Master's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Public Health and Nursing

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Association between pain catastrophizing and postoperative pain intensity

A prospective cohort study

Master's thesis in Clinical nursing
Supervisor: Lise Husby Høvik
Co-supervisor: Torbjørn Rian
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PART ONE – THE EXTENDED SUMMARY

1 Introduction

Osteoarthritis is a painful condition, and prolonged pain is the main indication for knee replacement surgery (1–4). Patients with this condition wants surgery, in hope for a better life, with more physical activity without pain (5). Serious complications are rare and most of the patients experience pain relief and improved function after surgery (6). Total knee arthroplasty (TKA) is considered a painful procedure and pain after surgery may limit early mobilization. Mobilization and physical activity after TKA may avoid complications as physical stiffness and persistent pain (1–4). However, a total of 15% of the patients are not satisfied with the result one year after surgery, and 5% are dissatisfied due to persistent pain and low physical function (2–4,6,7).

During the last 20 years, programs to enhance postoperative recovery and convalescence have been introduced. Amongst these is the so called “Fast-track surgery”, a multimodal approach to patient care in the perioperative pathway. Evidence-based interventions in surgery and anaesthesia, pain management, patient education and early mobilization are key elements of this program (8). Studies find positive effects of fast-track surgery, such as reduced morbidity and reduced length of stay without increased number of complications or readmissions after knee arthroplasty (8,9). As a result of fast-track, it has been suggested that patients feel more empowered in their own training in the postoperative phase, which has led to patients feeling secure and able to manage the training process (5).

In a fast-track program, the nurse anaesthetist is a resource person who provides psychological support to help the patients through the perioperative experience (10). Regional anaesthesia is standard procedure during knee replacement and the patient is awake during surgery. This can be a stressful situation for the patient, and can influence postoperative coping (5). The International Federation of Nurse Anaesthetists (IFNA) standards state how the nurse anaesthetist provides appropriate health information through nurse-patient relationship, pre- per- and postoperatively (10). Through communication and information, the patient can be confident in the situation and be empowered (5,8).

Pain and function after TKA can be affected by mental distress, socioeconomic status, symptoms of anxiety or depression, and high levels of preoperative pain catastrophizing (11–13). Several studies suggest that patients with psychological symptoms need to be identified and consulted before

surgery (11,12,14,15). Pain catastrophizing has an impact on health related quality of life after surgery (15). Although studies have shown an association between preoperative pain catastrophizing and postoperative pain (12,15–17), other studies have failed to detect a relationship between anxiety or pain catastrophizing and chronic postsurgical pain (14,18).

The extended summary will address the overall. Theoretical perspectives and method are described more detailed in the extended summary, while the article will be more concrete and refined. The discussion in the article will focus on the study´s aim, while the extended summary will discuss the method. The article will follow the "BMC Musculoskeletal Disorders" guidelines (Appendix 4), which is a peer-reviewed journal focusing on all aspects of prevention, diagnosis, and management of musculoskeletal disorders.

1.1 Aim of the study

The aim of this study is to investigate a possible association between preoperative pain catastrophizing and postoperative pain eight weeks after TKA and compare pain outcomes and pain catastrophizing.

Research questions:

1. Do patients have a higher score of pain catastrophizing before surgery, compared to 8 weeks after surgery?
2. Is preoperative pain catastrophizing associated with postoperative pain intensity?

2.0 Scientific background

2.1 Pain

The International Association for the Study of Pain (IASP) has defined pain as "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage"(19). Degrees of biological, psychological, and social factors is influencing the personal experience of pain. The concept of pain is learned individually through life experience, and individual experience of pain should be respected. Pain and nociception are different phenomena. Pain cannot be inferred solely from activity in sensory neurons. Although pain usually serves an adaptive role, it may have adverse effects on function as well as social and psychological well-being (19).

The goal of using pain mapping tools is for the individual patient to receive individual and optimal pain treatment. Mapping tools can be both objective and subjective. The various pain mapping tools we use today can be divided into two main categories: one-dimensional and multidimensional scales. The difference is that the one-dimensional only measure pain intensity, while the multidimensional also measure the quality of the pain, the impact on different functions and sleep. Visual analogue scale (VAS) and numerical rating scale (NRS) are examples of one-dimensional scales. To map how the pain affects different functions, multidimensional mapping tools are used. In Norway, the most used forms are McGill´s pain form and Brief Pain Inventory (BPI) (20).

The World Health Organization (WHO) and IASP have developed a system for classifying pain conditions, in which acute pain is defined as pain that lasts for a short time, and up to 3 months (19). Chronic or prolonged pain is defined as pain that lasts beyond 3-6 months. Osteoarthritis of the knee joint is classified as a chronic or prolonged pain. Patient education, aggressive postoperative rehabilitation, and avoidance of technical errors in surgery are important factors for a successful knee replacement (1).

2.2 Pain catastrophizing

Pain catastrophizing is seen as a negative cognitive process and is thought to be a variable that can affect pain outcome. Catastrophizing is a repetitive negative thinking strategy to regulate negative emotional reactions (21). In 1995 Sullivan (22) made a validated scale for pain catastrophizing, the "Pain Catastrophizing Scale" (PCS). PCS is divided in three subscales, rumination; "I keep thinking about how much it hurts", magnification; "I wonder whether something serious may happen", and helplessness; "There is nothing I can do to reduce the intensity of the pain"(22). Pain catastrophizing

is defined as " *an exaggerated negative mental set brought to bear during actual or anticipated painful experience*" (23). There is a growing literature that find an association between pain catastrophizing and postoperative pain (12,17,24–26). However, other studies find no association (14,18).

Sullivan´s research showed that catastrophizers and non-catastrophizers both had their coping strategies for pain, where coping strategies such as focus on breathing, counting backwards, or focusing on daily tasks, was the most frequent strategy (22). However, studies did not find any effect of pain coping skills training, or cognitive behavioural patient education for pain catastrophizing (27,28). Other factors, such as anxiety and depression seems to have an impact on pain catastrophizing and pain outcomes (11,17,25,29). However, a study by Glette et al. (26) suggest that pain, pain catastrophizing and depression changes in the same direction.

2.3 The Fast-track model

The fast-track model is a knowledge-based multimodal treatment approach for surgical procedures. It consists of thorough patient information, standardization of surgical and anaesthesiological methods, optimal pain treatment, and early oral nutrition and mobilization. Several studies have shown that use of the fast-track model reduces morbidity, surgical stress response, reduces length of stay and prevents complications (8,9). The patient is central, and information is important, so that the patient can contribute in their own rehabilitation after the surgery (8).

Undergoing TKA, the patient receives regional anaesthesia and is awake during the procedure. This technique has shown to be preferable, prevents nausea and vomiting, as well as a reduction of opioid-induced hyperalgesia (8).

