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PAIN IN PATIENTS WITH OSTEOARTHRITIS TREATED WITH TOTAL KNEE ARTHROPLASTY

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To
My family

ABSTRACT

Background: The pathogenesis and mechanisms of pain in osteoarthritis (OA) are virtually unknown. In the absence of specific and effective pharmacological treatment, joint replacement often remains the only option. Total knee arthroplasty (TKA) has a significant effect in terms of pain relief. However, in one out of 5 cases TKA does not offer satisfactory pain relief. Inflammation, tissue damage and intense pain in conjunction with surgery have been suggested to cause neuroplastic changes in the central nervous system leading to hypersensitivity. In some patients this central sensitization is sustained and is believed to be responsible for pain persisting after TKA. The search for analgesics with a potential of preventing acute and persistent pain, has been directed not only to agents mitigating pain in conjunction with surgery, but also to agents that may block the mechanisms of central sensitization. Tramadol, a weak opioid drug, and also an inhibitor of the reuptake of serotonin and norepinephrine, has been suggested for prevention of persistent pain.

Aims: The aim of the present study was to explore preoperative clinical features associated with persistent pain after TKA. In particular, the aim was to test the predictive value of separating pain at rest from pain with movement with regard to pain relief after TKA. Also an analysis of radiological and histological changes in relation to pain at rest and pain with movement was conducted. Finally, the effect of intravenous tramadol 100 mg x 4, given during 24 hours after TKA, on acute postoperative pain and persistent pain 18 months after surgery was evaluated.

Results: Preoperatively, a low pain threshold to electrical stimulation and a high Visual analogue scale (VAS) score for pain at rest, but not with movement, was found to predict a worse outcome in terms of pain at rest 18 months after TKA. The grade of radiographic OA was significantly related to relief of pain with movement from preoperatively to 18 months postoperatively. Best pain relief by TKA was achieved in patients with severe radiographic changes. The combination of intravenous tramadol 100mg x 4 and morphine via patient controlled analgesia (PCA) pump did not offer better pain relief after TKA than morphine alone. Nor did tramadol prevent persistent pain 18 months after surgery.

Conclusions: Pain at rest should not be a prerequisite for TKA. Instead, a high preoperative score for pain at rest and a low pain threshold may be signs of central sensitization and indicate an increased risk of persistent postsurgical pain. Patients scheduled for TKA should be informed that the main gain to expect is relief of pain with movement. The evaluation of the outcome after TKA should be based on changes in pain from preoperatively to postoperatively, instead of merely considering postoperative pain. Most importantly, follow up studies on pain relief by joint replacement should separately consider pain at rest and pain with movement. Tramadol 100mg x 4 given intravenously as an add-on to morphine during 24 hours postoperatively does not prevent acute or persistent postoperative pain after TKA.

In clinical practice, the use of already well-established diagnostic tools should be expanded for the purpose of identifying patients at high risk of persistent pain after TKA. Hopefully this could provide guidelines on when to offer pharmacological prevention of persistent postsurgical pain or even avoid surgery.

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- I Lundblad H, Kreicbergs A, and Jansson K-Å.
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 J Bone Joint Surg Br 2008 Feb; 90(2): 166-71

- II Stiller C-O, Lundblad H, Weidenhielm L, Tullberg T, Grantinger B, Lafolie P, and
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 **The addition of tramadol to morphine via patient-controlled analgesia does not
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 Acta Anaesthesiol Scand 2007; 51: 322–330

- III Lundblad H, Kreicbergs A, Söderlund V, Ulfgren A-K, Stiller C-O,
 and Jansson K-Å.
 **The value of preoperative grade of radiographic and histological changes in
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 Knee Surg Sports Traumatol Arthrosc.(in press)

- IV Lundblad H, Kreicbergs A, Stiller C-O, Edman G, and Jansson K-Å.
 **No effect of postoperative administration of tramadol on persistent pain after
 total knee arthroplasty**
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LIST OF ABBREVIATIONS

ASA	American Society of Anaesthesiologists
BDNF	Brain derived neurotrophic factor
BMI	Body mass index
CGRP	Calcitonin gene related peptide
COX	Cyclooxygenase
CPSP	Chronic postsurgical pain
DNIC	Descending noxious inhibitory control
ES	Effect size
IL-6	Interleukin - 6
K & L	Kellgren & Lawrence
LIA	Local infiltration analgesia
MRI	Magnetic resonance imaging
NGF	Nerve growth factor
NMDA	N-Methyl-D-Aspartate
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OMERACT	Outcome Measures in Rheumatology Committee
PCA	Patient controlled analgesia (pump)
PM	Pain Matcher®
QST	Quantitative sensory testing
SP	Substance P
TKA	Total knee arthroplasty
VAS	Visual analogue scale
WHO	World Health Organisation

INTRODUCTION

BACKGROUND

Musculoskeletal disorders are the most common cause of pain (1). The prevalence of musculoskeletal pain has increased between two- and fourfold during the last 40 years (2). Osteoarthritis (OA) is a major cause of pain and disability in the elderly population (3, 4). In OA the knee is the most commonly affected joint and a frequent cause of disability (5). The prevalence of knee OA increases with age and reaches 40-60% in the upper seventies (6).

Neither the causes of OA nor the sources and mechanisms of pain are fully understood. Conservative treatment such as medication and physiotherapy has limited effect on pain and progression of the disease (7, 8). Until further knowledge about the pathogenesis of OA and mechanisms of pain are obtained to permit specific pharmacological targeting, surgical treatment mostly remains the best option. Total knee arthroplasty (TKA) has a consistent, significant effect in terms of pain relief (9, 10).

However, TKA, apart from causing severe acute postoperative pain, entails a risk of serious complications such as thrombo-embolism and infection, in some cases even prompting amputation (11-15). Furthermore, there is a subpopulation of patients undergoing joint replacement that experiences persistent unexplained pain (16-18). A number of risk factors for the development of persistent postsurgical pain have been identified. These include female gender, lower age, preoperative pain (19), psychic vulnerability, anxiety, a surgical approach causing nerve damage and the intensity of acute postoperative pain (20, 21).

In the search for the sources of pain many attempts have been made to correlate radiographic features of OA with pain (22, 23) but the findings remain contradictory. Although it has been reported that the risk of knee pain increases with the radiographic severity of OA (24, 25), many patients with radiographic OA do not have pain (26). It has been suggested that synovial inflammation and/or increased intraosseous pressure cause pain in OA (27). Increasing evidence has also accumulated about central and peripheral mechanisms leading to sensitization of neurons and receptors leaving not only the affected joint but also distant sites more sensitive to normally innocuous stimuli (5, 28).

Identification of preoperative patient characteristics associated with an increased risk of persistent pain after TKA can be expected to improve the selection criteria. This prompted an investigation of the predictive value of preoperative pain, pain thresholds, and grade of radiographic and histological changes in relation to postoperative pain.

Preventive analgesia is a term used for pain management in conjunction with surgery aimed at reducing the incidence of persistent postsurgical pain. Tramadol has been suggested as a compound with a potential to prevent acute postoperative pain as well as persistent postsurgical pain (29). Apart from being a weak opioid agonist tramadol also inhibits the neuronal re-uptake of serotonin and norepinephrine, which could influence the activity in descending anti-nociceptive pathways (30, 31).

OSTEOARTHRITIS (OA)

Osteoarthritis (OA) is a chronic irreversible condition characterized by destruction of articular cartilage and subchondral bone. The underlying cause of degeneration can be attributed to several factors. OA is commonly divided into primary and secondary OA. In primary OA, which usually develops at the age of 55-60 years, the underlying cause is unknown, possibly genetically whereas in secondary OA the cause is usually identified. Risk factors for development of secondary OA are injuries, obesity, inactivity, malformations and haemophilia. Secondary OA usually develops at an earlier age.

The pathogenesis of OA has long been thought to be cartilage driven(32), starting with focal areas of damage to the cartilage. In an attempt of repair, chondrocytes form clusters in the damaged areas and the concentration of growth factors in the matrix increase. This attempt subsequently fails and leads to an imbalance in favour of degradation. Increased synthesis of tissue-destructive proteinases, increased apoptotic death of chondrocytes and inadequate synthesis of components of the extra cellular matrix lead to the formation of a matrix that is unable to withstand normal mechanical stress (32).

Recent evidence (33) shows an additional and integrated role of bone and synovial tissue. The initial signs of OA are changes in the subchondral bone. Osteophyte formation, bone remodelling, subchondral sclerosis, and attrition are crucial for radiological diagnosis (32). Several of these bone changes take place not only during the final stage of the disease, but also at the onset of the disease, possibly before cartilage degradation. This finding led to the suggestion that subchondral bone changes could initiate cartilage damage.

PAIN MECHANISMS IN OA

Pain

The ability to experience pain is an important advantage in the evolution. Responding adequately to a painful stimulus protects the body from further damage. Patients who are unable to perceive pain from e.g. joints as in the hereditary disease “Norrbottnian congenital insensitivity to pain” (34) end up with severe destruction of the large joints. This clearly highlights the protective function of the nervous system.

The International Association for the Study of Pain defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (www.iasp-pain.org) (35). The fact that pain is an individual experience, influenced not only by psychosocial factors but also by previous experiences, inevitably makes inter-individual comparison of pain scores questionable.

Despite considerable efforts the mechanisms of pain in OA still remain to be fully clarified. A number of observations have contributed to the elusiveness of pain in OA. Firstly, not all OA patients experience pain. Secondly, pain can be reduced by placebo surgery and thirdly a considerable number of patients undergoing seemingly adequate joint replacements develop persistent pain. It has been reported that the risk of knee pain increases with the radiographic severity of OA (24, 25). Yet, many with radiographic OA do not have pain (26). In some studies it has been

shown that local and systemic inflammatory features are significantly related to pain (36) whereas other studies have failed to demonstrate such relationships (37-39). The poor correlation can be attributed to several causes, involving the sensitivity of radiographs to quantify the disease, the heterogeneity of the disease process and an individual's interpretation and behaviour towards a potentially painful stimulus (35).

Nociception

Nociception is a neurophysiologic term that describes the activity in a nerve pathway, which transmits signals from a potentially noxious stimulus, but is not always perceived as painful (35). Pain is the subjective experience that accompanies nociception but can also arise without a stimulus. Nociceptive pain arises from actual or threatening damage to non-neural tissue and is due to the activation of nociceptors (40). Impulses of sufficient intensity from the nociceptive fibres will produce post-synaptic depolarisation in the spinal neurons after synapses in the dorsal horn. Via one of four spinal tracts the impulse is then transmitted to the supra-spinal pain matrix consisting of nuclei of the thalamus, hypothalamus, cerebellum, cerebral cortex, medulla, and brain stem.

Sources of pain in OA

Four different types of nerves innervate the joint. Large type 1 (A- α fibres) and type 2 fibres (A- β fibres), smaller myelinated type 3 fibres (A- δ fibres), and finally thin and slowly conducting non-myelinated type 4 or C fibres. A- α fibres have a motor function whereas A- β fibres mediate tactile stimuli. The high threshold fibres, types 3 and 4, are the primary nociceptors, and are activated by noxious movements or manipulation of the joint. Under normal conditions A- δ fibres mediate the sharp pain associated with acute injury, while C fibres are responsible for the less well-defined aching pain (35). In peripheral and central neuropathic pain conditions the A- β fibres are thought to be responsible for allodynia i.e. pain due to a stimulus that does not normally provoke pain (41).

In 1991 Bjurholm (42) developed a method for demineralization of bone while preserving the antigenicity of neuroactive peptides. In this way nerves could be demonstrated by immunohistochemical staining. This permitted identification of nerve fibres according to specific sensory and autonomic mediators. The neuropeptides were predominantly found in vascular structures, but free nerve endings were also seen in all parts of long bones, the highest abundance being in areas with high osteogenic activity.

