Topical Administration of Raloxifene Does Not Significantly Improve Bone Toughness or Screw Pull-out Strength

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Introduction

Upper extremity fractures account for one-third of all fractures in the elderly.[1-3] In addition, there is an increased risk of proximal humerus fractures in patients with osteoporosis.[1,4,5] Failure of fixation has been shown in some series to be greater than 40 percent[6] and is attributed to limited pullout strength of screws in poor quality of bone stock.[7] While considerable efforts have been made towards improving implant design, relatively little research has addressed localized treatment of the underlying changes in the mechanical properties of cancellous bone in the humeral head. Previous studies have shown that Raloxifene, a selective estrogen receptor modulator used to prevent and treat osteoporosis, can increase the toughness of bone in vitro.[8] To date, it is unknown if this improvement in mechanical toughness will translate into a clinically significant difference in screw pull-out strength. The purpose of this study was to make direct comparisons between osteoporotic bones treated topically with Raloxifene and untreated bone. It was hypothesized that toughness and implant fixation strength can be improved with this straightforward approach.

Methods

The first portion of this study involved four-point bending tests of bone beams to determine toughness. Cancellous bone specimens were carefully harvested from fetal bovine femora using a bone saw and sanded to a uniform size (25 × 4 × 1.5 mm). Digital calipers were used to ensure that specimen size fell within a ± 0.05 mm tolerance. Prior to mechanical testing, bone specimens were sonicated for thirty seconds, wrapped in gauze with phosphate-buffered saline (PBS) solution, and subjected to two freeze-thaw cycles at −20°C. Matched pairs of specimens were then submerged in solutions for one week at a temperature of 4°C with continuous stirring. Specimens were soaked in either a Raloxifene solution at a concentration of 20 μM (RAL) or a PBS solution as a control (CTL). All solutions had 1% penicillinstreptomycin. Specimens were thawed to room temperature prior to testing. The beams were positioned within a test fixture (Fig 1.) on a universal testing frame (Instron 5542; Norwood, MA) equipped with a 50 N load cell and quasi-statically loaded

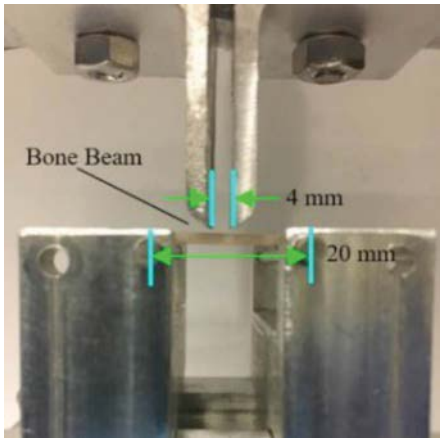

Figure 1. 4-point bending test setup.

to failure. The second portion of the experiment involved pull-out testing of 3.5 mm cancellous screws (DePuy Synthes, Warsaw, IN) from human cadaveric humeri that were confirmed to be osteoporotic by DEXA scans. The humeri were decorticated with the exception of the lateral wall. The screws were inserted unicortically to a depth of 30 mm in 5 standard trajectories based on a small fragment locking proximal humerus plate (DePuy Synthes, Warsaw, IN). Each sample came as a matched pair and one side was soaked in RAL solution and the contralateral side in control solution. Pull-out testing was conducted on a universal testing frame (TA Electro-Force 3550; Eden Prairie, Minnesota) equipped with a 1,110 N/14.1 N-m load/torque cell. The screws were pulled out at 0.03 mm/sec until failure and the load at failure was determined.

Results

The toughness in four-point bend testing was not significantly different between groups ($p = 0.876$) (Fig. 2). The toughness values were 0.151 ± 0.068 J/m3 and 0.155 ± 0.0439 J/m3 for the RAL and CTL groups, respectively. For the screw pull-out tests, the Raloxifene soaked samples trended towards a higher load at failure, however these results were not statistically significant (p-value = 0.099) (Fig. 3). Failure loads were 122 ± 74.3 N and 89.5 ± 63.8 N for the RAL and CTL groups, respectively.

Discussion

Research into biological therapies to address osteoporotic disease is scarce, despite the

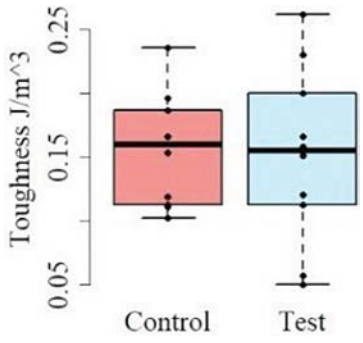

Figure 2. Toughness results.

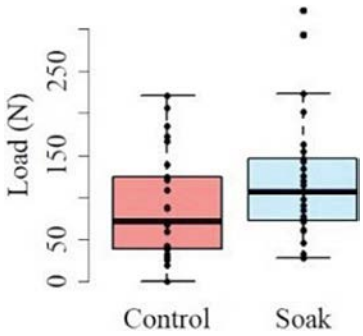

Figure 3. Screw pull-out results.

profound improvements to surgical outcomes that they may offer patients. While screw pull-out strength trended towards a higher failure load in the RAL group, the results were not statistically significant. Bone toughness was not increased by soaking the specimens in Raloxifene. This is in contrast to previously published data by Gallant et al., which found that topical administration of Raloxifene solution increased toughness, however these results are not directly comparable. The current study included fetal bovine and human cadaveric bone, whereas the study by Gallant et al. was performed on dog tibiae.[8] In addition, the current study used cancellous bone instead of cortical bone. This study included several limitations. The number of samples that could be harvested from each bone was limited by the size of the bone and the presence of arteries. In addition, cancellous bone introduced greater structural variability into the specimens. Future work on this project with larger sample sizes may demonstrate a statistically significant trend that could directly influence clinical practice. Rather than using individual screw pull-out testing as a proxy for failure, an entire locking plate-screw construct could be tested. While significantly more costly, testing a locking plate-screw construct would be more clinically relevant.

Significant/Clinical Relevance

This research shifts the focus of the discussion regarding osteoporotic fracture care from implant design to identifying biologic solutions that address the true underlying issue of bone quality. The results show that topical administration of Raloxifene does not significantly increase bone toughness or screw pull-out strength, which contradicts the results of previous work.

Acknowledgments

This study was funded by AO Trauma North America.

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