■ INSTRUCTIONAL REVIEW

Pain after total knee arthroplasty

A NARRATIVE REVIEW FOCUSING ON THE STRATIFICATION OF PATIENTS AT RISK FOR PERSISTENT PAIN

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The patient with a painful arthritic knee awaiting total knee arthroplasty (TKA) requires a multidisciplinary approach. Optimal control of acute post-operative pain and the prevention of chronic persistent pain remains a challenge. The aim of this paper is to evaluate whether stratification of patients can help identify those who are at particular risk for severe acute or chronic pain.

Intense acute post-operative pain, which is itself a risk factor for chronic pain, is more common in younger, obese female patients and those suffering from central pain sensitisation. Pre-operative pain, in the knee or elsewhere in the body, predisposes to central sensitisation. Pain due to osteoarthritis of the knee may also trigger neuropathic pain and may be associated with chronic medication like opioids, leading to a state of nociceptive sensitisation called 'opioid-induced hyperalgesia'. Finally, genetic and personality related risk factors may also put patients at a higher risk for the development of chronic pain.

Those identified as at risk for chronic pain would benefit from specific peri-operative management including reduction in opioid intake pre-operatively, the peri-operative use of antihyperalgesic drugs such as ketamine and gabapentinoids, and a close post-operative follow-up in a dedicated chronic pain clinic.

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Pain is considered to be chronic when it persists beyond the normal healing time. Chronic pain therefore lacks the acute warning function of physiological nociception. Between 6% and 10% of patients may have moderate to severe pain that continues for at least three months post-operatively, and this is defined as chronic post-surgical pain (CPSP).[1] For a mean 30% (6% to 54%) of chronic pain patients the origin of CPSP might be neuropathic.[2] Neuropathic pain is usually more severe and affects the quality of life more adversely. CPSP should be considered a serious health problem because the prolonged use of opioids and analgesic adjuvants (i.e. gabapentinoids) post-operatively, may result in dependence and addiction.[3,4]

The number of primary total knee arthroplasties (TKAs) being undertaken annually is increasing worldwide by 6% without a negative impact from the economic down-turn.[4] This increase is because of increased longevity and increased activity in old age.[5] With the development of less invasive surgical techniques and fast-track programmes, the length of stay after TKA has been reduced, allowing an increased turnover of patients.[6] Enhanced recovery programmes might lead to the perception of TKA as a minor surgical intervention.[7] Nevertheless, recent studies have reported that 15% to 20% of patients are not satisfied after TKA without evident clinical or radiological reasons.[8] Pain is the main cause of dissatisfaction for most of these patients. Better targeting of the patients at risk with stratification might help to design better peri-operative preventive strategies.[9,10]

Pain may have a psychological component, related to mood, anxiety and depression, or the response to stress and somatisation. An increased amplification of pain is related to tissue injury, blood pressure, impaired pain regulatory systems and pro-inflammatory states.[11] All chronic pain was once acute, but not all acute pain becomes chronic. The transition is complex and involves pre-, intra- and post-operative, psychosocial, socio-environmental and patient-related genetic factors. The aim of this review is to identify risk factors for severe acute pain and chronic pain after TKA.

General predictive factors for CPSP

According to the index developed by Althaus et al,[12] five predictors contribute to CPSP: pre-operative pain in the area which is to be operated

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upon, chronic pre-operative pain elsewhere in the body, such as in the spine or hip, acute post-operative pain, capacity overload and comorbid stress symptoms such as anxiety, rumination, magnification, and helplessness.

Patients awaiting TKA frequently also report pain elsewhere in the body.[13] More intense post-operative pain is seen in association with central sensitisation (CS), younger age, obesity and female gender, and severe acute pain is a major risk factor for the development of CPSP.[14] The type of surgery will also affect the severity of acute pain. More than 50% of patients report severe pain during the first three post-operative days and this can predispose to CPSP.[15] The risk factors for the development of CPSP remain controversial. For example, although women consistently report higher acute post-operative pain scores, regardless of the type of surgery[16,17] and female gender is an independent risk factor for CPSP after TKA according to retrospective studies,[14] this has not been validated in prospective studies.[16] Capacity overload or having to deal with more stress than the subject can cope with in the six months before surgery is also a risk factor. It can lead to an emotional, mental and physical exhaustion (burn out) owing to excessive stress over a long period. Excessive stress can lead to anxiety, panic attacks, depression, alcoholism or other substances abuse.[18] Patients presenting with migraine, irritable bowel syndrome and fibromyalgia might have a genetic predisposition to chronic pain. Furthermore, they often also suffer from insomnia, exhaustion, dizziness, catastrophisation and depression, all indicators of pre-operative stress.[19] The individual high risk factors for severe acute post-operative pain and CPSP are discussed below under various headings.

