

Onabotulinum Toxin (BoNT-A) for Prevention of Heterotopic Ossification

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Introduction

Heterotopic ossification (HO) is the formation of lamellar bone in soft tissue areas, usually involving large joints (hips, shoulders, elbows, knees). Therapeutic strategies for prevention of HO are still limited with varying degrees of success. Burn patients with higher TBSA are at higher risk¹. Current therapies are lacking².

Onabotulinum toxin A (BoNT-A is a well-established therapy for pain and spasticity that is also identified to act on anti-inflammatory pathways³.

Our aim was to identify therapeutic efficacy of BoNT-A in a burn model. This model was developed by Levi et al. developed HO in 100% of mice by inducing a 30% TBSA burn with a tenotomy of the achilles tendon

Hypothesis: BoNT-A inhibits the development of HO in a burn mouse model

Methods

Induce heterotopic ossification in an established burn mouse model – 30% TBSA burn with achilles tenotomy in mice under anesthesia⁴.

- Two groups
- Experimental group received 0.3U/kg of BoNT-A at regular intervals (3 days, 30 days, 60 days) and a control group that received the same volume of saline at the same time intervals
 - After therapy was complete, mice were humanely euthanized and the injected hindleg was sent for micro-CT at University of Illinois
 - The volume of Heterotopic ossification was calculated in each sample
 - Means were calculated and students T-Test was used for statistical analysis between groups

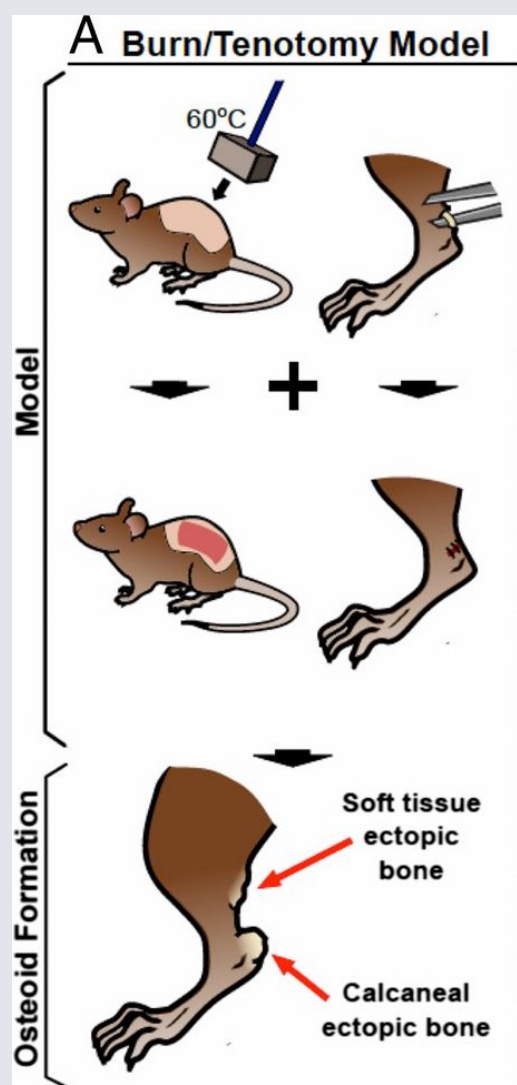


Figure 1. Burn-Tenotomy Model
Taken from Levi et al.⁵

Results

When comparing the average volume of HO the two groups, the volume of HO was separated into bone that developed at the site of the tenotomy and bone that developed in the more proximal posterior compartment

When looking at mean volume of HO that developed between the two groups, the group treated with BoNT-A had a reduced average volume of HO across the board.

When stratifying within groups for HO that developed local to the injury and remotely (in the calf), the decrease in HO development was 5-fold reduction at the local site and about an 8-fold reduction in the remote site. Overall HO development was decreased by almost 6-fold.

In figure 1, there are differences in HO development between the samples with the greatest recorded HO in each group. HO labeled in green represents HO developing in the calf. HO labeled in blue represents HO developed at the tenotomy site. Both sites appear to have smaller HO volumes in the BoNT-A group

	Tenotomy (uL)	Proximal calf (uL)	Total Volume (uL)
Botox	0.35	0.11	0.46 (SD =0.29)
Saline	1.73	0.86	2.59 (SD =.57)
p-value	0.0005	0.003	0.0004

Table 1. Average volume of HO in each area

This table looks at the average volume of HO developing in the tenotomy site, the proximal calf, and the total amount

