OPAL STUDY OPTIMIZING PATHWAY FOR ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

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ENGLISH ABSTRACT

Objectives In the reconstruction of the anterior cruciate ligament (ACL) painkillers is used to reduce the amount of pain. Our aim was to improve the basis for postoperative paint treatment using KOOS and the pain threshold before surgery. Further investigate the vivo metabolic changes in the skeletal muscle.

Methods 6 patients (age 19-32) with ACL lesion were included in the prospective cohort study from 19th October to 7th December 2015. The patients underwent the standard procedure for reconstruction of the ACL. Before surgery patients reported KOOS, EQ-5D-5L and PainDetect Questionnaires. Further the pain threshold and pain sensibility were investigated with a digital pressure pain threshold algometer (PPT) and the pain stimulus from a mechanic spring-clamp (MSC). MiD was used to investigate the vivo metabolic changes in the skeletal muscle tissue during the surgery and shortly after. Glucose, lactate, pyruvate and glycerol and lactate/pyruvate ratio (L/P ratio) was used as indicators of tissue ischemia.

Results

In four of the five KOOS subscales the ACL lesion patients scored significantly worse compared to the reference population. EQ-5D-5L showed xx. PD-Q preoperative showed that the pain was nociceptive pain.

Preoperatively patients reported high pressure point threshold (PPT) and there were none significant difference before and after applying the pain stimulus.

Microdialysis showed highly increase of the concentration of glycerol and L/P-ratio (lactate/pyruvate-ratio) during the operation.

Discussion

With our results from KOOS, pain threshold and microdialysis, there is a basis for an improvement the pain management. There are still many aspects that needed to be investigated before we can make a definitive conclusion.

Key words ACL reconstruction, microdialysis, pain threshold, KOOS, EQ-5D, PainDetect.

DANSK ABSTRAKT

Introduktion I forbindelse med rekonstruktion af forreste korsbånd er smertestillende anvendt for at reducere smerterne. Vores formål var at forbedre grundlaget for den postoperative smertebehandling ved at undersøge KOOS og smertetærsklen før operationen. Yderligere at undersøge de vivo metaboliske ændringer i skeletmuskulaturen.

Metode 6 patienter (alder 19-32) med forreste korsbåndsskader var inkluderet i det prospektive kohorte studie fra den 19. oktober til den 7. december 2015. Patienterne gennemgik standard proceduren for rekonstruktion af forreste korsbånd. Før operation skulle patienterne udfylde spørgeskemaer for KOOS, EQ-5D-5L and PainDetect. Yderligere blev smertetærsklen og smertesensibiliteten undersøgt vha. et digitalt trykalgometer og et smertesimuli påført af en mekanisk klemme.
Mikrodialyse blev brugt til at undersøge det vivo metaboliske ændring i skeletmuskulaturen gennem operationen Glukose, laktat, pyruvat, glycerol and laktate/pyruvate-ratio blev brugt som indikatorer for iskæmi i muskelvævet.

Resultater
I fire af fem KOOS subskaler reporterede forreste korsbånds patienter signifikant dårligere sammenlignet med den raske befolkningen. EQ-5D-5L viste xx. PD-Q før operationen viste at smerterne var nociceptive smerte. Før operationen patienterne angav høje værdier for smertetærsklen og der var ingen signifikante forskelle på smertetærsklerne efter at der var blevet påført smertestimuli med den mekaniske klemme.
Mikrodialyse viste høje stigninger i koncentrationerne af glycerol og L/P-ratio gennem operationen.

Diskussion

Med vores resultater fra KOOS, smertetærskelmålingerne og mikrodialyse, er der grundlag for en forbedring af smertebehandlingen. Der er stadig mange aspekter der skal undersøges før at vi kan lave en definitiv konklusion.

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ABBREVIATIONS

ACL	Anterior Cruciate Ligament
MiD	Microdialysis
L/P-ratio	Lactate/Pyruvate-ratio
QoL	Quality of Life
PPT	Pain Pressure Threshold
KOOS	Knee Injury and Osteoarthritis Outcome Score
VAS	Visual Analogue Scale
EQ-5D	EuroQol Group 5-Dimension Self-Report Questionnaire
PD-Q	PainDetect Questionnaire
PPT	Pain Pressure Threshold
MSC	Mechanic Spring-Clamp
CRF	Case Report Form
CPM	Conditioned Pain Modulation

OPAL STUDY - OPTIMIZING PATHWAY FOR ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

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Introduction

Background

Every year 2700 patients in Denmark is undergoing reconstruction of the anterior cruciate ligament (ACL) (1).

The improvements in surgical techniques and rehabilitation programs in ACL reconstruction have a highly success rate in the sports medicine (2). Less than 3 % of the patients need a second surgery within the first two years (3)(4).

Nevertheless, postoperative patients still experience pain and reduced Quality of Life (QoL) after the surgery (1). The postoperative period is characterized with pain. The pain is coming from bones and muscles, and this may cause a longer hospitalization after surgery and delay the rehabilitation. The metabolic changes in the tissue during the reconstruction of ACL aren't known. Metabolites as glucose, pyruvate, lactate, glycerol and L/P-ratio are indicators of ischemia. The glycerol indicates the cell damage (5) (6) (7) (8). During ischemia, lactate increases and pyruvate decreases, and leading to an increased L/P-ratio - a ratio above 25 is considered abnormal (9). These metabolic changes have a influence on the outcome of pain (8).

We know that the first hours and days after surgery is the most painful period. It is important that the patient in this period is receiving a sufficient pain treatment. After the discharge from the hospi-

tal, it is the patient himself that administrated the analgesic treatment prescribed by the surgeon. Often the patients first take the analgesics when the pain is present, and therefore there will be a period with pain until the analgesics have the full effect.

The research question was whether pre-operative CPM and per-operative microdialysis can be related to postoperative pain after ACL reconstruction.

The hypothesis was CPM and microdialysis indicate a basis for improvement of pain treatment after ACL reconstruction.