Stratification of patients according to pre-operative CS status

Pre-operative pain in the knee combined with pain elsewhere in the body is common among patients with osteoarthritis (OA) or rheumatoid arthritis.[13] Although the level of pre-operative pain does not affect the early discharge of patients included in a fast-track programme,[20] it is a risk factor for CPSP and for a poor long-term outcome. Various mechanisms ranging from peri-articular and local knee inflammation (i.e. peripheral sensitisation) to CS, including a central inflammatory process caused by glial activation, contribute to the severity of pain in patients with OA.[8,10] CS is a non-adaptive processing of nociceptive inputs, which contributes to the severity of both acute and chronic pain. It leads to a reduced effectiveness of the endogenous inhibitory pain systems and/or a stimulation of facilitatory ones. Quantitative sensory testing (QST), an approach used to assess the mechanisms underlying CS, has shown significant facilitation, (e.g. positive temporal summation) and reduced inhibition in patients with OA of the knee.[21,22] QST determines the sensation and pain thresholds for cold and warm temperatures as well as the threshold for vibration sensation both by stimulating the skin. These stimuli activate specific receptors that communicate the message via peripheral nerve fibres to the central nervous system. CS contributes to pain in patients with OA of the knee; this explains the discordance between the intensity of pain and the severity of the OA on radiographs[23] as well as the discrepancy between a satisfactory post-operative radiographic appearance and unexplained persistent pain after TKA.[24] Among the available types of QST, dynamic measures of pain sensitivity (e.g. temporal summation) are more valid predictors than static measures (e.g. pain thresholds).[25] Pre-operative positive temporal summation is associated with both higher acute post-operative pain with movement and CPSP.[23] The thresholds of pressure pain, a QST-test where deep tissue pressure is applied with an algometer until the patient says his pain threshold is reached, seems only predictive of severe acute post-operative TKA pain during mobilisation.[26,27]

Chronic pain may require a prolonged course of analgesic medication, specifically opioids. This may cause a state of nociceptive sensitisation called 'opioid-induced hyperalgesia'. The extensive use of opioid medication pre-operatively increases the risks of a more painful and prolonged recovery.[28] Low doses of opioids and the use of weak opioids such as tramadol may trigger pre-operative hyperalgesia and enhance acute post-operative pain.[29] Patients who take opioids pre-operatively are more likely to be still using them 12 months after surgery, and they will report greater pain and will be more dissatisfied after TKA.[30] The pre-operative use of benzodiazepines seems to be an even stronger predictor of later opioid use than the presence of pre-operative chronic pain itself.[31]

Stratification of patients according to the presence of a neuropathic pain component

Beyond the local nociceptive pain caused by wear of articular cartilage and inflammation, there is also some evidence of a neuropathic component in the pain of OA. Neural invasion of the articular cartilage has been found in arthritic knee joints in both human[32] and experimental models.[33] The prevalence of neuropathic pain in patients with OA, after exclusion of other confounding variables such as Parkinson's disease, diabetic neuropathy and sciatica is between 29% and 34%.[34,35] This pre-operative neuropathic pain is often associated with CPSP after TKA.[36] A history of previous knee surgery including arthroscopy, ligament reconstruction and open meniscectomy is also strongly associated with neuropathic pain before TKA.[35] CPSP is therefore also frequently seen after arthroscopy of the knee.[37] TKA on its own may cause neuropathic pain post-operatively due to local nerve damage, often to the infrapatellar branch of the saphenous nerve, or because of local inflammation.[38,39] Risk factors associated with the operation include increased duration of surgery and tourniquet time, revision surgery, TKA *versus* unicompartmental arthroplasty and intra-operative nerve damage.[19] The true incidence of neuropathic pain after

