

## INTISARI

**Latar Belakang:** Stroke iskemia merupakan gangguan neurologis penyumbatan pembuluh darah menuju otak, menyebabkan berkurangnya suplai darah dan oksigen ke otak. Eksosom HWJ UC MSC merupakan ekstraseluler vesikel dari sel *Wharton's Jelly* tali pusat, yang mulai dikembangkan sebagai pengobatan regeneratif stroke iskemia. Namun mekanisme eksosom HWJ belum diketahui secara pasti. Penelitian ini bertujuan untuk mengevaluasi pengaruh Eksosom HWJ UC MSC terhadap neurogenesis bulbus olfaktorius dengan melihat ekspresi gen *Pcna*, *Doublecortin*, dan *Neun*.

**Metode:** BCCAO digunakan untuk membuat tikus model iskemia serebral global transien yang menyerupai stroke iskemia. Injeksi intravena eksosom HWJ dilakukan 24 jam pasca pembuatan tikus model menggunakan tiga variasi dosis: Exo 1 (dosis rendah  $8,5 \times 10^4$  partikel/ekor), Exo 2 (dosis sedang  $8,5 \times 10^5$  partikel/ekor), Exo 3 (dosis tinggi  $8,5 \times 10^6$  partikel/ekor). Tikus diterminasi pada hari ke-8 pasca injeksi. Bulbus olfaktorius diisolasi RNA lalu dibuat cDNA. Analisis ekspresi gen menggunakan qPCR, sedangkan gambaran histologi *Pcna* menggunakan imunohistokimia. Data dianalisis statistik menggunakan ANOVA dilanjutkan analisis *multiple comparison*.

**Hasil:** Kelompok tikus yang diinjeksi eksosom HWJ pada berbagai variasi dosis menunjukkan ekspresi gen *Pcna* lebih tinggi terhadap kelompok kontrol BCCAO. Gambaran histologi *Pcna* menunjukkan sel positif *Pcna* pada kelompok yang diinjeksi eksosom di berbagai variasi dosis. Sedangkan gen *Doublecortin* dan gen *Neun* menunjukkan hasil sebaliknya. Kelompok tikus yang diinjeksi eksosom HWJ pada berbagai variasi dosis menunjukkan ekspresi gen *Doublecortin* serta gen *Neun* lebih rendah dibandingkan dengan kelompok kontrol BCCAO.

**Kesimpulan:** Tikus model yang diinjeksi eksosom HWJ UC MSC menunjukkan tren *upregulation* terhadap gen *Pcna*, namun *downregulation* terhadap gen *Doublecortin* dan *Neun*. Hal tersebut mengindikasikan adanya peningkatan proliferasi sel di bulbus, namun tidak mengarah pada pembentukan neuroblas serta maturasi neuron. Diduga mekanisme aksi eksosom HWJ terhadap stroke iskemia lebih mengarah ke jalur selain neurogenesis.

**Kata kunci:** Stroke iskemia, eksosom HWJ UC MSC, *Pcna*, *Doublecortin*, *Neun*

## ABSTRACT

**Background:** Ischemic stroke is a neurological disorder caused by the blockage of blood vessels leading to the brain, resulting in a reduced supply of blood and oxygen to the brain. HWJ UC MSC exosomes are extracellular vesicles derived from Wharton's Jelly umbilical cord stem cells, which are being developed as a regenerative therapy for ischemic stroke. However, the exact mechanism of HWJ exosomes is still unknown. This study aims to evaluate the effect of HWJ UC MSC exosomes on olfactory bulb neurogenesis by examining the gene expression of *Pcna*, *Doublecortin*, and *Neun*.

**Methods:** BCCAO method was used to create a transient global cerebral ischemia rat model, mimicking ischemic stroke. Intravenous injection of HWJ exosomes was performed 24 hours after model induction using three dose variations: Exo 1 (low dose,  $8.5 \times 10^4$  particles/rat), Exo 2 (medium dose,  $8.5 \times 10^5$  particles/rat), and Exo 3 (high dose,  $8.5 \times 10^6$  particles/rat). The rats were terminated on day 8 post-injection. RNA was isolated from the olfactory bulb and then converted into cDNA. Gene expression was analyzed using qPCR, while histological visualization of *Pcna* was performed using immunohistochemistry. Data were statistically analyzed using ANOVA followed by multiple comparison analysis.

**Results:** Groups injected with HWJ exosomes at various dose variations showed higher *Pcna* gene expression compared to the BCCAO control group. Histological analysis of *Pcna* showed *Pcna*-positive cells in the groups injected with exosomes at different doses. In contrast, the expression of *Doublecortin* and *Neun* genes showed the opposite results. The group of rats injected with HWJ-derived exosomes at various doses exhibited lower expression of *Doublecortin* and *Neun* genes compared to the BCCAO control group.

**Conclusion:** The model rats injected with HWJ UC MSC exosomes showed an upregulation trend in *Pcna* gene expression, but a downregulation in *Doublecortin* and *Neun* gene expression. This indicates an increase in cell proliferation in the olfactory bulb, but not in the formation of neuroblasts or neuron maturation. The mechanism of action of HWJ-derived exosomes in ischemic stroke is suspected to be directed more toward pathways other than neurogenesis.

**Keywords:** Ischemic stroke, HWJ UC MSC-derived exosomes, *Pcna*, *Doublecortin*, *Neun*