ABSTRAK

Latar Belakang: Cedera Iskemia-Reperfusi ginjal (*Kidney Ischemia-Reperfusion Injury*/IRI) merupakan salah satu mekanisme utama yang menyebabkan fibrosis dan progresi gagal ginjal kronis. Terapi regeneratif yang memanfaatkan eksosom sebagai metode pengantaran berbagai zat aktif, terutama eksosom turunan *human Wharton's Jelly-derived Mesenchymal Stem Cell* (hWJMSC), memiliki potensi untuk menjadi menurunkan progresivitas cedera I/R ginjal.
Tujuan Penelitian: Mengkaji efek pemberian eksosom terhadap fibrosis pada gagal ginjal dengan model cedera iskemi/reperfusi ginjal periode kronis
Metode: Tikus Wistar jantan, berusia 10 minggu, sejumlah 26 ekor dibagi menjadi 5 kelompok, yaitu kelompok SO (*sham-operated*), IR (cedera I/R ginjal), IRE-1 (cedera I/R ginjal + eksosom dosis rendah), IRE-2 (cedera I/R ginjal + eksosom dosis sedang), dan IRE-3 (cedera I/R ginjal + eksosom dosis tinggi). Pemeriksaan kreatinin serum dilakukan menggunakan darah retroorbitalis yang diambil 7 hari sebelum operasi (*baseline*), 1 hari sesudah operasi, dan 21 hari sesudah injeksi eksosom, diikuti terminasi. Eksosom turunan hWJMSC diberikan secara intravena 1 hari setelah operasi. Pewarnaan *picrosirius red* dilakukan untuk menilai fraksi area kolagen. Pemeriksaan ekspresi mRNA CTGF, α-SMA, dan Col1a ginjal dilakukan dengan metode RT-PCR dan *housekeeping gene* β-aktin. Analisis statistika dilakukan menggunakan *repeated measure* ANOVA, *one-way* ANOVA, dan Kruskal-Wallis, serta uji *post-hoc* LSD ataupun Dunn.
Hasil Penelitian: Kelompok IRE-3 menunjukkan kadar kreatinin serum pasca-eksosom tidak signifikan terhadap *baseline* (2,878±0,768 vs 0,382±0,050; p<0,001), sedangkan kelompok IR menunjukkan kadar kreatinin pasca-eksosom yang masih lebih tinggi dibanding *baseline* (0,238±0,038 vs 0,68±0,068; p<0,001). Kelompok IRE-3 menunjukkan fraksi area kolagen lebih rendah secara signifikan dibanding kelompok IR (7,93±0,81 vs 22,27±3,58; p<0,001). Ekspresi mRNA CTGF tidak menunjukkan perbedaan signifikan pada semua kelompok, namun ekspresi mRNA α-SMA (0,346±0,006 vs 0,500±0,071; p=0,024) dan ekspresi mRNA Col1A1 (0,685±0,036 vs 0,769±0,050; p=0,005) lebih rendah secara signifikan pada kelompok IRE-3 dibanding kelompok IR. Eksosom dosis tinggi menjadi dosis yang paling efektif dalam menghasilkan perbedaan.
Kesimpulan: Pemberian eksosom turunan hWJMSC dosis tinggi mampu memperbaiki fungsi ginjal dan fibrosis melalui penghambatan proliferasi miofibroblas serta modulasi keseimbangan degradasi matriks ekstraseluler.
Kata Kunci: cedera iskemia/reperfusi ginjal, terapi regeneratif, eksosom, fibrosis

ABSTRACT

Background: *Kidney ischemia-reperfusion injury (IRI) is one of the main mechanisms causing fibrosis and progression of chronic kidney failure. Regenerative therapy utilizing exosomes as a method of delivering various active substances, particularly exosomes derived from human Wharton's Jelly-derived Mesenchymal Stem Cells (hWJMSC), has the potential to reduce the progression of renal I/R injury.*

Objective: *To examine the effects of exosome administration on fibrosis in kidney failure using a chronic kidney ischemia/reperfusion injury model.*

Method: *Twenty-six male Wistar rats, aged 10 weeks, were divided into 5 groups, namely the SO (sham-operated) group, the IR (renal I/R injury) group, the IRE-1 (renal I/R injury + low-dose exosomes) group, the IRE-2 (renal I/R injury + medium-dose exosomes) group, and IRE-3 (renal I/R injury + high-dose exosomes). Serum creatinine levels were measured using retroorbital blood samples taken 7 days before surgery (baseline), 1 day after surgery, and 21 days after exosome injection, followed by termination. hWJMSC-derived exosomes were administered intravenously 1 day after surgery. Picrosirius red staining was performed to assess the collagen area fraction. Examination of CTGF, α-SMA, and Col1a mRNA expression in the kidney was performed using the RT-PCR method and the housekeeping gene β-actin. Statistical analysis was performed using repeated measure ANOVA, one-way ANOVA, and Kruskal-Wallis, as well as LSD or Dunn post-hoc tests.*

Results: *The IRE-3 group showed no significant difference in post-exosome serum creatinine levels compared to baseline (2.878±0.768 vs 0.382±0.050; p<0.001), while the IR group showed post-exosome creatinine levels that were still higher than baseline (0.238±0.038 vs 0.68±0.068; p<0.001). The IRE-3 group showed a significantly lower collagen area fraction compared to the IR group (7.93±0.81 vs. 22.27±3.58; p<0.001). CTGF mRNA expression did not show significant differences in the ischemic/reperfusion injury group, but α-SMA mRNA expression (0.346±0.006 vs. 0.500±0.071; p=0.024) and Col1A1 mRNA expression (0.685±0.036 vs. 0.769±0.050; p=0.005) were significantly lower in the IRE-3 group than in the IR group. The high-dose exosome was the most effective dose in producing differences.*

Conclusion: *High-dose hWJMSC-derived exosome administration improved kidney function and fibrosis through inhibition of miofibroblast proliferation and modulation of extracellular matrix degradation balance.*

Keywords: *ischemic/reperfusion injury of the kidney, regenerative therapy, exosomes, fibrosis*