TKA is unknown and probably underestimated. The peak incidence occurs between six weeks and three months post-operatively and affects about 11% of patients[40,41] and accounts for 6% of those who develop CPSP.[2,42] The correct diagnosis with the use of validated questionnaires (DN-4) is mandatory because both pre- and post-operative neuropathic pain are risk factors for CPSP and are associated with more severe pain at all times after TKA.[40,41]

Stratification of patients according to pre-operative individual stress factors

Evidence from studies on non-surgical chronic pain suggests that disability reflects both the severity of the pain and the patient's ability to cope with pain. Catastrophising is a negative cognitive and affective response to pain. It is multidimensional, comprising elements of rumination, magnification and helplessness.[43] Interestingly, catastrophising remains constant after surgery and is not affected by changes in the severity of pain. It may reflect depression. A recent systematic review lacked sufficient evidence to conclude which risk factors among psychological processes including catastrophising, anxiety and depression contribute to CPSP after TKA.[43] Catastrophising might, however, be a significant predictor of pain felt at night after TKA, independently of the presence of depression, because catastrophising is associated with insomnia, which may contribute to a generalised state of hyperalgesia.[44]

Patients with OA who have less severe degenerative changes and moderate pain at the time of surgery, consistently demonstrate poorer outcomes following primary TKA.[45] A recent study showed that chronic non-orthopaedic conditions such as fibromyalgia, migraine, irritable bowel syndrome, chronic low back pain, a head injury or stroke are more commonly found in patients with a poor outcome after TKA.[45] These conditions are all causes of stress, leading to a combination of psychological distress and amplification of pain[19] as found in 'idiopathic pain disorders'.[46] These disorders remain poorly understood, but are characterised by pain associated with abnormalities of motor function, autonomic balance, neuro-endocrine function and sleep.

The patient with a painful arthritic knee requiring TKA needs a multidisciplinary approach. The peri-operative course might be divided into pre-, intra- and post-operative periods. The pre-operative assessment of the risk factors and stratification of the patients might lead to an individualisation of peri-operative management. Those with pre-operative neuropathic pain, those who have taken opioid analgesics for a long time and those with CS might benefit from specific pre- or peri-operative management with anti-hyperalgesic drugs such as ketamine and gabapentinoids. The operation should consist of less invasive surgery, partial replacements where possible and avoiding damage to the infra-patellar branch of the saphenous nerve. The patients who develop CPSP need close follow-up in a dedicated chronic pain clinic. Efficient collaboration between orthopaedic surgeons, anaesthetists, pain clinicians and general practitioners is the key for a successful outcome after TKA.

