Efficacy of stepped care treatment for chronic discogenic low back pain patients with Modic I and II changes☆

Heidi Mylenbusch [*], Michiel Schepers, Elmar Kleinjan, Marije Pol, Henk Tempelman, Hanneke Klopper-Kes

Stichting Rugpoli Twente, Veluwe, Brabant, Randstad – Multidisciplinary Center for Spine and Musculoskeletal Disorders, the Netherlands

ABSTRACT

Objective: This study investigated whether patients with Modic changes (MC) of types I, I/II, and II would respond to an anti-inflammatory-based, stepped care treatment with three treatment steps: first, oral administration of NSAIDs, 2×200 mg celecoxib daily for two weeks; second, an intradiscal steroid injection (ID) with dexamethasone and cefazolin; and third, oral treatment with antibiotics (AB), 3×1 g amoxicillin daily for 100 days.
Design: This was an observational clinical study based on analyses of categorical data of patient-reported outcome measurements.
Subjects: Subjects were consecutive patients with chronic low back pain (CLBP), diagnosed by assessment of anamnestic signs of inflammation; a pain score ≥ 6 on the Numeric Pain Rating Scale (NPRS); a mechanical assessment; MC I, I/II, or II based on MRI; and lack of response to conservative treatment.
Methods: From January 1, 2015, to December 31, 2021, 833 eligible patients were selected for the stepped care treatment. A total of 332 patients completed requested follow-up questionnaires at baseline and 12 months (optional at 3 and 6 months). Primary outcomes were pain (at least 50 % pain relief) and/or a minimum of 40 % improvement in functionality as measured by the Roland Morris Disability Questionnaire (RMDQ) or the Oswestry Disability Questionnaire (ODI). Secondary outcome measures were use of pain medication and return to work.
Results: At 1 year of follow-up, 179 (53.6 %) of 332 patients reported improvement according to the responder criteria. Of the 138 patients that had received only NSAIDs, 88 (63.8 %) had improved. In addition, 50 (56.8 %) of the 183 patients that had received ID had improved, and 41 (38.7 %) of the 106 patients treated with AB had improved. None of the patients reported complications. 12.0 % of patients using AB stopped preterm due to undesirable side effects.
Conclusion: Treatment with a stepped care model for inflammatory pain produced clinically relevant, positive reported outcomes on pain and/or function. Our stepped care model appears to be a useful, safe, and cost-saving treatment option that is easily reproducible. Further studies, including randomized controlled trials and analyses of subgroups, may help to develop a more patient-tailored approach and further avoidance of less-effective treatments and costs.

1. Introduction

MC are pathological changes in the bones of the spine, situated in both the bodies and the endplates of the vertebrae. MC are characterized by MRI and were first described and defined by the radiologist Dr.

Michael Modic in 1988 [1]. MC of types I, II, and III are identified by MRI and can change over time [2–4]. MC type I produces a low signal on T1-weighted spin-echo images and a high signal on T2-weighted spin-echo images, representing active inflammatory endplate edema. MC type II appears with high signal on T1-weighted spin-echo images and high signal on T2-weighted spin-echo images, indicating fatty bone

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Abbreviations used

AB	antibiotics
CLBP	chronic low back pain
ID	intradiscal steroid injection
LBP	low back pain
MC	Modic changes
NPRS	Numeric Pain Rating Scale
ODI	Oswestry Disability Index
RMDQ	Roland Morris Disability Questionnaire

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marrow replacement. MC type III is the late stage of sclerosis, exhibiting irregular patterns, severe disc degeneration, and osteophytes, but is not thought to be associated with pain [5]. The prevalence of MC is approximately 6 % of Asian and Western populations [6,7]. MC are most often found in low back pain (LBP) populations (30–60 %) and are strongly associated with CLBP and radiating pain [1–20].

The medical history and MRI-based diagnosis of vertebrogenic pain have been recognized with an international classification (10th revision) by diagnostic code M54-51. Typical complaints of patients with MC are chronic daily and constant LBP, often described as a heavy weight on both sides in and near the spine; bilateral, morning pain and stiffness that improves with movement; [2] and occasional radiation to the legs. Pain becomes worse with exercise therapy [3], bodily actions, and sports [2]. MC complaints appear to be recalcitrant to exercise therapy [7,21] and worsen during both extension [22] and flexion movements [7]. Additional characteristics associated with MC include pain at night [22, 23], especially with turning; sleep disturbance; maximum pain in the morning; and stiffness lasting longer than 45 min [22].

