Greater Trochanteric Pain Syndrome in General Practice

Tineke Brinks

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	Prof.dr. J.A.N. Verhaar
	Prof.dr. H.C.P.M. Van Weert

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Chapter 1

General introduction

INTRODUCTION

This thesis focuses on patients with greater trochanteric pain syndrome. These patients suffer from local pain at the lateral side of the hip. The syndrome is characterized by chronic intermittent or continuous pain at and around the greater trochanter, sometimes radiating to the lateral aspect of the hip or lateral thigh and increasing with physical activity. Lying on the affected side can interfere with restful sleep. In 1952 Spear and Lipscomb described a series of 40 patients with a dull aching pain in the trochanter region and distinguished this condition from referred pain or local infectious diseases.[1] In the late 1970s, Little described this condition as bursitis trochanterica.[2] Finally, in 1991, Collee et al. described this condition as greater trochanteric pain syndrome (GTPS).[3]

The syndrome occurs in all age groups, but the incidence is highest in patients aged 40-60 years and up to four times higher in women.[4-6] In a retrospective study in general practice the incidence of trochanteric pain was calculated to be 1.8 per 1000 patients per year.[5] So, in a standard general practice about four new patients with trochanteric pain present themselves per year. The prevalence of GTPS in adults with musculoskeletal low back pain is reported to be 20-35%.[7] A cross-sectional study in a population at risk for osteoarthritis of the knee showed that 17.6% had GTPS.[7] The symptoms of GTPS can be considered as a chronic disease. Lievense et al. found that 29% of the patients with GTPS still suffered from this pain after 5 years.[5] Spear and Lipscomb showed that the complaints of GPTS in their cohort of 40 patients lasted from 2 weeks to 27 years.[1] In the study of Anderson the symptoms of the 45 patients persisted from 4 weeks to 5 years.[8]

The etiology of trochanteric pain is not precisely documented. Trochanteric pain was previously thought to be caused by inflammation of the bursa, but recent histological investigation could not confirm this hypothesis.[9] Furthermore, Cohen et al. recently concluded that fluoroscopically-guided corticosteroid injections in the trochanteric bursa did not improve the outcome of pain reduction compared to 'blind' corticosteroid injection in the trochanteric region.[10] Karpinsky and Piggott compared the pain pattern in GTPS with tennis elbow and other pain patterns in local overuse.[11] A study on the classification of hip disorders showed that edema around the greater trochanteric tendons was closely related to the symptoms of GTPS.[12] MRI studies also suggest that m. gluteus medius pathology is associated with GTPS.[13] The gluteus medius and minimus muscles are the major abductors of the hip. The main tendon of the gluteus medius muscle attaches to the superior aspect of the greater trochanter, with the lateral tendon inserting into the lateral aspect. The gluteus minimus muscle attaches to the anterior facet of the greater trochanter. Consequently, bursal inflammation, frictional trauma from overuse, and tears of either the gluteus medius or minimus muscles, or their tendinous insertions, may all result in GTPS.[14]

There are few reports on therapy for GTPS in the medical literature. Injection therapy for GTPS was first described in 1959 by Krout and Anderson.[15] In 1961 Gordon stated that the condition could be treated conservatively and that most cases respond to local corticosteroid injections. He asserted that surgical interventions should be reserved for the most intractable cases.[16] Govaert et al. concluded that trochanteric reduction osteotomy is a safe and effective procedure for patients with refractory trochanteric bursitis who do not respond to conservative treatment.[17] Craig et al. reported their positive experience with a method of Z-lengthening of the iliotibial band for refractory GTPS.[18] Furia et al. concluded that shockwave therapy is an effective treatment for GTPS.[19] In 2009 Rompe et al. reported the first randomized clinical trial in secondary care, which compared shockwave therapy, physical therapy and corticosteroid injection therapy for GTPS.[20] They concluded that corticosteroid injections were effective at short-term follow up but that, after 15 months, physiotherapy and shockwave therapy were superior to injection therapy. Until now, however, no randomized control trial has examined the effect of treatment with corticosteroid injections of GTPS in general practice, while in Dutch general practice injection therapy (apart from expectative treatment with analgesics) is the most frequently utilized treatment in GTPS.[5]

The main objective of this thesis is to evaluate the place of corticosteroid injection for GTPS in general practice. For this, we examine the efficacy of local corticosteroid injections for GTPS in general practice compared to usual care with an expectative treatment with analgesics, using a randomized controlled trial design. The cost-effectiveness of the injection therapy was also assessed. Balanced decisions about healthcare interventions require evidence on harms as well as benefits of the various interventions. Therefore, in this thesis we also present a systematic review of the literature on the reported adverse effects of corticosteroid injection therapy and on the effectiveness of other interventions for GTPS.[21]

Finally, given the frequently reported role of co-existent morbidity in lower extremity osteoarthritis and low back pain, we also investigate the influence of co-morbidity on efficacy of corticosteroid injection in GTPS. In a separate study we evaluate the influence of GTPS on symptom severity in patients in general practice with hip osteoarthritis.

OUTLINE OF THIS THESIS

This thesis describes the results of a randomized controlled trial conducted in patients suffering from greater trochanteric pain syndrome. This study was performed in Dutch general practice in 2006-2009.

In the first part of this thesis **Chapter 2** presents the study design. Then **Chapter 3** describes the main outcomes of the trial, which included 120 patients. **Chapter 4** calculates the cost-effectiveness of injection therapy in patients with GTPS based on the outcome of the randomized trial in general practice.

In the second part of this thesis **Chapter 5** presents an overview of the literature on the side-effects of extra-articular corticosteroid injections. This is followed in **Chapter 6** by a systematic review of studies evaluating the efficacy of interventions for GTPS. In **Chapter 7** we describe the prevalence and influence of GTPS in primary care patients with hip osteoarthritis. Finally, **Chapter 8** discusses the main results of this work and the clinical implications of our findings for the management of patients with GTPS by the general practitioner.

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Chapter 2

Effect of corticosteroid injection for trochanter pain syndrome: design of a randomized clinical trial in general practice

Aaltien Brinks, Rogier M van Rijn, Arthur M Bohnen, Gabriël LJ Slee, Jan AN Verhaar, Bart W Koes, Sita MA Bierma-Zeinstra

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ABSTRACT

Background: Regional pain in the hip in adults is a common cause of a general practitioner visit. A considerable part of patients suffer from (greater) trochanteric pain syndrome or trochanteric bursitis. Local corticosteroid injections is one of the treatment options. Although clear evidence is lacking, small observational studies suggest that this treatment is effective in the short-term follow-up. So far, there are no randomized controlled trials available evaluating the efficacy of injection therapy. This study will investigate the efficacy of local corticosteroid injections in the trochanter syndrome in the general practice, using a randomized controlled trial design. The cost effectiveness of the corticosteroid injection therapy will also be assessed. Secondly, the role of co-morbidity in relation to the efficacy of local corticosteroid injections will be investigated.
Methods/Design: This study is a pragmatic, open label randomized trial. A total of 150 patients (age 18–80 years) visiting the general practitioner with complaints suggestive of trochanteric pain syndrome will be allocated to receive local corticosteroid injections or to receive usual care. Usual care consists of analgesics as needed. The randomization is stratified for yes or no co-morbidity of low back pain, osteoarthritis of the hip, or both. The treatment will be evaluated by means of questionnaires at several time points within one year, with the 3 month and 1 year evaluation of pain and recovery as primary outcome. Analyses of primary and secondary outcomes will be made according to the intention-to-treat principle. Direct and indirect costs will be assessed by questionnaires. The cost effectiveness will be estimated using the following ratio: CE ratio = (cost of injection therapy minus cost of usual care)/(effect of injection therapy minus effect of usual care).
Discussion: This study design is appropriate to estimate effectiveness and cost-effectiveness of the injection therapy. We choose to use a pragmatic study design and are thus not able to study specific effects of the injection with corticosteroids. A distinction between placebo effect of the injection and specific effects of the corticosteroids is therefore not possible.
Trial Registration: The trial is listed in the Dutch Trial Registry with the number ISRCTN16994576.

BACKGROUND

One of the more common pain syndromes of the in the hip in adults is known as trochanteric pain syndrome (TPS) or trochanteric bursitis. It is considered to have the following characteristics: chronic, intermittent pain at the lateral site of the upper limb, sometimes radiating to the lateral aspect of the hip or lateral thigh and increasing at physical activity.[1-4] Lying on the affected site increases the pain and can thereby disturb sleep and/or rest. At physical examination palpation of the greater trochanter is painful.[1-4] The prevalence is higher among females than among males (rate 4:1) and the incidence is highest between the ages 40 to 60 years.[4,5] A recent prospective study in a Dutch general practice population showed an incidence of 5.6 patients per 1000 adults in one year (unpublished pilot data). In a retrospective study, Lievense et al. found an incidence of 1.8 per 1000 in one year.[5] Earlier, the same clinical manifestations were known as trochanteric bursitis, although clinical manifestations of inflammation almost never occur.[1,2,4] Tendinitis of the insertion of the m. gluteus medius is suggested as another cause of pain at this site. It might also be a combination of bursitis and tendinitis. Because the exact etiology is not known, Collee et al. suggested in 1991 to classify the clinical manifestations as "greater trochanter syndrome".[6] Observational studies showed that in most of the cases with local pain at this site co-morbidity exists. About two thirds of the patients with TPS have also low back pain or osteoarthritis of the hip.[1,3,6,7] Many GPs inject corticosteroids combined with an anesthetic agent at the most painful site with the expectation that the pain will decrease. There is no conclusive evidence that these injections are effective, although small observational studies suggest that injections with corticosteroids are effective in the short-term follow-up.[2,5,7,8] No randomized controlled trials are available evaluating the benefit of injection therapy for this disorder. Other common treatment options are pain relief with analgesics, physiotherapy, a surgical release of the iliotibial tract, removal of the bursa, or a trochanteric reduction osteotomy.[9] This study we will investigate the efficacy and cost effectiveness of local corticosteroid injections in TPS, using a randomized controlled trial design. We also investigate the role of co-morbidity in relation to the efficacy of this local corticosteroid injection.

METHODS/DESIGN

Study design

This study is a pragmatic, open label randomized trial. The local Medical Ethics Committee of the Erasmus University Medical Center, Erasmus MC, has approved the trial. The trial is included in the Dutch Trial register (ISRCTN 16994576).

All patients will give written informed consent.

Patient selection

GPs participating in the HONEUR research network of the Erasmus MC and other interested GPs in the area will be invited to participate in the study. The HONEUR GP research network consists of 40 GP practices which are connected to the Department of General Practice in order to participate in regular research projects. They will be asked to select patients aged 18 to 80 years visiting the GP with the following symptoms: pain persisting for more than one week in the lateral region of the hip or thigh with tenderness at palpation of the greater trochanter with one of the two following characteristics:[1-4,10]

1). Severe pain at palpation of the greater trochanter, but uncertainty as to whether the patient recognizes the pain as that for which he or she visits the GP.
2). Local tenderness when the area of the great trochanter is palpated and the patient recognizes the pain as that for which he or she visits the GP.

Excluded are patients who are unable to understand the Dutch questionnaires, patients who have consulted the GP with the same complaints in the previous year and had any intervention, or are operated on in the same region, or have systemic neurological or rheumatologic disorders.

Procedures

Patients who are eligible for the study and show interest to participate will receive written study information from their GP, as well as the baseline questionnaire and the informed consent form. If they show interest the GP will fax their contact data to the researcher together with the findings of physical examination on a standardized form. One of the investigators will contact the patient to ask if they have any additional questions and will assess the suitability to participate in the study. If the patient still wants to participate and is eligible, we ask them to return the baseline questionnaire and informed consent form. When we receive the baseline questionnaire, the patient will be classified as having comorbidity or not. If the question: "Do you suffer from low back pain" is answered positively as often or continuous, we classify the patient as having low back pain comorbidity. The ACR criteria for osteoarthritis of the hip, using history and physical examination (painful or decreased internal rotation and flexion of the hip as performed by the GP) are used to decide whether the patient has osteoarthritis of the hip as comorbidity.[11]

Randomization

After receiving the baseline questionnaire and informed consent, an independent person will randomize each patient based on computerized randomization lists to either receive the injection therapy or the usual care, consisting of analgesics as needed. This randomization is stratified for yes or no comorbidity and uses randomization block sizes of ten, yielding four strata: one lacking comorbidity, one with low back pain, one with osteoarthritis, and one stratum with both.

Intervention

The GP and the patient will be informed about the treatment that the patient will be given as soon as randomization has taken place. The GPs participating in the study have been trained by us to give the injection according to a standard procedure: i.e. to use 40 mg triamcenolon acetate combined with lidocaine 1 or 2% in a 5 ml syringe. They are trained to mark the most painful point with a pen or pencil and disinfect the site. The needle is inserted perpendicular to the skin and directed down to the point of maximal tenderness, 1 ml of the substance will be injected at that point, then the needle should be moved to another place in the painful area and the same procedure should be repeated until the syringe is empty. In case of lack of efficacy, or only temporary effect, this procedure may be repeated after a period of 3 weeks up to 3 months. After the injection the GP will fax us a form with details of the injection given, e.g. the volume that is injected, if the injection was painful, or if there was pain relief after injection or direct side effects.

The control group will receive usual care consisting of analgesics as needed; all patients are free to receive additional treatment from a physiotherapist, although this is not advocated by the investigators.

Questionnaires

The primary outcome measurements will be experienced recovery at 3 months and at 1 year, measured on a 7-point Likert scale (1 = fully recovered till, 7 = worse than ever) and severity of pain during the last week measured with a numeric rating scale (0 = no pain, 10 = worst conceivable pain). Medical consumption of the patient (e.g. medication, visits to the GP or physiotherapist, hospital treatment and diagnostic tests) will be measured as direct cost.

The PRODISC questionnaire will be used to measure the cost effectiveness and will measure the indirect costs, expressed in work staff absence and loss of productivity in paid work, or loss of productivity in not-paid work.[12]

The WOMAC (Western Ontario and McMaster University Osteoarthritis Index) is recommended by the Osteoarthritis Research Society for use in clinical trials in people with hip osteoarthritis to measure pain and disabilities.[13] The HOOS (hip disability and osteoarthritis outcome score)[14] is developed as an extended version of the WOMAC, to evaluate the whole domain of patient-relevant outcome in young and active patients and is recently validated in the Dutch language.[15] The HOOS consists of 5 subscales; Pain, other Symptoms, Function in daily living (ADL), Function in sport and recreation (Sport/Rec) and hip-related Quality of life (QOL). Both the WOMAC and HOOS will be used in this study. We use the EuroQol (EQ5D) as instrument to measure quality of life.[16] Finally, we ask the patients who received an injection, to report any side effects of the injection. Table 1 shows the timing of measurements.

Table 1. Timing of study questionnaires.

	baseline	6 wks	3 mth	6 mth	9 mth	12 mth
Severity of pain: VAS (1–10)	+	+	+	+	+	+
Experienced recovery: Likert (1–7)	+	+	+	+	+	+
HOOS including WOMAC	+	+	+	+	+	+
PRODISQ + medical consumption	+		+	+	+	+
EQ 5 D	+		+	+	+	+
Side effects of injection		+	+	+	+	

Sample size

The sample size was calculated to detect an increase in recovery rate of 25% in the intervention group after three months of follow-up (45% recovery in the control group versus 70% recovery in the intervention group). With power 0.8 and alpha 0.05 (two-sided tested) and with a dropout rate of 10%, a total number of 75 patients in each group are needed.

Data analyses

Difference between the groups in the primary outcome will be analyzed based on the basis of the "intention-to treat" principle. Differences in continuous outcome measures between the groups will be analyzed with linear regression techniques and differences in dichotomous outcomes (recovery dichotomized to totally recovered or almost totally recovered versus slightly recovered and less) will be analyzed with logistic regression techniques. Baseline differences between the groups will be assessed and checked whether these influence the outcome of the study. Baseline variables that change the outcome by 10% or more will be regarded as confounders and will therefore be added to the regression models. Regression models will also be used to study effect modification of co-morbidity. A cost-effectiveness analyses will be performed from a social and a patient perspective, looking at differences in direct and indirect health care cost between the two groups. If the trial does not show a difference in disease parameters (VAS and WOMAC) and quality of life (EuroQol) between the groups, the analysis will be reduced to a cost minimization analysis. This form of analysis evaluates the efficacy of treatment based solely on direct and indirect costs. If the study does find a positive difference in disease parameters and/or quality of life in the injection group, a cost-effectiveness ratio can be determined.

DISCUSSION AND CURRENT STATUS

In this study design we compare two types of therapy which are frequently used in general practice. This study design is appropriate to estimate effectiveness and cost-effectiveness of the injection therapy. We choose to use a pragmatic study design and are thus not able to study specific effects of the injection with corticosteroids. A distinction between placebo effect of the injection and specific effects of the corticosteroids is therefore not possible. The study is executed in general practice and may therefore not apply to patients in secondary care. No disease specific questionnaires are available for this disorder. Therefore generic outcome measures (recovery and pain severity) were chosen as primary outcome measures. However, region specific questionnaires for osteoarthritis were included as secondary outcome measures. These questionnaires allow us to analyze subscales like for instance the WOMAC pain and the WOMAC function; subsequently osteoarthritis specific questions on stiffness (WOMAC stiffness) can validly be omitted. Patients included in our trial have symptoms of TPS solely, or have these symptoms in co-occurrence with low back pain or osteoarthritis of the hip. To include patients with such co-morbidity maybe questionable because the TPS may be due to such morbidity. Therefore injection therapy for TPS in such morbidity possibly shows different effectiveness. We chose to include these patients because in common practice these patient also receive injection therapy. We, however, used a design in which we stratify for co-morbidity or not. The current status of the study is that of a total of the 80 GPs participating in the study. However, until now only 43 GPs included 90 patients. The total study population is expected to be recruited by February 2008. The first short term results (3 months of follow-up) will be available at mid-2008.

COMPETING INTERESTS

ZonMw, the Netherlands Organisation for Health Research and Development supported this study. The authors have no competing interests.

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Chapter 3

Corticosteroid injections for greater trochanteric pain syndrome: a randomized controlled trial in primary care

Aaltien Brinks, Rogier M van Rijn, Sten P Willemsen, Arthur M Bohnen,
Jan AN Verhaar, Bart W Koes, Sita MA Bierma-Zeinstra

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ABSTRACT

Purpose: We undertook a study to evaluate the effectiveness of corticosteroid injections in primary care patients with greater trochanteric pain syndrome (GTPS).

Methods: We evaluated the effect of corticosteroid injections compared with expectant treatment (usual care) in a pragmatic, multicenter, open-label, randomized clinical trial in the Netherlands. Patients (aged 18 to 80 years) with GTPS visiting 81 participating primary care physicians were randomly allocated to receive either local corticosteroid injections (n = 60) or usual care (n = 60). Primary outcomes of pain severity (numerical rating scale 0 to 10) and recovery (yes or no total or major recovery) were evaluated at 3-month and 12-month follow-up visits. Adverse events were collected at 6 weeks.

Results: At the 3-month follow-up visit, 34% of the patients in the usual care group had recovered compared with 55% in the injection group (adjusted OR = 2.38; 95% CI, 1.14-5.00, number needed to treat = 5). Pain severity at rest and on activity decreased in both groups, but the decrease was greater in the injection group, for an adjusted difference in pain at rest of 1.18 (95% CI, 0.31-2.05) and in pain with activity of 1.30 (95% CI, 0.32-2.29). At the 12-month follow-up, 60% of the patients in the usual care group had recovered compared with 61% in the injection group (OR = 1.05; 95% CI, 0.50-2.27). Pain severity at rest and on activity decreased in both groups and the 12-month follow-up showed no significant differences, with adjusted differences of 0.14 (95% CI, –0.75 to 1.04) for pain at rest and 0.45 (95% CI, –0.55 to 1.46) for pain with activity. Aside from a short period with superficial pain at the site of the injection, no differences in adverse events were found.

Conclusion: In this first randomized controlled trial assessing the effectiveness of corticosteroid injections vs usual care in GTPS, a clinically relevant effect was shown at a 3-month follow-up visit for recovery and for pain at rest and with activity. At a 12-month follow-up visit, the differences in outcome were no longer present.

INTRODUCTION

Greater trochanteric pain syndrome (GTPS), also known as trochanteric bursitis, is a common cause of hip pain in general practice. In 1958 Anderson described the physical signs of bursitis trochanterica, and in 1979 Little described the clinical findings in the context of other causes of hip pain.[1,2] Schapira et al[3] and Shbeeb and Matteson[4] reported extended descriptions of the clinical symptoms. Karpinski and Piggott[5] and Collee et al[6] described these clinical findings as GTPS. This syndrome is characterized by chronic intermittent or continuous pain at and around the greater trochanter, sometimes radiating to the lateral aspect of the hip or lateral thigh and increasing with physical activity. There is tenderness to palpation of the greater trochanter on physical examination, reproducing the patient's pain. Although GTPS was previously thought to be caused by inflammation of the bursa, recent histological investigation could not confirm this hypothesis.[7] In 2001 a study of the classification of hip disorders showed that edema around the greater trochanteric tendons (seen on sonography), but not sonographic signs of trochanteric bursitis, was closely related to the symptoms of GTPS.[8] Magnetic resonance imaging also suggests that pathologic findings of the gluteus medius is associated with GTPS.[9] Furthermore, Cohen et al recently concluded that fluoroscopically guided corticosteroid injections in the trochanteric bursa did not improve the outcome of pain reduction compared with an unguided corticosteroid injection in the trochanteric region.[10] The prevalence of GTPS was recently calculated to be 17.6% in a community-based population at risk for knee osteoarthritis and in persons with knee osteoarthritis.[11] In a retrospective study in general practice, the incidence of patients visiting their primary care physician for trochanteric pain was calculated to be 1.8 persons per 1,000 per year.[12] This latter study also showed that 36% of the patients still had complaints after 1 year, and 29% of the patients still suffered from this pain after 5 years. In that same study 37% of the patients were injected with corticosteroids, and of these patients, 66% reported improvement after treatment.[12] This outcome is similar to the outcome of a case series in which 61% of patients improved 6 months after a local corticosteroid injection.[13] In a report of 61 cases, 58 patients had excellent or good results after a corticosteroid injection.[14] The study comparing unguided corticosteroid injection with fluoroscopically guided injection showed a positive result in 47% and 41%, respectively.[10] In another trial corticosteroid injection was compared with other specific therapy (shock wave therapy and exercise therapy) and showed superior short-term effect (success rate 75% for corticosteroid injections and 13% and 7% for shock wave and exercise therapy, respectively). The effect of therapy reversed after 15 months of follow-up (success rate for corticosteroid injection was 48%, shock wave therapy 74%, and exercise therapy 80%).[15] Although local corticosteroid injections are frequently given for GTPS, no study has compared the effect of corticosteroid injections with usual

care, which is an expectant approach in a randomized trial. We therefore report the first randomized controlled trial comparing usual care with the effect of an additional local corticosteroid injection in primary care patients with GTPS.

METHODS

This study was a pragmatic, open-label, randomized trial in general practice conducted in the Netherlands with 81 participating primary care physicians. The local Medical Ethics Committee of the Erasmus University Medical Center, approved the trial, and all the patients gave informed consent for participation. The trial was included in the Dutch Trial register (ISRCTN 16994576). Details of the study protocol were reported in 2007 and are briefly summarized here.[16]

Participants

General practitioners in the Rotterdam area recruited the study participants by selecting patients (aged 18 to 80 years) who consulted them about GTPS. GTPS was diagnosed when the patient complained of pain persisting for more than 1 week in the lateral region of the hip, and tenderness to palpation of the greater trochanter, reproducing the patient's pain, was found on physical examination.[1-4] Excluded were patients who were unable to understand the Dutch questionnaires. Also excluded were patients who had consulted their general practitioner with the same symptoms in the previous year and had received any intervention, or who were operated on in the same region, or who had a systemic neurological or rheumatologic disorder. If the patient was interested in participating in our study, the physician sent to the researcher a fax of the patient's contact information and a standardized form with findings from the physical examination. The physician gave the patients written study information, the baseline questionnaire, and the informed consent form. One of the investigators contacted the patient to ask whether there were any additional questions and assessed the patient's suitability to participate in the study. Patients who were eligible and agreed to participate were asked to return the completed baseline questionnaire and informed consent form. After the questionnaire was returned, the patient was classified by comorbidity status. If the question, "do you suffer from low-back pain?" was positively answered as often or continuously, the patient was classified as having comorbid low-back pain. We used the American College of Rheumatology (ACR) history and physical examination criteria for osteoarthritis of the hip (older than 50 years, morning stiffness lasting longer than 60 minutes, and painful or decreased internal rotation and flexion of the hip as performed by the general practitioner) to decide whether the patient had suspected osteoarthritis of the hip as a comorbid condition.[17]

Randomization

Patients were independently randomized (based on computerized randomization lists) to receive either the injection therapy or usual care. This randomization was stratified by comorbidity and randomization block sizes of 10, yielding 4 strata: with no comorbid condition, with low-back pain, with osteoarthritis of the hip, and with both.

Intervention treatment

As soon as randomization had taken place, the general practitioner and the patient were informed about the treatment that the patient would be given. The physicians participating in the study were trained to give the injection according to a standardized procedure: 40 mg of triamcinolone acetate combined with 1% or 2% lidocaine in a 5-mL syringe. They were trained to mark the most painful point on the hip on the greater trochanter area with a pen or pencil and to disinfect the site. The needle was inserted perpendicular to the skin, directed down to the point of maximal tenderness, and 1 mL of the substance was injected at that point. The needle was then moved to another place in the painful area, and the same procedure was repeated until the syringe was empty. After the injection the physician sent to the study researchers a fax of a form with the details of the injection given, eg, the volume that was injected, whether the injection was painful, and whether there was pain relief after the injection or any immediate side-effects. In addition to the injection therapy, the physicians were allowed to prescribe analgesics (as in the usual care group). The physicians were also allowed to give a second injection between 3 weeks and 3 months after the first injection.

Usual care

The control group received usual care consisting of analgesics as needed. In the Netherlands, because there is direct access to a physiotherapist, all patients in both treatment groups were allowed to receive additional treatment from a physiotherapist (however, the investigators did not specifically recommend this action).

