

BJR

■ **OSTEOARTHRITIS****Cytotoxicity of drugs injected into joints in orthopaedics**

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Objectives

Intra-articular injections of local anaesthetics (LA), glucocorticoids (GC), or hyaluronic acid (HA) are used to treat osteoarthritis (OA). Contrast agents (CA) are needed to prove successful intra-articular injection or aspiration, or to visualize articular structures dynamically during fluoroscopy. Tranexamic acid (TA) is used to control haemostasis and prevent excessive intra-articular bleeding. Despite their common usage, little is known about the cytotoxicity of common drugs injected into joints. Thus, the aim of our study was to investigate the effects of LA, GC, HA, CA, and TA on the viability of primary human chondrocytes and tenocytes *in vitro*.

Methods

Human chondrocytes and tenocytes were cultured in a medium with three different drug dilutions (1:2; 1:10; 1:100). The following drugs were used to investigate cytotoxicity: lidocaine hydrochloride 1%; bupivacaine 0.5%; triamcinolone acetonide; dexamethasone 21-palmitate; TA; iodine contrast media; HA; and distilled water. Normal saline served as a control. After an incubation period of 24 hours, cell numbers and morphology were assessed.

Results

Using LA or GC, especially triamcinolone acetonide, a dilution of 1:100 resulted in only a moderate reduction of viability, while a dilution of 1:10 showed significantly fewer cell counts. TA and CA reduced viability significantly at a dilution of 1:2. Higher dilutions did not affect viability. Notably, HA showed no effects of cytotoxicity in all drug dilutions.

Conclusion

The toxicity of common intra-articular injectable drugs, assessed by cell viability, is mainly dependent on the dilution of the drug being tested. LA are particularly toxic, whereas HA did not affect cell viability.

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Keywords: Chondrocytes, Tenocytes, Intra-articular Drugs, Toxicity

Article focus

■ This study investigated the effects of intra-articular injection of local anaesthetics (LA), glucocorticoids (GC), hyaluronic acid (HA), contrast agent (CA), and tranexamic acid (TA) on the viability of primary human chondrocytes and tenocytes.

Key messages

- Cytotoxicity of intra-articular injected drugs towards chondrocytes and tenocytes depends on the concentration of the drug.
- LA (lidocaine, bupivacaine) and triamcinolone acetonide had strong toxic effects

on chondrocytes and tenocytes in low dilutions.

- Dexamethasone, TA, and CA had only minor effects on chondrocytes and tenocytes whereas HA did not affect cell viability.

Strengths and limitations

- Cytotoxicity of clinically relevant intra-articular injectable drugs was compared. To our knowledge, no comparable study has been published.
- This study was performed *in vitro*, and cells were isolated from their extracellular matrix, therefore effects may be reduced in healthy intact cartilage and tendon tissue.

Introduction

The intra-articular injection of medication is common in orthopaedics. Most of these drugs such as local anaesthetics (LA), glucocorticoids (GC), or hyaluronic acid (HA) are used to treat osteoarthritis (OA). It is estimated that 10% of the world's population who are 60 years or older have significant clinical problems that can be attributed to OA.¹ The use of intra-articular injections for the management of OA is increasing.² An epidemiological analysis of non-operative interventions used in patients with knee OA in the United States in 2009 revealed that, during the previous five years, 43.5% of the patients who underwent total knee arthroplasty (TKA) were preoperatively treated with intra-articular GC injection and 15.4% of patients received viscosupplementation injections such as HA.³

Despite their common usage, little is known about the cytotoxicity of common drugs administered into the joint. The aim of our study was to investigate the effects of LA, GC, HA, contrast agents (CA), and tranexamic acid (TA) on the viability of primary human chondrocytes and tenocytes *in vitro*.

Materials and Methods

The study design was approved by the Institutional Review Board (protocol number EK 33022017). The following drugs (Table I) were used to investigate their cytotoxicity on human chondrocytes and tenocytes: lidocaine hydrochloride 1% (Xylocitin-loc 1%; mibe GmbH, Brehna, Germany); bupivacaine 0.5% (Carbostesin; AstraZeneca GmbH, Wedel, Germany); triamcinolone acetonide (40 mg, TriamHEXAL; HEXAL AG, Holzkirchen, Germany), dexamethasone 21-palmitate (2.5 mg dexamethasone, Lipotalon; Recordati Pharma GmbH, Ulm, Germany); tranexamic acid (500 mg/5 ml, Cyklokapron-Injektionslösung; Pfizer Pharma PFE GmbH, Berlin, Germany); iodine contrast media (300 mg iodine/ml, Solutrast; Bracco Imaging Deutschland GmbH, Konstanz, Germany); hyaluronic acid (1% hyaluronic acid in physiologic saline); and distilled water. Normal saline (NS) served as a control. Chondrocytes and tenocytes were cultured in a medium with three different drug dilutions (1:2, 1:10, and 1:100). The experiments were performed using cells from three different donors.

