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General discussion



AIM

Magnetic Resonance (MR) imaging is not recommended in the Dutch clinical guideline ‘traumatic knee complaints’ for general practitioners (GPs), mainly because the diagnostic value and cost-effectiveness of direct access by the GP to knee MR imaging is unknown.¹ Whether MR imaging of the knee should enter the diagnostic pathway in primary care through direct access by the GP, depends on whether it improves patient outcome, reduces costs and affects subsequent diagnosis and management. Therefore, the primary aims of this thesis were to describe over a period of 1-year follow-up:

- whether MR imaging referral by the GP is non-inferior compared to usual care in patients with persistent traumatic knee complaints regarding self-reported knee related daily function, and
- whether MR imaging referral by the GP is cost-effective compared to usual care in patients with persistent traumatic knee complaints.

KEY FINDINGS

The results of the TACKLE trial (TraumAtic Complaints of the Knee — Leiden University Medical Centre and Erasmus Medical Centre) showed that MR imaging in general practice in patients (aged 18 to 45 years) with traumatic knee complaints was both non-inferior and non-superior to usual care regarding knee related daily function during 1-year follow-up. Secondary outcome measures showed that adding MR imaging to usual care had no impact on knee pain, knee symptoms, function in daily living, sport and recreation, and quality of life. However, more patients perceived to be recovered and more were satisfied after adding MR imaging. Also, we showed that MR imaging referral by the GP was not cost-effective in patients with traumatic knee complaints. There were higher healthcare costs due to more costs for the MR scan but also due to more patients visiting a physiotherapist and more patients undergoing an arthroscopy after MR imaging, without an improvement in the quality adjusted life years (QALY).

METHODOLOGICAL ISSUES

The design of the TACKLE Trial

We performed a high quality trial with clear results, suitable to translate into clinical practice. However, constructing a randomised controlled trial (RCT) to study (cost)effectiveness of MR imaging for traumatic knee complaints in general practice involves many design choices that may have impacted on the results of our study. When studying cost-effectiveness the usual choice is to design a pragmatic study in which the interventions are applied in a way that reflects clinical practice as much as possible. One facet of this is the absence of blinding. However, the fact that

the patients knew that they were allocated to the MR imaging group instead of the usual care group (without MR imaging) in a study environment may have affected the subjective clinical outcomes. Also, the subjective clinical outcomes may be influenced by the increased attention of the healthcare providers in the patients receiving an MR scan. Research has shown that the patient-practitioner interaction effect rooted in demonstrating care and empathy can positively enhance a patients experience.²⁻⁴ These patient-practitioner interactions also exists in daily practice and therefore reflect the pragmatic design of the study.

Another important choice is the primary outcome. In our study, we decided to use the Lysholm scale as the primary outcome to assess the knee related daily function which was originally developed for anterior cruciate ligament (ACL) injuries. We choose the Lysholm scale to measure knee related daily function because this scale is well documented according to psychometric properties in patients with traumatic knee injuries in general practice.⁵ However, detecting small improvement in patients with reasonable knee function using the Lysholm scale might be difficult. The International Knee Documentation Committee subjective knee evaluation form could have been an alternative, although we are not aware of any research on psychometric properties of this questionnaire in a primary care population. We think that the inability of the Lysholm scale to detect small differences did not influence the main conclusion of our study, since all secondary clinical outcome scores show consistent results of no differences between usual care and MR imaging.

A third methodological issue in the TACKLE trial is the fact that GPs were instructed to invite all patients with traumatic knee complaints to participate in the study, while in daily practice GPs tend to identify patients who they consider to be in need of additional diagnostics. No consensus exist among GPs about which patients are in need of additional diagnostics and there is no scientific ground on which these criteria can be based. In addition to the TACKLE trial, we also conducted a retrospective cohort study with data originating from a longitudinal database of electronic medical records of GPs in The Netherlands (chapter 3). We showed that during 2011 to 2013 GPs referred about one in eight patients to an MR imaging. Male gender and 'a longer duration of complaints' were identified as predictors for an MR imaging referral by the GP, but our model only accounted for 6.5% of the explained variability. The results of the TACKLE trial are solely generalisable to the random patient consulting the GP with traumatic knee complaints.

Also, we have to be aware that probably the patient not invited by the GP to participate in our RCT were patients with severe knee complaints who were already referred to secondary care by the GP during the first consultation. The Dutch clinical guideline 'traumatic knee complaints' for GPs recommends only referring the patient to secondary care during the first consultation in case of a fracture or an acute locked knee.

