Treatment outcomes of a Numeric Rating Scale (NRS)-guided pharmacological pain management strategy in symptomatic knee and hip osteoarthritis in daily clinical practice

G.F. Snijders[1], C.H.M. van den Ende[1], B.J.F. van den Bemt[2], P.L.C.M. van Riel[3], F.H.J. van den Hoogen[1], A.A. den Broeder[1], on behalf of the NOAC study group.

[1]Department of Rheumatology, and [2]Department of Pharmacy, Sint Maartenskliniek, Nijmegen; [3]Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.

Abstract

Objectives

To describe the results of a Numeric Rating Scale (NRS)-guided pharmacological pain management strategy in symptomatic knee and hip osteoarthritis (OA) in daily clinical practice.

Methods

In this observational cohort study, standardised conservative treatment was offered to patients with symptomatic knee and/or hip OA referred to secondary care. Pain management was guided by a NRS for pain, aiming for NRS ≤4. The first step in pharmacological treatment was paracetamol (acetaminophen) in case of no recent use in adequate dose. In case of treatment failure, patients switched to a non-steroidal anti-inflammatory drug (NSAID) and eventually to a second NSAID, each after a 4-week trial period. Predictors for response to treatment were identified. Moreover, reasons for protocol violations were collected.

Results

Three-hundred and forty-seven patients were included. The proportion of patients that reached a response after paracetamol, first and second NSAID was 25% (59/234), 16% (31/190) and 11% (10/87), respectively. Non-adherence to protocol occurred in 46% of cases when switch of analgesic was advised, mainly due to unwillingness of patients to change the analgesic. Identified predictors for response to analgesics included higher age, lower patient global assessment, less stiffness and more radiographic severity.

Conclusions

Adequate use of paracetamol and switching to a NSAID after failing paracetamol resulted in moderate treatment response percentages, whereas the result of a second NSAID was disappointing in patients with advanced knee and hip OA. Predictors for response included patient and disease related factors. A substantial part of patients with NRS >4 were unwilling to change their analgesics.

Key words

knee osteoarthritis, hip osteoarthritis, analgesia, non-steroidal anti-inflammatory drugs, paracetamol

Gijs F. Snijders, MD, PhD
Cornelia H.M. van den Ende, PhD
Bart J.F. van den Bemt, PharmD, PhD
Piet L.C.M. van Riel, MD, PhD
Frank H.J. van den Hoogen, MD, PhD
Alfons A. den Broeder, MD, PhD

Please address correspondence and reprint requests to:
Gijs F. Snijders, MD, PhD,
Department of Rheumatology,
Sint Maartenskliniek,
6500 GM Nijmegen, The Netherlands.
E-mail: gijssnijders@gmail.com

Received on April 8, 2011; accepted in revised form on September 6, 2011.

Competing interests: none declared.

Introduction

As there is no known cure for OA, recommendations in guidelines for knee and hip osteoarthritis (OA) consist of combinations of non-pharmacological – *e.g.* education, physical therapy and weight reduction – and pharmacological interventions to control symptoms (1-4). Pharmacological interventions include treatment with analgesics, principally using paracetamol (acetaminophen), non-steroidal anti-inflammatory drugs (NSAIDs) and (partial) opioids. In guidelines, paracetamol is generally recommended as analgesic of first choice in the treatment of pain and disability related to knee or hip OA, as NSAIDs are associated with more side effects like gastrointestinal and cardiovascular complications (5, 6).

The efficacy of paracetamol and NSAIDs in knee and hip OA has been demonstrated in several randomised controlled trials (RCTs) (7, 8). However, little is known about the optimal pain management strategy in clinical practice. More specifically, the clinically important questions regarding whether treatment policies as prescription of an NSAID after failure of paracetamol and switching to another NSAID after an insufficient response to the first NSAID are warranted, have never been the subject of research.

In our centre, on the basis of the aforementioned guidelines and the recently developed treatment strategy on OA in The Netherlands (9), a 12-week standardised treatment protocol was developed consisting of a Numeric Rating Scale (NRS)-guided pain management strategy (paracetamol, NSAIDs and eventually tramadol) in addition to education, advice about weight loss and lifestyle measures, and referral to a physical therapist. The protocol was implemented at a specialised outpatient clinic for conservative treatment of knee and hip OA (10).

The aims of this exploratory study were 1) to describe the results of a NRS-guided pain management strategy in symptomatic knee and hip osteoarthritis (OA) in daily clinical practice, and 2) to identify predictors for response in daily clinical practice in symptmatic secondary care knee and/or hip OA.