To investigate whether bone tissue may be a source of knee pain, injection of liquid into the patella has been tested and found to be very painful suggesting that increased intra-osseous pressure can be a cause of pain in OA. Further support of this observation is that the appearance of bone marrow lesions (43) on magnetic resonance images (MRI) is associated with pain. On histological examination these areas show abnormal bone with excessive fibrosis, small areas of osteonecrosis, and extensive bone remodelling. Other features on MRI that have been related to pain are knee effusions and synovial thickening.

Ahmed and colleagues (44) investigated the distribution of sensory and autonomic neuropeptides in joint tissue and found evidence for an involvement of the nervous system in inflammatory joint disease. Thus, nociceptive neuropeptides as substance P (SP) and calcitonin gene-related peptide (CGRP) together with other inflammatory mediators, such as bradykinin and histamine trigger a self-propagating inflammatory response contributing to joint pain.

Studies on un-anesthetized patients (45) have shown that the most pain sensitive structures in the knee are ligament insertions, synovium and the fat pad underneath the patellar tendon. However, the cartilage itself was not tender in these studies. As the synovial membrane is richly innervated it is believed to be responsible for the painful flares (33) of OA that causes the temporal variation of pain in OA.

One reason for the contradictory results in studies of morphologic features and pain in OA could be that pain at rest and pain with movement partly have different mechanisms and therefore should be considered separately. Furthermore, due to the subjective nature of pain, inter-individual comparison of pain scores can be questionable, whereas intra-individual comparison of pain over time may prove to offer more relevant information.

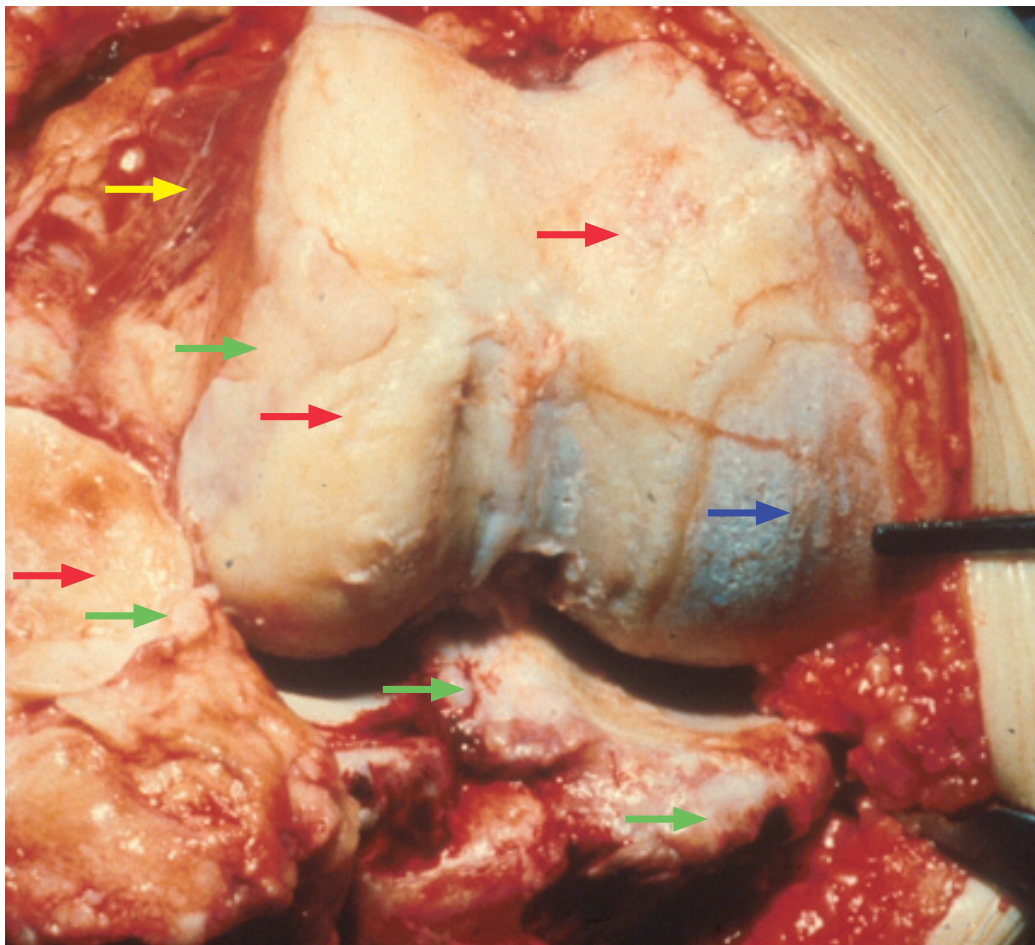


Figure 1. Knee OA as seen during TKA with synovial inflammation (→), osteophytes (→), cartilage wear (→). Bone attrition (→) is visible on the medial condyle.

Inflammation in OA

Although OA is generally considered a degenerative (non-inflammatory) disease as many as 50% of patients with OA show signs of inflammation in the synovial membrane (46). Inflammation in OA can be detected by MRI, ultrasound, and by analysis of biological markers in blood or synovial fluid (33). Among different methods of detecting and grading synovitis histological examination of biopsy-obtained samples is considered the “gold standard” (33). The histological changes that occur in the OA synovium include hypertrophy and hyperplasia with an increase in the number of synovial lining cells. These changes are often accompanied by infiltration of mononuclear cells in the sublining tissue with scattered foci of lymphocytes and macrophages.

In some studies (36, 38, 47) it has been shown that local and systemic inflammatory features are significantly related to pain, whereas other studies have failed to demonstrate such relationships (37, 39). Also, synovectomy at the time of TKA does not provide any benefit in clinical outcome or inflammatory response after surgery (48).

In a recent review in *Nature*, Sellam and Berenbaum (33) suggest that catabolic and pro-inflammatory mediators such as cytokines, nitric oxide, prostaglandin E2 and neuropeptides are produced by the inflamed synovium and alter the balance of cartilage matrix degradation and repair, leading to excess production of proteolytic enzymes responsible for cartilage breakdown. Degradation products from the cartilage in turn amplify synovial inflammation, creating a vicious circle. Macrophages have also been shown to mediate synovitis and angiogenesis in OA by the release of Vascular derived Endothelial Growth Factor (VEGF) (49). In response to inflammation of the synovial membrane and continuous nociceptive input, peripheral nerve endings become more sensitive to incoming stimulus, i.e. peripheral sensitization.

Peripheral sensitization

After tissue trauma, pain occurs through noxious stimulation of afferent nerves. In response to damaged tissue releasing inflammatory mediators such as cytokines and prostaglandins at the wound site, a reduction in threshold and amplification in the responsiveness occurs in peripheral terminals of high threshold primary sensory neurons (50, 51). This process, peripheral sensitization, causes a primary mechanical hyperalgesia that is restricted to the site of tissue injury and is thought to be adaptive in the sense that it protects the body from further damage.

Central sensitization

Central sensitization is an enhancement of the function of neurons and circuits in nociceptive pathways caused by increased membrane excitability and synaptic efficacy as well as reduced inhibition. This represents an adaptive plasticity of the nervous system in response to activity, inflammation and neural injury (28). Four mechanisms are considered of particular importance; changes in the expression of sodium ion channels, up regulation of calcium ion channels, activation of NMDA receptors and disinhibition.

Continuous and intense nociceptive input from a damaged joint may drive central sensitization assumed to play an important role in OA (5). In addition, enhanced central summation may facilitate temporal summation in OA patients as seen in other patients with chronic musculoskeletal pain. Another indicator of central sensitization is more intense pain and larger areas of referred pain in response to experimental muscle stimulation (52).

In order to demonstrate central sensitization, patient specific tests have been developed. By measuring pressure pain thresholds at many sites around the knee, spreading sensitization, temporal summation of pressure pain, pain responses and referred pain areas after intra-muscular pain stimulation and the potency of diffuse noxious inhibitory control (DNIC), signs of central sensitization have been demonstrated among patients with OA (5). Treatment of neuropathic pain has also been shown to be effective in OA [8]. However, reversing inflammation in the peripheral tissue does not always attenuate central sensitization. Therefore refractory pain may persist even after TKA (53). The importance of central sensitization in OA has been highlighted by Arendt-Nielsen (5) and it has also been suggested as a mechanism in chronic or persistent postsurgical pain (54). Pain at rest has been suggested to reflect a neuropathic component, which however, still has to be proven.

ASSESSMENT OF PAIN IN OA

Pain

Pain is a personal experience and an individual interpretation of a nociceptive stimulus that is influenced by previous experiences and psychosocial factors. Objective inter-individual comparison of pain measurements is therefore virtually impossible. Nonetheless, pain is the most important symptom of OA and the main indication for surgery. In clinical practice and research there is a need for reliable, yet simple tools for measuring pain intensity. The difficulties with pain measurements are reflected by the multitude of pain scoring systems available. Pain intensity can be assessed with numerical rating scales, verbal descriptor scales as the Likert scale or visual analogue scales (VAS) (55) each of which has its advantages and drawbacks. Another generic scale is the Borg CR-10 scale (56), which takes into account that pain, increases in a logarithmic rather than linear fashion. The quality of pain is considered in the McGill Pain Questionnaire (MPQ) (57), which reflects the sensory, affective, and evaluative dimensions of pain.

VAS

The use and validity of VAS for pain assessment have been reported previously (58, 59). Patients move a vertical line along the scale and select a position on a 100 mm line that corresponds to the intensity of their pain. The left endpoint represents no pain, whereas the right endpoint depicts the worst imaginable pain. The ratings on the back of the scale are read and recorded as numbers from 0 to 100. In clinical practice the VAS is often simplified by recording the scores as whole numbers between 0 and 10, Figure 2. The accuracy of pain measurements is impossible to determine, as the response is affected not only by the “true” pain intensity but also by the patients interpretation of this sensation. In a recent study the test–retest reliability of two consecutive pain scores on the VAS was found to be excellent with an intra-class correlation coefficient of $r = 0.96$ (60).

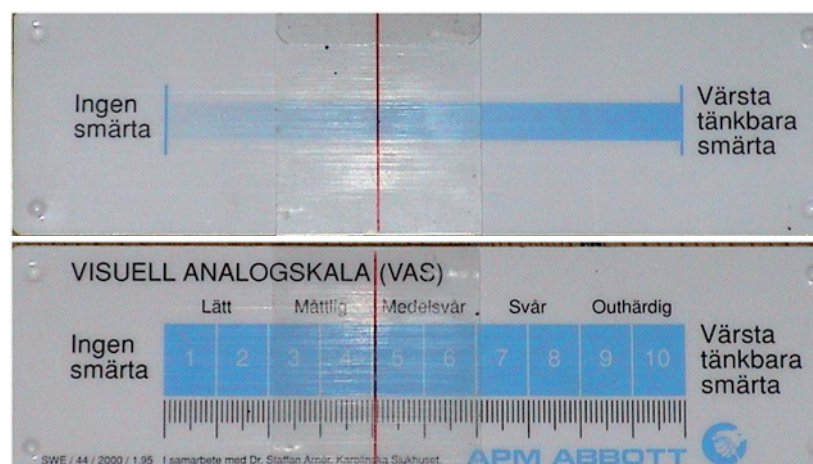


Figure 2. The Swedish version of VAS used for assessment of pain intensity in this thesis (upper figure is the side facing the patient and the lower figure is the backside of the device).

