INTISARI

Latar belakang: Cedera *transient global cerebral ischemia* menyebabkan oksigen di otak menjadi menurun dan memiliki konsekuensi seluler dan molekuler yang memengaruhi fungsi neuron. Neuron piramidal CA1 hippocampus merupakan area yang paling rentan pada kondisi hipoksia/iskemia di mana kerusakan pada area ini akan mengakibatkan gangguan pada fungsi memori spasial. Vitamin D memiliki peran dalam mengatur fungsi otak yaitu dapat mencegah kerusakan oksidatif pada jaringan saraf dan mengembalikan fungsi fisiologis.

Tujuan: Penelitian ini mengkaji pengaruh pemberian vitamin D terhadap fungsi memori spasial, gambaran ekspresi protein p53 pada sel piramidal di CA1 hippocampus, ekspresi mRNA caspase-3, dan ekspresi mRNA EPO pada model cedera *transient global cerebral ischemia*.

Metode: Dua puluh empat tikus Wistar *(Rattus norvegicus)* jantan (usia 2-3 bulan, berat badan 150-300 gram) dibagi secara acak menjadi 4 kelompok (n=6): SO (kontrol), BCCAO, dan kelompok VD1 (BCCAO + injeksi vitamin D 0,125 µg/kgBB/hari), dan VD2 (BCCAO + injeksi vitamin D 0,5 µg/kgBB/hari). Induksi model cedera *transient global cerebral ischemia* dilakukan dengan *bilateral carotis communis artery occlusion* (BCCAO) selama 20 menit. Vitamin D diberikan secara injeksi intraperitoneal selama 10 hari. Uji retensi dengan Morris *water maze* (MWM) dimulai hari ke-3 pasca operasi untuk mengukur jarak total di kuadran target. Tikus diterminasi pada hari ke-10, kemudian dilakukan isolasi jaringan hippocampus. Pewarnaan imunohistokimia p53 dilakukan pada preparat hippocampus untuk menilai gambaran ekspresi protein p53 pada sel piramidal di CA1 hippocampus yang mengalami apoptosis. Ekspresi mRNA caspase-3 dan EPO dinilai dengan metode RT-PCR. Uji statistik menggunakan one-way ANOVA diikuti post-hoc LSD. Nilai $p<0,05$ dianggap signifikan secara statistik.

Hasil: Kelompok BCCAO menunjukkan jarak uji retensi MWM yang signifikan lebih pendek dan ekspresi mRNA caspase-3 yang signifikan lebih tinggi secara statistik daripada kelompok SO. Setelah pemberian vitamin D, jarak uji retensi MWM kelompok VD1 dan VD2 signifikan lebih panjang dibandingkan dengan kelompok BCCAO. Gambaran ekspresi protein p53 pada area sel piramidal CA1 hippocampus tampak lebih banyak dan lebih tebal pada kelompok BCCAO dibandingkan kelompok SO dan vitamin D. Ekspresi mRNA caspase-3 kelompok VD1 dan VD2 signifikan lebih rendah daripada kelompok BCCAO.

Kesimpulan: Vitamin D dapat meningkatkan kemampuan retensi memori spasial dan bersifat neuroprotektif terhadap sel piramidal CA1 hippocampus dengan menurunkan ekspresi caspase-3 pada tikus cedera *transient global cerebral ischemia*.

Kata kunci: vitamin D, memori spasial, p53, caspase-3, *transient global cerebral ischemia*

ABSTRACT

Background: Transient global ischemic brain injury causes oxygen in the brain to decrease and has cellular and molecular consequences that affect neuron function. CA1 pyramidal neurons hippocampus an area that is most vulnerable to condition hypoxia/where ischemia damage in this area will result in impairment of spatial memory function. Vitamin D has a role in regulating brain function, which can prevent oxidative damage to nerve tissue and restore physiological function.

Objective: This study examines the effect of vitamin D administration on spatial memory function, features of p53 protein expression in pyramidal cells in the CA1 hippocampus, caspase-3 mRNA expression, and EPO mRNA expression in a transient global cerebral ischemia injury model.

Method: Twenty-four male Wistar rats (*Rattus norvegicus*) (2-3 months old, 150-300 gram body weight) were randomly divided into 4 groups (n=6): SO (control), BCCAO, and VD1 group (BCCAO + injection of vitamin D 0.125 µg/kgBB/day), and VD2 (BCCAO + injection of vitamin D 0.5 µg/kgBB/day). Induction of a transient global cerebral ischemia injury model was performed with bilateral common carotid artery occlusion (BCCAO) for 20 minutes. Vitamin D is given by intraperitoneal injection for 10 days. The retention test with the Morris water maze (MWM) started on the 3rd postoperative day to measure the total distance in the target quadrant. Mice were terminated on the 10th day, then hippocampus tissue was isolated. Immunohistochemistry staining of p53 was performed on hippocampus preparations to assess the appearance of p53 protein expression in pyramidal cells in the CA1 hippocampus that underwent apoptosis. Caspase-3 and EPO mRNA expression were assessed by the RT-PCR method. Statistical test using one-way ANOVA followed by posthoc LSD. The value of $p<0.05$ was considered statistically significant.

Results: The BCCAO group showed significantly shorter MWM retention test distance and statistically significantly higher caspase-3 mRNA expression than the SO group. After administration of vitamin D, the MWM retention test interval for the VD1 and VD2 groups was significantly longer than that of the BCCAO group. The expression of p53 protein in the hippocampus CA1 pyramidal cell area appeared to be more numerous and thicker in the BCCAO group compared to the SO and vitamin D groups. The expression of mRNA caspase-3 in the VD1 and VD2 groups was significantly lower than in the BCCAO group.

Conclusion: Vitamin D improves spatial memory retention ability and is neuroprotective against neuronal death of CA1 pyramidal cells of the hippocampus after BCCO through a mechanism of decreasing caspase-3 expression in a transient global cerebral ischemia injury.

Keywords: vitamin D, spatial memori, p53, caspase-3, transient global cerebral ischemia injury