2.4 Comorbidities

To predict operative risk the American Society of Anaesthesiologists (ASA) developed a physical status classification system to offer clinicians a simple categorization of a patient's physiological status (30). The classification is from 1-6, where 1 is a normal healthy patient, and 6 is a brain-dead patient. Charlson Comorbidity Index (CCI) is a measure of 1-year mortality risk and burden of disease and consists of 17 comorbidities. Comorbidities are weighted from 1 to 6 for mortality risk and disease severity, and then summed to form the total CCI score. Clinical research has used the CCI extensively to address the confounding influence of comorbidities, predict outcomes and for self-report of comorbidities (31).

3 Method

St.Olavs Hospital, Trondheim University Hospital, is part of "Helse Midt-Norge RHF", a health trust with responsibility of hospitals and specialist health services for approximately 720 000 inhabitants in the two central Norwegian counties, consisting of a total of 1018 beds. St.Olavs Hospital, dept. Øya is the largest hospital in the region with the highest number of knee arthroplasty operations. The current study is a sub study from a randomized controlled trial (RCT) by Rian et al. (32), and the data is collected from the patients in the period between 15. November 2015 to 4. January 2019. All patients undergoing TKA were asked to participate in the study at the preoperative outpatient clinic a few weeks before surgery.

St.Olavs Hospital has since September 2010 organized total knee- and hip replacement surgery after the fast-track model. At the outpatient clinic, the patient is informed and examined by an anaesthesiologist, surgeon, nurse, and physiotherapist. In addition, participation in a patient school emphasise surgical and anaesthesiological methods, type of prosthesis, training and how to behave at home. All patients are given patient information and they are specifically informed about what can be expected from postoperative pain.

The patients are mobilized in the recovery unit after surgery. A majority of the patients are discharged to home after a few days (7). Both patients and ward staff are primed to expect a hospital stay of 2 to 3 days. After discharge, patients can contact the ward nurse staff at the orthopaedic department by telephone. The first follow-up with a physiotherapist is after eight weeks. In these weeks, the fast-track model presupposes rehabilitation based on conventional physiotherapy and the patient's own efforts.

3.1 Study design

This study is a prospective cohort study, based on data from a single-center, prospective, randomized, double-blinded trial conducted at St.Olavs Hospital, Trondheim University, Norway. The study by Rian et al. (32) compared the effectiveness of tapentadol extended-release, oxycodone controlled-release, and placebo, as added to a multimodal analgesic regime both in-hospital and at home the first week after TKA.

3.2 Participants

Measurement of the sample size is calculated for the RCT study using one-way ANOVA analysis at Stata 13.1 Power. This sub study is based on the sample size from the RCT study and has not made a separate sample size calculation.

Four hundred and eighty-eight consecutive patients were considered for inclusion, of which 149 were included and randomized. A total of 134 patients in three study groups received their allocated intervention, of these a total of 125 filled out the PCS form at baseline and after 8 weeks and was included in the analysis.

3.2.1 Inclusion criteria

Patients between 18- and 80-years of age undergoing TKA who consented to participate in the study.

3.2.2 Exclusion criteria

The most frequent cause for not being eligible in the RCT study was use of drugs or medical condition in conflict with one of the analgesic drugs, cognitive impairment, inability to read or speak Norwegian, lack of cellphone or wireless Wi-Fi connection. Patients who were breastfeeding or pregnant, patients with a regular use of opioids or a history of opioid abuse, and patients scheduled for general anaesthesia were also excluded from the study (Appendix 1).

3.3 Ethics

All research that involves humans must follow guidelines for good ethical principles. There are developed guidelines for ethical standards in the Nordic countries, which is based on four principles: the principle of autonomy, of beneficence, of non-maleficence and of justice (33). The Declaration of Helsinki was developed as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The declaration undergoes the risk, burden and benefits costs, and all participants must be given informed consent (34).

Health information or other sensitive personal information that is identifiable can only be stored in encrypted form or in areas with a high degree of security. Health information must be stored pseudonymously, research data and identifying elements must be stored separately, so that the researchers only have access to research data (35).

This study was a randomized controlled trial, monitored by The Norwegian University of Science and Technology (NTNU), Unit for Applied Clinical Research, approved by the Regional committee for Medical and Health Research Ethics (2015/209/Rek-Midt) and the Norwegian Medicines Agency (15/01581-13), and registered at clinicaltrials.gov (NCT02604446) on November 13, 2015. The current master project was approved by REK 28. September 2020 (Appendix 3).

Participation in the study was voluntary and entailed written consent for participation. Upon participating, all patients were provided oral and written information about the study. This included their rights to withdraw at any time, without their withdrawal affecting the scheduled course of treatment or follow-up. All patient data was treated confidentially and pseudonymized. All data from the study were entered into a secure database that were created at St.Olavs Hospital. Access to this database was restricted to key study personnel. The randomisation of study drugs was only known by the hospital pharmacy (for emergency unblinding), the monitor unit (AKF NTNU) who generated the list, and the manufacturer of the study drugs. The database is stored for 15 years.

3.4 Measurements

Measurements in clinical research or practice are used as information for decision making, evaluation or prediction. The score must be evaluated within the context of the test´s intended use, and then conclude whether it is reliable and valid. Reliability provides in many ways the foundation for making generalizations (36).

The pain catastrophizing scale (PCS) is translated to Norwegian, and validated (37). The patients are asked to rate their thoughts regarding pain catastrophizing using a five-point Likert scale. PCS is a self-administered form where you answer questions about feelings and thoughts when you experience pain. The form consists of 13 questions that are graded on a 5-point Likert scale where 0 is “not at all” and 4 is “all the time”. This results in a scale from 0-52, where high scores indicate a high degree of pain catastrophizing. The form gives a total score, as well as a score on each of the three subscales. Previous research has used a cut-off score of 20 to identify patients as high pain catastrophizers (18,38,39).

The Numerical Rating Scale (NRS) is a commonly used 11-point one-dimensional pain intensity scale, where 0 is no pain and 10 the worst pain imaginable (40). The primary outcome in the RCT study by RIan et al. (32) was pain at movement (walking): “How much pain do you have now when you move”.

3.5 Data collection

NRS was used to register pain on mobilization and at rest, daily for seven consecutive days after surgery. Patient symptoms were obtained by self-registrations on a specially designed iPad application where all patients recorded all self-reports the first 8 days. The data collected through iPads were anonymized and wirelessly transferred to a separate database for storage. Pain on mobilization and at rest was also reported on an NRS at an outpatient follow-up eight weeks after surgery. PCS was self-administered and registered on inclusion and eight weeks after surgery at the outpatient follow-up.

3.6 Data analysis

Demographic, medical and clinical data are presented as frequency (%) and proportions (%) for categorical data and mean and standard deviation (SD) for continuous data.