Disease specific scales

The WOMAC index of OA is the most widely used score for assessing pain and progression of the disease (61) and is recommended by the World Health Organization (WHO). It includes 24

items divided into three categories: pain, stiffness, and function. Although data on pain at rest and pain during different activities are collected separately in the WOMAC index, most authors present the scores from the pain domain as one global index on a scale from 0 to 20. Other disease specific scales are the Knee Society Score, the IKDC, the Oxford Knee Score, and the KOOS. These are all available on the Internet at www.orthopaedicscores.com.

Quantitative sensory testing (QST)

Quantitative sensory testing (QST) is a term used to describe psychophysical methods of determining thresholds or stimulus response curves for sensory processing under normal and pathophysiological conditions. By recording participant's responses to external stimuli of controlled intensity QST allows us to get a numerical value of a specific sensory perception. As various modalities of stimulus affect different nerve fibres, QST can also be used to test nerve fibres separately. Different methods for detection of sensory and pain thresholds as well as suprathreshold and pain tolerance thresholds have been introduced. Common physical stimuli include warmth and coolness, heat pain, touch-pressure, and vibration. A simple method recently introduced is the Pain Matcher® (Figure 3), an electrocutaneous stimulator, which has been validated for assessment of pain and detection of sensory thresholds (62).



Figure 3. Photograph of the Pain Matcher®, displaying from left to right, detection level, pain threshold, and matched pain on the liquid crystal screen.

Measurements of thresholds to thermal, mechanical and electrical stimulation reflect the state of the peripheral and central nervous systems. As opposed to standard diagnostic tools, QST enables us to test specific components of the nociceptive system (63). A- β fibres mediate light touch and vibration whereas A- δ fibres mediate thermal as well as pinprick stimuli. The unmyelinated C-fibres are mediators of heat and cold pain sensations as well as the sensation of warmth.

Electrocutaneous stimulation is used for measurement of current perception thresholds and pain tolerance thresholds. Neuroselectivity is achieved by using different frequencies: 5 Hz stimulates small unmyelinated C-fibres, 250 Hz stimulates A- δ fibres, and the 2000 Hz frequency is neuroselective towards the large myelinated A- β fibres. The main difference between electrical and thermal-mechanical stimuli is that electrical stimuli bypass peripheral nociceptors (64). Notably, pain thresholds measured by the Pain Matcher® have been shown to predict the intensity of post-operative pain after caesarean section (65). It has been reported that electrical stimulation can detect central sensitization (66).

IMAGING IN OA

Radiological classification of osteoarthritis remains the reference standard despite the emergence of new techniques such as MRI. The explanation is availability and tradition, but also the fact that no clear cut-off or overall severity grade exists for OA according to MRI findings (67). The most widely used radiological classification criteria for knee OA are those proposed by Kellgren and Lawrence (K&L) in 1957 (68, 69). The WHO has declared the K&L “the gold standard” for radiographic grading of OA. However, the original criteria have been modified which may affect the classification and sometimes preclude comparison between studies (67). Furthermore, it has been criticized because of its emphasis on the presence of osteophytes and inability to separate different radiographic features in the classification. Although the reproducibility has been variable it was concluded in a study by Kessler (70) that so far no other system shows higher reliability.

In 1968 Ahlbäck introduced a simple system for the classification of osteoarthritic changes on a plain radiograph (71, 72). Although his system has been criticized for difficulties in discriminating low from medium stages, its reliability is probably quite good when using optimal radiographic positioning and an experienced radiologist (73). Weidow et al. (74) found poor reproducibility and validity in the Ahlbäck scale as compared to visual inspection of the joint preoperatively. Nonetheless, the intra-observer reliability as well as the sensitivity of the Ahlbäck scale was found to be acceptable in the same study.

Plain radiography is still the “work horse” in the clinical diagnosis of OA. However, with the increasing availability of MRI, many patients referred to an orthopaedic surgeon have already been investigated by MRI. For research purposes the Osteoarthritis Research Society International (OARSI) (75) initiated a working group that stated that measurement of knee joint space width obtained from plain radiography was reliable. However, they also concluded that MRI is best for imaging of osteoarthritis because of its unique ability to visualize multiple individual tissue pathologies related to pain. Thus, future research efforts in imaging of osteoarthritis are likely to shift further from conventional radiography-based studies to those that directly visualize the target tissues, specifically MRI and possibly also ultrasound (76).

NON-SURGICAL TREATMENTS OF KNEE PAIN IN OA

The magnitudes of the effect of available therapies for the management of hip and knee OA have been determined by systematic literature search (77) of the Osteoarthritis Research Society International (OARSI). The effect size (ES) is calculated by dividing the mean difference between treatments by the standard deviation of the difference. It is therefore suitable for non-parametric cross-study comparisons. An effect size of 0.2 is considered small, whereas 0.5 is moderate and >0.8 is large. The effect is determined separately for pain relief, function and stiffness.

Physiotherapy

Independent studies suggest modest, if any, benefit of many non-pharmacological therapies over attention control or placebo, although they have been demonstrated to have significant impact over no intervention at all (78). According to the latest OARSI report aerobic exercise gives a moderate effect (ES=0.52) on pain, whereas water-based exercise has a small (ES=0.19) effect. Massage has a very limited effect (ES=0.10) whereas heat/ice therapy has an effect size of 0.69.

Weight reduction is not easy but quite effective in terms of functional improvement especially in knee OA (79) but has limited effect on pain (ES=0.20).

Pharmacological treatment

Paracetamol (acetaminophen) is usually the first choice among oral analgesics for mild to moderate osteoarthritic pain (ES 0.14) (32). Cyclooxygenase (COX) is an enzyme responsible for the synthesis of inflammatory mediators called prostanoids, including prostaglandins, prostacyclin and thromboxane. Pharmacological inhibition of COX can provide relief of inflammation and pain. Non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen, exert their effects through inhibition of COX. NSAIDs are somewhat more effective (ES=0.29) than paracetamol. However, the use of oral NSAIDs is sometimes not possible because of the well-known gastrointestinal and cardiovascular side effects. It has also been proposed that NSAIDs may accelerate the course of OA (80) due to a toxic effect on articular cartilage (81). Opioid drugs have a moderate to large effect (ES= 0.78) on pain intensity. However, the use of opioids has its limitations due to side effects such as nausea, constipation, dizziness, and somnolence.

Recently the dietary supplements glucosamine- and chondroitin sulphate have been introduced for the treatment of OA. Although some evidence from animal models (82) and clinical studies indicate that administration of glucosamine sulphate may delay radiological progression of knee OA (83, 84), this remains controversial. Furthermore these compounds have only limited, if any, effect on pain (ES=0.13) (85, 86).

Intra-articular steroids seem to have a good effect on pain (ES=0.72). However this tends to decrease for each injection with no effect at all after two years. Intra-articular hyaluronic acid seems to have a longer lasting effect on pain than cortisone with an ES of up to 0.60. However, in a Cochrane report from 2009 (87) it was concluded that available treatment options for OA have limited analgesic effects and that there is an urgent need for more effective treatments in OA.

Increasing evidence of central sensitization in patients with chronic osteoarthritic pain (5) has lead to the use of pharmacological agents acting on supraspinal pathways. Agents that have been tried with positive effects in osteoarthritis are ketamine, gabapentin, imipramine, venlafaxine, and duloxetine (88). Venlafaxine and duloxetine are inhibitors of serotonin and norepinephrine reuptake and are also used in the treatment of depression and fibromyalgia. Ketamine is an NMDA antagonist whereas the exact mechanisms of action for gabapentin remain unknown. Ketamine, gabapentin, and imipramine, have all been shown to inhibit temporal summation, which is a key feature in the initiation of central sensitization.

Tramadol

Tramadol [2-(dimethylaminomethyl)-1-(3-methoxyphenyl) cyclohexanol], developed in the late 1970's is a centrally acting analgesic drug used to treat moderate pain. Tramadol is increasingly used for the treatment of OA because, in contrast to NSAIDs (89, 90), it does not cause gastrointestinal bleeding or renal problems, and does not affect articular cartilage. However, the effect on pain is small, 12.5 on a 100mm VAS, which represents the smallest noticeable change. Apart from traditional opioid side-effects there is a risk of developing a "serotonin syndrome" (91) if tramadol is combined with other monoamine oxidase inhibitors. The most frequent clinical features within this syndrome are changes in mental status, restlessness, myoclonus, hyperreflexia, diaphoresis, shivering, and tremor.

The small but significant analgesic effect of tramadol has been attributed to a dual mechanism. In addition to being a weak opioid agonist it also inhibits the neuronal re-uptake of serotonin and norepinephrine. Since the analgesic effects of tramadol are not fully reversed by the administration of naloxone, mechanisms other than the action on the μ -opioid receptor must be involved (92).

Tramadol is structurally similar to and shares some of its mechanism of action with venlafaxine (93, 94). Apart from monoaminergic pathways tramadol as well as venlafaxine interact with the NMDA receptors (95) and inhibit ion channel activity, mechanisms suggested to be involved in central sensitization (28). Furthermore, tramadol has been shown to prevent thermal hind paw hyperalgesia in the rat and has therefore been suggested to be a potential agent in the treatment of neuropathic pain and the prevention of central sensitization (29).

Although the analgesic action of tramadol is yet to be fully clarified several actions on receptors in the central nervous system have been demonstrated. Thus, tramadol has been also been suggested as a serotonin releasing agent, norepinephrine re-uptake inhibitor, NMDA receptor antagonist, 5-HT_{2C}-receptor antagonist, (α 7) 5 nicotinic acetylcholine receptor antagonists, TRPV1 receptor agonist, and a muscarinic acetylcholine receptor antagonist (96).

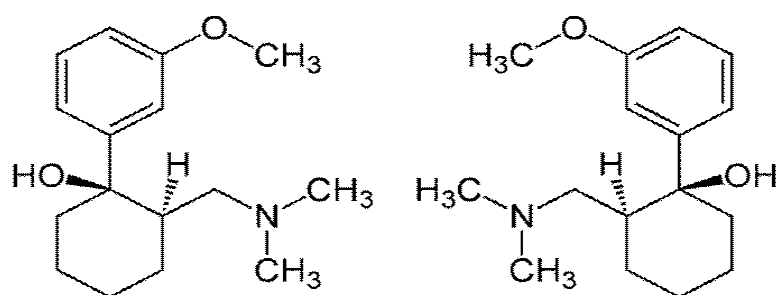


Figure 4. The two isomers in the racemic mixture of tramadol

SURGICAL TREATMENT OF OA

Arthroscopic lavage and debridement

Arthroscopic lavage and debridement consists of shaving rough and loose areas of cartilage and meniscus and sometimes removing osteophytes. In theory some of the effects could be due to removal of debris and inflammatory cytokines. The OARSI stated that the procedure had some effect in terms of pain relief (ES=0.21). However, in a Cochrane review (97) of surgical lavage and debridement in knee OA no benefit was detectable compared to placebo.

Cartilage repair

Repair of cartilage defects is only indicated for focal defects. The different techniques are divided into bone marrow stimulation, osteochondral transplantation, - and chondrocyte transplantation. Bone marrow stimulation is achieved by simply penetrating the, often sclerotic, subchondral bone which stimulates healing with mostly fibrous tissue. It is widely used because of its simplicity, but very little hyaline cartilage will be present in the repair tissue. Another way is to transplant osteochondral grafts. These can be either autologous as in the “mosaicplasty” or allogenic

(98). The problems with this method are technical difficulties and osseous integration. Autologous chondrocyte transplantation was introduced by Brittberg and colleagues in 1994 (99). This method utilizes cultivated chondrocytes that are re-implanted underneath a periosteal flap. Also this technique has been shown to decrease symptoms but there is no evidence of a superior effect compared to other treatments (100).

