Evaluation Of Azilsartan Transdermal Hydrogel In Volumetric Muscle Loss Injury In A Rat Model

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Abstract

A volumetric muscle loss (VML) is the loss of skeletal muscle with associated functional impairment, also known as traumatic or surgical muscle loss. Major muscle tissue loss occurs in personnel on battlefields who have suffered serious injuries. As a result of lost satellite cells, matrix degradation, and persistent upregulation of proinflammatory markers, the muscle cannot regenerate or achieve proper function. So, in the present study, we formulated the azilsartan hydrogel (0.5 and 1%) and further investigated the effect of the azilsartan (AZL) hydrogel in the VML rat model. For that, the volumetric muscle loss was done in the gastrocnemius muscle of 24 rats. The animals were divided into 5 groups: uninjured, VML, VML+ Ethanol, VML+AZL (0.5%) and VML+AZL (1%). The hydrogels were applied daily for 28 days at the injury site. Our results showed that AZL (1%) improved the gastrocnemius weight and their weight-to-length ratio. Also, the oxidative stress and antioxidant levels in skeletal muscle of VML were restored. In conclusion, these results showed that azilsartan hydrogel is effective in volumetric muscle loss induced in rats and could be taken as a therapeutic strategy.

Keywords: Volumetric muscle loss, Azilsartan, Hydrogel, Gastrocnemius, Oxidative stress.

INTRODUCTION

Traumatic muscle loss during battlefield or surgery is the primary reason for Volumetric Muscle Loss (VML) [1]. VML results in 20% or more muscle mass loss, inhibiting the self-repair pathway and causing significant functional impairment [2]. It damages the injury site cells and injures the nearby tissues that include nerves, bones, tendons, and blood vessels. An estimation showed that there is ~250,000 VML injury per year on the battlefield in the US [3]. 8% of medevac cases got handicapped due to VML injury. In a lifetime, $340,000-440,000 is invested by a disabled person due to VML injury [3]. VML injury results in the loss of regenerative cells such as satellite cells, the basal lamina, and fibroadipogenic progenitors [4].

Hydrogels have numerous advantages like they have a particle size within the nanometric range, follow the non-Newtonian pseudo plastic flow, having pH of acidic range, high bio adhesive property [5–8]. One of the main advantages of using hydrogel is their applicability *i.e.* easily applicable, and non-greasy. Azilsartan is an Angiotensin Receptor Blocker (ARB) highly selective for the AT1R and used to treat hypertension [9,10]. Lastra *et al.* showed that azilsartan improves insulin resistance and glucose transport activity in skeletal muscle *via* the Akt/AS160 signalling in the gastrocnemius muscle and soleus muscle [10]. Also, azilsartan significantly ameliorated the cardiac fibrosis in abdominal cardiac constriction (AAC) [11]. One interesting finding in the mice model of contusion injury showed that losartan shows muscle regeneration and improves muscle healing [12] and is proposed to use along with muscle-derived stem cells to treat skeletal muscle injuries. In the present study, we prepared azilsartan hydrogels as an appropriate treatment for VML-induced muscle injury. We have chosen the 1% Carbopol 940 as reported effective in loading in ARB drugs [13] due to its good adhesive property, consistency, nonirritant, and swelling volume [14–16].

MATERIALS AND METHODS

Materials

Azilsartan medoxomil was gifted by Honour lab limited, Telangana, India. All the chemicals used were purchased from Himedia and Sigma until unless specified. All solvents used in the present study were of analytical grade. Propylene glycol was purchased from Changshu Hongsheng Fine chemical Co. Limited, India.