Visual inspections of histogram and q-q plots were used to determine whether they were normally distributed or not. Preoperative pain (NRS) was the only variable normally distributed; all the other variables was skewed. Through non-parametric test the Wilcoxon signed rank test was used when comparing PCS at baseline and 8 weeks after surgery. A difference variable of PCS was created, to analyse changes before and after surgery. The statistical significance level was set at $p < 0.05$.

Linear regression analysis was used to determine association between preoperative pain catastrophizing and postoperative pain. We chose NRS at movement due to the importance of physical activity to avoid physical stiffness and persistent pain. We used a scatter plot to see if the residuals were normally distributed. Baseline characteristics such as age, gender, length of stay and preoperative pain were considered as potential covariates and adjusted for in the regression analyses. In the regression analysis the R squared (R^2) and beta coefficient (B, the slope) has given valuable information. The R^2 indicates how much of the total variation in the dependent variable, can be explained by the independent variable. The B is the degree of change in the outcome variable for every 1-unit of change in the predictor variable. The equation for the multiple linear regression is presented below.

$$Dependent\ variable\ (NRS) = B(constant) + B\ independent\ variable\ (PCS\ at\ baseline) + \varepsilon$$

Analysis comparing gender was performed using the Mann-Whitney U test. Statistical calculations were performed using IBM SPSS Statistics version 27.

4 Results

4.1 Descriptive statistics

Hundred and thirty four patients were included in the study by Rian et al. (32). In our study, we excluded 9 patients; seven of them had not filled out the PCS form at 8 weeks follow-up, and 2 had incomplete forms at 8 weeks follow-up, resulting in a final population of 125 patients. **Figure 1** shows the flow of patients through the study.

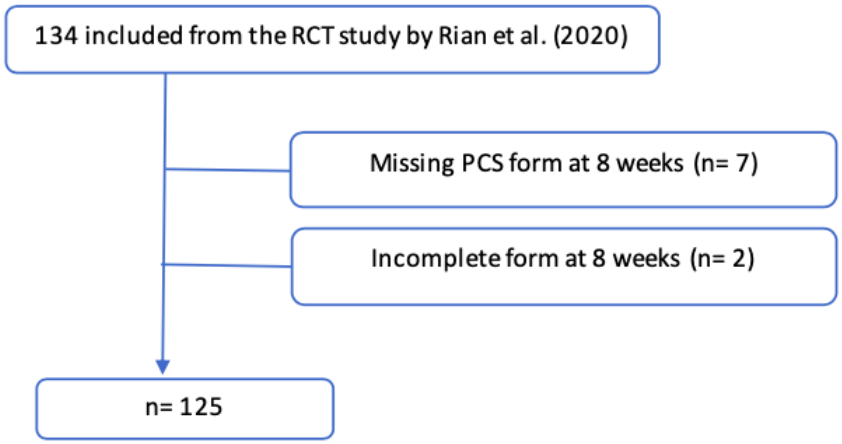

Figure 1 Flow of patients through the study.

Baseline demographic, medical and clinical data for the patients in the sample are given in **Table 1**.

Table 1 Baseline Characteristics of the study population (n=125)

Characteristics	*Value*
Age, mean (SD)	61.64 (9.7)
Female gender, n (%)	67 (53.6%)
ASA group 1, n (%)	37 (29.6%)
ASA group 2, n (%)	84 (67.2%)
ASA group 3, n (%)	4 (3.2%)
CCI, mean (SD)	2.22 (1.6)
Length of stay, mean (SD)	2.20 (0.7)

ASA: American society of Anaesthesiologists classification, CCI: Charlson comorbidity index.

4.2 Pain catastrophizing and pain development

We found a significant decrease in PCS from a mean of 11.18 before surgery to 6.26 after surgery (p<0.001).

Table 2 shows the development of pain intensity and pain catastrophizing before and after surgery.

Table 2 Pain scores and pain catastrophizing scores at baseline and 8 weeks after surgery

	Baseline	*8 weeks*	*p-value*
NRS movement, mean (SD)	5.27 (2.23)	2.31 (2.21)	p<0.001
NRS at rest, mean (SD)	2.56 (1.90)	1.76 (1.78)	p=0.038
PCS, mean, (SD)	11.18 (9.59)	6.26 (7.23)	p<0.001

a. NRS; Numeric rating scale, PCS; Pain catastrophizing scale, SD; Standard deviation

A total of 84.8% scored <20 on PCS at baseline, and 15.2% scored 20 or more. The difference in PCS score before and after surgery showed that a total of 21% had a higher PCS score after surgery. A total of 70% of the patients had a reduction in PCS score, and 9% had unchanged PCS. In **Figure 2** the percent of patients PCS difference is shown in a pie chart.

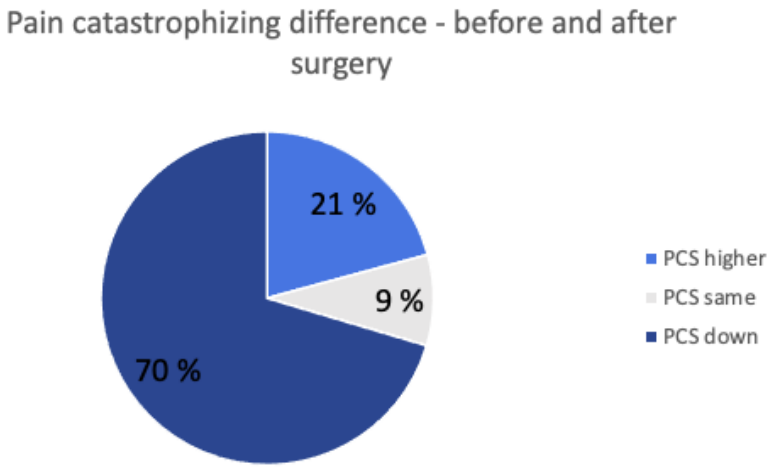

Figure 2 Changes in PCS from before to after surgery

Association between preoperative pain catastrophizing and postoperative pain performed by a linear regression analysis, present a weak association. The scatterplot of the residuals was normally distributed, (Appendix 2). The beta coefficient (B) shows that postoperative pain at movement

increases when having a patient with higher PCS score before surgery. The multiple regression analysis is presented in **Table 3**.

Table 3 Multiple linear regression analysis with pain at movement 8 weeks after surgery as dependent variable. Adjusted for age, gender and length of stay.

Variable	*B*	*R(R^2)*	*95% CI*	*Sig.*
	2.766 (Constant)	0.213 (0.045)		
PCS baseline			0.004-0.081	0.030
Age			-0.040-0.032	0.822
Gender			-0.601-0.829	0.753
Length of stay			-0.785-0.215	0.261

PCS; Pain catastrophizing scale, NRS; Numeric rating scale, CI; Confidence interval

We found an association between preoperative pain catastrophizing and postoperative pain at movement p=0.030, 95% CI (0.004-0.081). There were no association between preoperative PCS and preoperative pain at movement p=0.065, 95% CI (-0.003-0.086). We found an association between postoperative PCS and postoperative pain at movement p=0.005, 95% CI (0.021-0.114).