Isolation of human chondrocytes and tenocytes. Human cartilage from normal areas was harvested from three healthy donors aged 58 and 74 years (both male) and 59 years (female) undergoing TKA after obtaining their informed consent. On the same day, cartilage samples were cut into small pieces, transferred into six-well cell culture plates and treated with collagenase II (0.2% in Dulbecco's Modified Eagle Medium (DMEM)) for 24 hours at 37°C. After filtration through a 70 µm filter, the solution was centrifuged (five minutes at 1500 rpm), the supernatant was discarded, the remaining cell pellet was

resuspended in growth medium (DMEM, 15% FCS, 1% penicillin/streptomycin), and cells were seeded into cell culture flasks and incubated at 37°C and 5% CO₂. After seven days, the medium was changed for the first time and cells were cultured until confluency with the subsequent medium changed every two to three days.

A segment of tendon of the proximal long head of biceps was harvested from three healthy donors aged 51 and 59 years (both male) and 61 years (female) undergoing shoulder arthroscopy and biceps tenodesis. The isolation of tenocytes was undertaken as described for the chondrocytes in this study except for the use of collagenase solution; to digest the tendon, collagenase I (0.2% in DMEM) was used.

Investigation of cytotoxicity. Human chondrocytes or tenocytes of the three donors were seeded at 2*10⁴ cells/cm² and incubated for 24 hours in a growth medium to ensure sufficient cell adhesion. After that, the medium was changed to a growth medium containing the particular drug dilution. Following a 24-hour incubation period, cells were washed with phosphate-buffered saline (PBS), stained for viability analysis, fixed with 4% neutral buffered formaldehyde for histological analysis or frozen at -80°C until biochemical analysis.

Biochemical analysis of cell number. For biochemical determination of cell number, frozen samples were thawed, and cells were lysed in PBS containing 1% Triton X-100 (Sigma-Aldrich Corp., St. Louis, Missouri) for 30 minutes on ice at room temperature. The activity of lactate dehydrogenase (LDH) was quantified using the CytoTox 96® Non-Radioactive Cytotoxicity Assay (Promega Corp., Madison, Wisconsin) according to the manufacturer's instructions, and correlated with the cell numbers using a calibration line. The experiments were performed in triplicate.

Statistical analysis. Numerical data were statistically analyzed using GraphPad Prism 5.04 software (GraphPad Software Inc., La Jolla, California). All values are expressed as mean and SD. Statistical analysis was performed on quantified data using one-way analysis of variance (ANOVA). For *post hoc* testing, two tailed non-paired *t*-tests where NS served as negative control, were performed. Differences were considered significant when $p < 0.05$.

Histological analysis. For staining with haematoxylin and eosin (H&E), fixed cells were washed with PBS and incubated for three minutes with haematoxylin (Merck KGaA, Darmstadt, Germany). Then the slides were washed again with PBS and incubated for another three minutes with eosin (Merck). Finally, cells were washed with distilled water and examined using a light microscope (Keyence BZ 9000; Keyence Germany GmbH, Neu-Isenburg, Germany).

Live cell staining. Immediately after washing with PBS, live cells were stained with 2.4 µM calcein (Invitrogen, Thermo