Outcomes

Primary outcome was recovery at 3 and 12 months as measured on a 7-point Likert scale (1 = fully recovered to 7 = worse than ever), and severity of pain during the last week (both while at rest and during activity) measured with a numeric rating scale from 0 to 10 (0 = no pain, 10 = worst conceivable pain). These outcomes were assessed at 6 weeks and at 3, 6, 9, and 12 months after randomization and were collected by means of postal questionnaires. Other secondary patient-oriented outcomes in this study were quality of life (range 0 to 1,0 = worst quality of life to 1 = best quality of life), which we measured using a standardized instrument, EQ-5D (EuroQol Group, York, United Kingdom),[18] and a self-administered health status instrument for patients with osteoarthritis of the hip

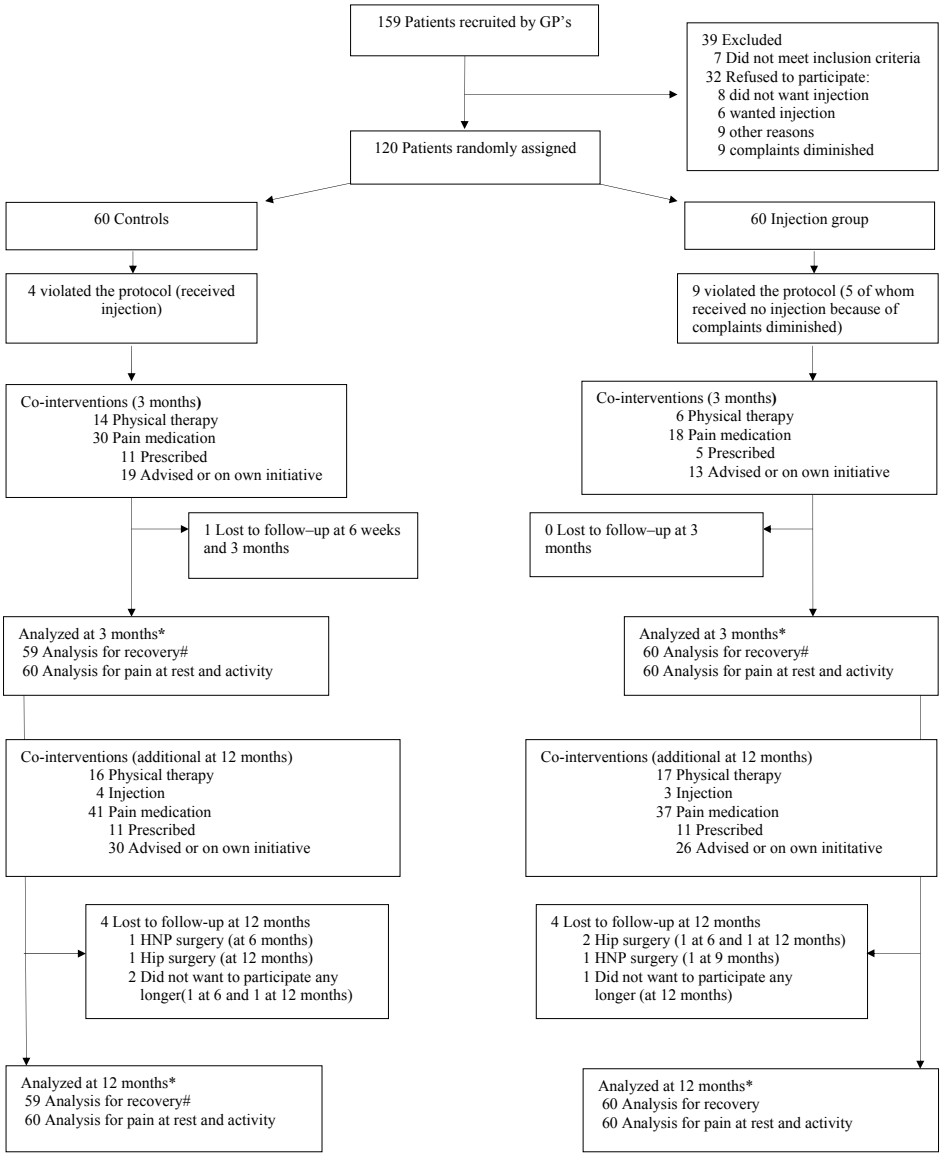
or knee, the Western Ontario and McMaster University Osteoarthritis Index (WOMAC). The WOMAC index consists of 3 domains: pain (5 items), stiffness (2 items), and function (17 items). We used the domains of pain and function. Each item can be scored on a 5-point Likert scale. (where 1 = none and 5 = extreme). Sum scores for each domain were calculated and standardized (0 to 100), with high values indicating more pain or lower physical functioning.[19] At a 6-week follow-up visit, all patients were asked about specific adverse events of the therapy (eg, hot flushes, disturbance in menstruation pattern, or general allergic reaction, such as itching all over the body, urticaria, headache, shortness of breath).

Data analyses

Between-group differences in the primary outcome were analyzed based on the intention-to-treat principle. Between-group differences in continuous outcome measures were analyzed with repeated measures for general linear models. Generalized estimating equations models (repeated measures) were used for dichotomous outcome (recovery dichotomized to totally recovered or almost totally recovered vs slightly recovered and less). All analyses were adjusted for baseline values of the outcome, except for the analysis on recovery. In addition, a yes or no presence of comorbidity (osteoarthritis, low back pain, or both) was added to the regression models. Other baseline values (age, sex, employment, body mass index, education level, and duration of symptoms, preference of treatment, and comorbidity, as well as baseline pain severity for recovery analyses) were assessed to establish whether these values affected the primary outcomes of the study by more than 10%. If so, they were also added to the models. Number needed to treat was calculated for the dichotomized outcome (recovery). Effect sizes were calculated as adjusted difference in outcome divided by baseline standard deviation of the outcome. From the clinical standpoint effect sizes of 0.2 to 0.5 are considered small, and 0.5 to 0.8 moderate, whereas greater than 0.8 indicates a large clinical effect.[20] Predefined subgroup analyses were performed for the subgroup with comorbidity (osteoarthritis of the hip, low-back pain, or both). All analyses were conducted using SAS version 9.2 (2007, Institute Inc, Cary, North Carolina, USA). We aimed to include 150 participants (68 patients per group, and anticipating a 10% loss to follow-up) to be able to prove a difference of 25% for recovery (a recovery of 45% in the control group and 70% in the intervention group) based on 2-sided testing with α of .05 and a power of 80%.

RESULTS

Figure 1 presents the participant flow of the study. From April 2006 until June 2008 general practitioners recruited 159 patients, 7 of whom did not meet our inclusion



*All people were included in the repeated measurement analysis.
# For the repeated measurements analysis on recovery at least one follow-up assessment was needed to be included in the analysis.
HNP=Hernia Nuclei Pulposi

Figuur 1: Participants flowchart.

criteria. After reading the study information, 23 patients refused to participate, for the most part because they had a clear preference for either injection therapy or for usual care. Although the time between visiting their physician and randomization was only a few days, 5 patients had a spontaneous decline of their symptoms and therefore no longer wished to participate in the study. Finally, 120 patients were included in the study and randomized (60 to usual care, 60 to injection therapy); their mean age was 56 years, and 77% of them were women (Table 1 displays their baseline characteristics). Complete follow-up data of the primary outcomes at 3 months were available for 119 patients and at 12 months for 111 patients. During the first 3 months, 13 patients did not receive the intervention as allocated, and 9 patients did not receive the injection therapy. Of the latter group, 5 reported that their symptoms disappeared before the injection was given. In the usual care group 4 patients received an injection from their physician, which was

Table 1. Characteristics of the study population at baseline.

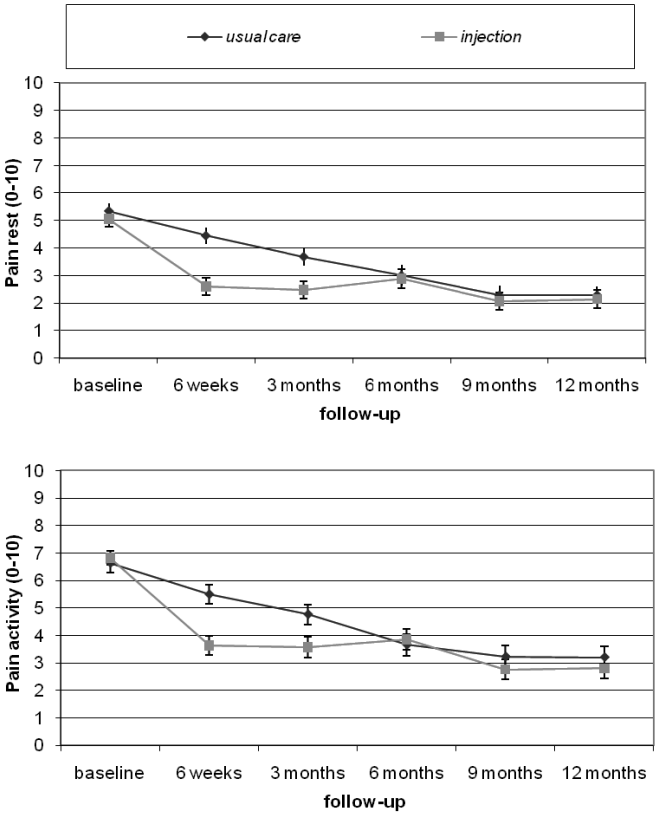
	Usual Care Group n=60	Intervention Group n=60	Total Group n=120
Age in years, mean (SD)	54.8 (14.7)	57.7 (13.9)	56 (14.3)
Women, n (%)	48 (80)	44 (73.3)	92 (76.7)
Paid job, n (%)	24 (40)	26 (43.3)	50 (41.7)
BMI, mean (SD)	26.3 (3.6)	26.9 (3.8)	26.6 (3.7))
WOMAC pain [0-100], mean (SD)[a]	52.4 (19.1)	48.8 (16.1)	50.6 (17.7)
WOMAC function [0-100], mean (SD)[a]	49.2 (19.6)	43.9 (17.0)	47.0 (18.4)
Pain at rest [0-10], mean (SD)[b]	5.33 (2.2)	5.05 (2.2)	5.19 (2.2)
Pain on activity [0-10] mean (SD)[b]	6.63 (2.6)	6.82 (1.9)	6.73 (2.3)
Quality of life, EQ-5D [0-1], mean (SD)[c]	0.72 (0.2)	0.76 (0.2)	0.74 (0.2)
Education level, n (%)			
- low	17 (28.3)	22 (36.7)	39 (32.5)
- middle	33 (55)	29 (48.3)	62 (51.7)
- high	10 (16.7)	9 (15)	19 (15.8)
Duration of complaints, n (%)			
- 1-2 months	30 (50.8)	27 (45.0)	57 (47.9)
- 2-6 months	14 (23.7)	20 (33.3)	34 (28.6)
- >6 months	15 (25.4)	13 (21.7)	28 (23.5)
Co-morbidity hip OA or low back pain, n (%)			
- none	25 (41.7)	22 (36.7)	47 (39.2)
- low back pain	21 (35)	22 (36.7)	43 (35.8)
- hip OA	8 (13.3)	10 (16.7)	18 (15)
- low back pain and hip OA	6 (10)	6 (10)	12 (10)

BMI = body mass index; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index, EQ-5D = EuroQol, OA = osteoarthritis

[a]= Scored on a range from 0-100, with high values indicating more pain or lower physical functioning

[b]= Scored on a range from 0-10, 0= no pain and 10 = worst conceivable pain

[c]= Scored on a range from 0-1, where 0 = worst quality of life and 1 = best quality of life

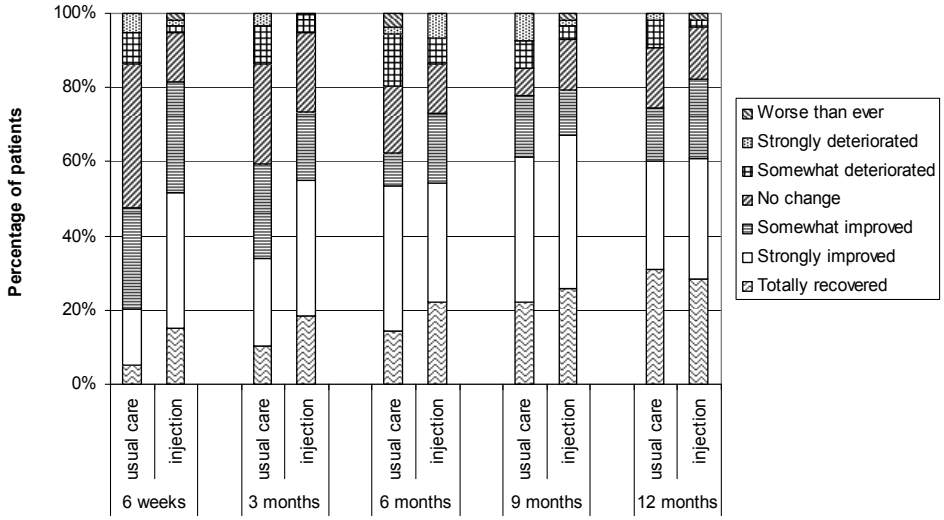


Figuur 2: Course of mean pain intensity (and standard error) at rest and on activity during the 12-month follow-up period for injection group (n=60) and usual care group (n=59), on a visual analog scale (VAS).

contrary to study instructions. Figure 2 shows the course of pain at rest and on activity up to 12 months of follow-up, and Figure 3 shows the course of recovery.

Results at 3-month follow-up

By the 3-month follow-up visit, 55% of injection group patients had recovered (defined as totally or strongly recovered) compared with 34% of the usual care group (21% difference), for a number needed to treat of 5. None of the baseline variables, when added to the model, changed the outcome by more than 10%. Binary models for recovery resulted in an odds ratio (OR) of 2.38 (95% CI, 1.14-5.00) (Table 2). Pain severity at rest and on activity decreased in both groups; however, the decrease was greater in the injection group: adjusted difference for pain at rest was OR = 1.18 (95% CI, 0.31- 2.05) and adjusted difference for pain with activity was OR = 1.30 (95% CI, 0.32-2.29). Effect sizes for pain severity were 0.54 and 0.57, respectively. The estimates for the above-mentioned primary outcomes were slightly higher when violators of the protocol were



Figuur 3: Course of recovery during 12-month for injection group (n=60) and ususal care group (n=60).

excluded from the analysis. Similar results were found when those who did not receive the injection because their complaints had diminished (n = 5) were also excluded. The secondary outcomes of WOMAC pain and WOMAC function measures showed a greater decrease in pain in the injection group than in the usual care group. The adjusted difference between the groups for WOMAC pain and WOMAC function were OR = 12.40 (95% CI, 4.86-19.93) and OR = 11.36 (95% CI, 4.01-18.70), respectively. Effect sizes for injection therapy were 0.67 and 0.56, respectively. There was no significant difference in quality of life between the 2 groups (Table 2).

Results at 12-month follow-up

At the 12-month follow-up visit, 61% of the patients in the injection group had recovered (defined as totally or strongly recovered) compared with 60% in the usual care group. Binary models for recovery resulted in OR = 1.05 (95% CI, 0.50-2.27). Pain severity at rest and pain severity with activity decreased in both groups. The adjusted difference for pain at rest was OR = 0.14 (95% CI, –0.75 to 1.04), and the adjusted difference for pain with activity was OR = 0.45 (95% CI, –0.55 to 1.46). The differences were not significant, however. All secondary outcomes showed no differences at 12 months of follow-up (Table 2).

Subgroup Analysis

In the subgroup with comorbidity (hip osteoarthritis, low-back pain, or both; n = 73), 58% of the intervention group had recovered vs 32% in the usual care group at the 3-month follow-up, with a number needed to treat of 4 (adjusted OR = 2.87; 95% CI, 1.10-7.55). Differences in pain at rest and with activity at 3 months of follow-up were

Table 2. Primary and secondary outcome measures at 3 and 12 months follow-up.

	Usual Care (n=59)			Injection (n=60)				
	Baseline	3 months	12 months	Baseline	3 months	12 months	Odds ratio (95% CI) at 3 months	Odds ratio (95% CI) at 12 months
Recovered [a] n/N (%)	-	20/59 (34)	33/55 (60)	-	33/60 (55)	34/56 (61)	2.38 (1.14 to 5.00)	1.05 (0.50 to 2.27)
	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)		Adjusted difference at 3 months (95% CI)[b]	Adjusted difference at 12 months (95% CI)
Pain at rest [0-10]	5.3 (2.2)	3.7 (2.5)	2.3 (2.3)	5.1 (2.2)	2.5 (2.5)	2.1 (2.5)	1.18 (0.31 to 2.05)	0.14 (-0.75 to 1.04)
Pain on activity [0-10]	6.6 (2.60)	4.8 (2.8)	3.2 (2.9)	6.7 (1.9)	3.6 (2.8)	2.8 (2.8)	1.30 (0.32 to 2.29)	0.45 (-0.55 to 1.46)
WOMAC pain [0-100]	52.4 (19.1)	37.6 (22.7)	22.9 (22.8)	48.8 (16.1)	23.6 (21.3)	18 (19.6)	12.40 (4.86 to 19.93)	2.67 (-4.98 to 10.32)
WOMAC function [0-100]	49.2 (19.6)	34.2 (21.3)	21.7 (22.7)	43.9 (17.0)	21.3 (19.3)	17.4 (19.6)	11.36 (4.01 to 18.70)	1.01 (-6.37 to 8.39)
EQ-5 D [0-1]	0.72 (0.2)	0.79 (0.17)	0.85 (0.17)	0.74 (0.2)	0.81 (0.2)	0.82 (0.2)	-0.02 (-0.08 to 0.04)	-0.004 (-0.05 to 0.06)

[a] Fully or strongly recovered.

[b] Adjusted for baseline values of the outcome.

Table 3. Reported number of adverse events at 6 weeks.

Adverse event	Intervention group	Usual care group
Hot flushes	11	12
Disturbance in menstruation pattern	3	5
General allergic reaction (e.g. itching all over the body, urticaria, headache, short of breath)	9	12
Superficial pain at site of injection, number		
yes, short period	23	0
yes, long period	3	0
missing	11*	0
Other reported side-effects		
Insensible spot	1	0
Extravasation of blood	1	0
Sore spot	1	0
Small lump at injection place	1	0

*9 of them were violators of the protocol; they did not receive an injection at 3-months follow-up
4 patients of the usual care group received an injection within 3 months; none of them reported any side-effects from the injection

1.36 (95% CI, 0.15-2.57) and 1.42 (95% CI, 0.14-2.70), respectively. Effect sizes were 0.69 (pain at rest) and 0.67 (pain with activity). Comparing the intervention group with the usual care group at the 12-month follow-up, differences in pain at rest and with activity were 0.12 (95% CI, –1.12 to 1.36) and 1.42 (95% CI, 0.14 to 2.70), respectively. For recovery OR = 0.99 (95% CI, 0.38-2.59).

Adverse Effects

At 6 weeks, the frequency of systemic adverse events was similar. In the injection group, no immediate side-effects were reported by the physicians; however, almost 40% of the injection group reported a short period with superficial pain at the site of the injection (Table 3).

DISCUSSION

In this first randomized controlled trial assessing the effectiveness of corticosteroid injections vs usual care for patients with GTPS, a clinically relevant effect was shown at 3 months of follow-up for recovery and for pain at rest and with activity. At 12 months of follow-up the differences in outcome were no longer present. This randomized controlled trial is the first to compare the effect of local corticosteroid injections with usual care in primary care patients with GTPS. Even though we were unable to include the 150 patients that we hoped to randomize,[21] we found a significant and clinically relevant

effect of injection with corticosteroids at 3 months in all primary outcome measurements. Although this effect was even higher at 6 weeks, at the 12-month follow-up no difference in effect was present. Our findings indicate a short-term effect of corticosteroid injections, which disappeared at 6 months. Rompe et al also found a short-term effect of corticosteroid injection at 1 month follow-up; however, this beneficial effect had decreased at 4 months, and by the 15-month follow-up visit the pain had increased again to almost baseline values.[15] In contrast to our study, Rompe et al included patients from secondary care and excluded patients with concurrent hip joint disease. It remains uncertain whether his study population explains the difference between the 2 studies for the long-term course of complaints after corticosteroid injection. Even though our inclusion period took longer than we anticipated, and we enrolled fewer than 150 participants, the funding authority allowed us to reduce the sample size to 120 participants because we had almost no loss to follow-up (especially on the short term). In view of the clear results, it is possible that a somewhat larger study population would not have led to different conclusions. We used a pragmatic open design and measured the effect of the corticosteroid injection as experienced by patients in clinical practice; therefore, it is not possible to distinguish among the effects of the injection itself (needling), or the use of lidocaine, the corticosteroid fluid, or the placebo effect. It is acknowledged that a placebo effect might occur with injection therapy. For example, a recent review reported that a more invasive placebo treatment was more effective than a noninvasive placebo treatment.[22] In the present study, during the first 3 months more patients in the usual care group than in the intervention group received physical therapy (although not specifically recommended) as a cointervention; the same was true for pain medication. The effect of injection therapy may therefore be even stronger than reported here. Observational studies have shown that about two-thirds of patients with GTPS also have low back pain or osteoarthritis of the hip.[6,23] The present study also found comorbidity in 63% of the patients. Because we expected to find lower effectiveness in the subgroup, we prestratified our randomization for comorbidity. In our analysis of patients with comorbidity, however, the effect of injection therapy with corticosteroids was unexpectedly slightly higher and significant. This finding implies that the subgroup of patients with comorbidity profit as much from the injection therapy as did the total intervention group. A systemic effect of corticosteroid injections on musculoskeletal pain has been proposed because (in patients with rotator cuff disease) a corticosteroid injection was found to be equally effective in the upper gluteal region and in the subacromial bursa.[24] Apart from a beneficial effect on GTPS, in our patients with comorbidity, the injections might also have had a beneficial effect on osteoarthritis or low-back pain. Because we aimed to interfere as little as possible with usual primary care practice, radiographs were not used to assess hip osteoarthritis. Instead, a clinical assessment was used to define osteoarthritis according to the ACR clinical criteria for hip osteoarthritis.[25] Because these

criteria were not developed for primary care research, our clinical classifi cation may not fully overlap with the ACR radiographic classification criteria[17]; nevertheless, they are the most suitable clinical criteria currently available.[26] Our assessment of low-back pain was based on the questionnaire alone, and we have no information about the type and severity of that pain. We can conclude, however, that other musculoskeletal symptoms of the hip (eg, morning stiffness or painful or restricted internal rotation) or in the low-back region should not prevent the clinician from applying local injection therapy when GTPS is diagnosed.

Recommendations for General Practice

This study shows the additional value of injection therapy in primary care patients who have clinical signs of GTPS. The application of corticosteroid injections made no difference in the long-term resolution of pain, but the injection gave patients early relief. Although these effects have been assessed in only one trial, physicians now have a more evidence-based rationale for offering corticosteroid injections to patients with symptoms of GTPS for the short-term relief of symptoms.

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Chapter 4

Cost-effectiveness analysis of corticosteroid injections in patients with greater trochanteric pain syndrome

David J Blok, Aaltien Brinks, Rogier M van Rijn, Jan AN Verhaar,
Bart W Koes, Sita MA Bierma-Zeinstra, Marc A Koopmanschap

Submitted

ABSTRACT

Background: Greater trochanteric pain syndrome (GTPS) is a common cause of hip pain. Until now only effectiveness of corticosteroid injections has been evaluated. This is the first cost-effectiveness study.

Objective: Cost-effectiveness analysis of corticosteroid injections in patients with GTPS.

Design: Randomized controlled trial. Patients were randomly allocated to receive either local corticosteroid injections (n=60) or usual care in the form of analgesics as needed (n=60). The randomization was stratified for yes/no co-morbidity of low back pain, osteoarthritis of the hip, or both.

Data sources: Self-reported resource use and quality of life.

Target population: Patients (age 18-80 years) who visited a general practitioner with complaints of the syndrome.

Time horizon: One year follow-up.

Perspective: Societal perspective.

Outcome Measures: Direct medical costs, productivity costs, EQ-5D scores and WOMAC scores.

Results: No significant differences were found in the annual direct medical costs, productivity costs, or total costs. Only at baseline the intervention group had significantly higher direct medical costs than the control group due to the corticosteroid injections. Patients in the intervention group had a higher annual quality of life but it was not statistically significant: intervention group: 0.8124 vs. control group: 0.7903. The average annual WOMAC scores showed significantly better results in the intervention group: 26.8 vs. control group: 33.8. The cost-effectiveness ratio was €28,688. At a threshold Incremental Cost-Effectiveness Ratio (ICER) of €20,000, the probability that it is accepted is 47%.

Limitations: Small sample size.

Conclusions: Corticosteroid injections will not have significant benefits in terms of quality of life and costs in the long run. However, uncertainty analysis has shown out that there is a 47% probability that the intervention is cost-effective compared to usual treatment.

INTRODUCTION

Greater trochanteric pain syndrome (GTPS), a trochanteric bursitis or tendinitis, is a common cause of hip pain. The major symptom is chronic intermittent pain at the lateral side of the hip, described as an aching pain that can vary from sudden and sharp to dull. The duration of the pain is variable, but it is usually long term. Lievense et al. showed that 35% of patients complained of pain after a one-year follow-up and 29% after five years.[1] Pain increases with physical activity. The greater trochanter is painful on palpation and lying on the affected side or prolonged standing aggravates discomfort.[2-4] Tenderness about the greater trochanter is the most common finding. Patients with GTPS suffer some degree of disability and limitation.[5-6]

A cross-sectional study in a population at risk for osteoarthritis (OA) of the knee showed that 17.6% had GTPS. The prevalence of unilateral and bilateral GTPS was 15% and 8.5% (females) and 6.6% and 1.9% (males) respectively.[7] The prevalence of GTPS is up to 4 times higher in women.[4,6-7] A Dutch study has shown that the incidence of GTPS is 1.8 patients per 1000 per year in a primary care setting.[1] GTPS occurs in all age groups, but the incidence is the highest among 40- to 60-year-olds.[2,4,6,8] According to observational studies, about two-thirds of patients with GTPS also have low back pain or OA of the hip.[9-10] Other factors associated with GTPS are ipsilateral iliotibial band syndrome (ITB) and obesity.[1,4,7]

Conservative treatment of patients with GTPS includes the use of nonsteroidal anti-inflammatory drugs, local corticosteroid injections, physical therapy, controlled and limited activities, weight loss, or some combination of these.[4,6,11] For those who do not respond to the conservative treatment, surgical procedures are available.[5,8]

Several observational studies have evaluated the effect of corticosteroid injections. Shbeeb et al.[12] found that 77.1% of the patients reported improvement in terms of pain reduction after 1 week, 68.8% after 6 weeks, and 61.3% after 26 weeks, concluding that corticosteroid injection therapy is highly effective. Similarly, Rasmussen et al.[10] concluded that one or two local steroid injections are effective and long lasting in reducing pain. Several other observational studies have also reported corticosteroid injections to be more effective than other GTPS treatments.[1,9,13] These conclusions, however, are based on short term follow-up (26-week maximum).[4,8] Lievense et al.[1] conducted a retrospective cohort study to determine GTPS post-status at 1 and 5 years, reporting that 66% of the patients receiving corticosteroid injections experienced improvement. In a randomized controlled study evaluating the effectiveness of corticosteroid injections in GTPS patients, Rompe et al.[14] concluded that the injections only have short term benefits. Similar outcomes were shown in a recent randomized controlled study by Brinks et al.[15] They showed clinical relevant and significant better outcome after corticosteroid injection compared to exceptive treatment at three months of follow-up, but not in the

long run. Up till now no earlier studies have evaluated cost-effectiveness. Therefore, we focus on determining the cost-effectiveness of corticosteroid injections compared to usual care in patients with GTPS.

METHODS

We performed a cost utility analysis to compare corticosteroid injections with usual care for GTPS alongside a clinical study.[8] The study was conducted from a societal perspective, meaning that it included all costs relevant to all parties, such as patients, insurers, and health care suppliers. Travel costs were not included.[16] In a pragmatic open-label randomized controlled study patients were randomized using computerized randomization lists to either receive the usual care or the injection therapy. The randomization is stratified as follows: no co-morbidity, low back pain, hip osteoarthritis, or both co-morbidities. The follow up period after randomization was one year.[8]

Role of the funding sources

This study was supported by the funding program for common disorders in general practice by the Netherlands Organization for Health Research and Development (ZonMw). The funding source had no involvement in the collection, analysis and interpretation of data, nor in the decision to submit the paper for publication.

Study population

The sample included 120 patients between the ages of 18 and 80 years. Selected patients had to have visited a GP for pain in the lateral region of the hip or thigh that had persisted for more than one week. Additionally, severe pain or local tenderness had to have been present in the greater trochanteric area upon touch or palpation reproducing the patient's pain. Patients who had consulted a GP for the same complaints earlier or who had had intervention were excluded from the study, as were patients with a history of surgery in the area or systemic neurological or rheumatologic disorders.[8]

Intervention group

Patients in the intervention group were injected with corticosteroids by their general practitioners (GP). The selected GPs were participating in the HONEUR research network, which has 40 GP practices connected to the Department of General Practice of the ErasmusMC. The participating GPs had been trained to give the corticosteroid injection according to a standard method. It comprised 40 mg triamcenolon acetate combined with 1% or 2% lidocaine in a 5-ml. syringe. In the cases of temporary effect or lack of efficacy, the therapy could be repeated once after a period of 3 weeks up to 3 months.[8]

Control group

The intervention was compared with the usual alternative treatment for GTPS, which were oral analgesics as needed. The patients were free to receive other treatment.[8] Patients of both groups were allowed to have physiotherapy but it was not recommended by the researchers.

Data sources

Data on direct medical costs, productivity costs, and quality of life were gathered using questionnaires filled out by the patients at baseline, 6 weeks, 3 months, 6 months, 9 months, and 12 months. The 6-week questionnaire asked only about the quality of life (QoL) and side effects. The ensuing comprehensive questionnaires collected general information plus data on WOMAC (Western Ontario and McMaster University Osteoarthritis Index, a health status instrument for patients with OA in the hip or knee)[17]; PRODISQ (a modular questionnaire to measure productivity cost)[18]; medical consumption (see below); EQ-5D (a descriptive instrument to measure quality of life)[19]; and side effects.[8]

Direct medical costs

We determined the total direct medical costs by multiplying resource use with unit costs. For medical consumption, patients were asked to supply their total amounts of medical utilization in the previous 3 months. The costs were calculated for each follow-up questionnaire. Annual costs were determined by adding up the costs per period disregarding baseline but including the costs of the intervention. The values for medical consumption were based on the resource and guideline costs of the Dutch Health Insurance Board updated to 2004.[20] The resource costs were adjusted to year 2008 using the yearly consumer price index of the Statistics Netherlands (CBS).