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References

1. **Treede RD, Rief W, Barke A, et al.** A classification of chronic pain for ICD-11. *Pain* 2015;156:1003–1007.
2. **Haroutiunian S, Nikolajsen L, Finnerup NB, Jensen TS.** The neuropathic component in persistent postsurgical pain: a systematic literature review. *Pain* 2013;154:95–102.
3. **Fuzier R, Serres I, Bourrel R, et al.** Analgesic drug consumption increases after knee arthroplasty: a pharmacoepidemiological study investigating postoperative pain. *Pain* 2014;155:1339–1345.
4. **Kurtz SM, Ong KL, Lau E, Bozic KJ.** Impact of the economic downturn on total joint replacement demand in the United States: updated projections to 2021. *J Bone Joint Surg [Am]* 2014;96-A:624–630.
5. **Leskinen J, Eskelinen A, Huhtala H, Paavolainen P, Remes V.** The incidence of knee arthroplasty for primary osteoarthritis grows rapidly among baby boomers: a population-based study in Finland. *Arthritis Rheum* 2012;64:423–428.
6. **Husted H, Jensen CM, Solgaard S, Kehlet H.** Reduced length of stay following hip and knee arthroplasty in Denmark 2000-2009: from research to implementation. *Arch Orthop Trauma Surg* 2012;132:101–104.
7. **Loftus T, Agee C, Jaffe R, Tao J, Jacofsky DJ.** A simplified pathway for total knee arthroplasty improves outcomes. *J Knee Surg* 2014;27:221–228.
8. **Wylde V, Bruce J, Beswick A, Elvers K, Gooberman-Hill R.** Assessment of chronic postsurgical pain after knee replacement: a systematic review. *Arthritis Care Res (Hoboken)* 2013;65:1795–1803.
9. **Noiseux NO, Callaghan JJ, Clark CR, et al.** Preoperative predictors of pain following total knee arthroplasty. *J Arthroplasty* 2014;29:1383–1387.
10. **Lewis GN, Rice DA, McNair PJ, Kluger M.** Predictors of persistent pain after total knee arthroplasty: a systematic review and meta-analysis. *Br J Anaesth* 2015;114:551–561.
11. **Diatchenko L, Slade GD, Nackley AG, et al.** Genetic basis for individual variations in pain perception and the development of a chronic pain condition. *Hum Mol Genet* 2005;14:135–143.
12. **Althaus A, Hinrichs-Rocker A, Chapman R, et al.** Development of a risk index for the prediction of chronic post-surgical pain. *Eur J Pain* 2012;16:901–910.
13. **Ayers DC, Li W, Oatis C, Rosal MC, Franklin PD.** Patient-reported outcomes after total knee replacement vary on the basis of preoperative coexisting disease in the lumbar spine and other nonoperatively treated joints: the need for a musculoskeletal comorbidity index. *J Bone Joint Surg [Am]* 2013;95-A:1833–1837.
14. **Puolakka PA, Rorarius MG, Roviola M, et al.** Persistent pain following knee arthroplasty. *Eur J Anaesthesiol* 2010;27:455–460.
15. **Wylde V, Rooker J, Halliday L, Blom A.** Acute postoperative pain at rest after hip and knee arthroplasty: severity, sensory qualities and impact on sleep. *Orthop Traumatol Surg Res* 2011;97:139–144.
16. **Morze CJ, Johnson NR, Williams G, et al.** Knee pain during the first three months after unilateral total knee arthroplasty: a multi-centre prospective cohort study. *J Arthroplasty* 2013;28:1565–1570.
17. **Gerbershagen HJ, Pogatzki-Zahn E, Aduckathil S, et al.** Procedure-specific risk factor analysis for the development of severe postoperative pain. *Anesthesiology* 2014;120:1237–1245.
18. **Montero-Marin J, Prado-Abril J, Piva Demarzo MM, Gascon S, García-Campayo J.** Coping with stress and types of burnout: explanatory power of different coping strategies. *PLoS One* 2014;9:e89090.
19. **Ayers DC, Franklin PD, Ploutz-Snyder R, Boisvert CB.** Total knee replacement outcome and coexisting physical and emotional illness. *Clin Orthop Relat Res* 2005;440:157–161.
20. **Holm B, Bandholm T, Lunn TH, et al.** Role of preoperative pain, muscle function, and activity level in discharge readiness after fast-track hip and knee arthroplasty. *Acta Orthop* 2014;85:488–492.