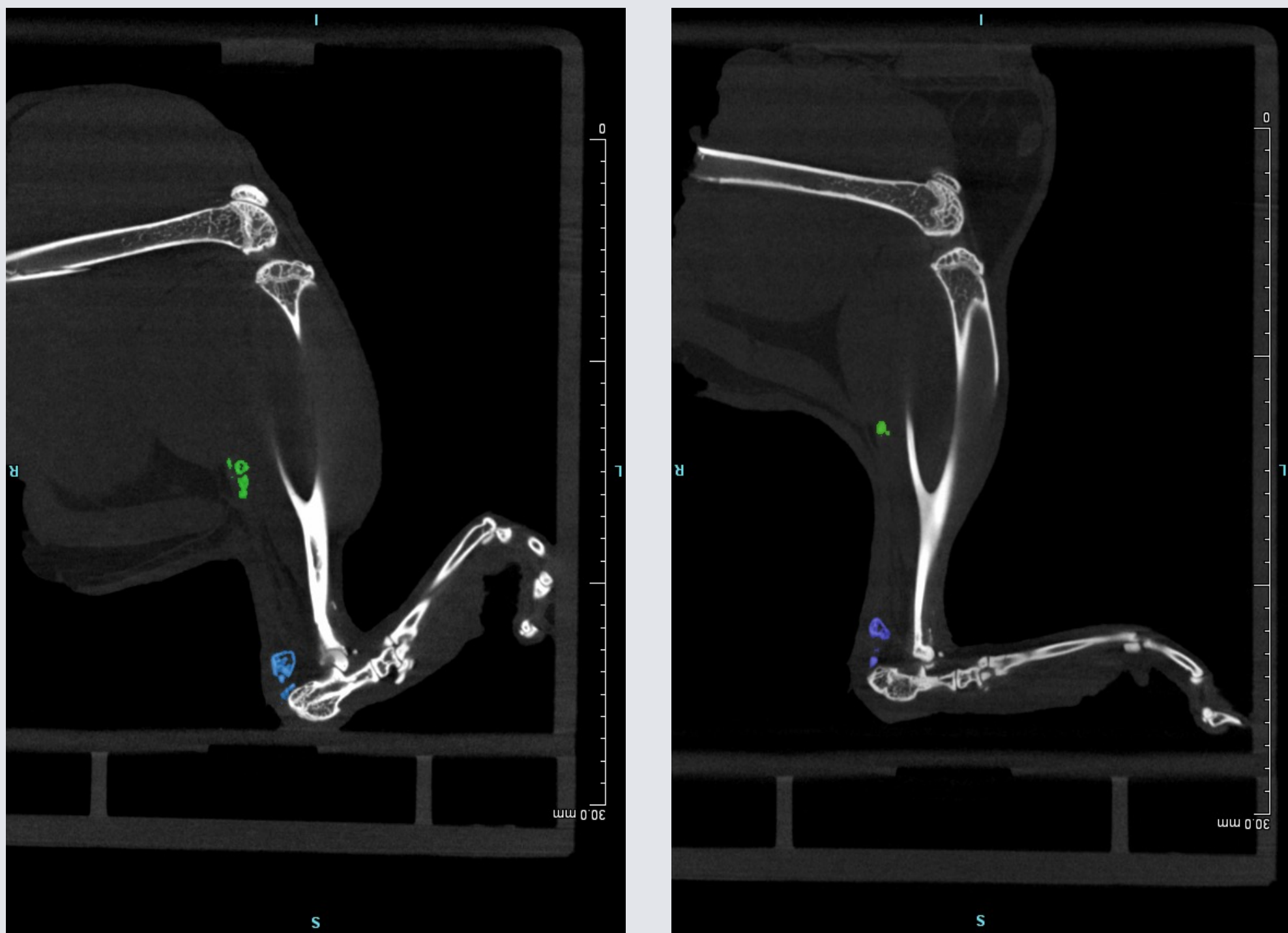


Figure 1. Comparison of HO and saline samples

Left – sample treated with saline; right – sample treated with BoNT-A

Discussion

- Current evidence exists that resection of HO initiates a cascade that leads to recurrent development⁶.
- BoNT-A can significantly reduce the volume of HO in a burn model that develops HO 100% of the time
- Furthermore, within this model, BoNT-A decreased the development of remote HO compared to local HO
 - This may be more applicable to burn patients developing HO in areas remote to their injuries
- This may have future therapeutic implications as a newer indication of BoNT-A to prevent HO, specifically secondary prevention after excision
- Next steps currently being investigated are identifying the mechanism by which BoNT-A can significantly reduce the volume of HO
 - Theories currently under investigation include arrest of the bone maturation process as well as inhibition of the inflammatory pathway leading to the development of HO.
- Identifying functional implications of reduced but not eliminated HO
- Applications that require further study include HO that develop in other settings of traumatic injuries as well as congenital HO.
- This study can hopefully form the basis that leads to potential translation to human subjects

References & Acknowledgments

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