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Review

Analgesic Efficacy of Postoperative Ibuprofen in Third Molar Surgery: A Meta-Analysis

Itzel Joselyn Mora-Falcón [1], Iván Agustín Amador-Beas [1], Ronell Bologna-Molina [2,3], Nelly Molina-Frechero [4], Othoniel Hugo Aragón-Martínez [5], Nicolás Serafín-Higuera [6], Sandra López-Verdín [7] and Mario Alberto Isiordia-Espinoza [1,*]

1 Departamento de Clínicas, Centro Universitario de los Altos, División de Ciencias Biomédicas, Universidad de Guadalajara, Tepatitlán de Morelos 47620, Mexico; itzel.mora@alumnos.udg.mx (I.J.M.-F.); ivan.amador@alumnos.udg.mx (I.A.A.-B.)
2 Departamento de Patología Molecular, Facultad de Odontología, Universidad de la República (UDELAR), Montevideo 11200, Uruguay; ronellbologna@odon.edu.uy
3 Departamento de Investigación, Facultad de Odontología, Universidad Juárez Autónoma de Durango, Durango 34000, Mexico
4 Laboratorio de Cariología y Medicina Oral, Departamento de Salud, Universidad Autónoma Metropolitana-Xochimilco, Ciudad de Mexico 04960, Mexico; nmolina@correo.xoc.uam.mx
5 Facultad de Medicina, Universidad Autónoma de San Luis Potosí, San Luis Potosí 78290, Mexico; hugo.aragon@uaslp.mx
6 Centro de Ciencias de la Salud Mexicali, Facultad de Odontología Mexicali, Universidad Autónoma de Baja California, Mexicali 21040, Mexico; nicolas_addiel@yahoo.com.mx
7 Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara 44340, Mexico; sandra.lverdin@academicos.udg.mx
* Correspondence: mario.isiordia162@yahoo.com

Abstract

Purpose: The aim of this study is to determine the analgesic efficacy of ibuprofen 200, 400, and 600 mg after lower third molar surgery. **Material and Methods**: Clinical trials that included patients undergoing third molar surgery comparing ibuprofen with placebo were included. The only exclusion criteria was loss of postoperative patient follow-up greater than 20%. PubMed, Wiley, Science Direct, EBSCOhost, Scopus, and Web of Science databases were used to search for clinical trials. The risk of bias of the included articles was assessed using the Cochrane Collaboration's seven-point risk of bias tool, and dichotomous data for the most important variables for determining analgesic efficacy and adverse effects were then concentrated into one database for statistical analysis. **Results**: The qualitative analysis was performed with 57 clinical trials and a total of n = 7735 patients. Moreover, the number of patients who took rescue analgesics and the global evaluation of the studied drugs showed statistical differences in favor of ibuprofen 200 (n = 797 and n = 694, respectively), 400 (n = 2803 and n = 2407, respectively), and 600 mg (n = 1149 and n = 291, respectively) compared to placebo. Adverse effects, such as nausea, vomiting, and headache, resulted in statistical differences in favor of ibuprofen 200 (n = 1461, n = 1319, and n =1342, respectively), 400 (n = 3917, n = 3124, and n = 2477, respectively), and 600 mg (n = 716) in comparison to placebo. The numbers needed to treat indicated high efficacy of ibuprofen in controlling pain after third molar surgery, while the numbers needed to harm were high, indicating the good safety profile of this drug. **Conclusions**: Ibuprofen has high analgesic efficacy and a good safety profile when used after third molar surgery.

Keywords: ibuprofen; placebo; postoperative analgesia; adverse effects; third molar surgery

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1. Introduction

Postoperative pain is the main challenge for a general dentist or maxillofacial surgeon after performing impacted lower third molar surgery [1,2]. This phenomenon is dictated by the trauma of the soft and bony tissues of the peri-surgical region [3–8], as well as other factors, such as the patient's adherence to postoperative indications for managing inflammatory complications set by the clinicians [9–11] and their knowledge of pharmacological options to meet the needs of each case [12–18].

Pain after third molar surgery occurs in the immediate postoperative period [5,17]. According to the clinical characterization of this postoperative pain model, peak pain occurs between 5 and 8 h postoperatively. However, episodes of pain can continue to occur at any time during the first 24 h postoperatively [5,17,18]. Third molar surgery is usually performed under local anesthesia, which facilitates pain assessment. It is usually rapid in onset and has mild-to-moderate intensity, affecting the patient's quality of life [17].