Patients are often severely restricted in their daily activities, jobs, and even social interactions [24], and the severity of pain is correlated with the shape and height of the MC as assessed by MRI [10,15]. Conservative care is often not effective in reducing the complaints [23,25, 26].

The pathogenesis of MC involves mechanical stress and inflammation [12], an autoimmune response following a mechanical, degenerative injury [23,27,28], and/or response to possible low-grade infection or discitis from typical strains of bacteria [19,29–32]. Mechanical stress leads to disruption and fissuring of the endplate, with regions of degeneration and regeneration and vascular granulation tissue [17,29]. Modic signs often appear in regions with higher impact from mechanical forces, such as scoliosis [24,27] and spondylolisthesis [28,30].

Inflammation is expressed by the morphological substrate of bone edema.

Rannou et al. [22] have reported significantly higher levels of high-sensitivity C-reactive protein in the blood of patients with MC I. In patients with MC–II–classified discs, elevated levels of inflammation parameters such as tumor necrosis factor-alpha, interleukins, and others have been detected [33]. Ohtori et al. [34] have reported increased levels of protein gene product 9.5, immune-reactive nerve fibers, tumor necrosis factor-alpha, and immune-reactive cells in MC I discs compared to normal discs and higher levels in MC I compared to MC II discs. CLBP with MC is a plausible result of the presence of these inflammatory cytokines and nerve ingrowth into vertebral endplates [14,17,25,35].

The role of infection pathways has been demonstrated in many studies. Propionic bacterium acnes have been found in discs with MC as a substrate of a spontaneous low-grade infection [8,23,36–46]. The relationship between Propionic bacterium acnes and development of MC has further been confirmed by studies in rabbits [38,47].

In their recent review article regarding the efficacy of AB treatment, Manniche and Hall [32] state that newer microbiological studies using competently performed more sophisticated techniques to detect smaller numbers of bacteria and low-grade infection have produced compelling

evidence supporting the presence of Propionic bacterium acnes in discs with MC and as well as the effect of long-term oral AB treatment of MC patients. Other authors have found only moderate evidence for a relationship between the presence of bacteria in disc material, CLBP with disc herniation, and CLBP MC I [36,48] or have attributed the small number of positive findings to contamination [30,49].

The literature has demonstrated no consensus regarding treatment strategies and poor outcomes from conservative treatments for CLBP associated with MC [10,26,50]. Treatments that have been studied include opioids [51], zoledronic acid [52], rehabilitation programs [53], exercise therapy [25,39,54], and rest [24,29]. Beyond these conservative treatments, other more invasive treatments such as intradiscal methylene blue injections [55,56], intradiscal electrothermy (IDET) [57], intraosseous basivertebral nerve ablation [58,59], discectomy [60], and total disc replacements [61,62] have also been studied, with positive effects reported. Evidence for efficacy instrumented posterior lumbar fusion has been generally poor [58,63,64].

The literature has suggested that the efficacy rates of conservative and even certain invasive treatments are poor [14,22,23,65–67]. Given the lack of an effective gold-standard treatment as well as the possible belief that MC are associated with MRI findings of inflammation of the bone surrounding a degenerated disc, we have developed a stepped care model aimed at reducing discogenic CLBP by reducing inflammation with the least burdensome treatment for the patient.

1.1. Rationale for the stepped care model

NSAID medications are widely used to reduce pain and inflammation. Guidelines for the treatment of CLBP advise using oral NSAIDs. However, current guidelines do not distinguish different types of CLBP, such as those with MC and those without [51,65–69]. No RCTs or studies have clearly described the effect of medical treatment with NSAIDs as monotherapy for patients with CLBP with MC. Chen et al. [67] studied the effect of conservative treatment with NSAIDs combined with traditional Chinese medicine massage and some exercise therapy in three different groups of patients with CLBP (group 1 without MC, group 2 with MC I, and group 3 with MC II). Patients with MC I improved significantly compared to patients without MC and with MC II. This finding supports NSAID treatment of patients with MC. The pharmacological effect of NSAIDs is blockage of cyclooxygenase isoenzymes Cox-1 and Cox-2 to reduce the inflammatory cascade of arachidonic acid to prostaglandins. Prostaglandins are mediating inflammation as well as sensitizing peripheral nociceptors [67].

