

Opioid requirement after arthroscopy is associated with decreasing glucose levels and increasing PGE2 levels in the synovial membrane

Erland Högberg¹, Anders Stålmán¹, Torsten Wredmark¹, Jon A Tsai², Peter Arner³ and Li Felländer-Tsai¹

Divisions of ¹Orthopedics and ²Surgery, Department of Clinical Science Intervention and Technology (CLINTEC), and ³Department of Medicine, Karolinska Institutet at Karolinska University Hospital, SE-141 86 Huddinge, Sweden

Correspondence LF-T: li.tsai@ki.se

Submitted 05-04-09. Accepted 05-11-14

Background Increased prostaglandin E2 (PGE2) release has been suggested to contribute to the enhanced nociceptor sensitivity that underlies chronic osteoarthritis pain. We have previously shown increased levels of lactate and glycerol in synovium postoperatively. Thus, we wanted to investigate whether the local trauma response is related to subjective pain.

Methods We monitored metabolic and inflammatory changes with microdialysis in the knee joint synovial membrane of 14 patients after arthroscopy, in relation to pain requiring systemic opioids. The adipose tissue of the contralateral thigh served as reference. The concentrations of glucose, lactate, pyruvate, glycerol and PGE2, and also local blood flow were analyzed over 3 hours postoperatively.

Results In the 6 patients requiring systemic opioid analgesia, the initial concentrations of glucose and PGE2 in the synovial tissue were increased compared to those not requiring opioids, and decreased following opioid administration. In the reference tissue there was no difference between groups regarding glucose, and the PGE2 concentration was below the detection limit. No significant differences in the levels of other compounds, in relation to the need for opioids, were found, either in synovial tissue or in reference tissue. Overall, the synovial tissue blood flow was stable.

Interpretation Pain after arthroscopy is reflected by increased glucose utilization and PGE2 production by the synovial membrane.

Postoperative changes in glucose, lactate and glycerol have previously been shown to occur locally after standard knee arthroscopy (Felländer-Tsai et al. 2002), which can be interpreted as a sign of hypermetabolism.

Prostaglandin E2 (PGE2) is a crucial mediator of inflammatory pain sensitization and a key mediator of central and peripheral pain sensitization (Vane-gas and Schaible 2001). Changes in PGE2 concentrations in synovial fluid have been shown to correlate with the degree of pain experienced (Trumble et al. 2004). Researchers originally thought that PGE2 causes pain only by stimulating neurons at inflamed peripheral sites. However, prostaglandins also act on the spinal cord, causing pain sensitization. Binding of the prostaglandin to its receptor activates a kinase, which phosphorylates the $\alpha 3$ form of the receptor for glycine, a neurotransmitter that inhibits the activity of target neurons. This reduces the activity of the receptor and also the inhibition, thus facilitating transmission of pain signals to the brain (Harvey et al. 2004).

Postoperative pain shows individual variations unrelated to the duration and extent of the surgical trauma. Some patients undergoing arthroscopy report pain and request opioids postoperatively even though they experience the same order of magnitude of surgical trauma as patients who do not require additional analgesia. We therefore hypothesized that requirement of opioids may be a surrogate variable for inflammatory response and

Details of the 14 patients who underwent arthroscopy due to suspected intraarticular pathology

Case	Ketobemidon opioid (mg)	Sex	Age (years)	Height (cm)	Weight (kg)	Body mass index (BMI)	Operating time (min)	Diagnosis/injury
1	Yes 2	F	24	173	58	19	47	Operative ^a
2	Yes 3	M	17	194	107	28	25	Diagnostic
3	No	M	41	174	75	25	45	Operative ^a
4	No	F	40	164	72	27	23	Diagnostic
5	Yes 2	M	32	183	104	31	65	Operative ^a
6	No	M	43	186	99	29	48	Operative ^a
7	No	M	29	180	115	35	30	Operative ^a
8	No	F	37	164	64	24	55	Diagnostic
9	Yes 2	M	36	177	92	29	43	Operative ^a
10	No	M	43	186	102	29	42	Operative ^a
11	No	M	52	187	100	29	46	Operative ^a
12	No	M	37	165	72	26	20	Diagnostic
13	Yes 2	F	42	178	92	29	50	Operative ^a
14	Yes 3	M	28	182	102	31	52	Operative ^a

