Arthrography in loosened hip prostheses. Assessment of possibilities for intra-articular therapy

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Abstract

Background
Loosening is a major complication in prosthesis surgery. Less invasive alternatives to revision surgery are required to prevent and treat prosthesis loosening. Some experimental therapies investigating alternative treatments exploit the intra-articular space as a route of administration. For efficient, local delivery of therapeutic agents a contained joint space is required. Furthermore, the volume of the joint space determines the concentration of the therapeutic ingredient in the joint.

Methods
A retrospective analysis of 221 hip arthrograms performed between 1994 and 2004 for diagnosis of prosthesis loosening was performed. All arthrograms were studied for leakage of contrast medium and the volume of injected contrast medium.

Results
There was a contained joint in 164 arthrograms (74%). The volume in these hips was $31 \pm 12.7$ mL. Male patients had a larger joint volume than female patients $(p = 0.019)$. There was no difference in containment and joint volume between hips with a primary and with a revised prosthesis.

Conclusions
For successful intra-articular therapy it is necessary that the injected agent remains in the joint space. As leakage of contrast medium was shown in about a quarter of hips, this study shows that an arthrogram may be useful in the inclusion procedure for intra-articular studies to determine containment of the joint and also the volume that can be injected.
Introduction

For patients undergoing replacement of joints with orthopaedic implants, subsequent loosening of the prosthesis is common at long-term follow-up. In addition, joint prostheses are increasingly scheduled at a younger age and with increases in the average age of developed populations replacement joints experience increased activity over longer life spans. Overall loosening of hip prostheses occurs in 7-13% of cases within 10 years, this rate is higher in male patients, patients younger than 55 years of age and in cemented prostheses (when adjusted for age). Revision surgery has a 5.7% post-operative mortality (during hospital stay) in elderly patients, and in patients with cardiac insufficiency (ASA3 - American Society of Anesthesiologists) there is an increased risk of major complications such as myocardial failure or coronary artery disease. These individuals are therefore ineligible for revision surgery and currently have no other treatment options. For these patients there is a clear need for alternative therapies that are less invasive.

Studies of alternative treatments for prosthesis loosening are currently ongoing, in particular intra-articular delivery of therapeutic proteins or genes. These protocols involve the inhibition of inflammatory processes within the joint to prevent or retard periprosthetic osteolysis or, killing and removal of interface tissue with gene-directed enzyme prodrug therapy (GDEPT), with subsequent injection of bone cement to refix loosened prostheses.

In both such studies good exposure of the target tissue is essential and the injected active ingredient must remain in the joint for a sufficiently long period. Beside size of the therapeutic particle, the integrity of the surrounding joint tissue (containment) is important in retaining active particles within the joint space. Leakage of injected fluid can be visualised by arthrography with contrast medium. The presence of bursae corresponding with the joint space is a common feature, especially in patients with hip prostheses. Leakage can also occur in the absence of bursae e.g. along the psoas muscle. In hips with leakage from the joint, exposure of the target tissue to the therapeutic agent will be sub-optimal and there will be an increased risk of exposure to surrounding tissues. Thus, before a patient can undergo an experimental intra-articular treatment it is important to confirm containment of fluid within the joint and demonstrate that the tissue surrounding the joint forms a continuous, closed compartment .

Efficacy of intra-articular therapy is also dependent on the joint volume. In large joint spaces the active ingredient will be more diluted than in smaller joint spaces or a higher dose will be required with the potential for increased toxicity. Joint spaces can also be too small for intra-articular therapy where delivery of the required amount of
active ingredient is limited or the local concentrations too high increasing the potential for normal tissue toxicity.

Therefore, for the clinical use of intra-articular treatments it is relevant to demonstrate containment of injected solutions within the joint space and determine the volume of that space to optimise the delivery of therapeutic agents to joint tissue. The aim of this study was therefore to determine the number of hip prostheses with clinical loosening that would be eligible for therapy using intra-articular delivery of proteins or genes.

**Methods**

Using the hospital database all hip arthrographies performed between January 31st 1994 and September 30th 2004 were identified. The radiological reports were studied for the indication for which the arthrography was made. All arthrographies made in hips with a prosthesis in situ were included. Exclusion criteria were a suspected infection of the prosthesis, dislocation of the prosthesis, procedures in which no contrast medium was injected, and arthrographies that could not be found in the archives of the radiological department. All arthrograms were performed or supervised by a radiologist with arthrography experience. The patient was positioned supine on the examination table. The hip region was covered with sterile drapes and the skin was infiltrated with a local anaesthetic. Under fluoroscopic guidance a needle directed at the femoral neck was inserted into the joint and an attempt was made to aspirate some of the synovial fluid for culturing of microorganisms. Ioxaglate sodium meglumine (Hexabrix® 320; Guerbet, Aulnay-sous-Bois, France) contrast medium was injected through the needle under fluoroscopic guidance. Injection of contrast medium was stopped when one of the following events occurred: Rapid increase of pressure while injecting the contrast medium; the patient complained of pain in the hip; or presence of contrast medium in the lymphatic system on the fluoroscopic images.