Patients and methods

Patients

All patients referred to the Rheumatology specialised outpatient clinic ('knie/heup artrose poli', knee/hip OA clinic) of Sint Maartenskliniek, with knee and/or hip OA fulfilling the clinical American College of Rheumatology (ACR) criteria (11, 12), were included in this observational cohort study. For knee OA, the following criteria were used: knee pain (>15 days of last month) plus at least three among age (>50 years), morning stiffness (<30 minutes), crepitus, bony tenderness, bony enlargement or no palpable warmth. For hip OA, the following criteria were used: hip pain (>15 days of last month) plus internal rotation hip <15° and erythrocyte sedimentation rate (ESR) ≤45 mm/hr, or hip pain (>15 days of last month) plus internal rotation hip ≥15° and painful internal rotation hip and morning stiffness (≤60 minutes) and age (>50 years).

The exclusion criteria were: pain in the knee or hip on a numeric rating scale (NRS, 0–10) of ≤4, inflammatory rheumatic diseases or deposition diseases possibly leading to inflammatory arthritis or secondary OA, co-morbidity exceeding the complaints of limitations of knee or hip OA, cognitive or sensomotor problems interfering with the use of questionnaires and planned orthopaedic procedures within the following 12 weeks. Calcium pyrophosphate deposition disease (CPPD) – excluding the phenotypes pseudogout and polyarthritis – and previous meniscus problems were allowed.

All patients were asked to participate in the CONTROL-PRO study (10), an observational cohort study tightly integrated with the specialised outpatient clinic.

Specialised knee/hip OA outpatient clinic treatment protocol

All patients, treated at the specialised knee/hip OA outpatient clinic, received standardised evidence-based tailored conservative treatment in a stepped-care format as usual care for 12 weeks. This stepped-care model is based on an online published Dutch multidisciplinary guideline for diagnosis and

treatment of knee and hip OA and has been proposed by a consensus panel of leading experts in the field of OA in The Netherlands (9).

The goal of treatment was to reduce the level of pain on a NRS to ≤4. Visits were planned at week 0 and 12 at the outpatient clinic and at week 4 and 8 by telephone, and were managed by a research physician (GS), a physician assistant or a nurse practitioner. When NRS pain remained higher than 4 and patients had taken the prescribed medication for at least two weeks adequately, the next step of the stepped-care model was offered (see below).

The first step of the treatment protocol consisted of education, life style advice concerning physical activity, weight loss advice in patients with a body mass index (BMI) of ≥28 (goal: 5% weight loss in 12 weeks), referral for first-line physical therapy – *i.e.* prescription for both aerobic and strengthening exercises according to the graded activity principle – and treatment with paracetamol in a fixed dose of thrice a day 1000 mg, in case of no recent use in adequate dose (2–4 times 1000mg/day during at least 14 consecutive days) for knee and/or hip complaints (in case of recent use of paracetamol, treatment with a NSAID was initiated in the first step). In the second step, if necessary and not earlier than after 4 weeks, a NSAID (NSAID 1) was advised. The choice for a specific drug was based on previous exposure to specific NSAIDs. The preferential agent was naproxen, 500 mg twice a day. During the observation period, two different polices were applied: before August 2009, paracetamol was continued when NSAID of first choice was initiated (n=44), whereas after August 2009, paracetamol was discontinued if the first NSAID was prescribed (n=33). The third step consisted of the replacement of naproxen with 15 mg of meloxicam once a day, or with 600 mg of ibuprofen thrice a day (second choice NSAID). The fourth step included the replacement of the NSAID with tramadol (50 mg thrice a day).

In this study, the proportion of patients responding to paracetamol, and NSAID 1 and 2 (NRS ≤4) were examined.

Baseline data and data on previous treatments

Baseline data were collected on demographic and disease-related characteristics using a standardised interview and physical examination. Data on previously used treatment modalities concerning knee and/or hip OA were obtained using a standardised interview consisting of a checklist with all common prescribed analgesics (only analgesics used for at least 14 consecutive days were counted; no exact dosages were required), intra-articular injections, supplements (*i.e.* glucosamine and chondroitin) and physical therapy (minimum attendance to two sessions was required). In addition, every referred patient was asked to bring a list from the pharmacist or general practitioner with previously prescribed medication to the first visit at the outpatient clinic.