Conventional postoperative pharmacological treatment after lower third molar surgery consists of using mainly three types of medications: nonsteroidal anti-inflammatory pain drugs (NSAIDs) [15–17], opioid analgesics [18], and glucocorticoids [14,19]. Undoubtedly, the main group of drugs used to control pain and other postsurgical complications after third molar surgery is NSAIDs [20].

Recently, a quantitative systematic review evaluated the analgesic effectiveness of ibuprofen and traditional NSAIDs in oral surgery [20]. However, the pooled data comparisons were limited due to the number of drugs and the doses used for each [20]. On the other hand, in clinical research, it is essential to compare the effect of an analgesic drug with a placebo to determine its analgesic efficacy [21].

This systematic review aims to synthesize information reported in clinical trials on the analgesic effectiveness of the postoperative administration of ibuprofen compared to placebo following lower third molar surgery.

2. Materials and Methods

This systematic review was carried out according to the PRISMA guidelines [22,23], and the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (2011) [24].

2.1. Selection Criteria

Inclusion criteria (PICO) [25]:

Population: Patients undergoing third molar surgery.

Interventions: Ibuprofen administered postoperatively (200 mg, 400 mg, and 600 mg).

Control: Postoperative administration of placebo.

Outcome: The number of patients requiring rescue analgesic medication, overall evaluation of study treatments (patient satisfaction), and adverse effects.

Exclusion criteria: Loss of postoperative patient follow-up greater than 20%.

2.2. Search Using Databases

Clinical trials published from January 1990 to May of this year were considered for inclusion in this systematic review. The PubMed, Wiley, Science Direct, EBSCOhost, Scopus, and Web of Science databases were utilized to read the abstracts of those studies that were located with the following keywords: "Ibuprofen", "placebo", "third molar surgery"; "third molar removal", "wisdom teeth surgery", "wisdom teeth removal", "wisdom teeth extraction", "oral surgery", "third molar extraction", and "dental extraction".

The PubMed search was conducted using study types "Clinical Trial", "Randomized Controlled Trial", "Controlled Clinical Trial", and "Clinical Study", and published in English or Spanish. In Wiley Online Library, the publication type ("Journals") and

Subjects ("Dentistry") filters were used. The ScienceDirect search was limited to "research articles" (article type), areas of "Medicine and Dentistry", and "Pharmacology, Toxicology and Pharmaceutical Sciences". At EBSCOhost, the search was filtered only by "scholarly publications" (source type). In Scopus, the search was filtered by three areas: "Medicine", "Dentistry", and "Pharmacology, Toxicology, and Pharmaceutics"; "Article" was selected as the document type, "Journal" as the source, and "Human" only as the keyword. Finally, in Web of Science, the information was filtered by document type ("article") and Web of Science category ("Dentistry, Oral Surgery, Medicine", "Pharmacology, Pharmacy", "Surgery", "General Internal Medicine" and "Anesthesiology"). In all databases, only articles in English and Spanish were considered. This review was registered in the PROSPERO database—University of York (ID: CRD42025649382).

2.3. Assessment of Bias

The Cochrane Collaboration's seven-point risk of bias tool was utilized [20,26–29].

2.4. Data Extraction

The data were initially concentrated in an Excel file and subsequently transferred to statistical software for analysis in this study. The number of patients requiring rescue analgesic medication, overall evaluation of study treatments (the total of patients reporting a global assessment as good, very good, or excellent), and adverse effects—nausea, dizziness, vomiting, or headache—were extracted.

When a clinical trial assessed the efficacy of a dose (e.g., ibuprofen 200 mg) using two or more dosage forms (e.g., tablets, capsules, soluble tablets, etc.), the data were summed and concentrated in the statistical analysis as a single data point that was used for comparison with placebo.

Two academics independently searched for clinical trials indicating a comparison between ibuprofen and placebo in third molar surgery, conducting a risk of bias assessment and data extraction. The disagreements between two professors thoroughly examined, and a consensus was ultimately reached with the facilitation of a third researcher [30–32].