The aim of this prospective study was to measure the pain profile and the surgical stress response in the soft tissue under the reconstruction of the ACL. With this, create basis for future optimization of the perioperative period after reconstruction of the ACL.

Materials and Methods

Study design

This prospective cohort study was conducted at Aalborg University, Aalborg, Denmark.

Participants

6 patients aged 19-32 scheduled for reconstruction of unilateral ACL was included (Figure 1 - flowchart). Baseline characteristics are presented in Table 1. Exclusion criteria according to the protocol; missing informed consent or ability to read/understand Danish, absent of collaboration, body-mass index >35, height <160 cm, severe obesity or oedema of crus, missing pedal pulse, pregnancy, drug abuse, diabetes mellitus, rheumatoid arthritis, peripheral vascular disease, neurologic diseases, musculoskeletal diseases, psychiatric diseases and known knee disease (cysts or other defects in the knee).

TABLE 1. Baseline Characteristics of the included Patients

Characteristic	Males (n=5)	Females (n=1)
Age at surgery, year	24.4 ± 4.9	32
Body-mass index ⊗	25.1 ± 1.5	25.9
Injured knee (right), %	60	0
Graft type		
Patellar tendon graft	2	1
Hamstring tendon graft		
KOOS scores∫		
$KOOS_4$	59.5± 6.2	56
Pain	74.4 ± 12.3	64
Symptoms	63.6 ± 9.6	61
Activities of daily living	82.6 ± 13.6	81
Sports and recreation	35.0 ± 12.7	10
Quality of life	28.8 ± 10.5	19
EQ-5D ∉		
EQ-5D index	0.680 ± 0.084	0.757
EQ-5D VAS	79 ± 16.4	80
Used pain medication in the past week		
Cause of injury, no.		
Soccer	2	
Team Handball		
Downhill skiing/telemark		1
Other/unspecified sports	3	

⊗ The body-mass index is the weight in kilograms divided by the square of the height in meters.

∫ Scores on the Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales range from 0 (worst) to 100 (best). $KOOS_4$ is the mean score on the pain, symptoms, ADL and QoL subscales.

∉ The three-level version of the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D) includes both the EQ-5D descriptive index (with scores ranging from -0.59 to 1.00) and the EQ-5D visual analogue scale (with scores ranging from 0 to 100); higher scores indicate better QoL.

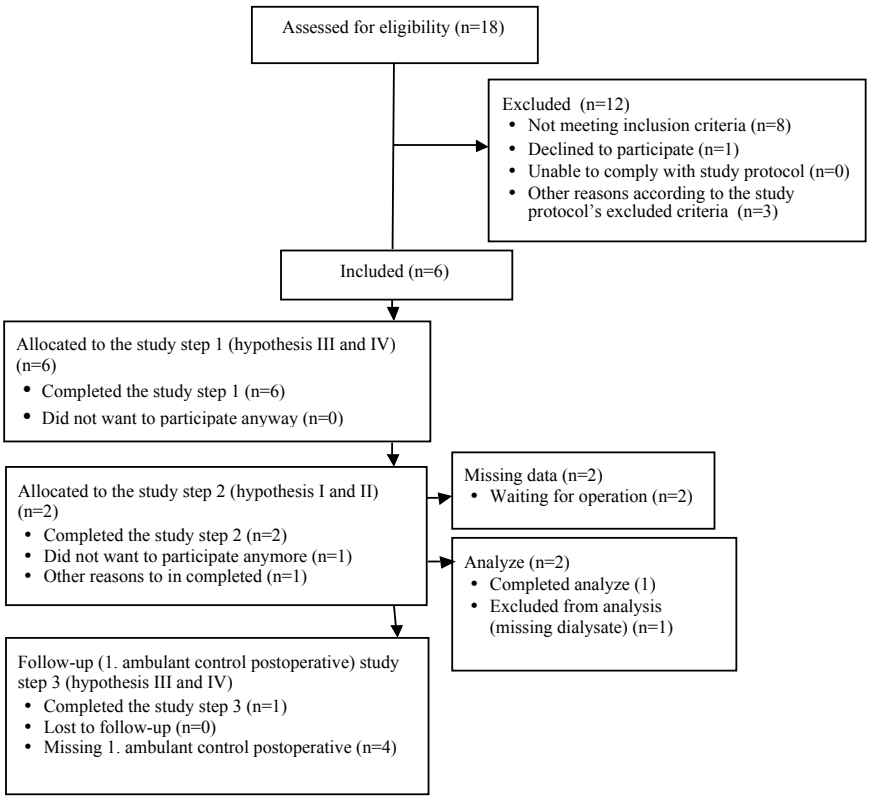

Figure 1. Consort flow chart of the ACL lesion patients.

Variables

Self-reported outcome

The patients answered in questionnaire about their medical history, permanent and analgesia medicine. Further they answered a knee-specific questionnaire, KOOS, and a generic questionnaire, EQ-5D, before surgery (preoperative) and at the first consultation postoperatively.

The patients rated their knee and associated problems by the Danish version of the KOOS (10). KOOS is a valid, reliable, and responsive disease-specific self-administered questionnaire for patients with knee injury and knee osteoarthritis. KOOS comprises five subscales; pain, other symptoms, function in daily living (ADL), function in sport and recreation (Sport/Rec) and knee related Quality of Life (QoL). Missing data were treated according to the user's guide (11).

The EQ-5D is a generic measure of health status (12)(13). The EQ-5D comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In the end of the questionnaire the EQ VAS (vertical, visual analogue scale) records the self-rated overall health.

PainDetect Questionnaire (PD-Q) is a reliable screenings tool to distinguish neuropathic pain from nociceptive pain (14). The PD-Q comprises different aspects of the pain; pain course pattern and radiating pain. To indicated the likelihood of a neuropathic pain component, the final score should between -1 and 38 (14).