For retrospective analysis of indication for arthrography and the results of the examination, the radiological reports and the patient’s medical records were used. From these records the following data were gathered: age, sex, injected volume during arthrography, time span between the total hip arthroplasty and the arthrography, whether the prosthesis was a primary hip prosthesis or a revision procedure, and, when applicable, findings during subsequent surgery. The results of the arthrography were qualified as loose or well-fixed for both the femoral and the acetabular components, respectively. The criterion for loosening of the acetabular component was leakage of contrast medium in all acetabular zones or in zone I and II or II and III. The criterion for loosening
of the femoral part was extension of contrast medium past the intertrochanteric line of the standard stem and halfway down the stem of the long-stemmed component.\(^3\)

**Primary surgery and revisions**
Some patients had multiple arthrograms. To compare containment of contrast medium and volume of the hip joint after primary and (multiple) revision surgery two subgroups of arthrographies were made. In the primary hip group the latest arthrogram before surgery was considered. In the revision surgery group the latest arthrogram after the most recent revision procedure was considered. In patients with multiple arthrograms each hip (right and left) could only be in each group once.

**Containment of contrast Medium**
All arthrographies made for diagnosis of aseptic loosening of the hip prosthesis were reviewed to qualify containment of the joint. Containment of the joint was defined as contained or non-contained, depending on leakage of contrast medium from the joint into the surrounding tissues. Presence and localisation of a bursa were noted. To investigate containment of the joint space, the spreading of the contrast medium was evaluated on the arthrogram prints. When the contrast medium was located in the joint space in all prints the joint was considered contained. When the prints showed leakage of contrast medium to surrounding tissues the joint was non-contained. There was never a contained joint in the presence of a bursa. In some cases a small amount of contrast medium leaked out of the joint when the needle was removed, which did not count as non-contained.

**Sensitivity of arthrogram for loosening**
Patients who underwent revision surgery within 2 years after arthrography were included in a sensitivity analysis. To study the occurrence of false-negative results loosening diagnosed with arthrography was compared to findings of loosening during surgery. The prosthesis was considered loose during surgery when there was macroscopic movement of the prosthetic component evaluated by means of traction and rotation.

**Volume**
The volume of the joint was assessed from the radiological report. In hips with a non-contained joint, injection of the contrast medium was terminated as contrast medium
was leaking out of the joint space. The amount of contrast medium injected in these cases is probably not the maximal volume. The volumes in non-contained hips were therefore not taken into account for determination of mean volumes in patients with a clinically loosened prosthesis.

Statistical Methods
Distribution of contained and non-contained joints was calculated for all arthrograms together and for different subgroups. Chi-Square tests and Student's t-tests were used to study the differences in containment.

For all arthrograms together and for subgroups, mean volume of the joint capacity and standard deviations were calculated. Univariate analysis of variance was used to investigate the differences in volume. For all statistical analyses $p < 0.05$ was the level of statistical significance.

Results

Arthrographies
Between January 31st 1994 and September 30th 2004 484 hip arthrograms were performed at the radiology department of one hospital. In 320 arthrographies a hip prosthesis was in situ when the arthrogram was made. 62 arthrographies were excluded from the study. In 36 of these an infection was suspected. In 11 patients fluoroscopic images were made without injection of contrast medium to analyse mechanical problems associated with the hip prosthesis (e.g. dislocation tendency). Dislocation of the prosthesis was found in two patients. In one patient only a low volume of contrast medium was injected to demonstrate polyethylene wear. Intra-articular injection was unsuccessful in two patients. Ten arthrograms could not be found in the hospital archives. Thus 258 arthrograms were included in the study.

125 Patients had an arthrogram made after primary hip replacement in one of their hips. The hospital archives from 1994 showed arthrogram of one hip after revision surgery in 53 patients. In these patients there were no data on arthrograms before the revision surgery. Ten patients had an arthrogram both before and after revision surgery. In six patients there was an arthrogram after primary hip prosthesis in the right and the left hip and four had an arthrogram in both hips after revision surgery. One patient had an arthrogram of both hips after primary hip replacement and of one of the hips after revision surgery. 26 Patients had more than one arthrogram performed without intervening surgery. In these cases the most recent
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Table 1. Comparison of various parameters between hips with primary and revised prostheses.

