Effect of dioxydini on the healing of articular cartilage defect

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Background. To evaluate the effects of intraarticular injection (i. a. i.) of dioxydini on the regeneration of a surgical defect performed on the knee joint cartilage of clinically healthy Chinchila rabbits.

Materials and methods. Experiments were carried out on 32 animals with cartilaginous defect. Under general anaesthesia a standard constant defect till to subchondral bone (3 mm wide and 2 mm deep) was performed on the articular cartilage medial condyles of the right knee joints of rabbits. Lateral condyles were left undamaged. After the healing of the wound, the animals were divided into the test and control groups. The test group animals with a defect were injected intraarticularly with 1% dioxydini solution and animals of the control group with sodium saline. Cartilage samples of the knee joints were collected for histopathological study at various stages of experiment (at 6, 8, and 12 weeks post-operation) and were observed light microscopically using formalin-fixed, decalcified and stained tissue slices.

Results. It was shown that i. a. i. of 1% dioxydini induced slight destructive changes in the healthy cartilage and slight thickening in the upper layers of cartilage by focal flowing of activated chondrocytes towards the defect site. The recovery of articular cartilage was statistically similar in the test (dioxydini) and control groups: 50% of cartilaginous defects up to subchondral bone were filled up with hyaline cartilaginous tissue, and this filling was predetermined by the state of the subchondral plate. If it was not damaged, the defect was filled up by hyaline cartilage activated chondrocytes flowing from the subchondral plate and, if it was damaged, the healing was done by fibrovascular tissue or fibrocartilage from the progenitors of blood cells flowing from lacunas of the subchondral bone.

Conclusions. The study revealed that i. a. i. of dioxydini has a chondrogenic potential by activating young chondrocytes flowing from subchondral plate, which were not active in the production of proteoglycans (PGs) in the defect site made to subchondral bone and restored by hyaline cartilaginous tissue only in 50% of cases. Maybe growth factors such as TGF-β, hormones, and bone marrow proteins (BMPs) are necessary to force chondrocytes to proliferate and produce the matrix proteins. Further investigations are needed to optimize the concentration of dioxydini with reparative capabilities which would induce only minimal destructive changes in the native cartilage.

Key words: dioxydini, articular cartilage defect, reparation

INTRODUCTION

Articular cartilage repair is a clinical challenge because of its limited intrinsic healing potential (1–3). Chondrocytes have been extensively studied and are a natural and logical cell source for cartilage repair. They are biologically active only in the healthy cartilage (1, 4).

But the stimulation of native chondrocytes in damaged cartilage by biochemical and physical methods can change their capabilities (5, 6). Few studies exist about the native chondrocyte stimulation, but Murray’s (7) work concerning animal osteoarthrosis induced by papain seems to be important as it focuses attention on the appearance of focally activated chondrocytes. I. a. i. of papain has been used to induce degeneration and subsequent repair of articular cartilage in animal
models (7–9). High concentrations of papain induce cartilage destruction (10), but on the other hand, stimulation of young forms of chondrocytes in the perichondrial area with their flowing into the middle layers of cartilage was observed. Subsequent studies (11, 12) revealed that decreasing the concentration of papain to 0.02% was more effective for inducing the reparative rather than the destructive processes in the cartilage.

In our few previous experiments performed on rabbits with experimental synovitis, we observed that i. a. i. of dioxydini (an antibacterial drug of chinoline group with a wide spectrum of activities for intravenous, intraarticular and local injections) induced an analogous effect as papain did (4, 13). Dioxydini induces some degenerative changes in native articular cartilage, but stimulates the flowing of young chondrocytes from the perichondrial area into cartilage layers. Data on the stimulation of young chondrocytes and the influence of dioxydini on cartilaginous defect regeneration are absent.

The objective of this study was to investigate the effect of i. a. i. 1% dioxydini solution on the degree of destructive and reparative processes in cartilage and to evaluate the repairing capability of a surgical defect as deep as to the subchondral bone.