^a e.g. meniscus surgery or shaving.

pain, based on the studies of Trumbe et al. (2004). Tissue microdialysis makes it possible to monitor the concentration of molecules in the interstitial fluid of the synovium (Felländer-Tsai et al. 2002). Local variations in metabolites may reflect the synovial tissue response to trauma (Felländer-Tsai et al. 2002, Högberg et al. 2005).

We monitored local changes in classic metabolic compounds and PGE2 in relation to pain requiring parenteral opioid analgesia postoperatively. Compounds were measured postoperatively by microdialysis in knee joint synovial membrane using standard arthroscopy as trauma model. As reference tissue, we used reciprocal measurements in adipose tissue of the contralateral thigh.

Patients and methods

The local ethics committee approved the study. Informed consent was obtained from each patient before inclusion.

Microdialysis

The principle of microdialysis is to mimic the passive function of a capillary blood vessel by perfusion of a tubular, semipermeable membrane introduced into a tissue. Microdialysis measurements of knee joint synovium have been described previously (Felländer-Tsai et al. 2002).

Patients

14 otherwise healthy patients with suspected intraarticular knee joint pathology were included consecutively in the study (Table). The extent of surgical trauma was similar, i.e. minor surgery as opposed to major arthroscopic knee surgery (such as cruciate ligament reconstruction).

Procedure

Arthroscopy was performed under general anesthesia and without tourniquet. The joint was irrigated with saline at a perfusion pressure of 90 mmHg. Upon completion of the arthroscopic procedure, a dialysis catheter with a cutoff of 20 kD (CMA 60; CMA Microdialysis AB, Stockholm, Sweden) was introduced into the synovial membrane under arthroscopic control as described previously (Felländer-Tsai et al. 2002). A reference dialysis catheter was inserted into the adipose tissue of the contralateral thigh.

Microdialysis samples were analyzed with a CMA 600 (CMA AB) for glucose, lactate, pyruvate and glycerol content. PGE2 was analyzed using ELISA (Prostaglandin E2 EIA Kit-Monoclonal; Cayman Chemical Co., Ann Arbor, CA). Blood flow was measured with the ethanol escape method described and validated previously (Bernt and Gutman 1974, Felländer et al. 1996).