Osteotomies

In relatively young active patients with a unicompartamental OA associated with a varus or valgus malalignment but with a good range of motion, osteotomy around the knee is an alternative to joint replacement. The aim is to alter the mechanical axis and thereby unload the osteoarthritic compartment. By pre- and postoperative gait analysis it has been shown that the load is reduced not only in the knee but also in the hip joint after osteotomy (101). Older techniques as the closing wedge osteotomy were associated with a risk of damage to the peroneal nerve or shifting of the mechanical axis causing a translational deformity. Currently, with the use of plates with locking screws or external fixators, open wedge osteotomies are widely used (102).

Arthroplasty

The first attempts to replace a damaged knee joint with an artificial implant were made in the 1940's. In 1953 Walldius, a Swedish orthopaedic surgeon published some promising results with a hinge prosthesis made of acrylate (103). In the 1970's the concept of replacing the tibiofemoral condylar surfaces with cemented fixation was popularized. After biomechanical studies by Gunston in 1971 (104), recognizing that the femoral condyles not only roll but also glide on the tibia, the total condylar knee, based on the principle of a low friction arthroplasty was developed by Insall (105). Arthroplasty is currently performed by replacement of one, two, or all three compartments of the knee, i.e. the lateral, medial, and patello-femoral compartments. TKA is the most effective treatment for patients with advanced OA (106). In a study on the long-term results of TKA, pain relief was found to remain 20 years or more after surgery (107). The indications for TKA vary between surgeons. Pain is generally accepted as the major criterion. But, according to a study by Mancuso from 1996 (108) most surgeons in New York City would require severe pain and transfer pain at least daily and rest pain at least several days/week before performing a TKA.

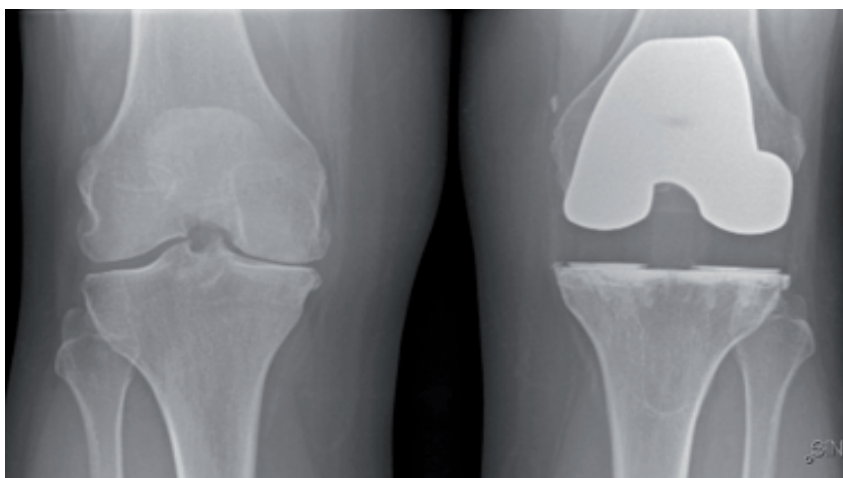


Figure 5. Radiograph of a patient with predominantly medial osteoarthritis in the right knee and a total knee arthroplasty performed in her left knee.

POSTSURGICAL PAIN

Acute postsurgical pain

The management of acute postoperative pain after TKA poses a significant challenge. It is not only a cause of discomfort and unnecessary suffering for the patient, but severe postoperative pain can also delay mobilization with an increased risk of thromboembolism, lengthening the patient's hospital stay. Acute postoperative pain has also been implicated as a risk factor for persistent postsurgical pain (109). Despite the awareness of the consequences of acute postsurgical pain, it is not seldom poorly managed (110).

Persistent postsurgical pain

In the literature chronic- and persistent postsurgical pain are two terms used interchangeably to describe a clinical picture of pain still occurring three months after surgical intervention (111). We have chosen the term "persistent" as "chronic" in our opinion denotes an irreversible condition.

Persistent postsurgical pain is an under-recognized problem affecting 10 to 50 % of surgical patients(109). After total knee arthroplasty (TKA), 44% of patients report persistent pain and 15% of these have severe to extreme pain (112). A number of risk factors have been identified. These include female gender, low age, intensity of preoperative pain (19) and acute postoperative pain, psychic vulnerability, anxiety and a surgical approach causing nerve damage (109).

Surgery elicits an acute inflammatory response with the release of prostaglandins and cytokines, which activate and sensitize primary afferents, which in turn promotes central sensitization. These sensitization mechanisms are adaptive in the sense that they protect the body from further damage. However, some patients experience pain which persists for months or even years after surgical intervention. Persistent pain after surgery is likely to result from a complex combination of mechanisms.

PREVENTIVE ANALGESIA

Pre-emptive and preventive analgesia have been developed to inhibit the mechanisms leading to persistent postsurgical pain (113, 114). Early experimental observations demonstrated that analgesics applied before injury was more effective in reducing central sensitization than post-injury administration. Pre-emptive analgesia is believed to minimize the risk of acute and chronic pain by reducing afferent nociceptive transmission provoked by the procedure whereas preventive analgesia is based on the assumption that the only way to prevent central sensitization is to completely block pain and afferent signals from the surgical wound at the time of incision until wound healing. In the majority of recent studies pre-emptive analgesics showed no benefit over preventive analgesia and it has been suggested that the term pre-emptive analgesia should be abandoned in favour of preventive analgesia.

Among agents with a potential to prevent central neuroplasticity leading to sensitization promising results have been found with perioperative administration of ketamin, celecoxib (115), venlafaxine(116), gabapentin (117), and pregabalin (118). Although tramadol is often considered to be an opioid, the opioid properties of tramadol seem to be very limited. Tramadol shares its

mechanism of action with venlafaxine by inhibiting the neuronal re-uptake of serotonin and norepinephrine (93). Tramadol given perioperatively may therefore have a potential for preventing persistent postsurgical pain. TKA is a standardized surgical procedure that seemingly would be optimal to use in interventional studies on sustained postsurgical pain.

HYPOTHESIS AND AIMS

Hypotheses

- The origin and mediation of pain at rest and pain with movement differ. The two pain modalities should therefore be assessed separately
- Pain with movement is predominantly related to grade of radiographic OA whereas pain at rest predominantly is related to grade of inflammation.
- Central sensitization is a contributing factor to pain in chronic OA pain as well as in unexplained persistent pain after TKA
- Pain thresholds to electrical stimulation can be used to identify patients at increased risk of persistent pain after TKA
- Tramadol mitigates acute postoperative pain
- Tramadol has a preventive effect on persistent pain after TKA

Aims

- To test whether separate assessment of pain at rest and pain with movement preoperatively is useful for predicting pain relief by TKA
- To test whether pain at rest and pain with movement in OA differ in terms of inflammatory or radiographic changes
- To assess the value of preoperative grade of radiographic and histological changes in prediction of pain relief by TKA
- To establish the usefulness of the Pain Matcher® as a tool for measurement of pain in OA and prediction of pain relief by TKA
- To test if the risk of persistent pain 18 months after TKA is related to the intensity of acute postoperative pain
- To determine whether intravenous tramadol 100 mg x 4 as add-on to morphine administered via a PCA pump results in better pain relief after TKA than morphine alone
- To test whether tramadol administered for 24 hours after surgery prevents persistent pain 18 months after TKA as compared to morphine alone

MATERIAL AND METHODS

The study was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent prior to participation.

PARTICIPANTS

Men and women aged 18–80 years, with American Society of Anaesthesiologists (ASA) physical status I or II and primary osteoarthritis, selected for elective TKA with spinal anaesthesia at Stockholm Spine Centre, were enrolled between February 2002 and August 2004. The exclusion criteria were as follows: creatinine level above 160 mmol/l; intolerance to tramadol or morphine; seizures or cardiac arrhythmias; or communication problems. Distribution of the 75 patients recruited for participation and reasons for exclusion, withdrawal, or discontinuation are presented in the flowchart in Figure 3. The populations ('intention to treat' or 'per protocol') used for statistical calculations are also given. Because of administrative failures or consent withdrawals 10 patients in paper II and 4 patients in paper III and I were excluded. The number of patients excluded in the different studies (paper I-IV) varied because of differences in protocols and consent withdrawals.

Preoperative patient characteristics are shown in Table 1. No significant differences besides smoking habits were found between groups.

Table 1 Baseline characteristics of the patients

Characteristic		Paper I and III (n= 69)	Randomized in paper II (n=63)	
			Tramadol n=32	Placebo n=31
Age in years	M (SD)	68 (8.1)	68 (8.6)	68 (8.7)
Weight in kg	M (SD)	84 (15.5)	81 (17.0)	86 (13.9)
BMI	M (SD)	30 (5.0)	30 (4.8)	29 (5.2)
Duration of knee pain in years	M (SD)	8.5 (6.2)	9.8 (7.6)	7.8 (5.6)
Smoking habits	Yes (%)	12 (17)	3 (9)	8 (26)
Male/Female	N (%)	34 (49)	16 (50)	14 (45)

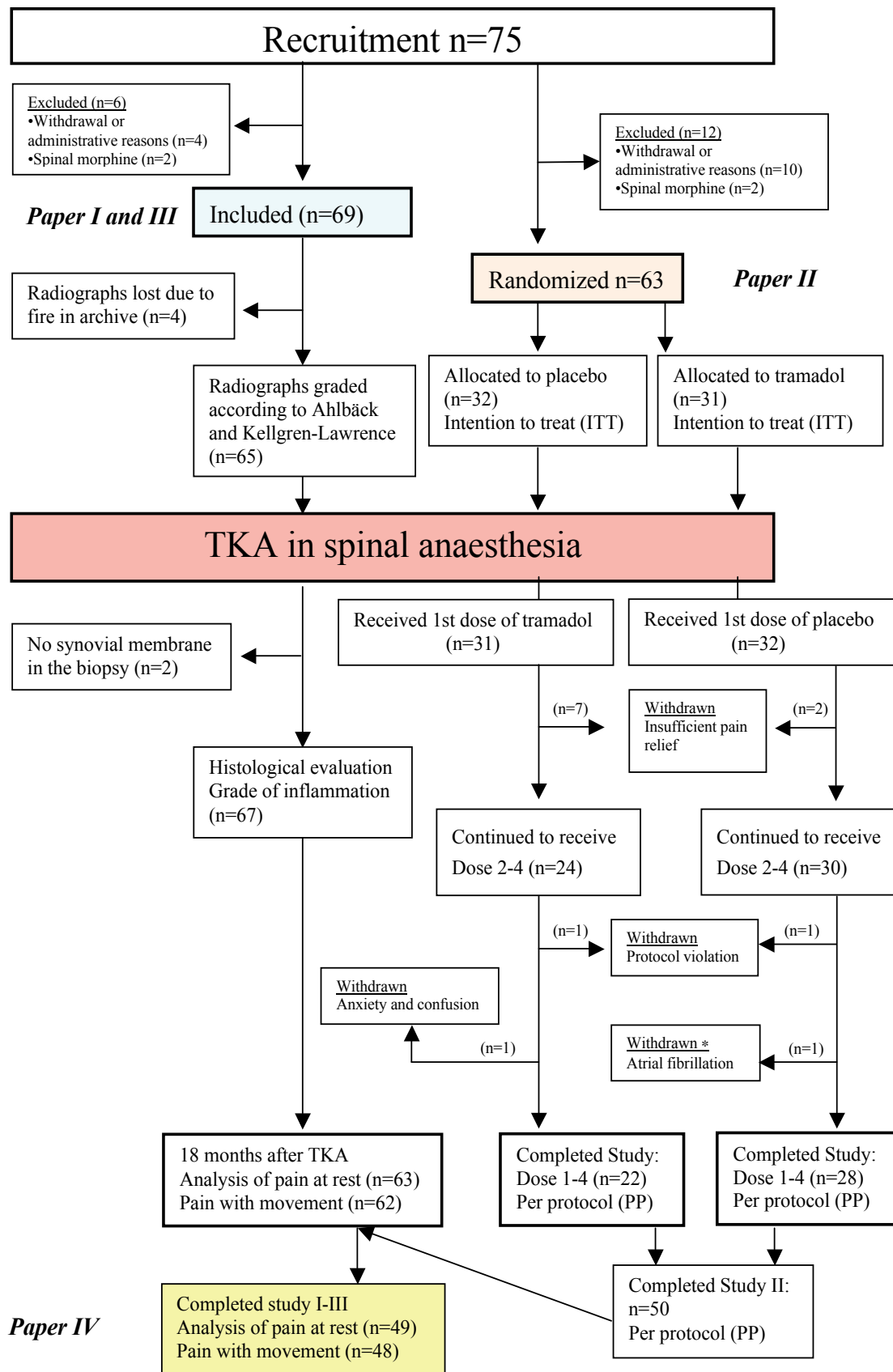


Figure 3. Flow chart showing the reasons for withdrawal and explanation of the patient study groups used for statistical analysis.