Studies of the treatment of discogenic CLBP with ID have reported various criteria for diagnosis or study inclusion as well as different techniques and corticoid preparations, followed by inconsistent results [49,70,71]. Studies with negative results have often failed to use MC as an inclusion criterion [72,73]. Studies of patients with MC using ID steroids have produced more positive results than those related to discogenic-pain-based or degenerative disc disease [74,75]. One RCT found intradiscal steroids to be effective for a subgroup of CLBP with MC, irrespective of MC I or II designation [74]. This observation has been confirmed by Carragee [75] and several other authors [4,14,76, 77]. Treatment with ID steroids is generally thought to demonstrate a low risk of serious complications [14,21,78].

In 2013, the first study from Albert et al. [24] showed that 162 patients with severe CLBP and typical MC I had been successfully treated with oral AB for 3 months. Success was defined as a statistically significant reduction of low back pain, functional impairment (RMDQ), leg pain level, and hours with pain during the previous 4 weeks. Two different doses of amoxicillin-clavulanic acid were compared, and the higher dose of 1 g three times per day produced superior results. No differences in positive treatment effects for patients with MC I, I/II, and II were found.

The study was repeated in Iraq with the same protocol and produced same results as those from Denmark [79]. Nearly identical reduction in

functional impairment and pain in the AB group with a follow-up period of 1 year was observed [78]. A Norwegian study [80] involving lower doses of amoxicillin found that MC I patients exhibited a statistical improvement in function (measured with RMDQ) whereas MC II patients did not. Positive effects of AB in the treatment of MC have been further confirmed in numerous other studies [32,74,81–85]. Other research groups have followed different protocols with varying (sometimes negative) results [41,45,72,86].

In general, the stepped care model presented here first employed NSAIDs as the simplest low-cost treatment with the least burden for patients. In cases of insufficient improvement, defined as a patient report of a persisting NPRS of 6 or higher, care progressed to invasive treatment with an ID, still aiming to treat the source of pain locally, safely, and with few side effects. Finally, and only in case of failure of all previous steps, oral AB therapy was provided, assuming that 100 days of high doses of AB would produce the highest impact on body homeostasis.

2. Methods

The study setting, Rugpoli, is a multidisciplinary center for spine and musculoskeletal disorders, with six locations spread throughout the Netherlands. Standard care treatments for discogenic pain are only partially covered by Dutch health insurance; ID and some other treatments are not reimbursed.

Between January 1, 2015, and December 31, 2021, 833 patients with discogenic CLBP and MC I, I/II, or II were selected for the stepped care treatment model after having failed to respond to conservative care at Rugpoli.

Standard care at Rugpoli includes physiotherapeutic McKenzie mechanical diagnostics as well as exercise therapy and musculoskeletal manipulation techniques, aimed at changing the loading patterns of the spine to reduce pain [87]. All patients received at least one epidural steroid injection prior to beginning the stepped care model. The purpose of the epidural injection was to reduce inflammation as close as possible to the disc with MC; administration was performed as a caudal or transforaminal epidural injection, according to SIS guidelines [78]. Evaluation of the effect of the conservative treatment occurred 3–4 weeks after the epidural injection (and sometimes later for patient-specific reasons).

Other sources of pain, such as facet joint pain or sacroiliac joint pain, were ruled out by history, physical examination, or diagnostic blocks [78].

The diagnosis of discogenic pain related to MC is based on three items: MRI findings (MC I, I/II, or II); typical history or complaints of continuous, inflammation-related pain; and mechanical examination by a McKenzie therapist, showing typical pain distribution and typical movement patterns. Patients were included if they exhibited three or more of the following symptoms for typical pain and movement patterns: 1) constant severe predominant LBP (longer than 3 months, NPRS 6 or more), 2) disturbed sleep (self-reported), 3) morning stiffness for more than 30–45 min, 4) "Federung" (springing test) at Modic level, 5) typical pain and stiffness produced by repeated flexion in the extension direction, and 6) typical pain and stiffness produced by repeated extension in the flexion direction. The exclusion criteria were age less than 18 years, pregnancy, allergy to contrast dye or cefazolin, NPRS of 5 or lower, MC III, predominant leg pain, systemic or local infection, and coagulopathy.

MRI of the lumbar spine was performed with a 0.4 T machine. Classification of the MRI findings was performed in accordance with the criteria defined by Modic et al. [5] and Fields [88].

