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# **BUPIVACAINE, LEVOBUPIVACAINE and TRAMADOL ARE CYTOTOXIC TO RATS' ARTICULAR CARTILAGE BOTH *INVIVO* and *INVITRO***

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# **SAME DAY SURGERY**

- Intraarticular use of anaesthetic agents is common for postoperative pain relief after arthroscopic knee surgery.
- Different combinations for intraarticular analgesic injections with different efficiency have been reported.
- However, the side effects of these drugs on articular cartilage have been mostly neglected by the clinicians despite some reports about their negative effects.

# Bupivacaine, Levobupivacaine and Tramadol

- In this study, we have evaluated and compared the effects of Bupivacaine, Levobupivacaine and Tramadol both *invivo* and *invitro* experimental rat models on articular cartilage and chondrocytes.

# ***Invivo Experiment:***

## **Injections:**

- Thirty mature Sprague-Dawley rats were randomized into 3 groups
- Bupivacaine (Group 1), Levobupivacaine (Group 2), Tramadol (Group 3) were injected into the right knee joints and serum physiological saline into the left.
- The rats were killed, 5 at 48 h and 5 at 10 days from each group.
- The knee joints were resected.

# ***Invivo Experiment:***

- The specimens were fixed, decalcified and paraffin embedded tissue slides were stained with Hematoxylen and Eosin (H&E) and Toluidin Blue.
- Slides were examined by the same pathologist, who was blinded to the injectate used in each joint.
- Samples were evaluated histopathologically for the presence of inflammation, osteoarthritis grade [OARSI grade (0-6)] and scoring (ICRS recommendations)

# ***Invitro Experiment:***

## **Rat Articular Cartilage Cell Growth:**

- Articular cartilage cells were obtained from the knees of 6-8 weeks Sprague-Dawley rats and were cultured and incubated.

## **Articular Cartilage Cell Seeding:**

- The cells were concentrated by centrifugation and then seeded onto a well plate.

# ***Invitro Experiment:***

## **Anesthetic Agent Treatment:**

- Cartilage cell seeded samples ( $10^4$  cells/mL) were incubated in three different anesthetic agents; Bupivacaine, Levobupivacaine, and Tramadol.
- The cells were then washed one time and returned to chondrocyte growth media.

## **Determination of Cell Growth (Cell Titer 96™ Nonradioactivity Cell Proliferation (MTS) Assay):**

- Nonradioactivity Cell Proliferation (MTS) assay was used to determine the cell density on the samples.
- All experiments were performed three times.