MATERIALS AND METHODS

Animals
Thirty-two adult male rabbits (2.3–2.5 kg body weight) were obtained from Institute of Immunology (Vilnius, Lithuania) and housed one per cage in air-conditioned quarters with a 12-h light–dark cycle. The animals were given standard laboratory food and water ad libitum. They were allowed to acclimatize for at least five days before testing. Approval of the Ethic Committee for Laboratory Animal Use, Lithuania, was obtained prior to commencement of the manipulations on animals.

Surgical procedure
Following aseptic surgical procedures under general anaesthesia (intravenous injection of thiopental [BIOCHEMIE GmbH, Vienna, Austria] at a dose 25 mg/kg body weight), standard defects were made on the right knee joint of 32 healthy rabbits. Knee joints were approached through a medial parapatellar incision, and each patella was dislocated laterally. By performing rotation movements with a trochar, a constant defect as deep as to the subchondral bone was made on the medial condyle of femurs (3 mm wide and 2 mm deep). Lateral condyle was left undamaged for evaluation of the effect of dioxydini on the healthy articular cartilage. The articular capsule and skin were sutured. After surgery the animals were housed in individual cages and were allowed free cage activity for 5–7 days to recover from surgery before the further procedures were initiated.

Intraarticular injections of dioxydini
After the healing of wound the animals were divided into test and control groups, each of 16 rabbits. The test group of animals received i. a. i. of 1% dioxydini (FGUP “Moschempharmpreparations”) into the right knee joint cavity in the volume of 1 ml on day 7. The animals of the control group received an injection of saline solution.

Macroscopic examination
All animals were sent to sleep with an overdose of thiopental administered intravenously. Rabbits of the test and the control groups were euthanized at 6, 8, 12 weeks post operation (p. o.). Their knee joints were visually inspected grossly and intraarticularly. The knee joints cartilage and the defect site in each group were examined macroscopically for color, integrity, contour, and smoothness. The degree of knee synovitis was also evaluated.

Histological examination
Samples of cartilage with subchondral bone were inserted into ethanol–formol (9:1) fixative. Following decalcification, dehydration and paraffin embedding, cartilage specimens were cut on a MIKROM microtome. Serial sets of 4–5 µm thick sections from each piece of cartilage were mounted on glass slides and stained with haematoxylin–eosin and toluidine blue (pH 4.5) for light microscopic examination by scoring pathological changes. Microscopic assessment was performed by using the Olympus BX51 microscope (Germany) view analysis system. Sections were evaluated for the quality of the repaired tissue according to the histological grading scale adopted by Jackson et al. (14).

RESULTS

Effect of intraarticular injection of dioxydini on cartilaginous defect repair

Macroscopic findings
Six weeks after surgery and the i. a. i. of 1% dioxydini, the synovium of joints was whitish and slightly atrophic in all cases (4 of 4). The synovium in the control group was slightly inflamed. Eight weeks p. o. the synovium was whitish and smooth (4 of 6 cases). The other two synovia were slightly fibrotic and swollen. Changes in the synovia were more expressed 12 weeks p. o.: slight swelling, whitish colour, fibrotic and atrophic changes were found in all cases. Synovium in the control group was normal.

Defect sites in 50% of cases were fully filled up with a tissue similar to the native cartilage and occupied by a whitish tissue at weeks 6 p. o. in the test (dioxydini) group. At week 8, 66.7% of p. o. defects were completely filled up with a tissue similar to native cartilage, and 33.3% were partly (1/2–3/4 of the defect) filled up. At week 12, the superficial changes in the cartilage showed that the defects were completely filled up with a tissue...
similar to native cartilage (33.3% of cases) or with a whitish tissue (66.7% of cases). Cartilage in controls (i. a. i. sodium saline) did not differ from normal cartilage in 50% of cases. The cartilaginous defects in other cases showed irregular contours and were completely or partly covered with whitish hypertrophic or fibrotic tissues.

