

Letter to the Editor



To the Editor:

We read with interest the article by Kim et al. [4] involving pain and hyperalgesia in patients undergoing staged bilateral total knee arthroplasty (TKA). It is well established that injury, including surgery, induces central sensitization which manifests in both primary and secondary hyperalgesia [13]. Also relevant is evidence of hyperalgesia induced by repeat injury of the same body part at two points in time [2]. Clinical evidence of tertiary or remote hyperalgesia, in which injury at one body site produces pain at another, distant site has also been established [13]. Less common, but no less important, is remote hyperalgesia induced by injuries at different points in time [9,10]. In a clever test of this latter phenomenon, Kim et al. evaluated 30 patients undergoing staged bilateral TKA in which the left or right knee was selected at random for the first TKA (TKA1) and was followed by identical surgery of the other knee (TKA2) one week later. The results showed that rest pain, movement-evoked pain, and analgesic consumption were significantly greater in the second knee 24 and 48 hours after TKA2 than in the first knee 24 and 48 hours after TKA1. The authors conclude that the enhanced pain sensitivity in the second knee was evidence of “tertiary” hyperalgesia (ie, remote hyperalgesia) due in part to central sensitization of subcortical and other brain regions induced by the noxious inputs arising from TKA1. A related finding has been reported in a rodent model involving neonatal paw incision. Rats that had been exposed to a paw incision at 3 days of age, displayed greater hyperalgesia in re-

sponse to a second paw incision (as well as to electrical stimulation of the ipsilateral tibial nerve) performed in adulthood than did control rats injured only once as adults [2].

These results clearly have important clinical and basic science implications both for the well-being of patients undergoing staged bilateral TKA as well as the mechanisms underlying the heightened pain and analgesic consumption. However, the authors do not distinguish clearly between tertiary hyperalgesia and what we, here, call the “double-hit hypothesis of hyperalgesia,” namely, greater pain after TKA2 than after TKA1 due to the central neural sensitizing effects of the latter on the former. In contrast to the double-hit hypothesis, tertiary hyperalgesia is not necessarily dependent upon the number of conditioning trials and can be demonstrated even after a single nociceptive stimulus or injury [5].

Relevant to Kim et al.’s findings of tertiary or remote hyperalgesia are animal [6] and human studies [7] of *allochiria* or mirror image pain [1], in which injury to one side of the body not only produces local pain, but also pain at the contralateral, mirror image point. A bilateral mechanism is implicated since ipsilateral nerve injury results in a significant, 50% reduction in the innervation of the territory of the contralateral nerve on the opposite side of the body in uninjured skin [6]. In humans, pain severity at the ipsilateral, nerve-damaged side correlated with ipsilateral-induced contralateral nerve damage suggesting that the ipsilateral pain severity was influenced by the degree of contralateral nerve damage [6,7]. Whether a similar bilateral mechanism is, in part, responsible for the hyperalgesia Kim et al. observed remains to be tested.

With respect to the double-hit hypothesis of hyperalgesia, we would like to raise two points; one that addresses other factors that may have contributed to tertiary hyperalgesia observed by Kim et al. [4] and the other that outlines more clearly the predictions about pain and hyperalgesia associated with staged bilateral TKA. First, psychological factors, emotional distress, and coping responses were not assessed even though these have been recommended as core outcome domains to be measured in pain-related clinical trials [11]. The most prominent risk factor for acute and chronic pain after TKA is perioperative pain catastrophizing [3,8,12]. Patients who engage in higher levels of pain catastrophizing are at significantly greater risk of heightened pain both in the acute phase after surgery and months later. It is possible that pain catastrophizing levels increased from TKA1 to TKA2 which would lead to increased pain intensity as well. More generally, one must consider the additional worry, stress, and depleted coping resources associated with having had a second TKA one week after the first—stressors that were not present at the same level before TKA1—and how these factors relate to the heightened pain in response to TKA2. In regard to biological pathways, stress-related activation of the hypothalamic–pituitary–adrenocortical axis and the sympathetic nervous system may play a key role. Whether central neuroimmune activity [2] also is involved in remains to be seen. In addition, health behaviors such as poorer sleep and increased sedentary behaviors after TKA1 could also have contributed to the observed hyperalgesic effect in knee 2 after TKA2. There is an inherent bias that cannot be overcome with this kind of design, as one cannot have a second TKA before the first.

Nevertheless, measuring psychological and emotional functioning as well as biological outcomes could help to determine the validity of the double-hit hypothesis of hyperalgesia (i.e., is pain intensity after TKA2 greater than after TKA1 even when controlling for psychobiological factors?).

The second point concerns performing a more complete test of the double-hit hypothesis, which predicts not only that TKA1 should cause TKA2 pain in knee 2 to be more intense, but also the inverse: namely, that TKA2 should cause TKA1 knee pain to be more intense. Moreover, preoperative pain in knee 2 within the first week after TKA1 would also be expected to increase in intensity from baseline (ie, pre-TKA1 to post-TKA1). Kim et al. do report rest and movement-evoked pain intensity scores in knee 1 before assessing pain in knee 2 at 24 and 48 hours after TKA2, but they do not present data showing whether there was an increase in the intensity of knee 1 pain after TKA2 or whether pain in knee 2 increased from baseline to post-TKA1 but before TKA2. Overall, the authors are to be commended on a well-designed and conducted study. Future research in this area should evaluate psychological and emotional factors known to affect pain and test other predictions associated with the double-hit hypothesis of hyperalgesia.

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