Pain Threshold

Before and after surgery patient's pain and sensibility were investigated with a digital pressure pain threshold (PPT) algometer (Somedic, Sweden) and a mechanic spring-clamp (MSC). They were positioned comfortably supine. Before starting the measurements, the participants were introduce to the experiment and they were asked how they rate their pain on the Visual Analog pain Scale (VAS) before starting the PPT measurements.

The pressure pain threshold was defined according to the certain pressure points to establish the participants pressure pain topography. A mechanic pressure stimulus was applied with a 1-cm^2 probe and a pressure gradient of 50 kPa/s. The pressure gradually increases until the participant experienced discomfort/pain (VAS 3) and pressed at the stop button. The probe was held perpendicular to the skin and the PPT measurements overlapped each other for the different pressure points. The pressure force (kPa) was recorded on the PPT algometer and was noted in CRF.

The PPT was producing eight stimuli in the knee area (corresponding to Figure 2, no. 3 medial, no. 7 lateral) and one at the tibia. As control point m. extensor carpi radialis longus dxt. were used. The procedure was preformed two times, and in between MSC was promote diffuse noxious inhibitory control (DNIC). The MSC was producing a pressure for 10 seconds and thereafter the patient was asked what the pain was at VAS.

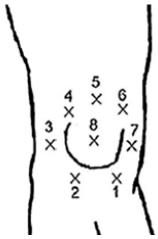

Figure 2. Pressure points.

Microdialysis

In the study CMA 63 catheters (CMA Microdialysis AB, Sweden) (length 30 mm, outer diameter 0.6 mm and molecular cut off 20 kDa) were used in skeletal muscle (m. quadriceps femoralis) of the leg with ACL lesion. After the patient was placed in anaesthesia one MiD catheter was inserted parallel to the muscle fibers in m. quadriceps femoralis (angle of 35°).

The catheter was connected to a syringe filled with 2.5 ml perfusion fluid T1 (CMA Microdialysis AB, Sweden) that was placed in CMA 106 MiD pumps, which constant perfused at a rate of 0.3 µl/min. Before starting, the microdialysis probe was calibrated in 30 minutes. The calibration is

needed to draw conclusions about concentrations in the periprobe fluid (15). To calibrated the probe, the 106 Microdialysis Pump was used to flush the catheters with sterile perfusion fluid (according to the instruction from M dialysis AB, Sweden, Appendix A).

After the calibration period, the dialysates were regularly collected every 20th minute during a period of minimum 2 hours. The catheter in m. quadriceps femoralis was collecting dialysate to analyze the metabolic changes.

The ISCUS*flex* MiD analyzer (CMA Microdialysis AB, Sweden) with Reagent Set A, was used to analyze the collected samples of glucose, lactate, pyruvate and glycerol.

Bias

The amount of included patients in the study may below, and therefore the power isn't as high as wanted.

Further the microdialys catheters are placed without ultrasound and therefore we can't be sure if they are placed correctly.

Quantitative variables

All the quantitative variables were reported in case report form (CRF).

Statistical methods

In all the analysis *p* values less than or equal to 0.05 were considered statistically significant. Analyses were preformed with the use of Stata software, version 14.0 (StataCorp) or Microsoft ® Excel ® for Mac 2011, version 14.4.7.

The assumption of distribution variables was checked visually by QQ-plots. The reported values of KOOS were placed in an Excel metric. Data were expressed with mean and SD, and by unpaired two-sample *t* test compared to the reference values for healthy people (16).

EQ-5D were expressed with mean and SD, and by unpaired two-sample *t* test compared to the reference values for healthy people (17).

PD-Q were expressed with mean and SD, and by unpaired two-sample *t* test compared to the reference.

Pain threshold analysis. The assumption of normal distribution of the variables was checked visually by QQ-plots. Continuous data were expressed as mean and SD. By unpaired two-sample *t* test compared PPT before and after the applied pain stimulus.

The metabolic changes monitored by microdialysis during surgery and reperfusion is illustrated in a diagram and descriptive described. The samples was analysed in ISCUS*flex* MiD analyzer (CMA Microdialysis AB, Sweden).

Study size. To determine the sample size, Stata software, version 14.0 (StataCorp) was used. With a sample of 10 patients we have 80 % power to detect a difference of 1 SD with a significant level at 5 % with the using of a two-sided unpaired *t*-test (Figure 3).

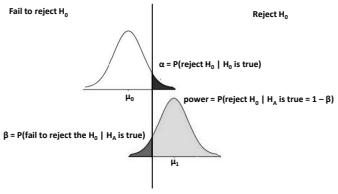

Figure 3. Sample size calculation.

Study Oversight

The study complied with the principles of the Declaration of Helsinki and was approved by the local Ethics Committee of the North Denmark Region (N-20150035) and the Danish data registry (approval N-2015-67).

Results

By the 19th October to 7th December 2015 6 patients were enrolled in the study; 1 patient completed the study (Figure 1). Preoperative baseline characteristics were similar.

Outcomes

Preoperative Score – KOOS data compared with reference data

Preoperatively patients generally reported worse KOOS scores compared to the established reference population (16) for all the KOOS subscales (Table 2). In four of the KOOS subscales (KOOS Pain, KOOS Symptoms, KOOS Sport/recreation and KOOS QoL) the ACL lesion patients scored significantly worse compared to the reference population (Table 2)(16). Especially the ACL lesion patients KOOS there were showed a significant (p = <0.0001) reduction on KOOS Sport/recreation and KOOS QoL (Table 3). The mean EQ-5D-5L index preoperative compared to the established Danish reference norms (Table 2) (17) were showed a significant difference (p = <0.001) in reported health status. The reported PD-Q preoperative showed that the pain that the patients with ACL rupture, were experience were nociceptive pain (Table 2).