SAE = serious adverse event.

PREOPERATIVE ASSESSMENTS

Preoperative pain according to VAS

All patients were interviewed the day before surgery about the total duration of knee pain and the current intensity of pain at rest and with movement. The latter was defined as pain during walking. Preoperative pain intensity was assessed using the visual analogue scale, VAS (Figure 2), (59). The use and validity of VAS for pain assessment have been reported previously (58, 59, 119). The ratings were recorded on a scale with the endpoints 0 and 10 on a 100 mm horizontal line. Patients moved a vertical line along the horizontal scale and selected a position that corresponded to the intensity of pain. The left endpoint represents no pain whereas the right endpoint depicts the worst imaginable pain. The ratings on the back of the scale were read and recorded as whole numbers (0-10). The rationale for recording ratings on the VAS as whole numbers was that this is the way the scale is used in clinical practice. In paper IV the preoperative pain ratings were transformed to a scale between 0 and 100 to enable comparison with the pain ratings during the first postoperative day reported in paper II.

Pain Matcher®

The Pain Matcher (PM), Figure 3, is an instrument for electrical stimulation that was developed for assessing the magnitude of pain (62, 120). The patient matches perceived pain in a certain region of the body to a physical sensation between the thumb and index finger produced by the PM (121). The Pain Matcher® provides constant current stimulation, despite variable skin resistance, and is controlled by a microprocessor, which provides rectangular pulses at a frequency of 10 Hz and amplitude of 10 mA. Increasing the stimulus is done by gradually raising the pulse width from zero to a possible maximum of 396 μ s in increments of 4 μ s over a total of 99 steps. The electrical current is extremely low and causes no tissue damage. The value reached (0 to 99) is directly related to the pulse width and is displayed on a liquid crystal screen. Measuring pain with the PM has been shown to be reliable (122, 123). We used the PM preoperatively on all patients to assess not only the matched pain, i.e., the pain corresponding to the knee pain with movement, but also to determine sensory and pain threshold to the electrical stimulus. As a control group, 12 men and 12 women, all healthy and without pain, were tested for the same thresholds.

Radiographic grade of OA

Anterior-posterior and lateral radiographs were taken with equal weight bearing on both legs in 15° of flexion or in the case of contracture at maximal extension. All radiographs were read by an experienced radiologist and graded according to the Ahlbäck and Kellgren & Lawrence (K&L) classification systems (72, 124), Table 2a-b. The different compartments of the knee, including the patello-femoral joint, were evaluated separately. We used the score from the most damaged compartment as measure of radiographic severity. The Ahlbäck classification and Kellgren-Lawrence classification used in this thesis are shown in Table 2a-b.

Table 2a The Ahlbäck classification of radiographic knee OA

Ahlbäck grade	Ahlbäck definition
Grade I	Joint space narrowing (joint space < 3 mm)
Grade II	Joint space obliteration
Grade III	Minor bone attrition (0–5 mm)
Grade IV	Moderate bone attrition (5–15 mm)
Grade V	Severe bone attrition (>15 mm)

Table 2b The Kellgren & Lawrence classification system of radiographic knee OA

Kellgren & Lawrence grade	Kellgren & Lawrence definition
Grade 1 'Doubtful'	Minute osteophyte, doubtful significance
Grade 2 'Minimal'	Definite osteophyte, unimpaired joint space
Grade 3 'Moderate'	Moderate diminution of joint space, with osteophytes
Grade 4 'Severe'	Joint space greatly impaired with sclerosis of subchondral bone

RANDOMISATION

The study presented in paper II was a single-centre, parallel, double-blind, randomized trial with two treatment groups: (i) tramadol 100 mg in 100 ml physiological saline solution for intravenous infusion, administered four times (every 6 h) during the first postoperative day; (ii) 100 ml physiological saline solution, administered four times (every 6 h) during the first postoperative day. The Pharmacy of the Karolinska University Hospital (Karolinska Apoteket, Solna, Sweden) received the name and date of birth of the included patient and prepared four 100-ml bags containing saline solution with or without tramadol; the infusion bags were identical except for the label with the patient's name and birth date. A manually generated Randomisation list with blocks of six, based on a Randomisation table according to the Quality Manual of Apoteket AB, Chapter 10 (Pharmacist Gudrun Ekberg), was used. The four infusion bags were available after termination of surgery.

SURGICAL PROCEDURE

Surgery was performed in spinal anaesthesia at the Karolinska Hospital according to our standard procedure using the PFC Sigma knee prosthesis (Johnson & Johnson). The femoral component was positioned using an intra-medullar guide. Rotational alignment was achieved using the posterior condyles as reference. In cases with a valgus knee or uneven cartilage erosion Whiteside's line and the epicondyles were considered for the same purpose. The tibial component was positioned with an extra-medullar guide. Rotational alignment was determined with the patellar tendon as a reference and by testing patellar tracking during flexion and extension. The patella was not resurfaced in any case.

During surgery two samples were taken from the synovial membrane. One full thickness (synovial membrane and fibrous capsule) biopsy of approximately 20 x 20 mm was taken from the synovial fold above the femoral cartilage shield. The other biopsy entailed an isolated sample of synovial membrane from the site of most pronounced inflammation, i.e. visible swelling and redness. All samples were immediately frozen to -58° C. After one week the samples were transferred to -70° C and kept there until analysis.

PROTOCOL

Following surgery, when pain intensity had reached 40 mm on the VAS, patients received a PCA-pump for intravenous administration of morphine (1 mg/ml) as well as the first dose of study medication (saline or tramadol 100 mg). On patient request, 1-2 mg of morphine was delivered each time the PCA pump was activated. All patients had the option to receive additional morphine from the study nurse. The administration of the study drugs was repeated every 6 hours. In order to minimize the risk of nausea from tramadol, the study patients received the infusion over 20 min.

POSTOPERATIVE ASSESSMENTS

Assessments during the first 24 hours

Prior to administration of the first infusion of the study drug, the patients assessed the pain intensity using a VAS from 0 (“no pain”) to 100 (“worst imaginable pain”). The degree of nausea and degree of sedation (tiredness) was also assessed using the 100-mm VAS. During the first 24 hours after surgery only pain at rest was assessed. This was done every hour during the first 6 hours and then prior to infusion of the study drugs as well as 1 hour after infusion. The final assessment was done 24 hours after the start of the trial i.e. 24 hours after administration of the first dose of the tramadol or placebo. No specific questions were asked with regard to adverse events, but the patients were informed to report any side effects they encountered.

Histological grade of inflammation

Synovial tissue from all patients were sectioned at 10µm using a Microm HM 560 cryostat. The sections were mounted directly on SuperFrost/Plus glass slides and stained with Hematoxylin-Eosin. All slides were coded and then examined by an experienced histologist who evaluated the extent of inflammation from 0 to 3 (49) according to lining cell depth, cellularity and lymphocyte infiltration as shown in Table 3.

Table 3 Histological grading of inflammatory changes in the synovial membrane (49)

Grade	Description	Definition
0	Normal	Synovial lining 4 or 5 cells thick, increased cellularity with some inflammatory cells
1	Mild inflammation	Synovial lining 6 or 7 cells thick, dense cellularity with inflammatory cells but not lymphoid aggregates
2	Moderate inflammation	Synovial lining 6 or 7 cells thick, dense cellularity with inflammatory cells but not lymphoid aggregates
3	Severe inflammation	Synovial lining >7 cells thick, dense cellularity and inflammatory cell infiltration, may contain perivascular lymphoid aggregates

Pain 18 months after TKA

At 18 months postoperatively a questionnaire was sent to all patients, who were asked to estimate pain intensity at rest and with movement according to the VAS as done before surgery. Instead of merely calculating mean postoperative pain for the entire group, pain relief was assessed for each patient individually, after which the mean pain relief was determined for the entire group. Since the change in VAS from pre- to postoperative, delta pain, depends on the magnitude of preoperative pain we also determined the relative change in pain i.e. the ratio delta pain to preoperative pain.

STATISTICAL ANALYSIS

For papers I and III, a power analysis was carried out showing that 28 subjects should be included to find a strong relationship ($r \geq 0.50$) with a significance level of 5 percent and a power of 80 percent using a two-tailed test. All variables were summarized using standard descriptive statistics such as mean, standard deviation (SD), and frequency. Due to skewed distributions correlations were calculated as Kendall's rank order correlation coefficients (τ). The predictive value of preoperative measurements was evaluated with a logistic regression analysis (stepwise forward). The inclusion criterion was 5 percent. The logistic regression analysis yields the relationships as odds ratios with a 95 percent confidence interval. All variables entered in the logistic regression were dichotomized. The significance level was 5 percent (two-tailed).

For paper II the size of the trial, i.e. the number of patients included, was based on the clinical assumption that a difference of 17 mm in mean VAS between the two treatment groups during the first postoperative day should be clinically significant. The power analysis was based on a standard deviation of the pain intensity of 20 mm, as reported in a similar patient sample (125). A sample size of 30 in each group should be sufficient to detect a decrease in pain intensity of 1.7 with 90% power and a $1/4$ 0.05, using the unpaired Student's t-test (GraphPad StatMate 1.0, GraphPad, San Diego, CA). Differences in pain intensity, sedation, nausea, and morphine consumption were compared between the two study groups with the Mann–Whitney U-test.

RESULTS AND DISCUSSION

PREOPERATIVE CHARACTERISTICS

The mean values of the preoperative characteristics are similar to other reports on patients with knee OA scheduled for TKA (126). After a mean period of 8.5 years with gradually increasing stiffness and pain in the affected knee, the patient was referred to an orthopaedic surgeon. Notably, the main complaint and the reason for consultation was pain with movement. Radiological examination typically revealed a medial compartmental osteoarthritis with a slight varus deformity. A few patients (17%) reported moderate to severe pain also at rest.

VAS

Preoperative pain ratings are shown in Table 4. No significant gender difference in the pain ratings according to VAS was found. As mentioned above, the main complaint of patients scheduled for TKA because of OA was pain with movement. Almost 25 percent (16/69) of the patients had no pain at rest. Pain at rest was significantly less intense than that with movement ($z=7.03$, $p<0.001$). Out of 69 patients, 65 (94%) scored 5 or higher for pain with movement (VAS 0-10), but only 12 (17%) scored 5 or higher for pain at rest (VAS 0-10).

