In Vivo Effects of Single Intra-Articular Bupivacaine Injection

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Introduction: Single intra-articular local anesthetic injections are commonly used as diagnostic and therapeutic modalities. Recent in vitro studies (1, 2) show chondrotoxic effects of local anesthetics. In addition, a rabbit in vivo study (3) and a clinical case series (4) show chondrotoxicity after continuous infusions of bupivacaine into the glenohumeral joint. This study was conducted to determine whether a single injection of bupivacaine is toxic to articular chondrocytes in vivo.

Materials and Methods: All animal injections were performed following Institutional Animal Care and Use Committee approved protocols. Twelve Sprague Dawley rats received a 100 μl injection of sterile 0.9% saline into the right knee (Control Knee) and 100 μl of single dose 0.5% bupivacaine (AstraZeneca) into the Left Knee (Experimental Knee). At each time point (2 weeks, 6 months), 6 rats were euthanized and the distal femurs were harvested. Rat knees were immediately placed into pre-warmed live/dead-cell fluorescent staining solution (Molecular Probes 0.1% propidium iodide (PI) and 0.1% 5-chloromethylfluorescein diacetate-(CMFDA) for one hour at 37°C. Samples were washed and imaged via confocal microscopy at the medial femoral condyle, lateral femoral condyle and trochlear groove. Percentage of live and dead cells, were determined through analysis of 3-D reconstructions of confocal images. The knees were then assessed by histological analysis and graded using a modified Mankin score . Data were analyzed by one-way ANOVA followed by Bonferroni t-test (using GraphPad Prism) with significance set at a p<0.05.

Results: At two weeks, there were no significant differences in cell viability or modified Mankin score between saline and bupivacaine groups at all three anatomical locations (medial femoral condyle, lateral femoral condyle or trochlea) (p>0.05). Average percentage of live chondrocytes was 84±13% in bupivacaine injected knees compared to 81±16% in saline injected knees (Figure 1A). At 6 months after injections, average percentage of live cells was 92±9% for bupivacaine groups and 89±8% for saline groups (p<0.05, Figure 1B). Histological analysis at 6 months revealed higher total Mankin scores indicative of greater degeneration to the medial and lateral femoral condyles (Table 1). Bupivacaine injected knees showed hypercellularity and chondrocyte cloning with loss of the tidemark (Figure 2). The articular surface remained intact in most of the specimens. The histological appearance in bupivacaine injected knees of hypercellularity extending below the expected tidemark was suggestive of a reparative response. Figure 2 displays hematoxylin and eosin slide of the trochlear groove of Rat 2 six months after injection of bupivacaine (A) and saline (B).

Discussion: These results show histological changes suggestive of both reparative responses and degeneration in bupivacaine injected knees. While no significant differences in cell death was observed between single intra-articular injections of 0.5% bupivacaine and saline controls 2 weeks or 6 months post-injection, the histological results showed increased changes to cellularity, tidemark and structure in bupivacaine treated knees. Histological changes were subtle and marked cartilage loss was not seen in any of the specimens. Histological signs of a reparative response without apparent increased chondrocyte death at two weeks and six months after exposure suggest that injured chondrocytes may have recovered or dead chondrocytes may have been replaced within the study time frames in this skeletally immature small animal model. Results of this study, in conjunction with previously published studies (1-4), support using intra-articular local anesthetics at the lowest concentrations, smallest volumes, and for the shortest period of time needed for the desired clinical effect until additional data from small and large animal studies are available.


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Total Mankin Score: Saline vs. Bupivacaine