Radiographs

Bilateral (posterior-anterior fixed flexion and lateral) knee and pelvic radiographs were performed in all participants. Scoring of radiographs was done using Kellgren-Lawrence Grading Scale (K&L-score) (13) by an experienced rheumatologist and a research physician (GS).

Numeric Rating Scale (NRS) and questionnaires

NRS on pain (0–10) was assessed every visit. At baseline, patients were asked to fill out the Knee/Hip injury and Osteoarthritis Outcome Score (KOOS/HOOS) (Likert-scale version) questionnaire (14, 15). These questionnaires include the Western Ontario McMaster Universities (WOMAC) (16) score index in its complete and original format (with permission, http://www.koos.nu). WOMAC pain, stiffness and function subscales were calculated at baseline and after 12 weeks, and presented as normalised scores (0 to 100, where 0 equals no symptoms). To assess quality of life, the Short Form-36 (SF-36) (17) questionnaire was completed by all participants. The SF-36 consists of eight subscales with a score range of 0 to 100, where 100 represents the best possible health situation. The physical (PCS) and mental component summary (MCS) scores were calculated as weighted means of the four physical and four mental subscale scores, respectively (higher scores indicate better health situation).

Outcome

The outcome of this study was the proportion responders (*i.e.* percentages patients reaching a NRS ≤4 after each step from the abovementioned treatment protocol), after a four-week use of paracetamol, after a four-week use of NSAID of first choice after failing paracetamol, and after four weeks a NSAID 2 after failing both paracetamol and the NSAID of first choice. Independent predictors for response to treatment were identified. Furthermore, reasons for non-compliance to the study protocol were collected.

Statistics

Statistical analyses were performed using STATA/IC 10.1 for Windows. Descriptive statistics were provided by using mean (SD), median or frequencies/percentages depending on the distribution of data. The response percentage to the first prescribed NSAID was calculated using data of patients with and without previous use of paracetamol. Around the proportion of responders 95%-confidence intervals (95%-CI's) were calculated. An exploratory sample size calculation was made as follows: to be able to estimate a response proportion with a 95%-CI of ≤0.1, an alpha of <0.05 and a power of 0.8, 80 patients were necessary per group.

To predict a treatment response (NRS ≤4 after paracetamol or first NSAID), a prediction model was built. Predefined candidate (baseline) predictive variables were: WOMAC subscales, NRS PGA, age, gender, BMI, K&L-score, index joint (knee or hip), number of previously used NSAIDs, previous use of paracetamol, paracetamol continued when NSAID was initiated (paracetamol add-on, solely to predict response to NSAID), duration of knee/hip complaints, and MCS. These variables were first bivariately tested and, if an association with treatment response was found (p-value of removal >0.20), they entered a multivariate logistic re-

gression analysis. Using backward selection (based on *p*-values), the final model was built. For the (possible) predictors, odds ratios (OR's) with 95%-CI were calculated.

In individuals with incomplete data on possible predictors (*i.e.* WOMAC pain: n=23, WOMAC stiffness: n=81, WOMAC physical function: n=28, BMI: n=25, duration of knee/hip complaints n=30, NRS PGA: n=6, and MCS: n=39), single imputation was performed using regression modelling to replace missing values. Individuals with missing data on response status – *i.e.* missing values on NRS pain (n=32 after initiation of NSAID 1; n=12 after initiation of NSAID 2) – were classified as non-responders.

Ethical considerations

The standardised treatment protocol was performed as routine clinical care in Sint Maartenskliniek. The local Medical Research Ethics Committee (MREC), region Arnhem-Nijmegen (The Netherlands), approved the study design of CONTROL-PRO (local study number 2009/095).

Results

Between July 2007 and October 2010, 559 patients were treated at the specialised knee/hip OA outpatient clinic. A total of 347 patients fulfilled inclusion and exclusion criteria (Fig. 1). The reason for insufficient data was the loss of follow-up (n=12). Sixty patients were not treated in accordance to the protocol: intra-articular injections (n=12), tramadol (n=23), and NSAID combined with paracetamol (n=25), respectively. In 30 patients no pharmacological therapy was started at study start. Those patients were not included in the statistical analyses. Three-hundred seven out of 347 (88%) patients were referred to the specialised outpatient clinic by an orthopaedic surgeon, whereas the remaining 19 (5%) and 21 (6%) patients were referred by a rheumatologist and a general practitioner, respectively. Baseline characteristics are depicted in Table I. A total of 234 (67%) patients was treated with paracetamol in the first step. A NSAID was the pharmacologic treatment in the first step of 113 (33%) patients (Fig. 1).