Productivity costs

Productivity costs represented losses due to absence from work and reduced efficiency in paid and unpaid work. They were measured with the PRODISQ questionnaire.[18] Patients were asked to report their absence from work and its duration. Costs of absence were calculated by multiplying the number of hours absent with the average productivity cost per hour worked, set at €35 for both males and females.[20]

Efficiency loss was measured using the quality and quantity method. Patients were asked to mark the quality and quantity of their work on the last working day of each period on a visual analog scale from 0 (worst) to 10 (best). Efficiency loss was calculated as (1-(quality/10) x (quantity/10)) x working hours per day.[21] Costs were obtained by multiplying the average productivity cost per hour worked with the efficiency loss. Efficiency losses of unpaid work primarily concerns housekeeping tasks, shopping, and childcare. Patients were asked if and for how long these tasks were taken over by

someone else. Costs were calculated by multiplying the number of hours that tasks were taken over with the current price of simple professional home care.[20]

Quality of life

QoL was determined by the EQ-5D questionnaire. The five dimensions of the EQ-5D (mobility, self-care, usual activities, pain and anxiety/depression) have three levels each (no problem, some problem, and extreme problem).[22] Utility values were based on valuations of each possible health state by the Dutch general public.[19] The annual QoL was calculated as the average of all measurement moments. The study also estimated health status using the WOMAC, an index measuring disability and pain secondary to hip OA. Its three dimensions include pain, stiffness, and function in daily living.[17] For each question standardized response options are given on a 5 point Likert scale from 0 (worse score) to 4 (best score). A normalized score is then calculated for each dimension, where 0 indicates absence of symptoms and 100 indicates extreme symptoms.[17] The annual WOMAC score is an average of the scores of each measurement moment.

Cost-effectiveness analysis

The analysis was based on the intention-to-treat principle. Differences between the intervention and control groups were analyzed using parametric and non-parametric tests. Differences in costs and health effects were measured at the baseline and follow-up. SPSS 17.0 was used for statistical analysis. The level of statistical significance was set at 5%.

An uncertainty analysis was performed using the bootstrapping method. A cost-effectiveness plane was created to show the degree of uncertainty for costs and health effects and the cost-utility ratio. Using the cost-effectiveness (CE) plane, an acceptability curve was created, indicating the probability that an incremental cost-effectiveness ratio (ICER) was acceptable at a certain threshold.

RESULTS

This study included 120 respondents, 60 in the intervention group and 60 in the control group. At baseline 100% of the questionnaires were returned (4% not fully complete), at 3 months 98% (30%), 6 months 96% (17%), 9 months 93% (8%), and 12 months 93% (12%). Sixteen patients violated the protocol. Seven in the control group received corticosteroid injections besides the usual care, four within three months and three after three months. In the intervention group, nine patients did not receive the corticosteroid injections. In addition, three patients in the intervention group and two in the control group received an additional injection after three months. Because our study was based on an intention-to-treat analysis, all violators were taken into account.

The general characteristics at baseline for the intervention group and control group are presented in Table 1. The population's average age was 56 years and about 75% was female. Most patient characteristics were comparable at baseline.

Direct medical costs

The health care utilization due to GTPS for the intervention group and control groups is shown in appendix A. For both groups, a GP, physiotherapist, and medication had the highest utilization. At baseline 100% of the patients in both groups visited a GP, decreasing gradually to about 10% at 12 months. The average number of GP visits per patient shows a downward trend over time in both groups.

In the intervention group, physiotherapist visits peaked at 6 months (20%) and 9 months (12%). The average number of visits per patient also peaked at 6 months (1 visit) and 9 months (2 visits). In the control group, physiotherapist visits showed an increase at 3 months (22%) and a continual decrease from 6 months to 7% at 12 months. The average number of visits per patient also showed a similar downward pattern from more than one visit at baseline to around 0.12 visits at 12 months.

At baseline 20% of both groups used prescription drugs, which gradually declined to about 5% at 12 months. Over-the-counter (OTC) drug use showed a similar pattern from around 38% at baseline to 17% at 12 months. However, the control group's use of both prescription and OTC medication showed an increase at 3 months, which is expected since analgesics are part of the usual treatment. Furthermore, OTC drugs were more frequently used than prescription medication in both groups. Overall, there were no significant differences in health utilization between the groups for any type of medical consumption at any measurement moment.

Table 2 shows a summary of the direct medical costs at 3-month intervals. The costs were calculated using the costs per unit of medical consumption (appendix B). In the intervention group, costs are largely determined by the costs of GP visits, corticosteroid injections, physiotherapy, and surgery; costs of medication and other care were less significant. The costs of corticosteroid injections (€24) were only important at baseline. The costs in the control group were mainly determined by GP visits, physiotherapy, surgery, and medication.

The total costs at baseline were significantly higher for the intervention group than for the control group (€80 vs. €62) (P value = 0.00), primarily because of the corticosteroid injections (P value = 0.00). There were no significant total cost differences found at the other moments, but in terms of specific cost items we found that the costs for physiotherapy and medication were significantly higher in the control group compared to the intervention group at 3 months (P_{phys} = 0.014; P_{med} = 0.005).

Table 1. General characteristics of the patients at baseline in the intervention and the control group.

		Intervention group n=60	Control group n=60	P value
Average age (years)		57,7 (med 58; S.D. 13,9)	54,8 (med 55,5; S.D. 14,7)	0,34
Gender	Female	73%	80%	0,20
	Male	27%	20%	
Body Mass Index		26,9 (med 25,9; S.D. 3,8)	26,3 (med 25,4; S.D. 3,6)	0,45
Paid work		43%	41%	0,68
Average hours per week		31,0 (med 34,0; S.D. 9,6)	28,5 (med 34,0; S.D. 12,5)	0,65
Average net income per hour		€ 12,39 (med 10,82; S.D. 3,94)	€ 11,62 (med 11,44; S.D. 4,05)	0,61
Education	Low	37%	28%	0,10
	Middle	48%	55%	
	High	15%	17%	
Prior episode of trochanter pain syndrome		22%	35%	0,04
Duration of current episode	1-2 months	45%	51%	0,22
	2-6 months	33%	24%	
	> 6 months	22%	26%	
Co-morbidity hip OA or low back pain	None	37%	42%	0,82
	Low back pain	37%	35%	
	Hip OA	17%	13%	
	Hip OA and low back pain	10%	10%	

Med = median; S.D. = standard deviation; OA = osteoarthritis.

Table 2. Mean direct medical costs per patient for the previous 3 months per follow-up moment in the intervention and the control group (median).

	Intervention group					**Control group**				
	Baseline	3 months	6 months	9 months	12 months	Baseline	3 months	6 months	9 months	12 months
General Practitioner	€ 31 (22)	€ 15 (0)	€ 9 (0)	€ 5 (0)	€ 3 (0)	€ 28 (22)	€ 11 (0)	€ 9 (0)	€ 3 (0)	€ 2 (0)
Sport Physician	€ 0 (0)	€ 0 (0)	€ 0 (0)	€ 0 (0)	€ 0 (0)	€ 0 (0)	€ 0 (0)	€ 0 (0)	€ 0 (0)	€ 0 (0)
Physiotherapist	€ 7 (0)	€ 8 (0)	€ 32 (0)	€ 48 (0)	€ 8 (0)	€ 9 (0)	€ 46 (0)	€ 32 (0)	€ 12 (0)	€ 11 (0)
Medical Specialist	€ 1 (0)	€ 2 (0)	€ 3 (0)	€ 4 (0)	€ 8 (0)	€ 0 (0)	€ 0 (0)	€ 2 (0)	€ 9 (0)	€ 2 (0)
Company Physician	€ 0 (0)	€ 0 (0)	€ 0 (0)	€ 0 (0)	€ 1 (0)	€ 7 (0)	€ 0 (0)	€ 0 (0)	€ 0 (0)	€ 0 (0)
Cesar/Mensendieck	€ 0 (0)	€ 2 (0)	€ 8 (0)	€ 10 (0)	€ 0 (0)	€ 0 (0)	€ 0 (0)	€ 14 (0)	€ 2 (0)	€ 0 (0)
MRI-scan/CT-scan	€ 0 (0)	€ 4 (0)	€ 4 (0)	€ 4 (0)	€ 0 (0)	€ 0 (0)	€ 0 (0)	€ 0 (0)	€ 4 (0)	€ 0 (0)
X-Ray	€ 3 (0)	€ 5 (0)	€ 2 (0)	€ 2 (0)	€ 3 (0)	€ 6 (0)	€ 3 (0)	€ 5 (0)	€ 4 (0)	€ 1 (0)
Surgery	€ 0 (0)	€ 29 (0)	€ 0 (0)	€ 34 (0)	€ 30 (0)	€ 0 (0)	€ 35 (0)	€ 0 (0)	€ 32 (0)	€ 0 (0)
Medication	€ 7 (4)	€ 4 (0)	€ 4 (0)	€ 2 (0)	€ 3 (0)	€ 6 (0)	€ 9 (4)	€ 5 (0)	€ 3 (0)	€ 2 (0)
Corticosteriod injection	€ 24 (29)	€ 2 (0)	€ 2 (0)	€ 0 (0)	€ 0 (0)	€ 0 (0)	€ 2 (0)	€ 2 (0)	€ 0 (0)	€ 0 (0)
Other costs	€ 7 (0)	€ 0 (0)	€ 2 (0)	€ 0 (0)	€ 4 (0)	€ 5 (0)	€ 7 (0)	€ 0 (0)	€ 7 (0)	€ 13 (0)
Total	€ 80 (54)	€ 71 (4)	€ 65 (0)	€ 108 (0)	€ 60 (0)	€ 62 (26)	€ 114 (23)	€ 70 (0)	€ 76 (0)	€ 32 (0)
S.D.	€ 61	€ 236	€ 120	€ 348	€ 234	€ 140	€ 290	€ 133	€ 313	€ 112
25 percentile	€ 51	€ 0	€ 0	€ 0	€ 0	€ 22	€ 0	€ 0	€ 0	€ 0
75 percentile	€ 107	€ 66	€ 63	€ 15	€ 14	€ 43	€ 99	€ 89	€ 23	€ 4

Cost of absence from work

Table 3 shows the groups' absenteeism rates. Overall it is low (at most 2 patients). Patients reported absences at baseline, 6, 9, and 12 months in the intervention group, and at baseline and 3 months in the control group. In both groups the number of patients with paid work remained constant over time: about 26 in the intervention group and 25 in the control group. Differences between the groups in terms of absence were not significant. The average number of days absent showed more variation over time in the intervention group. However, the average number of days absent per absentee was not significantly different between the groups.

In the control group we found a declining trend in costs of absenteeism as opposed to the intervention group, whose trend seemed to be random with a peak at 12 months (€292). Costs were not significantly different between groups.

Efficiency loss

Table 3 summarizes the efficiency losses on the last working day before each measurement moment. The efficiency losses were measured using VAS scores (appendix C).

Table 3. Cost of absence from paid work and efficiency loss from paid work in the past 3 months in the intervention and the control group, mean (standard deviation).

	Baseline	3 months	6 months	9 months	12 months
Intervention group					
Number with paid job, n (%)	26 (43%)	25 (42%)	26 (44%)	25 (43%)	26 (47%)
Absent	3,8%	0,0%	7,7%	4,0%	7,7%
Number of days absent	0,23 (1,18)	0,0 (0,0)	0,15 (0,54)	0,8 (4,0)	2,60 (9,70)
Costs due to absence from work per patient	€ 31,50 (€ 244,00)	€ 0,00 (€ 0,00)	€ 18,27 (€ 99,82)	€ 72,41 (€ 551,49)	€ 281,25 (€ 1504,92)
Efficiency loss due to GTPS	35%	24%	15%	8%	8%
Average hours efficiency loss due to GTPS	1,06 (1,64)	0,55 (1,19)	0,46 (1,15)	0,39 (1,35)	0,48 (1,67)
Costs due to efficiency loss per patient	€ 16,14 (€ 41,79)	€ 8,10 (€ 28,48)	€ 7,33 (€ 28,15)	€ 5,60 (€ 30,78)	€ 7,71 (€ 39,51)
Control group					
Number with paid job, n (%)	24 (41%)	25 (43%)	23 (41%)	23 (44%)	25 (45%)
Absent	8,3%	4,0%	0,0%	0,0%	0,0%
Number of days absent	0,83 (2,57)	0,80 (4,00)	0,0 (0,0)	0,0 (0,0)	0,0 (0,0)
Costs due to absence from work per patient	€ 70,47 (€ 384,76)	€ 43,45 (€ 330,89)	€ 0,00 (€ 0,00)	€ 0,00 (€ 0,00)	€ 0,00 (€ 0,00)
Efficiency loss due to GTPS	42%	33%	17%	8%	8%
Average hours efficiency loss due to GTPS	1,19 (1,52)	0,69 (1,26)	0,56 (1,36)	0,14 (0,56)	0,23 (0,74)
Costs due to efficiency loss per patient	€ 16,97 (€ 39,32)	€ 10,35 (€ 30,95)	€ 8,26 (€ 31,55)	€ 2,32 (€ 13,32)	€ 3,87 (€ 18,05)

The average VAS score is above 9 in both groups, which indicates little efficiency loss. The scores showed a significant increase over time only in the intervention group at 3 months (P = 0.024). There are no significant differences in the VAS scores between the two groups.

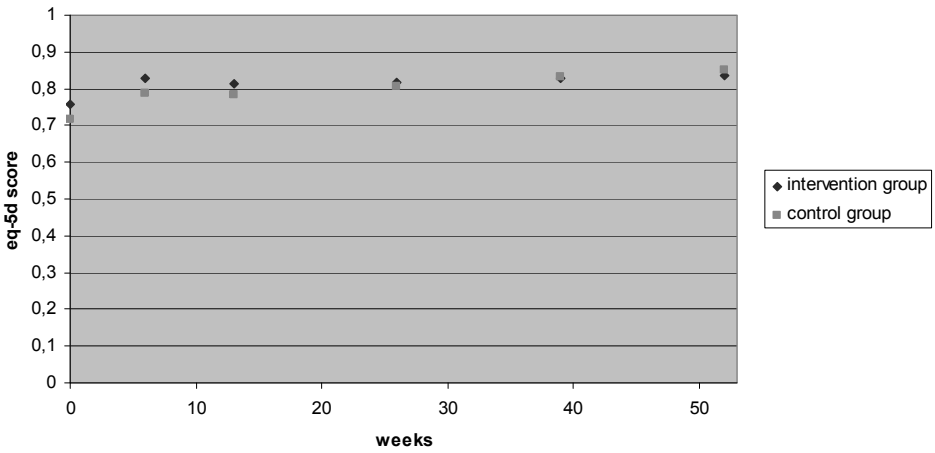
At baseline about 35% and 42% of the patients reported some efficiency losses due to GTPS in the intervention and control groups respectively. The losses decreased in both groups (8% at 12 months) and in terms of average hours showed a similar decreasing pattern with a slight increase at 12 months. The cost of efficiency losses corresponded with the hours lost pattern and was lowest at 9 months (ig: € 6; cg: € 2). The differences in costs between the two groups were not significant.

Hindrance during unpaid work

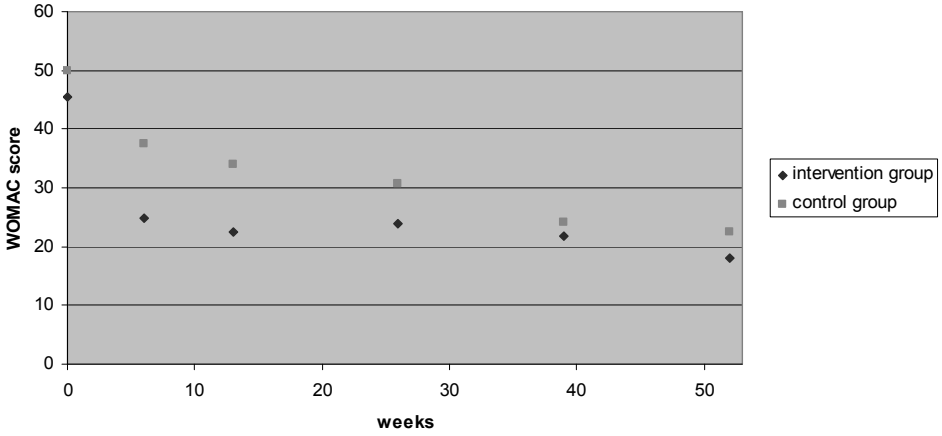
Hindrance during unpaid work because of GTPS is summarized by measurement moment in appendix D. At baseline 30% of the intervention group and 22% of the control group suffered hindrance; i.e., they had to have someone take over their housekeeping tasks. The average costs follow a clear downward trend in the intervention group from €25 per patient at baseline to €7 at 9 months. A 12 months it increased again. The control group shows in overall a declining pattern from €16 per patient at baseline to only €3 per patient at 12 months. Neither the changes over time within the groups nor the costs per patient between the groups were significant.

Quality of life

Figure 1 shows the QoL scores on the EQ-5D for both groups. Only at 6 weeks the scores were significantly higher in the intervention group (P = 0.022). The overall QoL for both



Figuur 1: Quality of life as measured by the EQ-5D.



Figuur 2: The mean WOMAC total scores in the intervention and the control group.

groups averaged about 0.8. Inspection of the EQ-5D dimensions showed that on all measurement moments and for both groups the pain dimensions had the worst scores. At baseline, 6 weeks, and 3 months, the intervention group had significantly less pain than the control group (Chi square test: $P1_{pain} = 0.029$; $P6w_{pain} = 0.023$; $P3_{pain} = 0.039$). At 3 months and 6 months the intervention group showed also significantly less discomfort on the activity and depression dimensions (Chi square: $P3_{activity} = 0.00$; $P6_{depression} = 0.00$ respectively).

Table 4. The mean annual costs and quality of life per patient in the intervention and control group (standard deviation).

	Intervention group	Control group	Incremental
Direct Medical costs	€ 343 (€ 584)	€ 303 (€ 490)	40
Productivity costs	€ 2315 (€ 7161)	€ 1721 (€ 3912)	594
Absence	€ 350 (€ 1962)	€ 43 (€ 331)	307
Efficiency loss paid work	€ 1374 (€ 5058)	€ 1349 (€ 3854)	25
Efficiency loss unpaid work	€ 590 (€ 1379)	€ 328 (€ 741)	262
Total costs	€ 2658 (€ 7368)	€ 2024 (€ 4001)	634
25 percentile	€ 54	€ 50	
50 percentile	€ 247	€ 391	
75 percentile	€ 1610	€ 2420	
Quality of Life	0,8124 (0,1168)	0,7903 (0,1406)	0,0221
CE Ratio			€ 28688
WOMAC	26,8 (16,6)	33,8 (16,5)	-7*
CE Ratio			- € 91

* Significant (p=0.016)

Figure 2 displays the total scores of the WOMAC, showing a downward trend over time for all WOMAC dimensions in both groups. At 3 months the intervention group had significantly better WOMAC scores than the control group (P = 0.002). In terms of specific WOMAC dimensions, the intervention group scored significantly better at 6 weeks and 3 months for pain and function ($P_{pain/function\ 6\ wks}$ = 0.00; $P_{pain/function\ 3\ months}$ = 0.001) and at 6 months for pain ($P_{pain\ 6\ months}$ = 0.036). On every other follow-up moment the results were not significantly different.

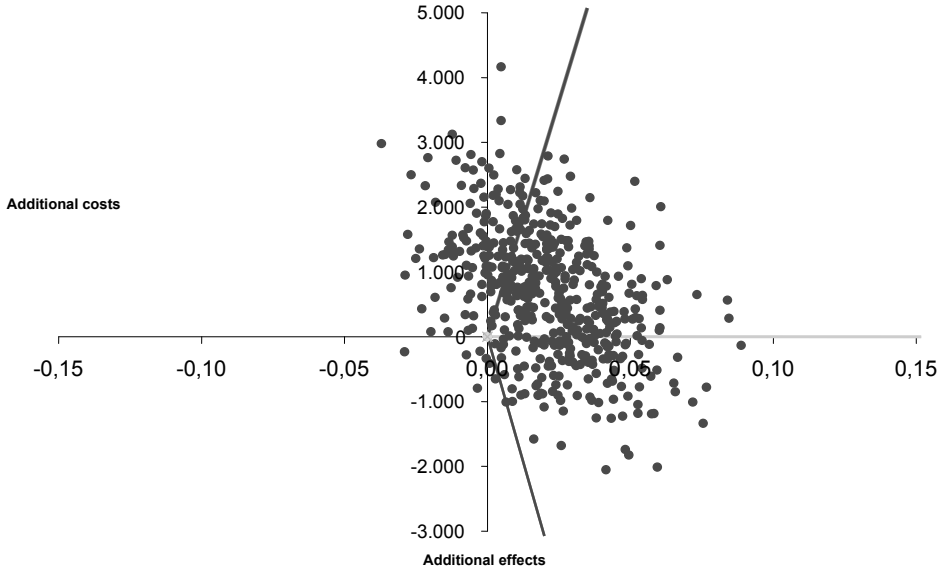
Annual costs

Table 4 presents the annual costs per patient, which are €2,658 for the intervention group and €2,024 for the control group (P total = 0.781). The differences in the annual costs stem primarily from absenteeism and efficiency losses during unpaid work. For all items the intervention group had higher costs. Statistical testing, however, showed no significant differences in the annual costs between the groups (P_{med} = 0.629; P_{prod} = 0.895; $P_{absence}$ = 0.324; P_{el} = 0.403; P_{unpaid} = 0.385) because of the large variation among the respondents. Both productivity costs (ig: €7,161; cg: €3,912) and annual costs (ig: €7,368; cg: €4,001) had high standard deviations.

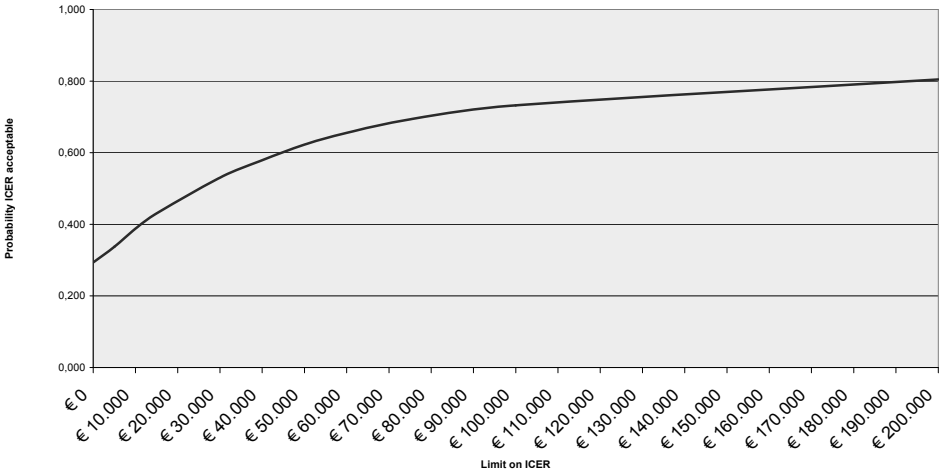
Cost-effectiveness analysis

Table 4 shows the total annual costs and health effects of the two groups. The total annual costs for the intervention group are €634 higher than in the control group. The average QoL per patient in the intervention group is 0.0221 QALY higher than the control group. The differences in annual costs and health effects between the two groups are not significant ($P_{annual\ costs}$ = 0.781; $P_{health\ effects}$ = 0.443). The corresponding cost-effectiveness ratio is €28,688 per QALY. The annual WOMAC score shows that patients in the intervention group had significantly fewer symptoms than patients in the control group (26.8 vs. 33.8; P_{womac} = 0.016). The corresponding cost-effectiveness ratio is - €91 per WOMAC point. The latter result cannot be generalized, however, since there is no comparison with other studies.

The results of bootstrapping with 2.500 draws are presented in Figure 3. The constructed bootstrap confidence interval ranged from -1.501.523 to +1.578.565, which is substantial. The CE plane in Figure 3 shows that in 29% the intervention was dominant, which implies better health effects and lower costs. In 13% the intervention was inferior. In 86% of the cases the intervention had positive health effects and 30% had cost savings. Figure 4 shows the corresponding acceptability curve. At a threshold ICER of €20,000, the probability that it is accepted is 47%. If we take disease severity into account, however, the threshold may be lower. Our results show that disease burden averages about 0.2 QALY. The corresponding threshold ICER, according to the influential Dutch Council for Public Health and Health Care (RvZ) proposal (but not officially ad-



Figuur 3: CE-plane of total costs which examined the degree of uncertainty for costs and health effects and the cost-utility ratio.



Figuur 4: Acceptability curve which shows the probability that an ICER is acceptable.

opted by reimbursement authorities), is about €16,000.[23] The probability that the ICER is acceptable at €16,000 is 44%.

DISCUSSION

The objective of this study was to determine the cost-effectiveness of corticosteroid injections for GTPS. It is the first randomized controlled trial to do so.

The results showed that there were no significant differences between the intervention group and control group regarding annual direct medical costs and productivity costs. Only at baseline and only due to the corticosteroid injections the intervention group have significantly higher direct medical costs than the control group.

Overall, direct medical costs were relatively low. The intervention itself was not expensive. In addition, this study also showed that productivity costs in terms of absence were quite low and efficiency losses were quite moderate. The average VAS score was above 9, but in terms of costs it is still substantial.

The results of the QoL using the EQ-5D indicated a small but not significant benefit for the intervention group at the one-year follow-up. In contrast, the annual WOMAC score did show a significantly better result in favour of the intervention group. We can also conclude that all tools to measure health effects showed that in the short-term the intervention group showed a significantly better result, but in the long-term the differences were no longer significant. These results align with earlier observational studies based on a short-term follow-up that concluded that corticosteroid injections are more effective than any other treatment.[1,5,9-10,12]

The results of the uncertainty analysis showed that in 86% of the cases the intervention had a positive health effect. We also concluded that a threshold of €20,000 yields a 47% probability and €16,000 a 44% probability that the ICER will be accepted. In addition, the probability that the intervention will decrease costs is 30%. When only direct medical costs are taken into account, a threshold of €20,000 yields an 82% probability that the ICER will be accepted. We must keep in mind, however, that differences in annual costs and QoL are not significant.

Subgroup analysis showed that the group with no co-morbidity had significant higher QoL compared to the group with co-morbidity. Also total costs were significantly higher, but direct medical costs were significantly lower. In total, five patients of our research population had surgery, all from the co-morbidity subgroup. Three had hip OA, one low back pain, and one both. As mentioned in the literature study, GTPS is often associated with or discovered secondary to another condition. The surgeries performed on these patients were in large part treatment for co-morbidity. Since we are using the intention-to-treat principle these patients were still taken into account. The influence of leaving them out, however, would have been limited. Direct medical costs would have been €237 and €228 in the intervention and control groups respectively, total costs €2589 and €1810. Neither difference is significant.

A limitation of the study was its small sample size. Although it is sufficient to test the efficacy of the intervention, it seems that for an economic evaluation it should be larger.

Another limitation was perhaps the quality of the data. Health utilization was self-reported, which may have caused the outliers. In the intervention group one patient reported 60 physiotherapist visits within three months. The extraordinarily high number led us to consider that the patient had counted self-exercise at a treatment centre as a visit with a physiotherapist. The questionnaire did not specifically differentiate the two. We applied the costs per unit of a normal visit to a physiotherapist for all 60 visits but the medical costs may well have been lower. Sensitivity analysis, however, showed that the impact was very small. Setting 30 times at half the unit price lowers the total direct medical costs by €7.

Our study showed no significant differences in costs and QoL at a one-year follow-up, indicating no benefit in these measurement units. However, with a CE ratio of €28,688 per QALY, the study showed at a threshold of €20,000 that there is a 47% probability that the intervention is cost-effective compared to usual treatment.

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Appendix A. Healthcare utilization in the last 3 months. Intervention group and control group (median).