21. **Arendt-Nielsen L, Nie H, Laursen MB, et al.** Sensitization in patients with painful knee osteoarthritis. *Pain* 2010;149:573–581.
22. **Suokas AK, Walsh DA, McWilliams DF, et al.** Quantitative sensory testing in painful osteoarthritis: a systematic review and meta-analysis. *Osteoarthritis Cartilage* 2012;20:1075–1085.
23. **Finan PH, Buenaver LF, Bounds SC, et al.** Discordance between pain and radiographic severity in knee osteoarthritis: findings from quantitative sensory testing of central sensitization. *Arthritis Rheum* 2013;65:363–372.
24. **Petersen KK, Arendt-Nielsen L, Simonsen O, Wilder-Smith O, Laursen MB.** Presurgical assessment of temporal summation of pain predicts the development of chronic postoperative pain 12 months after total knee replacement. *Pain* 2015;156:55–61.
25. **Yarnitsky D, Granot M, Granovsky Y.** Pain modulation profile and pain therapy: between pro- and antinociception. *Pain* 2014;155:663–665.
26. **Rakel BA, Blodgett NP, Bridget Zimmerman M, et al.** Predictors of postoperative movement and resting pain following total knee replacement. *Pain* 2012;153:2192–2203.
27. **Wylde V, Sayers A, Lenguerrand E, et al.** Preoperative widespread pain sensitization and chronic pain after hip and knee replacement: a cohort analysis. *Pain* 2015;156:47–54.
28. **Zywiel MG, Stroh DA, Lee SY, Bonutti PM, Mont MA.** Chronic opioid use prior to total knee arthroplasty. *J Bone Joint Surg [Am]* 2011;93-A:1988–1993.
29. **Hina N, Fletcher D, Poindessous-Jazat F, Martinez V.** Hyperalgesia induced by low-dose opioid treatment before orthopaedic surgery: an observational case-control study. *Eur J Anaesthesiol* 2015;32:255–261.
30. **Franklin PD, Karbassi JA, Li W, Yang W, Ayers DC.** Reduction in narcotic use after primary total knee arthroplasty and association with patient pain relief and satisfaction. *J Arthroplasty* 2010;25 (suppl):12–16.
31. **Skurtveit S, Furu K, Bramness J, Selmer R, Tverdal A.** Benzodiazepines predict use of opioids--a follow-up study of 17,074 men and women. *Pain Med* 2010;11:805–814.
32. **Suri S, Gill SE, Massena de Camin S, et al.** Neurovascular invasion at the osteochondral junction and in osteophytes in osteoarthritis. *Ann Rheum Dis* 2007;66:1423–1428.
33. **Im HJ, Kim JS, Li X, et al.** Alteration of sensory neurons and spinal response to an experimental osteoarthritis pain model. *Arthritis Rheum* 2010;62:2995–3005.
34. **Oteo-Álvaro A, Ruiz-Ibán MA, Miguens X, et al.** High Prevalence of Neuropathic Pain Features in Patients with Knee Osteoarthritis: A Cross-Sectional Study. *Pain Pract* 2014. (Epub ahead of print) PMID: 24750662.
35. **Valdes AM, Suokas AK, Doherty SA, Jenkins W, Doherty M.** History of knee surgery is associated with higher prevalence of neuropathic pain-like symptoms in patients with severe osteoarthritis of the knee. *Semin Arthritis Rheum* 2014;43:588–592.
36. **Wright A, Moss P, Sloan K, et al.** Abnormal quantitative sensory testing is associated with persistent pain one year after TKA. *Clin Orthop Relat Res* 2015;473:246–254.
37. **Dualé C, Ouchchane L, Schoeffler P, EDONIS Investigating Group, Dubray C.** Neuropathic aspects of persistent postsurgical pain: a French multicenter survey with a 6-month prospective follow-up. *J Pain* 2014;15:24–21.
38. **Borsook D, Kussman BD, George E, Becerra LR, Burke DW.** Surgically induced neuropathic pain: understanding the perioperative process. *Ann Surg* 2013;257:403–412.
39. **Deumens R, Grosu I, Thienpont E.** Surgically Induced Neuropathic Pain: Understanding the Perioperative Process. *Ann Surg* 2013. (Epub ahead of print) PMID: 24368633.
40. **Phillips JR, Hopwood B, Arthur C, Stroud R, Toms AD.** The natural history of pain and neuropathic pain after knee replacement: a prospective cohort study of the point prevalence of pain and neuropathic pain to a minimum three-year follow-up. *Bone Joint J* 2014;96-B:1227–1233.
41. **Lavand'homme PM, Grosu I, France MN, Thienpont E.** Pain trajectories identify patients at risk of persistent pain after knee arthroplasty: an observational study. *Clin Orthop Relat Res* 2014;472:1409–1415.
42. **Wylde V, Hewlett S, Learmonth ID, Dieppe P.** Persistent pain after joint replacement: prevalence, sensory qualities, and postoperative determinants. *Pain* 2011;152:566–572.
43. **Burns LC, Ritvo SE, Ferguson MK, et al.** Pain catastrophizing as a risk factor for chronic pain after total knee arthroplasty: a systematic review. *J Pain Res* 2015;8:21–32.
44. **Edwards RR, Haythornthwaite JA, Smith MT, Klick B, Katz JN.** Catastrophizing and depressive symptoms as prospective predictors of outcomes following total knee replacement. *Pain Res Manag* 2009;14:307–311.
45. **Jacobs CA, Christensen CP, Karthikeyan T.** Chronic Non-Orthopedic Conditions More Common in Patients with Less Severe Degenerative Changes That Have Elected to Undergo Total Knee Arthroplasty. *J Arthroplasty* 2015;30:1146–1149.
46. **Diatchenko L, Nackley AG, Slade GD, Fillingim RB, Maixner W.** Idiopathic pain disorders--pathways of vulnerability. *Pain* 2006;123:226–230.