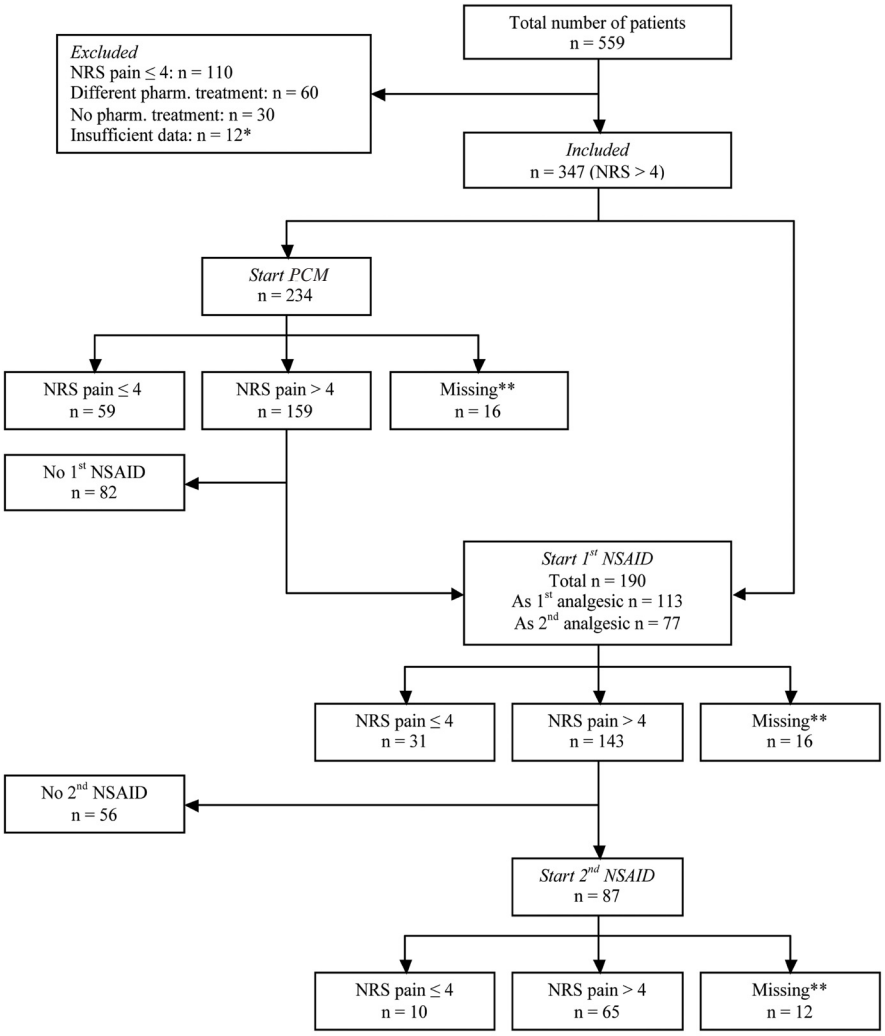

Fig. 1. Study flowchart.
*Insufficient data: no available NRS pain at baseline or <1 follow-up visit. **Missing value on NRS pain. NRS: numeric rating scale; NSAID: non-steroidal anti-inflammatory drug; PCM: paracetamol; pharm: pharmacologic.

Outcome

Fifty-nine of the 234 patients (25%, 95%-CI 19–31) reached a NRS ≤4 after a four-week treatment with paracetamol. A total of 190 individuals was treated with NSAID 1 – *i.e.* 77 after failing paracetamol and 113 after insufficient perceived effect from recent use of paracetamol prior to this study – which resulted in a response rate of 31/190 (16%, 95%-CI 10–22) patients responding. Eighty-seven patients were treated with a second NSAID, which resulted in 10/87 cases (11%, 95%-CI 4–18) in a NRS ≤4.

The following variables were bivariately associated with a response to paracetamol: higher age, better NRS PGA, lower WOMAC pain, lower WOMAC stiffness, lower WOMAC physical function, higher K&L-score, no past use of paracetamol, and low number of previously used NSAIDs (Table II). Higher age, lower NRS PGA, lower WOMAC stiffness and higher K&L-score were independently associated with a higher chance of response to paracetamol (Table IV). Lower NRS PGA, and lower WOMAC pain, stiffness and physical function were bivariately associated with a higher change for a treatment response to NSAID 1. Continuation of paracetamol when the first NSAID was initiated was not associated with a response to NSAID 1 (Table III). Only lower NRS PGA was identified as independent predictor for a response to NSAID of first choice (Table IV). The index joint (knee or hip) was not associated with response to paracetamol or NSAIDs.