5.0 Discussion

Eight weeks after surgery, we found an overall decrease in both pain catastrophizing and pain intensity compared to before surgery. Previous studies have shown that surgery itself has a positive effect on reducing both pain and pain catastrophizing (24).

In this study, we found an association between preoperative pain catastrophizing and postoperative pain, as previous research has concluded (12,15,17,25,41–43). There is increased research investigating interventions to reduce pain catastrophizing preoperatively in order to reduce postoperative pain after surgery (27,44). Interventions such as coping skills training and cognitive behavioural patient education has been tested, however, currently with no effect on pain catastrophizing (28,45). Other interventions, such as testing an antidepressant (escitalopram), found no effect of this drug trial (44).

The nurse anaesthetist is a resource person for the patient and can provide accurate and understandable information in the perioperative trajectory (10). Accurate and understandable information to assist patients can be important in ensuring the patient, and may reduce pain catastrophizing. Patients undergoing TKA are mostly awake due to regional anaesthesia, which can be stressful and confusing. Already from the preparation of the patient to final surgery we can make the patient confident through communication. As mentioned previously, there are many factors who influence the pain catastrophizing (15,46,47). Through appropriate health information the nurse anaesthetist can provide a good environment, which can be crucial to patient coping skills (10). This can impact the pain catastrophizing and might empower the patient postoperative (10).

We found that as much as 20% increased in PCS after surgery. TKA is considered a painful surgery, and one explanation may have been that patients experienced more pain than expected after surgery (5).

Factors such as socioeconomic status, psychological status and life quality may influence the score of pain catastrophizing and pain (11–13,15,29,48). This study only used the NRS, a one-dimensional scale for pain mapping. It could have been an advantage to add a multidimensional scale to describe the patient´s experience of the pain. Some patients may find it easier to explain the pain they are experiencing than to rank the pain based on a number on a scale (20). A multidimensional scale could have been used, such as McGill´s pain form or brief pain inventory (BPI) which could have given a

broader understanding of the pain (20). This could provide an increased understanding and knowledge of the patients experienced pain (5,18).

Four hundred eighty-eight consecutive patients were considered for inclusion, of which 149 were included. Due to the selection of patients in the RCT study comparing pain drugs there may have been bias to our results, as patient with severe diseases were excluded. However, this study had a total of 125 patient included, compared to the study by Høvik et al. (18) who had 71 patient. Høvik et al. (18) could not find an association between preoperative pain catastrophizing and postoperative pain, which may be due to sample size. The two studies used different pain mapping procedures which makes it difficult to compare their results regarding the association between pain and pain catastrophizing. Few studies have been published that show no association between preoperative pain catastrophizing and postoperative pain. One possible explanation may be that studies that do not show a difference have more problems with being published (49).

Recent studies have a theory of symptom clusters, which suggest that multiple symptoms occurring together may cause a synergetic effect with greater negative impact (50). Symptoms consisting of pain, fatigue and depression is found as clusters which is associated with poor function and quality of life in patients with osteoarthritis (51). Anxiety and depression are not included as variables in this study. A study by Darnall et al. (29) shows that patients with depression or anxiety score higher on PCS compared to patients without depression or anxiety. However, a study from Glette et al. (26) suggested that when pain or pain catastrophizing changed, depressive symptoms changed in the same direction, and vice versa. A systematic review show that pain catastrophizing is a predictor for functional outcomes, but there is conflicting evidence that pain catastrophizing, anxiety and depression are predictors of postoperative pain (46).

This is a sub-study of a RCT comparing pain medication. One of the exclusion criteria was use of drugs not compatible with the scheduled pain medication. These criteria excluded patients using anti-depressant drugs and anti-psychotic drugs. This may have affected pain catastrophizing scores before surgery.

6.0 Conclusion

Preoperative pain catastrophizing is associated with higher postoperative pain intensity. There is a significant decrease in pain catastrophizing and pain intensity from before surgery to after surgery for TKA. However, 20% of the patient increased in pain catastrophizing after surgery. Many studies investigate treatments to decrease pain catastrophizing before surgery but gave no reduction. Further research investigating this problem is warranted.

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PART TWO – THE ARTICLE

Association between pain catastrophizing and postoperative pain intensity – a prospective cohort study

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Abstract

Background: Osteoarthritis is a painful condition, and prolonged pain is the main indication for knee replacement surgery. Serious complications are rare and most of the patients experience pain relief and improved function after surgery. However, a total of 15% of the patients are not satisfied with the result one year after surgery, and 5% are dissatisfied due to persistent pain and low physical function. The aim of the current study is to investigate if there is an association between preoperative pain catastrophizing (PCS) and postoperative pain eight weeks after total knee arthroplasty (TKA).

Methods: The study is a sub-study from a randomized controlled trial (RCT) consisting of 134 patients in 3 groups, receiving an allocated pain management intervention after knee replacement. Follow-up included pain on movement and pain at rest measured on a numerical rating scale (NRS). Pain catastrophizing were measured 1-3 weeks before surgery and 8 weeks after surgery, using the pain catastrophizing scale (PCS).

Results: Pain outcome on mobilization were reduced from mean (SD) 5.27 (2.23) preoperatively to 2.31 (2.21) eight weeks after surgery ($p<0.001$). Further, we found a significant decrease in mean (SD) PCS from 11.18 (9.59) before surgery to 6.26 (7.23) after surgery ($p<0.001$). Linear regression analyses found a weak association between preoperative pain catastrophizing and postoperative pain intensity, $p= 0.030$ (95% CI 0.004-0.081).

Conclusions: Preoperative pain catastrophizing is associated with higher postoperative pain intensity. There is a significant decrease in pain intensity and pain catastrophizing from before surgery to after surgery for TKA. The impact of high PCS score on the intensity of postoperative pain remains unclear and calls for further research in this field.

Trial registration:

Registered at clinicaltrials.gov (NCT02604446) on November 13, 2015.

Keywords: Pain catastrophizing, total knee arthroplasty, pain

Background

In 2019, 7797 total knee arthroplasties (TKA) were performed in Norway, an increase of 3.8% from 2018 (1). Osteoarthritis is a painful condition, and prolonged pain is the main indication for knee replacement surgery (2–5). Serious complications are rare and most patients experience pain relief and improved function after surgery (6). However, a total of 15% of the patients are not satisfied with the result one year after surgery, and 5% are dissatisfied due to persistent pain and low physical function (1,3–6). TKA is considered a painful procedure and pain after surgery may limit early mobilization. Physical activity after TKA may avoid complications as physical stiffness and persistent pain (2–5).

