

Local Anesthetics and Corticosteroids: A Chondrotoxic Combination

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INTRODUCTION:

Local anesthetic and corticosteroid combination injections are often used in clinical practice, but research investigating the chondrotoxic properties of these combinations is minimal. The limited work investigating the combination of local anesthetics and corticosteroids indicates that agents like lidocaine potentiate the chondrotoxicity of corticosteroids. Seshadri et al. demonstrated that the combination of Methylprednisolone and 1% lidocaine was toxic to bovine articular chondrocytes, causing nearly complete necrosis of all test cells. Similarly, Farkas et al. found that separate cultures of Betamethasone in combination with 1% lidocaine, 0.5% bupivacaine, or ropivacaine were all significantly chondrotoxic when compared to corticosteroid or local anesthetic treatment groups alone. Syed et al. reported that Triamcinolone acetonide alone, 0.25% bupivacaine alone, and the combination of these two medications resulted in significant chondrotoxicity when compared to cells cultured in control media. These studies suggest that corticosteroids and local anesthetics may have a synergistic effect on chondrocyte death. It is plausible that other commonly used corticosteroids may also prove chondrotoxic, especially when combined with local anesthetics.

The purpose of this study was to evaluate the effect of single injection doses of 1% lidocaine or 0.25% bupivacaine in combination with single injection doses of Dexamethasone sodium phosphate (Decadron®), Methylprednisolone acetate (Depo-Medrol®), Betamethasone sodium phosphate and Betamethasone acetate (Celestone® Soluspan®), or Triamcinolone acetonide (Kenalog®) on human chondrocyte viability.

METHODS:

Human chondrocytes were seeded at a density of 0.5×10^6 cells/well in 6 well plates. All medications were delivered to human chondrocytes in vitro for the medication's respective average duration of action using a bioreactor containing a continuous infusion pump constructed to mimic joint fluid metabolism. A two-color fluorescence assay was used to evaluate cell viability. A mixed-effects regression model was used to evaluate the mean differences in cell viability between treatment groups.

To estimate the mean differences in cell death between the 11 experimental conditions, a mixed-effects regression model with a random effect for the well was used due to the non-independence of observations, specifically the 4 outcome estimates per well. From this model, simultaneous (family-wide) 95% confidence intervals and p-values were estimated for the pair-wise difference between the conditions. Values are reported as mean percent cell death \pm standard deviation.

RESULTS:

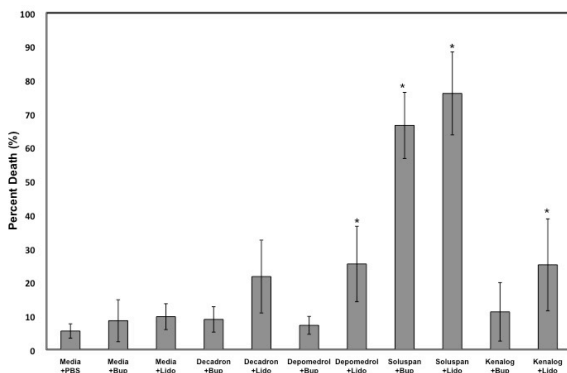


Figure 1. The effect of each individual local anesthetic, and each combination of local anesthetic and corticosteroid on cell viability after 14 days. Asterisks denote culture conditions that were significantly more chondrotoxic than cultures of local anesthetics alone.

At 14 days, chondrocytes treated with 1% lidocaine and Betamethasone sodium phosphate and Betamethasone acetate illustrated a dramatic decrease in viability ($76.08 \pm 12.32\%$ death) compared with control media ($5.51 \pm 2.13\%$ cell death, $p < 0.01$), 1% lidocaine alone ($9.77 \pm 3.8\%$ $p < 0.01$), and 0.25% bupivacaine alone ($8.56 \pm 6.23\%$ cell death, $p < 0.01$). Cultures of 0.25% bupivacaine and Betamethasone sodium phosphate and Betamethasone were similarly chondrotoxic ($66.57 \pm 9.82\%$ cell death; $p < 0.01$) compared to controls. Compared with 1% lidocaine alone ($9.77 \pm 3.8\%$ cell death), both 1% lidocaine and Methylprednisolone acetate ($25.4 \pm 11.2\%$, $p < 0.013$) and 1% lidocaine and Triamcinolone acetonide ($25.2 \pm 13.6\%$, $p < 0.016$) also illustrated significant chondrotoxic effects.

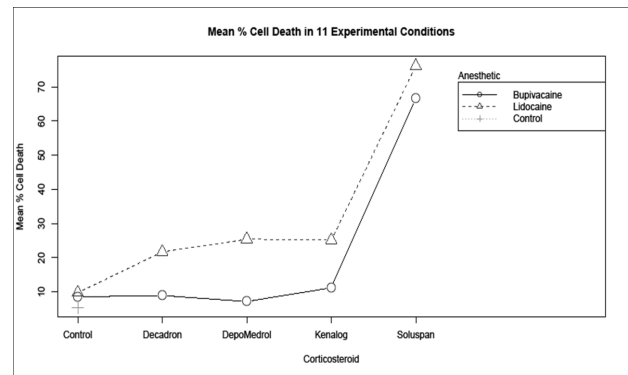


Figure 2. Mean percent chondrocyte death in 11 experimental conditions.

DISCUSSION:

Analysis of the viability of chondrocytes after treatment with single dose concentrations of four commonly used corticosteroids and local anesthetics revealed two significant findings. First, Betamethasone sodium phosphate and Betamethasone acetate (Celestone® Soluspan®) dramatically decreased cell viability when used in combination with both 1% lidocaine and 0.25% bupivacaine in comparison to cultures containing each anesthetic alone. Second, cultures containing Methylprednisolone acetate and Triamcinolone acetonide exhibited a significant decrease in chondrocyte viability when combined with 1% lidocaine, but demonstrated no increased cell death when combined with 0.25% bupivacaine.

These results clearly suggest that Betamethasone sodium phosphate and Betamethasone acetate (Celestone® Soluspan®) is highly chondrotoxic in the presence of local anesthetics. There is also evidence to suggest that Betamethasone sodium phosphate and Betamethasone acetate is chondrotoxic in culture alone. The amount of additional cell death due to local anesthetics is unclear.

It is hypothesized that benzalkonium chloride, a preservative in the Betamethasone sodium phosphate and Betamethasone acetate solution, is responsible for the negative impact on cell viability when administered alone. While Betamethasone sodium phosphate and Betamethasone acetate did not show significant cell death when analyzed independently, a solution containing both Betamethasone combination and benzalkonium chloride began to be significantly chondrotoxic at levels 5% of standard clinical doses. The crystalline structure of Betamethasone sodium phosphate and Betamethasone acetate preparations may also be responsible for its chondrotoxicity.

SIGNIFICANCE:

Despite generally positive clinical outcomes, intra-articular injections of local anesthetics and corticosteroids should be used cautiously, particularly when using Betamethasone sodium phosphate and Betamethasone acetate and 1% lidocaine.