		Intervention group					**Control group**				
		baseline *n=60*	3 months *n=59*	6 months *n=59*	9 months *n=58*	12 months *n=56*	baseline *n=60*	3 months *n=58*	6 months *n=56*	9 months *n=53*	12 months *n=55*
General Practitioner	Contact	100%	34%	31%	12%	9%	100%	33%	20%	9%	11%
	Mean	1,43 (1,0)	0,69 (0,0)	0,39 (0,0)	0,22 (0,0)	0,13 (0,0)	1,27 (1,0)	0,52 (0,0)	0,41 (0,0)	0,13 (0,0)	0,11 (0,0)
Sport Physician	Contact	0%	0%	2%	0%	0%	0%	0%	0%	0%	0%
	Mean	0,00 (0,0)	0,00 (0,0)	0,02 (0,0)	0,00 (0,0)	0,00 (0,0)	0,00 (0,0)	0,00 (0,0)	0,00 (0,0)	0,00 (0,0)	0,00 (0,0)
Physiotherapist	Contact	7%	7%	20%	12%	7%	5%	22%	14%	11%	7%
	Mean	0,27 (0,0)	0,34 (0,0)	1,29 (0,0)	1,95 (0,0)	0,32 (0,0)	0,38 (0,0)	1,84 (0,0)	1,3 (0,0)	0,49 (0,0)	0,44 (0,0)
Medical Specialist	Contact	2%	3%	3%	5%	9%	0%	0%	2%	11%	4%
	Mean	0,02 (0,0)	0,03 (0,0)	0,05 (0,0)	0,07 (0,0)	0,13 (0,0)	0,00 (0,0)	0,00 (0,0)	0,04 (0,0)	0,15 (0,0)	0,04 (0,0)
Company Physician	Contact	0%	0%	2%	2%	4%	2%	2%	2%	0%	0%
	Mean	0,00 (0,0)	0,00 (0,0)	0,02 (0,0)	0,02 (0,0)	0,05 (0,0)	0,33 (0,0)	0,02 (0,0)	0,02 (0,0)	0,00 (0,0)	0,00 (0,0)
Cesar/ Mensendieck	Contact	0%	3%	5%	3%	0%	0%	2%	4%	2%	0%
	Mean	0,00 (0,0)	0,07 (0,0)	0,31 (0,0)	0,40 (0,0)	0,00 (0,0)	0,00 (0,0)	0,02 (0,0)	0,57 (0,0)	0,08 (0,0)	0,00 (0,0)
MRI-scan/CT-scan	Contact	0%	2%	2%	2%	0%	0%	0%	0%	2%	0%
	Mean	0,00 (0,0)	0,02 (0,0)	0,02 (0,0)	0,02 (0,0)	0,00 (0,0)	0,00 (0,0)	0,00 (0,0)	0,00 (0,0)	0,02 (0,0)	0,00 (0,0)
X-Ray	Contact	7%	7%	7%	5%	7%	15%	9%	13%	8%	4%
	Mean	0,07 (0,0)	0,14 (0,0)	0,05 (0,0)	0,05 (0,0)	0,09 (0,0)	0,15 (0,0)	0,09 (0,0)	0,13 (0,0)	0,11 (0,0)	0,04 (0,0)
Other	Contact	2%	0%	2%	0%	4%	5%	3%	0%	6%	0%
	Mean	0,05 (0,0)	0,00 (0,0)	0,02 (0,0)	0,00 (0,0)	0,05 (0,0)	0,07 (0,0)	0,07 (0,0)	0,00 (0,0)	0,15 (0,0)	0,00 (0,0)
Surgery	Contact	0%	2%	0%	2%	2%	0%	2%	0%	2%	0%
Medication	Prescription	22%	17%	12%	7%	5%	17%	24%	18%	8%	4%
	OTC	43%	22%	19%	10%	16%	32%	35%	23%	17%	17%

Appendix B. Unit costs of health care utilisation (2008).

General Practitioner (one visit)		€ 21,91
Sport Physician (one visit)		€ 21,91
Physiotherapist		€ 24,67
Medical Specialist		€ 60,73
Company Physician		€ 21,91
Cesar/Mensendieck		€ 24,94
MRI/CT scan		€ 208,33
X-Ray		€ 37,80
Hip surgery		€ 1.705,13
HNP surgery		€ 2.033,80
Other care	Bone scan	€ 127,27
	Massage	€ 25,00
	Medical ultrasonography	€ 39,93
	Meniscus surgery	€ 710,65
	Orthopedic insoles	€ 95,00
	Osteopathy	€ 90,00
	Podiatry	€ 56,00
	"Vitaalveld" therapy	€ 95,00
Medication	Arcoxia	€ 1,07
	Arthrotec 50	€ 0,30
	Brexine	€ 0,27
	Celebrex	€ 0,83
	Chefarine	€ 0,11
	Corticosteroid injection	€ 28,81
	Diazepam	€ 0,06
	Diclofenac 50mg	€ 0,22
	Diclofenac 75mg	€ 0,14
	Glucosamine 1500mg	€ 13,00
	Ibuprofen 600	€ 0,06
	Ibuprofen 400	€ 0,17
	Meloxicam 7.5mg	€ 0,18
	Naproxen 500	€ 0,12
	Omeprazol	€ 0,04
	Paracetamol	€ 0,04
	Perskindol	€ 10,95
	Saridon	€ 0,12
	Symphosam	€ 11,40
	Tramadol HCl 50pch	€ 0,17

Appendix C. Reduced efficiency at paid work for the intervention and the control group as measured by the visual analogue scale, mean (median).

	baseline	3 months	6 months	9 months	12 months
Intervention group					
Quantity	8,96 (10)	9,60 (10)	9,59 (10)	9,58 (10)	9,32 (10)
Quality	9,27 (10)	9,56 (10)	9,63 (10)	9,54 (10)	9,52 (10)
Control group					
Quantity	9,00 (10)	9,24 (10)	9,35 (10)	9,75 (10)	9,69 (10)
Quality	8,83 (10)	9,32 (10)	9,22 (10)	9,88 (10)	9,85 (10)

Appendix D. Hindrance during unpaid work in the previous 3 months as a result of GTPS in the intervention and the control group, mean (standard deviation).

	baseline	3 months	6 months	9 months	12 months
Intervention group	n=60	n=59	n=59	n=58	n=56
No unpaid work	3%	2%	5%	3%	5%
No hindrance	67%	76%	78%	78%	73%
Housekeeping tasks taken over	30%	22%	17%	19%	21%
Average hours taken over per week	7,06 (6,86)	4,15 (2,30)	6,00 (4,58)	2,91 (0,83)	7,09 (10,29)
Costs per week per patient	€ 25,00 (€ 60,01)	€ 11,44 (€ 25,35)	€ 11,44 (€ 34,53)	€ 6,90 (€ 15,02)	€ 17,41 (€ 65,35)
Control group	n=60	n=58	n=55	n=53	n=55
No unpaid work	0%	2%	0%	2%	4%
No hindrance	78%	79%	86%	85%	91%
Housekeeping tasks taken over	22%	19%	15%	13%	6%
Average hours taken over per week	6,58 (6,88)	3,36 (1,69)	5,38 (6,14)	4,00 (2,28)	3,25 (0,96)
Costs per week per patient	€ 16,46 (€ 49,81)	€ 7,97 (€ 18,83)	€ 9,77 (€ 36,54)	€ 5,66 (€ 18,27)	€ 2,95 (€ 11,01)

Chapter 5

Adverse effects of extra-articular corticosteroid injections: a systematic review

Aaltien Brinks, Bart W Koes, Aloysius CW Volkers, Jan AN Verhaar, Sita MA Bierma-Zeinstra

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ABSTRACT

Background: To estimate the occurrence and type of adverse effects after application of an extra-articular (soft tissue) corticosteroid injection.

Methods: A systematic review of the literature was made based on a PubMed and EMbase search covering the period 1956 to January 2010. Case reports were included, as were prospective and retrospective studies that reported adverse events of corticosteroid injection. All clinical trials which used extra-articular corticosteroid injections were examined. We divided the reported adverse events into major (defined as those needing intervention or not disappearing) and minor ones (transient, not requiring intervention).

Results: The search yielded 87 relevant studies: 44 case reports, 37 prospective studies and 6 retrospective studies. The major adverse events included osteomyelitis and protothecosis; one fatal necrotizing fasciitis; cellulitis and ecchymosis; tendon ruptures; atrophy of the plantar fat was described after injecting a neuroma; and local skin effects appeared as atrophy, hypopigmentation or as skin defect. The minor adverse events ranged from skin rash to flushing and disturbed menstrual pattern. Increased pain or steroid flare after injection was reported in 19 studies. After extra-articular injection, the incidence of major adverse events ranged from 0-5.8% and that of minor adverse events from 0-81%. It was not feasible to pool the risk for adverse effects due to heterogeneity of study populations and difference in interventions and variance in reporting.

Conclusion: In this literature review it was difficult to accurately quantify the incidence of adverse effects after extra-articular corticosteroid injection. The reported adverse events were relatively mild, although one fatal reaction was reported.

BACKGROUND

In 1954 the first report on the effects of corticosteroids on healthy tissues appeared.[1] Local extra-articulair injections of glucocorticoid agents are currently used for rheumatic disorders including a wide spectrum of localized lesions of the tendons, enthesis, tendon sheaths, bursae, ligaments and fasciae as well as nerve compression syndromes.[2] Corticosteroid injections are frequently included as treatment option in clinical guidelines in the field of musculoskeletal disorders. Injectable corticosteroids are nowadays registered for local treatment of (rheumatic) arthritis, synovitis, bursitis, epicondylitis, tendonitis, neuromas, ganglion cysts, entrapment syndromes, fasciitis and back pain.[3,4] In 2006 Dutch pharmacists delivered 208,380 prescriptions of injectable triamcinalone, representing €2,867,000 of the €86,250,000 total prescribed medication for the musculoskeletal system (3.3%),[5] it is however not known how many of the injectable corticosteroids are given intra- or extra-articular. In a retrospective cohort study (on the five-year prognosis of trochanteric syndrome) 37% of the 164 cases were injected with corticosteroids.[6] Systematic therapeutic overview showed that 14-38% of patients with a tennis elbow in general practice were treated with corticosteroid injections.[7] In another study in general practice patients with tendosynovitis or nerve entrapment were injected with corticosteroid injection in 11% and 13% respectively.[8] Nevertheless there is only limited evidence to support the superiority of extra-articular glucocorticoid injections based on randomized trials.[9] Recently in RCT is reported efficacy of corticosteroid injections for trigger finger.[10] In addition, safety aspects of corticosteroid injections have so far not been adequately investigated by systematic reviews, except for complications associated with the use of corticosteroids in the treatment of athletic injuries.[11] Balanced decisions about healthcare interventions require evidence on harms as well as benefits.[12] Therefore, the aim of the present study was to estimate the occurrence of and describe the type of adverse effects due to extra-articular corticosteroid injections.

METHODS

Search

The aim was to identify relevant articles describing adverse events of extra-articular corticosteroid injections. With our medical librarian (AV) we performed an extensive literature search in PubMed and EMbase covering the period 1956 until January 2010. The query was based on the definitions of terms related to adverse outcomes as stated in the Cochrane Handbook.[13] The key words and query comprised a combination of MESH terms and free-text words for injection locations (all joints, tendon, bursal, and ligamental location), with MESH terms for glucocorticosteroid products and the way of

administration combined with all MESH terms and words related to adverse events. The search query is added as an additional file (see Additional file 1). In addition, the titles of references in the included articles or identified relevant reviews were checked for possibly relevant references. Health professionals and patients can report suspicions of adverse drug reactions to the Netherlands Pharmacovigilance Centre 'Lareb'. The 'Lareb' collates adverse drug reaction data in the Netherlands; it performs this task on behalf of the Medicines Evaluation Board (MEB).[14] The MEB is responsible for authorizing and monitoring safe and effective medicinal products on the Dutch market, and shares in the responsibility for authorizing medicinal products throughout the European Union. Therefore we also contacted 'Lareb' for relevant data of adverse events reported after extra-articular corticosteroid injection.

Inclusion criteria

Two researchers read a share of the abstracts for inclusion in this review. Only studies that reported original patient material (e.g. case reports, case studies, cohort studies, clinical trials and case control studies) that reported on the occurrence of adverse events after intervention with local non-intra-articular corticosteroid injections were included. Studies concerning epidural injection and intramuscular injections were excluded. Because the adverse events of therapy are not always mentioned in the article abstracts, the full article of all relevant clinical trials were carefully read to find any reported adverse events.[15]

Data extraction and data syntheses

Relevant study characteristics (including authors, year of publication, size of study population, type of intervention) were extracted. In addition, the type and number of adverse events were extracted, as was the follow-up time (prospective studies) and percentage lost to follow-up (as qualitative characteristics). Where possible, the percentage of persons with adverse events was calculated separately for major adverse events (defined by us as having a lasting effect, or needing intervention) and minor adverse events (defined as transient ones not needing intervention). In the clinical trials, the frequency percentage of adverse events was calculated only for the group receiving intervention with corticosteroids. Further, a summary of the frequency of such adverse events was based on prospective studies only. Only in the case of homogenous definitions of adverse effects, interventions and study populations we did consider pooling the risk for adverse-effects. The types of major and minor adverse events were summarized separately. The data received from 'Lareb' were also analyzed separately. These data include the indication for the corticosteroid injections, gender of the patient, and route of administration. We only report here on adverse events of injections that we know for certain were applied extra-articularly. In this review we used the terminology for adverse

drug reactions noted in the Cochrane Handbook.[13] We used the term 'adverse event' for an unfavorable outcome that occurs during or after the use of a drug or other intervention but is not necessarily caused by it. 'Adverse effect' is used for an adverse event for which the causal relation between the intervention and the event is at least a reasonable possibility. 'Adverse drug reaction' was used for an adverse effect specific to a drug. 'Side effect' was defined by any unintended effect, adverse or beneficial, of a drug that occurs at doses normally used for treatment, and 'complications' as an adverse events or effects following surgical and other invasive interventions. In the data-extraction, however, we report the terminology used by the authors.

RESULTS

Output

The search (1956 to January 2010) yielded 1,313 articles. After reading the abstracts, there were 290 possibly relevant articles on adverse effects after extra-articular injection. After studying the full-text articles and references of the included articles and relevant reviews, there were 87 relevant articles, i.e. 44 case reports, 37 prospective studies and 6 retrospective studies reporting on the adverse events of extra-articular local corticosteroid injections.

'Lareb' provided a list of reported adverse events after triamcinolone injections.

Types of adverse events

Case studies

Only two articles mentioned an adverse event after a corticosteroid injection in the bursa round the hip. One of these studies reported a complication after a ten-fold higher dose was accidentally given,[16] and the other reported a case of a necrotizing fasciitis after a corticosteroid injection in the trochanteric bursa - which proved to be a lethal complication.[17] Necrotizing fasciitis after corticosteroid injection for trigger finger was presented as another severe complication.[18] Six studies described hypopigmentation of the skin,[19-24] and two studies described atrophy of the skin.[21,23] Atrophy of the plantar fat pad was reported after injecting an interdigital neuroma, and another group reported perilymphatic atrophy.[25,26] Atrophy of the skin and subcutaneous fat with hyperpigmentation was described in one patient after intralesional injection of a neuroma at the feet.[27] A skin defect was observed after two injections of triamcinolone injected into a hypertrophic scar.[28] Osteomyelitis of the humerus was reported after three injections with hydrocortisone for a tennis elbow.[29] Osteomyelitis of the calcaneus was reported after an injection for plantar fasciitis.[30] Localized abscess containing Staphylococcus aureus was described after injection of corticosteroid for the treatment of chronic tendi-

nitis of the Achilles tendon.[31] Another article mentioned a sterile abscess after injecting a patient with a plantar fasciitis.[32] Protothecosis (a rare infection caused by an achlorophyllic algae) was seen in two patients after intralesional injections with corticosteroids.[33] Atypical Mycobacterium soft tissue infection was reported after corticosteroid injection for de Quervain's disease.[34] An allergic reaction was reported after giving an injection to a patient who had tendonitis.[35] A tendon rupture of the hand was described after an injection into the carpal tunnel, and a tendon rupture after an injection for tennis elbow.[36,37] A delayed flexor superficiales and profundus rupture occurred after a steroid injection for trigger finger.[38] Seven weight lifters presented at the hospital with ruptured patellar tendon, they all had a history of multiple local steroid injections.[39] A rupture of the Achilles tendon associated with corticosteroid injections was reported in three studies.[40-42] Another case report described an avulsion of the calcaneal tendon after steroid injections administered because of an acute flare-up of rheumatoid arthritis.[43] One study described thirteen patients who developed 15 ruptured tendons subsequent to injection of a depository steroid in or around the tendons injected.[44]. One study reported ischemia of the hand after carpal tunnel injection and one study after a corticosteroid injection for de Quervain tenosynovitis.[45,46] Nerve injury after steroid injection for carpal tunnel syndrome is described in 3 studies.[47-49] Soft tissue calcifications were reported as a complication due to adjusted materials in the solvent or due to an accumulation of insoluble steroid.[50-52]

Prospective studies

Of the 37 prospective studies, 11 reported no adverse effects. Hypopigmentation was reported in three studies.[53-55] Atrophy was described in four studies.[54,56-58] Increased or persistent pain after injection or pain at the site of injection was described in 19 studies. Adverse events not mentioned in the case reports were flushes and disturbance in menstrual pattern.[59] Cellulitis, ecchymosis and subcutaneous nodule were three other symptoms not mentioned earlier in the case reports.[55,60] Table 1 presents information on the minor and major adverse events in the prospective studies.

Retrospective studies

In one retrospective study septic bursitis was described after corticosteroid injection in traumatic olecranon bursitis.[61] Tachon's syndrome (subacute back pain and/or thoracic pain following local injections of corticosteroids) was reported in one study.[62] Table 2 presents information on the adverse events in the retrospective studies.

Lareb Institute

The following adverse events were registered by the 'Lareb' institute following extra-articular indications: after corticosteroid injection for bursitis trochanterica flushing

Table 1. Summary of the included prospective studies.

Author, year of publication	Type of study, number of cases	Indication	Corticosteroid injection agent (no. of injected cases, sides)	Methods of reporting adverse events	Complications reported Major/minor Period of time	Follow-up (%)
Rompe 2009[69]	RCT (229)	GTPS	Prednisolon 25 mg/ meaverin 0.5% (75)	In method section: adverse effects were recorded by the physician Results: summarized in a table	Minor: increased or radiating pain: 44%, skin irritation 3%, swelling 9%	92% after 15 months
Gunter 2004[70]	RCT (18)	Iliotibial band friction syndrome	Methylprednisolone acetate 40 mg / lignocaine 1% (9)	In method section: side effects/adverse reactions: are reported in both intervention groups as a separate issue Results: mentioned as a separate issue	No side-effects after 7 and 14 days	100% at 2 weeks
Chao 2009[71]	RCT (97)	Trigger thumb	Triamcenolon 10 mg (42)	In method section: no information Results: mentioned in a sentence	Minor: 2.2% had pain after 1 month	100% after 12 months
Peters 2008[72]	RCT (50)	Trigger finger	Triamcinolone acetonide: 10, 1 or 2 injections (41)	In method section: adverse event as secondary outcome Results: mentioned as a separate issue	Minor: hot flushes 22%, steroid-flare 14.6%	82% after 12 months follow-up
Jianmongkol 2007[73]	RCT (101)	Trigger finger, 2 types of injection therapy were compared (48/53)	Triamcinolone 10 mg/lidocaine (101)	In method section: no information Results: reported in one sentence	No complications	Follow-up 6 weeks (% lost to follow-up not mentioned)
Goldfarb 2007[74]	RCT (154)	Trigger finger or De Quervain's tenosynovitis	Methylprednisolone acetate 40 mg/lidocaine 1%/ bupivacaine 0.5% (154)	In method section: incidence of post injection pain flare was the aim of the study, no other complications are monitored Results: flare reaction mentioned as a separate issue	Minor: in 33% increase in pain score of 2 points or more (VAS scale 0-10).	81% follow-up after 1 and 6 weeks

Table 1. (continued)

Author, year of publication	Type of study, number of cases	Indication	Corticosteroid injection agent (no. of injected cases, sides)	Methods of reporting adverse events	Complications reported Major/minor Period of time	Follow-up (%)
Baumgarten 2007[75]	RCT (59)	Trigger finger in diabetics versus non diabetics	Betamethasone 6 mg / lidocaine 1% (44)	In method section: in follow-up section: complications related to treatment were reported Results: complications reported as a separate issue	No adverse events at 6 weeks, 3 months and 1 year	98% follow-up at 12 month (range 13-41 months)
Kazuki 2006[76]	Pros (100)	Trigger finger	Betamethasone 2.5 mg / lidocaine 1% (129 fingers)	In method section: not mentioned. Results: one sentence: no complications of steroid injections were observed	No complications after 6 months	100% follow-up after 6 months (range 1-42)
Gurcay 2009[77]	RCT (36)	Carpal tunnel syndrome	Betamethasone 6 mg (18)	In method section: not mentioned Results: no complications or side effects to treatment were observed	No side effects	100% follow-up after 3 months
Nalamachu 2006[78]	RCT (40)	Carpal tunnel syndrome	Methylprednisolone 40 mg / lidocaine 1% (20)	In method section: adverse events were classified according to MedDRA and the incidence of treatment emergent events was summarized Results: adverse events were described	Minor: numbness (5%), local pain (5%), tingling in hands at 4 weeks (5%)	85% follow-up after 4 weeks
Dammers 2005[79]	RCT (132)	Carpal tunnel syndrome	Methylprednisolone 20 mg (45), 40 mg (43), 60 mg (44) with lidocaine 10 mg	In method section: not mentioned Results: no side effects were recorded	No side-effects after 1 and 12 months	97% follow-up after 12 months
Hui 2005[60]	RCT (50)	Carpal tunnel syndrome	Methylprednisolon 15 mg (25)	In method section: surgical complications are assessed after one week, no other adverse events mentioned. Results: one patient with cellulitis is reported and four patients with pain at the injection side	Minor: pain at injection side 16% Major: cellulitis 4%	100% at 6 and 20 weeks

Table 1. (continued)

Author, year of publication	Type of study, number of cases	Indication	Corticosteroid injection agent (no. of injected cases, sides)	Methods of reporting adverse events	Complications reported Major/minor Period of time	Follow-up (%)
Wong 2005[80]	RCT (40)	Carpal tunnel syndrome	Methylprednisolone 15 mg single dose (20) or double dose (20)	In method section: any side effects were recorded at 8, 24 and 40 weeks Results: reported as a sentence at the end of the result section	Minor: local pain (30% in 20 mg group and 10% in 20 mg group)	100% follow-up at 8 weeks
Agarwal 2005[81]	Pros (48)	Carpal tunnel syndrome	Methylprednisolone acetate 40 mg / xylocaine 2% (67 hands)	In method section: not mentioned Results: at the end of the result section adverse effects were mentioned	Minor: mild discoloration of the skin over the injection site (6%)	100% follow-up after 3 months, 78% after 12 months
Ly-Pen 2005[82]	RCT (163)	Carpal tunnel syndrome	Paramethasone acetonide 20 mg (82, 69 wrists required second injection)	In method section: not mentioned Results: safety and tolerability was a separate chapter	No relevant side-effects	79.5% follow-up at 12 months
Sevim 2004[83]	RCT (120)	Carpal tunnel syndrome	Betamethasone 6 mg. (60)	In method section: not mentioned Results: complications and side effects are described	Minor: moderate pain lasting less than 24 hours after injection (3.4%), haematoma (1.7%)	90% follow-up at 11 months (range 9 to 14 months)
Armstrong 2004[84]	RCT (81)	Carpal tunnel syndrome	Betamethasone 6 mg / lidocaine 1% (43 with a total of 364 injections)	In method section: side effects and complications are recorded Results: adverse effects described	Minor: severe pain after injection (5%), acute transient sympathetic reaction after injection (2%)	89% follow-up after 18 months
Wong 2001[85]	RCT (62)	Carpal tunnel syndrome	Methylprednisolone 15 mg (30)	In method section: any side effects were recorded by telephone interview Results: summarized in a table	Minor: injection pain (6.7%)	100% after 12 weeks
Kalaci 2009[64]	RCT (100)	Plantar fasciitis	Triamcinolone 20 mg (50)	In method section: not mentioned Results: description of the side effects not found	No side effects or complications All of the patients found the injection painful	100% after 6 months

Table 1. (continued)

Author, year of publication	Type of study, number of cases	Indication	Corticosteroid injection agent (no. of injected cases, sides)	Methods of reporting adverse events	Complications reported Major/minor Period of time	Follow-up (%)
Porter 2005[86]	RCT (132)	Plantar fasciopathy	Betamethason 5.7 mg / lignocaine 1% (64)	In method section: patients were asked to report any possible side effects at 3 and 12 months Results: no infections or rupture are found, description of the side effects	Minor: post-injection pain (12.5%) that required analgesia and/or ice application	95% follow-up at 12 months
Genc 2005[87]	Pros (30)	Plantar fasciitis	Methylprednisolone 20 mg / prolocaine 2% (47 heels)	In method section: ultrasonografy measurement of the facia at 1 and 6 months Results: reported as one sentence	No rupture observed	100% follow-up at 6 months
Lindenhovius 2008[88]	RCT (64)	Lateral elbow pain	Dexamethasone 4 mg/ lidocaine 1% (31)	In method section: not mentioned Results: adverse events are described	Minor: discoloration of skin 3.2%, increased elbow pain 3.2%	77% after 1 and 6 months
Tonks 2007[53]	RCT (48)	Epicondylitis lateralis	Triamcinolone acetonide 10 mg / lignocaine 2% (24)	In method section: complications of treatment were one of the outcome measurements Result section: complications are described	Major: skin depigmentation and atrophy in 4% after 7 weeks	77% follow-up at 7 weeks
Bisset 2006[54]	RCT (198)	Tennis elbow	Triamcinolone 10 mg / lidocaine 1% (65)	In method section: not mentioned Results: side effects were mentioned in a separate section	Minor: pain (18.5%). Major: loss of skin pigment (3%), atrophy of subcutaneous tissue (1.5%)	100% follow-up in injection group at 12 months

Table 1. (continued)

Author, year of publication	Type of study, number of cases	Indication	Corticosteroid injection agent (no. of injected cases, sides)	Methods of reporting adverse events	Complications reported Major/minor Period of time	Follow-up (%)
Wang 2003[89]	Pros (94)	Hand and elbow injections	Betamethasone / lidocaine 1%	In method section: registration of pain levels after injection of corticosteroid to hand and elbow was the aim of the study, no other side effects were recorded Results: post injection pain is shown in table and list	Minor: 50% increased post-injection pain during 1.2 days	71% follow-up at 5 days
Smidt 2002[90]	RCT (185)	Epicondylitis lateralis	Triamcinolone acetonide 10 mg / lidocaine (62)	In method section: details of any adverse effects were reported on standardised forms Results: adverse effects summarized in a table	Minor: facial flush (3%), skin irritation (5%), red swollen elbow (3%), change of skin colour (11%), other not specified side-effects (13%)	96% follow-up at 52 weeks
Jensen 2001[91]	RCT (30)	Tennis elbow	Methylprednisolone 20 mg / lidocaine 1% (16)	In method section: daily pain registration for six weeks Results: described in result section	Minor: pain increase after injection (81%)	100% follow-up 6 weeks
Hay 1999[57]	RCT (164)	Tennis elbow	Methylprednisolone 20 mg / lignocaine (51)	In method section: complications of treatment is one of the secondary outcome Results: described in a separate section side effects	Major: local skin atrophy in the overall group (3 of 111), one with steroids (1.9%)	100% follow-up at 12 months
Stahl 1997[92]	RCT (58)	Medial epicondylitis	Methylprednisolone 40 mg/lidocaine (30)	In method section: interviews and physical examination for possible local complications Results: complications are reported in a separate part	Major: non reported Minor: facial flushing in one female patient	100% follow-up 12 months

Table 1. (continued)

Author, year of publication	Type of study, number of cases	Indication	Corticosteroid injection agent (no. of injected cases, sides)	Methods of reporting adverse events	Complications reported Major/minor Period of time	Follow-up (%)
Verhaar 1995[93]	RCT (106)	Tennis elbow	Triamcinolone 1% (53)	In method section: side effects not specified Results: no infection or skin hypopigmentation	No side effects in the injection group	100% follow up after 12 months
Price 1991[58]	RCT (145)	Tennis elbow	Triamcinolone 10 mg / lignocaine 1% or Hydrocortisone 25 mg / lignocaine 1% compared with lignocaine 1% or with Triamcinolone 20 mg. Second study Triamcinolone 10 mg versus 20 mg	In method section: severe post-injection pain and skin atrophy were noted Results: table with the adverse effects	Minor: post-injection pain (11%–58%). Major: skin atrophy (17%-40%)	Follow-up at 24 weeks (% lost to follow-up not clear)
Jirarattanaphochai 2004[55]	RCT (160)	De Quervain's tenosynovitis	Triamcinolone acetonide 10 mg (100)	In method section: the adverse events reported at 3 weeks, 6 and 12 months are secondary outcome measurements Results: adverse effects are mentioned in a table	Minor: post-injection pain (13%), subcutaneous nodule (2.5%), ecchymosis (1.3%). Major: skin hypopigmentation (1.3%)	100% follow-up, 3% lost between 6 and 12 months
Avci 2002[94]	CT (19)	Pregnant or lactating women with De Quervain's tenosynovitis	Methylprednisolone 10 mg (10)	In method section: not mentioned Result section: not specified	No side effects or local complications of corticosteroid injection were noted	100% follow (range 9-17 months)

Table 1. (continued)

Author, year of publication	Type of study, number of cases	Indication	Corticosteroid injection agent (no. of injected cases, sides)	Methods of reporting adverse events	Complications reported Major/minor Period of time	Follow-up (%)
Anderson 1991[95]	Pros (56)	De Quervain teno-synovitis	Methylprednisolone acetate 40 mg	In method section: adverse reaction were recorded, particularly signs of atrophy Result: adverse reactions are summarized in a table	Minor; pain 18%, pain, swelling, heat 5% ecchymosis 9% temporary radial nerve paresthesia 2% vasovagal reaction 2% Major: subcutaneous fat atrophy 16%	95% follow-up at 4.2 years
Crawford 1999[96]	RCT (106)	Heel pain	Methylprednisolone 25 mg (53)	In methods and results sections: not mentioned	No side-effects reported	52% follow-up after 6 months
Capasso 1997[97]	RCT (116)	Patellar tendopathy	Methylprednisolone 40 mg/lignocaine (39)	In method section: not mentioned Results: acceptability of treatment is separately discussed in a chapter	Minor: burning sensation (10.3%), injection pain (5.1%)	82% follow-up after 12 months
Mens 1998[59]	Pros (77 ♀)	Musculo-skeletal disease	Triamcinolone acetate intra-articular (46) and extra-articular (24)	Method section: patients were asked to report appearance of flushing and any abnormality of the menstrual pattern Results: shown in a table	Disturbance in menstruation at 6 weeks (50.6%), flushes (28.6%)	100% follow-up after 6 weeks

RCT: randomized controlled trial, CT: controlled trial, Pros: prospective clinical study

Table 2. Summary of the included retrospective studies.

