

INTISARI

Latar belakang: Kondisi inflamasi pada gagal ginjal kronis (GGK) mengakibatkan cedera pembuluh darah kecil, disfungsi endotelial, dan *remodeling* pembuluh darah ginjal dengan penurunan *endothelial nitric oxide synthase* (eNOS). Terapi *stem cells* dan produk turunannya, terutama eksosom sedang banyak diteliti pada berbagai model gagal organ. Akan tetapi, efek protektif eksosom dari *Human Umbilical Cord Mesenchymal Stem Cell* (HUC-MSC) belum diteliti pada keadaan remodeling vaskular dan ekspresi mRNA eNOS.

Tujuan: Tujuan dari penelitian ini adalah untuk mengkaji pengaruh eksosom dari HUC-MSC terhadap remodeling vaskular dan ekspresi mRNA eNOS pada tikus model *5/6 subtotal nephrectomy*.

Metode: Model *5/6 Subtotal Nephrectomy* dilakukan untuk menggambarkan kondisi gagal ginjal kronis pada hewan coba tikus. Tikus Wistar jantan ($n = 30$, 2-3 bulan, 150-250 gram) menjalani prosedur operasi pengangkatan *5/6* bagian ginjal kemudian dibagi menjadi lima kelompok, yaitu kelompok kontrol/*sham operation* (SO, $n = 6$), kelompok *5/6-SN* (SN, $n = 6$), kelompok *5/6-SN* dengan injeksi HUC-MSC dosis 48,30 μg total protein (SNE1, $n = 6$), kelompok *5/6-SN* dengan injeksi HUC-MSC 96,60 μg total protein (SNE2, $n = 6$), Kelompok *5/6-SN* dengan injeksi HUC-MSC 193,20 μg total protein (SNE3, $n = 6$). Injeksi dilakukan secara intravena melalui vena di ekor sebanyak 2x/minggu selama 4 minggu. Tikus kemudian diterminasi pada minggu ke-6 dan dilakukan analisis menggunakan RT-PCR untuk melihat ekspresi mRNA eNOS. Pemeriksaan remodeling vaskular dilakukan dengan memeriksa *wall thickness* (tebal dinding) dan *Lumen/Wall Area Ratio* (LWAR) pada arteri resisten (diameter $<50 \mu\text{m}$) pada *slide* ginjal dengan pewarnaan Sirius Red, 15 arteri per *glass slide*. Analisis hasil dan data dilakukan menggunakan *software* SPSS 30.

Hasil Penelitian: Ekspresi mRNA eNOS pada kelompok SN signifikan lebih rendah dibandingkan dengan kelompok SO ($p < 0,001$). Pemberian eksosom HUC-MSC signifikan menunjukkan ekspresi mRNA eNOS yang lebih tinggi pada kelompok SNE1 ($p = 0,007$), SNE2 ($p = 0,012$), dan SNE3 ($p = 0,002$) dibandingkan kelompok SN. Kelompok SN signifikan mengalami remodeling vaskular yang lebih buruk daripada kelompok SO, dengan tebal dinding yang lebih tinggi ($p < 0,001$) dan LWAR yang lebih rendah ($p = 0,002$). Pemberian eksosom HUC-MSC signifikan menunjukkan *wall thickness* yang lebih rendah pada kelompok SNE2 ($p = 0,006$) dibandingkan kelompok SN serta nilai LWAR yang lebih tinggi pada kelompok SNE1 ($p = 0,039$) dan SNE3 ($p = 0,028$) dibandingkan kelompok SN.

Kesimpulan: Pemberian eksosom HUC-MSC pada kelompok *5/6-SN* menunjukkan remodeling vaskular yang lebih rendah dan ekspresi mRNA eNOS lebih tinggi dibandingkan kelompok yang tidak diberikan injeksi eksosom.

Kata kunci: Eksosom *Human Umbilical Cord Mesenchymal Stem Cell*, *Endothelial Nitric Oxide Synthase*, Gagal Ginjal Kronis, Remodeling Vaskular

ABSTRACT

Background: The inflammatory state in chronic kidney disease (CKD) leads to small vessel injury, endothelial dysfunction, and renal vascular remodeling with a decrease in endothelial Nitric Oxide Synthase (eNOS). Stem cell therapy and its derivatives, particularly exosomes, are being widely investigated in various organ failure models. However, the protective effects of exosomes derived from Human Umbilical Cord Mesenchymal Stem Cells (HUC-MSCs) have not yet been studied in the context of vascular remodeling and eNOS expression.

Objective: The objective of this study was to examine the effect of HUC-MSCs on vascular remodeling and eNOS mRNA expression in 5/6 subtotal nephrectomy rat model.

Method: The 5/6 Subtotal Nephrectomy model was performed to represent chronic kidney disease in rats. Male Wistar rats (n = 30, 2-3 months old, 150-250 g) underwent surgical removal of 5/6 of the kidney and were then divided into five groups. Control/sham operation group (SO, n = 6), 5/6-SN group (SN, n = 6), 5/6-SN group with injection of HUC-MSC at a dose of 48.30 µg total protein (SNE1, n = 6), 5/6-SN group with injection of HUC-MSC at a dose of 96.60 µg total protein (SNE2, n = 6), and 5/6-SN group with injection of HUC-MSC at a dose of 193.20 µg total protein (SNE3, n = 6). Injections were administered intravenously via the tail vein twice per week for 4 weeks. At week 6 rats were sacrificed and RT-PCR analysis was performed to assess eNOS mRNA expression. Vascular remodeling was assessed by quantifying wall thickness and Lumen/Wall Area Ratio (LWAR) in resistant arteries (<50 µm in diameter) from Sirius Red-stained kidney sections (10-15 vessels per slide). Data analysis was performed using SPSS version 30.

Results: The mRNA expression of eNOS in the SN group was significantly lower than that in the SO group (p < 0.001). Administration of HUC-MSC-derived exosomes significantly resulted in higher eNOS mRNA expression in the SNE1 (p = 0.007), SNE2 (p = 0.012), and SNE3 (p = 0.002) groups compared to the SN group. The SN group exhibited significantly worse vascular remodeling than the SO group, characterized by higher wall thickness (p < 0.001) and lower LWAR (p = 0.002). Administration of HUC-MSC-derived exosomes significantly resulted in lower wall thickness in the SNE2 group (p = 0.006) compared to the SN group, as well as higher LWAR values in the SNE1 (p = 0.039) and SNE3 (p = 0.028) groups compared to the SN group.

Conclusion: Administration of HUC-MSC exosomes in the 5/6-SN group showed lower vascular remodeling and higher eNOS mRNA expression compared to the untreated group.

Keywords: Chronic Kidney Disease (CKD), Human Umbilical Cord Mesenchymal Stem Cell Exosomes, Vascular Remodeling, Endothelial Nitric Oxide Synthase