Table 2. Crude Mean (± SD) and *p value* for Male and Female Patients Self-reported Knee Injury and Osteoarthritis Outcome Score and EQ-5D Preoperatively And Reference*

	Preoperative				
	Males (mean, SD) (n = 5)	**Reference males** (16) **(mean, SD)**	***p* value males**	**Females (mean, SD)** (n = 1)	**Reference females**(16) **(mean, SD)**
KOOS Pain	74.4 ± 12.3	92.2 ± 11.2	0.012	64	92.2 ± 11.2
KOOS Symptoms	63.6 ± 9.6	87.2 ± 13.9	0.001	61	87.2 ± 13.9
KOOS ADL	82.6 ± 13.6	94.2 ± 10.0	0.094	81	92.1 ± 14.0
KOOS Sports/recreation	35.0 ± 12.7	85.1 ± 20.8	<0.001	10	89.1 ± 13.5
KOOS QoL	28.8 ± 10.5	85.3 ±19.2	<0.001	19	95.2 ± 11.6
EQ-5D index	0.680 ± 0.084	0.930*	<0.001	0.757	
EQ-5D VAS	79 ± 16.4			80	
PainDetect[1]	7 ± 2.9				

** Danish reference index EQ-5D* (17). *[1]PainDetect; value <12 indicate nociceptive pain.*

Preoperative Score – Pressure Pain Threshold (Conditioned Pain Modulation)

Preoperatively patients reported high pressure pain threshold (PPT) and there were none significant difference (Table 3) on all the pressure points after the applying of the pain stimulus at the thumb.

Table 3. Crude Mean (± SD) and *p value* for Male and Female PPT

	Preoperative				
	Males (mean, SD) (n = 5)			Females (mean, SD) (n = 1)	
	Before MSC	After MSC	*p* value males	Before MSC	After MSC
1 point	624.2 ± 170.3	543.0 ± 174.8	0.4781	392	458
2 point	565.2 ± 129.4	562.6 ± 154.4	0.9777	353	404
3 point	530.0 ± 178.2	574.8 ± 169.2	0.6942	347	399
4 point	545.4 ± 169.1	558.8 ± 146.7	0.8968	436	397
5 point	579.2 ± 207.7	685.4 ± 258.1	0.4938	418	431
6 point	590.4 ± 181.3	548.0 ± 155.1	0.7015	458	422
7 point	596.4 ± 199.4	625.6 ± 195.6	0.8210	328	324
8 point	494.2 ± 165.3	561.2 ± 222.8	0.6038	191	308
Tibia point	714.4 ± 189.1	669.2 ± 165.1	0.6977	401	346

MSC: A mechanic spring clamp that applied a pain stimulus for 10 seconds at the thumb.

Operative Outcome – Metabolic changes

Microdialysis of the metabolic changes during the reconstruction of the ACL lesion and after end reconstruction showed a highly increase of the concentration of glycerol and L/P-ratio (lactate/pyruvate-ratio) until 80 minutes after the beginning of the operation. After the 80 minutes the concentration of glycerol and L/P-ratio decreases and nearly at zero at the last observation after 160 minutes. At the same time where we see a decrease of glycerol and L/P-ratio, the concentration of pyruvate is increasing. The increase in the concentration of glycerol and L/P-ratio indicate cell damage and ischemic as a response to surgery (Figure 3). The concentration of glucose and lactate is stabile through the reconstruction period and after surgery.

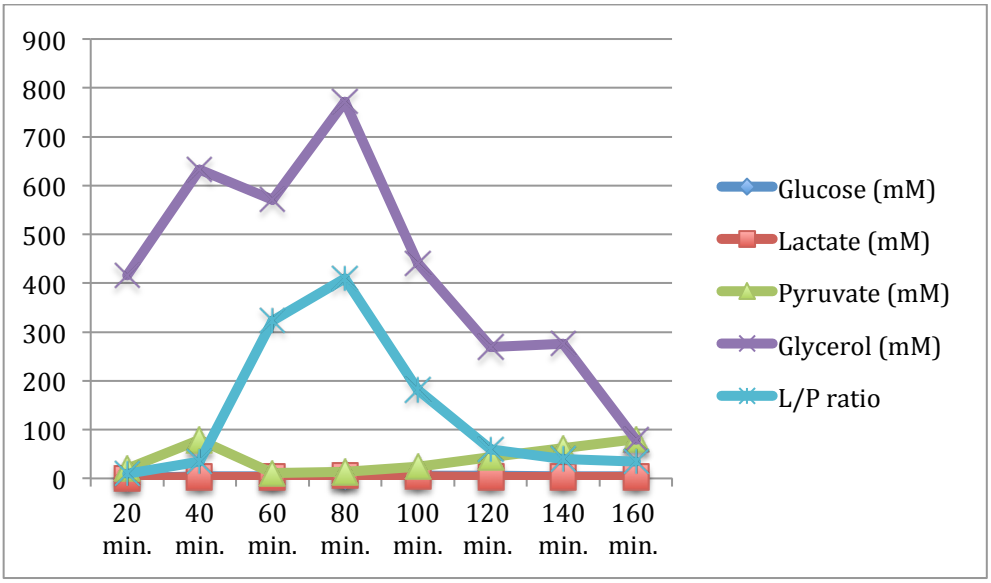

Figure 4. Microdialysis – metabolite changes.

Discussion

In this study the patients preoperatively reported significantly worse in four of the KOOS subscales (KOOS Pain, KOOS Symptoms, KOOS Sport/recreation and KOOS QoL) compared to the reference population. Further MiD showed a highly increase of the concentration of glycerol and L/P-ratio (lactate/pyruvate-ratio) until 80 minutes after the beginning of the operation, as a sign of cell damage and ischemia. Even after the end of surgery the metabolite of glycerol and L/P-ratio (lactate/pyruvate-ratio) were increases a while and there after decrease.