Table I. Baseline characteristics of patients (n= 347).

Variable	
Women, n (%)	231 (67)
Age (years), mean (SD)	55 (10)
BMI, mean (SD)	29 (5)
Knee OA, n (%)	286 (82)
Duration of knee/hip complaints (years), median (*p*-value 25–75)	4 (2–10)
K&L-score ≥2, n (%)	226 (65)
NRS pain (0–10), mean (SD)	7 (1)
NRS patient global assessment (0–10), mean (SD)	7 (2)
WOMAC pain (0–100), mean (SD)	55 (18)
WOMAC stiffness (0–100), mean (SD)	60 (21)
WOMAC function (0–100), mean (SD)	56 (18)
MCS (possible range 2–74)*	50 (11)
PCS (possible range 4–71)*	33 (7)
Past treatment, n (%)	
Analgesics	
none	58 (17)
paracetamol (acetaminophen)	214 (62)
paracetamol in adequate dose[1]	71 (20)
one or more NSAID	249 (72)
opioids[2]	54 (16)
Supplements[3]	130 (37)
Physical therapy	223 (64)
Past surgical treatments for knee OA, n (%)	
one or more arthroscopies[4]	165 (58)
open procedures[5]	39 (14)
Past surgical treatments for hip OA, n (%)	
one or more arthroscopies	0
open procedures	7 (11)

*Norm-based scores, higher scores indicate better health, individual scores in the 45–55 range indicate average health; [1]Adequate dose: 2–4 times 1000 mg/day during at least 14 consecutive days; [2]Including tramadol; [3]Glucosamine and chondroitin; [4]Including partial meniscectomy; [5]Including joint prosthesis; BMI: body mass index; OA: osteoarthritis; K&L-score: Kellgren-Lawrence Grading Scale; NRS: Numeric Rating Scale; NSAID: non-steroidal anti-inflammatory drug; MCS: Mental Component Score; PCS: Physical Component Score of Short Form-36; WOMAC: Western Ontario McMaster Universities Osteoarthritis Index.

Table II. Results of univariate logistic regression analysis of possible predictors (at baseline) for treatment response to paracetamol (n= 234).

Variable	OR	95% CI
Gender (male)	1.10	0.61–2.01
Age	1.04	1.01–1.07
Index joint (knee)	1.87	0.91–3.82
NRS PGA	0.80	0.67–0.95
WOMAC pain	0.98	0.96–1.00
WOMAC stiffness	0.98	0.97–1.00
WOMAC physical function	0.98	0.96–0.99
BMI	0.98	0.93–1.00
Duration of complaints, in years	0.99	0.93–1.04
K&L-score	1.47	1.13–1.91
Previous use of paracetamol (yes)	0.51	0.28–0.94
Number of previously used NSAIDs	0.74	0.56–0.97
MCS	0.99	0.96–1.01

OR: odds ratio; CI: confidence interval; NRS: Numeric Rating Scale; PGA: patient global assessment; WOMAC: Western Ontario McMaster Universities Score; BMI: body mass index; K&L-score: Kellgren-Lawrence Grading Scale; NSAIDs: non-steroidal anti-inflammatory drugs; MCS: Mental Component Score of Short Form-36.

Table III. Results of univariate logistic regression analysis of possible predictors (at baseline) for treatment response to NSAID 1 (n= 190).

Variable	OR	95% CI
Gender (male)	0.92	0.39–2.14
Age	1.02	0.96–1.06
Index joint (knee)	0.90	0.32–2.55
NRS PGA	0.71	0.56–0.89
WOMAC pain	0.97	0.95–0.99
WOMAC stiffness	0.98	0.96–1.00
WOMAC physical function	0.97	0.95–1.00
BMI	1.04	0.97–1.11
Duration of complaints, in years	1.03	0.99–1.06
K&L-score	1.39	0.98–1.97
Previous use of paracetamol (yes)	1.34	0.37–4.83
Paracetamol add on* (yes)	1.45	0.61–3.43
Number of previously used NSAIDs	0.75	0.57–1.00
MCS	1.03	0.99–1.07

*In the first 44 patients with no response to paracetamol, as the first step of the protocol, paracetamol was continued when first NSAID 1 was started at the second step.
OR:odds ratio; CI: confidence interval; NRS: Numeric Rating Scale; PGA: patient global assessment; WOMAC: Western Ontario McMaster Universities Score; BMI: body mass index; K&L-score: Kellgren-Lawrence Grading Scale; NSAIDs: non-steroidal anti-inflammatory drugs; MCS: Mental Component Score of Short Form-36.