Author, Year of publication	Type of study	Indication	Corticosteroid used	Complication (number of cases)
Berthelot 2004[62]	Questionnaire sent to 500 rheumatologist	Different rheumatologic diseases	Cortivazol Hydrocortisone Betamethasone Paramethasone	Tachon's syndrome (n=318) *
Cill 2004[98]	48 cases	Achilles tendinopathy	Triamcinolone 10 mg and 20 mg with bupivacaine 0.25%	No major complications, 1 patient (2%) reported purple skin dicoloration
Bjorkman 2004[99]	27 cases	Rupture of the tendon extensor pollicis longus	2 oral corticosteroids and 2 local corticosteroid injections	Rupture of the tendon extensor pollicis longus n=4 associated with use of corticosteroids
Acevedo 1998[100]	765 cases	Plantar fasciitis	Triamcinolone 40 mg (122)	Plantar fascia rupture (n=44) **
Astrom 1998[101]	298 cases	Achilles tendinopathy	Unknown	Preoperative steroid injection was predictive of a partial rupture***
Weinstein 1984[61]	Follow-up of 47 cases	Traumatic olecranon bursitis	25 patients received Triamcinolone 20 mg after aspiration	Septic bursitis (9%) Skin atrophy (25%) Chronic pain (28%)

* 1 event per 8,000 injections.
** 44 of the 51 plantar fascia ruptures were associated with corticosteroids injection.
***Odds ratio 2.0 (CI 1.3-9.8).

was reported, after injection for tennis elbow, rash, menstrual disorder, and skin depigmentation and in one patient dyspnoea and eyelid ptosis were reported. In one patient hallucination, increased intracranial and intraocular pressure, and paresis occurred after corticosteroid injection for a calcaneal spur. In another patient, after corticosteroid injection for carpal tunnel syndrome hirsutism, nail changes and vaginal hemorrhage were reported. After injection for trigger finger an allergic skin reaction was observed. Reported adverse events after corticosteroid injections for tendonitis were: anaphylactic reaction in one patient, erythema and skin atrophy in another, and rash and tendon disorder in the third patient.

Frequency of adverse events

Due to the heterogeneity of the study populations, the type of interventions, the uncertain causality of the reported reaction with the administered corticosteroid injection and the impossibility to count risk differences in all the studies, we refrained from pooling the risk for adverse-effects. Minor adverse events were: - pain after injection with a frequency ranging from 3.4-81%, - numbness and tingling in hands was reported in one study on CTS patients in 5% of the cases, - mild discoloration of the skin over the site of

injection in three studies in 3.2%, 6% and 11.2%, respectively, - disturbance in menstruation in one study in 50.6% of the patients, and flushes in 3 studies with a frequency of 3.2%, 22% and 28.6%, respectively, - transient sympathetic reaction in one study with a frequency of 2%, - ecchymosis in one study with a frequency of 1.3%.

Major adverse events in the prospective studies were: - skin depigmentation reported in 3 studies with a frequency ranging from 1.3-4%, - atrophy was mentioned in 5 studies with a frequency ranging from 1.5-40%, - cellulitis was reported in one study in 4% of the patients.

DISCUSSION

In this review, reported dermal adverse events of local corticosteroid injections were irritation, change of skin colour, skin and perilymphatic atrophy, soft tissue calcification, skin defect, hypopigmentation, sterile abscess, ecchymosis, and allergic rash. The infectious adverse events were cellulites, localized abscess, septic bursitis, atypical Mycobacterium infection, necrotizing fasciitis, and protothecosis. Local adverse events included local pain, tingling or numbness in hands, local neural damage and tendon rupture. Systemic adverse events included allergic reactions, facial flush and disturbance in menstrual pattern.

Edwards and Aronson defined an adverse drug reaction as "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product".[63] According to the WHO they classify adverse drug reactions into six types: dose-related, non dose-related, dose-related and time-related, time related, withdrawal, and failure of therapy. In the present review we were unable to categorize the adverse drug reaction in this way. We neither were able to judge the causal relation between the reported reactions and the administered drug, so we are about speaking of adverse events rather than adverse drug reactions. In addition, in Table 1 we reported the terminology as described in the individual articles, because it was not always clear which classification system they used. Although the adverse events reported in our review are 'miscellaneous' ones, we think that these types of adverse events (occurring after a regular dose of extra-articular corticosteroid injections) can be divided in systemic adverse events and local adverse events. The systemic adverse events can be divided into allergic reactions (IgE mediated) or other hypersensitivity reactions, disturbance in menstruation, flushes and Tachon's syndrome and systemic infection. The local effects consisted of local pain, degeneration, atrophy and change in skin colour, local infection, impact on collagen metabolism expressed as tendon ruptures, and perilymphatic atrophy. Depending on

the place where the injection is administered, adverse events can manifest, for example, injections for plantar fasciitis are almost painful.[64] Injections in general can cause substantial adverse effects. For example, Nicolau's syndrome (livedoid dermatitis secondary to acute arterial thrombosis after injection in a blood vessel) has been described after an intra-articular corticosteroid injection.[65] Such an adverse event would be extremely rare after injection in a bursa or other superficial structures. The venous counterpart, known as Tachon's syndrome (subacute back pain and/or thoracic pain following local injections of corticosteroids), was reported in a retrospective study.[62] In general it is obvious that adverse events associated with corticosteroid injection can be minimized by ensuring appropriate injecting procedures are followed by a well-trained practitioner. Neural damage after injecting carpal tunnel syndrome (CTS) might be avoided by proper injection technique.[66] In this review we divided the adverse events into minor ones (the harm was temporary) and major ones (the adverse event needed intervention or was not transient). This clinical categorization, although not approved by the WHO or FDA, might help to make a more balanced decision regarding the (possible) harm of an injection with corticosteroids for extra-articular use. In addition, it can be easily explained to patients. The Cochrane Collaboration provides guidance from the Adverse Effects Subgroup of the Non-randomized Studies Methods Group.[13] An appendix provides information on adverse effects, advice and tips about the search strategy and the type of studies to be included. However, we failed to find all the relevant articles with the search strategy advised by the Cochrane Collaboration and had to expand the search strategy. In our review, we did not use an overall quality assessment. We did describe however, the methods of reporting adverse events for each prospective study, the duration of follow-up, and the percentage lost to follow-up. The drawback of our study is that we could not assess the risk of bias. Clinical trials, cohort studies and case studies have their own risk of bias.[13] The limitations of the case reports are that there is uncertainty as to the adverse event was caused by the corticosteroid injection. Similarly, the lack of a control group in the prospective study on reporting specified menstruation disorders afterwards cannot prove the causal relationship.[59] If we assume that the internal validity for assessing adverse events in RCT at least should be based on the percentage available for follow-up (i.e. 80% or more) and systematic registration of adverse events and a comparison against a control group, then using these criteria less than half of the prospective studies in this review were of inferior quality. Some RCTs assess smaller numbers of patients thus decreasing the chance of detecting a rare adverse event. Moreover, a part of the RCTs cover a relatively short study period thus precluding the identification of delayed or prolonged, and generally have highly specific inclusion/exclusion criteria that may imply that the results cannot be generalized to other populations. Therefore, the assessment of safety needs to cover not only RCTs but also explore other sources such as, for example, post-marketing surveillance studies, spontaneous reporting schemes, and

epidemiological studies. Systematic reviews on the safety of therapeutic interventions should preferably combine data from various types of studies.[67] In prospective studies, adverse effects attributed to the specific intervention should preferably be estimated by risk ratios, where the risk for adverse effects in the intervention group is compared with that for those who did not receive the intervention. In the present review, because all subjects included in the prospective studies received the intervention, only the percentage of adverse effects could be estimated. For this reason, in the RCTs we estimated the percentage of adverse effects for the intervention group only and did not compare these data with the control group. However, because the types of adverse event reported in these RCTs were highly intervention-specific we do not expect an overestimation of the adverse effects. In fact, based on the inadequate/lack of systematic registration in the included studies, we suspect there may even be an underestimation of the adverse effects. Therefore we advocate that future RCTs and prospective studies should report on adverse events following the recommendations in the CONSORT guidelines.[68]

CONCLUSION

In this literature review it was difficult to accurately quantify the incidence of adverse effects after extra-articular corticosteroid injection. Although one fatal adverse event after an extra-articular corticosteroid injection was reported, extra-articular corticosteroid injections are regularly administered worldwide. In the present review the incidence of major adverse events (according to our definition) was up to 5.8%, ranging from depigmentation and atrophy of the skin to cellulitis; generally speaking these adverse effects could perhaps be classified as 'relatively mild'. Based on these data the administration of extra-articular corticosteroid injections seems to be a 'relatively safe' intervention.

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ADDITIONAL FILE: SEARCH STRATEGY IN PUBMED AND EMBASE

(joint OR joints OR joint* OR tendon OR tendinitis OR bursitis OR bursa OR ligament OR ligaments OR ligaments* OR intraarticular OR shoulder OR shoulders OR knee OR knees OR foot OR elbow OR elbows OR wrist OR wrists OR hip OR hips OR heel OR heels)
(injections[mesh] OR injection*[tw]) AND (glucocorticoids[mesh] OR glucocorticoid*[tw] OR corticosteroid*[tw]) AND (adverse effects[sh] OR adverse[tw] OR side effect*[tw] OR safety[tw] OR tolera*[tw] OR poison*[tw] OR toxic*[tw] OR chemically induced[sh] OR chemically induced[tw] OR contraindicat*[tw] OR contra-indicat*[tw] OR complicat*[tw])
(extra-articul*[tw] OR extraarticul*[tw]) AND (injections[mesh] OR injection*[tw]) AND (glucocorticoids[mesh] OR glucocorticoid*[tw] OR corticosteroid*[tw]) AND (adverse effects[sh] OR adverse[tw] OR side effect*[tw] OR safety[tw] OR tolera*[tw] OR poison*[tw] OR toxic*[tw] OR chemically induced[sh] OR chemically induced[tw] OR contraindicat*[tw] OR contra-indicat*[tw] OR complicat*[tw])

PubMed
(tendons[mesh] OR tendo*[tw] OR teno[tw] OR tendinopathy[mesh] OR tendin*[tw] OR enthesiti*[tw] OR bursa*[tw] OR bursitis[mesh] OR bursit*[tw] OR periarthrit*[tw] OR ligaments[mesh] OR ligament*[tw] OR knee[mesh] OR knee*[tw] OR foot[tw] OR feet[tw] OR foot diseases[mesh] OR fasciiti*[tw] OR heel*[tw] OR epicondyl*[tw] OR elbow*[tw] OR wrist*[tw] OR hip[tw] OR hips[tw] OR extra-articul*[tw] OR extraarticul*[tw]) AND (injections[mesh] OR injection*[tw]) AND (adrenal cortex hormones[mesh:noexp] OR glucocorticoids[mesh] OR hydroxycorticosteroids[mesh] OR glucocorticoid*[tw] OR hydroxyglucocorticosteroid*[tw] OR corticosteroid*[tw]) AND (adverse effects[sh] OR adverse[tw] OR side effect*[tw] OR safety[tw] OR tolera*[tw] OR poison*[tw] OR toxic*[tw] OR chemically induced[sh] OR chemically induced[tw] OR contraindicat*[tw] OR contra-indicat*[tw] OR complicat*[tw])

EMbase
(tendon/syn OR tendo*:ti,ab,de OR teno:ti,ab,de OR periarthritis/exp OR tendinitis/syn OR tendin*:ti,ab,de OR enthesiti*:ti,ab,de OR bursa*:ti,ab,de OR bursit*:ti,ab,de OR periarthrit*:ti,ab,de OR ligament/syn OR ligament*:ti,ab,de OR knee*:ti,ab,de OR foot:ti,ab,de OR feet:ti,ab,de OR fasciiti*:ti,ab,de OR heel*:ti,ab,de OR epicondyl*:ti,ab,de OR elbow*:ti,ab,de OR wrist*:ti,ab,de OR hip:ti,ab,de OR hips:ti,ab,de OR (extra NEAR/1 articul*):ti,ab,de OR extraarticul*:ti,ab,de) AND (injection/syn OR injection*:ti,ab,de) AND (glucocorticoid/syn OR glucocorticoid*:ti,ab,de OR corticosteroid*:ti,ab,de) AND ('adverse drug reaction'/syn OR 'adverse effect':lnk OR adverse:ti,ab,de OR 'side effect':ti,ab,de OR 'side effects':ti,ab,de OR safety:ti,ab,de OR tolera*:ti,ab,de OR poison*:ti,ab,de OR toxic*:ti,ab,de OR 'chemically induced':ti,ab,de OR contraindicat*:ti,ab,de OR (contra NEAR/1 indicat*):ti,ab,de OR complicat*:ti,ab,de)

Chapter 6

Interventions for greater trochanteric pain syndrome: what is the evidence?

Aaltien Brinks, Rogier M van Rijn, Bart W Koes, Jan AN Verhaar, Sita MA Bierma-Zeinstra

Submitted

ABSTRACT

Objective: This systematic review summarizes evidence for the benefits and safety of interventions used for patients with lateral hip pain due to trochanteric tendinopathy or bursitis, also known as greater trochanteric pain syndrome (GTPS).

Methods: An electronic database search was conducted up to October 2010. Studies were selected when they were a randomized clinical trial (RCT), a quasi-RCT or a controlled clinical trial, and investigated adult patients with pain at the lateral side of the hip due to GTPS. Interventions for GTPS were assessed and compared to each other, to placebo, or to no treatment. Main outcomes are pain, recovery and adverse events. Quality of the studies was assessed with the risk of bias tool recommended by the Cochrane Collaboration. Because data were clinically heterogeneous, a qualitative review was performed. The level of evidence was classified as strong, moderate, limited, or no evidence.

Results: Four studies were included with a total of 489 patients. Only corticosteroid injection therapy, home training, and shockwave therapy were evaluated in a comparative study design. Although corticosteroid injection was one of the interventions in all four RCTs, none of the comparison combinations were used twice; therefore, no strong or moderate evidence was reached. Thus, there is limited evidence for short-term effectiveness of corticosteroid injections vs. usual care, vs. shockwave therapy, and vs. home exercise. On the long-term, however, there is limited evidence for superiority of home training vs. corticosteroid injection, and of shockwave therapy vs. corticosteroid injection. For other interventions no evidence was found. No serious adverse events were reported.

INTRODUCTION

In adults, a common musculoskeletal pain syndrome in the hip is lateral hip pain, also known as greater trochanteric pain syndrome (GTPS). The symptoms are characterized by chronic, intermittent pain at the lateral side of the leg, sometimes radiating to the lateral aspect of the hip or lateral thigh and increasing during physical activity. Lying on the affected side increases the pain and can disturb sleep. At physical examination palpation of the greater trochanter is painful.[1-4] Earlier, the same clinical manifestations were known as trochanteric bursitis, although clinical manifestations of inflammation almost never occur.[5] Tendinitis of the insertion of the maximus gluteus medius muscle has been suggested as another cause of pain at this site.[6] It might also be caused by a combination of bursitis and tendinitis. Because the exact etiology is mainly unknown, in 1991 Collee et al. suggested that all the clinical manifestations should be classified as 'greater trochanteric pain syndrome' (GTPS).[7] Observational studies showed that in most patients with local pain at this site, musculoskeletal co-morbidity also exists. About 65% of the patients with GTPS also have low back pain or osteoarthritis of the hip.[7,8]

The prevalence is higher among females than among males (rate 4:1) and incidence is highest between age 40 to 60 years.[3,8] A retrospective study in primary care reported an incidence of 1.8 per 1000 adults in one year.[8] The management of GTPS varies; many physicians inject corticosteroids combined with an anesthetic agent at the most painful site with the expectation that the pain will decrease. Although there is no conclusive evidence that these injections are effective, small observational studies suggest that injections with corticosteroids are effective in the short-term follow-up.[2,8-10] Other common treatment options are prescription of analgesics, physiotherapy, or surgical interventions such as surgical release of the iliotibial tract, removal of the bursa, or a trochanteric reduction osteotomy.[11,12] Hypotheses for corticosteroid injections and surgery are: corticosteroid injections decrease the local inflammation of the bursa or the tendon; release of the iliotibial tract lowers pressure at the trochanter; and removal of the bursa prevents future inflammation. Although numerous physical therapy interventions are available, their intention and exact mechanism of action are mostly unclear.

In addition, an overview of the efficacy of available treatments for GTPS is lacking. Therefore, this systematic review summarizes evidence for the benefits and safety of interventions used in patients with lateral hip pain due to GTPS. The various interventions are compared to each other, to placebo, or to no treatment. The main outcomes of pain, function and recovery are used to assess the benefits of the interventions, and reports on adverse events are used to assess safety.

METHODS

Literature search

Relevant literature was identified by searching in the electronic databases of Medline, EMbase and Web of Science up to October 2010. Table 1 presents the search strategy. Two authors (AB, RMvR) independently selected the studies, initially based on title and abstract. From the title, keywords and abstract, they assessed whether the study met the inclusion criteria regarding design, participants and intervention. For potentially relevant articles, the full text was retrieved for final assessment. For published protocols eligible for this review, we established whether outcome data were already published. Both review authors then independently made the final selection of the trials using a standardized form. Disagreement was resolved by consensus. Only randomized controlled trials (RCTs) and controlled clinical trials that use quasi-randomized methods to allocate participants to treatment (e.g., alternation; date of birth; or similar) were included. Participants had to be adults (18 years and over) suffering from pain at the lateral side of the hip due to GTPS, trochanteric bursitis or tendonitis. Participants with lateral hip pain as defined by the trial authors, or described as meeting the common diagnostic criteria for GTPS (diffuse pain in the buttock and lateral thigh with marked point tenderness of the greater trochanter), were eligible for inclusion. Studies on patients with acute trauma, neoplasm, or inflammatory or neurological diseases were excluded. However, studies investigating patients with co-morbidities (e.g. osteoarthritis or low back pain) were included.

Table 1. Search strategy used for the presented study.

Studies	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR clinical trial[pt] OR clinical trial*[tw] OR ((singl*[tw] OR doubl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR latin square[tw] OR placebo*[tw] OR random*[tw] OR research design*[tw] OR comparative study[pt] OR evaluation studies[pt] OR follow-up*[tw] OR followup*[tw] OR cross-over[tw] OR crossover[tw] OR control[tw] OR controls[tw] OR controlled[tw] OR controled[tw] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animals[mesh] NOT humans[mesh])
Location and clinical diagnosis	(hip[tw] OR hips[tw] OR thigh[tw] OR thighs[tw] OR buttock*[tw] OR femur head*[tw] OR gluteus[tw] OR gluteal[tw] OR trochant*[tw]) AND (bursitis[mesh] OR bursiti*[tw] OR periarthriti*[tw] OR tendinopathy[mesh] OR tendino*[tw] OR tenosynovit*[tw] OR tendon entrap*[tw] OR tendonit*[tw])
Treatment	(therapeutics[mesh] OR therapy[sh] OR therapy[tw] OR therapies[tw] OR therapeut*[tw] OR physiother*[tw] OR rehabil*[tw] OR mobili*[tw] OR surger*[tw] OR surgic*[tw] OR treated[tw] OR treatment*[tw] OR management*[tw])

Assessment of risk of bias

Risk of bias of the included studies was independently assessed by two reviewers (AB, RMvR), using the tool recommended by the Cochrane Collaboration.[13] AB was not involved in the assessment regarding the trial of which she was first author. Disagreement

was resolved by consensus. Studies with five or more points on the risk of bias assessment were regarded as studies with low risk of bias.[14]

Data extraction

One reviewer (AB) extracted the data on the interventions, type of outcome measures, duration of follow-up and outcomes, using a standardized data extraction form.

The following outcomes were included:

Primary outcomes

Pain (e.g. visual analogue scale (VAS), numerical rating scales (NRS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain); function (e.g. WOMAC function/disability for participants with osteoarthritis, Health Assessment Questionnaire, Physical Performance Test, other scales). The examples given in parentheses are not presented as a proposed hierarchy.

Secondary outcomes

Quality of life (e.g. SF36, EQ5-D, Sickness Impact Profile); overall recovery (e.g. measured on a self-reported Likert scale, or other scales); activities of daily living; number of participants experiencing any serious adverse events; number of participants who withdrew due to adverse events.

Type of interventions

All interventions for trochanteric hip pain in adults were included. Interventions are likely to include conservative strategies such as local or systemic analgesics, and injection with corticosteroids combined with a local anesthetic agent, or surgical techniques including surgical release of the iliotibial tract, removal of the bursa, or a trochanteric reduction osteotomy. Interventions by allied health professionals may include exercises, relaxation, bio-psychosocial rehabilitation program, physical applications such as ultrasound, biofeedback, myo-feedback, radial shockwave therapy, and work place adjustments.[15,16] Combinations of treatments are also eligible for inclusion. Comparisons include placebo, usual conservative care, no treatment, or surgical interventions.[9,12,16-18]

Data analysis

Data are analyzed and presented per type of intervention. For discrete data, results are expressed (if possible) as number and percentages of favorable change at follow-up. For continuous outcomes, the mean and SD of outcome scores are extracted at follow-up. The results of each RCT were plotted as point estimates: i.e., odds ratios (ORs) with corresponding 95% confidence intervals (95% CI) for discrete outcomes, and mean differences with corresponding 95% CI for continuous outcomes. In our opinion, because the

studies were clinically heterogeneous with respect to the type of comparisons, pooling was not possible. Therefore, we decided not to pool the data statistically, but to perform a qualitative review (best-evidence synthesis) by attributing various levels of evidence to the effectiveness of the interventions described, taking into account the methodological quality and the outcome of the original studies. The best-evidence synthesis described by van Tulder et al.[19] and classification of the level of evidence is conducted as follows:

Level 1: Strong evidence: provided by generally consistent findings in multiple, relevant, high-quality RCTs. *Level 2*: Moderate evidence: provided by generally consistent findings in one relevant, high-quality RCT and one or more relevant low-quality RCT. *Level 3*: Limited evidence: provided by generally consistent findings in one or more relevant low-quality RCT. *Level 4*: No or conflicting evidence: if there are no RCTs or if the results are conflicting.

RESULTS

Literature search

The database search yielded 313 potentially relevant studies. From titles and abstracts, 12 potentially relevant articles and one protocol were identified; data from the protocol were included because these data are from the present authors.[22] Finally, after reviewing the full text, 4 articles met the inclusion criteria (Figure 1).

Assessment of risk of bias

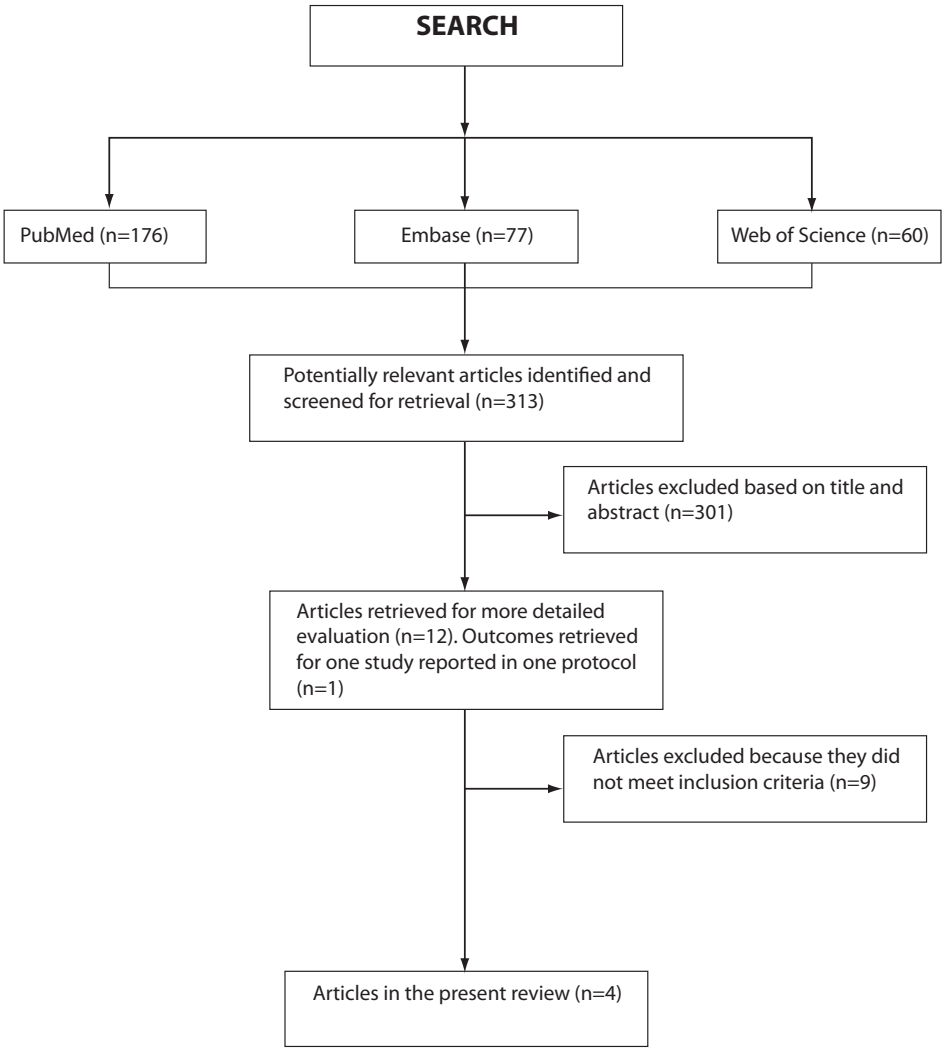
Table 2 presents the overall assessment of the risk of bias of each study. The initial agreement of the reviewers on the total assessment of risk of bias was 82.8% (36 of 44 items). All disagreements were solved in a consensus meeting. One of the 4 included studies appeared to have a high risk of bias and 3 were considered to have a low risk of bias.

Description of the included studies

Table 3 presents the characteristics of the studies and Table 4 gives the results of the studies per outcome measure classified by duration of follow-up.