Patients provided informed consent for treatment with the stepped care model related to interventions on the spine as well as follow-up information through self-reported questionnaires, to be used for further research regarding treatment outcomes. Effective education of patients and availability of a low-threshold service were considered very important; therefore, we developed written patient information explaining Modic disease, treatment steps, expected chances of improvement, and use of probiotics as well as providing the telephone number of a contact person.

2.1. The stepped care model

The stepped care model consists of three treatment steps.

Step 1: Anti-inflammation medication with oral NSAIDs: according to the common treatment of inflammation-related rheumatic diseases [67,86] and in the absence of contraindications, we began with the prescription of 200 mg celecoxib twice per day for 2 weeks. Evaluation of the effect occurred 1–2 weeks after finishing the NSAID medication, during the next consultation at the clinic.

Step 2: Patients with insufficient pain reduction (defined as a persisting NPRS of 6 or higher) or returning complaints after finishing the NSAID treatment (or contraindications for NSAIDs) received an ID as soon as possible after evaluation of the first step. The ID procedure was performed without sedation, according to SIS guidelines [78], with sterile technique and multiple fluoroscopic safety views, and using a 22- or 25-gauge needle. The correct intradiscal needle position was confirmed using a small amount (maximum of 0.5 cc) of Omnipaque, followed by the injection of a mixture of 10 mg dexamethasone (1 cc), 2 % xylocaine (0.5 cc), and 40 mg cefazolin (0.2 cc). Evaluation and follow-up were performed by phone by our research team after 3–4 weeks.

Step 3: In case of insufficient effect of the former steps or contraindications, patients could begin directly with 1 g oral amoxicillin three times per day for 100 days. In case of penicillin allergy, patients received 100 mg oral doxycycline twice per day for 100 days.

All data were collected during routine daily clinical practice. This observational study was exempt from Institutional Review Board (IRB) approval per institutional policy as only anonymized data was utilized in performing outcomes analysis. As such, identifiable subjects are not involved in this study and the study was conducted in keeping with established ethical considerations in the study of human subjects.

All data were obtained from patient-reported outcome measurements and were not collected specifically for this research. Outcomes were stratified by treatment type.

After enrollment and completion of the baseline questionnaire, all patients were assessed by an independent research team after 3, 6, and 12 months. Patients received follow-up questionnaires by mail (including up to two reminders) and were contacted by phone by the research team if step 3 with AB treatment was required. Phone follow-up was used to clinically assess side effects or complications related to long-term AB use.

The primary outcome was measured by a NPRS for pain and the RMDQ or ODI for functionality [89]. In the first year, only the RMDQ was used. Since August 1, 2019, the ODI has been used according to international agreements for comparability of research outcome measurements [90]. Secondary outcome measures were defined as oral analgesic use and return to work.

This observational study evaluated the results from our daily practice for a stepped care model concept with three possible treatment steps for patients with severe CLBP and MC.

2.2. Statistical analyses (SPSS)

The primary outcome measures of average NPRS, worst NPRS, and RMDQ/ODI were tested for normality using the Shapiro–Wilk test. Associated p-values ranged from 0.000 to 0.014; therefore, non-normal distribution of data was presumed. The primary outcomes of average NPRS, worst NPRS, and RMDQ/ODI were continuous data; therefore, a paired-samples t-test was used to compare measurements at baseline and

at 12 months of follow-up. A *p*-value of .05 was applied as a threshold for statistically significant differences. Descriptive statistics were performed for the secondary outcomes of employment status (consisting of variables "paid job" and "sick leave") and use of oral analgesic medications (consisting of variables "other drugs" and "opioids").

The above-mentioned statistical procedures were performed to gain a general sense of the data. We used all available data, dismissing the presence of missing data, the longitudinal nature of the data set, and the possibility of confounders and effect modifiers in the data set. Therefore, we also performed linear mixed models analyses on the continuous data present in the primary outcomes. Within the model, only a random intercept was included because of the longitudinal nature of the data set.

For categorical analyses, response was defined as a reduction of at least 50 % in baseline pain or improvement in function of at least 40 %, as measured by RMDQ and ODI.