Table 1. Description of investigated drugs

Drug	Class of drug	Scope of application/effect/mode of action
Lidocaine	Local anaesthetic	1) Temporary amelioration of pain. ⁴ 2) Intra-articular use for reduction of anterior shoulder dislocations should be strongly considered as a first-line therapy. ⁵
Bupivacaine	Local anaesthetic	1) Use in arthroscopic surgery. 2) Continuous intra-articular infusions for analgesia after shoulder surgery. ⁶
Triamcinolone acetonide	Glucocorticoid	1) A class of steroid hormones that mediate many physiological effects in most vertebrates.
Dexamethasone	Glucocorticoid	2) One of the most widely prescribed classes of drugs. 3) Involved in many physiological processes including glucose homeostasis, development, metabolism, and programmed cell death. 4) Pharmacological benefits are primarily anti-inflammatory and immunosuppressive. ⁷
Tranexamic acid (TA)	Antifibrinolytic haemostatic	1) Synthetic derivative of the amino acid lysine that exerts its antifibrinolytic effect through the reversible blockade of lysine binding sites on plasminogen molecules. ⁸ 2) Is used to support haemostasis and prevent excessive intra-articular bleeding. 3) Intravenous or intra-articular administration, whereas one single intra-articular dose and two intravenous doses of TA have equivalent efficacy and safety in management of blood loss at total knee arthroplasty. ⁹
Iodine contrast media	Contrast media	1) Needed to prove successful intra-articular injection or aspiration, or to visualize articular structures dynamically during fluoroscopy. 2) Contrast agents (CAs) that go beyond qualitative visualization and enable quantitative assessments of functional tissue performance represent the next generation of CA. 3) One clinical area where CAs can have a significant impact is in the diagnosis of soft-tissue-based diseases such as osteoarthritis. ¹⁰
Hyaluronic acid	Cartilage-protective	1) High-molecular-weight polysaccharide. 2) Important component of synovial fluid and extracellular matrix of articular cartilage. 3) Contributes to the elasticity and viscosity of synovial fluid. 4) Acts as a fluid shock absorber and helps to maintain the structural and functional characteristics of the cartilage matrix. ¹¹

Fisher Scientific, Waltham, Massachusetts) in PBS and incubated for 30 minutes at 37°C in the dark. After that, the staining solution was substituted by PBS. Images were taken with the fluorescence microscope Keyence BZ 9000.

Results

Cell numbers, after culturing chondrocytes and tenocytes at different dilutions of the investigated drugs, are presented in Figures 1 and 2, respectively.

Compared with NS at a dilution of 1:2 LA (lidocaine, bupivacaine), as well as triamcinolone acetonide, TA and iodine contrast media showed strong cytotoxic effects towards chondrocytes and tenocytes as determined by significantly reduced cell numbers. For dexamethasone, a significantly lower number of cells was detected only for chondrocytes in dilution 1:2. HA did not affect cell numbers of both types in each dilution. For chondrocytes, additionally, cell numbers were also decreased when cultured with GC at a dilution of 1:10 and with LA at a dilution of 1:10 and 1:100. Culturing tenocytes with LA and triamcinolone acetonide at a dilution of 1:10 also resulted in significantly reduced cell numbers. At a dilution of 1:100, none of the investigated drugs showed any cytotoxic effects.

Staining with H&E (Figs 3 and 4) showed that cell morphology changed, and cell growth was reduced for both cell types after culturing cells with lidocaine and bupivacaine in dilution 1:2 and 1:10. Morphology of chondrocytes changed from a spindle-like phenotype to narrowed rounded cells while tenocytes had lost their typical spindle-shaped appearance and converted to a polygonal shape. For chondrocytes, toxic effects are also visible for

triamcinolone acetonide, TA and iodine contrast media in dilution 1:2, whereas tenocytes showed reactions only for triamcinolone acetonide and TA in dilution 1:2.

Live staining (Figs 5 and 6) of chondrocytes and tenocytes has shown that, for both types of cells, culturing with lidocaine and bupivacaine in dilution 1:2 and 1:10 and culturing with triamcinolone acetonide in dilution 1:2 resulted in a reduction of visible living cells.

Discussion

We found that toxicity of common intra-articular injectable drugs, assessed by cell viability, is mainly dependent on the dilution of the drug being tested. Drug-incubated chondrocytes and tenocytes showed comparable viability values.

The intra-articular injection of LA, including lidocaine and bupivacaine has been commonly used for the evaluation of atypical pain and is generally accepted as safe.⁴ Glucocorticoids are known as potent anti-inflammatory agents that act through a variety of mechanisms on different cellular levels.¹² However, GC and LA may induce apoptosis in chondrocytes¹³ and should therefore be used with caution, especially in joints with compromised cartilage.¹⁴ Our investigations showed that LA at a dilution of 1:100 resulted in only moderate reduction of cell viability whereas a dilution of 1:10 and 1:2 led to a high cytotoxicity. Our results have demonstrated that the cytotoxic effect of LA is dose-dependent. Karpie and Chu¹⁵ also found a dose- and time-dependent cytotoxic effect of lidocaine on bovine articular chondrocytes. Moreover, they had pointed out that an intact articular surface was not protective for lidocaine. In contrast, the

