

INTISARI

Latar Belakang: Anemia adalah komplikasi awal pada penyakit Gagal ginjal kronik (GGK). Faktor utama munculnya anemia adalah terjadinya aktivasi fibroblas menjadi miofibroblas yang menyebabkan inadekuatnya produksi eritropoietin untuk digunakan dalam proses eritropoeisis. Eksosom terdiri dari DNA, *circular RNA*, mRNA, *long non-coding RNA*, *micro-RNA* serta mengandung protein, seperti IFN- γ dan HGF yang dapat deaktivasi fibroblas menjadi miofibroblas pada fibrosis ginjal. Terapi eksosom dapat dijadikan salah satu dalam menekan perkembangan fibrosis pada pasien GGK.

Tujuan Penelitian: untuk mengetahui pengaruh pemberian eksosom dari turunan *Human Umbilical Cord Mesenchymal Stem Cell* terhadap kadar kreatinin serum darah, kadar hemoglobin (Hb), ekspresi mRNA EPO, dan ekspresi protein PDGFR- β di ginjal tikus model 5/6 subtotal nefrektomi.

Metode: Subjek penelitian ini adalah 25 ekor tikus Wistar jantan (*Rattus norvegicus*) berumur 3 bulan dengan berat badan 150-300 g. Hewan coba dibagi menjadi 5 kelompok yakni *Sham Operation* (SO, n=5), 5/6 Subtotal Nefrektomi (SN, n=5), SN+Eksosom dosis 1= 48,30 μg total protein (SN+Exo1, n=5), SN+Eksosom dosis 2=96,60 μg total protein (SN+Exo2, n=5), dan SN+Eksosom dosis 3=193,20 μg total protein (SN+Exo3, n=5). Pada akhir perlakuan (hari ke-42) dilakukan satu kali pemeriksaan kadar serum kreatinin dan konsentrasi hemoglobin yang diambil dari darah vena retro orbital. Pemeriksaan ekspresi mRNA EPO menggunakan *Reverse Transcriptase-Polymerase Chain Reaction* (RT-PCR) dan di analisis dengan *software ImageJ*. Serta pengamatan ekspresi protein PDGFR- β . Data dianalisis dengan uji statistik *one way ANOVA* dan *Kruskall Wallis* ($p < 0,05$).

Hasil Penelitian: Kadar serum kreatinin lebih tinggi pada kelompok SN (0,73 mg/dL \pm 0,04) vs SO (0,32 mg/dL \pm 0,06) ($p < 0,001$) dan terjadi penurunan kadar kreatinin serum darah di kelompok SN+Exo1 (0,49mg/dL \pm 0,12), SN+Exo 2 (0,52mg/dL \pm 0,18) dan SN+Exo 3 (0,53 mg/dL \pm 0,07) vs SN (0,73 mg/dL \pm 0,04) ($p < 0,01$). Konsentrasi hemoglobin tidak menunjukkan perbedaan secara statistik ($p > 0,05$). Ekspresi mRNA EPO tidak berbeda signifikan secara statistik ($P > 0,05$). Deskripsi pewarnaan imunohistokimia pada sel interstisial peritubular ginjal kelompok SN menunjukkan penanda sel fibroblas (PDGFR- β) lebih tinggi dibandingkan kelompok SO serta rendah pada kelompok yang diberi perlakuan eksosom dosis pertama dan kedua dibandingkan kelompok SN.

Kesimpulan: Pada tikus model 5/6 subtotal nefrektomi yang diberi perlakuan 3 dosis eksosom dapat menurunkan kreatinin serum darah, namun belum mempengaruhi kadar hemoglobin dan ekspresi Eritropoietin (EPO). Gambaran hasil imunohistokimia protein PDGFR- β tampak kurang dominan pada kelompok SN+Exo 1 dan SN+Exo2 dibandingkan kelompok yang tidak diberikan perlakuan eksosom.

Kata Kunci: Gagal Ginjal Kronis, eksosom, anemia, eritropoietin.

ABSTRACT

Background: Anemia is an early complication in Chronic Kidney Disease (CKD) The main factor in the emergence of anemia is the activation of fibroblast to become miofibroblast which causes the production of erythropoietin to be insufficient for use in the erythropoiesis process. Exosomes consist of DNA, circular RNA, mRNA, long non-coding RNA, micro-RNA, and contain proteins, such as IFN- γ and HGF which can reprogram miofibroblast into Fibroblast. Exosome therapy can be used to suppress the development of fibrosis in GGK patients.

Objective: To determine the effect of administering exosomes derived from Human Umbilical Cord Mesenchymal on blood serum creatinine levels, hemoglobin (Hb) levels, EPO mRNA expression, and PDGFR- β protein expression in the kidney of 5/6 subtotal nephrectomy rat model.

Methods: The subjects of this research were 25 male Wistar rats (*Rattus norvegicus*) aged 3 months with a body weight of 150-300 g. Experimental animals were divided into 5 groups, namely Sham Operation (SO, n=5), Subtotal Nephrectomy 5/6 (SN, n=5), SN+Exosome total protein 48.30 μ g (SN +Exo1, n=5), SN+Exosomes dose 2=96.60 μ g total protein (SN+Exo2, n=5), and SN+Exosomes dose 3=193, 20 μ g total protein (SN+Exo3, n=5). At the end of treatment (day 42), one examination of serum creatinine levels and hemoglobin concentration was taken from retroorbital vein blood. EPO mRNA expression was examined using Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) and analyzed with *ImageJ software*. As well as observing PDGFR- β protein expression. Data were analyzed using *one way ANOVA* and *Kruskall Wallis* statistical tests ($p < 0.05$).

Results: Serum creatinine levels were higher in the SN (0,73 mg/dL \pm 0,04) vs SO (0,32 mg/dL \pm 0,06) ($p < 0,001$) and there was a decrease in blood serum creatinine levels in this group SN+Exo1 (0,49mg/dL \pm 0,12), SN+Exo 2 (0,52mg/dL \pm 0,18) and SN+Exo 3 (0,53 mg/dL \pm 0,07) vs SN (0,73 mg/dL \pm 0,04) ($p < 0,01$). Hemoglobin concentration did not show statistical differences ($p > 0.05$). HIF-1 α mRNA expression was higher in the SN group compared to the SO group ($p < 0.05$) and was not statistically significantly different between the three doses. EPO mRNA expression was not statistically significantly different ($P > 0.05$). Description of immunohistochemical staining on renal peritubular interstitial cells in the SN group showed that the fibroblast cell marker (PDGFR- β) was higher than in the SO group and lower in the groups treated with the first and second doses of exosomes compared to the SN group.

Conclusion: In 5/6 subtotal nephrectomy model Rat given 3 doses of exosomes were able to reduce blood serum creatinine, but did not affect hemoglobin levels and Erythropoietin (EPO) expression. The PDGFR- β protein immunohistochemistry results appeared to be less dominant in the SN+Exo 1 and SN+Exo 2 groups compared to the group that was not given exosome treatment.

Key Words: Chronic Kidney Disease (CKD), exosome, anemia, erythropoietin.