We found no correlation between the intensity of pain at rest and pain with movement. This is an interesting observation. The sources of pain in OA are not fully understood, but it can be speculated that pain at rest is caused by a different mechanism than pain with movement. The sensory qualities of pain at rest in knee OA are often described as aching, tiring, and tenderness indicating an underlying neuropathic component. Pain with movement on the other hand is more often described as sharp, which indicates nociceptive pain mediated by A- δ fibres. A distinction between pain at rest and pain with movement is of clinical significance. It may prove that these two modalities of pain in OA represent activation of different nerve terminals that have altered thresholds.

Table 4. Mean preoperative pain ratings in the 69 patients

Variable	Mean	SD	Range
Visual analogue scale			
Pain, at rest	2.4	1.86	0 to 7
Pain, with movement	7.1	1.72	3 to 10
Pain Matcher®			
Sensory threshold	7.1	3.17	3 to 19
Pain threshold	16.4	10.63	5 to 78
Matched pain	20.6	12.47	5 to 65

Quantitative Sensory Testing (QST) - Pain Matcher®

Mean preoperative values of matched pain, pain and sensory thresholds are shown in Table 4. As in previous studies (127), the patient group compared to the normal reference group, exhibited a significantly higher sensory threshold (7.1 vs. 4.5) and a significantly lower pain threshold (16.4 vs. 21.1). On average the pain threshold was 2.4 (range 1.1-9.6) times higher than the sensory threshold. The matched pain on motion was 1.42 times higher than the pain threshold (range 0.43-3.43). Furthermore, women had significantly lower sensory thresholds than men (6.4 vs. 7.8, $z=2.38$, $p=0.017$) and also lower pain thresholds (13.5 vs. 19.4, $z=2.89$, $p=0.004$). The matched pain on motion, however, was significantly lower than that for men (14.9 vs. 26.2, $z=3.28$, $p=0.001$).

The tool used in the present study for matching of pain and determining sensory thresholds and pain threshold, i.e., Pain Matcher®, has been reported to be both reliable and reproducible (62). However, in this study we found it difficult for patients to match the pain inflicted by the Pain Matcher® to knee pain. As in previous studies (121) some patients found the electrical impulse unpleasant and therefore stopped the test before experiencing pain. Others had problems in discriminating pain from unpleasantness. The difficulties in understanding the instructions was reflected by as many as 9 of 52 patients scoring higher for pain threshold than for matched pain despite reporting considerable knee pain on the VAS scale. Also the discordance between matched and scored joint pain indicates that “matched pain” as determined by Pain Matcher® is of questionable value. Nonetheless, our data suggests that the tool can offer meaningful measurements of thresholds for sensation and pain.

A low pain threshold to an electrical stimulus to a site distant from the arthritic joint has been associated with a central sensitization. The low thresholds to pain in patients with OA compared to healthy controls therefore may indicate a central sensitization as a contributing factor to pain in long standing OA.

Radiographic changes

The average grade of radiographic OA as well as the distribution of patients in each grade is shown in Table 5a-b. Most patients presented with predominantly medial compartmental osteoarthritis. Seven patients (10%) had a lateral compartmental OA and out of 65 patients evaluated for radiographic OA 61 had signs of patello-femoral OA of any degree according to the Ahlbäck scale and 26 patients according to the Kellgren & Lawrence scale. Although criticism exists of both scales they are extensively used and intra-observer reliability has been found to be acceptable, albeit dependent on experienced radiologists (73, 74). In order to obtain data that are applicable in clinical practice we decided in favour of plain radiographs and the most frequently used classifications, i.e. Ahlbäck and Kellgren & Lawrence (Figures 2 and 3) according to an experienced radiologist.

Table 5a. Mean preoperative grade of radiographic OA

Variable	n	Mean	SD	Range
Worst compartment OA				
Ahlbäck	65	3.4	0.76	1-4
Kellgren & Lawrence	65	3.5	0.64	2-4
Patello-femoral OA				
Ahlbäck	65	1.22	0.42	0-4
Kellgren & Lawrence	65	0.66	0.88	0-4

Table 5b. Number of patients according to grade of morphological changes

Grade	Worst compartment OA		Patello-femoral OA		Histological OA
	Ahlbäck	K & L	Ahlbäck	K & L	n
0	0	0	4	39	36
1	1	0	45	12	22
2	8	5	13	12	6
3	22	21	1	1	3
4	34	39	1	1	-
5	0	-	0	-	-

Histological changes

The number of patients in each grade of histological inflammation is shown in Table 5b. The average grade of inflammation was 0.7 (range 0-3; SD 0.84). Three patients had severe and six moderate inflammatory changes. The occurrence of inflammatory changes in the present series is thus similar to or less in comparison to that of previous reports in the literature (46, 49).

Correlation between preoperative findings

As seen in Table 6 the Ahlbäck and Kellgren-Lawrence scores were strongly correlated ($\tau=0.74$; $p<0.001$). However, the present study does not enable any conclusions about which classification is preferable in terms of validity or reliability. As expected, the grade of radiographic OA as assessed by either of the two scales exhibited a significant positive correlation with the duration of disease ($\tau=0.30$ and 0.31 , $p<0.01$). However, age, gender, BMI, or smoking habits showed no significant correlation with the pain ratings or the grade of radiographic and histological changes. Radiographic studies focusing on individual features of OA, e.g. osteophytes, subchondral bone sclerosis, synovial thickening, meniscal tears, etc., have reported significant associations with pain (128). In a recent population based study using a global Kellgren & Lawrence score Neogi et al. (25) found a strong association between pain and radiographic OA. In the present study the failure to demonstrate a similar relationship may be explained by the selection of patients with high pain scores typical for those requiring surgical intervention. Finding a significant relationship between pain scores among patients selected for TKA and other variables is obviously more difficult than in a population-based study in which pain scores are distributed over the entire

VAS scale. However, the discordance between pain and grade of radiographic OA is probably explained by the heterogeneity of patients with OA. This is manifested by different grade of e.g. central and peripheral sensitization, synovitis and intraosseous pressure, or simply in different personal interpretations of pain.

Table 6. Correlations between pain and morphological features of OA

Variable	2	3	4	5
VAS				
1 Pain at rest	0.10	-0.09	-0.09	0.11
2 Pain with movement	-	0.16	0.05	-0.17
Radiographic grade				
3 Kellgren & Lawrence		-	0.74***	0.01
4 Ahlbäck			-	0.06
Histological grade				
5 Inflammation				-

*** $p < 0.001$

As shown in Table 6 there was no significant correlation between the grade of radiographic changes and the histological grade of inflammation, which also has been suggested as a source of pain in OA. However, efforts to find a relation between pain and inflammatory changes in OA have been contradictory (36, 38, 129). We noted a tendency for patients with histological signs of inflammation to report a higher score for pain at rest. In the entire group, 52 out of 69 (75%) patients reported pain at rest prior to surgery. Among the 31 patients with inflammatory changes in the synovial membrane, as many as 26 (87 %) had pain at rest. However, as shown in Table 6 this relation was not significant. Neither did we find any other significant relationships between morphological features and the preoperative pain ratings.

It was expected that patients with a low pain threshold would report a higher preoperative VAS score for pain intensity either at rest or with movement. It was also speculated that patients with synovitis would have lower thresholds for pain since inflammation has been shown to induce not only peripheral but also central sensitization (5, 28). However, the mean values of sensory and pain thresholds, and matched pain with movement were not significantly related to the grade of radiological OA or histological signs of inflammation. Nor were these morphological features related to the preoperative pain ratings (VAS). Furthermore, pain with movement according to VAS, and the matched pain with movement according to the Pain Matcher® showed no significant relationships.

As shown in Table 7, significant but modest correlations were found between the sensation and pain thresholds on one hand and the matched pain on motion on the other. A low sensory threshold tended to be associated with a low pain threshold.

It has been proposed that a pain threshold/sensory threshold of less than 2.0 suggests an altered central nervous system processing (66). Pain thresholds to electrical stimulation have been used in the detection of central sensitization (130). As signs of central sensitization have been demonstrated among non-operated patients with osteoarthritis (5) and treatment of neuropathic pain has been shown to be effective in OA (88) it appears that patients with OA to a various extent may be sensitized even before TKA.

Table 7. Relationships between different aspects of pain and sensory characteristics as determined by the visual analogue scale (VAS) and Pain Matcher (Kendall's rank order correlation coefficients)

Variable	2	3	4	5
Visual analogue scale (VAS)				
1. Pain at rest	0.10	-0.08	-0.04	0.05
2. Pain with movement	-	-0.06	-0.13	-0.08
Pain Matcher				
3. Sensation threshold		-	0.42***	0.46***
4. Pain threshold			-	0.52***
5. Matched pain – with movement				-

*** $p < 0.001$

THE EFFECT OF TRAMADOL ON ACUTE POSTOPERATIVE PAIN AND MORPHINE CONSUMPTION

The aim in paper II was to find evidence for the efficacy of combining tramadol and morphine by PCA for pain relief after orthopaedic surgery. This combination was used in our practice and considered to offer better pain relief and fewer side effects after orthopaedic surgery than morphine alone. There was however no evidence in the literature for this combination.

The combination of tramadol at the recommended dose of 100 mg x 4 with morphine by patient controlled analgesia (PCA) did not result in superior pain reduction after TKA (Figure 5). Although the morphine consumption during 24 h after TKA was 30% lower in the tramadol group than in the placebo group, this may not be of clinical importance as the side effects, such as sedation and nausea, were just as common in the tramadol group; despite the lower use of morphine (Table 8). Also, more patients in the tramadol group dropped out as a result of insufficient pain relief.

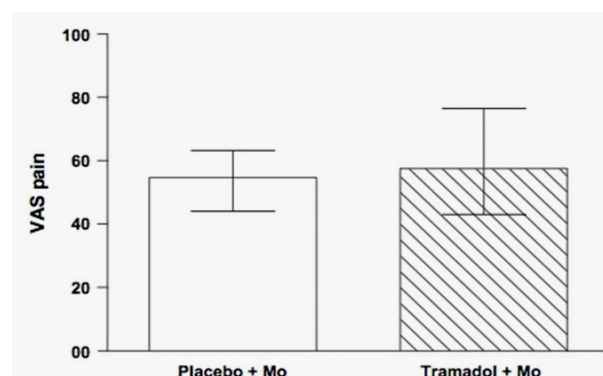


Figure 5. Median and interquartile range of the average visual analogue scale (VAS) score registered throughout the study period after the administration of one to four doses of tramadol 100 mg ('intention to treat'). Mo = morphine.

Table 8. Intention to treat outcome of one to four doses of tramadol (100 mg) administered at 6-h intervals (24 h).

	Placebo	Tramadol
Group size	32	31
Pain VAS primary outcome	54 (50–59)	59 (51–67)
Nausea VAS	3 (1–6)	6 (3–9)
Sleep rate (%)	35	33
Withdrawal rate (24 h)	4/32 (13%)	9/31 (29%)
Withdrawal due to insufficient pain relief	2/32 (6 %)	7/32 (23%)

Data expressed as mean (95% confidence interval). No statistically significant difference was reached for any variable. VAS, visual analogue scale

In a study (131) where the effects of tramadol were compared with those of morphine via PCA, Hadi and colleagues found no differences in pain relief or side effects. Some studies have indicated that oral tramadol lacks analgesic effect in the postoperative situation (125, 132). Suboptimal doses of tramadol may have contributed to this outcome. Despite the higher dose of morphine used by the patients, clinically acceptable analgesia was hard to achieve with intravenous morphine, either with or without tramadol. Many patients were either in pain or asleep.