Shbeeb et al. compared the use of three different doses of corticosteroid injections in patients referred to their clinic to receive an injection for GTPS complaints.[10] The patients received 6, 12 or 24 mg of betamethasone with 1% lidocaine. They concluded that patients receiving the highest dose were more likely to report improvement 6 months after injection.[10]

The study of Rompe et al. compared three different treatments for patients with persisting lateral hip pain in a secondary care setting.[16] One group received a home



Figuur 1: Flowchart showing inclusion of the relevant studies.

training program consisting of piriformis stretch, iliotibial band stretch, straight leg raise, and wall squat with ball and gluteal strengthening. One group was injected with prednisolone 25 mg mixed with a local anesthetic agent. The third group received 3 sessions of shockwave treatment in 3 weekly sessions. Subjects who reported themselves completely recovered or much improved were classified as 'success'. One month from baseline, results after corticosteroid injection (success rate 75%; pain rating 2.2 points) were significantly better than those after home training (success rate 7%; pain rating 5.9 points) or shockwave therapy (success rate 13%; pain rating 5.6 points). Regarding treatment success at 4 months, radial shockwave therapy led to significantly better re-

Table 2. Results of the risk of bias assessment of the included studies, with scores per item.

Authors	Shbeeb[10]	Rompe[16]	Cohen[20]	Brinks[22]
Adequate randomization	?	-	+	+
Allocation concealed	?	?	+	+
Patient blinded	?	-	+	-
Care provider blinded	?	-	-	-
Outcome assessor blinded	?	-	+	-
Dropout rate described	-	+	+	+
Intention to treat analysis	?	+	+	+
Groups similar at baseline	?	+	+	+
Co-interventions avoided or similar	?	-	?	-
Compliance acceptable	?	+	+	+
Timing of outcome assessment similar	+	+	+	+
Total score	1	5	9	7

A score of ≥5 is regarded as a low risk of bias. [14]

Table 3. Characteristics of the four studies in the present review.

First author	Study population	Treatment	Follow-up duration	Results
Shbeeb[10]	74 patients in rheumatology clinic with trochanteric bursitis (62 ♀, mean age 66.2 years)	A. 6 mg betamethasone injection with 4 cm^3 1% lidocaine (n=20) B. 12 mg betamethasone injection with 4 cm^3 1% lidocaine (n=32) C. 24 mg betamethasone injection with 4 cm^3 1% lidocaine (n=22)	1, 6 and 26 weeks	Self-reported improvement VAS score 0-100
Rompe[16]	228 patients with refractory GTPS in orthopedic clinic (162 ♀, mean age 47.7 years)	A. home training group (n=76) B. 25 mg prednisolone with meaverin 0.5% injection in 5 ml (n=75) C. shockwave therapy group (n=78)	1, 4 and 15 months	Degree of recovery and severity of pain over the past week on Likert scale 0-6 Severity of pain on 0-10 NRS
Cohen[20]	65 patients with GTPS in one academic and two military treatment facilities (56 ♀, mean age 50.8 years)	A. fluoroscopically-guided injection with 60 mg depo-methylprednisolone with 0.5% bupivacaine in 2.5 ml (n=33) B. blind injection with 60 mg depo-methylprednisolone with 0.5% bupivacaine in 2.5 ml (n=32)	1 and 3 months	Severity of pain at rest and on activity on 0-10 NRS
Brinks [22]	120 patients with GTPS in general practice (92 ♀, mean age 56 years)	A. 40 mg triamcinolone with 1% or 2% lidocaine (n=60) B. expectant care with analgesics as needed (n=60)	3 and 12 months	Severity of pain at rest and on activity on 0-10 NRS Self-reported recovery on Likert scale 0-7

NRS= numeric rating scale

sults (success rate 68%, pain rating 3.1 points) compared to home training (success rate 41%, pain rating 5.2 points) and corticosteroid injection (success rate 51%, pain rating 4.5 points). Fifteen months from baseline, radial shockwave therapy (success rate 74%, pain rating 2.4 points) and home training (success rate 80%, pain rating 2.7 points) were significantly more successful compared to corticosteroid injection (success rate 48%, pain rating 5.3 points). Rompe et al. suggested that the role of corticosteroid injection needs to be reconsidered because of the decline of superiority after one month. Adverse effects were reported in 111 patients, and all reported effects were mild. In the home training group 27 patients reported increased or radiating pain. In the corticosteroid injection group 33 patients suffered from increased or radiating pain after injection, 7 reported swelling and 2 patients reported skin irritation. In the shockwave group 26 patients reported skin irritation, 13 reported increased pain, and 2 patients reported local swelling.[16]

Cohen et al. included 65 patients with GTPS from 3 different institutions and investigated whether fluoroscopically-guided injection was superior to a 'blind' trochanteric bursa injection. Patients with successful outcome at 1-month follow-up (defined as ≥50% reduction on an NRS pain score) were evaluated at 3-months follow-up.[20] The authors found that over 50% of all injected patients (37 of 65 patients) did not have significant pain relief after 1 month. They concluded that fluoroscopically-guided trochanteric bursa injections were not associated with superior outcomes compared to injections guided by landmarks alone in patients who presented with clinical GTPS. The authors found no difference in pain score between the two groups at 1 and 3 months.[20]

Brinks et al. conducted a pragmatic study in which corticosteroid injection therapy was compared with usual care (= analgesics as needed); each group consisted of 60 patients. [21] At 3-months follow-up, in the usual care group 34% of the patients were recovered compared to 55% in the injection group (adjusted OR 2.38; 95% CI 1.14-5.0, NNT=5). Pain severity at rest and during activity decreased in both groups, but the decrease was greater in the injection group with an adjusted difference in pain at rest of 1.18 (95% CI 0.31-2.05) and in pain on activity of 1.30 (95% CI 0.32-2.29). At 12-months follow-up, in the usual care group 60% of the patients had recovered compared to 61% in the injection group (OR 1.05; 95% CI 0.50-2.27). Pain severity at rest and on activity decreased in both groups; at 12-months follow-up there were no significant differences: adjusted differences of 0.14 (95% CI -0.75 to 1.04) for pain at rest and 0.45 (95% CI -0.55 to 1.46) for pain on activity. At 6 weeks the frequency of systemic side-effects was similar in both groups. However, almost 40% of the injection group reported a short period with superficial pain at the site of the injection.[22]

Table 4 presents results extracted from the reported data. Based on best-evidence synthesis, no strong or moderate evidence could be reached. There is limited evidence for short-term effectiveness of corticosteroid injections vs. usual care, vs. shockwave

Table 4. Results of the four studies per outcome measure, classified by duration of follow-up.

First author	Treatments	Mean pain (SD)		Mean difference (95% CI)	
		Short term (<26 weeks)	Long term (>26 weeks)	Short term (<26 weeks)	Long term (>26 weeks)
Rompe[16]	A. home training group B. corticosteroid injection group C. shockwave therapy group	1 month A 5.9 (2.8) B 2.2 (2) C 5.6 (3.7) 4 months A 5.2 (2.9) B 4.5 (3) C 3.2 (2.4)	15 months A 2.7 (2.8) B 5.3 (3.4) C 2.4 (3)	1 month A vs B 3.7 (2.92, 4.48) A vs C 0.3 (-0.73, 1.33) B vs C -3.4 (-4.34, -2.46) 4 months A vs B 0.7 (-0.24, 1.64) A vs C 2.0 (1.16, 2.84) B vs C 1.3 (0.44, 2.16)	15 months A vs B -2.6 (-3.59, -1.61) A vs C 0.3 (-0.62, 1.22) B vs C 2.9 (1.88, 3.92)
Cohen[20]	A. blind injection with 60 mg depo-methylprednisolone with 0.5% bupivacaine in 2.5 ml (n=32) B. fluoroscopically-guided injection with 60 mg depo-methylprednisolone with 0.5% bupivacaine in 2.5 ml (n=33)	1 month at rest A 2.2 (2.6) B 2.7 (2.5) 1 month (on activity) A 2.6 (2.5) B 1.9 (1.7) 3 months (at rest) A 2.6 (2.5) B 1.9 (1.7) 3 months (on activity) A 4.8 (2.6) B 4.7 (2.8)		1 month at rest A vs B -0.5 (-0.75, 0.75) 1 month on activity A vs B -1.0 (-2.35, 0.35) 3 months at rest A vs B 0.7 (-0.35, 1.75) 3 months on activity A vs B 0.1 (-1.22, 1.42)	
Brinks [22]	A. expectant care with analgesics as needed (n=60) B. 40 mg triamcinolone with 1% or 2% lidocaine (n=60)	3 months at rest A 3.7 (2.5) B 2.5 (2.5) 3 months on activity A 2.5 (2.5) B 3.6 (2.8)	12 months at rest A 2.3 (2.3) B 2.1 (2.5) 12 months on activity A 3.2 (2.9) B 2.8 (2.8)	3 months at rest A vs B 1.2 (0.30, 2.10) 3 months on activity A vs B 1.2 (0.19, 2.21)	12 months at rest A vs B 0.20 (-0.66, 1.66) 12 months on activity A vs B 0.40 (-0.64, 1.44)

Table 4. (continued)

First author	Treatments	Recoverers (%)*		OR (95% CI)	
Rompe[16]	A. home training group	1 month	15 months	1 month	15 months
	B. corticosteroid injection group	A 5/76	A 61/76	A vs B 0.02 (0.01, 0.07)	A vs B 4.41 (2.14, 9.09)
	C. shockwave therapy group	B 56/75	B 36/75	A vs C 0.48 (0.16, 1.47)	A vs C 1.40 (0.66, 2.99)
		C 10/78	C 58/78	B vs C 20.04 (8.62, 46.59)	B vs C 2.9 (0.16, 0.63)
		4 months		4 months	
		A 31/76		A vs B 0.67 (0.35, 1.28)	
		B 38/75		A vs C 0.32 (0.17, 0.63)	
		C 53/78		B vs C 0.48 (0.25, 0.93)	
Brinks [22]	A. expectant care with analgesics as needed (n=60)	3 months	12 months	3 months	12 months
		A 20/59 (34)	A 33/55 (60)	B vs A 2.38 (1.14, 5.00)	B vs A 1.05 (0.50, 2.27)
	B. 40 mg triamcinolone with 1 or 2% lidocaine (n=60)	B 33/60 (55)	B 34/56 (61)		

Shbeeb et al.[10] not entered in the table: the entire group results are reported as one overall figure.

*Rompe et al.: success in % (=completely recovered or much improved).

*Brinks et al.: recovery % (=fully or strongly recovered).

therapy, and vs. home exercise. On the long-term, however, there is limited evidence for superiority of home training vs. corticosteroid injections, and for shockwave therapy vs. corticosteroid injection. For the other interventions no evidence was found.

DISCUSSION

Only corticosteroid injection therapy, home training, and shockwave therapy were evaluated in a comparative study design. Two studies showed a positive effect of corticosteroid injection therapy at short-term follow-up, and one study found home therapy and shockwave therapy to be superior to corticosteroid injection therapy at 15-months follow-up.

Only 4 relevant studies meeting our selection criteria were identified with the search strategy. This is a very small number considering the widespread use of corticosteroid injections and other treatment options for GTPS. In addition, although corticosteroid injections were assessed as one of the treatments in all 4 studies, the studies were very heterogeneous with respect to their comparisons and none investigated in corticosteroid injections vs. placebo. This leaves only limited evidence for the short-term effectiveness of corticosteroid injections vs. home training or against expectant treatment, and with limited evidence for the long-term effectiveness of home training or shockwave therapy vs. corticosteroid injection. No intervention studies on surgical treatment were found.

Most studies had some shortcomings. For example, Shbeeb et al. compared different doses of corticosteroids but the quality of the study was low.[10] In addition, the lack of published outcome data made it impossible to verify a dose-response relation in the present review.

The study of Cohen et al. showed the highest methodological quality.[20] Their study examined whether fluoroscopic guidance improves the outcome of corticosteroid injections for GTPS. The authors concluded that fluoroscopically-guided trochanteric bursa injection is not associated with superior outcome compared to injections guided by landmarks alone in patients presenting with clinical GTPS. This result is not surprising when considering that the origin of GTPS complaints is frequently reported to be outside the bursa.[23]

The study of Rompe et al. was classified as high quality; however, the randomization procedure was not adequate and it was unclear whether the allocation assignment was concealed.[16]

Several trials reported both short and long-term results. Rompe et al. found a remarkable improvement after corticosteroid injection at 1 month follow–up (74.7%) which, however, declined to 48% after 15 months. They found that both home therapy and

shockwave therapy were superior to corticosteroid injections at 15-months follow-up.[16] This reverse effect on the long term in patients receiving corticosteroid injections is also reported in other disorders. In a study on tennis elbow, corticosteroid injection was initially superior to both 'wait and see' and physiotherapy; however, this effect was lost after six 6 weeks with a concomitantly high recurrence rate in the corticosteroid group, which did not occur with 'wait and see' or physiotherapy.[24]

Rompe et al. suggested that the role of corticosteroid injection needs to be reconsidered because of the decline of superiority after 1 month.[16] However, Brinks et al. reported a clinically relevant effect of corticosteroid injection at 3-months follow-up compared to usual care. The latter study is the only one conducted in primary care; the authors found a superior effect of corticosteroid injection at 3-months follow-up compared to usual care, but that positive effect had disappeared at 12-months follow-up.[22]

CONCLUSION

Physicians can offer patients suffering from GTPS a corticosteroid injection for short-term pain relief, but they need to inform the patient that benefit on the long term is uncertain or even absent. They should discuss the low risk of adverse events, but mention the possibility of a flare reaction. To improve treatment in patients with GTPS more study is needed on the effect of initial corticosteroid injection, combined or followed by exercise therapy. The injection may provide short-term pain relief whereas exercise therapy may provide long-term pain relief and functional improvement.

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Chapter 7

Prevalence and influence of greater trochanteric pain in hip osteoarthritis

Aaltien Brinks, Rianne B Rozendaal, Bart W Koes, Jan AN Verhaar, Sita MA Bierma-Zeinstra

Submitted

ABSTRACT

Background: Patients with osteoarthritis (OA) often have periods of increased pain (flares). However, little is known about the association between the co-existence of a tendinitis of the gluteus medius or gluteus minimus muscle, the greater trochanter pain syndrome (GTPS), and these fluctuations in pain.

Objective: To evaluate the frequency of GTPS in hip OA patients, the association of GTPS with symptom severity in hip OA, and the association of changes in the presence of GTPS with fluctuation in symptom severity.

Methods: Data from a trial were used in which primary care hip OA patients were randomly assigned to receive either glucosamine sulfate or placebo over the 2-year study period. Symptom severity (0-100) was assessed with WOMAC scores for pain, function and stiffness, and with a visual analogue scale (VAS) for pain in the previous week. GTPS was defined as tenderness at the greater trochanter in combination with pain recognition, and painful resisted hip abduction. A linear regression model was used to analyze the adjusted influence of GTPS on symptom severity. At 2-year follow-up, the prognostic value of GTPS on symptom severity was assessed; also evaluated was whether individual changes in severity scores were associated with changes in the presence of GTPS between baseline and follow-up.

Results: Of the 214 hip OA patients, 36 (17%) showed GTPS at baseline. Using adjusted regression models, patients with GTPS at baseline had significantly higher mean WOMAC pain and stiffness scores (8.1 and 6.9 points, respectively), and higher scores for VAS pain severity (12.8 points). At 2-year follow-up, GTPS at baseline did not predict symptom severity but was significantly associated with higher symptom scores (13.1, 10.6 and 18.0 points for WOMAC pain, function, and stiffness, respectively; and 12.1 points for VAS pain severity). Individual changes in the presence of GTPS were associated with individual changes in symptom severity (WOMAC scores of 13.1, 9.4 and 11 points, respectively; and 15.6 points on the VAS).

Conclusion: In this primary care population, almost 1 in 5 hip OA patients had co-existent GTPS which was associated with higher symptom scores.

INTRODUCTION

Symptomatic osteoarthritis (OA) in hip and knee, with joint pain as the most prominent symptom, are the most disabling types of OA and affect 5-10% of the elderly population.[1] Despite over a decade of research, disease-modifying drugs remain relatively unsuccessful.[2] Therefore, only symptomatic treatment for OA is currently available, with only minor to moderate effectiveness.[3] Lack of effective conservative treatment may eventually result in costly joint replacement (for those who can sustain such surgery); however, survival of the replacement is usually only about 15 years.

Better understanding of the pain in OA, which differs between and within patients, might lead to improved symptomatic treatment. First, not all patients with structural changes due to OA develop pain. In those with symptomatic OA, many show a pattern with periods of increased pain (flares) and periods with much less (or absence of) pain, resulting in a highly unstable trajectory, with abrupt changes or short-term fluctuations.[4,5] Although this fluctuating pattern in OA patients is well recognized in clinical practice, little is known about the reasons for these fluctuations.[6,7] A systematic review showed a moderate level of evidence (based on cross-sectional studies) that the presence or severity of knee OA pain is associated with the presence of joint effusion/synovitis, or bone marrow lesions (BML).[8] Recently, a prospective study that repeatedly measured symptomatic severity in knee OA patients, showed that changes of BML and synovitis are associated with fluctuation of knee pain. Pain resolution occurred more frequently when BML became smaller.[9] Other suggested causes of pain in OA are ligament and tendon pathology. In a cross-sectional study, Hill et al. showed that periarticular lesions confirmed on MRI (including bursitis and iliotibial band syndrome) was observed three times more often in those with radiological knee OA reporting knee pain, than in those reporting no knee pain.[10]

For hip OA even less is known about the fluctuation in pain severity, and the association of the presence of pain with specific pathology of intra- and extra-articular structures in hip OA. In the hip region a tendinitis of the insertion of the gluteus medius or minimus muscle, or a trochanteric bursitis (or a combination of both), is known as the greater trochanteric pain syndrome (GTPS).[11] It is established that about two thirds of the patients with this syndrome also have low-back pain or OA of the hip.[12,13] In older adults at high risk of developing symptomatic knee OA, or who already had knee OA, GTPS was present in 17.6% of the cases.[14]

However, it remains unknown what percentage of patients with hip OA have this syndrome, and whether the co-existence of GTPS is associated with more severe pain in hip OA. Therefore, the present study investigates these two topics in primary care patients with symptomatic hip OA.

METHODS

Study design

For this study, we used data from a trial in which eligible patients were randomly assigned to receive either 1500 mg of oral glucosamine sulfate (administered once daily as two 750-mg tablets) or placebo over a study period of 2 years. In this trial, all outcome assessors, patients, data analysts, and researchers were blinded to group assignment.

The Medical Ethics Committee of the Erasmus MC approved the study design, and all patients provided written informed consent.

Details on the study protocol and trial outcomes have been published earlier [4,15,16]; briefly: the results showed that glucosamine sulfate was no better than placebo in reducing symptoms and progression of hip OA.

Setting and participants

General practitioners in the Rotterdam area recruited patients for this study. Patients were eligible for inclusion if they met the American College of Rheumatology clinical criteria for hip OA during a screening examination at the research center.[17] Patients who had undergone or were awaiting hip replacement surgery were not eligible. Excluded from the study were patients who had a Kellgren and Lawrence (K&L) score of 4 of the hip[18], renal disease, liver disease, diabetes mellitus, or a disabling co-morbid condition that would make visits to the research center impossible, as well as patients already receiving glucosamine sulfate and those unable to fill out questionnaires in the Dutch language. Patients who violated the study protocol were encouraged to complete the data collection in order to limit the loss to follow-up.

Outcomes and follow-up

In a baseline questionnaire we assessed patient characteristics, disease characteristics, and co-morbidity. At baseline and at 2-year follow up, weight-bearing anteroposterior digital radiography of the pelvis was performed according to a highly standardized protocol to assess radiographic severity of hip OA. Radiographic severity was scored according to the K&L grading scale (0-4).[18] In addition, radiography of the hands and knees was performed to record the presence of radiographic OA according to the K&L grade ≥ 2.

Symptom severity was assessed with the WOMAC 3.1 questionnaire (using a 5-point Likert scale) on pain, function and stiffness. In addition, a visual analogue scale (VAS) was used to measure pain severity in the previous week (score 0-100, where 0=no pain).[19,20] The WOMAC subscales are presented as standardized scores (0-100, where 0=no symptoms). Data for these outcome measures were collected at baseline and every 3 months thereafter during the 2-year study period.

At baseline and at 2-year follow-up, patients visited Erasmus MC for a physical ex-

amination which included range of motion of the hip and painful involvement of extra-articular tissues at the hip. The greater trochanteric region was assessed for tenderness at the top of the greater trochanter, as well as just above, behind and beneath the same trochanter. In case of tenderness, patients were asked if they recognized the pain as one of their complaints.[21] In addition, in all patients we assessed whether resisted hip abduction in the extended position was painful.

Statistical analysis

Data from the assessments at baseline and at 2-year follow-up were used. Analyses were performed using SPSS version 17.0.2 (SPSS, Chicago, USA).

GTPS was defined as the presence of tenderness at the site of the greater trochanter (on the top, or just above, behind or beneath) in combination with the recognition of this tenderness as one of the complaints, and with a painful resisted hip abduction at the same site. As an alternative, a less stringent definition was utilized according to the definition above, but independent of a painful resisted abduction. Co-existence of GTPS was defined as GTPS of the left or right side, or of both sides. Differences in the distribution of patient characteristics in those with or without co-existent GTPS were assessed with chi-square tests for dichotomous variables, and with t-tests for continuous variables. The independent difference in distribution was assessed with multivariable logistic regression with those variables included with $p < 0.2$.

Linear regression models with backward selection (in: p-value <0.1, out: p-value <0.05) were used to analyze the cross-sectional influence of the co-existence of GTPS on symptom severity in hip OA patients at baseline and at 2-year follow-up. Also evaluated was the prognostic value of the presence of GTPS on pain severity at 2-year follow-up. Analysis of the WOMAC and VAS pain severity was adjusted for body mass index (BMI), sex, age, presence of low-back pain, having a K&L grade ≥ 2 in one of the hips, having a K&L grade ≥ 2 in one of the knees, and having hip symptoms that persisted ≥ 3 years. In the longitudinal analyses we also adjusted for baseline severity.

Also analysed was whether individual changes in severity scores were associated with changes in the presence of GTPS between baseline and 2-year follow-up. No change in the presence of GTPS was defined when GTPS was present or absent at both baseline and follow-up, and change in the presence of GTPS was defined as a change in GTPS status between these two time points. Per individual, the difference in symptom severity was calculated between the presence and absence of GTPS. For those who had no change in the presence or absence of GTPS, scores were randomly deducted (for time point) from each other. To assess the association between these fluctuations backward regression models were used, adjusted for baseline parameters that might be related to a change in symptoms over time, e.g. BMI, severity of radiological hip OA, presence of radiological knee OA, and presence of low-back pain.

For some patients, because not all physical examination variables were available for the diagnosis of GTPS, we performed a complete case analysis. In addition, some patients either lacked the 2-year symptom severity scores or underwent total hip arthroplasty during follow-up. All these patients were excluded from the longitudinal analyses.

In all analyses a p-value ≤ 0.05 was considered statistically significant.

Role of the funding source

The Erasmus MC-*Breedtestrategie* funded the study, but had no role in the study design; collection, analysis, or interpretation of the data; or in writing the paper.

RESULTS

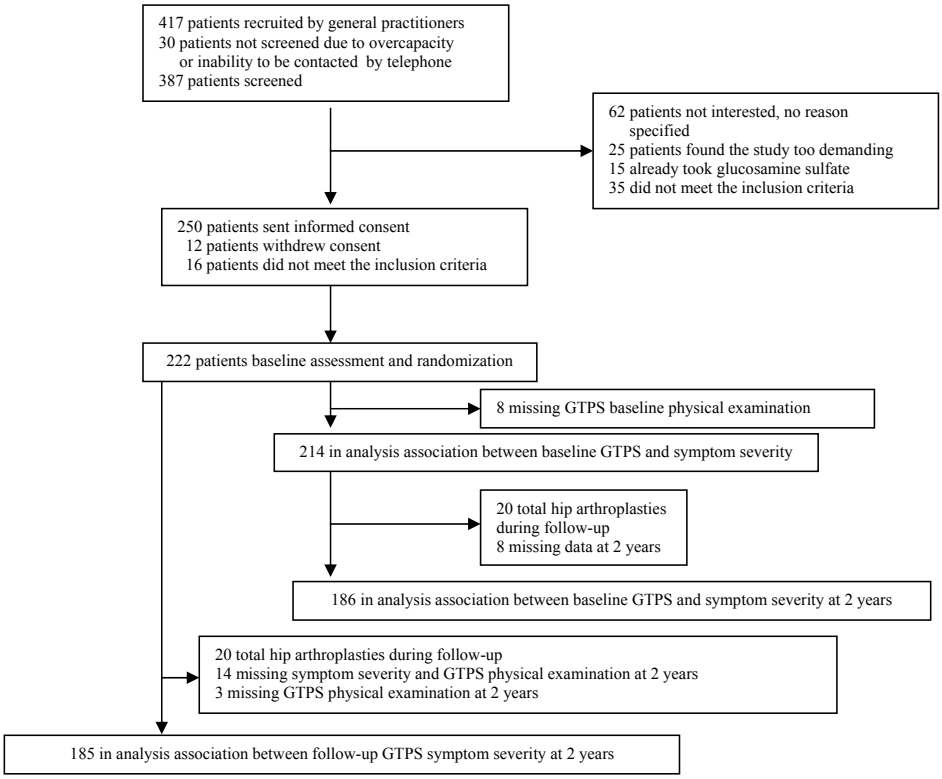
Of the 387 patients screened for this study, 222 received a baseline assessment with physical examination and were randomized. However, for 8 patients the baseline GTPS assessment was missing and for another 3 patients the follow-up GTPS assessment was missing. At 2-year follow-up: 20 patients had undergone total hip arthroplasy, the symptom severity score was missing for 14 patients, and in an additional 3 patients the GTPS assessment was missing (Figure 1).

For this study population, mean change in symptom severity between baseline and 2-year follow-up was -0.1 (SD 23.6), 0.7 (SD 19.4) and -2.7 (SD 25.1) for WOMAC pain, function and stiffness, respectively, and was 4.4 (SD 28.1) for VAS pain severity.

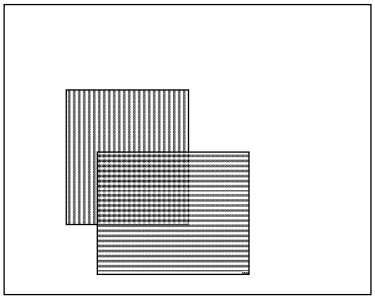
Of the 214 hip OA patients, 53% had K&L score 1, 34% had K&L score 2, and 13% had K&L score 3. Their mean age was 63.3 (SD 8.9) years, 48% of them reported bilateral hip pain, 70% was female, and 53% had symptom duration ≤ 3 years. In total, 36 patients (17%) had GTPS at the right or left side. Table 1 presents the characteristics for patients with and without GTPS separately. Females more often had GTPS than men; irrespective of concurrent low-back pain and/or BMI, compared with men the women had an OR of 5.3 (95% CI 1.5-18.3) for the co-existence of GTPS.

Despite a similar percentage of GTPS in hip OA patients at baseline and at 2-year follow-up (i.e. 16-17%), only 6% of these patients had GTPS at both baseline and follow-up (Figure 2).

Hip OA patients with co-existent GTPS at baseline had higher baseline symptom scores than those without. Using adjusted regression models, hip OA patients with co-existent GTPS at baseline had a significantly higher mean WOMAC score (8.1 points) and VAS pain severity (12.8 points) and more stiffness (6.9 points) compared with those without GTPS (Table 2). Other features associated with higher pain at baseline were female gender, concurrent low-back pain, and symptom duration ≥ 3 years.



Figuur 1: Flowchart of inclusion of the study participants.



Figuur 2: Distribution of the greater trochanteric pain syndrome (GTPS) at baseline (vertical lines), and at 2 years follow-up (horizontal lines). Excluded were persons with total hip arthroplasty during follow-up, or missing the examination at baseline or at 2 year follow-up.
Total n=178, n=28 with baseline GTPS, n=31 with GTPS at follow-up, giving an overlap of n=11

Presence of GTPS at baseline did not predict symptom severity at 2-year follow-up (Table 3). However, adjusted regression models showed that the presence of GTPS at follow-up was associated with all symptom scores, indicating a higher mean score of

Table 1. Patient characteristics and baseline severity of symptoms in hip OA patients (fulfilling ACR criteria) with and without greater trochanteric pain syndrome (GTPS).