2.5. Statistical Analysis

The number of patients requiring rescue analgesic medication and the overall evaluation of the study treatments (patient satisfaction) were analyzed using the random effects method due to the high heterogeneity observed (I^2 test > 30%) [24,28,29,33,34]. On the other hand, the data analysis on adverse effects showed low heterogeneity, so the fixed effects model was used (I^2 test < 30%) [24,28,29,33,34]. The Mantel-Haenszel test, the Odds Ratio (OR), and the confidence intervals (CIs) were calculated—estimators of the effect size—using the Review Manager 5.3 software for Windows. Moreover, the number needed to treat (NNT), the number needed to harm (NNH), and the CIs were obtained using the Risk Reduction Calculator (University of Illinois) [35–37]. A p-value of <0.05 in the overall test and an OR > 1 was considered a statistical difference [28,29,34]. Using data from the variables rescue analgesia and global treatment assessment, publication bias was assessed by visual inspection of funnel plots [24].

3. Results

3.1. Database Search

In the databases consulted for the search, 8993 articles were found. After removing articles unrelated to the topic, the duplicated articles, and performing a screening of the articles, 71 articles were obtained for a complete evaluation. During the full review, 9 articles that did not use placebo as a comparison group were discarded and 5 additional articles

were eliminated because they did not meet the PICO criteria. Only 57 articles were included in the qualitative analysis and 49 clinical trials provided data for the quantitative analysis (meta-analysis) of this systematic review (Figure 1) [38–94].

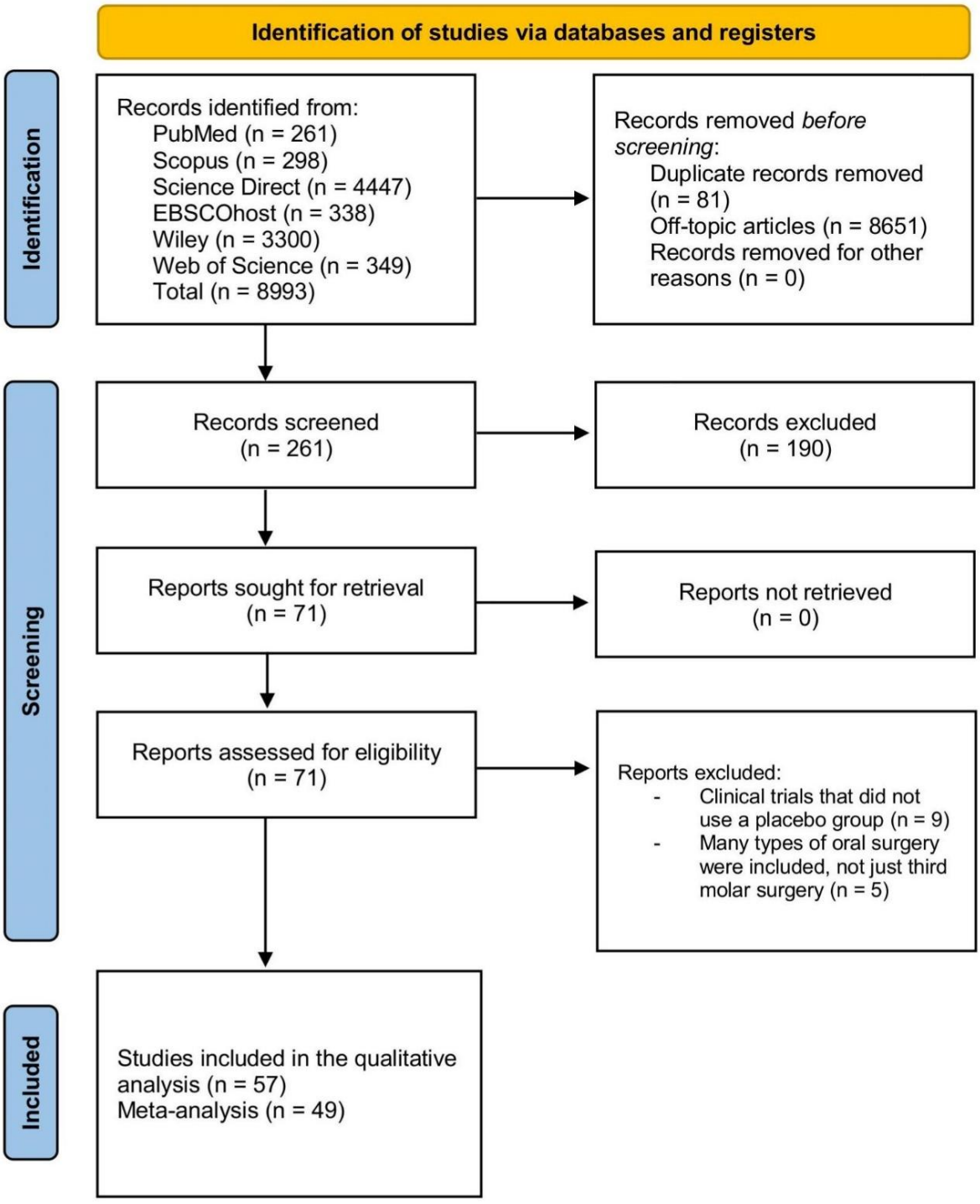

Figure 1. Study flow chart.