Hence, this controlled clinical trial demonstrated that neither intravenous morphine by PCA nor the combination of morphine by PCA with tramadol resulted in clinically acceptable pain relief in patients with pain after TKA surgery. In consequence the combination of tramadol and morphine by PCA for pain relief after orthopaedic surgery is no longer used in our practice.

The use of local infiltration anaesthesia has significantly improved pain management during the first postoperative 24 hours (133). However, after the first postoperative day there is still a need for improvements in pain management not only for patient satisfaction in conjunction with surgery but probably also for the prevention of persistent pain in predisposed patients.

PAIN AND PREDICTION OF PAIN 18 MONTHS AFTER TKA

18 months after TKA pain at rest and pain with movement was assessed for 63 and 62 patients respectively. The mean VAS scores were 0.5 (median 0; SD 1.3) for pain at rest and 1.7 (median 1; SD 3.8) for pain with movement. 21 (34%) patients had no pain at rest or with movement. Fifteen (22%) of the patients still had pain at rest (range 1–6) and 41 (66%) on motion (range 1–8). The results of the present study confirm the effectiveness of the TKA in the treatment of pain in OA. However, 18 months after TKA as many as eleven patients (16%) reported VAS scores equal to or more than 4 for pain at rest or with movement. This percentage of patients not satisfied with the TKA, is comparable to that reported by others (134). By identifying preoperative factors related to a poor outcome, selection criteria might be refined. To enable analysis of the predictive value of preoperative features of OA, pain 18 months postoperatively was assessed.

Three of the preoperative variables, i.e. pain at rest according to VAS, ($\chi^2=9.91$, $p=0.015$), sensory and pain thresholds according to Pain Matcher[®] ($\chi^2=4.00$, $p=0.045$, and $\chi^2=6.34$, $p=0.012$, respectively), were significantly related to pain at rest 18 months postoperatively. In the logistic

regression analysis, only two of these variables contributed significantly and uniquely to prediction, namely pain at rest and pain threshold (Table 9); the greater the pain at rest and the lower the pain threshold before surgery the worse the outcome in terms of persisting pain at rest. Notably, pain with movement at 18 months was not related to any of the tested predictor variables. Nor was the radiographic grade of OA or the histological grade of inflammation in the synovial membrane of any value for the prediction of pain intensity 18 months after TKA.

Table 9. Odds ratios (OR) for variables predicting a poor outcome, i.e. a high score for pain at rest 18 months postoperatively.

Predictive variables	B*	S.E. †	p	OR	95% CI ‡
Preoperative pain at rest (VAS)§	1.87	0.72	0.009	6.48	1.32 – 31.96
Preoperative pain threshold (Pain Matcher®)	2.22	0.87	0.010	9.19	1.69 – 50.07
Constant (y-intercept)	-3.76	0.96	0.000	-	-

B, slope of the regression equation

† SE, standard error

‡ 95% CI, 95% confidence interval

§ VAS, visual analogue scale

Since acute postoperative pain has been shown to predict persistent postsurgical pain (109) it was decided to use the means of the VAS scores determined during the first 24 postoperative hours and relate these values to the outcome in term of pain 18 months after TKA. A tendency was found for patients with severe acute postoperative pain to be at higher risk of persistent pain at rest, but not with movement 18 months after TKA.

Suggested risk factors of persistent postsurgical pain include female gender, low age, intensity of preoperative and acute postoperative pain, psychic vulnerability, and a surgical approach that entails an increased risk of nerve damage (109). In accordance with the results of Bourne and colleagues(135), preoperative pain at rest in the present study was found to be associated with a worse outcome after TKA. Another finding in line with the report of Nielsen et al. (65) on caesarean section was that a low preoperative pain threshold to an electrical stimulus predicted persistent postsurgical pain. Also, Werner (136) in a review concluded that QST has a higher predictive value with regard to postsurgical pain than psychosocial factors.

In a previous study by Pritchett (137), the level of Substance P (SP) was determined in the synovial fluid of patients scheduled for TKA. Good or excellent pain relief was achieved in 97% of patients with an elevated preoperative level of SP and in 61% of those with a normal preoperative level. It turned out that if surgery had been done only on patients with a high level of SP, presumably reflecting the nociceptive component of pain, most cases of persistent pain would have been avoided.

It appears that biological markers may be of value in predicting persistent postsurgical pain. It may prove that patients with a certain biological predisposition may develop a central sensitization before, during, or after surgery leading to unexplained persistent pain. If patients at increased risk of developing persistent postsurgical pain could be identified, surgery could be avoided in

some cases. Alternatively, preventive measures could be applied before and after surgery. Hypothetically, TKA relieves nociceptive pain, whereas the effect on neuropathic pain and central sensitization is more unpredictable.

PREDICTION OF CHANGE IN PAIN FROM PRE- TO 18 MONTHS POSTOPERATIVELY

It has been proposed that the outcome after TKA should not only be based on postoperative pain scores but also on absolute and relative change in pain (135). By calculating absolute and relative changes in pain, a shift was made from inter- to intra-individual comparisons. This was done to avoid the obvious bias of comparing pain scores between individuals, which is highly dependent on each individual's unique interpretation of pain.

The mean change in pain, in absolute terms, was -2.4 (95% CI -2.97 to -1.92) for pain at rest and -5.3 (95% CI -5.91 to -4.65) for pain with movement. The mean change in pain score in relative terms was -53% (95% CI -0.66 to -0.40) for pain at rest and -64% (95% CI -0.57 to -0.71) for pain with movement. Notably, four out of 63 patients at 18 months postoperatively scored higher for pain at rest compared to the preoperative assessments and two out of 62 patients scored higher for pain with movement; one of the two scored higher for pain both at rest and with movement. Although the average change in pain both at rest and with movement (VAS) was clinically significant, (119, 138) patients scheduled for TKA should be informed that the main gain to be expected from the procedure is relief of pain with movement.

As described above the grade of radiographic and histological changes were not significantly related to the mean pain intensities at rest or with movement preoperatively, nor at 18 months after TKA. However, a high score for radiographic OA was found to correlate significantly to a relief of pain with movement both in absolute and relative terms reflecting the predictive value of radiographic grade of OA.

This relationship would not have been detected if the analysis had been confined to the postoperative pain scores. Instead the predictive value of radiographic grade became evident when the change in pain from pre- to postoperative was recorded; the higher the radiographic grade the greater the relief of pain with movement. From the observations made we suggest that evaluation of the outcome after joint replacement should be based on intra-individual change from pre- to postoperative scores for statistical analysis. Most importantly, follow up studies on pain relief by joint replacement should consider pain at rest and pain with movement separately.

THE EFFECT OF TRAMADOL ON PAIN 18 MONTHS AFTER TKA

In paper IV a test was conducted to assess whether tramadol administered for 24 hours directly postoperatively as add-on to intravenous morphine via PCA might prevent persistent pain 18 months after TKA as compared to morphine alone. It may be argued that the chances of this would be limited as we already reported that intravenous tramadol in addition to morphine via PCA did not result in better pain relief during the first postoperative day. However, gabapentin given as a single preoperative dose before thyroidectomy was found to prevent persistent postsurgical pain although it had no effect on acute postoperative pain (139). Previous studies have indicated that

not only the reduction of acute postoperative pain per se, but also the mechanism (drug) by which this reduction is achieved has an impact on persistent postsurgical pain.

In the search for drugs that act specifically on central sensitization, tramadol has been suggested as an agent that possibly could induce anti-hypersensitivity (29). Furthermore, intravenously administered tramadol and its active metabolite have been detected in the synovial fluid where it was found to significantly lower the levels of SP (140). This indicates a modulatory effect on inflammation, which in turn has been proposed to underlie sensitization of the nervous system causing in some cases persistent postsurgical pain. Therefore data on pain at rest and with movement 18 months after TKA was compared in patients randomized to tramadol or placebo.

The mean VAS scores 18 months after TKA are shown in Table 10. Although patients in the tramadol group scored higher in pain intensity 18 months after TKA, the differences were not statistically significant.

In summary, the present study could not demonstrate that the combination of tramadol and morphine was superior to morphine alone in preventing persistent pain after TKA. However, further investigations exploring the effects of tramadol administered during the entire painful postoperative period should be made before the preventive effects of tramadol on persistent postsurgical pain can be discarded.

Table 10. Per protocol outcome of four doses of tramadol (100 mg) administered at 6h intervals during 24 h

	Placebo	Tramadol
Acute postoperative variables	(n=28)	(n=22)
Mean acute postoperative pain	52 (47-57)	49 (43-55)
VAS 0-100 (95% C.I.)		
Total morphine dose (mg)	72 (61-82)	51 (39-62)*
Total morphine dose (mg/kg)	0.9 (0.76-1.04)	0.63 (0.48-0.78)*
Outcome at 18 months postoperatively	(n=26)	(n=22rest/21move)
Pain at rest VAS 0-100 (95% C.I.)	2 (0-5)	9 (1-16)
Pain with movement VAS 0-100 (95% C.I.)	14 (7-21)	20.2 (10-34)

Data expressed as mean (95% confidence interval)

LIMITATIONS

PAIN ASSESSMENT

An obvious limitation of relating pain intensity to different morphological features of OA is the inherent shortcoming of pain assessments. Difficulties in finding correlations between pain and different features of OA may partly be explained by differences in the interpretation of pain among individuals. Nociceptive signals are subject to modulation by central and peripheral excitatory and inhibitory systems. In addition, pain as expressed on the VAS is influenced by different psychosocial, economic, cognitive and emotional experiences (141). Yet, VAS is reasonably reliable (142) and widely used permitting comparison with the results of other similar studies. To some extent the problem with VAS can be avoided as described by calculating the absolute and relative changes in pain on an intra-individual level after a given intervention.

RADIOGRAPHIC EXAMINATIONS

Although routine pre- and postoperative radiography of the knee was done, no long radiographs including the hip, knee, and ankle, (HKA) were taken to evaluate alignment. A wide variety of mechanical and biological factors may underlie persistent pain after TKA (143, 144). Presumably, these factors are evenly distributed in the present patient series. This study was aimed at finding other conceivable explanations to pain in OA beyond those related to implant design and positioning.

STATISTICAL POWER

Given the low incidence of pain 18 months after TKA in the present study, the statistical power in detecting a significant effect of tramadol on persistent pain after TKA was quite limited. However, not even a tendency toward a better effect of tramadol was found. In our analysis, we decided not to include patients who withdrew prior to receiving all 4 doses of the study drug. This drop out might have generated a bias. Yet, it provided homogenous treatment groups for comparison. Admittedly, we are not able to present intention to treat (ITT) data based on the 63 randomized patients. Therefore our report (paper IV) could be regarded as hypothesis generating rather than hypothesis testing.

DURATION OF TRAMADOL TREATMENT

The present study was unable to demonstrate an additional effect of intravenous tramadol, administered during 24 hours as add-on to morphine via PCA, in comparison to morphine alone. Therefore, it may be argued that an effect on persistent postsurgical pain of tramadol given during only 24 hours after TKA would be unlikely. However, gabapentin given as a single dose preoperatively has been shown to prevent persistent postsurgical pain even though it had no effect on acute postoperative pain (139).

