Topical Application of CD362⁺ Human Mesenchymal Stem Cells (Cyndacel-M) Seeded in Excellagen™ Scaffold Augments Wound Healing and Increases Angiogenesis in a Diabetic Rabbit Ulcer Model


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Introduction

• Diabetic foot ulcers (DFU) is one of the most common complication of diabetes.
• 15–25% of all patients with diabetes will develop DFU.
• 15-fold higher risk of lower-extremity amputation with DFU.
• Cell-based therapy provides a novel therapeutic strategy for increasing wound closure and augmenting angiogenesis.

Objectives

1. To compare the efficacy of topical administration of CD362⁺, CD362⁻ and PA-SSC in wound healing in the alloxan-induced rabbit model of diabetic ulceration.
2. To determine if combined [topical + IV] delivery of cells is more effective in wound healing and will improve glycemic control.
3. To understand the mechanism of SSC mediated wound healing in diabetes mellitus.

Methods

Induction of hyperglycemia: Diabetes was induced in rabbits by using 150mg/kg alloxan (Sigma-Aldrich) in 10ml saline and administered via an ear vein using a intravenous cannula. Blood glucose was checked daily using a glucometer from a pinprick of the marginal ear vein.

Surgical procedure: After 5 weeks of hyperglycemia, wounds were created by using sterile, disposable 6-mm punch biopsies. Each wound was treated with one of the randomized treatment groups.

Diabetic Rabbit Ear Ulcer Model

New Zealand white rabbits (3.5-5 Kg)

Diabetes Induction: Alloxan (150 mg/kg) Wound creation and application of scaffold + MSC (CD362⁺/CD362⁻/PA-SSC)

Experimental week 0 1 2 3 4 5 6
• Glucose levels
• Weight
• Water intake
• Behaviour
• Euthanasia
• Infection
• Wound closure
• Healing

Results

Study 1: Comparison of topical administration of CD362⁺, CD362⁻ and PA-SSC in diabetic wound healing

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Control (No treatment)</th>
<th>Excellagen scaffold alone</th>
<th>Excellagen scaffold + 1,000,000 CD362⁺ cells</th>
<th>Excellagen scaffold + 1,000,000 CD362⁻ cells</th>
<th>Excellagen scaffold + 1,000,000 PA-SSC</th>
</tr>
</thead>
</table>

Study 2: To determine if combined topical + IV delivery is more effective in wound healing and will improve glycemic control

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Topical administration of Excellagen + 1*10⁶ optimal cells</td>
</tr>
<tr>
<td>2</td>
<td>Topical treatment with Excellagen + 1<em>10⁶ cells and intravenous delivery of 2</em>10⁶ cells/Kg body weight</td>
</tr>
</tbody>
</table>

Summary and conclusion

Study 1: Effect of topical administration of CD362⁺, CD362⁻ and PA-SSC in diabetic wound healing

1. Excellagen accelerates the wound healing rate as compared to untreated wounds.
2. Wounds treated with 1 *10⁶ (CD362⁺) cells in an Excellagen scaffold showed highest and most significant % wound closure when compared with the untreated group at 1 week period.
3. Increased percentage wound closure may be associated with more efficient neovascularisation-angiogenesis.

4. A significantly increased surface density (SV), length density (LV) and reduced radial diffusion distance (Rdiff) is observed in Excellagen + (CD362⁺) cells treated wound groups in comparison to untreated wounds.

Study 2: Topical vs Combination study

1. Effect of combination [topical & IV] treatment: slight increase in % wound healing is observed in combination versus topical treated animals but this difference is not significant.

2. Topical treatment alone: The wounds treated with Excellagen + (CD362⁺) cells showed increased % wound closure compared to wounds treated with Excellagen alone and confirms the results seen with objective 1.

Thus, the application of CD362⁺ cells in an Excellagen matrix may lead a new therapeutic product with improved wound healing potential and in a less healing time.

References

2. REDDSTAR, Repair of Diabetic Damage by Stromal Cell Administration (www.reddstar.eu)

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Diabetes (to include obesity, pathophysiology & epidemiology)

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