3. Results

Of the 332 patients with follow-up data (see Fig. 1), 301 started with NSAID therapy while 31 patients exhibited contraindications and began directly at step 2 with ID therapy. Of the 301 patients that started on NSAID therapy, 88 (29.2 %) responded and did not receive additional steps. Of the 213 non-responders, 152 progressed to ID treatment, together with 31 patients who had not been treated with NSAIDs, forming a group of 183 patients receiving an ID, whereas 50 patients stopped treatment despite insufficient relief with NSAIDs and 11 patients progressed directly to AB therapy. A total of 183 patients received ID, of which 50 (27.3 %) were responders and 133 were non-responders. Of the 133 non-responders, 95 received AB therapy and 38 did not progress due to contraindications or concerns about AB therapy. The 95 patients, together with the 11 patients who did not receive ID, formed a group of 106 patients receiving AB therapy. Of the 106 patients with AB therapy, 41 (38.7 %) responded and 65 did not.
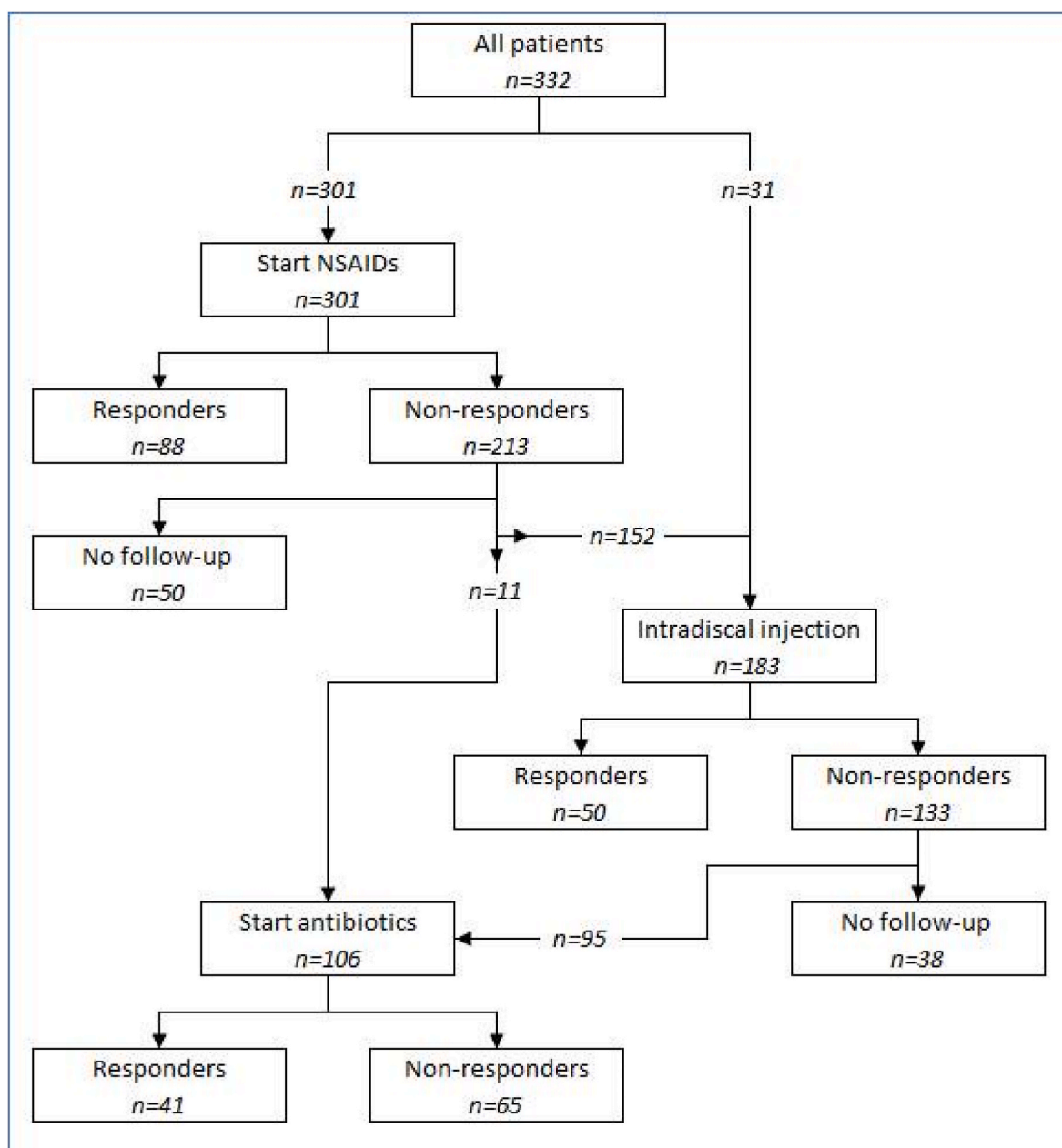

Fig. 1. Treatment pathways and responder numbers.