3.2. Evaluation of Bias

The risk of bias assessment showed that 54 studies scored low to moderate risk of bias [38–40,42–45,47–84,86–94] while only 3 studies scored high risk of bias (Figure 2) [41,46,85].

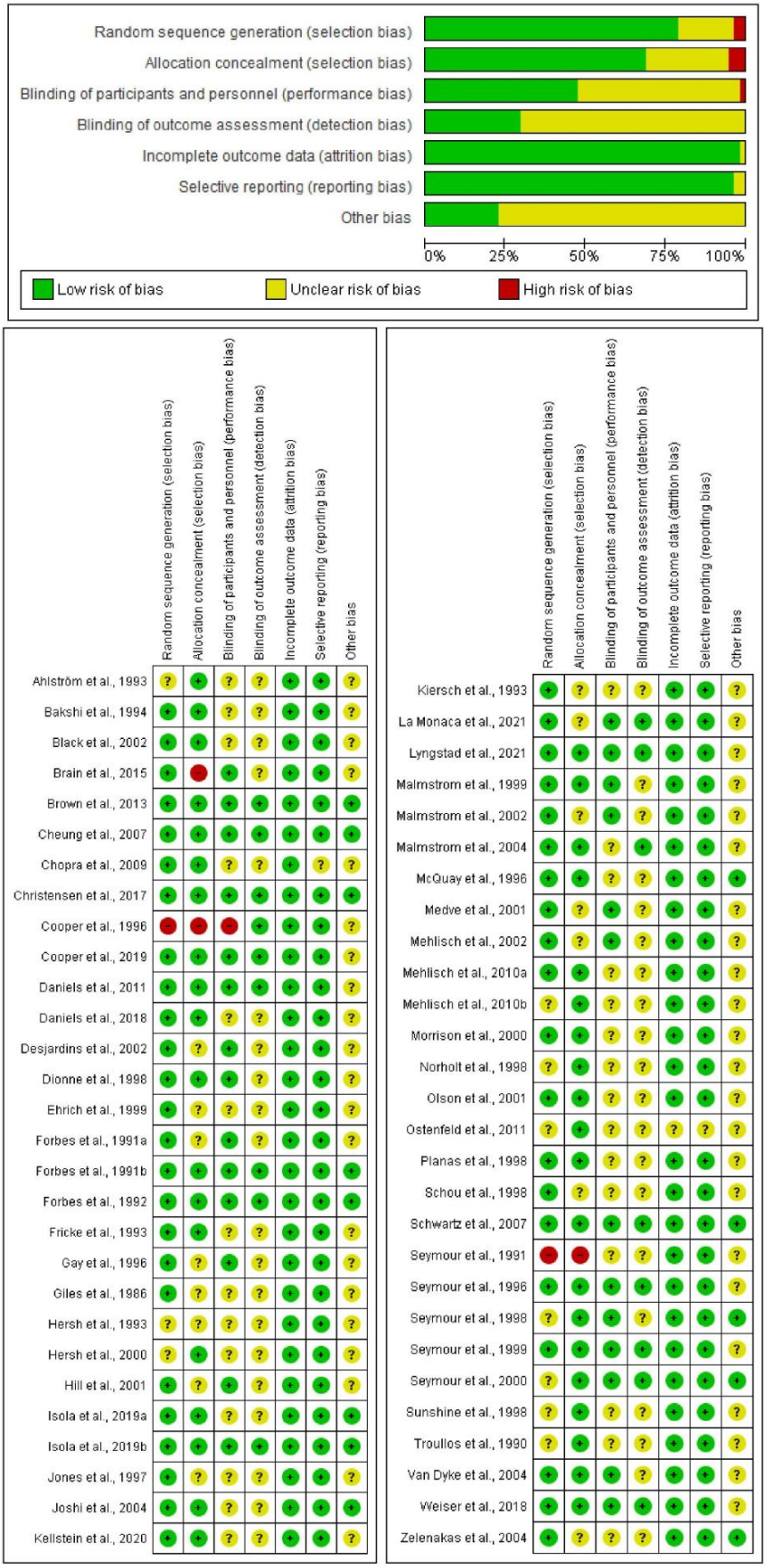

Figure 2. Bias risk assessment [38–94].

