Authors' response: We read with great interest the comments written by Dr. Shetty and colleagues, and firstly we would like to thank them for their interest in our article.

The removal of the mandibular third molars is the most common surgical procedure in dentistry. It is also considered a standardized surgical operation and, indeed, a suitable model for investigating the safety and efficacy of anesthetic solutions.

Based on the results of our article, it is not possible to determine if the solutions of local anesthetics, either articaine or the rest of anesthetics solutions, are the determining factor for developing a nerve injury.¹

One of the limitations in our research was that the selected articles used variable vasoconstrictor concentrations, which could potentially have had an impact on the outcomes. For this reason and following the Cochrane recommendation, $\frac{2}{2}$ we performed a sensitivity analysis to reduce the consequent heterogeneity. Besides that, there are articles that could not find any influence of vasoconstrictor concentration on the efficacy of local anesthetics.³ There are, indeed, other factors that could influence onset time of duration of local anesthesia. In this line, authors agree that there could be confounding factors that we did not retrieved from the selected articles, that could clarify the named "unexplained heterogeneity." However, the article by Al-Shayyab and Baqain,⁴ which the authors cited in their letter, curiously admits that there is little information available about the influence of variables, such as sex, on the efficacy of local anesthetics. According to Higgins and Green,² there must be at least 10 trials to assess the publication bias, as when there are fewer studies, the statistical power of the test is too low to distinguish chance from true skewness. We disagree with the authors when they stated that the non-subgroup analysis was a fundamental error since the Cochrane Group does not recommend it when there are less than 10 studies in each comparison. To combine data from

1

split-mouth studies with parallel group trials we used the generic inversevariance method; therefore, although we introduced the standard deviation (Table 2), the software RevMan depicted the standard error. However, authors must take into consideration that the standard deviation is implied in the standard error, which is needed to calculate the confidence interval.

On the other hand, the main goal of search strategies is to identify all of the available data on this topic and to make this search reproducible. We are convinced that we achieved this goal, as an extensive screening in the literature was performed in our study. Moreover, the PRISMA checklist stated that it is necessary to present a complete electronic search strategy for at least 1 database,⁵ and we did present the search strategies for all the databases that we used.

Finally, although we are aware of the limitations and weaknesses of our article, we are convinced that our study provides valuable information for making clinical decisions and future research.

Laura Santos-Sanz, DDS

Fellow of the master's degree programme in Oral Surgery Efhre International University University/Fundació Privada Catalana per a la Salut Oral Belize City, Belize

Jorge Toledano-Serrabona, DDS

Fellow of the master's degree program in Oral Surgery and Implantology Faculty of Medicine and Health Sciences University of Barcelona Coordinator of master's degree program in Oral Surgery and Implantology Efhre International University University/Fundació Privada Catalana per a la Salut Oral Researcher Bellvitge Biomedical Research Institute Barcelona, Spain

Cosme Gay-Escoda, MD, DDS, MS, PhD, EBOS

Chairman and Professor Department of Oral and Maxillofacial Surgery University of Barcelona Barcelona, Spain Director of the master's degree program in Oral Surgery and Implantology Efhre International University University/Fundació Privada Catalana per a la Salut Oral Belize City, Belize Coordinator/Researcher Bellvitge Biomedical Research Institute Head Department of the Oral Surgery, Implantology, and Maxillofacial Surgery

Barcelona, Spain

1. Camps-Font O, Figueiredo R, Sánchez-Torres A. Which is the most suitable local anaesthetic when inferior nerve blocks are used for impacted mandibular third molar extraction? A network meta-analysis. *Int J Oral Maxillofac Surg.* 2020;49:1497-1507.

2. Higgins JP, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions Version 6.1. The Cochrane Collaboration. Available at: http://www.handbook.cochrane.org. Accessed February 18, 2021.

3. Santos CF, Modena CS, Giglio PM, et al. Epinephrine concentration (1:100,000 or 1:200,000) does not affect the clinical efficacy of 4% articaine for lower third molar removal: a double-blind, randomized, crossover study. *J Oral Maxillofac Surg.* 2007;65:2445-2452.

4. Al-Shayyab MH, Baqain ZH. Factors predictive of the onset and duration of action of local anesthesia in mandibular third-molar surgery: a prospective study. *Eur J Oral Sci.* 2018;126:110-117.

5. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg.* 2010;8:336-341.