In total, 332 patients completed follow-up questionnaires up to one year. Out of this group, 178 patients (53.6 %) met our criteria for clinically relevant positive effects, defined as reduction of pain (minimum of 50 % pain relief by NPRS) or improvement of functionality (minimum 40 % improvement in RMDQ/ODI). Pain scores for average and worst pain and for function improved mostly during the first 3 months. The curve flattened later but nevertheless continued to decline within the 1 year of follow-up.

Out of 216 patients treated with AB, 26 patients (12.0 %) stopped due to undesirable side effects, such as diarrhea or rash, and were not included in the final analyses.

Consecutive patients, mainly Dutch people (Caucasian population), were included. Of 1182 patients who were initially identified as eligible (see Fig. 2), 833 completed the baseline questionnaires and were included in the study, and 332 patients completed follow-up questionnaires after 12 months (with or without the 3- and 6-month questionnaires).

3.1. Possible confounders and effect modifiers

The statistical model was expanded with variables of gender (male or female) and age category ($<30, <40, <50, <60, <70, \geq70$ years old). No confounders were identified at steps 1, 2, and 3 for the variables of average back pain, worst back pain, and disability score. Effect modifiers on gender and age were found. We found a significant difference ($p =$ .026) in disability scores between men and women in the AB group at 3 and 12 months of follow-up and a significant difference ($p = .040$) in disability scores between patients younger than 30 years old and the other age categories in the ID group at 6 months of follow-up. Because the effect modifiers were scattered throughout the data (different steps, follow-up periods, and outcome measures), we have chosen to present the general outcomes of all three steps.

3.2. Outcomes

The primary outcomes (see Figs. 3–5) exhibited the same tendencies regarding pain and function.

Table 1 shows opioid use declined from 19.3 % to 13.3 %, which is a 31 % reduction. Use of other medications such as NSAIDs, paracetamol, or TCA showed no significant differences. Sick leave decreased from 17.5 % of the population to 11.4 %.