Analgesia

All patients received standardized premedication

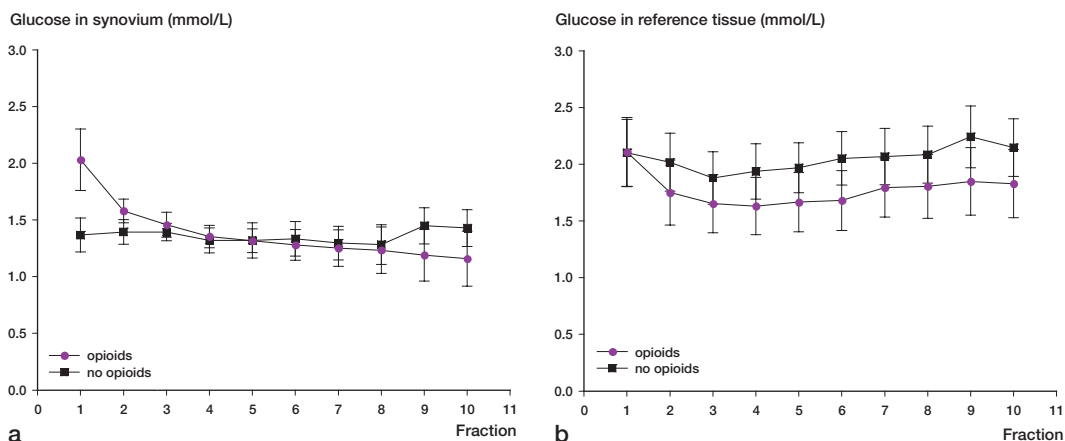


Figure 1 a and b. Dialysate levels (mean and SD) of glucose over 3 h after knee arthroscopy. There was a significant decrease in glucose over time in the synovial membrane (a) among the patients receiving opioids (closed circles), but not among those who did not require additional opioids (squares). In the reference tissue (b) there was no significant change in glucose in either group of patients.

(paracetamol/codein) and 20 mL bupivacain with adrenaline (5 mg/mL + 5 µg/mL) was injected into the knee joint postoperatively. All patients were informed that if considered necessary by the patient, additional analgesia was available upon request. The nurse in charge of postoperative pain relief was blinded to the study design. Subsequently, 6/14 patients required additional pain relief postoperatively and thus received 2–3 mg ketobemidon subcutaneously according to clinical routine.

Statistics

Data are expressed as mean (SD). All data were analyzed using procedure Mixed in SAS (SAS System 8.2; SAS Institute Inc., Cary, NC). We performed a three-way repeated measures ANOVA with Condition (knee and fat) and Time (10 time points) as the within-subjects variables and Group (Opioid, Reference) as the between-subjects variable (Kirk 1995, Littell et al. 1996). A p-value of less than 0.05 was considered statistically significant.

Results

10 of 14 patients underwent operative arthroscopy, while the remaining 4 underwent only diagnostic arthroscopy (Table). 5 in the first group and 1 in

the second group received ketobemidon postoperatively. Operating time for the patients receiving ketobemidon was 49 (43–65) min and it was 44 (20–55) min for the patients who did not receive ketobemidon (Table). There was no significant difference in the duration of the operation when comparing patients requiring additional postoperative pain relief with opioids (6/14) with those not receiving additional opioids (Table). There was no difference in mean age or BMI, or in sex distribution between those who received ketobemidon and those who did not.

Patients requiring additional systemic analgesia postoperatively showed a significantly different pattern of changes in glucose (Figure 1a) and PGE2 (Figure 2) in the synovial tissue compared to those not requiring additional analgesia. The concentrations of glucose and PGE2 were increased in the analgesia group at the start, and the concentrations decreased gradually during the study. In those patients who did not receive additional analgesia, the concentrations of glucose and PGE2 were unchanged throughout the experiment. We found no significant variation in the concentration of glucose in the reference tissue (Figure 1b). For PGE2, most measurements in the reference tissue were below the detection limits (data not shown).

There were no significant differences in lactate, pyruvate and glycerol concentrations in relation to additional postoperative analgesia in either

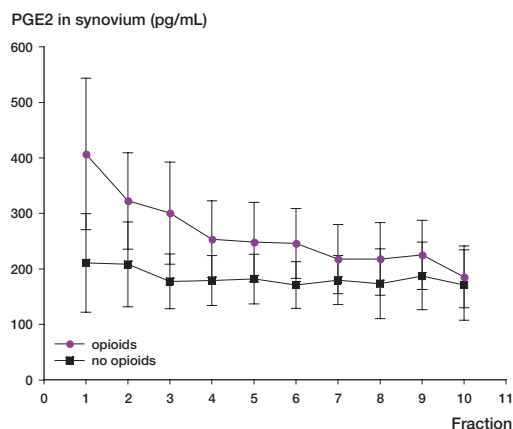


Figure 2. Dialysate levels of PGE2 (mean and SD) over 3 h after knee arthroscopy. There was a significant trend toward decreased levels of PGE2 over time in the synovial membrane of the patients receiving opioids, but not among those who did not require additional opioids. In the reference tissue, the majority of PGE2 measurements were below the detection limits (data not shown).

the synovial tissue or reference tissue (data not shown). Our previous findings (Felländer-Tsai et al. 2002) concerning the general postoperative course of these compounds were confirmed (data not shown).