The conduct of the study

During the conduct of the TACKLE trial, we were faced with some challenges.

Firstly, fewer eligible patients participated in our trial than anticipated. In order to collect sufficient data, we made the following changes to the study protocol after the trial commenced and reported this to the medical ethical committee, and the trial register: i) the time constraint to include patients with knee complaints present for at least four weeks was abandoned in dialogue with the participating GPs since, according to the participating GPs, it did not reflect daily practice and ii) eligible patients who were missed by the GP during the consultation were identified by searching the electronic medical records for knee classification codes and were invited afterwards (n=132). The latter patients had a longer time from trauma to study inclusion (median 75 days; IQR 49, 107 days) than the patients invited during consultation (median 22 days; IQR 8, 45 days) and had less knee complaints. This might have diminished the effect we found between the groups, however, explorative subgroup analysis in the patients with knee complaints present for at least four weeks (n=218) showed that MR imaging was also non-inferior to usual care and not cost-effective during the 1-year follow-up. In addition to this, explorative subgroup analyses in patients with complaints persisting for at least four weeks and recruited during the consultation (n=94) confirmed the results of non-inferiority of MR imaging compared to usual care during the 1-year follow-up. However, the probability of MR imaging being cost-effective compared with usual care increased, with a range from 75% for €0 willingness to pay (WTP) per QALY to 83% for €20 000 WTP/QALY from a healthcare perspective. From a societal perspective, this was 58% and 62% respectively. Because such explorative analyses are liable to bias due to the lack of power and no stratification, these results should be interpreted with caution.

Also, in order to collect sufficient data, we reduced the sample size during the recruitment period from a total of 520 to 360 patients. Initially, we choose a non-inferiority margin of 4.8 points on the Lysholm scale to calculate the sample size, as the 95% confidence interval in the reference study was within 4.8 points from the mean difference.⁶ However, the margin was adapted to 6 points on the Lysholm scale in dialogue with the subsidiary. Six points is still substantially lower than the 10 to 15 point difference considered to be clinically relevant on the Lysholm scale.⁷ Also, the increase in the non-inferiority margin from 4.8 to 6 points had no effect on the statements of non-inferiority and non-superiority of MR imaging compared to usual care, as the 95% confidence interval also did not cross the 4.8 points on the Lysholm scale.

The second methodological issue we were confronted with during the conduct of the study was the crossing over of patients from the usual care group to the MR imaging group. Twenty patients in the usual care group received an MR imaging, while the GP explicitly was instructed by the researchers not to request an MR imaging in patients randomised to the usual care group. From the 20 patients receiving an MR scan, in at least 10 patients the GP consciously violated the research protocol by requesting an MR imaging. In the remaining 10 patients, we were not able to track down the requester of the MR imaging. The protocol violation did not influence the results, since the per protocol and intention to treat analyses showed similar results.

PATIENT SATISFACTION

Based on the key findings of the TACKLE trial, the statement in the Dutch clinical guideline 'traumatic knee complaints' for GPs that MR imaging is not recommended is strengthened with robust scientific evidence for patients aged 18 to 45 years with traumatic knee complaints. However, the results of the TACKLE trial also showed that more patients perceived to be recovered and more were satisfied after adding MR imaging. Patient satisfaction with the treatment is an important outcome in medical decision making. The increased patient satisfaction in the MR group may be influenced by patient preferences, expectations and illness perceptions.

The preference for MR imaging is reflected in i) the number of patients who declined randomisation because they had a strong preference for an MR scan, ii) the increased drop out in the usual care group and iii) the referral to MR imaging by the GP in the patients randomised to usual care.

Patients with traumatic knee complaints tend to underestimate the duration of the recovery. A prospective cohort study in patients assigned for arthroscopy on suspicion of meniscus injury and later verified by arthroscopy showed that 59% of the patients had unfulfilled expectations after the surgery.⁸ The majority of the patients (91%) had expected to be fully recovered within three months after surgery. Satisfaction with the knee function was associated with expectations of leisure activities being fulfilled.