4. Discussion

The goal of this observational study was to determine whether patients with MC I, I/II, or II would respond to an anti-inflammatory-based, stepped care treatment with three treatment steps. The steps began with the simplest oral treatment with NSAIDs, followed by invasive treatment with ID and, if necessary, a third step of AB treatment with the largest impact on homeostasis.
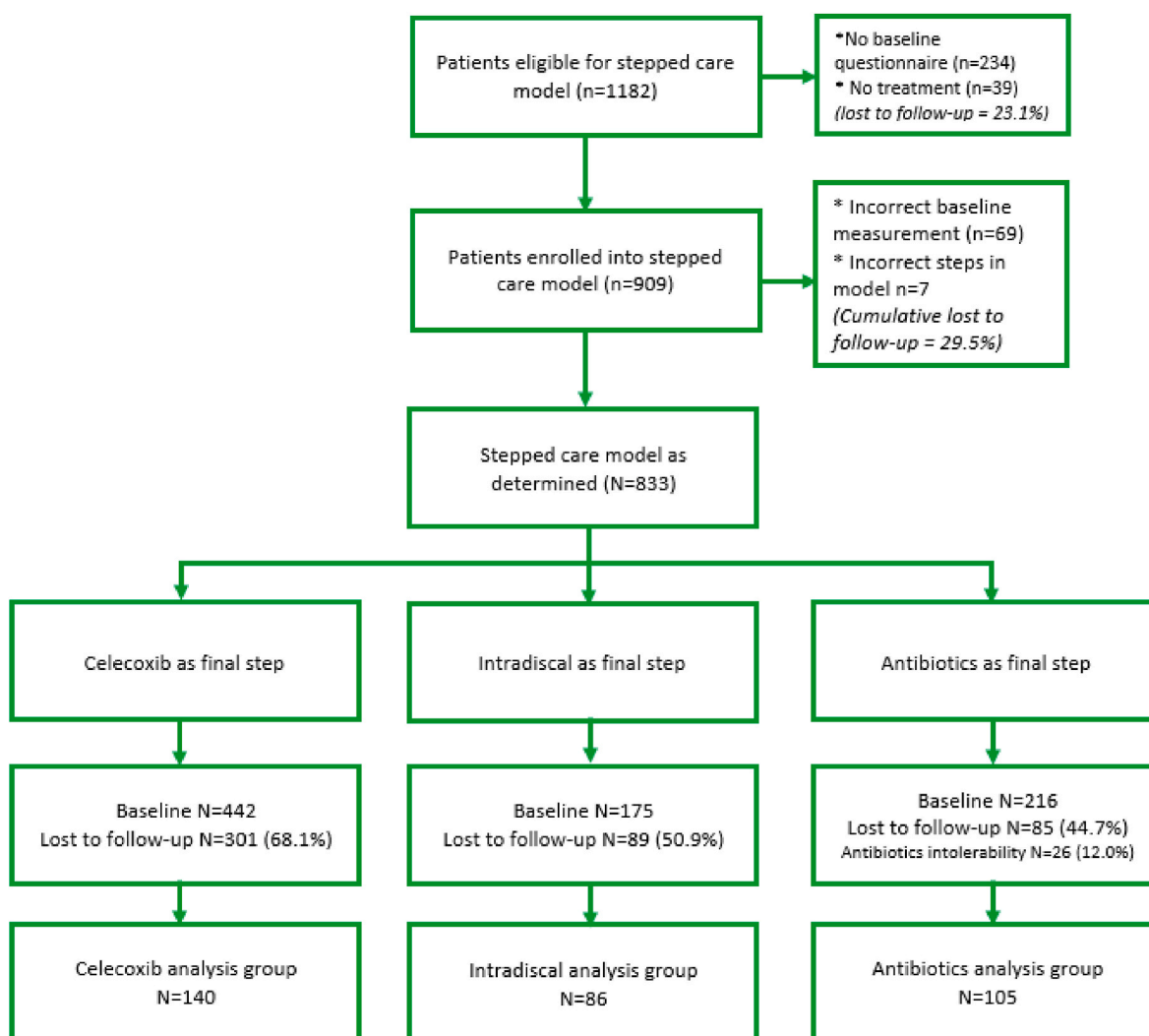
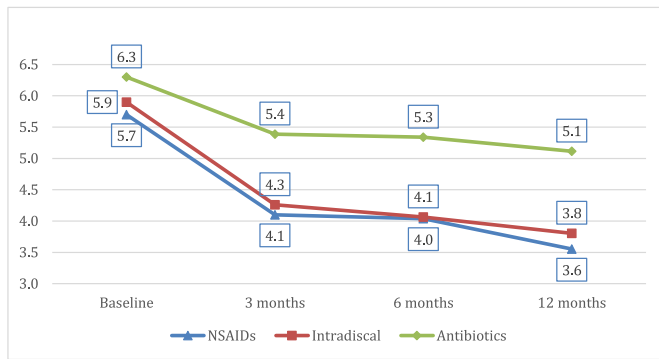**Fig. 2.** Dropout rates and losses to follow-up.

Fig. 3. Average development of average back pain during 1 year of follow-up.
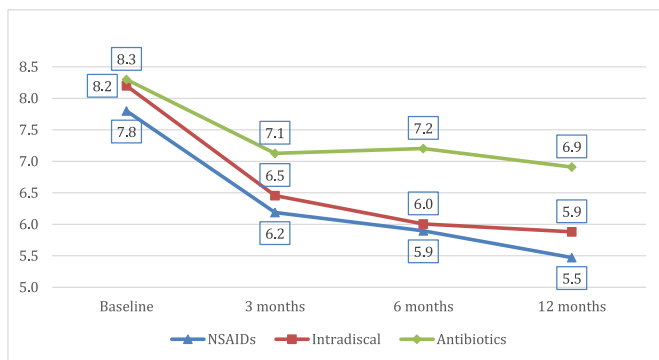

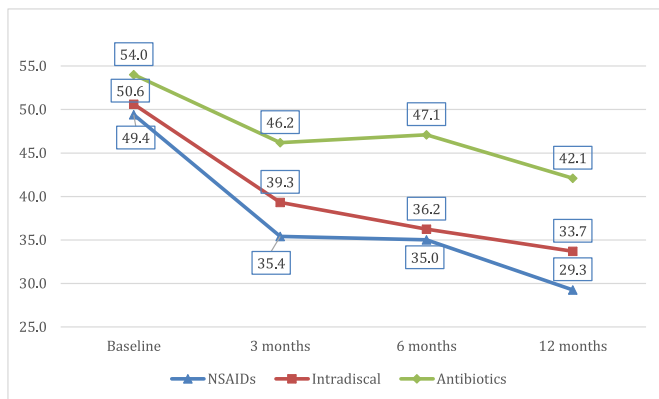**Fig. 4.** Average development of worst back pain during 1 year of follow-up.

