INTRODUCTION
Pathologic bone fractures and other lesions caused by cancer metastases can be currently managed with the injection of bone cements to relieve pain and restore the structural integrity of the bone. Chemotherapeutic agents can be added to these bone cements to reduce the need for additional systemic chemotherapy or radiation therapy [1-2].

Even though antibiotic eluting bone cements are successfully used in orthopedic practice, adding chemotherapy drugs to bone cement pose a different set of problems. This is mainly due to the toxicity concerns associated with the use of chemotherapy agents. To avoid local or systemic toxicity, the drug elution profile of a particular bone cement/drug concentration need to be determined. The drug elution profile depends on many factors including initial drug concentration, mixing conditions, surface area of the bone cement implant, etc. In this study, the effect of initial methotrexate amount on bone cement elution was measured.

It is our hypothesis that the relationship between clinically relevant initial drug concentration and amount of methotrexate eluted is not linear. The aim of this experiment is to measure in vitro drug elution from bone cement (Vertebroplastic radiopaque resinous material) containing four different initial methotrexate amounts. In addition, the effect of initial methotrexate concentration on the flexural properties of post cured bone cement was determined.

METHODS
Vertebroplastic radiopaque resinous material was kindly provided by DePuy Spine Inc., MA. Methotrexate was obtained from Bedford laboratories, Bedford, OH.

Preparation of experimental bone cement mixtures: The bone cement used in this study is a two part system containing 22.5 g of powder (methylmethacrylate polymer and barium sulfate) and 9.1 ml liquid monomer (methylmethacrylate monomer). The powder component (2.5 g) of the bone cement was first mixed thoroughly with methotrexate (50 or 100 or 150 or 200 mg). The liquid monomer (1 ml) was then added to the prepared powder and mixed well. The resulting chemotherapeutic bone cement mixture was used within 5 minutes to prepare the elution and mechanical test specimens.

Preparation of in vitro test specimens: Glass vials were used as molds to prepare the cylindrical specimens. The prepared methotrexate/bone cement mixtures were poured into the glass vials and were allowed to harden for 24 h at 37° C. The polymerized cylindrical bone cement specimens were then taken out of the glass molds by breaking the glass molds carefully. Three cylindrical elution test specimens were prepared in each group.

Figure 1: Comparison of methotrexate elution. The drug elution increased at least four times when the initial concentration doubled from 100 mg to 200 mg.
**In vitro elution experiment:** The cylindrical bone cement specimens were placed in vials containing 20 ml saline. The vials were placed in an incubator maintained at 37°C. Methotrexate elution was measured at different time points for 670 h. The eluted methotrexate concentration was measured in triplicates using a micro-plate reader (Spectramax 190, Molecular devices, CA) at a wavelength of 405 nm. The elution media was replaced whenever the methotrexate concentration was measured.

**Three-point bending test:** 2 x 2 x 40 mm rectangular test bars were prepared by injecting bone cement mixtures into square borosilicate glass tubes (Friedrich & Dimmock, Milvile, NJ). The post cured specimens were soaked in 50 ml saline for 20 days. Flexural strength and modulus of the bone cement specimens after soaking was determined by a 3-point bending test. The specimens were loaded to failure by using an electromechanical testing machine (800LE4 Dynamic Test System, Test resources Inc., Shakopee, MN) at a crosshead speed of 1 mm/min. The distance between the support beams of the three point test jig is 28 mm. The flexural strength (in MPa) for a three point bend test was calculated by the following formula

\[ \sigma = \frac{3FL}{2BH^2} \]  

where \( l \) is the distance between the supports in mm, \( F \) is the failure load (N), \( B \) is the width, and \( H \) is the height of the beam in mm. The flexural modulus (E in GPa) for a three point bend test was calculated from

\[ E = \left( \frac{F}{D} \right) \left( \frac{l^3}{4BH^3} \right) \]

where \( l \) is the distance between the supports in mm, \( B \) and \( H \) are the specimen width and height respectively in mm, and \( F/D \) is the slope in the linear region of the load-displacement curve.

**RESULTS AND DISCUSSION**

The results indicate that the relationship between initial methotrexate amount and methotrexate elution is non-linear. Methotrexate elution increased four fold when the initial methotrexate amount was increased from 100 to 200 mg. This may be due to the drastic changes in pore structure and interconnectivity caused by the addition of 200 mg methotrexate. The effect of changes in pore structure on the mechanical properties of bone cement was evaluated using a three point bending test. Addition of methotrexate decreased the flexural strength of vertebroplastic bone cement. However, the flexural modulus (dry control specimens) was not affected by the addition of methotrexate. The mechanical properties decreased after soaking in saline for 20 days (Table 1). It should be noted that the stiffness and strength of bone cement is usually very high when compared to the properties of cancellous bone [3]. Therefore, the decrease in mechanical properties of this experimental chemotherapeutic bone cement after soaking should not in anyway compromise the mechanical stability of the fracture construct. Due to the potential local toxicity to surrounding vital organs, the surgeons should be careful in determining the initial amount methotrexate added.

**CONCLUSIONS**

The results showed that Vertebroplastic bone cement is suitable for use with chemotherapeutic agents. Initial methotrexate amount seems to play a major role in the pore structure formation. This should be kept in mind to avoid any local drug toxicities to adjacent healthy tissues.

**REFERENCES**


**ACKNOWLEDGEMENTS**

Authors would like to thank Depuy Spine, MA for their financial support and bone cement.

| Table 1: Mechanical properties of bone cement pre and post elution. Control did not contain any methotrexate. |
|-------------------------------------------------|------------------|------------------|
| Before soaking                                  | Flexural Strength (MPa) | Flexural Modulus (MPa) |
| Control                                        | 55.6 ± 2.9        | 2408.6 ± 62.5     |
| 100 mg MTX                                     | 47.7 ± 2.8        | 2589.6 ± 178.1    |
| 200 mg MTX                                     | 39.4 ± 2.7        | 2540 ± 76.5       |
| After soaking for 20 days                      |                   |                  |
| Control                                        | 43.7 ± 2.8        | 1839.3 ± 51.4     |
| 100 mg MTX                                     | 30.3 ± 3.4        | 1438.8 ± 55.1     |
| 200 mg MTX                                     | 28.9 ± 1.8        | 1391.4 ± 94.9     |