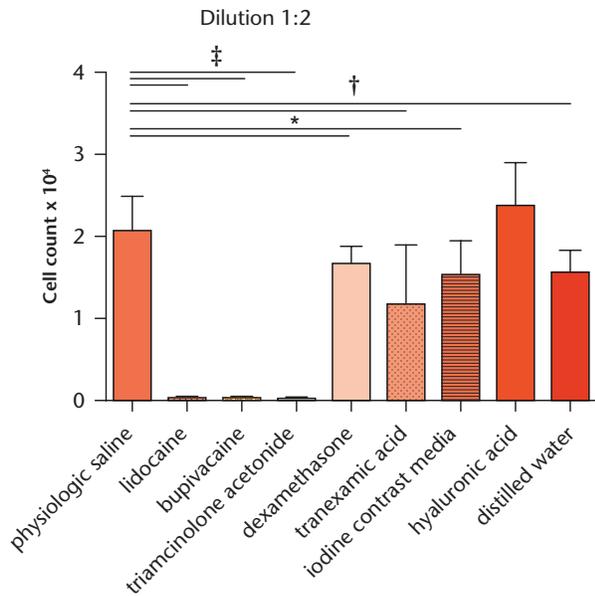


Fig. 1a

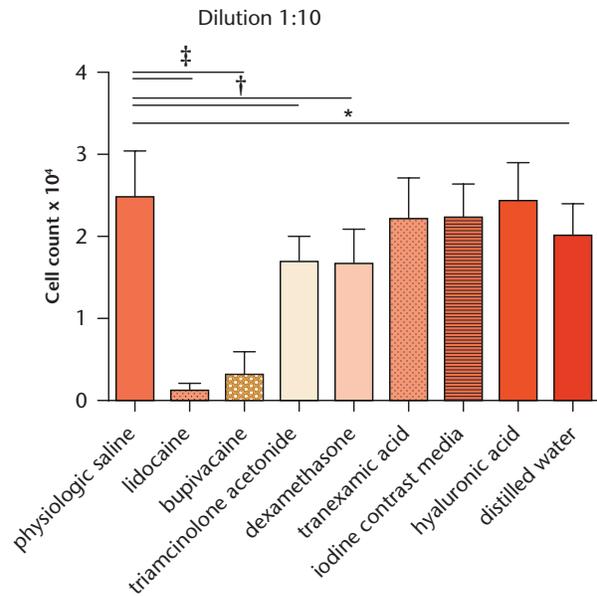


Fig. 1b

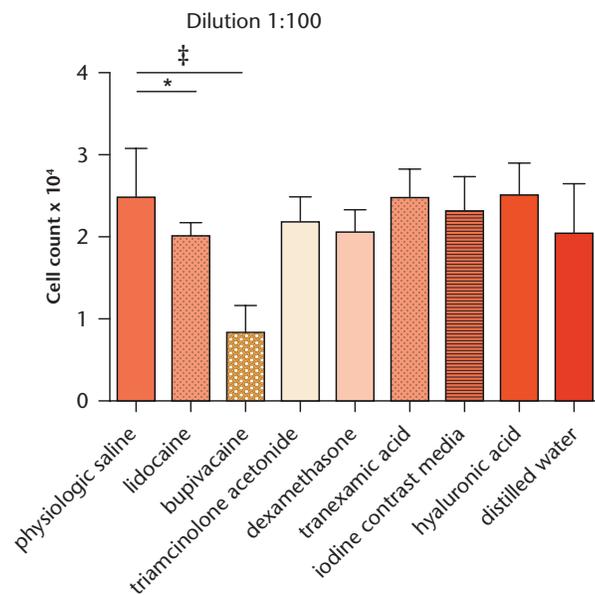


Fig. 1c

Cell numbers of chondrocytes after 24-hour incubation with different dilutions of the different drugs determined by lactate dehydrogenase (LDH) assay. a) Dilution 1:2, b) Dilution 1:10, c) Dilution 1:100. Results are presented as mean and SD for each drug. For all dilutions, one-way analysis of variance (ANOVA) showed significant differences between the groups (p -value < 0.0001). For *post hoc* testing, * (p -value < 0.05), † (p -value < 0.01) and ‡ (p -value < 0.001) indicate statistical significance (non-paired *t*-test) towards normal saline.

intact bovine articular surface has some chondroprotective effects for bupivacaine, which is cytotoxic to bovine articular chondrocytes after an exposure of 15 to 30 minutes.⁶ We had similar dose-dependent findings when using GC. Triamcinolone acetone, in particular, reduced cell viability significantly at a dilution of 1:2 and 1:10. In a controlled *in vivo* study with rats, Sola et al¹⁶ found that, after one week, 4 mg/ml triamcinolone resulted in a lower chondrocyte viability as compared with 1 mg/ml triamcinolone. As triamcinolone is a depository drug with prolonged action,

and works as an anti-inflammatory agent in controlling symptoms and providing a longer remission effect,¹⁷ it is widely used in clinical situations.