In both groups, synovial tissue blood flow (ethanol ratio) was stable in both tissues (data not shown).

Discussion

An exaggerated sensation of pain is a cardinal symptom of acute inflammation. Our findings indicate for the first time that local tissue changes in metabolic and inflammatory compounds measured by microdialysis in the synovium postoperatively may be correlated to the magnitude of pain experienced. In this study, we monitored local synovial and reference adipose tissue metabolism after arthroscopic surgery using the microdialysis technique and analyzed the relationship between subjective postoperative pain requiring additional analgesia on PGE2 and the concentrations of metabolites in synovial dialysate.

Metabolic and inflammatory changes in joints have both short-term and long-term implications for joint physiology. This includes acute inflam-

mation and pain leading to the development of osteoarthritis (OA) (Averbeck et al. 2004). We have previously shown increasing levels of lactate and glycerol in the synovium postoperatively (Felländer-Tsai et al. 2002), which was confirmed in the present study. However, we found no effect of additional analgesia treatment on these metabolites, indicating that their postoperative changes reflect the degree of trauma and not the degree of pain. For glucose, we observed an analgesia-specific pattern. The concentration of glucose was elevated initially and decreased with time, but only in the group that needed additional opioids postoperatively. This may be explained by impaired local glucose metabolism due to pain and stress, followed by a normalization of the glucose level after relief of pain.

High levels of PGE2 have been shown in synovial fluid from patients with inflammatory joint disease (Egg 1984). Basal and evoked release of PGE2 from knee joint preparations has been shown to rise, while osteoarthritic changes develop in animal models (Averbeck et al. 2004). The release of PGE2—an endogenous algogenic substance—in synovial tissue plays an important role in OA-associated pain, as inferred from the known efficacy of cyclooxygenase inhibitors in reducing OA pain (Creamer 2000). The increased release of PGE2 has been suggested to enhance the nociceptor sensitivity underlying chronic OA pain (Creamer 2000). During inflammatory pain states, PGE2 disinhibits the spinal transmission of nociceptive input through the spinal cord dorsal horn to higher brain areas through PKA-dependent phosphorylation and inhibition of the glycine receptor GlyR α 3. This process apparently underlies central thermal and mechanical hypersensitivity, which develops within hours after induction of peripheral inflammation (Harvey et al. 2004). In this study, we found elevated PGE2 concentrations in the group that experienced severe pain, which decreased following additional analgesia. This suggests that pain and stress induce specific effects on prostaglandin production that are not related to the trauma.

Changes in microdialysate concentrations over time reflect local metabolism or removal by the microcirculation. The ethanol ratio indicates that there was no important change in synovial blood flow during the experiments. Thus, the decrease in

glucose levels over time following opioid analgesia probably reflects accelerated utilization of glucose by the synovial membrane.

Comparison with the reference tissue is essential for interpretation of the data. In adipose tissue, no difference in glucose was observed between those receiving opioids and those not. This suggests that pain and pain relief during arthroscopy have no generalized effects on glucose utilization and PGE₂ production. Instead, it appears that there are important interactions between the local trauma effect and pain/stress that, in turn, cause local changes in glucose and prostaglandin metabolism. Unfortunately, it is not possible at present to determine the extent to which ketobemidon itself alters metabolism in the synovial membrane.

We found a significant correlation between postoperative metabolic and inflammatory changes in knee joint synovium and subjective pain requiring additional opioid analgesia—involving glucose and prostaglandin metabolism, but not pyruvate and lactate metabolism or local blood flow. It should, however, be kept in mind that the number of patients in our study was low, which may weaken the conclusion. Even so, the findings are clinically relevant since they confirm the mechanism of pain targeting with anti-inflammatory pharmacomodulation postoperatively. In the future, perioperative optimization should thus be specifically tailored in order to reduce the effects of morbidity due to surgical trauma, once detailed tissue reactions become clear.