	Hip OA with GTPS (n = 36)	Hip OA without GTPS (n=178)	p-value
Patient characteristics			
Female, n (%)	32 (89)	117 (66)	0.006
Age in years, mean (SD)	62.9 (8.9)	63.5 (8.9)	0.7
BMI, mean (SD)	29 (5.1)	27.7 (4.5)	0.15
Duration > 3 years, n (%)	20 (56)	93 (52)	0.7
Radiographic severity hip OA			0.67
-Kellgren Lawrence 1, n (%)	20 (56)	92 (52)	
-Kellgren Lawrence 2-3, n (%)	16 (44)	86 (48)	
Bilateral hip pain, n (%)	16 (44)	87 (49)	0.63
Low-back pain, n (%)	27 (75)	113 (64)	0.19
Radiographic knee OA, n (%)	8 (22)	58 (33)	0.22
Radiographic hand OA, n (%)	18 (50)	93 (52)	0.81
Baseline symptom severity			
WOMAC pain, mean (SD)	43.8 (23.3)	32.2 (22.6)	0.006
WOMAC function, mean (SD)	43 (22.3)	32.9 (22.6)	0.016
WOMAC stiffness, mean (SD)	45.7 (29)	40.7 (24.6)	0.008
VAS pain, mean (SD)	52.8 (25.7)	30 (24.7)	0.001

Testing the difference in distribution of patients characteristics in a multivariable model (female gender, BMI, radiographic severity hip OA, low back pain), only female gender was unequally distributed (OR 5.3, CI 95%:1.5 to 18.3, p=0.009).

Table 2. Cross-sectional association (beta) of the co-existence of greater trochanteric pain syndrome (GTPS) in patients with hip osteoarthritis (OA), with symptomatic severity at baseline (n= 214).

	WOMAC pain	WOMAC function	WOMAC stiffness	VAS pain
GTPS	8.1 (0.3 to 16.1)	-	6.9 (-1.3 to 15.1)	12.8 (3.9 to 21.7)
Gender	5.3 (2.7 to 15.5)	6.3 (0.4 to 12.4)	8.7 (2.0 to 15.4)	-
BMI	-	1.2 (0.7 to 1.9)	0.8 (0.2 to 1.5)	0.7 (-0.2 to 1.4)
Low-back pain	13.5 (7.4 to 19.6)	11.8 (5.9 to 17.5)	18.7 (12.3 to 25.1)	10.7 (3.6 to 17.7)
Duration of symptoms > 3 years	6.2 (0.5 to 12)	11.1 (5.6 to 16.5)	6.1 (0.1 to 12.1)	6.8 (0.2 to 13.5)

Backward regression model with age, gender, BMI, low-back pain, bilateral hip pain, severity of radiographic hip OA, presence of radiographic knee OA, symptom duration ≥ 3 years, and presence of GTPS as independent variables.

13.1, 10.6 and 18.0 points for WOMAC pain, function and stiffness, respectively, and of 12.1 points for VAS pain severity (Table 4).

Also, fluctuation in the presence of GTPS was associated with individual change in symptom severity with 13.1, 9.4 and 11 points for the WOMAC, respectively, and 15.6 points for VAS pain severity (Table 5).

Table 3. Prognostic association (beta) of baseline co-existence of greater trochanteric pain syndrome (GTPS) with symptomatic severity at 2 year follow-up (n = 186). Persons with total hip arthroplasty during follow-up are excluded.

	WOMAC pain	WOMAC function	WOMAC stiffness	VAS pain
GTPS	-	-	-	-
Age	0.3 (0.01 to 0.7)	0.4 (0.1 to 0.7)	0.4 (0.07 to 0.2)	-
BMI	0.9 (0.2 to 1.5)	-	0.8 (0.1 to 1.5)	0.8 (0.1 to 1.6)
Low-back pain	7.4 (0.8 to 14.1)	-	-	8.8 (1.4 to 16.3)
More severe radiographic hip OA	5.9 (-0.2 to 11.9)	6.6 (1.2 to 12)	-	11.3 (4.3 to 18.3)
Duration of symptoms > 3 years	-	-	-	8.1 (1.2 to 15.1)
Baseline severity	0.4 (0.3 to 0.6)	0.7 (0.6 to 0.8)	0.4 (0.3 to 0.6)	0.3 (0.2 to 0.5)

Backward regression model with baseline age, gender, BMI, low-back pain, bilateral hip pain, severity radiographic hip OA, presence of radiographic knee OA, symptom duration ≥ 3 years, and GTPS as independent variables.

Table 4. Cross-sectional association (beta) of co-existence of greater trochanteric pain syndrome (GTPS) in patients with hip osteoarthritis (OA) with symptomatic severity at 2 year follow-up (n=185).

	WOMAC pain	WOMAC function	WOMAC stiffness	VAS pain
GTPS at follow-up	13.1 (5.4 to 20.9)	10.6 (3.4 to 17.6)	18.0 (10.0 to 26.1)	12.1 (3.0 to 21.2)
Age	0.3 (0.03 to 0.7)	0.4 (0.08 to 0.6)	0.4 (0.01 to 0.7)	-
Low-back pain	7.4 (1.1 to 13.7)	5.4 (-0.2 to 11.0)	-	8.3 (1.1 to 15.4)
More severe radiographic hip OA	6.1 (0.4 to 11.8)	7.2 (2.0 to 12.3)	-	11.0 (4.3 to 17.7)
BMI	0.7 (0.1 to 1.3)	-	0.6 (0.01 to 1.3)	0.7 (-0.2 to 1.4)
Duration > 3 years	-	-	-	6.1 (-0.6 to 12.9)
Baseline severity	0.4 (0.3 to 0.5)	0.6 (0.5 to 0.7)	0.4 (0.3 to 0.6)	0.3 (0.2 to 0.5)

Backward regression model with baseline age, gender, BMI, low-back pain, bilateral hip pain, severity radiographic hip OA, presence of radiographic knee OA, symptom duration ≥ 3 years, baseline severity score, and GTPS at follow-up as independent variables.

Table 5. Association (beta) of change scores in symptom severity with change in presence of GTPS between baseline and 2-year follow-up.

	WOMAC pain change	WOMAC function change	WOMAC stiffness change	VAS pain change
BMI (baseline)	1.4 (0.6 to 2.1)	1.0 (0.3 to 1.6)	-	0.9 (0.01 to 1.8)
Low-back pain (baseline)	-	-	-	-
Severity hip OA (baseline)	-	5.7 (-1 to 11.5)	6.9 (-0.6 to14.4)	10.7 (2.3 to 19.2)
Radiographic knee OA (baseline)	-13.5 (-21.1 to -5.8)	-6 (-12.5 to 0.6)	-	-10.1 (-19.5 to -0.6)
Change in GTPS	-13.1 (-21.4 to -4.9)	-9.4 (-16.5 to -2.4)	-11 (-20.1 to -1.9)	-15.6 (-25.8 to -5.4)

Backward regression model with baseline BMI, low-back pain, severity hip OA, radiographic knee OA, and change in presence of GTPS (no change = GTPS is present or absent at both baseline and follow-up, change = GTPS disappeared compared to baseline or follow-up).

When using the alternative, less stringent case definition for GTPS, 36% showed GTPS at baseline at the left or right side, and 48% at 2-year follow-up. Using adjusted regression models, hip OA patients complying with the less stringent definition for GTPS at baseline had significantly higher mean WOMAC pain, function and stiffness scores of 10.6 (CI 95%: 4.7-16.5), 8.1 (CI 95%: 2.5-13.6) and 6.6 (CI 95%: 0.3-2.9) points, respectively, and a higher mean VAS score of 7.9 (CI 95%: 1.1-14.7) points, compared with those who did not comply. Again, the presence of the less stringent GTPS at baseline did not predict symptom severity at 2-year follow-up; however, adjusted regression models showed that the presence of the less stringent GTPS at 2-year follow-up was significantly associated with WOMAC pain, function and stiffness scores of 6.6 (CI 95%: 0.5-12.8), 4.8 (CI 95%: 0.8-10) and 18 (CI 95%: 10-26.1) points, respectively. Based on the alternative definition, analyses on individual change yielded no significant associations between fluctuation in symptom severity and fluctuations in the presence of GTPS.

DISCUSSION

This study shows that 1 in 5 primary care hip OA patients appear to have concurrent GTPS, and that those with GTPS have higher symptom scores than those without. To our knowledge this is the first study to describe the presence of GTPS in hip OA patients. Even when we applied a stringent definition, the prevalence was 16%. With the less stringent definition, based on tenderness and recognition of the pain alone, the prevalence was as high as 36%. Segal et al. found a prevalence of GTPS of 17.6%, based on tenderness alone in their study population aged 50-79 years with knee OA or at risk for knee OA, and found that it was clearly related to the presence of ipsilateral knee OA.[14]

We used two cross-sectional measurements (with a 2-year period between) in the same study population and found higher pain levels in those with co-existent GTPS. Because the presence of GTPS did not predict future pain in hip OA, GTPS might a reason for the fluctuation in pain in hip OA. However, based on these assessments we cannot conclude whether higher pain levels in the hip induce GTPS (e.g. via a disturbed walking pattern or sensitization), or whether patients have higher pain levels due to the co-existent GTPS. The use of repeated measures (with shorter intervals between them) might further elucidate this relationship.

A high percentage (63%) of our hip OA patients reported low-back pain. Also, the presence of low-back pain influenced the severity of symptoms in hip OA, as did the presence of GTPS. Musculoskeletal co-morbidity is known to influence the severity of symptoms in OA[22-24] and, similar to the present study, co-existent low-back pain is also known to predict future pain in those with hip OA.[25] The presence of co-existent low-back or buttock pain, often in combination with spine OA, may also be a reason

for persisting pain at that location after total hip arthroplasty and, consequently, to dissatisfaction with the surgery.[26]

At present, no data are available on the influence of co-existent GTPS on the effect of any treatment for hip OA. On the other hand, we recently reported on the influence of co-existent hip OA or low-back pain in a trial with local corticosteroid injection in patients with GTPS.[27] Because we expected to find lower effectiveness in this subgroup, we pre-defined this subgroup analysis and pre-stratified our randomization for co-morbidity.[27] Results showed a significant short-term effect of local corticosteroid injection in the total group, but also in the subgroup of patients with co-existent low-back pain or hip OA.[13] This implies that the subgroup of patients with co-morbidity benefits as much from injection therapy as the total group.

A limitation of the present study (and in earlier GTPS studies) is that there is no consensus on the diagnostic criteria for GTPS. Related to this, few data are available regarding the validity or reliability of diagnostic criteria for this condition; we did not evaluate these properties in the present study. Although some studies mentioned trochanteric tenderness and recognition of the pain as diagnostic criteria[21,28-30], others also report on additional diagnostic tests such as a positive Trendelenburg sign, painful resisted abduction, and painful resisted internal rotation.[31,32] For intra-observer reliability, a kappa of 0.68, 0.62 and 0.03, respectively, for these tests was reported in only 12 patients with lateral hip pain in combination with trochanteric tenderness. In 24 patients with the same complaints the Trendelenburg sign showed the highest sensitivity and specificity with respect to a gluteus medius tear on MRI, followed by painful resisted abduction (sensitivity 73%, specificity 46%).[31] However, those authors used a non-tear as comparison including gluteus medius tendinitis or bursal distention. Recently, Lequesne et al. reported a sensitivity of 88% and a specificity of 95% of a painful resisted abduction for GTPS on MRI (gluteus medius tear, gluteus medius tendinitis, or bursitis) compared to controls without lateral hip complaints, very similar to resisted internal rotation; for the Trendelenburg sign they reported 100% sensitivity and 97% specificity.[32] Although the Trendelenburg sign appeared to be superior with respect to validity and reliability, both studies had a very few participants, did not describe any blinding of the test results, and used totally different control subjects. Neither of these study populations were similar to ours. In addition, in our study we only used resisted painful abduction, and restricted motion for flexion and internal rotation, as physical examination tests. This was our rationale for using the two definitions: one based on tenderness, recognition of the pain, and painful resisted abduction, and the other based on tenderness and recognition alone. Although the two definitions had a different prevalence, they had the same associations with OA symptom severity and no predictive value.

Based on these results we recommend more studies on co-existent peri-articular pathology in OA, with respect to their role in fluctuations in pain, severity of pain and

disability, and their influence on treatment in OA. Treating peri-articular pathology may reduce pain levels and improve the daily functioning of OA patients. Finally, we also emphasise the need for consensus on and validation of diagnostic criteria for peri-articular disease in OA.

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Chapter 8

General discussion

INTRODUCTION

This thesis focuses mainly on the following question: What is the evidence for the use of corticosteroid injection for patients with greater trochanteric pain syndrome (GTPS) in general practice? In addition, the cost-effectiveness of corticosteroid injections for GTPS was assessed and the side-effects of these injections evaluated in a systematic review. We also describe the role of co-morbidity on the effect of injection therapy, and the effect of co-existent GTPS on symptom severity in hip osteoarthritis (OA).

This general discussion presents an outline of the current knowledge on GTPS and of the different views regarding the etiology of this regional pain syndrome. We then discuss the results of our randomized trial in relation to patient care and the shortcomings related to evaluating the side-effects. Finally, we present some implications for future research.

ETIOLOGY

There are several differing views regarding the etiology of this pain syndrome. In 1958, Anderson described the physical signs of 45 patients with subacute and chronic pain in the hip region and distinguished this condition from the infectious or acute form of bursitis trochanterica.[1]

In 1979 Little defined the physical signs of local girdle pain with marked point tenderness of the greater trochanter as 'bursitis trochanterica'.[2] Karpinski et al. reviewed 15 patients with pain and tenderness at the tip of the great trochanter and named it the 'greater trochanteric pain syndrome'.[3] These authors asserted that the cause of the syndrome is speculative and (in the absence of demonstrable pathology) suggested that the pain pattern results from local overuse, possibly with repetitive microtrauma.[3] Collee et al. contend that the pathogenesis is uncertain and may involve various structures (such as tendon and bursae), and that referred pain from the lumbosacral region, as well as altered hip-joint mechanism, plays a role.[4] Woodley et al. demonstrated that multiple bursae are associated with the greater trochanter.[5] The anatomical study of Dunn et al. shows that subgluteus maximus bursae at the level of the greater trochanter are an expected finding in the older age group and that they vary in number, position and histological appearance.[6] They assumed that these bursae are acquired as a consequence of excessive friction between the greater trochanter and the gluteus maximus as it inserts into the fascia lata.[6]

GTPS appears to co-occur with various other musculoskeletal conditions. In the study of Collee et al. the incidence of GTPS in patients with low-back pain was 24.5%, and they found that GTPS occurred more often in women and in patients with low-back pain persisting for more than 3 months.[4] Segal et al. described the epidemiology and associ-

ated factors in persons at risk for knee OA and found a GTPS prevalence of 17.6% in a non-clinical based population.[7] In a primary care population with hip OA we also found a similar prevalence of GTPS (this thesis).

Therefore, based on this relatively high co-occurrence with other disorders, we postulate that GTPS is a syndrome that does not often exist on its own. It can be associated with low-back pain or with OA. The pain can be caused by tendon pathology or by trochanteric bursa distention and is probably of multifactorial etiology. Osteoarthritis or low-back pain might cause a deviant walking or movement pattern and may lead to relative overuse of the m. gluteus medius or minimus. This overuse gives rise to microtrauma and secondary calcification in the tendons which can lead to a non-septic inflammation in the overlying structures with swelling and modeling cicatrix tissue. Friction between the fascia latae and the greater trochanter due to overuse of the m. gluteus maximus will cause irritation or non-septic inflammation of the bursa trochanterica.

Obesity has also been associated with GTPS.[8] Runhaar et al. demonstrated that obese patients have a different walking pattern.[9] However, the cross-sectional, population-based study of Segal et al. did not demonstrate any relationship between body mass index and GTPS.[7] The prevalence of GTPS is higher among females than males (rate 4:1) and the incidence is highest in those aged 40-60 years.[10,11] The greater number of women with GTPS has not yet been explained, but may be due to the higher incidence of OA among women. In a relatively high percentage of patients (≤ 36%) the complaints are reported to persist at 12-months follow-up.[11] These figures are similar to those in other pain syndromes such as, for example, shoulder pain.[12] Furthermore, pain in GTPS becomes chronic, even after successful tissue repair.[13]

DIAGNOSIS

GTPS is a clinical diagnosis, which implies that no advanced technology or gold standard is available to confirm this clinical presentation; the physician arrives at the diagnosis by combining history taking with findings at physical examination. In 1952 Spear et al. reported on 63 patients with non-infectious trochanter bursitis and peritendinitis.[14] They described the clinical symptoms as dull, aching pain in the trochanter region, increased by physical activity such as climbing stairs, standing and walking; in some patients the pain increased when lying on the affected side. They observed that patients with peri-trochanteric calcifications (seen on X-ray) had the same clinical symptoms as patients with non-infectious bursitis.[14] Little distinguished bursitis trochanterica from other causes of girdle pain; he described the clinical symptoms as local tenderness at the trochanter, and the other characteristic feature was relief of symptoms by treatment with local infiltration with corticosteroids and anesthetic.[2]

In order to confirm the diagnosis of the syndrome, initially X-rays were made; however, it was noted that calcification at the greater trochanter was seen in only some of the patients with GTPS.[1,2] In addition, it is unknown what proportion of people in a healthy population have the same sort of calcifications at the greater trochanter. Thus, we can conclude so far that, based on X-rays alone, the diagnosis of GTPS cannot be made.

The gluteus medius and minimus insertions and the trochanteric bursa can be evaluated with ultrasound (US). Calcific tendinosis within the gluteal tendons may be better seen on US than on magnetic resonance imaging (MRI).[15] MRI in musculoskeletal disorders has provided new insights into a number of musculoskeletal syndromes and has several advantages compared with conventional radiography, US and bone scanning in the imaging of soft tissue lesions. MRI is useful to evaluate the signs of gluteal tendinopathy as well as to exclude other causes of lateral hip pain, such as local trauma, avascular necrosis of the femoral head and degenerative spinal disease.[16] Bird et al. support the hypothesis that gluteus medius tendon pathology is important in defining GTPS; they examined patients with GTPS to determine the prevalence of gluteus medius pathology by utilizing MRI.[17] In 45.8% of the 24 patients they found a gluteus medius tear and in 64.5% a gluteus medius tendinitis was seen on MRI.[17] In a retrospective study on MRI findings in GTPS, Blankenbaker et al. detected peritrochanteric abnormalities in patients with GTPS; they concluded that the absence of peritrochanteric MRI abnormalities makes trochanteric pain syndrome unlikely.[18] However, detection of these abnormalities on MRI is a poor predictor of trochanteric pain syndrome as these findings are present in a high percentage of patients without trochanteric pain. Thus, MRI seems to be a highly sensitive test, but has low specificity.

Although various clinical tests are described in association with GTPS, the diagnostic value of these tests is difficult to interpret because there is no accepted gold standard to determine the underlying pathology.[19] Bird et al.[17] combined the findings of MRI and physical examination in 24 patients with GTPS; they found that Trendelenburg's sign performed best overall in terms of sensitivity, specificity, and intraobserver reliability in detecting gluteus medius tears, followed by painful resisted abduction.[17] However, they used a non-tear as comparison, including gluteus medius tendonitis or bursal distention. Finally, Lequesne et al. reported a sensitivity of 88% and a specificity of 95% for painful resisted abduction in patients with refractory GTPS on MRI (gluteus medius tear, gluteus medius tendonitis or bursitis) compared to controls without lateral hip complaints; for the Trendelenburg sign they reported 100% sensitivity and 97% specificity.[20]

In our randomized controlled clinical trial assessing the effectiveness of local corticosteroid injection for GTPS, we asked the participating GPs to select patients aged 18-80 years visiting their practice with lateral hip pain with the following symptoms: pain persisting for more than one week in the lateral region of the hip or thigh with tenderness at palpation of the greater trochanter with the following characteristics: severe

pain at palpation of the greater trochanter, but uncertainty as to whether the patient recognizes the pain as that for which he or she visits the GP, or local tenderness when the area of the great trochanter is palpated and the patient recognizes the pain as that for which he or she visits the GP. We derived these criteria from Little's study because we found them to be in line with clinical practice.[2] GPs in the Netherlands are not used to making a supplementary diagnostic investigation before they consider injection therapy or any other intervention for GTPS. For our study on the co-existence of GTPS in patients with hip OA we used a similar criterion as described above, but also added the resisted abduction test because this standardized test was available for all patients. Although fewer patients were diagnosed with GTPS when the resisted abduction test was also performed, the association with increased symptom severity was similar.

THERAPY

A wide variety of therapies are available for GTPS. Surgical techniques include surgical release of the iliotibial tract, removal of the bursa, repair of a tendon tear, or a trochanteric reduction osteotomy.[21-23] However, little is known about the effectiveness of these surgical interventions because they have not been compared with any of the other interventions. Interventions by allied health professionals can include exercises, relaxation, physical applications such as ultrasound, biofeedback, myo-feedback, radial shockwave therapy, and workplace adjustments. Only radial shock wave therapy and exercise therapy have been examined in randomized trials.[24,25] Radial shock wave therapy showed effectiveness in chronic GTPS.[25] Rompe et al. found shock wave therapy and home training to be superior to corticosteroid therapy at 15-months follow-up.[26] Primary care intervention strategies include local or systemic analgesics, and injection with corticosteroids combined with a local anesthetic agent.

Although the effect of analgesics on GTPS has not yet been investigated, we believe that patients may benefit from the use of analgesics. The effect of corticosteroid injection therapy is attributed to local inhibition of the inflammation.[26] In addition, there is a central effect (at brain level) of corticosteroids, although the clinical relevance of the central effect might only be relevant in high doses or with repetitive application.[27] To our knowledge, Spear et al. were the first to report on injection therapy for bursitis trochanterica; they injected one patient with procaine which had an immediate positive effect.[14] Barker described three patients with chronic trochanter bursitis who had an immediate positive response to corticosteroid injections.[28] Leonard reported that all 18 patients that were injected with hydrocortisone had complete relief from complaints.[29]

Before conducting our clinical study, no evidence was available from a high-quality randomized clinical trial regarding the use of corticosteroid injection for GTPS in general practice and secondary care. In our study we compared usual care versus corticosteroid injection therapy in a non-blinded, pragmatic study design.[30] This type of design is appropriate to examine whether injection therapy is more effective than no injection therapy, as delivered and experienced in actual clinical practice.

EFFECTIVENESS OF CORTICOSTEROID INJECTIONS

The results of our study show that, at 3-months follow-up, 55% of the patients in the injection group had recovered (defined as a total or strong recovery) compared with 34% in the usual care group (difference of 21%). This results in a 'number needed to treat' of 5 patients at 3-months follow-up. Pain severity at rest and on activity decreased in both the groups but the decrease was greater in the injection group: adjusted difference pain at rest 1.18 (95% CI 0.31-2.05) and adjusted difference pain on activity 1.30 (95% CI 0.32-2.29) on a 0-10 scale. At 12-months follow-up the difference between the groups no longer existed: in the injection group 61% of the patients were recovered (defined as a total or strong recovery) compared with 60% in the usual care group. Pain severity at rest and on activity decreased in both groups: adjusted difference pain at rest -0.14 (95% CI to -0.75 to 1.04) and adjusted difference pain on activity 0.45 (95% CI -0.55 to 1.46); however, these differences were no longer significant.[31]

In a recent systematic review based on 41 studies on the efficacy and safety of corticosteroid injections for management of tendinopathy, there was strong evidence that corticosteroid injection is beneficial in the short term for treatment of tendinopathy, but is less effective than other treatment options in the intermediate and long term;[32] however, this latter study did not investigate GTPS. In our study we did not find this reverse effect at 12-months follow-up.

LIMITATIONS OF OUR TRIAL

For our randomized controlled trial we aimed to recruit 150 patients. This sample size was calculated to detect an increase in recovery rate of 25% in the intervention group after 3- months follow-up (45% recovery in the control group vs. 70% recovery in the intervention group). With power 0.8 and alpha 0.05 (two-sided test) and a dropout rate of 10%, a total of 75 patients per group was required. Unfortunately, during a 2-year period it was possible to recruit only 120 patients. Nevertheless, based on the low dropout rate and the possibility to evaluate the data with one-sided testing, halfway through the

study the funding authorities allowed us to lower the sample size to 120 participants. The difficulties in recruiting patients in general practice have been well documented by van der Wouden et al.[33]

Important points related to our study are that: 1) it focused on incident cases, 2) the GP had to be alert during consultation, 3) and the GP was the first to inform the patient about our study. These three factors are reported to be associated with less successful patient recruitment.[33] Fortunately we could successfully examine our research question using the smaller sample size, as evidenced by the fact that we detected significant differences. This was mainly due to the effect of the corticosteroid injection, and to the very low rate of dropout rate during the study period (only 1 person dropped out at 3-months follow-up).

In addition, we were confronted with many violators. In the intervention group 9 (15%) of the 60 participants did not receive an injection for various reasons, and 8 (13.3%) persons in the control group did get an injection within 12 months. However, these violators did not influence our conclusion that injection therapy is effective at 3-months follow-up. In a separate per protocol analysis comparing the injection group with the non-injection group, with the violators excluded, the effects of injection therapy were more pronounced. Related to our pragmatic study design, which makes no comparison with placebo injection, we cannot distinguish a possible placebo effect of the injection therapy from the effect of the injected corticosteroid itself. In addition, we do not know the effect of needling.

CO-MORBIDITY AND SUBGROUP ANALYSES

GTPS is more common in patients with co-morbidity. Using data from a randomized controlled trial in hip OA patients, our group showed that 1 of 5 primary care hip OA patients appears to have concurrent GTPS, and that hip OA patients with GTPS have higher symptom scores than those without GTPS.[34]

Observational studies have shown that about two-thirds of patients with GTPS also have low-back pain or OA of the hip.[4,35] Our study of patients with GTPS showed co-morbidity in 63% of these patients. Because we expected to find a lower effectiveness of local corticosteroid injections in this subgroup, we pre-defined these subgroups and stratified our randomization for co-morbidity (due to hip OA, low-back pain, or to both). However, in our analysis of patients with co-morbidity, the effect of injection therapy with corticosteroids was, unexpectedly, at least as high as in the total population and the effect was significant. In the subgroup with co-morbidity (n=73), at 3-months follow-up 58% of the intervention group were recovered vs. 32% in the control group, with a number needed to treat of 4 patients (adjusted OR 2.87, 95% CI 1.10-7.55). Differences

in pain at 3-months follow-up at rest and on activity were (on a 0-10 scale) 1.36 (95% CI 0.15-2.57) and 1.42 (95% CI 0.14-2.70), respectively. This implies that the subgroup of patients with co-morbidity has at least as much benefit from the injection therapy as the total group. In a randomized double-blind study Ekeberg et al. compared the effectiveness of US-guided corticosteroid injection in the subacromial bursa with systemic corticosteroid injection in patients with rotator cuff disease and found no significant differences in the outcome.[36] We can postulate that corticosteroids injections are not only locally effective, but that local corticosteroid injections have a systemic effect on OA and low-back pain.

COST-EFFECTIVENESS

Another aim of our investigations was to determine the cost-effectiveness of corticosteroid injections for GTPS. The results showed no significant differences between the intervention group and control group regarding annual direct medical costs and productivity costs. Only at baseline, and only due to the corticosteroid injections, did the intervention group have significantly higher direct medical costs than the control group. Overall, direct medical costs were relatively low and the intervention itself was not expensive. This investigation also showed that productivity costs in terms of absence from work were relatively low and efficiency losses were moderate. Thus, although there was no substantial economic saving effect of corticosteroid injection therapy for GTPS, on the other hand the injections did not increase overall medical costs. It must be noted, however, that our relatively small sample size (120 patients) precluded a more precise estimation of these costs.

ADVERSE EFFECTS

As every healthcare intervention carries some risk of harm, clinical decision-making needs to be supported by a systematic assessment of the balance between benefit and harm.[37] In this thesis we assessed the possible harmful effects of corticosteroid injection in a separate review.

Whereas there is a guide for reviews on intervention studies, there is no guide for a systematic review on side-effects. According to the CONSORT guidelines for randomized trials, adverse events need to be published as part of the results of the trial.[38] However, the low number of adverse events in clinical trials, due to the relatively low number of participants, implies that not all adverse events are observed and/or reported. Serious

adverse events might be published as case reports, but less serious adverse events may (in some cases) not be published at all. The registration of adverse events in general practice is considered to be underestimated, probably because there is no obligation to report adverse events due to interventions in general practice.

Estimation of all the adverse events and side-effects of corticosteroid injection therapy involves prospectively following all patients prescribed corticosteroids for injection therapy and evaluating the adverse events on the short and long-term.