The reconstruction of ACL rupture is one of the most successful surgeries in Orthopaedic Sports Medicine. Through the passed years the non-operative treatment of physiotherapy have been first choice of treating ACL rupture if the patients wasn't elite athlete at the point of trauma. None of our patients in the study were elite athletes at the time of the trauma, however it doesn't change the fact that the patients have reported significantly worse on four KOOS subscales compared to reference population. Generally the Danish population reported highly values in all the KOOS subscales (16). In a meta-analyse of David E. Ramski et al. (18), patients who underwent non-operative and de-

layed treatment expired more instability later return to previous activity levels compared to patients treated with early surgical stabilization.

Pain treatment is an on-going discussion point in science of medicine. In this study we performed a pain profile for the patients with ACL rupture. The preoperatively PPT measurement showed that the patients had a relatively high pain threshold on all the pressure points. It could indicate that the patients with ACL rupture are accustomed to endure pain on daily basis, and therefore score higher on their pain threshold. And with none significant difference in the PPT after pain stimulus from the MSC. With this in mind, the staff (surgeons and nurses) around the patients should be aware of the fact that the patients have this high pain threshold and therefore can be difficult to cover the pain before and after reconstruction.

MiD is recognized as a useful tool to assess metabolic changes in skeletal tissue in clinical settings (8)(6)(19)(7). We determined that microdialysis is an effective way to monitor interstitial levels of metabolites during the reconstruction of ACL induced ischemia. The period of interest was when the knee was exposed to ischemia during the reconstruction and time of reperfusion. The main findings showed that the relatively short surgery caused ischemia and cell damage measured by metabolites. Ischemia is induced in the knee area until 80 minutes after start of surgery. The ischemia was almost reversible after 160 minutes after the start of the surgery. The MiD catheters are placed without ultrasound and therefore we can't be sure of that they are placed correctly Even though not using ultrasound to inserted the MiD catheter in the muscle should have any effects, the finding of the metabolic changes during surgery is so significantly high, that we recognized that the monitored metabolic changes is correct. To our knowledge, this study is the first to assess the ischemic changes during ACL reconstruction.

Microdialysis is a minimal invasive technique that has limited risks for patients and even with small

concentration volumes the ischemic changes can be monitored. The sampling of interstitial fluids can continuous be collected. Microdialysis contains a major limitation when estimating data because only an approximation can be stated. Recovery depends of many factors that affect the equilibrium, to achieve the highest recovery we used the largest membrane recommend to skeletal tissue and the lowest perfusion rate allowed. Most of the clinical studies available use relative recovery and by using very low flow recovery will be reaching near hundred per cent.

Glycerol is a component of the cell plasma membrane and released into the interstitial space when the cells undergoing damaged during surgery. Glycerol can be used as a marker if cell destruction. In previous studies (8) the high levels of glycerol had been explained by the catecholamine response, that initiate a lipolysis reaction in the skeletal muscle (20) produced by the used of tourniquet. In this study the surgeon wasn't using tourniquet during the surgery and therefore it can't be apart of the explanation of the high level of glycerol during surgery until 80 minutes after started surgery.

A precise marker of cell ischemia is L/P-ratio (5). In our study we observed a highly increase of the L/P-ratio until 80 minutes after started surgery. After 160 minutes from the start of the surgery the L/P-ratio levels were almost back to normal. Muscles are relatively resistant to ischemia, but even shorter periods (as the procedure of ACL reconstruction) of ischemia may in an overload of calcium in the muscle (6). This should be taken into the consideration if the procedure of the ACL reconstruction could be change, so the patients would experience an even shorter period of ischemia if possible.

Key results

We can conclude that the method of PPT and MiD can be used to measure pain and metabolic changes that indicate ischemia and cell damage in skeletal muscle tissue during the reconstruction

of ACL. Thereby confirm our hypothesis, that CPM and microdialysis can indicate a basis for improvement of pain treatment after ACL reconstruction. But because of the small sample size, it is necessary to verify the method with a larger sample size.

With our results from KOOS, pain threshold and microdialysis in mind, there is a basis for an improvement of the recommendation of treatment non-operative and operative, and the pain management. There are still many aspects that needed to be investigated before we can make a definitive conclusion.

Limitations

We can concluded that the method of PPT and MiD can be used to the measure pain and metabolic changes that indicate ischemia and cell damage, but because of the small sample size it is necessary to verify the method with a larger sample size.

Interpretation

Preoperatively the patient reported significantly worse in four of the KOOS subscales (KOOS Pain, KOOS Symptoms, KOOS Sport/recreation and KOOS QoL) compared to the reference population.

MiD showed that the vivo metabolic changes of ischemia and cell damage are increasing even after the end of the operation.

Funding

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APPENDICES

Appendix A: Instructions for use 63 MICRODIALYSIS CATHETER, M dialysis AB, Sweden

Appendix B: Questionnaire

Appendix A. Instructions for use 63

MICRODIALYSIS CATHETER, M dialysis AB, Sweden

μdialysis

M Dialysis AB
Hammarby Fabriksv 43, SE-120 30 Stockholm, Sweden.
Phone: +46 8 470 1020 Fax: +46 8 470 1055
E-mail: info@mdialysis.com
Web: www.mdialysis.com

DK

Brugerinstruktion
63 MICRODIALYSIS CATHETER

TILTÆNKT BRUG
63 Microdialysis Catheter er beregnet til at udføre mikrodialyse i adipost væv, afslappet skeletmuskler eller hepatisk væv under åben operation.

ANVENDELSE
BEMÆRK: For det implanteres i de adipøse væv, bør membranen forvædes. Vi anbefaler to måder hvorpå dette kan gøres:

- Dyp membranen i steril perfusionsvæske i et par sekunder, **eller**
- Anvend 106 eller 107 Microdialysis Pump til at gennemskylle kateteret med steril perfusionsvæske. Fjern ikke den beskyttende slange rundt om kateteret under gennemskylning.

Udvis forsigtighed, således at kateteret ikke bliver usterilt.

Implantering subkutant eller intramuskulært
Følgende procedure skal udføres under aseptiske betingelser ved medicinsk uddannet personale.