During the last 20 years, programs to enhance postoperative recovery and convalescence have been introduced. Amongst these is the so called "Fast-track surgery", a multimodal approach to patient care in the perioperative pathway. Evidence-based interventions in surgery and anaesthesia, pain management, patient education and early mobilization are elements of this program (7). Studies find positive effects of fast-track surgery, such as reduced morbidity and length of stay after knee arthroplasty (7,8).

Pain and function after TKA can be affected by mental distress, socioeconomic status, symptoms of anxiety or depression, and high levels of preoperative pain catastrophizing (9–11). Several studies suggest that patients with psychological symptoms need to be identified and consulted before surgery (9,10,12,13). Pain catastrophizing is defined as a maladaptive cognitive-affective response to pain that involves negative thinking regarding the pain experience (14). Pain catastrophizing has an impact on health related quality of life after surgery (13,15). Although studies have shown an association between preoperative pain catastrophizing and postoperative pain ((12,15–17)10,13,16,17), other studies have failed to detect a relationship between pain catastrophizing and chronic postsurgical pain (12,18).

The aim of this study is to see if there is an association between preoperative pain catastrophizing and postoperative pain eight weeks after TKA.

Method

Patients and setting

This study is a prospective cohort study, based on data from a single-center, prospective, randomized, double-blinded trial conducted at St.Olavs Hospital, Trondheim University, Norway. The study by Rian et al. (19) compared the effectiveness of tapentadol extended-release, oxycodone controlled-release, and placebo, as added to a multimodal analgesic regime both in-hospital and at home the first week after TKA. The data was collected from 15. November 2015 to 4. January 2019. Patients scheduled for surgery with total knee arthroplasty (TKA) between 18 and 80 years of age were considered for inclusion in the study. Exclusion criteria were cognitive impairment, inability to read or speak Norwegian, lack of cell-phone or wireless Wi-Fi connection at home or use of drugs or medical conditions that conflicted with one or more of the study drugs or any of the multimodal basal pain medications given in the study. One hundred and thirty-four patients completed the trial.

Upon participating, all patients were provided oral and written information about the study. Informed written consent was obtained from participants. This study was approved by the Regional committee for Medical and Health Research Ethics (2015/209/Rek-Midt) and the Norwegian Medicines Agency (15/01581-13), and registered at clinicaltrials.gov (NCT02604446) on November 13, 2015.

Patient population

Four hundred eighty-eight consecutive patients were considered for inclusion, of which 149 were included and randomized. A total of 134 patients in three study groups received their allocated intervention, of these a total of 125 patients filled out the PCS form at baseline and after 8 weeks and was included in the analysis.

Measures

Pain catastrophizing was measured by the Norwegian version of the pain catastrophizing scale (PCS) (20). The PCS is a self-administered form where you answer questions about feelings and thoughts when you experience pain. The form consists of 13 questions that are graded on a 5-point Likert scale where 0 is “not at all” and 4 is “all the time”. This results in a scale from 0-52, where high scores indicate a high degree of pain catastrophizing. Previous research have used a cut-off score of 20 to identify high pain catastrophizers (18,21,22). PCS was self-administered and registered on inclusion and eight weeks after surgery at the outpatient follow-up.

Pain was measured by Numerical Rating Scale (NRS), a commonly used 11-point one-dimensional pain intensity scale, where 0 is no pain and 10 is worst imaginable pain (23). The outcomes were pain on mobilization (walking) and pain at rest. Patients were asked “How much pain do you have now when you move”, and “How much pain do you have at rest”. Pain on movement was emphasized in this study, as movement of the knee is important for a successful knee arthroplasty.

NRS was used to register pain on mobilization and at rest, daily for seven consecutive days after surgery. Patient symptoms were obtained by self-registrations on a specially designed iPad application where all patients recorded all self-reports the first 8 days. The data collected through iPads were anonymized and wirelessly transferred to a separate database for storage. Pain on mobilization and at rest was also reported on a NRS at an outpatient follow-up eight weeks after surgery.

Baseline registration included ASA score (24) and Charlson Comorbidity Index (CCI) (25).

Statistical analysis

Statistical calculations were performed using IBM SPSS Statistics version 27. Demographic, medical and clinical data are presented as frequency (n) and proportions (%) for categorical data and mean and standard deviation (SD) for continuous data. Visual inspections of histogram and q-q plots were used to determine whether they were normally distributed or not. Preoperative pain (NRS) was the only variable normally distributed; all other variables was skewed. The Wilcoxon signed rank test was used when comparing PCS at baseline and 8 weeks after surgery. A difference variable of PCS was created, to analyse changes before and after surgery. The statistical significance level was set at $p < 0.05$.

Linear regression analysis was used to determine association between preoperative pain catastrophizing and postoperative pain. Pain on movement was identified as the main outcome variable. Baseline characteristics such as age, gender, length of stay and preoperative pain were considered as potential covariates and adjusted for in the regression analyses.

Results

Hundred and thirty-four patients were included in the study. Nine patients were excluded due to missing or incomplete PCS forms, resulting in a final population of 125 patients.

Baseline and demographic data are presented in **Table 1**.

Table 4 Baseline characteristics of the study population (n=125)

Characteristics	*Value*
Age, mean (SD)	61.6 (9.7)
Female gender, n (%)	67 (53.6)
ASA group 1, n (%)	37 (29.6)
ASA group 2, n (%)	84 (67.2)
ASA group 3, n (%)	4 (3.2)
CCI, mean (SD)	2.22 (1.6)
Length of stay, mean (SD)	2.20 (0.7)

ASA: American society of Anaesthesiologists classification, CCI: Charlson comorbidity index.

Pain and pain catastrophizing measured at baseline and 8 weeks after surgery, are presented in **Table 2**.

Table 5 NRS pain and PCS score at baseline and 8 weeks after surgery

	Baseline	*8 weeks*	*p-value*
NRS on movement, mean (SD)	5.27 (2.234)	2.31 (2.213)	p<0.001
NRS at rest, mean (SD)	2.56 (1.909)	1.76 (1.784)	p=0.038
PCS, mean, (SD)	11.18 (9.595)	6.26 (7.230)	p<0.001

NRS; Numerical rating scale, PCS; Pain catastrophizing scale

A total of 84.8% scored <20 on PCS at baseline, and 15.2% scored 20 or more. A total of 70% of the patients had a reduction in PCS after surgery, and 21% had higher PCS score (***Figure 3***). There were no association between pain catastrophizing and pain on movement in the group with increased PCS scores.