Contributions of authors

EH performed the operations, contributed to the analysis of metabolic compounds, contributed to the statistical calculations and wrote the initial manuscript. AS performed the operations, contributed to the analysis of metabolic compounds, contributed to the statistical calculations, and designed the figures. TW performed the operations and contributed to the final revision of the manuscript. JAT performed the PGE₂ analysis and contributed to the writing of the manuscript. PA contributed to interpretation of the data and to the final revision of the manuscript. LFT designed the study, wrote the application to the local ethical committee, performed the operations, contributed to data analysis and wrote the final draft of the manuscript.

We thank Elisabeth Dungner for excellent technical assistance. This study was supported by grants from Karolinska Institutet and the Swedish Medical Research Council.

No competing interests declared.

Averbeck B, Rudolphi K, Michaelis M. Osteoarthritic mice exhibit enhanced prostaglandin E₂ and unchanged calcitonin gene-related peptide release in a novel isolated knee joint model. *Rheumatol*, 2004; 31 (10): 2013-20.

Bernt E, Gutman J. Determination of ethanol with alcohol dehydrogenase and NAD. In: *Methods of enzymatic analysis*. New York: Academic press 1974: 1499-505.

Creamer P. Osteoarthritis pain and its treatment. *Curr Opin Rheumatol* 2000; 12: 450-5.

Egg D. Concentrations of prostaglandins D₂, E₂, F₂ alpha, 6-keto-F₁ alpha and thromboxane B₂ in synovial fluid from patients with inflammatory joint disorders and osteoarthritis. *Rheumatol* 1984; 43 (2): 89-96.

Felländer G, Linde B, Bolinder J. Evaluation of the microdialysis ethanol technique for monitoring of subcutaneous adipose tissue blood flow in humans. *Int J Obes Relat Metab Disord* 1996; 20 (3): 220-6.

Felländer-Tsai L, Högberg E, Wredmark T, Arner P. In vivo physiological changes in the synovial membrane of the knee during reperfusion after arthroscopy. A study using the microdialysis technique. *J Bone Joint Surg (Br)* 2002; 84:1194-8.

Harvey R J, Depner U B, Wasse H, Ahmadi S, Heindl C, Reinold H, Smart T G, Harvey K, Schutz B, Abo-Salem O M, Zimmer A, Poisbeau P, Welzl H, Wolfer D P, Betz H, Zeilhofer H U, Muller U. GlyR alpha3: an essential target for spinal PGE₂-mediated inflammatory pain sensitization. *Science* 2004; 304 (5672): 884-7.

Högberg E, Wredmark T, Dungner E, Arner P and Felländer-Tsai L. Changes in metabolism and blood flow following catecholamine stimulation in the synovial membrane measured with microdialysis. *Knee Surg Sports Traumatol Arthrosc*. 2005 Aug 20; (Epub ahead of print)

Kirk R E. *Experimental design: Procedures for the behavioral sciences*. Brooks/Cole Publishing Company Pacific Grove (USA) 1995.

Littell, Ramon C, Milliken, George A, Stroup, Walter W, Wolfinger, Russell D. *SAS System for Mixed Models*, Cary, NC: SAS Institute Inc 1996.

Trumble T N, Billingham R C, McIlwraith C W. Correlation of prostaglandin E₂ concentrations in synovial fluid with ground reaction forces and clinical variables for pain or inflammation in dogs with osteoarthritis induced by transection of the cranial cruciate ligament. *Am J Vet Res* 2004; 65 (9): 1269-75

Vanegas H, Schaible H G. Prostaglandins and cyclooxygenases (correction of cyclooxygenases) in the spinal cord. *Prog Neurobiol* 2001; 64 (4): 327-63.