Also, patients create their own perceptions about their illness and the treatment. The Common Sense Model of self-regulation (CSM) contains a theoretical framework describing these illness perceptions.⁹ Research has shown that the beliefs of patients about their illness are associated with pain intensity and limitations in physical function in patients with musculoskeletal pain.¹⁰ The CSM describes five dimensions of perceptions related to: the identity or label the patient associates with the illness, the perceived duration of the illness, the expected effects and outcome, the personal ideas about the aetiology and how one controls or recovers from the illness. For example, the ideas of the patient about the cause of the pain and/or limitations in physical functioning in patients consulting their GP with knee complaints after a trauma may lead towards a strong desire for a more specific diagnosis, based on MR imaging rather than on history taking and a physical examination. After structural abnormalities are determined on MR imaging, the solution will be sought in dealing with the structural abnormalities instead of the functional disabilities. Yet, MR imaging of the knee may lead to incidental asymptomatic findings, in which structural pathology is not related to pain and function.^{11,12} The preferences, expectations and illness perceptions may influence the patient's satisfaction and therefore must be made transparent by the GP during the first consultation, so targeted information and advice is possible.

EFFECT OF MR IMAGING IN PRIMARY CARE ON SUBSEQUENT DIAGNOSIS AND MANAGEMENT

The guideline panel of the Dutch clinical guideline ‘traumatic knee complaints’ for GPs concluded, after weighing the arguments and the available research there is insufficient reason to recommend MR examination by the GP. However, the guideline panel stated in case indications for surgery are identified, MR imaging might play a role in primary care. In the TACKLE trial, MR findings that needed referral to an orthopaedic surgeon as defined by the research group before the trial commenced, predominantly were meniscal lesions and ACL lesions (chapter 4).

Meniscal lesions

Treatment paradigms of meniscal lesions have evolved during the past decades from complete resection to partial meniscectomy, and nowadays, meniscal lesions are repaired if possible, but also more and more treated conservatively.¹³ Research has shown that in patients with degenerative meniscal lesions, the outcomes after meniscectomy were no better than those after placebo surgery.¹⁴ We evaluated the effectiveness of exercise therapy for meniscal lesions in adults in a systematic review and meta-analysis (chapter 8). We included RCTs published until June 2015 and found no difference between exercise therapy and meniscectomy on pain and function outcomes in patients with degenerative meniscal lesions. Since then, several RCTs and systematic reviews are published confirming no clinical relevant differences between meniscectomy and exercise therapy in patients with degenerative meniscal lesions.¹⁵⁻²¹ As knee surgery has several limitations, such as the invasiveness of the procedure, the need for day admission in the hospital, the risk of complications and an increased risk of osteoarthritis,²² a recent published international clinical guideline recommends strongly against arthroscopic surgery in patients with degenerative knee arthritis and meniscal tears.^{23,24} However, in the above mentioned RCTs comparing surgery versus conservative treatment in patients with degenerative meniscal lesions up to one third of the patients crossed over to the surgery group or opted for delayed surgery. Explorative analyses showed that patients who were most likely to cross over to meniscectomy had shorter symptom duration and a higher level of baseline pain.^{25,26} Noteworthy, the delayed surgery did not seem to improve the clinical outcomes compared to the conservative treatment.²⁵ Our above mentioned systematic review and meta-analysis showed that there were no studies evaluating the effectiveness of exercise therapy compared to no exercise therapy in non-surgical patients with a meniscal lesion. The considerable amount of cross-overs to the surgery group and the lack of evidence about the effectiveness of exercise therapy in patients with meniscal lesion reflect the uncertainties about the optimal conservative treatment strategy in patient with degenerative meniscal lesions.

While there are many studies on the effectiveness of meniscectomy in patients with degenerative meniscal lesions, the effectiveness of meniscectomy in younger patients or in patients with traumatic meniscal lesions remains unknown. There are two ongoing RCTs off which the results

will appear soon, one compares surgery to exercise therapy in younger patients (18 to 40 years) with meniscal lesions²⁷, the other RCT compares meniscectomy to exercise therapy in patients with traumatic (non-degenerative) meniscal lesions.²⁸ An upcoming treatment option for patients with a meniscal injury due to a trauma is a meniscal repair. In the Netherlands a meniscal repair is indicated in young patients, with a recent trauma and a peripheral horizontal tear in the vascular zone of the meniscus, where the torn meniscus is of good quality.²⁹ However, there is a lack of evidence concerning the effectiveness and indications for meniscal repair. A recent meta-analysis comparing meniscectomy versus a meniscal repair identified only seven eligible studies, only one of it was an RCT.³⁰ The short-term results of this RCT showed better knee function after partial meniscectomy than after arthroscopic meniscal repair in patients with intrasubstance meniscal lesions, however there were serious concerns about the risk of bias.³¹