1. Tag et fast greb i huden med underliggende fedtvæv og lav et hul kun gennem huden med førstikkeren. Afbræk håndtagene på den delbare indfører inden indsættelse for at undgå skade på kropsvævet. Indfør indføreren helt til håndtaget på den delbare slange ind i det adipose eller det afslappede skeletmuskelvæv.

2. Fjern forsigtigt indførerens nål mens den delbare slange holdes på plads. Indførerens nål må ikke indføres igen efter den er fjernet. Observer for blødning. **Hvis der forekommer en omfattende blødning, skal indføreren fjernes.**

3. Skru af og fjern den beskyttende slange fra kateteret, ved at dreje den mod uret. **BEMÆRK: Udvis forsigtighed når den beskyttende slange fjernes, således at membranen ikke ødelægges i den distale ende af kateteret.**

4. Indfør forsigtigt Microdialysis Catheter i den delbare slange. **Rør ikke ved kateterets hvide membran.**

Anvisningerne nedenfor under nr. 5 kræver to personer.

5. Hold Microdialysis Catheter i denne position, omkring væskekrydset. Tag fat i den delbare slanges flige (man skal bruge tre hænder) og træk figene væk fra hinanden, væk fra det indførte kateter, indtil slangen deles (splittes) i hele sin længde. Derefter bortskaffes plastikfligene straks.

6. Hvis det er nødvendigt, hæftes kateteret forsigtigt. Anvend venligst fikseringsanordningerne (12,13) der er inkluderet i pakken.
Monter silikoneslangen (12) på **skaftet**. Placer fikseringsanordning (13) over silikoneslangen og fastgør den med stramme suturer. Suturerne bør ikke placeres direkte på skaftet, hvilket kan blokere strømmen.

7. Hvis det er nødvendigt kan Microdialysis Catheter også fikseres til **huden** med suturer omkring kateterets stopper (6).

8. Dæk indføringsstedet med en beskyttende bandage, f. eks. Tegaderm®, OpSite® eller lignende.

9. Forbind indløbsslangen til 106 Syringe, fyldt med perfusionsvæske , og indsæt et mikroprøveglas ind i mikroprøveglasholderen.

10. Placer sprøjten i 106 eller 107 Microdialysis Pump, og luk låget.

Appendix B. Questionnaire

Helbredsspørgeskema EQ-5D - Danmark

Under hver overskrift bedes du sætte kryds i DEN kasse, der bedst beskriver din helbredstilstand I DAG.

BEVÆGELIGHED

- Jeg har ingen problemer med at gå omkring ☐
- Jeg har lidt problemer med at gå omkring ☐
- Jeg har moderate problemer med at gå omkring ☐
- Jeg har store problemer med at gå omkring ☐
- Jeg kan ikke gå omkring ☐

PERSONLIG PLEJE

- Jeg har ingen problemer med at vaske mig eller klæde mig på ☐
- Jeg har lidt problemer med at vaske mig eller klæde mig på ☐
- Jeg har moderate problemer med at vaske mig eller klæde mig på ☐
- Jeg har store problemer med at vaske mig eller klæde mig på ☐
- Jeg kan ikke vaske mig eller klæde mig på ☐

SÆDVANLIGE AKTIVITETER *(fx. arbejde, studie, husarbejde, familie- eller fritidsaktiviteter)*

- Jeg har ingen problemer med at udføre mine sædvanlige aktiviteter ☐
- Jeg har lidt problemer med at udføre mine sædvanlige aktiviteter ☐
- Jeg har moderate problemer med at udføre mine sædvanlige aktiviteter ☐
- Jeg har store problemer med at udføre mine sædvanlige aktiviteter ☐
- Jeg kan ikke udføre mine sædvanlige aktiviteter ☐

SMERTER/UBEHAG

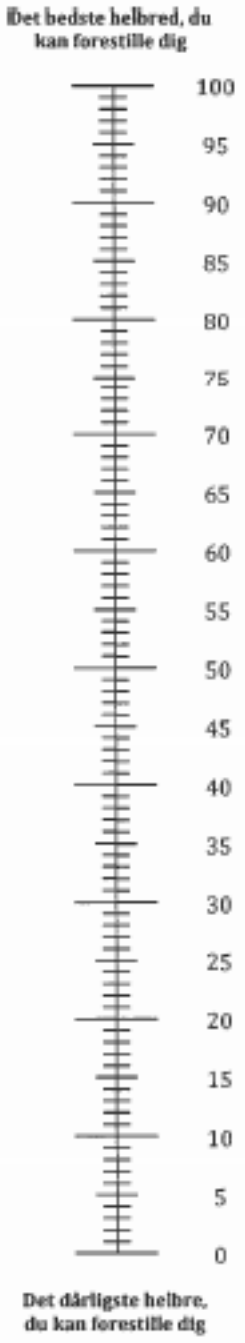
- Jeg har ingen smerter eller ubehag ☐
- Jeg har lidt smerter eller ubehag ☐
- Jeg har moderate smerter eller ubehag ☐
- Jeg har stærke smerter eller ubehag ☐
- Jeg har ekstreme smerter eller ubehag ☐

ANGST/DEPRESSION

- Jeg er ikke ængstelig eller deprimeret ☐
- Jeg er lidt ængstelig eller deprimeret ☐
- Jeg er moderat ængstelig eller deprimeret ☐
- Jeg er meget ængstelig eller deprimeret ☐
- Jeg er ekstremt ængstelig eller deprimeret ☐

- Vi vil gerne vide, hvor godt eller dårligt dit helbred er I DAG.
- Denne skala er nummereret fra 0 til 100.
- 100 svarer til det bedste helbred, du kan forestille dig.
  0 svarer til det dårligste helbred, du kan forestille dig.
- Sæt et X på det sted på skalaen, der viser, hvordan din helbredstilstand er I DAG.
- Skriv derefter det tal, du har markeret på skalaen, ind i boksen nedenunder.