<table>
<thead>
<tr>
<th></th>
<th>Primary prostheses (N=149)</th>
<th>Revised prostheses (N=72)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex male (%)</td>
<td>35/149 (24%)</td>
<td>24/72 (33%)</td>
<td>0.121</td>
</tr>
<tr>
<td>Age in years (mean ± SD)</td>
<td>68 ± 13</td>
<td>68 ± 11</td>
<td>0.670</td>
</tr>
<tr>
<td>Side left (%)</td>
<td>71/149 (48%)</td>
<td>34/72 (47%)</td>
<td>0.952</td>
</tr>
<tr>
<td>Loose stem (%)</td>
<td>36/149 (24%)</td>
<td>22/72 (31%)</td>
<td>0.311</td>
</tr>
<tr>
<td>Loose cup (%)</td>
<td>64/137 (47%)</td>
<td>38/72 (53%)</td>
<td>0.405</td>
</tr>
<tr>
<td>Mean survival time stem (± SD)</td>
<td>103 ± 78 months</td>
<td>105 ± 72 months</td>
<td>0.853</td>
</tr>
<tr>
<td>Mean survival time cup (± SD)</td>
<td>108 ± 78 months</td>
<td>87 ± 67 months</td>
<td>0.047</td>
</tr>
</tbody>
</table>

Mean (and standard deviation) of age and survival of prosthesis components are reported for both groups and p-values for the differences between the groups are calculated. Distribution of sex and percentage of loose components in both groups and their p-values are showed.

arthrogram was taken into account and the other images were marked as duplicates. There were 31 duplicate arthrograms, which were excluded. In six cases it was not possible to determine if the arthrogram was of a prosthesis following primary or revision surgery. In total 149 arthrograms were included for analysis of primary prostheses and 72 for analysis of revision prostheses. Data regarding sex and age of the patient, and side, loosening and survival time of the components are displayed in table 1.

Containment of contrast medium

Of the 149 arthrograms in primary hip arthroplasties 113 (76%) joints were contained. 36 (24%) arthrograms showed a joint that was not contained, 20 (56%) of which had a bursa (Figure 1, 2A). In the other arthrograms with a non-contained joint the leakage was mainly into the muscles (Figure 3). In the revision hip arthroplasties there was a contained joint in 51 of 72 hips (71%). Twenty-one hips were not contained and 16 (76%) of them had a bursa.

A number of parameters for differences between the containment groups were analysed for primary and revised prostheses. These data are shown in table 2a and 2b. There was no significant difference in sex distribution and in age between the groups. The percentage of hips with a loosened component was higher in the contained group (Table 2).
Figure 1. Fluoroscopic image of an arthrography of a hip with clinical loosening of the prosthesis.

Example of a hip with a subtrochanteric bursa. Left hip of a 58-year old male patient with an uncemented Mallory head prosthesis implanted five months before the arthrography was done. 70 mL contrast medium could be injected, no loosening could be shown.

Table 2a. Comparison of various parameters between contained and non-contained hips for primary hip prostheses.

<table>
<thead>
<tr>
<th></th>
<th>Containment good (N=113)</th>
<th>Containment poor (N=36)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex male (%)</td>
<td>29/113 (26%)</td>
<td>6/36 (17%)</td>
<td>0.267</td>
</tr>
<tr>
<td>Age in years (mean ± SD)</td>
<td>68 ± 13</td>
<td>66 ± 14</td>
<td>0.387</td>
</tr>
<tr>
<td>Loosening of at least one of the components</td>
<td>65/113 (58%)</td>
<td>14/36 (39%)</td>
<td>0.051</td>
</tr>
<tr>
<td>Loose stem (%)</td>
<td>30/113 (27%)</td>
<td>6/36 (17%)</td>
<td>0.228</td>
</tr>
<tr>
<td>Loose cup (%)</td>
<td>53/103 (52%)</td>
<td>11/34 (32%)</td>
<td>0.053</td>
</tr>
<tr>
<td>Mean survival time stem (± SD)</td>
<td>106 ± 77</td>
<td>92 ± 81</td>
<td>0.356</td>
</tr>
<tr>
<td>Mean survival time cup (± SD)</td>
<td>114 ± 76</td>
<td>89 ± 82</td>
<td>0.129</td>
</tr>
</tbody>
</table>

Mean (and standard deviation) of age and survival of prosthesis components are reported for both groups and p-values for the differences between the groups are calculated. Distribution of sex and percentage of loose components in both groups and their p-values are shown.
Table 2b. Comparison of various parameters between contained and non-contained hips for revised prostheses.

