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**Kombinasi MetcovazinÂ® dan Stimulasi Listrik dalam Memperpendek Fase Proliferasi dan Remodeling
Penyembuhan Luka pada Tikus Model Diabetes**
Lutfi Nurdian Asnindari, Prof. Dr. dr. Denny Agustiningsih, M. Kes., AIFM., AIFO-K.
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ABSTRAK

Latar Belakang: Penyembuhan luka pada pasien diabetes mengalami hambatan akibat gangguan proliferasi sel, deposisi matriks ekstraseluler, dan regenerasi jaringan. Kombinasi Metcovazin® dan stimulasi listrik berpotensi mempercepat penyembuhan luka, namun efektivitas terapi, durasi stimulasi yang optimal, serta mekanisme molekuler yang mendasarinya masih belum diketahui.
Tujuan: Penelitian ini bertujuan mengevaluasi efektivitas kombinasi Metcovazin® dan stimulasi listrik dengan berbagai durasi terhadap penyembuhan luka pada tikus model diabetes serta mengkaji mekanismenya melalui jalur pensinyalan *voltage-gated calcium channel* (VGCC) Cav1.2 –PDGF-BB/PDGFRβ–ERK1/2.
Metode: Penelitian eksperimental laboratorik dengan rancangan acak, kelompok kontrol, dengan pengukuran hanya setelah perlakuan menggunakan 30 ekor tikus Wistar jantan yang dibagi secara acak menjadi enam kelompok, yaitu K0 (tikus normal + Metcovazin®), KDM (tikus model diabetes + Metcovazin®), KES (tikus model diabetes + stimulasi listrik 15 menit), K5 (tikus model diabetes + Metcovazin® + stimulasi listrik 5 menit), K15 (tikus model diabetes + Metcovazin® + stimulasi listrik 15 menit), dan K30 (tikus model diabetes + Metcovazin® + stimulasi listrik 30 menit). Diabetes diinduksi menggunakan nicotinamide (110 mg/kgBB) dan streptozotocin (45 mg/kgBB). Luka *full-thickness* berdiameter 0,8 cm dibuat pada daerah dorsum tikus, kemudian diberikan perlakuan selama enam hari. Pada hari ketujuh dilakukan pemeriksaan kadar α-SMA, ekspresi kolagen tipe I, kolagen total, reepitelisasi, ekspresi VGCC Cav1.2, PDGFRβ, kadar PDGF-BB dan ERK1/2. Selain itu, dilakukan pengukuran impedansi kulit. Data dianalisis menggunakan uji *One-way ANOVA* atau *Kruskal–Wallis* yang dilanjutkan dengan uji *post hoc* Dunnett atau Dunn sesuai distribusi data.
Hasil: Kombinasi Metcovazin® dan stimulasi listrik durasi 15 menit merupakan intervensi yang paling efektif dalam mempercepat penyembuhan luka dibandingkan terapi Metcovazin® saja, ditunjukkan oleh peningkatan kadar α-SMA (p=0,049), ekspresi kolagen tipe I (p=0,003), kolagen total (p=0,000), dan skor reepitelisasi (p=0,012). Dibandingkan antar kelompok KDM, KES dan kombinasi, kombinasi terapi juga meningkatkan ekspresi kolagen tipe I (p=0,040), kolagen total (p=0,000), dan reepitelisasi (p=0,019). Dibandingkan K0, KDM menunjukkan penurunan ekspresi PDGFRβ (p=0,008), α-SMA, kolagen tipe I, dan reepitelisasi (p<0,05), disertai peningkatan impedansi kulit, sedangkan ekspresi VGCC Cav1.2, kadar PDGF-BB, total ERK1/2, dan kolagen total tidak berbeda bermakna (p>0,05). Stimulasi listrik memodulasi jalur pensinyalan secara parsial melalui peningkatan ekspresi VGCC Cav1.2 (p=0,007) dan PDGFRβ (p=0,006), sedangkan variasi durasi stimulasi hanya memengaruhi ekspresi PDGFRβ (p=0,003).