Several studies have demonstrated that there are differences between individual drugs of LA and GC. Lidocaine and bupivacaine, in particular, have a dose-dependent effect on chondrocytes^{18,19} and tenocytes, whereas ropivacaine does not show this effect.²⁰ High concentrations of triamcinolone acetone may cause irreversible effects in human tenocytes,¹⁷ while dexamethasone shows no effect

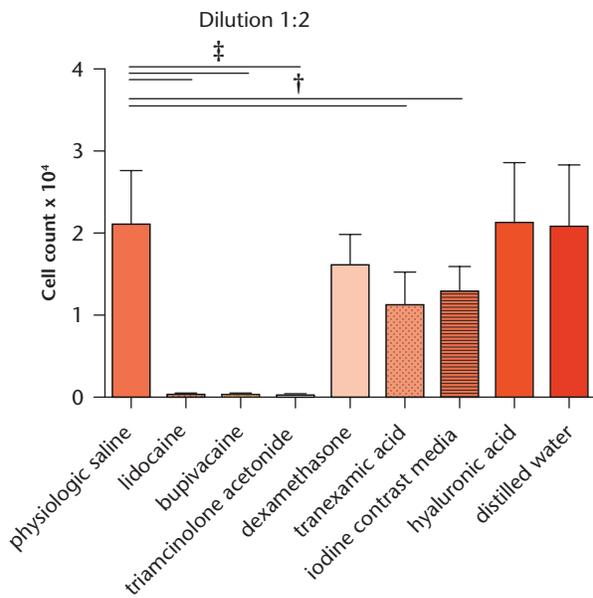


Fig. 2a

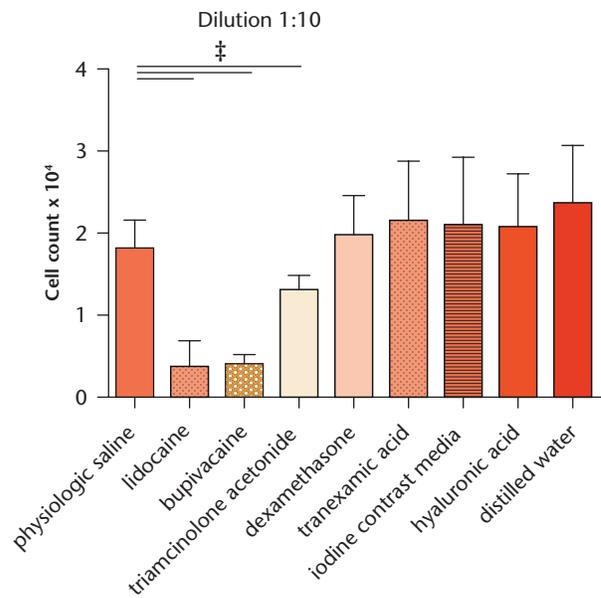


Fig. 2b

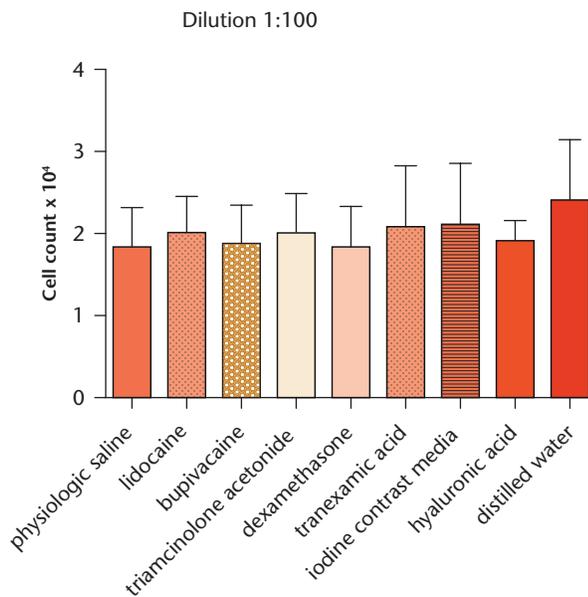


Fig. 2c

Cell numbers of tenocytes after 24-hour incubation with different dilutions of the different drugs determined by LDH assay. a) Dilution 1:2, b) Dilution 1:10, c) Dilution 1:100 Results are presented as mean and SD for each drug. While for dilutions 1:2 and 1:10, one-way ANOVA showed significant differences between the groups (p -value < 0.0001), dilution 1:100 resulted in no significant difference (p -value = 0.4887). For *post hoc* testing, * (p -value < 0.05), † (p -value < 0.01) and ‡ (p -value < 0.001) indicate statistical significance (non-paired *t*-test) towards normal saline.