<table>
<thead>
<tr>
<th></th>
<th>Containment good (N=51)</th>
<th>Containment poor (N=21)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex male (%)</td>
<td>14/51 (28%)</td>
<td>10/21 (48%)</td>
<td>0.099</td>
</tr>
<tr>
<td>Age in years (mean ± SD)</td>
<td>67 ± 11</td>
<td>72 ± 9</td>
<td>0.068</td>
</tr>
<tr>
<td>Loosening of at least one of the components</td>
<td>35/51 (69%)</td>
<td>13/21 (62%)</td>
<td>0.582</td>
</tr>
<tr>
<td>Loose stem (%)</td>
<td>20/51 (39%)</td>
<td>2/21 (10%)</td>
<td>0.013*</td>
</tr>
<tr>
<td>Loose cup (%)</td>
<td>25/51 (49%)</td>
<td>13/21 (62%)</td>
<td>0.320</td>
</tr>
<tr>
<td>Mean survival time stem (± SD)</td>
<td>110 ± 70</td>
<td>93 ± 79</td>
<td>0.388</td>
</tr>
<tr>
<td>Mean survival time cup (± SD)</td>
<td>91 ± 62</td>
<td>77 ± 77</td>
<td>0.470</td>
</tr>
</tbody>
</table>

Mean (and standard deviation) of age and survival of prosthesis components are reported for both groups and p-values for the differences between the groups are calculated. Distribution of sex and percentage of loose components in both groups and their p-values are shown.

Figure 2. Schematic representation of procedure to find percentage of patients with contained and non-contained joints (2A). Schematic representation of procedure to give an idea of the number of patients that can be included in a clinical trial based on arthrography data (2B).
Sensitivity of arthrogram for loosening

To investigate whether arthrograms with poor containment exhibited a higher percentage of false-negative results, sensitivity of the arthrogram for loosening was calculated. One hundred and two patients underwent surgery of the hip within 2 years after arthrography. The mean delay between arthrography and surgery was 6.8 ± 5.4 months. Of these 102 patients 21 (21%) were not contained and 81 (79%) were contained. In the non-contained group 11 hips had loosening of the stem as observed during surgery, six of which showed loosening on the arthrogram (sensitivity 55%). In the contained group 41 hips had loosening of the stem as observed during surgery, 28 of which had loosening on the arthrogram (sensitivity 68%). For the cups sensitiv-

Figure 3. Fluoroscopic image during arthrography in a hip with clinically loose prosthesis.

Example of a hip with a poor containment and leakage of contrast medium along the psoas muscle. Left hip of a 50-year-old female patient with a cemented Stanmore prosthesis implanted six months before the arthrography was done. 40 mL of contrast medium was injected. Loosening could not be shown on the arthrogram. Arrows show leakage of contrast medium along the psoas muscle.
Arthrography in loosened hip prostheses.

The sensitivity was 77% in the group with non-contained joints and 81% in the contained hips. Overall sensitivity and specificity for loosening of the stems was 65% and 96%, respectively. For the cups overall sensitivity was 80% and specificity was 93%. There were no differences in sensitivity and specificity between primary and revised hips.

Volume

Of the primary hip prostheses 113 had a contained joint, in 88 of which a joint volume was noted in the radiological reports. Of the revised hip prostheses 51 had a contained joint of which 35 had a known volume. In total 123 arthrograms were contained and had a known joint volume. The mean injected volume in the contained hips was 29 ± 12.4 mL (range, 2-60 mL) for the primary prostheses and 34 ± 13.2 mL (range 13-60 mL) for the revised prostheses ($p = 0.085$). Male patients had a larger volume than females when corrected for primary or revision surgery (34 ± 13.5 mL and 29 ± 12.3 mL respectively) ($p = 0.019$). There was no association between age and the injected volume ($p = 0.192$). Mean volumes and the 95% confidence intervals for hips with loosening of one or two components are shown in Figure 4.