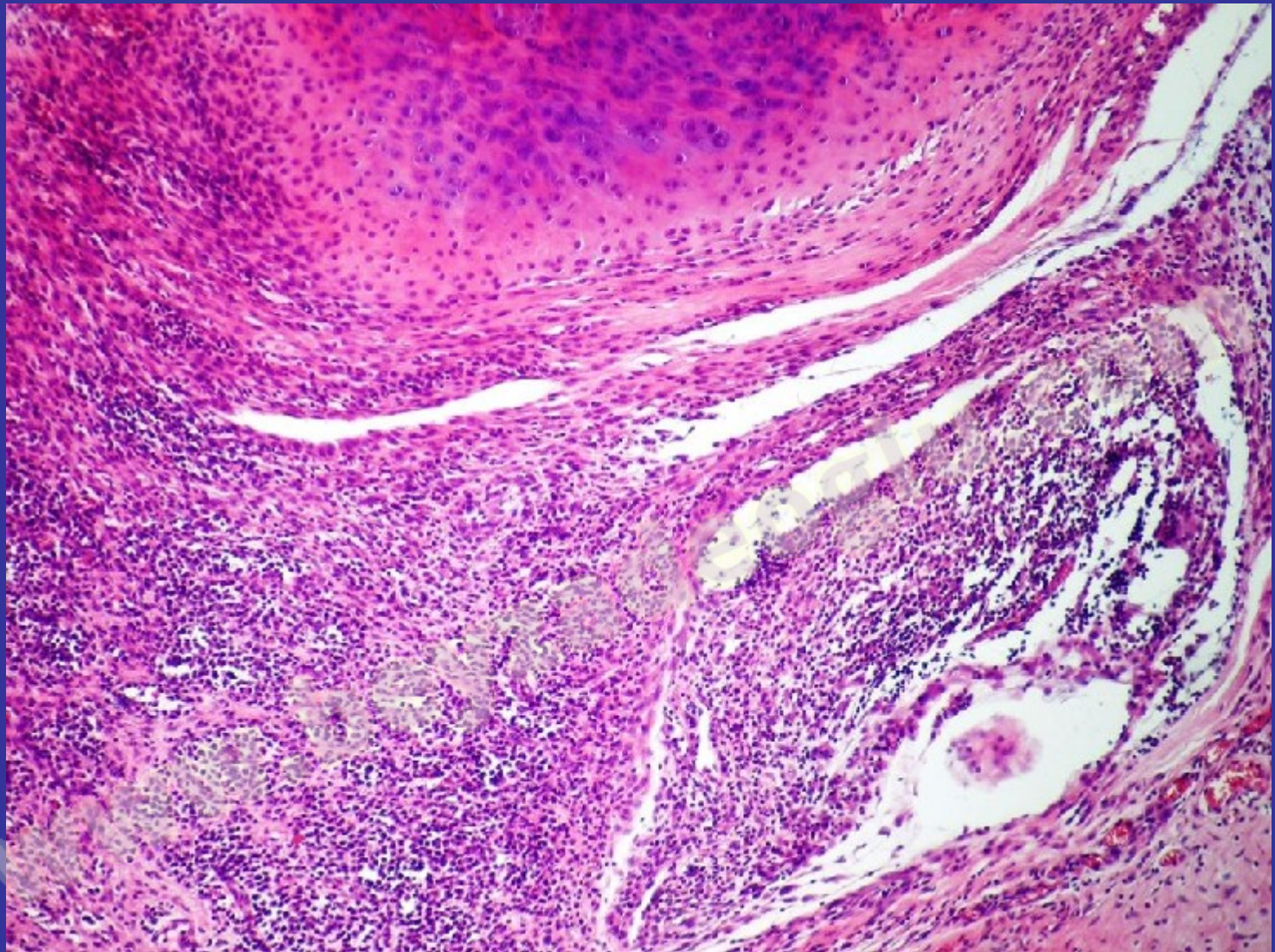
## Statistical Analysis:

- The histopathologic results were analysed Mann-Whitney U and Wilcoxon Rank tests with significance set as a  $P$  value less than .05 by SPSS for Windows 10.0.