CONCLUSIONS

- There is no correlation between the intensity of preoperative pain at rest and with movement. Preoperative pain at rest, but not with movement predicts persistent pain at rest 18 months after TKA. Therefore pain at rest and pain with movement should be assessed separately.
- The preoperative grade of radiographic OA does not correlate with the intensity of preoperative pain in patients scheduled for TKA, nor does the histological grade of synovial inflammation.
- Relief of pain with movement from pre- to postoperative was significantly related to the grade of radiographic OA. Best pain relief by TKA is achieved in patients with severe radiographic changes. This, however, only applies to pain with movement.
- The Pain Matcher[®] is a useful tool for measurements of pain thresholds. Patients with a low pain threshold are at increased risk of persistent pain at rest 18 months after TKA.
- The mean VAS score during the first 24 postoperative hours does not predict persistent pain at 18 months after TKA.
- The combination of intravenous tramadol 100mg x 4 and morphine via PCA does not offer better pain relief after TKA than morphine alone. Nor does tramadol prevent persistent pain 18 months after surgery.
- Pain at rest should not be an absolute prerequisite for TKA. Patients scheduled for TKA should be informed that the main gain to expect is relief of pain with movement.
- The evaluation of the outcome after TKA should be based on intra-individual changes in pre- and postoperative pain scores. Most importantly, follow up studies on pain relief by joint replacement should consider pain at rest and pain with movement separately.
- Efforts should be made to develop relevant tools for identification of patients at high risk of persistent pain after TKA in order to either avoid surgery or to offer pharmacological prevention of persistent postsurgical pain.

CLINICAL IMPLICATIONS

From the present studies as well as previous observations it seems that TKA is a successful procedure for treatment of nociceptive pain in knee OA. However, a subset of patients experience persistent postsurgical pain possibly caused by a central sensitization. To identify these patients the Pain Matcher[®] may be useful.

Pain at rest is often considered a prerequisite for joint replacement (108). The results of the present study seem to refute this view. Instead the indication for TKA should be more restrictive in patients with severe pain at rest. In these cases QST may reveal sensitization and prompt pharmacological intervention to prevent persistent postsurgical pain. In some patients TKA may even be contraindicated.

Although we never resurfaced the patella we found no correlation between the occurrence of radiographic patello-femoral OA and pain or change in pain 18 months after TKA. This supports that other factors than omission of patellar resurfacing are responsible for persistent pain after TKA. It also indicates that radiographic findings on the patello-femoral joint do not provide any guidance as to which patients would benefit from resurfacing of the patella.

Intravenously administered tramadol at the dose of 100 mg x 4 to morphine via PCA pump does not give any additional pain relief compared to morphine via PCA pump alone. Nor does it offer any advantage in terms of side effects. In addition, the present study indicates that morphine via PCA, as the sole means of postoperative analgesia, does not provide sufficient pain relief after TKA. Thus, other means of postoperative analgesia should be utilized following TKA. In consequence, the combination of intravenous tramadol and morphine is no longer used in our practice.

When confronted with a patient with persistent postsurgical pain, the explanation is commonly sought by evaluation of the radiographs looking for malalignment and signs of early loosening of implants without considering neuronal mechanisms as the primary cause. If no obvious reason is found on the radiograph there commonly remains no option beyond referral to a pain clinic. Revision surgery may result in even more severe pain.

FUTURE STUDIES

To minimize the occurrence of persistent postsurgical pain further attempts should be made to identify the relevant risk factors. Psychological tests are already available and can give a hint about the need of preoperative psychosocial intervention. Biological markers of nociceptive pain in serum or in the synovial or spinal fluid as well as markers of central sensitization could be one way to identify patients at increased risk. Suggested markers include BDNF (145), SP, CGRP, and IL-6 (146). Further studies on the predictive value of each of these factors are needed.

Treatments that specifically target pathophysiological mechanisms known to be involved in central sensitization are already available. However, there is no consensus about the use of these agents. Thus there is a need of testing these agents in conjunction with TKA. One that has been shown to be more effective than morphine in the reduction of cancer pain is anti-NGF therapy, which also lowers the concentration of markers of central sensitization (147).

One risk factor for persistent pain, i.e. acute postoperative pain, has been a main target in the field of preventive analgesia. A good effect of local infiltration analgesia (LIA) on acute postoperative pain has been convincingly shown (148) and is currently being tested as a possible way of preventing persistent pain after surgery (149). Also the duration of postoperative LIA may be of significance but has so far not been investigated. To avoid the afferent bombardment during the entire painful postoperative period LIA given during a longer postoperative period should be evaluated. It would also be of interest to test different analgesic agents given intra-articularly in conjunction with surgery. An optimal, individually designed “cocktail” interfering with several mechanisms could be administered through a catheter used not only for postoperative analgesia but also to prevent central sensitization.

SUMMARY IN SWEDISH

BAKGRUND

Artros i knäleden är en vanlig orsak till smärta i rörelseapparaten. Artros kännetecknas av en obalans mellan nedbrytning och uppbyggnad av brosk vilket leder till att brosket successivt bryts ned. Artros delas in i primär och sekundär artros. Primär artros vars utlösande orsak är okänd debuterar oftast sent i livet och enligt WHO's beräkningar lider varannan kvinna och var fjärde man över 60 år av någon form av artros. Sekundär artros drabbar ofta yngre patienter där man har en förklaring som t ex en tidigare knäskada, övervikt eller andra sjukdomar. Det finns många som har artrosförändringar som syns på röntgen men som inte har några symptom, och tvärtom. Artros fortskrider långsamt. Det finns ännu inte något botemedel.

Det finns flera problem med artros. Dels är orsaken till uppkomsten av primär artros okänd. Dels är mekanismerna bakom smärttillståndet vid artros ofullständigt klarlagda. Allt detta minskar förutsättningarna att finna ett botemedel mot sjukdomen och utveckla smärtstillande läkemedel. De mest framträdande symptomen; smärta, stelhet och svullnad tilltar successivt och kan till slut inte behandlas framgångsrikt på annat sätt än med knäprotesoperation. Man sågar då bort ledytorna och ersätter dem med en konstgjord led av metall och plast.

Resultaten efter knäprotesoperationer är idag lika bra som efter höftproteskirurgi med en protesöverlevnad på upp emot 98 % efter 10 år. Knäprotesoperationen är dock förenad både med svår postoperativ smärta och risker för allvarliga komplikationer som infektion och blodpropp. Dessutom drabbas upp till 10 % av oförklarad svår kvarstående smärta efter knäoperationen.

En förklaringsmodell till kvarstående smärta efter operationer är så kallad central sensitisering. Man har visat att intensiv smärta efter operation, inflammation och nervskador kan ge upphov till en kvarstående ökad retbarhet hos nerver. Detta leder till en sänkt smärtröskel. Många patienter med artros har redan före operationen tecken på sensitisering. Denna normaliseras dock oftast efter operationen då den kroniska smärtan och inflammationen försvinner. Dock verkar det finnas individer som är predisponerade till ett kvarvarande tillstånd med ökad eller tom förvärrad smärtkänslighet efter protesoperation.

Inom anestesi pågår intensiv forskning kring förebyggande smärtlindring. Genom att förhindra smärta i samband med operationen tror man sig kunna minska risken för att utveckla kronisk smärta efter operationen. En substans som i djurförsök visats kunna vara intressant i detta avseende är tramadol. Om vi kunde identifiera patienter med en hög risk att drabbas av kvarstående smärta redan före operationen skulle man kunna förbehandla dessa patienter så att mekanismerna bakom kronisk eller persisterande smärta blockeras eller tom undvika operation.

MÅLSÄTTNING

Målsättningen med studien var att undersöka om noggrann analys av såväl vilovärk som rörelsesmärta samt mätning av smärtröskel före en knäprotesoperation kan vara av värde för att förutspå

kvarstående smärta efter operation. Avsikten var också att undersöka om radiologisk artrosgrad och histologisk grad av inflammation i leden var relaterade till smärta före och 18 månader efter operationen. Slutligen var avsikten att undersöka effekten av läkemedlet tramadol dels för behandling av smärta direkt efter operationen och dels för att blockera de mekanismer som leder till kronisk smärta efter operation.

METOD

Studien omfattade 69 patienter som alla var planerade för total knäledsprotos på grund av artros i knäleden. Före operationen fick alla patienter skatta sin smärta i rörelse och i vila på en så kallad Visuellt Analog Skala (VAS). Vi undersökte även smärtröskel med en elektrisk impuls som ökades successivt med hjälp av ett litet instrument, Pain Matcher, som man höll mellan tummen och pekfingret. Med detta instrument fick även patienterna jämföra smärtan i knäleden med smärtan i fingrarna. På detta sätt fick vi numeriska värden inte bara på smärtröskeln utan även på den s.k. matchade smärtan och detektionströskel dvs. den minsta förnimmbara impulsen. Alla data från smärtundersökningarna relaterades sedan till varandra och även till graden av artros på röntgenbilden och graden av inflammation i histologiska snitt av ledhinnan.

Patienterna indelades (randomiserades) sedan slumpmässigt i två grupper. Den ena fick 100 mg tramadol var 6:e timme under de första 24 timmarna efter operationen som tillägg till morfin vilket gavs till alla intravenöst via en patientkontrollerad pump. Den andra gruppen fick placebo istället för tramadol. Under 24 timmar mättes morfinförbrukningen och smärtan skattades varje timme av patienterna på en VAS skala.

18 månader efter operationen skattades åter smärtan i rörelse och i vila enligt VAS. Vi relaterade sedan denna smärta till de preoperativa undersökningsfynden för att finna faktorer som skulle kunna förutspå ett sämre resultat i form av kvarstående smärta efter knäprotesoperation. Vi analyserade även om smärtintensiteten under det första dygnet efter operationen var av betydelse för graden av smärta efter 18 månader. Slutligen undersökte vi om tramadol under 24 timmar efter operationen kunde förebygga smärta 18 månader efter knäledsoperationen.

RESULTAT

Huvudfynden från denna undersökning var att de patienter som hade mest ont i vila och de som hade lägst smärtröskel före operationen även hade mer vilovärk 18 månader efter operationen. De som hade mest uttalad artros på röntgen fick störst förbättring av rörelsesmärtan. Detta kunde vi visa genom att analysera rörelsesmärtan och vilovärk var för sig och beräkna den eventuella förbättringen, dvs. skillnaden mellan smärtan före operationen och den 18 månader efter.

Vidare kunde vi visa att 100 mg tramadol givet var 6:e timme under de första 24 timmarna efter en total knäprotesoperation som tillägg till intravenöst morfin via en patientkontrollerad pump inte hade någon fördel jämfört med enbart morfin vad gäller smärta eller biverkningar. Däremot förbrukades mindre morfin av dem som fick tramadol. Tramadol givet under endast 24 timmar hade dock ingen förebyggande effekt på smärtan 18 månader efter operation med total knäledsprotos.

SLUTSATS

Patienter med svår smärta i vila eller en låg smärtröskel före operationen har större risk att drabbas av kvarstående smärta efter knäprotesoperation. Sänkt smärtröskel mot elektrisk impuls har rapporterats vara av värde för att påvisa s.k. central sensitisering. En av orsakerna till kvarvarande smärta skulle kunna vara en ökad retbarhet i nervsystemet.

Vilovärk anses av många utgöra huvudindikationen för knäprotesoperation. Våra resultat talar för att vilovärk snarare är en varningssignal som bör leda till en utredning om andra orsaker till smärtan. Patienten bör informeras om att det framförallt är rörelsesmärtan som lindras av ingreppet.

Tramadol givet i rekommenderad dos tillsammans med morfin intravenöst har ingen fördel jämfört med enbart morfin vad gäller graden av smärtlindring eller biverkningsprofil vare sig akut postoperativt eller 18 månader efter operation med total knäledsprotes.

Vi tror att man i framtiden med hjälp av biologiska markörer, noggrann smärtanalys och psykologiska tester bör kunna karaktärisera patienter bättre före operationen så att de smärtmekanismer som leder till kronisk eller kvarvarande smärta kan blockeras före, under och efter operationen.

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