

INTISARI

Pendahuluan: Kemoterapi mempunyai efek gonadotoksik yang dapat menurunkan cadangan ovarium hingga menyebabkan infertilitas. Eksosom *Human Wharton's Jelly-Mesenchymal Stem Cells* (HWJ-MSCs) diketahui mempunyai potensi regeneratif, namun pengaruhnya terhadap pemulihan kualitas oosit dan tingkat fertilisasi belum banyak diteliti pada kondisi *Diminished Ovarian Reserve* (DOR) akibat kemoterapi.

Tujuan: Penelitian ini mengevaluasi efek regeneratif dari eksosom HWJ-MSCs terhadap jumlah folikel ovarium, kualitas oosit, tingkat fertilisasi pada mencit model DOR.

Metode: Empat puluh mencit betina galur Balb/c diaklimatisasi selama 7 hari, kemudian dibagi menjadi lima kelompok (n=8): kontrol sehat (A); DOR tanpa terapi (B); DOR + eksosom $1,7 \times 10^6$ partikel/ml (C); $3,4 \times 10^6$ partikel/ml (D); dan $6,8 \times 10^6$ partikel/ml (E). Model DOR diinjeksi dengan siklofosamid 120 mg/kg pada hari ke-8 dan ke-15. Eksosom diinjeksi secara intraperitoneal pada hari ke-22. Empat mencit dari setiap kelompok diterminasi pada hari ke-36. Ovarium diambil untuk analisis histologis dengan pewarnaan Hematoksin–Eosin. Folikel sehat dihitung pada lima potong jaringan ovarium (interval 10 potongan, tebal 5 μ m). Empat mencit sisanya dilakukan superovulasi menggunakan follitropin-alfa dan choriogonadotropin-alfa, kemudian oosit dievaluasi untuk pengamatan kualitas oosit (jumlah CEO, tingkat maturasi oosit, diameter oosit dan tebal zona pelusida) dan tingkat fertilisasi secara *in vitro*.

Hasil: Pemberian eksosom HWJ-MSCs dosis $6,8 \times 10^6$ partikel/ml secara signifikan memperbaiki jumlah folikel sehat ($p = 0,04$) dan rasio folikel primordial ($p = 0,004$) pada mencit model DOR. Terdapat perbaikan tingkat maturasi oosit secara signifikan pada dosis $3,4 \times 10^6$ partikel/ml ($p = 0,029$). Ketiga dosis eksosom belum mampu memberikan perbaikan pada tingkat fertilisasi secara signifikan.

Kesimpulan: Eksosom HWJ-MSCs menunjukkan efek regeneratif parsial dengan memperbaiki jumlah folikel ovarium dan tingkat maturasi oosit, namun belum mampu memperbaiki tingkat fertilisasi secara signifikan pada mencit model DOR. Perbaikan tingkat fertilisasi yang tidak signifikan secara statistik tetap memiliki implikasi klinis dalam upaya memulihkan fertilitas pada pasien DOR.

Kata kunci: eksosom HWJ-MSCs, *diminished ovarian reserve*, regenerasi ovarium, kemoterapi.

ABSTRACT

Introduction: Chemotherapy has gonadotoxic effects that can reduce ovarian reserve, leading to infertility. Human Wharton's Jelly–Mesenchymal Stem Cell (HWJ-MSC)–derived exosomes are known to have regenerative potential; however, their effects on restoring oocyte quality and fertilization rates in chemotherapy-induced Diminished Ovarian Reserve (DOR) remain poorly investigated.

Objective: This study aimed to evaluate the regenerative effects of HWJ-MSC–derived exosomes on ovarian follicle counts, oocyte quality, and fertilization rates in a mouse model of DOR.

Methods: Forty female Balb/c mice were acclimatized for seven days and then randomly assigned to five groups ($n = 8$): healthy control (A); untreated DOR (B); DOR + exosomes 1.7×10^9 particles/ml (C); 3.4×10^9 particles/ml (D); and 6.8×10^9 particles/ml (E). The DOR model was induced by cyclophosphamide injections (120 mg/kg) on days 8 and 15. Exosomes were administered intraperitoneally on day 22. Four mice from each group were euthanized on day 36, and the ovaries were collected for histological analysis using Hematoxylin–Eosin staining. Healthy follicles were counted in five ovarian sections (interval of 10 sections, 5- μ m thick). The remaining four mice underwent superovulation with follitropin-alpha and choriogonadotropin-alpha, after which oocytes were assessed for cumulus–oocyte complex (COC) count, oocyte maturation stage, oocyte diameter, zona pellucida thickness, and in vitro fertilization rate.

Results: Administration of 6.8×10^9 particles/ml HWJ-MSC–derived exosomes significantly improved the number of healthy follicles ($p = 0.04$) and primordial follicle ratio ($p = 0.004$) in DOR mice. A significant improvement in oocyte maturation rate was observed at the 3.4×10^9 particles/ml dose ($p = 0.029$). None of the three exosome doses significantly improved the fertilization rate.

Conclusion: HWJ-MSC–derived exosomes demonstrated partial regenerative effects by improving ovarian follicle counts and oocyte maturation rates but did not significantly enhance fertilization rates in the DOR mouse model. Nevertheless, the non-significant improvement in fertilization rate may still have clinical implications for efforts to restore fertility in DOR patients.

Keywords: HWJ-MSC-derived exosomes, diminished ovarian reserve, ovarian regeneration, chemotherapy.