## ***Results: Invivo***

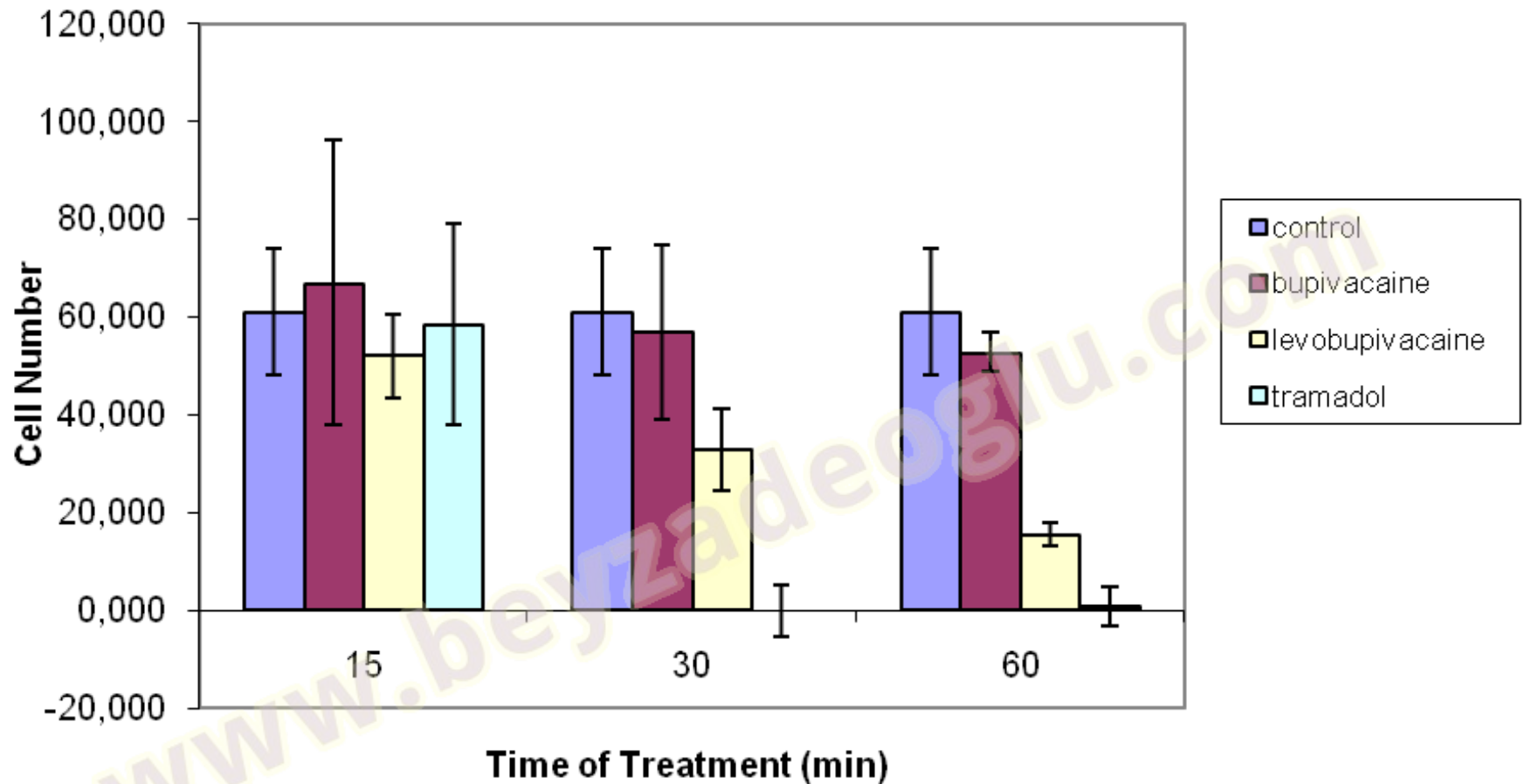
- Although the major destroying effects were histopathologically observed with Tramadol and Bupivacaine; the only statistically significant higher OARSI grade, OA stage and OA scores were detected with Levobupivacaine when compared the Levobupivacaine injected group after 10 days with the Levobupivacaine injected group after 48 hours ( $p < 0.01$  [ $p = 0.008$ ]).



**Cartilage hypertrophy and active chronic inflammation with abscess formation after 48 hours in Tramadol injection site (x100, H&E)**

## ***Results: Invitro***

- The number of both Bupivacaine and Levobupivacaine treated cells showed decrease throughout 15,30, and 60 minutes exposures.
- Between two, Bupivacaine treated cells showed less decrease in cell growth then Levobupivacaine treated ones.
- Tramadol, on the other hand, destroyed all of the cells at the end of 30 minutes of exposure.



**Cartilage cell growth by MTS assay upon exposure of three different anesthetic agents: Bupivacaine, Levobupivacaine, and Tramadol.**



# **I do use intraarticular local anaesthetics after arthroscopy**

**Beyzadeoglu T, Yilmaz C, Bekler H, Gokce A, Sayin MM.**

**Intraarticular tramadol plus pericapsular incisional bupivacaine provides better analgesia than intraarticular plus pericapsular incisional bupivacaine after outpatient arthroscopic partial meniscectomy.**

**Knee Surg Sports Traumatol Arthrosc 2007; 15:564-8.**

# CONCLUSION

- Three commonly used local anesthetic agents after arthroscopy for pain control have devastating effects on articular cartilage, both *invivo* and *invitro* experimental models, being Tramadol the worst among three.
- Although chondrotoxicity of Bupivacaine was less harmful than Levobupivacaine and Tramadol, these findings suggest that local anaesthetics negatively affect articular cartilage and chondrocytes.

# CONCLUSION

- Given that chondrocyte loss has been implicated in the development of chondrosis and osteoarthritis, orthopaedic surgeons should be careful in their preference for pain control with intraarticular drug injections after arthroscopic procedures.

# THANK YOU

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