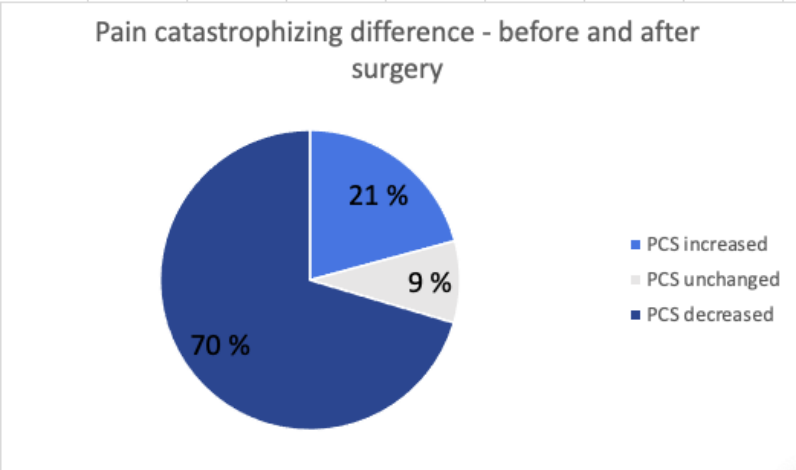

Figure 3 Changes in PCS from before to after surgery

Association between preoperative pain catastrophizing and postoperative pain performed by a linear regression analysis, is presented in ***Table 6***.

Table 6 Association between preoperative pain catastrophizing and postoperative pain 8 weeks after TKA

Variable	*R(R^2)*	*B*	*95% CI*	*Sig.*
PCS baseline	0.213 (0.045)	2.766 (Constant)	(0.004-0.081)	0.030

Dependent variable: NRS at movement at 8 weeks

Adjusted for confounding factors such as age, gender, and length of stay

PCS; Pain catastrophizing scale, NRS; Numeric rating scale

There were no association between preoperative PCS and preoperative pain at movement (p=0.065, 95% CI (-0.003-0.086)). There were an association between postoperative PCS score and postoperative pain at movement (p=0.005, 95% CI (0.021-0.114)).

Discussion

We found a weak association between preoperative pain catastrophizing and postoperative pain on mobilization. Our study suggest that pain catastrophizing is a factor which affect pain and function after TKA which is in line with other research (10,13,16,17,26–28). A Norwegian study (18) with nearly the same fast track trajectory as ours, found no association between pain catastrophizing and postoperative pain after TKA in 71 patients. We wanted to investigate if these results could be reproduced. However, differences in measurement methods (average pain versus pain on mobilization) together with a higher sample size in our study, makes it difficult to compare the two studies.

We found an overall decrease in pain and pain catastrophizing from before to after surgery. The surgery itself seems to provide a reduction in both pain and pain catastrophizing (29). Perceived pain can increase pain catastrophizing, while it seems that pain relief can lead to less pain catastrophizing (27,30). Studies have found pain catastrophizing to be a consistent psychologic predictor in of persistent pain in patient undergoing TKA (13,26), while others have failed to replicate this result (12,18). However, TKA is a surgical procedure which decreases pain, and may therefore reduce PCS. Different studies show that interventions such as total knee arthroplasty or physical therapy gives pain relief and also have an impact on pain catastrophizing (26,27,29,31).

Many variables affect pain and function after TKA. Sorel et al. (9) highlighted mental distress, symptoms of anxiety and/or depression as important factors for patients outcome after TKA. A study by Darnall et al. (32) shows that PCS increases with additional illnesses such as anxiety or depression. Birch et al. (10) found that patients with high levels of preoperative pain catastrophizing have lower physical function, more pain and poorer general health both before and after TKA, compared to patients without elevated pain catastrophizing. A study by Feldman et al. (11) found that patients with higher socioeconomic status had less pain and higher function after TKA, than patients with lower socioeconomic status. Several studies suggest that patients with psychological symptoms need to be identified and consulted before surgery (9,10,13,33). Yakobov et al. (13) suggests that psychosocial interventions designed to reduce pain catastrophizing might contribute to improved quality of life after surgery. A study by Lunn et al. (34) gave escitalopram, an antidepressant, to high pain catastrophizing patients, they found however no reduction in the postoperative pain. A study by Glette et al. (30) suggest that depression symptoms increases with increased pain and pain catastrophizing. Two studies who investigated the effect of coping skills training or cognitive behavioural patient education found no effect on pain catastrophizing (35,36). However, which

interventions are the most effective and will give the best improvements on the overall result remains unclear (29).

Limitation

This is a sub-study of a RCT comparing pain medication. The power analysis before the RCT was made on measurements of postoperative pain scores, not measurements of PCS-score. Our findings must be interpreted in that context. One of the exclusion criteria was use of drugs not compatible with the scheduled pain medication. This criterion excluded patients using anti-depressant drugs and anti-psychotic drugs. This may have affected pain catastrophizing scores in the study population.

Anxiety and depression were not included as variables in this study which could have made a contribution to interpretation of results.

Conclusions

We found a significant decrease in PCS from before surgery to after surgery. We found an association between preoperative pain catastrophizing and postoperative pain intensity. The impact of high PCS score on the intensity of postoperative pain remains unclear and calls for further research in this field.

Ethics approval

As stated in the method section, all participants signed a written informed consent. The study was approved by the regional committee for Medical and Health Research Ethics (2015/209/Rek-Midt) and the Norwegian Medicines Agency (15/01581-13).

Consents for publications

Not applicable.

Availability of data and material

Request for details in the study dataset can be submitted to the corresponding author. Human subject protection requirements, appropriate data privacy as well as institutional requirements must be met.

Abbreviations

ASA: American society of anaesthesiology classification; PCS: pain catastrophizing scale; TKA: total knee arthroplasty; NRS: numeric rating scale; CCI: charlson comorbidity index.

Competing interests

The authors declare that they have no competing interests.

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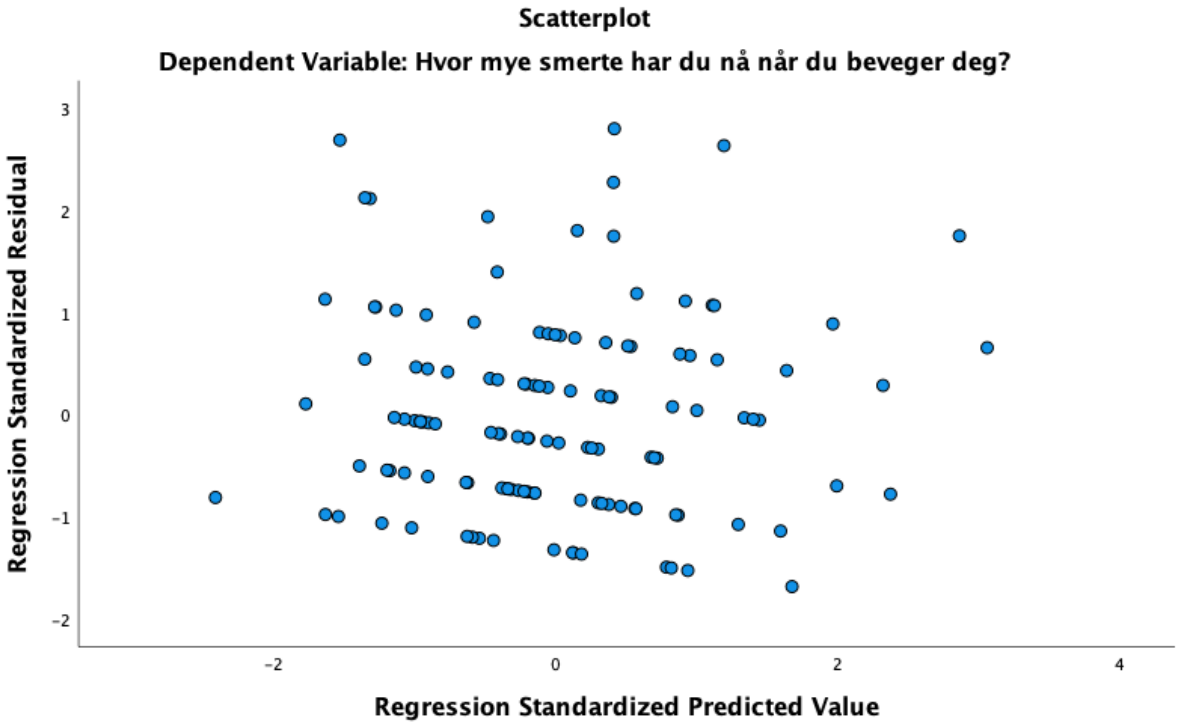
Appendix 1