![Graphic representation of joint capacity in different grades of prosthesis loosening.](image)

Error bars represent means and their 95% Confidence intervals for four categories of loosening. The mean volume of hips with well-fixed prostheses is significantly lower than the volumes in all other groups ($p = 0.003$). There is no difference in volumes between the three groups that show loosening ($p = 0.171$).
In hips with at least one loose component (diagnosed by arthrography and surgery) the injected volume was larger than in hips with no loosened components ($33 \pm 12.0 \text{ mL}$; and $26 \pm 12.6 \text{ mL}$ respectively) ($p = 0.003$) (Figure 5). There were no significant differences between hips with only loosening of the stem or cup, or loosening of both components with respect to volume of the arthrogram ($p = 0.171$). These results were similar for loosening diagnosed by arthrography alone.

**Figure 5.** Fluoroscopic image during arthrography in a hip with clinically loose prosthesis.

Example of a contained hip with average volume. Right hip of a 76-year-old female patient with a cemented Stanmore prosthesis implanted twelve years before the arthrography was done. 20 mL of contrast medium was injected. There is loosening of both cup and stem. Arrows show leakage of contrast medium in the periprosthetic space.
Discussion

In this study joint space containment and volume of hips with a clinically loose prosthesis were evaluated. Of 221 hips, 164 (74%) had a contained joint and 123 of these had a known volume. In these hip joints the mean volume was 31 mL. Containment of hip joints in patients with a clinically loosened prosthesis has been studied before. Barentsz et al. studied arthrographies of 24 patients with clinically loosened prostheses. Four of 24 patients showed leakage of the contrast medium in the surrounding tissues, one of them had a bursa. In another study of 178 arthrographies a bursa was found in 35% of cases and a non-bursal cavity in seven percent of hips. In total 43% of these hip joints had leakage of the contrast medium outside the joint. 

The volume of the joint cavity is dependent on the method of measurement used. In the current study volume was defined as the amount of contrast medium that could be injected into the joint until rapid increase of pressure, pain, or lymphatic filling. Hendrix et al. used the same criteria and found volumes of 7-70 mL in 31 patients. In the same way Barentsz et al. measured a mean volume of 12 mL (6-30 mL). Seelen et al. performed an arthrography in 30 patients with cementless hip prostheses with clinical suspicion for loosening. The mean volume was 18 mL (10-30 mL). Maus et al. found a small pseudocapsule (0-10 mL) in 32% of arthrographies; a medium size (11-25 mL) in 47% and a large pseudocapsule (>25 mL) in 21% of 178 arthrograms. Volumes found in the current study cannot be compared with studies in which volume of the joint is measured by a different method.

The results of our study show that there is a higher percentage of loosening in hips with a contained joint than in non-contained hips. The association between non-contained joints (bursae and non-bursal communicating cavities) and loosening has not been consistent in the literature. Some authors find a higher amount of loosening in hips with a bursa. Others conclude that the presence of bursal opacification does not have predictive value in identifying loosening or infection. However, it must be noted that in the case of a bursa or leakage in the soft tissues, the pressure required for leakage of contrast medium from the periprosthetic space, cannot be built up. This can lead to false-negative results. In this study the intra-articular pressure required to demonstrate loosening could not be achieved in joints with poor containment. Findings of loosening during revision surgery revealed that in non-contained joints sensitivity of the arthrography for loosening of the stem and cup was lower than in the contained group.

A drawback of the current study is that the injected volume was not always mentioned in the report of the arthrography by the radiologist.

Arthrography can be used to calculate the concentration and dose of the active
ingredient in patients that are considered for intra-articular therapy for hip prosthesis loosening and to exclude patients with leakage from the joint. The volumes that would be suitable for intra-articular injections in clinical studies will differ from study to study. The range of volumes to be included in a clinical study depend on several parameters, including toxicity and the predicted therapeutic window of the injected agent.

The data in this study can be used to predict how many patients will be excluded from intra-articular therapy protocols based on arthrography results. When hips from this study with a known volume are considered 27% (45 of 168) of cases will be excluded due to leakage of contrast medium. If there is also a limitation to the volume of active ingredient to be injected, the number of excluded patients will be larger. When a volume of mean ± 1 S.D. is considered to provide a drug concentration within the therapeutic range, without a risk for toxic side effects, the volumes to be included in the patients in this study would be 18-44 mL, corresponding to a percentage of included patients of 54% (Figure 2B).

Given the above-mentioned limitation, this study shows that 27% of hips with a clinically loosened prosthesis have a non-contained joint.

**Conclusion**

In this study containment of injected solutions within the joint space and the volume of that space is evaluated to optimise the delivery of therapeutic agents to joint tissue. The results of the study show that about one quarter of the hips with a clinically loosened prosthesis has a non-contained joint. When a clinical study with an intra-articular therapy is considered, an arthrogram is useful in the inclusion procedure to determine containment of the joint and the volume that can be injected.