on viability on bovine tenocytes in culture.²⁰ A recent review analyzing the infection rate following total hip arthroplasty found no evidence of an increased infection rate following a previous injection of the joint with GCs, however, the authors stated that the existing level of evidence is low, and high-quality multi-centre randomized trials are needed.²¹

For TA and CA, reduced cell viability was only observed at a dilution of 1:2. Parker et al²² had shown in their *in*

vitro investigations that there is a dose-dependent effect for TA on human articular chondrocytes. Additionally, they had transferred the results to clinical practice and concluded that a tissue concentration of 10 mg/ml to 20 mg/ml of TA could be expected to be safe.²² In contrast, HA showed no toxicity at all in investigated dilutions. Experimental *in vitro* investigations have demonstrated that HA treatment may regulate different biochemical pathways involved during cartilage damage.²³

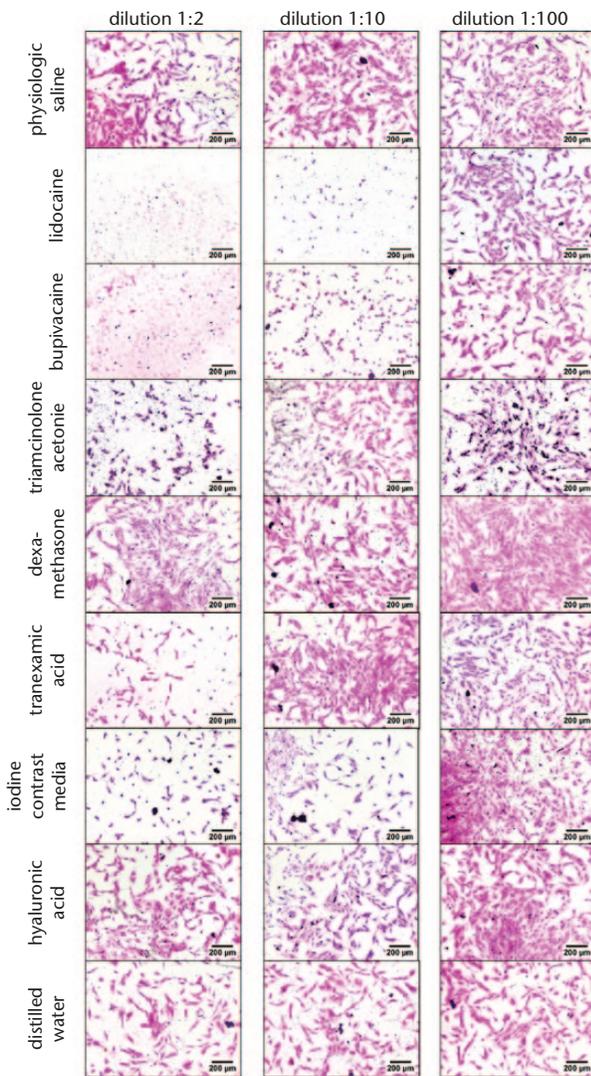


Fig. 3

Haematoxylin and eosin (H&E) staining of chondrocytes. Cell nuclei are coloured blue/violet by haematoxylin. Cytoplasm is coloured red/pink by eosin. Normal saline serves as control.

The knee joint has about 5 to 9 mls of synovial fluid with a pH of 7 to 8. For intra-articular injection, usually 5 ml to 10 ml of LA or 1 ml to 2 ml of GC are used. According to that, dilution of LA with native synovial fluid is approximately 1:2 and dilution of GC with native synovial fluid is approximately 1:10. Since there is some evidence that high concentrations of LA have toxic effects on chondrocytes and tenocytes, it might be wise to inject a lower concentration of LA or dilute it with saline or HA.

Our study has some limitations. When comparing the *in vitro* results with clinical intra-articular injection, it should be remembered that, for our experiments, cells were isolated from their native extracellular matrix. As shown by Piper and Kim,²⁴ the cytotoxicity of LA is less when using native cartilage with an intact extracellular matrix. This suggests that the cytotoxicity for

