*Ethical approval*
Not required.

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## Danger of highlighting the use of coxibs in daily dental practice

We read the valuable research by Isola et al. on the efficacy of celecoxib and ibuprofen for postoperative pain, swelling, and mouth opening after the surgical removal of impacted third molars with great interest[1]. Nevertheless, we have some concerns regarding the cardiovascular adverse effects of COX-2 inhibitors.

As mentioned by Isola et al.[1], the surgical removal of third molars is one of the most common surgeries in daily dental practice. Pain, swelling, and restriction in mouth opening are the main problems in the postoperative period that the dental practitioner has to deal with. Considering the gastrointestinal, hematopoietic, and renal adverse effect profile of COX-1 inhibition, the formulation of non-steroidal anti-inflammatory drugs with relative COX-2 selectivity became a highly desirable target during the 1990s[2]. However, studies in the first half of this decade revealed adverse effects of COX-2 inhibition on the cardiovascular system, including an increased risk of myocardial infarction, exacerbation of stable congestive heart failure, and worsening high blood pressure[3]. Randomized trials and meta-analyses confirmed these findings, triggering a red flag for a potential cardiovascular safety issue with coxibs; this also led to the withdrawal of some of the COX-2 inhibitors from the market by the US Food and Drug Administration[4]. Recent studies have also recommended caution in prescribing COX-1 and 2 inhibitors for patients with existing cardiovascular conditions, until more evidence for safety via randomized trials is available[5].

As suggested by Isola et al.[1], the most remarkable finding of their study is that treatment with celecoxib decreased the incidence and severity of postoperative pain following third molar surgery. This conclusion is very important and could affect the clinical behaviour of dental clinicians. We believe that when selecting celecoxib after dental surgery, its adverse effects must be considered. Therefore, the possible side effects of COX-2 inhibitors should have been emphasized in the text by the authors.

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## In response to Letter to the Editor ''Danger of highlighting the use of coxibs in daily dental practice''

We appreciate the Letter to the Editor by Gülses et al. in response to our article entitled ''Evaluation of the efficacy of celecoxib and ibuprofen on postoperative pain, swelling, and mouth opening after surgical removal of impacted third molars: a randomized, controlled clinical trial''[1]. We also thank these authors for their recognition of the results of our randomized controlled clinical trial.

The comments raised by these authors regarding the adverse effects of COX-2 inhibition on the cardiovascular system, including the increased risks of myocardial infarction and disturbance of blood pressure, are well taken. However, some elaboration is in order.

The surgical removal of third molars is one of the most common surgical interventions in daily dental practice. Previous studies have demonstrated that celecoxib used at a dose ranging between 120 mg and 200 mg is efficient in the reduction of early stage acute pain and perioperative symptoms following third molar surgery[2,3].

During the last few decades, COX-2 selective inhibitors were introduced to provide the anti-inflammatory effects of non-steroidal anti-inflammatory drugs (NSAIDs) with less gastrointestinal toxicity. However, the first studies on COX-2 inhibitors, used for a wide range of conditions such as osteoarthritis and rheumatoid arthritis, found an increased risk of cardiovascular disease (CVD)

development following the administration of these drugs[4,5].

Conversely, a larger recent study that evaluated the safety of celecoxib, naproxen, and ibuprofen demonstrated that the use of naproxen or ibuprofen was associated with a greater risk of major adverse cardiovascular events compared to the use of celecoxib[6]. Moreover, it was also shown that the use of ibuprofen or naproxen was associated with a greater risk of developing adverse gastrointestinal and renal events compared to celecoxib[6]. Similarly, Solomon et al.[7], in another large cohort study analysing the risk of toxicity of the major NSAIDs and celecoxib, found that patients who were treated with NSAIDs such as naproxen or ibuprofen had a significantly higher risk of CVD events and systemic toxicity than those who were treated with celecoxib.

Previous studies that evaluated the administration of celecoxib following third molar surgery did not report any significant adverse effects[8,9]. These studies reported only minor symptoms such as nosebleed, drowsiness, malaise, headache, dizziness (excluding vertigo), and nausea in a few cases[9], which did not require any specific treatment[2,3,8,9].

Based on this evidence, it is generally considered that there are still no significant data allowing definitive conclusions to be drawn on the 'possible' augmented risk of CVD events following the administration of celecoxib when compared to other NSAIDs, especially when celecoxib is administered for a short period of time, such as following the surgical removal of impacted third molars.

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