**Histological findings**

*The histology of hyaline cartilage on healthy lateral condyle of the right knee joints*

Examination of hyaline cartilage on 16 lateral condyles of the right knees (Table 1) showed the same histological picture at 6, 8 and 12 weeks following sodium saline injection. The surface of the cartilage was even, some chaps, erosions, and a deep fissure were found. The fibrotic pannus was observed in 5 of 16 cases on joint cartilage surface.

Chondrocytes of 2, 3, 4 lines in the first layer of cartilage were flat and sometimes picnotic. Four lines of normal or activated chondrocytes were found in the second layer. Four lines of rare chondrocytes in the columns in the third layer were observed on the background of the bright distinct matrix.

PGs were distributed equally in the second and third layers (grade +1). The subchondral plate consisted of four lines of large bright chondrocytes (Fig. 1A).

So, the picture of the healthy hyaline cartilage of the knee joints of rabbits was the same after 6, 8, and 12 weeks as post i. a. i. of sodium saline where destructive changes were observed on the surface of cartilage and in the first layer of chondrocytes. Healthy chondrocytes in second and third layers of cartilage as well as in the subchondral plate were found; the subchondral bone had active osteoclasts which formed a porous bone, small and wide lacunas filled with bone marrow cells and trabeculas with osteocytes.

**Histological changes in cartilage on healthy lateral condyle of the right knee joint after i. a. i. of 1% dioxydini**

The effect of single i. a. i. of 1% dioxydini on the histological changes of cartilage in the right knee joint was investigated at 6, 8 and 12 weeks (Table 2). Dioxydini induced several deep fissures which grew up with fibrotic or fibrocartilaginous tissues. Chondrocytes in the upper layers (first and second ) of cartilage were activated. They became smaller and formed piles in the deeper

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**Table 1. The histology of hyaline cartilage on healthy lateral condyle of the right knee joints**

<table>
<thead>
<tr>
<th>Knee joint</th>
<th>n</th>
<th>Surface</th>
<th>n/n</th>
<th>Lateral condyles</th>
<th>PGs (grade)</th>
<th>Subchondral lamina</th>
<th>Subchondral bone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Right</strong></td>
<td>16</td>
<td>Erosions</td>
<td>6/16</td>
<td>2-3 lines of flat chondrocytes</td>
<td>0</td>
<td>4 lines of bright large chondrocytes</td>
<td>Porous thick trabeculas, small lacunas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deep tissue</td>
<td>3/16</td>
<td>4 lines of active chondrocytes in the columns</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note.** Histology of healthy cartilage on lateral condyle of the right knee joint of rabbits was the same after 6, 8 and 12 weeks post i. a. i. of sodium saline. PGs – proteoglycans. n/n – number of cases with changes in cartilage / total number of patterns investigated.

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**Fig. 1.** Histological changes in hyaline cartilage with defect up to subchondral bone with or without i. a. injection of 1 ml 1% dioxydini solution (A, B). Defect filled up with hyaline cartilage. Hematoxylin-eosine. Toluidine blue. ×400.
layers. Chondrocytes of all layers produced sufficiently PGs (about grade +2), especially in the deep layers, but some were destructive with a picnotic nucleus in the subchondral plate.

At 8 weeks p. o., three of six defects were filled up with hyaline cartilaginous tissue. In all cases the native cartilage showed slight features of destruction, but defects were filled up differently: in three cases with hyaline

Table 2. Histological changes in healthy hyaline cartilage on lateral condyles of the right knee joint after i. a. i. of 1% dioxydini

<table>
<thead>
<tr>
<th>Weeks (p. o.)</th>
<th>n</th>
<th>Surface</th>
<th>n/n</th>
<th>Lateral condyles</th>
<th></th>
<th></th>
<th>Subchondral lamina</th>
<th>Sub-chondral bone</th>
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</table>

Note. Changes in healthy hyaline cartilage after i. a. i. of 1% dioxydini in the lateral condyle of the right knee joints were identical to medial one. PGs – proteoglycans. n – number of animals. n/n – number of cases with changes in cartilage / total number of patterns investigated.

