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**Possible missing alternative pain modulation in conclusion, and a possible gold opportunity missed**

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It’s a curious finding of association with the use of ?-blockers (particularly non-selective ones) with outcome of TKR, keeping in mind that in a study with multiple variables of more than 20 being analysed it is not impossible that this finding can occur by chance. Although the author states “the purpose of the present study was to analyze the relationship between the use of ?-blockers in patients with knee pain and the risk of undergoing a TKA as a result of advanced knee OA”, in absence of previously published protocol (the article did not refer to one, nor a simple search of the authors’ ORCID background reveal any), it is not certain that the true intent of this study was originally to focus on ?-blockers. Nevertheless I do find their result intriguing.

However what is more confusing is the authors’ conclusions. They stated: “Our results indicate that the use of ?-blockers, especially nonselective blockers, was associated with a lower likelihood of TKA. Patients treated for prolonged periods had a lower likelihood of TKA. This study provides insight to a possible relationship between the activity of the autonomic nervous system and the progression of OA. In addition, it provides a hypothesis for the development of future therapeutic lines targeting the adrenergic system in the treatment of OA.”

This is quite surprising as a significant proportion of their discussion also focused on possible pain modulation by ?-blockers which presents an important alternative (or concurrent) hypothesis in why ?-blockers users are less likely to have TKR. Many experienced clinicians are well aware of that high grade radiological appearance of knee osteoarthritis does not always translate to severity of knee pain and other symptoms, hence there is a nuance in shared decision-making when proposing treatment approach for patients with apparently radiologically proved advanced osteoarthritis. This philosophy is reflected in the protocol for TKR in the authors’ own institution, Hospital Regional Universitario de Málaga. More importantly at least one third of those who have undergone TKR has Kellgren-Lawrence grade 2 or less, hence the decision to operate could not have depended just on the “advanced OA involving at least 1 of the 3 compartments of the knee” criteria.

Unfortunately, despite the study being drawn from the hospital database of patients who attended the orthopaedic outpatient clinic with a history of new-onset knee pain between 2010 and 2019, with outcome of any primary TKA between 2018 and 2019 in these patients, the authors did not make any apparent determination if these patients demonstrated variation in progression of knee osteoarthritis according to ?-blocker usage, considering the time gap between presentation at the clinic can be as wide as 9 years, with average follow-up period in this nested study being about 2 years.

Perhaps this is for another time; if not, a gold opportunity missed.

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