 7 days. At the end of the study, the animals were anesthetized with ketamine (80 mg/kg) and xylazine (10 mg/kg). Then, brain tissue was removed rapidly, and blood sampling was taken from the portal vein to measure several factors such as bleeding time, the NETosis indicator protein (H3cit), infarct size, and MPO enzyme activity, as well as the CBC and behavioral test.

Results: Our results showed that infarct size increased in the IR group compared to the control group (p = 0.05). However, administration of ivermectin did not decrease infarct size compared to the IR group and even slightly increased infarct size. Also, the results obtained from the bleeding time and CBC showed that platelet count increased in the IR group in comparison to the control group (p = 0.001), and the ivermectin-treated group did not decrease platelet count in comparison to the IR group but increased blood clotting slightly. The results obtained from the Barnes test showed that the IR group rats' memory and learning were impaired compared to the control group (p = 0.05), and ivermectin treatment did not improve the memory and learning capacity and even slightly impaired that.

Conclusion and Discussion: Our preliminary findings showed that ivermectin loses its neuroprotective effect in long-term administration.

Keywords: Extracellular traps, Ivermectin, Reperfusion injury