Table 3. Histological changes in hyaline cartilage of right knee joint with defect up to subchondral bone

<table>
<thead>
<tr>
<th>Weeks</th>
<th>n</th>
<th>Native cartilage</th>
<th>Defect</th>
<th>Native cartilage</th>
</tr>
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<tbody>
<tr>
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</table>

Table 3 (continued)

<table>
<thead>
<tr>
<th>Weeks</th>
<th>n</th>
<th>Native cartilage</th>
<th>Defect</th>
<th>Native cartilage</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>5</td>
<td>Normal hyaline cartilage and pannus</td>
<td>Defect is not filled up</td>
<td>Normal hyaline cartilage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Destructive cartilage and pannus</td>
<td>Incomplete, atrophic hyaline matrix without cells</td>
<td>Destructive cartilage and pannus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slightly destructive cartilage</td>
<td>Hyaline cartilaginous tissue</td>
<td>Slightly destructive cartilage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Destructive cartilage</td>
<td>Incomplete hyaline cartilaginous tissue. The surface is eroded. Exostosis</td>
<td>Destructive cartilage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Destructive cartilage</td>
<td>Hyaline cartilage</td>
<td>Destructive cartilage</td>
</tr>
</tbody>
</table>

*Note.* 50% of defects up to subchondral bone were partially or completely filled up with hyaline cartilaginous tissue (n = 14).

cartilaginous tissue, in others with fibrocartilaginous tissue, limited on both sides by the subchondral plate, and with fibrovascular tissue and long synovial villous in the articular cavity (one case) and multicellular chondrocytes on the bottom of the native cartilage (two cases). Maybe the subchondral plate was damaged during the surgical procedure, therefore the filling of the defect was predetermined by bone marrow stem cells located in lacunas of the subchondral bone.

After 12 weeks, three of six defects were partially or completely filled by hyaline cartilaginous tissue on the background of a slight destruction of the native cartilage. One defect was not filled up, although the native cartilage was normal, and two others were partly filled up with a hyaline matrix without cells.

Histological changes in hyaline cartilage after i. a. i. of 1% dioxydini of the right knee joint with defect up to subchondral bone

The results of histopathological changes in hyaline cartilage with a defect up to subchondral bone and i. a. i. of 1% dioxydini into the right knee joint of rabbits are summarized in Table 4. Single injection of dioxydini in 50% of cases induced the filling of defects with hyaline cartilaginous tissue, and an empty space between the subchondral plate and filled tissue. 16.7% of defects were filled up with fibrovascular and 33.3% with fibrocartilaginous tissue where fibrovascular or fibrocartilaginous metaplasia of native cartilage with a slight activation of chondrocytes in islets was observed.

Table 4. Histological changes in hyaline cartilage of the right knee joint with defect up to subchondral bone after i. a. i. of 1% dioxydini