Protocol violations

A total of 138 out of 302 (46%) patients did not start with a (new) NSAID after failing paracetamol or the first NSAID – *i.e.* persistent NRS >4 – (Fig. 1). Reasons for these protocol-violations were: acceptable pain-level despite NRS >4 (12%), and unwillingness to take a NSAID (39%). In 39 out of 138 cases (28%), no reason for the protocol-violation was documented, possibly reflecting inadequately offering the next step of the protocol by the caregiver. Other reasons for no switch to a (new) NSAID were: contra-indication (10/138, 7%) and start of different pharmacological treatment (19/138, 14%).

Discussion

This is the first study analysing a NRS-guided pain management strategy in daily knee and hip OA care. Our study shows that NRS-tailored use of paracetamol results in a response percentage of 25%, and that treatment with a NSAID after failing paracetamol leads to a treatment response of 16% in secondary care knee and hip OA patients. Treatment with a second NSAID after failing paracetamol and the first NSAID resulted only occasionally in a treatment response – *i.e.* 11%. We therefore conclude that the prescription of paracetamol and the prescription of a NSAID after insufficient results with paracetamol are of value in knee or hip OA patients referred to secondary care, even after considering joint replacement. Some predictors for response to paracetamol and a NSAID were identified – including patient – and disease-related

Table IV. Prediction models with independently predictors for response to paracetamol (n=234) and first NSAID (n=190).

Variable	OR	95% CI
Response to paracetamol		
Age	1.03	1.00–1.07
NRS PGA	0.80	0.66–0.97
WOMAC stiffness	0.98	0.96–0.99
K&L-score	1.43	1.07–1.92
R^2=0.11; AUC 0.74		
Response to first NSAID		
NRS PGA	0.71	0.56–0.89
R^2=0.05; AUC 0.66		

OR: odds ratio; CI: confidence interval; NRS: Numeric Rating Scale; PGA: patient global assessment; WOMAC: Western Ontario McMaster Universities Score; K&L-score: Kellgren-Lawrence Grading Scale; AUC: area under the curve; NSAIDs: non-steroidal anti-inflammatory drugs.

factors – however, no strong predictors were found.

The percentage protocol violations – *i.e.* no switch of analgesic or switch to another agent when appropriate, according to the protocol – was 46%. This proportion is comparable with data from a *post-hoc* analysis in a RCT in rheumatoid arthritis, in which rheumatologists were advised about the right methotrexate dose before each visit, but were allowed to deviate from the protocol (18). In the majority of the protocol violations in our study, no medication switch – although appropriate according to the protocol – was performed, because patients perceived their pain level as acceptable and/or were unwilling to try a (new) NSAID. Possibly, these results reflect fear for adverse events of NSAIDs and the individual variation in the patient acceptable symptom state (PASS). The mean PASS for pain lies below 4 (32 mm [95%-CI 30–35] for knee OA and 35 mm [95%-CI 33–37] for hip OA on a 100 mm visual analogue scale), but our study indicates that a considerable proportion of patients report PASS beyond 4 (19).

The internal validity of our study seems adequate, illustrated by ample precision. However, the uncontrolled design should urge to caution regarding conclusions to be drawn about the effect of the interventions. Improvement of symptoms could also, at least partly, be explained by regression to the mean (natural history) or expectation bias (placebo effect). However, spontaneous regression of complaints seems to be an unlikely explanation, because the waiting time for our outpatient clinic was approximately two to three months before inclusion. Also, the response percentages found in this study seem comparable to the differences between the intervention and placebo arm in analgesic trials (20), and improvement was rarely seen after the second NSAID. Therefore, we conclude that the occurrence of type I errors is unlikely.

The response percentages with paracetamol could be inflated by effects of the other treatment modalities offered during the baseline visit. However, the effects of physical therapy are not to be expected within the first 4 weeks, as there was usually a waiting list of a few weeks before attendance.

Adherence to prescribed medication is known to be a potent effect modifier in clinical practice. Since adherence to prescribed treatment was not routinely measured in this study, non-adherence to prescribed treatment modalities could have resulted in lower response percentages. Nevertheless, this pragmatic study was intended to estimate and compare the results of paracetamol and NSAIDs in addition to non-pharmacologic interventions in daily clinical practice, thus including the effects of non-adherence.