Fig. 5. Average development of disability during 1 year of follow-up.

Table 1
Secondary outcomes at baseline and 12 months.

Outcome measures	Baseline (*n* = 833)	12 months (*n* = 332)
Paid job	86.1 %	83.8 %
Sick leave	17.5 % of patients with paid job	11.4 % of patients with paid job
Use of medication (in general)	45.8 %	39.0 %
Use of opioids	19.3 % of patients using medication (in general)	13.3 % of patients using medication (in general)
Use of other pain medication	89.9 % of patients using medication (in general)	94.5 % of patients using medication (in general)

Step 1 produced the highest number of patient-reported results of treatment in this study, with 63.8 % responders. We cannot compare these results with others in the literature, as no comparable studies have been performed for MC treated with NSAIDs.

Step 2 (ID) was almost as effective as step 1, with 56.8 % responders. Our positive results for ID differ from other inconsistent results reported in the literature regarding the use of ID [72,74,75,77]. This difference may have occurred because the selection criteria for study subjects, including degree of pain, type of discogenic degeneration, presence or absence of MC, definition of MC, and differentiation between MC-related and non-MC-related CLBP, have often been insufficient [72]. Other studies have included only very small numbers of patients [73,74]. These factors have resulted in recommendations against ID for discogenic pain [70]. In our study, the MC population was well defined, and there were no complications following ID. Our results align with those of Cohen [91] and Osti [92], who have confirmed the absence of infectious complications with discographies or ID using intradiscal antibiotic prophylaxes and standard techniques. Therefore, we consider ID to be a safe and effective treatment for a selected group of MC patients who have failed to respond to the first treatment step with NSAIDs.

Step 3 (AB) was administered to patients who had not responded to the previous steps. This group improved in 38.7 % of cases. This therapy seems to have been less effective compared to the results reported by Albert et al. [24] However, the patient groups are not comparable; our patients formed a highly negative selection group who had already received other therapies, including invasive procedures of the spine such as epidural steroid injections and ID, without success before being treated with AB.

Some authors have been critical of AB use for the treatment of CLBP with MC, such as the authors of the AIM study by Bråten et al. [80] Their study design differed from that of the present study and the Albert et al. study [23].

Comparison of the effectiveness of the three treatment steps separately was not possible from our data and was not the aim of this study. The groups seem to have demonstrated differences possibly related to the severity of the MC, and further research should address these differences. It is possible that individual care, enrolling patients at one of the steps in our model, might prevent the administration of care with a lower chance of success.

Kristoffersen et al. [93] found significant improvement from AB treatment for disability in a subgroup of patients larger MC I on the MRI, with short tau inversion recovery showing more MC-related high signal. The results were clinically relevant only for disability and not for LBP. This finding may be of note for further evaluation in our data.

A subject of further research for all treatment groups would be the investigation of subgroups, for example MC I, I/II, and II; patients with or without a torsion or spondylolisthesis with high impact of mechanical forces; age groups; and others. In addition, analyzing the non-responding patient groups might provide new insights into the avoidance of treatments with poor chances of success.

4.1. Weaknesses of this study

The participants did not all consistently follow step 1 first and then step 2 before step 3 in cases of failure. This report is a description of the daily practice with individual – sometimes pragmatic – solutions for patients, mostly due to contraindications. Possible bias exists due to a significant lack of follow-up. It is nearly impossible to avoid loss in an observational study, as disappointed patients choose other treatments, costs play a role, and the motivation to complete repeated questionnaires is low.

4.2. Strengths of this observational study

The data were collected from a large number of patients. The stepped care model provides useful, easily accessible, and safe treatment options with favorable tolerance for patients with high burden. The consecutive steps in our treatment model are unique and have demonstrated better results combined with less burden for patients compared to separate treatments.

5. Conclusion

Rugpoli designed a stepped care model for treating CLBP patients with MC I, I/II, and II based on the literature combined with its own clinical experience and outcome data. In total, 53.6 % of the included MC patients improved by 50 % or more regarding pain or 40 % or more regarding functionality.

Given the lack of effective alternative treatment options, our results are rather promising for this selected group of MC patients with severe impairment and signs of inflammation. Thorough patient selection is paramount to the success of the stepped care model; it is important to treat or exclude patients suffering mainly from other sources of pain before treating the discogenic inflammation component with the stepped care model for MC. Our stepped care model appears to be a useful, safe, and cost-saving treatment option.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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