<table>
<thead>
<tr>
<th>Weeks</th>
<th>n</th>
<th>Native cartilage</th>
<th>Defect</th>
<th>Native cartilage</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>6</td>
<td>Fibrovascular cartilage and pannus</td>
<td>Fibrovascular tissue on the surface of cartilage, fibrocartilage in deeper layers</td>
<td>Destructive cartilage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Activated hyaline cartilage</td>
<td>Fibrocartilage. Islets of chondrocytes in deeper layers</td>
<td>Edematous cartilage with islets of activated chondrocytes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Edematous hyaline cartilage with islets of active chondrocytes</td>
<td>Hyaline cartilaginous tissue</td>
<td>Edematous cartilage with islets of activated chondrocytes</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>Edematous cartilage with islets of activated chondrocytes</td>
<td>Fibrovascular tissue from lacunas of subchondral bone</td>
<td>Edematous activated hyaline cartilage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Destructive cartilage and pannus</td>
<td>Hyaline cartilaginous tissue with small chondrocytes and rough matrix. Subchondral plate is active</td>
<td>Destructive cartilage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fibrocartilaginous metaplasia with islets of cartilage, chondrocytes are activated from second layer</td>
<td>Fibrocartilage with small chondrocytes. Activated chondrocytes of subchondral plate go up and form the islets</td>
<td>Fibrocartilage with islets of hyaline cartilage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fibrovascular tissue. A lot of blood vessels with fibrotic walls. Synovial villi</td>
<td>Fibrovascular tissue</td>
<td>Fibrovascular metaplasia</td>
</tr>
</tbody>
</table>
DISCUSSION

Various methods for healing articular cartilage injury (15–20), including the transplantation of cultivated chondrocytes (21–24), have been used, but no one of them was successful because of the poor integration of the newly formed tissue with the native cartilage (25).

It is well known that the maintenance of the normal integrity of articular cartilage depends on the balance of synthesis and degradation processes carried out by the chondrocytes. The chondrocytes have exceptional capabilities to maintain the catabolic and anabolic functions of cartilage and to synthesize a new matrix (7, 26). Numerous studies in the literature show a biochemical and biophysical stimulation of chondrocytes in native cartilage (5, 6, 27–29). Our preliminary data on i. a. i. of dioxydini revealed its chondrogenic potential (4, 13).

Dioxydini has an ability to stimulate the synovial/cartilage junction and the spreading of proliferated chondrocytes into the middle layer of cartilage. But partial-thickness defects of articular cartilage do not heal spontaneously (30). So, we made a cartilage defect of a knee joint of rabbits in an attempt to activate production of matrix proteins by chondrocytes and filling up of the defect with hyaline cartilaginous tissue by i.a.i. of 1% dioxydini.

We found slight histological changes in the cartilage of the lateral condyle of the control group (right knee joint) which was the same after 6, 8 and 12 weeks and evaluated as a response to the defect made on the medial condyle.

The native cartilage of the control group with the defect up to subchondral bone underwent fibrotic metaplasia with islets of chondrocytes. Even in several cases of pannus, the defect was filled up with hyaline cartilaginous tissue. At the end of the experiment (on week 12) only slight destruction of native cartilage was observed and 50% of defects were filled up with hyaline cartilaginous tissue. In all the cases subchondral plate was evenly thick with activated chondrocytes, proceeding to the layers of native cartilage. So we suggest that the filling of the defect with hyaline cartilaginous tissue is predetermined by the state of the subchondral plate. If it is not damaged, the defect is filled with hyaline cartilaginous tissue, and if damaged, it is filled with fibrovascular or fibrocartilaginous tissues from the hematogenic precursor in subchondral bone lacunas. The fact that 50% of defects up to subchondral bone are filled up with hyaline cartilage corroborates this version.

Injection of 1% dioxydini stimulates chondrocytes but induced a more pronounced destruction of cartilage surface layer in the healthy and the test groups. 50% of defects were partly or completely filled up with hyaline cartilaginous tissue, and chondrocytes from subchondral lamina passed to the defect site and formed hyaline cartilaginous tissue. Because the destruction on healthy cartilage induced by dioxydini is rather significant, we suppose that the concentration of dioxydini must be lowered to avoid cartilage destruction and to stimulate mesenchymal cells in the synovial/cartilage junction and subchondral plate. An important question remains why such a great amount of young chondrocytes which appears in the cartilage does not produce enough matrix protein. A possible answer could be that growth factors (such as TGF-β), hormones and bone marrow proteins (BMPs) are necessary to force chondrocytes to proliferate and produce the matrix proteins (31–35).