Generalisability of the results of our study seems limited to symptomatic knee and hip OA patients in secondary care. In this light, our cohort is comparable with other cohorts, consisting mainly of obese women with knee OA (21, 22). Level of pain and BMI, however, are higher and patients were younger, possibly reflecting some selection as the vast majority of patients was referred by orthopaedic surgeons, mostly because of the absence of an indication for joint replacement surgery. Also, relatively high rates of surgical procedures in the past (in the knee OA group) exist in current study.

Predicting a treatment response to pharmacologic interventions with pretreatment variables could be valuable, as it could result in prevention of unnecessary exposure to potentially toxic agents. However, we were unable to identify strong independent predictors for response to paracetamol or NSAIDs. Higher K&L-scores as predictor for response to paracetamol has never been reported before, although it is an additional argument to try paracetamol before considering joint replacement even in advanced knee and hip OA. In a recently published study on predictors of response to cyclo-oxygenase-2 (COX-2) inhibitors, the only consistent predictor for an OMERACT-OARSI response was WOMAC physical function (23). Other studies report various but not consistent predictors for treatment response to NSAIDs (24, 25). Possibly, the response to pharmacologic agents is determined by other non-measured variables.

Future research should be focussed on the improvement of the pharmacological treatment strategy of symptomatic knee and hip OA – *e.g.* the place of (partial) opioids, paracetamol combined with a NSAID, and intra-articular injections combined with analgesics. Furthermore, pain management strategies could possibly be improved by shortening the trial period of a pharmacological agent, as the response after a two-week treatment has been identified as a strong predictor of OMERACT-OARSI response at 12-week treatment in several studies (26, 27). Also, a single-subject trial could be used to discover the best treatment for an individual person, in which patients are exposed to different analgesics during short trial periods (28). Finally, the development of novel classes symptom reducing agents should be encouraged, although the precaution of side effects is warranted (29).

Conclusions

In conclusion, the protocolised prescription of paracetamol and a NSAID after failing paracetamol resulted in moderate treatment response percentages, whereas the results of switching between NSAIDs were disappointing in secondary care knee and hip OA patients in daily clinical practice. Response to paracetamol or a NSAID could not be predicted. We therefore conclude that the prescription of paracetamol and the prescription of a NSAID after insufficient results with paracetamol are appropriate in patients with severe knee or hip OA, even after prior consideration for joint replacement. Reasons for non-compliance to initiation of analgesics should be further investigated.

Acknowledgements

We thank Dr D.J.R.A.M. de Rooij, MD, PhD, for radiograph scoring; M.A. Arts-Sanders for data collection and database building; V.H.H.P. Straten for data collection; the orthopaedic surgeons for referring patients; F.W. Snijders, MSc, and N.W.D. Eikelenboom, MSc, for data-entry and management; and Dr M.E.A. de Jager, MD, PhD, for figure preparation.