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Kesimpulan: Kombinasi Metcovazin® dan stimulasi listrik selama 15 menit merupakan intervensi yang paling efektif dalam mempercepat penyembuhan luka pada tikus model diabetes. Efek tersebut kemungkinan berkaitan dengan modulasi parsial jalur pensinyalan VGCC Cav1.2–PDGF-BB/PDGFRβ–ERK1/2 diikuti oleh peningkatan deposisi kolagen dan reepitelisasi.

Kata kunci: diabetes melitus; penyembuhan luka; stimulasi listrik; Metcovazin®; *growth factor*

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Combined Metcovazin® and Electrical Stimulation Accelerate the Proliferative and Remodeling Phases of Wound Healing in a Diabetic Rat Model

ABSTRACT

Background: Diabetic wound healing is impaired because of dysregulated cell proliferation, extracellular matrix deposition, and tissue regeneration. Combining Metcovazin® with electrical stimulation may accelerate wound healing; however, its therapeutic efficacy, optimal stimulation duration, and underlying molecular mechanisms remain unclear.

Objective: This study aimed to evaluate the effectiveness of combined Metcovazin® and electrical stimulation at different stimulation durations in promoting wound healing in a diabetic rat model and to investigate the underlying mechanism through the Cav1.2 voltage-gated calcium channel (VGCC)–PDGF-BB/PDGFRβ–ERK1/2 signaling pathway.

Methods: A randomized posttest only controlled group design was conducted using 30 male Wistar rats randomly assigned to six groups: K0 (non-diabetic rats treated with Metcovazin®), KDM (diabetic rats treated with Metcovazin®), KES (diabetic rats receiving 15 min of electrical stimulation), K5 (diabetic rats treated with Metcovazin® plus 5 min of electrical stimulation), K15 (diabetic rats treated with Metcovazin® plus 15 min of electrical stimulation), and K30 (diabetic rats treated with Metcovazin® plus 30 min of electrical stimulation). Diabetes was induced by intraperitoneal administration of nicotinamide (110 mg/kg body weight) and streptozotocin (45 mg/kg body weight). A full-thickness excisional wound (0.8 cm in diameter) was created on the dorsal skin of each rat, followed by six consecutive days of treatment. On day 7, α-smooth muscle actin (α-SMA), type I collagen expression, total collagen expression, re-epithelialization, Cav1.2 VGCC expression, PDGFRβ expression, PDGF-BB levels, and ERK1/2 levels were evaluated. Skin impedance was also measured. Data were analyzed using one-way analysis of variance (ANOVA) or the Kruskal–Wallis test, followed by Dunnett's or Dunn's post hoc tests, as appropriate.

Results: The combination of Metcovazin® and 15 min of electrical stimulation was the most effective intervention for enhancing wound healing compared with Metcovazin® alone, as evidenced by significantly increased α-SMA levels ($p = 0.049$), type I collagen expression ($p = 0.003$), total collagen expression ($p < 0.001$), and re-epithelialization scores ($p = 0.012$). Compared with the KDM, KES, and combination treatment groups, combination therapy also significantly enhanced type I collagen expression ($p = 0.040$), total collagen expression ($p < 0.001$), and re-epithelialization ($p = 0.019$). Relative to K0, the KDM group exhibited significantly lower PDGFRβ expression ($p = 0.008$), α-SMA levels, type I collagen expression, and re-epithelialization (all $p < 0.05$), accompanied by increased skin impedance. In contrast, Cav1.2 VGCC expression, PDGF-BB levels, total ERK1/2 levels, and total collagen expression were not significantly different ($p > 0.05$).

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Electrical stimulation partially modulated the signaling pathway by increasing Cav1.2 VGCC expression ($p = 0.007$) and PDGFRβ expression ($p = 0.006$), whereas different stimulation durations affected only PDGFRβ expression ($p = 0.003$).

Conclusions: The combination of Metcovazin® and 15 min of electrical stimulation was the most effective intervention for accelerating wound healing in a diabetic rat model. This therapeutic effect was associated with partial modulation of the Cav1.2 VGCC–PDGF-BB/PDGFRβ–ERK1/2 signaling pathway, leading to enhanced collagen deposition and re-epithelialization.

Keywords: diabetes mellitus; wound healing; electrical stimulation; Metcovazin®; growth factor