CONCLUSIONS

The healing of a cartilage defect made up to the subchondral bone in rabbits proceeded from activated chondrocytes of the subchondral plate. A single i. a. i. of dioxydini revealed its chondrogenic potential, and chondrocytes were able to flow towards the defect site.
from the synovial/cartilage junction and subchondral plate and to restore it with hyaline cartilaginous tissue only in 50% cases. These young chondrocytes are not active and cannot produce sufficient amounts of PGs. We suppose that growth factors such as TGF-β1, hormones and BMPs are necessary to force chondrocytes to proliferate and produce matrix proteins. Further investigations are needed to find the optimal concentration of dioxydini for reparative purposes of cartilage defects.

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DIOXYSIDINO POVEIKIS GYDANT

SANARO KREMŽLĖS DEFEKTĄ

Santrauka

Tikslas. Įvertinti įsánarinės dioksidino injekcijos poveikį sąnario kremžlės defekto, atliko chirurginiu būdu sveikiems triušiams, sugijimu.

Medžiaga ir metodai. Panaudojant bendrą anesteziją 32 triušiams dėsiniojo kelio sąnario vidiniuose gumburūse buvo suformuotas kremžlės defektas (3 mm pločio ir 2 mm gyho) įki subchondrinio kaulo. Šoniniai gumburai palikti sveiki. Užgūjus pjūvius, gyvūnai suskirstyti į bandomąją ir kontrolinę grupes po 16 triušių kiekvienoje. Bandomosios grupės gyvūnams į sąnario ertmę suleistas 1 ml 1% dioksidino tirpalas, kontrolinei – toks pat patikis fiziologinio tirpalo. Sąnario kremžlės audinio be defekto ir su defektu pavyzdžiai paimti histologiniu ištyrinimu praėjus 6, 8 ir 12 savaitčių po operacijos.

Rezultatai. Gautais duomenimis, įsánarinė 1% dioksidino injekcija sukėlė nedidelius destrukcinius pokyčius sveikoje kremžlėje ir židinių jaunu chondročių plūdimumą link defekto truputį sustorindama viršūtinius kremžlės sluoksnius. Sąnario kremžlės defekto atsistatymas buvo statistiškai panašus tiek bandomojoje, tiek ir kontrolinėje grupėse. 50% kremžlės defekų įki subchondrinio kaulo užsipildė hialininiu kremžlės audiniu, ir šis užsipildymas priklausę nuo subchondrinės ploktelės būklės: jei ji buvo nepažeista, defektas pildėsi hialininiu kremžlės audiniu, jei pažeista – fibrovaskulinio audiniu ar fibrokremzle iš subchondrinio kaulo lakūnų, pripildytų kaulų čiaupų ląstelių. Įsánarinė 1% dioksidino injekcija stimulavo chondročiutus ir 50% visų tūrų defektų buvo iš dalies užsipildė hialininiu kremžlės audiniu chondročiatams migruojant į natyvinęs kremžlės šonų ir subchondrinės ploktėlės.

Išvados. Įsánarinė dioksidino injekcija pasižymi chondrogennyinių poveikiu, tačiau atsiradę jauni chondročiai yra nepakankamai aktyvūs ir gamina nedaug proteoglikanų. Trašio sąnario chondročiai iš subchondrinės ploktelės ir natyvinės kremžlės kraštų plūsta link defekto ir tik iš dalies atstato jį hialininiu kremžlės audiniu (50% atveju, kaip ir kontrolinėje grupėje). Manome, kad būtini papildomi veiksmai, tokie kaip TGF-β, hormonai ir kaulų čiaupų proteinai (BMPs), kurie sustiprina chondročių proliferaciją ir paskatinti matriko baltyms gamybą. Tolesniais tyrimais būtina optimizuoti dioksidino koncentraciją, sukeliančią tik minimalus destrukcinius pokyčius kremžleje ir kremžės defekto reparaicijai.

Raktas: dioksidas, sąnario kremžlė, destrukcija, reparaicija