Anterior cruciate ligament injuries

Another frequent indication for surgery contains a cruciate ligament tear. A Cochrane review from 2016 assessing the effects of surgical versus conservative interventions for treating acute ACL injuries identified one eligible RCT.³² Low-quality evidence was found for no difference between surgical management and conservative treatment in patient-reported outcomes of knee function at two and five years after injury. Also, treatment with exercise therapy alone was a prognostic factor for less knee symptoms compared with early reconstruction plus exercise therapy.³³ However, 39% (23/59) of the patients in the conservative treatment group opted for ACL reconstruction for knee instability at two years and 51% (30/59) of the participants opted for ACL reconstruction after five years, indicating that there might be a subgroup of patients who may benefit from surgery. The Dutch guideline for orthopaedic surgeons recommends ACL reconstruction only in patients with symptomatic instability or persistent giving way (not improving after physical therapy and not responding to adjustment of activities).³⁴ Tough, the evidence for the benefit from surgery for any such subgroup is lacking. The Cochrane review identified two ongoing trials assessing the effects of surgical versus conservative interventions for treating acute ACL injuries.^{35,36}

IMPLICATIONS FOR CLINICAL PRACTICE

Our study provides high quality evidence confirming that routine MR imaging of the traumatic knee should not enter the diagnostic pathway in primary care through direct access by the GP, as it does not improve patient outcomes nor reduces costs nor prevent from referral to secondary care. In the particular situation that the GP desires to request an MR scan to improve patient satisfaction regardless of the costs, the GP has to be aware that he/she needs to refer 5 to 7 patients with traumatic knee complaints to MR imaging to yield one more satisfied patient. The most common traumatic knee complaints that are referred to an orthopaedic surgeon by the GP are meniscal lesions and cruciate ligament injuries. Especially in patients with degenerative meniscal

lesion, MR imaging will not affect subsequent management, since international clinical guidelines recommend conservative treatment in these patients. The treatment by the GP may be refined by enhanced and targeted information and advice, by making the preferences, expectations and illness perceptions transparent during the first consultation.

FUTURE DIRECTIONS FOR RESEARCH

With the TACKLE trial, we determined with sufficient confidence that adding an MR imaging referral by the GP to usual care did not improve knee function and it is not cost-effective in patients aged 18 to 45 years with traumatic knee complaints. However, there are some questions remaining.

There exists consensus about the recommendation not to perform surgery in patients with degenerative meniscus lesions. However, since not all patients with degenerative meniscal lesions benefit from the current conservative treatment, future research should establish measurable indicators for unsuccessful conservative treatment to be able to design a targeted (conservative) treatment strategy for these patients. In patients with traumatic meniscal lesions, the two ongoing RCTs will help to determine the effectiveness of surgery compared to conservative treatment in patients with traumatic meniscal lesions. Furthermore, indications for repair need to be distinguished. In case a subgroup of patients who benefit from repair is identified, the efficacy of MR imaging in primary care in patients who benefit from repair needs to be re-established. Although, indications for surgery may also solely be based clinical findings rather than abnormalities seen on MR imaging. In patients with ACL injuries, the results of the high risk of bias study showing no differences between conservative treatment and reconstruction need to be confirmed by the two ongoing trials. If these ongoing trials also show a substantial amount of patients opting for delayed reconstruction, we also need to distinguish measurable indicators identifying patients with ACL injuries who may benefit from surgery.

Until then, strengthening the recommendation against MR imaging referral in the guideline for GPs with robust scientific evidence might not withhold the GP to refer the patient to MR imaging. Barriers for guideline adherence should be investigated. Future research should focus on identifying reasons for the GP to refer the patient to MR imaging to be able to design targeted treatment strategies. In the TACKLE trial we collected data on the GPs initial working diagnosis and the GP's preferred management at baseline. However, these data are only available of a small number of patients and still have to be analysed. Moreover, these preferences may have been influenced by the possibility of MR imaging in the TACKLE trial.

Finally, more insight into which variables influence patient satisfaction is needed to improve the treatment of patients with traumatic knee complaints in general practice. For example, patient preferences, expectations and illness perceptions may be important mediators of the increased patient satisfaction after MR imaging. The value of patient education and intermediate care needs to be studied in this context.

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