DIT HELBRED I DAG =



KOOS
Spørgeskema til knæpatienter

Dato_____ CPR nr._____

Navn_____

Vejledning: Dette spørgeskema indeholder spørgsmål om, hvordan Du oplever dit knæ. Informationerne vil hjælpe os til at følge med i hvordan Du har det og hvor godt Du klarer dig i dagligdagen.
Ved hvert spørgsmål skal Du sætte et kryds i det alternativ, der passer bedst på dig. Du må kun sætte ét kryds ved hvert spørgsmål. Hvis Du er i tvivl om hvad Du skal svare, skal Du sætte krydset ved det alternativ, der føles mest rigtigt.

Symptom
Tænk på de **knægener** Du har haft i løbet af den sidste uge, når Du besvarer de næste spørgsmål.

S1 Har knæet været hævet ?

Aldrig	Sjældent	Ind imellem	Ofte	Altid
☐	☐	☐	☐	☐

S2 Har Du haft murren i knæet, hørt klik eller andre lyde fra knæet, når Du bevæger det ?

Aldrig	Sjældent	Ind imellem	Ofte	Altid
☐	☐	☐	☐	☐

S3 Har knæet haget sig fast eller været låst ?

Aldrig	Sjældent	Ind imellem	Ofte	Altid
☐	☐	☐	☐	☐

S4 Kan Du strække knæet helt ?

Altid	Ofte	Ind imellem	Sjældent	Aldrig
☐	☐	☐	☐	☐

S5 Kan Du bøje knæet helt ?

Altid	Ofte	Ind imellem	Sjældent	Aldrig
☐	☐	☐	☐	☐

Stivhed
Følgende spørgsmål handler om **ledstivhed**. Ledstivhed medfører besvær med at komme igang eller øget modstand, når Du bøjer eller strækker knæet. Angiv i hvor høj grad Du har oplevet ledstivhed i knæet i løbet af **den sidste uge**.

S6 Hvor stift er dit knæ, når Du lige er vågnet om morgenen ?

Slet ikke	Lidt	Moderat	Meget	Ekstremt
☐	☐	☐	☐	☐

S7 Hvor stift er dit knæ **senere på dagen**, når Du har siddet eller ligget og hvilet ?

Slet ikke	Lidt	Moderat	Meget	Ekstremt
☐	☐	☐	☐	☐

Smerte

P1 Hvor ofte har Du ondt i knæet ?

Aldrig	Hver måned	Hver uge	Hver dag	Altid
☐	☐	☐	☐	☐

Hvor mange knæsmerter har Du haft i løbet af **den sidste uge**, under følgende aktiviteter ?

P2 Dreje/vride på belastet knæ

Ingen	Lette	Moderate	Stærke	Ekstreme
☐	☐	☐	☐	☐

P3 Strække knæet helt

Ingen	Lette	Moderate	Stærke	Ekstreme
☐	☐	☐	☐	☐

P4 Bøje knæet helt

Ingen	Lette	Moderate	Stærke	Ekstreme
☐	☐	☐	☐	☐

P5 Gå på jævnt underlag

Ingen	Lette	Moderate	Stærke	Ekstreme
☐	☐	☐	☐	☐

P6 Gå op eller ned ad trapper

Ingen	Lette	Moderate	Stærke	Ekstreme
☐	☐	☐	☐	☐

P7 Om natten (smerter, som forstyrrer din søvn)

Ingen	Lette	Moderate	Stærke	Ekstreme
☐	☐	☐	☐	☐

P8 Siddende eller liggende

Ingen	Lette	Moderate	Stærke	Ekstreme
☐	☐	☐	☐	☐

P9 Stående

Ingen	Lette	Moderate	Stærke	Ekstreme
☐	☐	☐	☐	☐

Funktion i dagligdagen

Følgende spørgsmål omhandler dit fysiske formåen. **Angiv hvilken grad af besvær Du har oplevet under følgende aktiviteter i løbet af den sidste uge, på grund af dine knæproblemer.**

A1 Gå ned ad trapper

Intet	Lidt	Moderat	Stort	Ekstremt
☐	☐	☐	☐	☐

A2 Gå op ad trapper

Intet	Lidt	Moderat	Stort	Ekstremt
☐	☐	☐	☐	☐

A3 Rejse dig fra siddende

Intet	Lidt	Moderat	Stort	Ekstremt
☐	☐	☐	☐	☐

Angiv graden af **besvær** Du har oplevet ved hver aktivitet i løbet af **den sidste uge**

		Intet	Lidt	Moderat	Stort	Ekstremt
A4	Stå stille	☐	☐	☐	☐	☐
A5	Gå ned i knæ, f.eks. for at samle noget op fra gulvet	☐	☐	☐	☐	☐
A6	Gå på jævnt underlag	☐	☐	☐	☐	☐
A7	Gå ind/ud af en bil	☐	☐	☐	☐	☐
A8	Tage på indkøb	☐	☐	☐	☐	☐
A9	Tage strømper på	☐	☐	☐	☐	☐
A10	Stå ud af sengen	☐	☐	☐	☐	☐
A11	Tage strømper af	☐	☐	☐	☐	☐
A12	Ligge i sengen (vende dig, have knæet i samme stilling i lang tid)	☐	☐	☐	☐	☐
A13	Stige ind og ud af badekar/brusebad	☐	☐	☐	☐	☐
A14	Sidde	☐	☐	☐	☐	☐
A15	Sætte dig og rejse dig fra toilettet	☐	☐	☐	☐	☐
A16	Udføre tungt husarbejde (vaske gulv, støvsuge, bære øl/sodavandskasser o.lign.)	☐	☐	☐	☐	☐
A17	Udføre let husarbejde (lave mad, tørre støv af etc.)	☐	☐	☐	☐	☐

Funktion, sport og fritid

Følgende spørgsmål handler om din fysiske formåen. **Angiv hvilken grad af besvær Du har oplevet under følgende aktiviteter i løbet af den sidste uge på grund af dine knæproblemer.**

SP1 Sidde i hug

Intet	Lidt	Moderat	Stort	Ekstremt
☐	☐	☐	☐	☐

SP2 Løbe

Intet	Lidt	Moderat	Stort	Ekstremt
☐	☐	☐	☐	☐

SP3 Hoppe

Intet	Lidt	Moderat	Stort	Ekstremt
☐	☐	☐	☐	☐

SP4 Dreje/vride på belastet knæ

Intet	Lidt	Moderat	Stort	Ekstremt
☐	☐	☐	☐	☐

SP5 Ligge på knæ

Intet	Lidt	Moderat	Stort	Ekstremt
☐	☐	☐	☐	☐

Livskvalitet

Q1 Hvor ofte bliver Du mindet om dit knæproblem ?