Exclusion criteria:

- Contraindications for any of the study drugs
- Lactose intolerance
- Known hypersensitivity against any of the additives
- Chronic Obstructive Pulmonary Disease (COPD) grade 3 or 4
- Paralytic ileus
- Known alcohol or medical addiction/abuse
- History of asthma, urticaria or allergic reaction caused by acetyl salicylic acid or other NSAIDs
- Peptic ulcer
- Haemophilia
- Gastrointestinal bleeding
- Cerebrovascular bleeding
- Inflammatory bowel disease (ulcerous colitis, Chron disease)
- Concomitant use of the following drugs: ACE-inhibitors, AT2-blockers, SSRI, Anti-psychotic drugs, MAO-inhibitors, Atazanavir and Nelfinavir (medicine used for HIV-infection)
- Known kidney failure (creatinine level above reference value)
- Known heart failure (NYHA III-IV)
- Pregnancy
- Women in fertile age with risk of pregnancy
- Nursing women
- Operated under general anaesthesia without use of spinal anaesthesia
- Using opioids on a regular basis expect users of codeine or tramadol, or known former abuse of opioids
- Cognitive failure or other factors which make follow up impossible (for example language difficulties)
- No cell phone or internet connection at home (making follow up difficult)

Appendix 2

Scatterplot of the residuals in the multiple linear regression



Appendix 3

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK midt	Karoline Tammert	73597509	19.03.2015	2015/209/REK midt
			Deres dato:	**Deres referanse:**
			20.01.2015	2015-000295-94

Vår referanse må oppgis ved alle henvendelser

Torbjørn Rian
St. Olavs Hospital

2015/209 Bruk av langtidsvirkende smertestillende etter kneproteseoperasjon

Forskningsansvarlig: St. Olavs Hospital Prosjektleder: Torbjørn Rian

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK midt) i møtet 27.02.2015. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikkloven § 4.

Prosjektomtale

Studien skal gi kunnskap om nytten av langtidvirkende opioider (morfinpreparater) etter kneproteseoperasjon. Studien designes som en dobbelt blindet randomisert kontrollert studie. Vi vil sammenligne effekt og bivirkninger av depot tapentadol vs placebo vs depot oxycodon. Studien skal inkludere totalt 150 pasienter fordelt på tre grupper. Hovedendepunkt blir smerter ved mobilisering daglig i 8 dager etter operasjonen, og

delendepunkt vil være smerter i hvile samt bivirkninger som svimmelhet, kvalme, forstoppelse (obstipasjon), døsighet og søvnkvalitet. Målet er å se hvilket av de tre behandlingsmetodene som gir best smertelindring med minst bivirkninger. Resultatene vil være nyttig for smertebehandling etter kneproteser, men også for annen stor kirurgi. Det er ikke publisert lignende studier som er industri-uavhengige. De tre studiegruppene gjenspeiler tre ulike behandlingsregimer som har vært brukt de siste årene ved St. Olav, så vi vet at ingen pasienter får en dårlig behandling.

Besøksadresse:
Det medisinske fakultet
Medisinsk teknisk forskningssenter 7489
Trondheim

Telefon: 73597511
E-post: rek-midt@medisin.ntnu.no
Web: http://helseforskning.etikkom.no/

Vurdering

Komiteen oppfatter at denne studien tar sikte på å gi kunnskap om nytten av langtidvirkende opioider (morfinpreparater) etter kneproteseoperasjon. Det er en dobbelt blindet randomisert kontrollert studie. Formålet er å sammenligne effekt og bivirkninger av tre ulike studiearmer: depot tapentadol, placebo og depot oxycodon. Studien skal inkludere totalt 150 pasienter fordelt på disse tre gruppene. Hovedfokuset er på smerter ved daglig mobilisering i 8 dager etter operasjonen. Delfokuset er på smerter i hvile og bivirkninger som svimmelhet, kvalme, forstoppelse (obstipasjon), døsighet og søvnkvalitet. Resultatene vil være nyttig for smertebehandling etter kneproteseoperasjon, men også for annen kirurgi. De tre studiegruppene gjenspeiler tre ulike behandlingsregimer som har vært brukt de siste årene ved St. Olavs Hospital. Studien er samtykkebasert.

Forsvarlighet

Komiteen har vurdert søknad, forskningsprotokoll, målsetting og plan for gjennomføring. Under forutsetning av at vilkårene nedenfor tas til følge, framstår prosjektet som forsvarlig og hensynet til deltakernes velferd og integritet er ivaretatt.

Forbedring av informasjonsskriv

Komiteen ber om at informasjonsskrivet revideres i samsvar med følgende punkter:

1. At avkrysningsalternativet «Nei, jeg ønsker ikke å delta i studien» fjernes.
2. At REKs mal for informasjonsskriv benyttes. Malen er tilgjengelig på våre nettsider (Frister og skjemaer -> Maler for informasjon og samtykke).
3. At det beskrives ytterligere hva studien innebærer, hva deltakerne skal gjøre og eventuelle bivirkninger.
4. At det opplyses om at data fra 8-ukerskontrollen skal benyttes.
5. At det må opplyses om at studien er godkjent av Regional komité for medisinsk og helsefaglig forskningsetikk.
6. At informasjonsskrivet dateres.

