

# The Efficacy of ADIPOR1 and ADIPOR2 Peptide-Agonist AdipoRon in Preventing Contracture in a Rabbit Model of Arthrofibrosis

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**INTRODUCTION:** AdipoRon is an adiponectin receptor 1, 2 (ADIPOR1 and ADIPOR2) agonist with potential antifibrotic effects identified in recent studies. Specifically, AdipoRon was suggested to have an antifibrotic role in a mouse model of knee contracture. However, whether AdipoRon is effective in mitigating joint stiffness in a rabbit model of arthrofibrosis, a current translational gold standard animal model in studying arthrofibrosis in humans, is unknown. As such, we examined the efficacy of intravenous (IV) AdipoRon at mitigating flexion contracture in a rabbit model of knee arthrofibrosis.

**METHODS:** 56 female New Zealand White (NZW) rabbits were divided into 3 dosing groups: vehicle (dimethyl sulfoxide, DMSO), 2.5 mg/kg AdipoRon, and 5 mg/kg AdipoRon. Dosing groups were selected based on previously published results studying safety of IV AdipoRon in surgically-stressed rabbits. AdipoRon was dissolved in DMSO and then administered IV preoperatively and for 5 subsequent days postoperatively (30 rabbits, Aim 1) (**Figure 1**). AdipoRon was additionally dosed in the same manner after Kirschner wire (K-wire) removal at 8 weeks (26 rabbits; Aim 2). Rabbits were permitted free range within cages before and after K-wire removal. The primary outcome of joint passive extension angle (PEA,°) was measured at 8, 10, 12, 16 and 24 weeks following index surgery at a set torque of 50 Newton centimeters (N-cm) using a validated plunger device. A low passive extension angle indicates a larger flexion contracture (i.e. greater stiffness). At 24 weeks, rabbits were sacrificed and limbs were harvested in order to measure posterior capsular stiffness (N-cm/°) using a dedicated dynamic load cell device.

**RESULTS SECTION:** Regarding aim 1, the 5 mg/kg treated rabbits had a significant increase in PEA when compared to controls at 16-weeks (p<0.05) (**Figure 2A**). This effect was lost at later time points. Regarding aim 2, the 5 mg/kg treated rabbits had a significant increase in PEA when compared to controls at 10-weeks (p<0.05) (**Figure 2B**). These effects were lost at later time points. Posterior capsular stiffness was not significantly different at any dose group in either aim (**Figure 3**).

**DISCUSSION:** We are the first to report the efficacy of IV AdipoRon in a rabbit model of knee arthrofibrosis. The present study demonstrated a significant dose-dependent decrease in joint PEA at early time points; however, with time the knee range of motion in control rabbits gradually caught up to the experimental group.

**SIGNIFICANCE/CLINICAL RELEVANCE:** Building on previously published work, the present investigation provided the first assessment of AdipoRon's efficacy in mitigating knee stiffness in the current gold standard rabbit model of arthrofibrosis. Results of this investigation provide further evidence as to the potential role of AdipoRon as a preventative for arthrofibrosis in large mammals.

## IMAGES