Aldrig	Hver måned	Hver uge	Hver dag	Altid
☐	☐	☐	☐	☐

Q2 Har Du forandret din måde at leve på for at undgå at overbelaste knæet ?

Slet ikke	Noget	Moderat	I stor udstrækning	Totalt
☐	☐	☐	☐	☐

Q3 I hvor stor grad kan Du stole på dit knæ ?

Fuldt ud	I stor udstrækning	Moderat	Til en vis grad	Slet ikke
☐	☐	☐	☐	☐

Q4 Hvor store problemer har Du almindeligvis med dit knæ ?

Ingen	Små	Moderate	Store	Ekstreme
☐	☐	☐	☐	☐

Tak for at Du har besvaret samtlige spørgsmål !

Dansk version af KOOS samt et overblik af fysioterapeuterne Nina Beyer, Karin Jensen, Christian Wiznerg og Peter Magnusson. Information om KOOS kan fås hos Nina Beyer, Idrætsmedicinsk Forskningsenhed, Bispebjerg Hospital, Kobenhavn 2400 NV. Fax. 3531 6097, hvorfra seneste kan rekvireres. Yderligere information om KOOS kan fås hos: Leg sjukgymnast och doktorand Ewa Roos, Inst. för rörelseorganens sjukdomar. Avd. för sjukgymnastik., Lunds Universitet, Box 3130, 220 03 Lund, Sverige. Fax. +46 4622 24202.

painDETECT

PAIN QUESTIONNAIRE

Date: _____ Patient: Last name: _____ First name: _____

How would you assess your pain now, at this moment?

0 1 2 3 4 5 6 7 8 9 10

none max.

How strong was the strongest pain during the past 4 weeks?

0 1 2 3 4 5 6 7 8 9 10

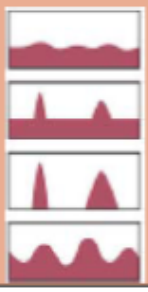
none max.

How strong was the pain during the past 4 weeks on average?

0 1 2 3 4 5 6 7 8 9 10

none max.

Mark the picture that best describes the course of your pain:



- Persistent pain with slight fluctuations ☐
- Persistent pain with pain attacks ☐
- Pain attacks without pain between them ☐
- Pain attacks with pain between them ☐

Please mark your main area of pain

Does your pain radiate to other regions of your body? yes ☐ no ☐

If yes, please draw the direction in which the pain radiates.

Do you suffer from a burning sensation (e.g., stinging nettles) in the marked areas?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Do you have a tingling or prickling sensation in the area of your pain (like crawling ants or electrical tingling)?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Is light touching (clothing, a blanket) in this area painful?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Do you have sudden pain attacks in the area of your pain, like electric shocks?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Is cold or heat (bath water) in this area occasionally painful?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Do you suffer from a sensation of numbness in the areas that you marked?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Does slight pressure in this area, e.g., with a finger, trigger pain?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

(To be filled out by the physician)

never	hardly noticed	slightly	moderately	strongly	very strongly
☐ x 0 = 0	☐ x 1 = ☐	☐ x 2 = ☐☐	☐ x 3 = ☐☐	☐ x 4 = ☐☐	☐ x 5 = ☐☐

Total score ☐☐ out of 35

Development/Reference: R. Freynhagen, R. Baron, U. Gockel, T.R. Tölle / Curr Med Res Opin, Vol.22, No. 10 (2006)

painDETECT

SCORING OF PAIN QUESTIONNAIRE

Date: _____ Patient: Last name: _____ First name: _____

Please transfer the total score from the pain questionnaire:

Total score ☐☐

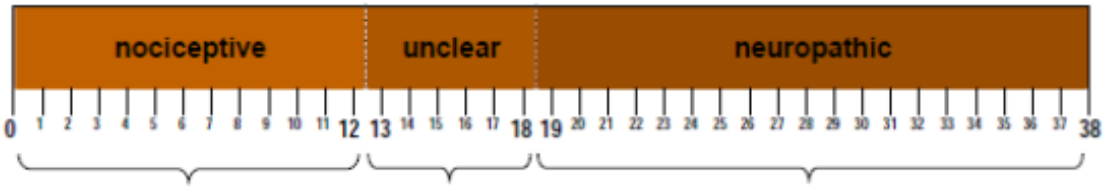
Please add up the following numbers, depending on the marked pain behavior pattern and the pain radiation. Then total up the final score:

	Persistent pain with slight fluctuations	0
	Persistent pain with pain attacks	- 1 if marked, or
	Pain attacks without pain between them	+ 1 if marked, or
	Pain attacks with pain between them	+ 1 if marked
	Radiating pains?	+ 2 if yes

Final score ☐☐

Screening Result

Final score



A neuropathic pain component is unlikely (< 15%)

Result is ambiguous, however a neuropathic pain component can be present

A neuropathic pain component is likely (> 90%)

This sheet does not replace medical diagnostics.
It is used for screening the presence of a neuropathic pain component.

Development/Reference: R. Freynhagen, R. Baron, U. Gockel, T.R. Tölle / Curr Med Res Opin, Vol.22, No. 10 (2006)