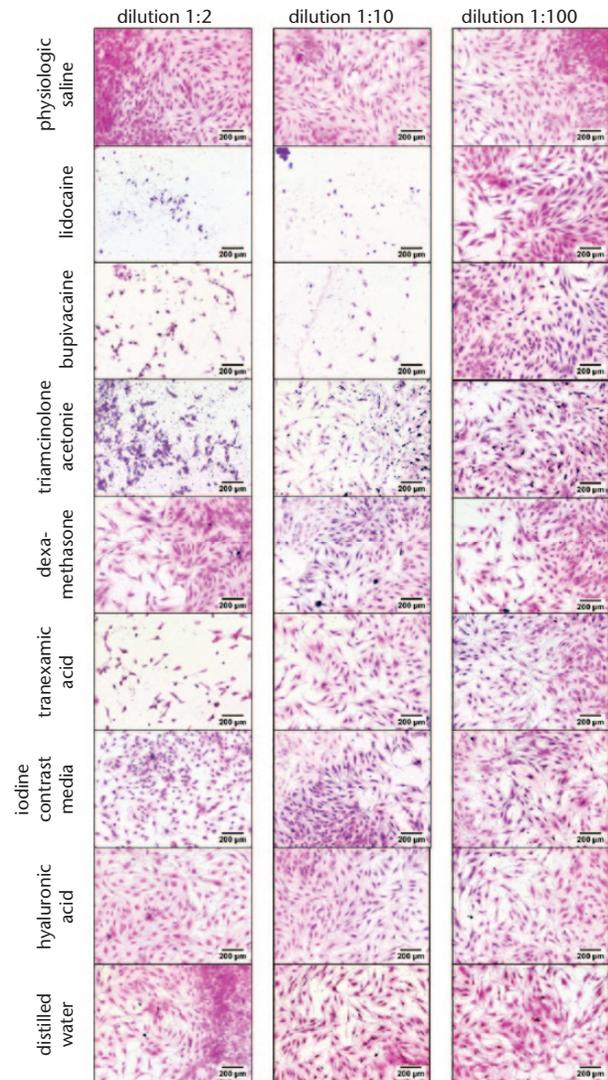


Fig. 4

Haematoxylin and eosin (H&E) staining of tenocytes. Cell nuclei are coloured blue/violet by haematoxylin. Cytoplasm is coloured red/pink by eosin. Normal saline serves as control.

chondrocytes and tenocytes demonstrated in our study may be reduced in healthy intact cartilage and tendon. Moreover, the amount of time required by the drug for cellular exposure depends on various factors in humans, such as metabolism of the injected drugs or anatomic nature of the joint injected. To investigate further the effects of intra-articular injected drugs on cartilage and tendons *in vivo*, a small animal model would be sufficient as a next step; this would allow for histological analysis after a series of injections. Additionally, there are new OA protective therapies, like Torin 1. These will need to be assessed prior to clinical application and will also have to be compared with the clinically established drugs for intra-articular injection.²⁵

In conclusion, we found that the cytotoxicity of intra-articular injected drugs towards chondrocytes and

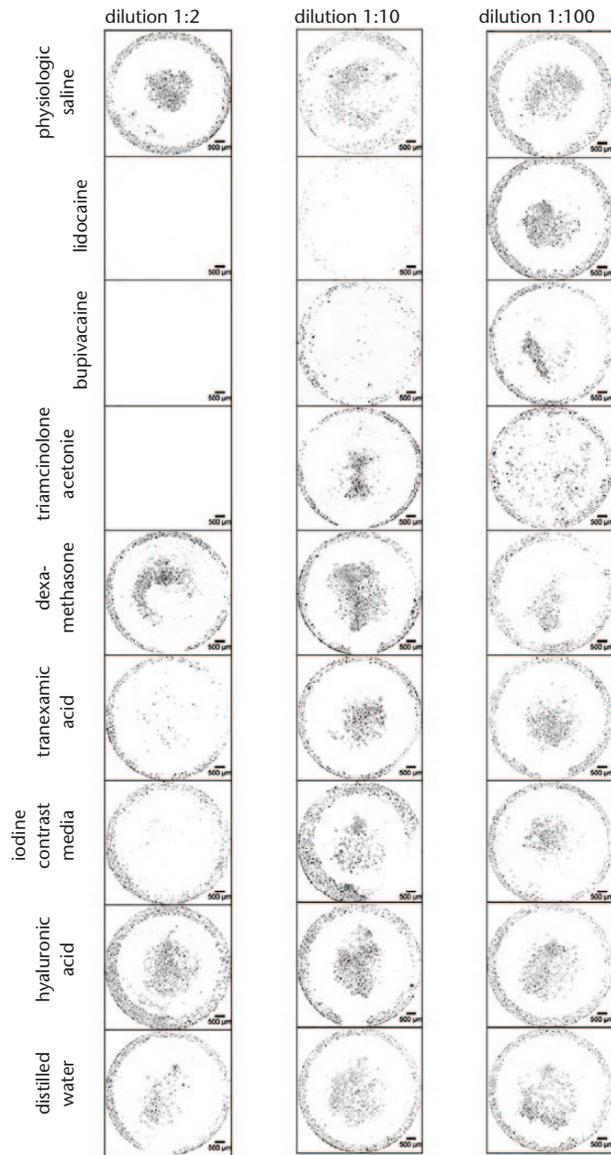


Fig. 5

Live staining of chondrocytes. Live cells are visible as green fluorescent cells and represented here in black. Normal saline serves as control.