Rekrutteringsprosedyre

Potensielle deltakere blir informert om studien av anestesilege på preoperativ poliklinikk. Komiteen ber om at de forespurte pasientene får informasjonsskrivet tilsendt i forbindelse med innkalling til kneproteseoperasjon. På denne måten får de tid til å tenke seg om, samtidig som de gis anledning til å stille oppklarende spørsmål til de som er best egnet til å gi gode svar. Svaret kan gis til eksempelvis en sykepleier ved avdelingen eller sendes per post. Dette ønsker komiteen skal gjøres for å unngå at pasientene føler seg presset til å delta. Komiteen ber om en bekreftelse på at dette vil bli gjort.

Vilkår for godkjenning

1. Bekreftelsen vedrørende rekrutteringen samt revidert informasjonsskriv skal sendes per e-post før studien igangsettes. Vennligst benytt post@helseforskning.etikkom.no og "REK midt 2015/209" i emnefeltet
2. Godkjenningen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden og protokollen. Prosjektet må også gjennomføres i henhold til REKs vilkår i saken og de bestemmelser som følger av helseforskningsloven (hfl.) med forskrifter.
3. Komiteen forutsetter at ingen personidentifiserbare opplysninger kan fremkomme ved publisering eller annen offentliggjøring.
4. Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og

omsorgssektoren». Av kontrollhensyn skal prosjektdata oppbevares i fem år etter sluttmelding er sendt REK. Data skal derfor oppbevares til denne datoen, for deretter å slettes eller anonymiseres, jf. hfl. § 38.

Vedtak

Regional komité for medisinsk og helsefaglig forskningsetikk Midt-Norge godkjenner prosjektet med de vilkår som er gitt.

Komiteen var enstemmig i sin beslutning.

Sluttmelding og søknad om prosjektendring

Prosjektleder skal sende sluttmelding til REK midt på eget skjema senest 01.03.2017, jf. hfl. §

12. Prosjektleder skal sende søknad om prosjektendring til REK midt dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang

Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK midt. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK midt, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

Sven Erik Gisvold Dr.med.

Leder, REK midt

Karoline Tammert

Seniorkonsulent

Kopi til:vigleik.jessen@stolav.no; siv.morkved@stolav.no; personvernombudet@stolav.no

FW: Endringsmelding 24.09.2020

Hei,

Ved behandling av endringsmelding ble den opne endringsmelding besvart ved en feiltagelse, det forekommer derfor feil i utsendt svarbrev om endringsmelding. Riktig endringsmelding er tatt til følge og dette oppdateres i rekportalen. Ønsker herved å holde deg orientert om dette.

Følgende endringer er tatt til følge:

- Ny estimertsluttdato 01.06.2024
- Ny prosjektmedarbeider Kristine Elise Rørmark.

REK midt har vurdert søknad om prosjektendring, og har ingen forskningsetiske innvendinger mot endring av prosjektet. Ny frist for innsending av sluttmelding er 01.12.2024.

Med vennlig hilsen

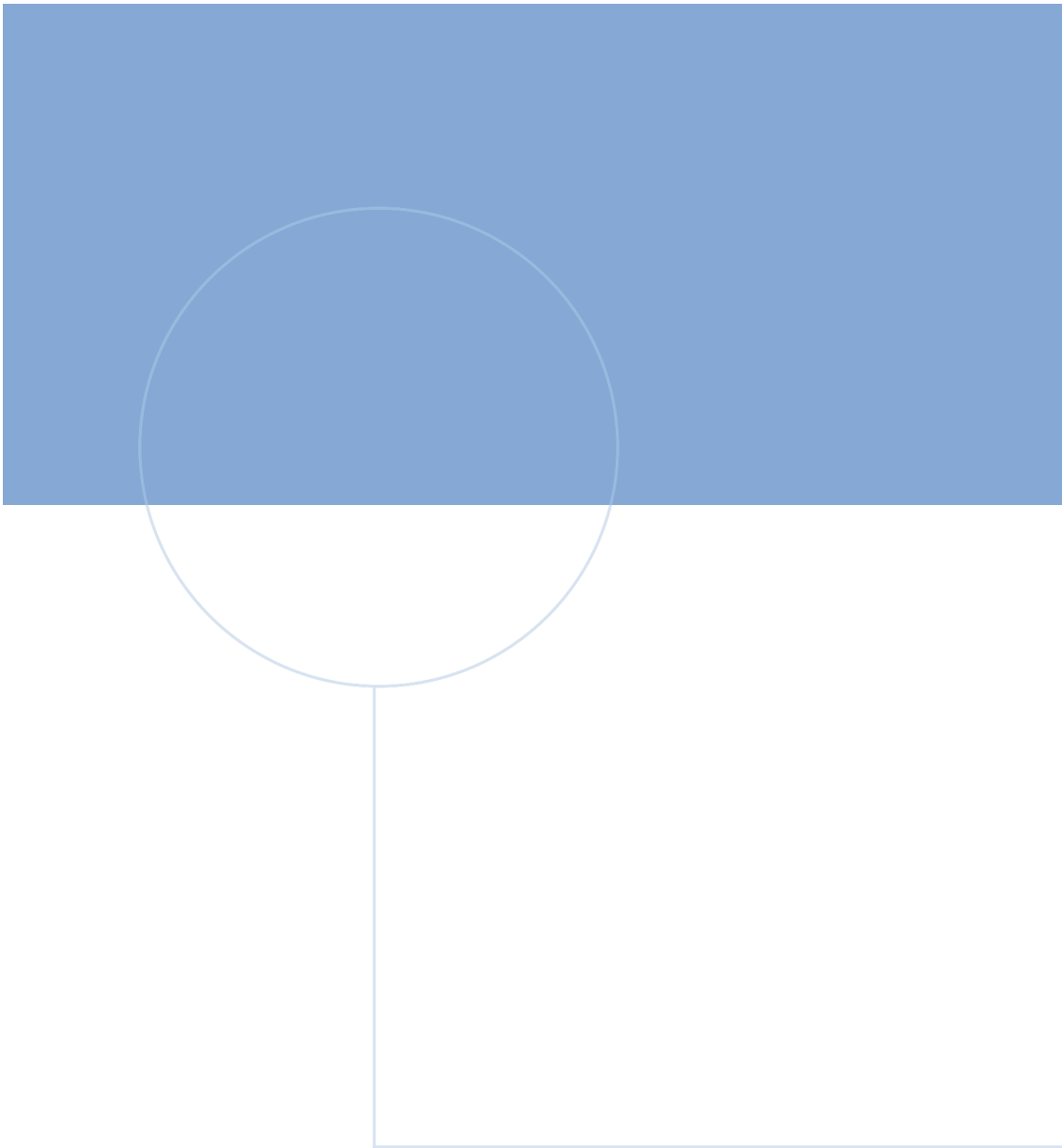
Rikka Frøyen Sande

konsulent, REK midt

Appendix 4

Guidelines for BMC musculoskeletal disorders.

https://bmcmusculoskeletdisord.biomedcentral.com/submission-guidelines/preparing-your-manuscript/research-article



NTNU

Norwegian University of
Science and Technology