References

1. JORDAN KM, ARDEN NK, DOHERTY M *et al*.: EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis* 2003; 62: 1145-55.
2. ZHANG W, DOHERTY M, ARDEN N *et al*.: EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2005; 64: 669-81.
3. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. *Arthritis Rheum* 2000; 43: 1905-15.
4. ZHANG W, MOSKOWITZ RW, NUKI G *et al*.: OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage* 2008; 16: 137-62.
5. HERNANDEZ-DIAZ S, RODRIGUEZ LA: Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiologic studies published in the 1990s. *Arch Intern Med* 2000; 160: 2093-9.
6. MCGETTIGAN P, HENRY D: Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA* 2006; 296: 1633-44.
7. BJORDAL JM, LJUNGGREN AE, KLOVNING A, SLORDAL L: Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials. *BMJ* 2004; 329: 1317.
8. TOWHEED TE, MAXWELL L, JUDD MG, CATTON M, HOCHBERG MC, WELLS G: Acetaminophen for osteoarthritis. *Cochrane Database Syst Rev* 2006; (1): CD004257.
9. VAN DEN ENDE CM, BIERMA-ZEINSTRA SM, VLIET VLIELAND TP, SWIERSTRA BA, VOORN TB, DEKKER J: [Conservative treatment of hip and knee osteoarthritis: a systematic, step-by-step treatment strategy]. *Ned Tijdschr Geneeskd* 2010; 154: A1574.
10. SNIJDERS GF, DEN BROEDER AA, VAN RIEL PL *et al*.: Evidence-based tailored conservative treatment of knee and hip osteoarthritis: between knowing and doing. *Scand J Rheumatol* 2011; 40: 225-31.
11. ALTMAN R, ALARCON G, APPELROUTH D *et al*.: The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. *Arthritis Rheum* 1991; 34: 505-14.
12. ALTMAN R, ASCH E, BLOCH D *et al*.: Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum* 1986; 29: 1039-49.
13. KELLGREN JH, LAWRENCE JS: Radiological assessment of osteo-arthrosis. *Ann Rheum Dis* 1957; 16: 494-502.
14. DE GROOT, I, FAVEJEE MM, REIJMAN M, VERHAAR JA, TERWEE CB: The Dutch version of the Knee Injury and Osteoarthritis Outcome Score: a validation study. *Health Qual Life Outcomes* 2008; 6: 16.
15. DE GROOT, I, REIJMAN M, TERWEE CB *et al*.: Validation of the Dutch version of the Hip disability and Osteoarthritis Outcome Score. *Osteoarthritis Cartilage* 2007; 15: 104-9.
16. BELLAMY N, BUCHANAN WW, GOLDSMITH CH, CAMPBELL J, STITT LW: Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol* 1988; 15: 1833-40.
17. WARE JE, JR., SHERBOURNE CD: The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; 30: 473-83.
18. FRANSEN J, LAAN RF, VAN DER LAAR MA, HUIZINGA TW, VAN RIEL PL: Influence of guideline adherence on outcome in a randomised controlled trial on the efficacy of methotrexate with folate supplementation in rheumatoid arthritis. *Ann Rheum Dis* 2004; 63: 1222-6.
19. TUBACH F, RAVAUD P, BARON G *et al*.: Evaluation of clinically relevant states in patient reported outcomes in knee and hip osteoarthritis: the patient acceptable symptom state. *Ann Rheum Dis* 2005; 64: 34-7.
20. CLEGG DO, REDA DJ, HARRIS CL *et al*.: Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N Engl J Med* 2006; 354: 795-808.
21. WESSELING J, DEKKER J, VAN DEN BERG WB *et al*.: CHECK (Cohort Hip and Cohort Knee): similarities and differences with the Osteoarthritis Initiative. *Ann Rheum Dis* 2009; 68: 1413-9.
22. VAN DIJK GM, VEENHOF C, SPREEUWENBERG P *et al*.: Prognosis of limitations in activities in osteoarthritis of the hip or knee: a 3-year cohort study. *Arch Phys Med Rehabil* 2010; 91: 58-66.
23. BINGHAM CO 3RD, SMUGAR SS, WANG H, PELOSO PM, GAMMAITONI A: Predictors of response to cyclo-oxygenase-2 inhibitors in osteoarthritis: pooled results from two identical trials comparing etoricoxib, celecoxib, and placebo. *Pain Med* 2011; 12: 352-61.
24. DETORA LM, KRUPA D, BOLOGNESE J, SPERLING RS, EHRICH EW: Rofecoxib shows consistent efficacy in osteoarthritis clinical trials, regardless of specific patient demographic and disease factors. *J Rheumatol* 2001; 28: 2494-503.
25. WALKER JS, SHEATHER-REID RB, CARMODY JJ, VIAL JH, DAY RO: Nonsteroidal anti-inflammatory drugs in rheumatoid arthritis and osteoarthritis: support for the concept of "responders" and "nonresponders". *Arthritis Rheum* 1997; 40: 1944-54.
26. BINGHAM III CO SMUGAR SS, WANG H, TERSHAKOVEC AM: Early response to COX-2 inhibitors as a predictor of overall response in osteoarthritis: pooled results from two identical trials comparing etoricoxib, celecoxib and placebo. *Rheumatology* (Oxford) 2009; 48: 1122-7.
27. BATTISTI WP, KATZ NP, WEAVER AL *et al*.: Pain management in osteoarthritis: a focus on onset of efficacy – a comparison of rofecoxib, celecoxib, acetaminophen, and nabumetone across four clinical trials. *J Pain* 2004; 5: 511-20.
28. WEGMAN AC, VAN DER WINDT DA, DE HAAN M, DEVILLE WL, FO CT, DE VRIES TP: Switching from NSAIDs to paracetamol: a series of n of 1 trials for individual patients with osteoarthritis. *Ann Rheum Dis* 2003; 62: 1156-61.
29. LANE NE, SCHNITZER TJ, BIRBARA CA *et al*.: Tanezumab for the treatment of pain from osteoarthritis of the knee. *N Engl J Med* 2010; 363: 1521-31.