We performed a systematic review of studies reporting on adverse events of local extra-articular corticosteroid injection therapy. Of the 87 studies that were identified (44 case reports, 37 prospective studies) two were small observational studies and six were retrospective studies. We divided the adverse events into minor (the harm was temporary) and major events (needing intervention, or were not transient). This distinction was made because in our opinion this is clinically relevant and easy to explain to patients. In the various studies the incidence of major adverse events ranged from 0-5.8% and that of minor events from 0-81%. The major adverse events included osteomyelitis and protothecosis; one fatal necrotizing fasciitis; cellulitis and ecchymosis; tendon ruptures; atrophy of the plantar fat and local skin effects appeared as atrophy, hypopigmentation, or as a skin defect. The minor adverse events ranged from skin rash to flushing and disturbed menstrual pattern. Increased pain or steroid flare after injection was reported in 19 of the 87 studies. In the study population included in our randomized controlled trial we found no difference in adverse events between the groups, except for pain at the injection site.

It was not possible to pool the risk for adverse effects due to heterogeneity of the study populations, to differences between the interventions, and due to the variance in the reporting methods.

FUTURE RESEARCH

One area for future research could be investigation of the additional effect of physical therapy. The study of Rompe et al. showed a superior benefit of physical therapy vs. corticosteroid injection at 15-months follow-up.[24] That therapy consisted of progressive, slow and repetitive exercises with piriformis stretch, iliotibial band stretch and straight leg raise.

It is also worthwhile to evaluate the role of local application of non-steroidal anti-inflammatory drugs in GTPS, as the beneficial effect of topical application in musculoskeletal pain has been shown for other local pain syndromes.[39] Because Rompe et al. found an effect of shock wave therapy in GTPS,[25] this effect needs to be confirmed in additional studies. Although Wang et al. demonstrated that shock wave therapy induces neovascu-

larisation and improves blood supply to tissue in rabbits,[40] the underlying mechanism of shock wave therapy still needs to be further elucidated.

Neither our study nor the review of Coombes et al.[32] showed any additional effect of corticosteroid injections on the long term. More research is needed to establish why some studies show a reversed effect on the long term, and others did not.

Finally, in order to acquire a more precise evaluation of the side-effects of corticosteroid injection, a larger prospective cohort of patients receiving a prescription for injectable corticosteroids is required.

CLINICAL IMPLICATIONS

The work presented in this thesis has shown the benefit of corticosteroid injection for GTPS at 3-months follow-up. For patients with local trochanteric pain (with or without co-morbidity) GPs can offer corticosteroid injections that are expected to have a clinically relevant effect; however, they need to explain that the benefit may diminish after about 12 months. After considering the expected benefit of treatment, and the impact of possible adverse side-effects, the patient and GP can come to an agreement about the most appropriate form of treatment for their GTPS.

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Chapter 9

Summary

Samenvatting

Dankwoord

Curriculum Vitae

PhD portfolio

SUMMARY

This thesis deals with patients with greater trochanteric pain syndrome (GTPS). This is a condition with chronic intermittent or continuous complaints of local pain at the lateral side of the hip. The incidence is highest in female patients aged 40-60 years; in general practice the incidence of trochanteric pain was estimated to be 1.8 per 1,000 patients per year.

Although the etiology of trochanteric pain is unknown, it could be caused by local inflammation (a so-called bursitis) or pathology of the tendinous insertions or the gluteus muscles.

Possible therapeutic options available so far are surgery, physical therapy, shockwave therapy, and injection therapy with corticosteroids. In the Netherlands, especially the last option is often applied by general practitioners. Although clear evidence is lacking, the results of small observational studies suggest that this treatment is effective in the short term. Until now, however, no randomized control trial has examined the effect of treatment with corticosteroid injections of greater trochanteric pain syndrome.

This thesis describes the results of a well-designed randomized controlled trial conducted in patients suffering from greater trochanteric pain syndrome. The study was performed in Dutch general practice in 2006-2009. It was supported by a funding program for 'Common disorders in general practice' by the Netherlands Organization for Health Research and Development (ZonMw).

Chapter 2 presents details of the study design. It was a pragmatic, open-label randomized trial. Patients visiting their general practitioner with complaints suggestive of the trochanteric pain syndrome were invited to participate. We aimed at a total of 150 patients in the age range 18 to 80 years. Patients included in this study gave informed consent and were randomly allocated to receive local corticosteroid injections, or to receive usual care which consisted of analgesics as needed. The randomization was stratified for the presence or absence of co-morbidity of low back pain, osteoarthritis of the hip, or both. Treatment was evaluated by means of questionnaires at several time points within one year: the evaluation of pain severity, or recovery, at 3 and 12 months was the primary outcome. An analysis of primary and secondary outcomes was made according to the intention-to-treat principle. Direct and indirect costs were assessed by means of questionnaires. The cost-effectiveness was estimated using the ratio: CE ratio = (cost of injection therapy minus cost of usual care)/(effect of injection therapy minus effect of usual care). This enabled us to investigate the effectiveness and cost-effectiveness of the corticosteroid injection therapy. Since the protocol did not include a placebo group, we were unable to make a distinction between the possible placebo effect of the injection and the specific effects of the corticosteroid medication itself.

Chapter 3 describes the main outcomes of the trial, which included 120 patients. Patients (aged 18-80 years) visiting the general practitioner with greater trochanteric pain syndrome were randomly allocated to receive either local corticosteroid injections (n=60) or usual care (n=60). Primary outcomes at 3 and 12 months follow-up were pain severity (on a numerical rating scale ranging from 0 to10) and recovery (yes versus no total or major recovery). At the first time point (3-months follow-up), in the usual care group 34% of the patients were recovered compared to 55% in the injection group. Pain severity at rest and on activity decreased in both groups, but the decrease was significantly greater in the injection group. At the second time point (12-months follow-up), there was no difference in outcome between the two groups. In the usual care group 60% of the patients had recovered compared to 61% in the injection group. Also, pain severity at rest and on activity decreased in both groups in the same magnitude. In this first controlled trial performed in general practice to measure the effectiveness of corticosteroid injections versus usual care, a clinically relevant effect was shown at 3-months follow-up for recovery, as well as for pain at rest and on activity. However, this proved to be a short-term effect: at 12-months follow-up no differences in outcome were found with regard to both the primary and secondary outcomes.

Chapter 4 addresses the cost-effectiveness of injection therapy in patients with greater trochanteric pain syndrome. This study used the data obtained from the randomized controlled trial performed in general practice (described in Chapters 2 and 3).

Data on direct medical costs, productivity costs, and quality of life were collected using questionnaires filled out by the patients at baseline, at 6 weeks, and at 3, 6, 9 and 12 months after inclusion in the study. The questionnaires collected general information and data on the so-called WOMAC (Western Ontario and McMaster University Osteoarthritis Index: a health status instrument for patients with osteoarthritis in the hip or knee); the Prodisq (a modular questionnaire to measure productivity cost); medical consumption; the EQ-5D (a descriptive instrument to measure quality of life); and on side effects.

No significant differences were found during any follow-up measurement in the annual direct medical costs, productivity costs, or total costs. Only at baseline the direct medical costs were significantly higher for the intervention group, primarily caused by the costs of the corticosteroid injections. Patients in the intervention group had a trend towards a higher annual quality of life; however, this was not significant. The average annual WOMAC scores showed significantly better results in the intervention group. The cost-effectiveness ratio was €28,688.

At 12 months follow-up it was concluded that corticosteroid injections offer no significant benefits in terms of quality of life, or in terms of all sorts of medical and indirect

costs. However, uncertainty analysis showed that there was a 44% probability that the intervention could be cost-effective compared to usual treatment (in this study, analgesics as needed). Overall, direct medical costs were relatively low and the intervention itself was not expensive. A limitation of the study was the small sample size. Although it was sufficient to test the clinical efficacy of the intervention, it should be larger for a more detailed economic evaluation.

Chapter 5 presents an overview of the literature on the occurrence and type of adverse effects after application of an extra-articular corticosteroid injection. For this purpose, a systematic review of the literature was made based on a PubMed and Embase search covering the period from 1956 to January 2010. Case reports were included, as were prospective and retrospective studies that reported adverse events of corticosteroid injection. All clinical trials using extra-articular corticosteroid injections were included. Reports of adverse events were divided into major ones (defined as those needing intervention, or not disappearing) and minor adverse effects (transient, not requiring intervention). The literature search yielded 87 relevant studies: 44 case reports, 37 prospective studies and 6 retrospective studies. Major adverse events were osteomyelitis and protothecosis; one fatal necrotizing fasciitis; cellulitis and ecchymosis; tendon ruptures; atrophy of the plantar fat; and local skin effects appearing as atrophy, hypopigmentation or as skin defect. Minor adverse events effects ranged from skin rash to flushing and disturbed menstrual pattern. Increased pain or steroid flare after injection was reported in 19 studies. The incidence of major adverse events ranged from 0 to 5.8% and the incidence of minor adverse events ranged from 0 to 81%. It was not possible to pool the data due to heterogeneity of the study populations, differences in the interventions applied, and a substantial variance in the methods of reporting. Therefore, in this literature review it was difficult to accurately quantify the incidence of adverse effects after extra-articular corticosteroid injections. The reported adverse events were relatively mild, although one fatal reaction was reported.

In **Chapter 6** we performed a systematic review of the studies evaluating the efficacy and safety of all reported interventions for greater trochanteric pain syndrome. An electronic database search was conducted up to October 2010. All studies were selected which conducted a randomized clinical trial, a quasi-randomized clinical trial, or a controlled clinical trial. For inclusion in the review, studies had to investigate adult patients with pain at the lateral side of the hip due to greater trochanteric pain syndrome. All interventions were assessed and compared with each other, to placebo, or to no treatment. The main outcomes were pain, recovery and adverse events. The quality of the studies was assessed with the risk-of-bias tool recommended by the Cochrane Collaboration.

Because data were clinically heterogeneous, a qualitative review was performed. The level of evidence was classified as strong, moderate, limited, or no evidence.

Eventually only four studies were included in the review, with a total of 489 patients. Corticosteroid injection therapy, home training, and shockwave therapy were evaluated in a comparative study design. None of the combinations for comparison were used twice; therefore, no strong or only moderate evidence was reached. There was limited evidence for the short-term effectiveness of corticosteroid injections versus usual care, versus shockwave therapy, and versus home exercise. On the long term, there was limited evidence for superiority of home training compared to corticosteroid injection, and of shockwave therapy compared to corticosteroid injection. For all other reported interventions, no evidence was found. No serious adverse events were reported.

Chapter 7 investigates the prevalence and influence of greater trochanteric pain syndrome (GTPS) in primary care patients with hip osteoarthritis. These patients often show a pattern with periods of increased pain; however, little is known about the association between the co-existence of GTPS and these fluctuations in pain. This study was a randomized placebo-controlled, double-blind trial of osteoarthritis patients in primary care who received glucosamine sulfate therapy for two years. Symptom severity was assessed with the WOMAC scores for pain, function and stiffness, and with a visual analogue scale for pain in the previous week. A linear regression model was used to analyze the adjusted influence of the presence of GTPS on the symptom severity in hip osteoarthritis patients. In addition, we analyzed the prognostic value of the presence of GTPS on symptom severity 24 months later, as well as whether individual changes in severity scores were associated with changes in the presence of GTPS between the two time points. It was found that about 1 in every 5 hip osteoarthritis patient in primary care had a co-existent GTPS and that this co-occurrence was associated with higher symptom scores on several questionnaires. GTPS at baseline did not predict symptom severity 24 months later, but GTPS at 24-months follow-up was significantly associated with higher symptom scores at this time point.

Finally, in **Chapter 8** we discuss the main results of this work and the clinical implications of the findings of the randomized controlled trial for the management of patients with greater trochanteric pain syndrome by the general practitioner.

SAMENVATTING

Trochantair syndroom (in het Engels "greater trochanteric pain syndrome") is het onderwerp van dit proefschrift. Patiënten met trochantair syndroom hebben lokale pijn aan de buitenzijde van de heup, waarbij de pijn meestal toeneemt bij lichamelijke activiteit. Trochantair syndroom is een chronische aandoening, dat wil zeggen de meeste patiënten houden last gedurende vele jaren na het stellen van de diagnose.

De aandoening komt voor in alle leeftijdsgroepen, maar wordt meestal gezien bij vrouwen tussen de 40 en 60 jaar. In de huisartsenpraktijk komt de aandoening voor bij 1.8 per 1000 patiënten per jaar. Praktisch betekent dit voor een gemiddelde huisartsenpraktijk vier nieuwe patiënten per jaar.

De precieze oorzaak van de aandoening is niet bekend; aanvankelijk werd een ontstekingsreactie van de lokale slijmbeurs verantwoordelijk geacht voor de klachten, maar veranderingen zoals calcificaties en zwelling van de peesaanhechtingen van de bilspieren lijken eveneens een rol te spelen.

De behandelingen die tot nu toe zijn beschreven voor trochantair syndroom zijn: operatie, fysiotherapie, shockwave therapie en injecties met corticosteroïden. Deze laatste behandeling wordt veel gedaan in de huisartsenpraktijk. Kleine observationele studies lieten resultaat zien van de corticosteroïd injecties op de korte termijn, maar tot nu toe was er geen afdoende bewijs voor de effectiviteit van deze behandeling.

In dit proefschrift worden de resultaten beschreven van een gerandomiseerde studie naar het effect van corticosteroïd injecties bij patiënten met trochantair syndroom. Tussen 2006 en 2009 werd de studie uitgevoerd bij patiënten met trochantair syndroom afkomstig uit Nederlandse huisartsenpraktijken. De studie werd gesubsidieerd door de Nederlandse organisatie voor gezondheidsonderzoek en zorginnovatie, ZonMw, uit het fonds "Alledaagse ziekten". Daarnaast beschrijft dit proefschrift middels literatuuronderzoek de mogelijke bijwerkingen van dergelijke lokale injecties met corticosteroïden en de effecten van alle type behandelingen bij trochantair syndroom. Ook werd het voorkomen van trochantair syndroom en het samenhangen met de ernst van klachten bij patiënten met artrose van de heup in de huisartsenpraktijk beschreven.

In **Hoofdstuk 2** wordt de studieopzet beschreven. We voerden een pragmatische, open-label, gerandomiseerde studie uit in de huisartsenpraktijk. Het was de bedoeling om 150 patiënten met een trochantair syndroom in de leeftijdscategorie van 18 tot 80 jaar te includeren. Patiënten werden, na uitleg over de opzet van de studie en nadat ze schriftelijk toestemming hadden gegeven, na loting behandeld met ofwel corticosteroïd injecties, ofwel de standaard behandeling (d.w.z. pijnstilling naar behoefte). Tevens werd beoordeeld met behulp van een vragenlijst of er wel of geen sprake was van comorbiditeit zoals lage rugpijn, heupartrose of beiden. Na indeling in een van deze vier

subgroepen werden de patiënten gerandomiseerd. De beide behandelingen werden geëvalueerd middels vragenlijsten, die meerdere malen per jaar werden verstuurd. De primaire uitkomstmaten, pijn in rust en bij beweging en het ervaren herstel, werden geanalyseerd na 3 en 12 maanden follow-up. De directe en indirecte kosten werden eveneens berekend aan de hand van vragenlijsten. Op deze manier kon een uitspraak gedaan worden over de effectiviteit van de injectiekuur t.o.v. de gebruikelijke behandeling en de kosteneffectiviteit van deze vorm van therapie.

Omdat we geen placebo controle groep hebben gebruikt, kunnen we geen onderscheid maken tussen de placebo werking van de injectie zelf en werking van de corticosteroïd injectie.

In **Hoofdstuk 3** worden de klinische uitkomsten van de studie beschreven. Tussen 2006 en 2008 werden totaal 120 patiënten geïncludeerd. De patiënten werden na aanmelding door de huisarts at random verdeeld over twee groepen: de ene groep kreeg corticosteroïd injectie therapie en de ander groep kreeg pijnstilling naar behoefte. De primaire uitkomstmaten (pijn en herstel) werden geanalyseerd na 3 en 12 maanden. Pijn in rust en de pijn bij inspanning werden gemeten op een visueel analoge schaal (VAS score van 0 tot 10), de mate van herstel werd gemeten aan de hand van 7 categorieën variërend van volledig herstel tot erger dan ooit. In onze studie werden patiënten hersteld geacht, als ze in de categorie sterk verbeterd of volledig herstel hadden aangekruist.

Na 3 maanden vond 55% van de patiënten in de injectiegroep zich volledig hersteld, t.o.v. 34% in de controlegroep, een statistisch significant verschil. Ook de afname in pijn (zowel in rust als bij inspanning) was significant groter in de injectiegroep na 3 maanden follow-up. De afname in pijn na 12 maanden verschilde niet tussen beide groepen. Na 12 maanden was er geen verschil meer in percentage herstel tussen beide groepen (injectiekuur 61%, standaard behandeling 60%). We concludeerden dat injectietherapie met corticosteroïden na 3 maanden klinisch effectief was, en een gunstiger resultaat liet zien vergeleken met de standaard behandeling met zo nodig pijnstilling. Na 12 maanden was er echter geen verschil meer te meten tussen beide groepen.

In **Hoofdstuk 4** wordt de kosteneffectiviteit van de injectie therapie bij patiënten met trochantair syndroom berekend. In de studiepopulatie beschreven in de hoofdstukken 2 en 3, werd na 1 jaar follow-up via vragenlijsten de kosten van elke behandelingsvorm uitgerekend. De directe medische kosten, de kosten ten gevolge van verlies van arbeidsproductiviteit (via de Prodisq vragenlijst) en verlies van efficiëntie van overige werkzaamheden, werden verzameld met behulp van vragenlijsten. Vragenlijsten werden afgenomen bij het begin van de studie, na 6 weken en vervolgens na 3, 6, 9 en 12 maanden. Kwaliteit van leven werd gescoord op het gebied van mobiliteit, zelfverzorging, dagelijkse activiteiten, pijn en angst/depressie middels de EQ-5D vragenlijst.

Daarnaast werd de impact van de heupklachten onderzocht in de dimensies pijn, stijfheid, en functionaliteit via de WOMAC score (Western Ontario and McMaster University Osteoarthritis Index, een schaal om de conditie van patiënten met heupartrose of knieartrose te meten).

Alleen bij het begin van de studie waren de directe medische kosten hoger in de groep van de corticosteroïd injecties, bepaald door de kosten van het bezoek aan de dokter en de injectie. Na een jaar werden er geen significante verschillen meer gevonden tussen de beide behandelingsgroepen wat betreft directe medische kosten, productiviteitsverlies en kwaliteit van leven.

De kosten-effectiviteitsratio werd berekend met de volgende formule: (kosten van injectietherapie – kosten van standaard behandeling)/(effect van injectietherapie – effect van standaard behandeling). De ratio was na 1 jaar 28.688 euro, en de waarschijnlijkheid dat de injectie interventie kosteneffectief is, was 44%. De conclusie was dan ook dat, alhoewel er geen significante verschillen werden gevonden in de directe kosten en sommige aspecten van kwaliteit van leven, corticosteroïd injecties mogelijk (met een waarschijnlijkheid van 44%) toch kosteneffectief zijn, vergeleken met standaard behandeling. De directe medische kosten zijn laag en de injectietherapie zelf is niet duur. Voor een meer gedetailleerde economische evaluatie, was de studiepopulatie te klein.

In **Hoofdstuk 5** wordt een overzicht gegeven van de bestaande literatuur naar de bijwerkingen van de injecties met corticosteroïden voor extra-articulaire toediening. Een systematische zoektocht werd uitgevoerd via PubMed en Embase, van alle artikelen over dit onderwerp die gepubliceerd waren van 1956 tot januari 2010. Case reports, prospectieve en retrospectieve studies werden geïnventariseerd naar de ernst van de bijwerking. We hebben de bijwerking "major" ofwel belangrijk genoemd als de bijwerking tot blijvende schade leed, of er noodzaak was voor behandeling. De bijwerking werd "minor" of mild genoemd als deze van voorbijgaande aard was of als er geen interventie nodig was. Er werden in totaal 87 studies gevonden, 44 case reports, 37 prospectieve studies en 6 retrospectieve studies. Diverse "major" bijwerkingen werden beschreven zoals osteomyelitis, protothecosis, necrotiserende fasciitis, peesscheuring, cellulitis en ecchymosis, huidatrofie en verminderde pigmentatie van de huid. Er werd 1 fatale bijwerking gerapporteerd. In veel studies werden mildere bijwerkingen beschreven zoals plaatselijke pijn, roodheid van de huid en verstoorde menstruele cyclus. De incidentie van de belangrijke bijwerkingen werd geschat op 0 – 5.8%, die van de mildere bijwerkingen op 0 – 81%. Gezien de vele verschillen in studies, patiëntenpopulatie, rapportage van de bijwerking e.d. was het niet mogelijk om de data bij elkaar op te tellen en te evalueren. We hebben de conclusie getrokken dat het moeilijk is om een accurate schatting van de bijwerkingen van extra-articulaire toediening van corticosteroïd injecties te geven, de gerapporteerde bijwerkingen zijn relatief mild, alhoewel één injectie met dodelijke afloop beschreven werd.

Hoofdstuk 6 vat de bestaande studies over de reeds onderzochte interventies bij trochantair syndroom samen in een systematische review. Studies die voldeden aan de criteria gerandomiseerd, gecontroleerd of quasi-gerandomiseerd, werden gezocht in Medline, Embase en Web of Science tot aan oktober 2010. Voor inclusie in deze review, werden artikelen geselecteerd met volwassen patiënten met pijn aan de zijkant van de heup ten gevolge van trochantair syndroom. De gevonden interventies werden beoordeeld en vergeleken met elkaar, of vergeleken met placebo of met geen behandeling. De belangrijkste uitkomstmaten waren effecten op pijn, en op herstel en het optreden van bijwerkingen. Tevens werd de kwaliteit van de studies beoordeeld met een meetsysteem ontwikkeld door de Cochrane Collaboration. De bewijsvoering werd geclassificeerd in de categorie sterk, matig, beperkt of geen bewijskracht.

Er werden 4 vergelijkende studies gevonden met een totaal van 489 patiënten. Alleen corticosteroïd injectietherapie, fysiotherapie en shockwave therapie waren behandelingen die onderling werden vergeleken. Geen van de vergelijkende studies was meer dan één keer uitgevoerd, dus er is er geen sterk bewijs gevonden voor de werkzaamheid van een van de behandelingen. Er werd beperkt bewijs gevonden dat corticosteroïd injecties op de korte termijn effectiever waren dan de standaard behandeling, shockwave behandeling en oefeningen thuis. Op de lange termijn was er beperkt bewijs voor een betere uitkomst van oefeningen thuis t.o.v. corticosteroïd injecties, en van shockwave behandeling t.o.v. corticosteroïd injecties. Er was geen bewijs voor klinische effectiviteit van andere interventies, zoals orthopedische operaties en biofeedback. In de vier studies werden geen ernstige bijwerkingen gerapporteerd.

In **Hoofdstuk 7** wordt het voorkomen onderzocht van trochantair syndroom in patiënten met heupartrose ("hip osteoartritis") in de Nederlandse huisartsenpraktijk. Deze patiënten hebben vaak meer pijnklachten, het is echter onduidelijk wat de samenhang is tussen de fluctuaties in pijn en het tegelijk voorkomen van trochantair syndroom.

Voor dit doel werd een patiëntenpopulatie gebruikt, waarbij in een gerandomiseerde placebo gecontroleerde studie het effect van glucosaminesulfaat op klachten van heupartrose was bestudeerd. Voor de interventie en na 24 maanden werd de effectiviteit van dit geneesmiddel geëvalueerd met behulp van pijnklachtenscores, functionaliteitmetingen en stijfheid (middels de WOMAC score en een visuele analoge schaal voor pijn in de afgelopen week). Er werd gekeken naar het voorkomen van trochantair syndroom als bijkomende aandoening en het effect van deze comorbiditeit op de klachten en prognose na 24 maanden.

Tijdens het begin van de studie bleek 17% van de 214 geïncludeerde patiënten met heupartrose ook last te hebben van een trochantair syndroom. Patiënten met trochantair syndroom scoorden significant hoger op de WOMAC score en pijnschalen, zowel bij het begin van de studie als na 24 maanden follow-up. Het hebben van trochantair

syndroom aan het begin van de studie was niet voorspellend voor de ernst van de symptomen na 24 maanden.

De conclusie van deze studie was dat bijna 1 op de 5 patiënten met heupartrose in de huisartsenpraktijk, ook last heeft van trochantair syndroom; dit gaat gepaard met significant hogere symptoomscores.

Het proefschrift eindigt met een interpretatie van alle gegevens van de uitgevoerde studies, met name de toepasbaarheid en de beperkingen van de corticosteroïd injectiekuur in de behandeling van patiënten met trochantair syndroom voor de dagelijkse praktijk van de huisarts.

DANKWOORD

Alle deelnemende patiënten en huisartsen wil ik als eerste danken, zij blijven voor een groot deel anoniem, maar zijn natuurlijk onmisbaar voor het uitvoeren van een klinische trial. Het is bewonderenswaardig hoe trouw de patiënten hun vragenlijsten hebben teruggestuurd. De collega huisartsen wil ik danken voor de moeite en extra tijd die zij hebben geïnvesteerd in het aanleveren van patiënten.

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Dan komen we bij de Westzeedijk, de afdeling waar echt wetenschappelijke productie wordt gedraaid. Vijf jaar heb ik daar de meeste maandagen en vrijdagochtenden doorgebracht en heb ik mij kunnen laven aan de wetenschap. Stafleden, senior- en junioronderzoekers en studenten zorgen aldaar voor een positief werkklimaat.

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Pauline en Jasmijn: twee dochters waar ik erg trots op ben!

CURRICULUM VITAE

Tineke Brinks werd op 2 november 1956 geboren in Amsterdam. Na haar studie geneeskunde aan de Universiteit van Amsterdam heeft zij haar arts examen gehaald in 1985. In de wachttijd voor de huisartsenopleiding was zij werkzaam als arts-assistent op de afdeling Interne Geneeskunde van het Academisch Medisch Centrum te Amsterdam op de afdeling van Prof. Johan Vreeken.

Na de tweejarige huisartsenopleiding aan de Universiteit van Amsterdam volgde zij haar eigen huisarts, Lean Kwint op. In 1990 startte zij als solistisch huisarts, samen met de assistentes Claudia Burolo en Karin Schmidt, de praktijk op de Kometensingel in Amsterdam. De praktijk verhuisde naar een nieuwe locatie op het Orionplantsoen en aldaar heeft zij 8 jaar samengewerkt met Ernst Lemaire.

In 2000 verhuisde zij naar Rotterdam. In 2001 startte zij de kaderopleiding palliatieve zorg van het NHG en werd ze SCEN arts en in 2009 werd zij benoemd tot lid van de KNMG Commissie Opleiding en Registratie SCEN.

Op het Erasmus Medisch Centrum was zij docent op de afdeling Praktische Klinische Vaardigheden van 2001 tot 2006. In 2002 werd zij tevens aangesteld als docent op de afdeling Huisartsgeneeskunde, waar ze tot nu nog werkzaam is.

In 2006 begon ze met het onderzoek naar de effectiviteit van corticosteroïd injecties bij trochantair syndroom.

Als freelance huisarts werkte ze vanaf haar verhuizing naar Rotterdam op verschillende locaties. Sinds 2005 werkt zij op vaste dagen in de huisartsenpraktijk van Bart van Leenen te Rotterdam.

Zij is getrouwd met Hans de Groot en heeft twee dochters: Pauline en Jasmijn.

PHD PORTFOLIO

Name PhD student:	Tineke (Aaltien) Brinks
Erasmus MC department:	General Practice
PhD period:	2006-2011
Promotors:	Prof.dr. S.M.A. Bierma-Zeinstra
	Prof.dr. B.W. Koes

PhD training

EpidM, afd. epidemiologie & biostatistiek, VU Medisch Centrum, Amsterdam:

Epidemiologisch onderzoek: opzet en interpretatie, 2007	40 hours
Inleiding in SPSS	16 hours
Principes van epidemiologische data-analyse: data-analyse, 2007	48 hours
Lineaire regressie en variantie-analyse, 2008	50 hours
Logistische regressie en analyse van overlevingsduren, 2008	50 hours
Systematische reviews en meta-analyse, 2010	24 hours

Professional Education

Basistraining didactiek voor docenten in de preklinische fase van de opleiding Erasmusarts, 2009	40 hours

Conferences/Presentations

Annual European Congress of Rheumatology 2009 poster presentation	10 hours
NHG Wetenschapsdag, two poster presentations and oral presentation, Utrecht, 2009	40 hours
NHG congress, poster presentation, Groningen, 2010	10 hours
PRImary Care MUSculoskeletal Research Congress, oral presentation, Rotterdam, 2010	20 hours

Teaching medical students: 2006-2011

Clinical Decision Making & Vocational training	600 hours
Supervising interns	600 hours