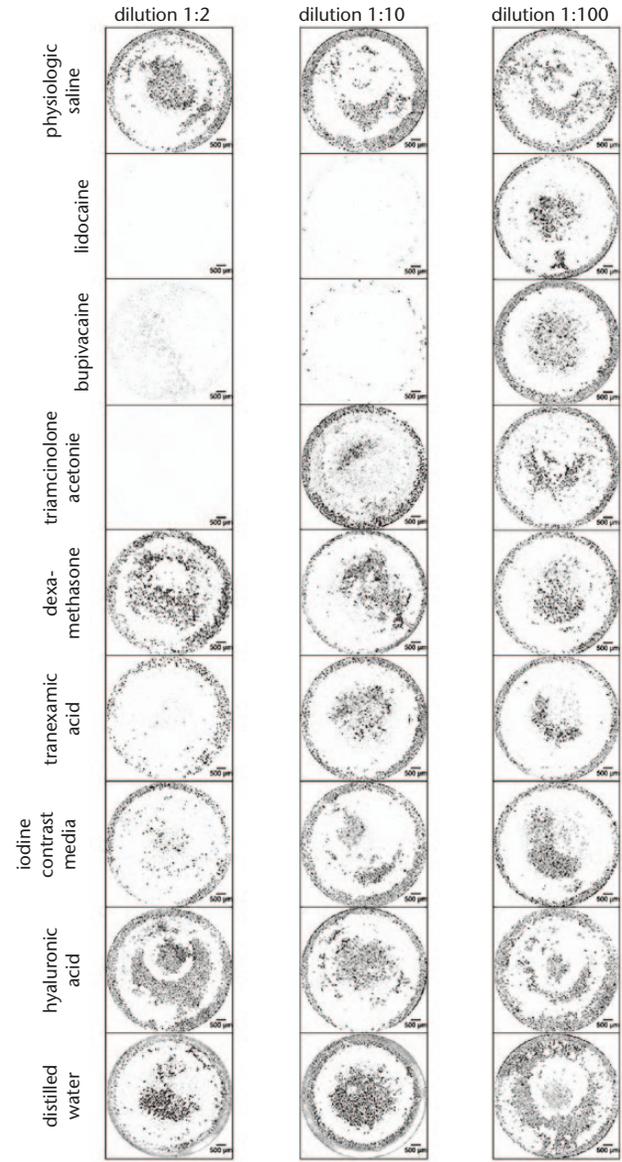


Fig. 6

Live staining of tenocytes. Live cells are visible as green fluorescent cells and represented here in black. Normal saline serves as control.

tenocytes depends on the concentration of the drug. LA such as lidocaine and bupivacaine demonstrated the highest toxic effects of the drugs investigated. The indication for intra-articular injection should therefore be defined carefully. Also, GCs had toxic effects on chondrocytes and tenocytes with triamcinolone acetone more than dexamethasone. TA had only minor effects on chondrocytes and tenocytes. TA is applied intra-articularly, to avoid postoperative bleeding following arthroplasty. We can conclude from our results that an intra-articular injection of TA can also be done in native joints. The effect on chondrocytes and tenocytes is comparable with iodine contrast media, which has been used for decades without clinically reported negative effects. HA does not appear to have any adverse effects *in vitro*.

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Author contributions

- P. Busse: Collected and analyzed the data, Wrote the manuscript.
- C. Vater: Designed the study, Collected and analysed the data, Reviewed and edited the manuscript.
- M. Stiehler: Designed the study, Reviewed and edited the manuscript.
- J. Nowotny: Collected the tissue samples, Reviewed and edited the manuscript.
- P. Kasten: Designed the study, Reviewed and edited the manuscript.
- H. Bretschneider: Collected and analyzed the data, Reviewed and edited the manuscript.
- S. B. Goodman: Designed the study, Reviewed and edited the manuscript.
- M. Gelinsky: Reviewed and edited the manuscript.
- S. Zwingenberger: Designed the study, Analyzed the data, Wrote, reviewed, and edited the manuscript.

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ICMJE COI statement

- The authors declare that there is no conflict of interest regarding the publication of this article.

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