3.3. Qualitative Analysis

The qualitative characteristics of 57 clinical trials were assessed to determine the analgesic effectiveness and adverse effects of ibuprofen 200 (n = 994), 400 (n = 3143), and 600 mg (n = 805) compared to placebo (n = 2793) following, at least, a third molar surgery [38–94]. The total number of participants in this qualitative analysis was n = 7735 (Table S1) [38–94].

Ibuprofen 400 mg was the most commonly used in the trials included in this systematic review [38–41,43,47,50–52,54–57,59–61,63,64,66,68–81,83–88,92–94] followed by ibuprofen 200 mg [40,46,49–51,53,58–60,67,73,75,77,83,86,89,90], and finally ibuprofen 600 mg [42,44,45,48,62,65,69,82,86,91]. A total of 19 trials performed the surgical procedure using local anesthesia alone [38–40,44,52,57,58,61–63,68,69,73,79,80,82,83,90,91], 28 studies used sedation/general anesthesia [41,43,45,47–51,53–55,59,60,65,66,70,72,76,78,81,84–89,92,94], and 10 trials did not report these data [42,46,56,64,67,71,74,75,77,93]. On the other hand, 14 studies used paracetamol, an NSAID or an opioid analgesic as monotherapy [43,44,49,52,58,62,64–66,79,82,83,86,90], 27 clinical trials used a combination of an NSAID and an opioid analgesic [41,42,45,47,48,50,54,55,57,59,60,68–72,76–78,81,84,85,88,89,92–94], and 16 articles did not report this information (Table S1) [38–40,46,51,53,56,61,63,67,73–75,80,87,91].

3.4. Quantitative Analysis

The number of patients taking rescue analgesics after third molar surgery who received ibuprofen 200 mg and placebo was evaluated in 7 clinical trials [49,53,59,60,77,86,89]. Evaluation of the pooled data shows that fewer patients in the ibuprofen 200 mg group needed to take rescue analgesics compared with the placebo group (n = 797, I^2 = 0%, Z = 7.97, OR = 0.20, 95% CIs = 0.13 to 0.29, p = 0.00001, Figure 3). Moreover, 24 clinical studies assessed ibuprofen 400 mg compared to the placebo [38,39,41,43,47,57,59,60,64,68–72,76,77,79,84–88,93,94]. The pooled data analysis showed that fewer patients in the ibuprofen 400 mg group took rescue analgesics compared to placebo (n = 2803, I^2 = 56%, Z = 8.98, OR = 0.21, 95% CIs = 0.15 to 0.30, p = 0.00001, Figure 3). The number of patients requiring rescue analgesics with ibuprofen 600 mg and placebo was assessed using data from 9 articles [42,44,45,48,62,65,69,82,86]. The result was similar to that obtained with the two previous doses of ibuprofen, indicating a decrease in the number of patients requiring rescue medication compared to the placebo group (n = 1149, I^2 = 72%, Z = 3.84, OR = 0.26, 95% CIs = 0.13 to 0.52, p = 0.0001, Figure 3). The NNT and CIs can be seen in Table 1.

Table 1. The number needed to treat (NNT), the number needed to harm (NNH), and the confidence intervals (CIs) of ibuprofen for pain control after third molar surgery.

Analgesic Efficacy	**Ibuprofen**								
	200 mg			**400 mg**			**600 mg**		
	n	**NNT**	**CIs**	***n***	**NNT**	**CIs**	***n***	**NNT**	**CIs**
The number of patients who took rescue analgesics	797	3.7	3 to 4.7	2803	3.1	2.8 to 3.4	1149	3.4	2.8 to 4.2
Overall evaluation	694	2.6	2.2 to 3.1	2407	1.9	1.8 to 2	291	1.6	1.4 to 2
Adverse effects	***n***	**NNH**	**CIs**	***n***	**NNH**	**CIs**	***n***	**NNH**	**CIs**
Nausea	1461	27.6	16.3 to 89.8	3917	28.4	18.4 to 61.6	-	-	-
Vomiting	1319	42.6	22.3 to 477.7	3124	29.6	19 to 66.3	716	17	10 to 50.8
Headache	1342	24.8	14.8 to 76.9	2477	26.7	17.2 to 59.3	716	12.3	7.7 to 31.2

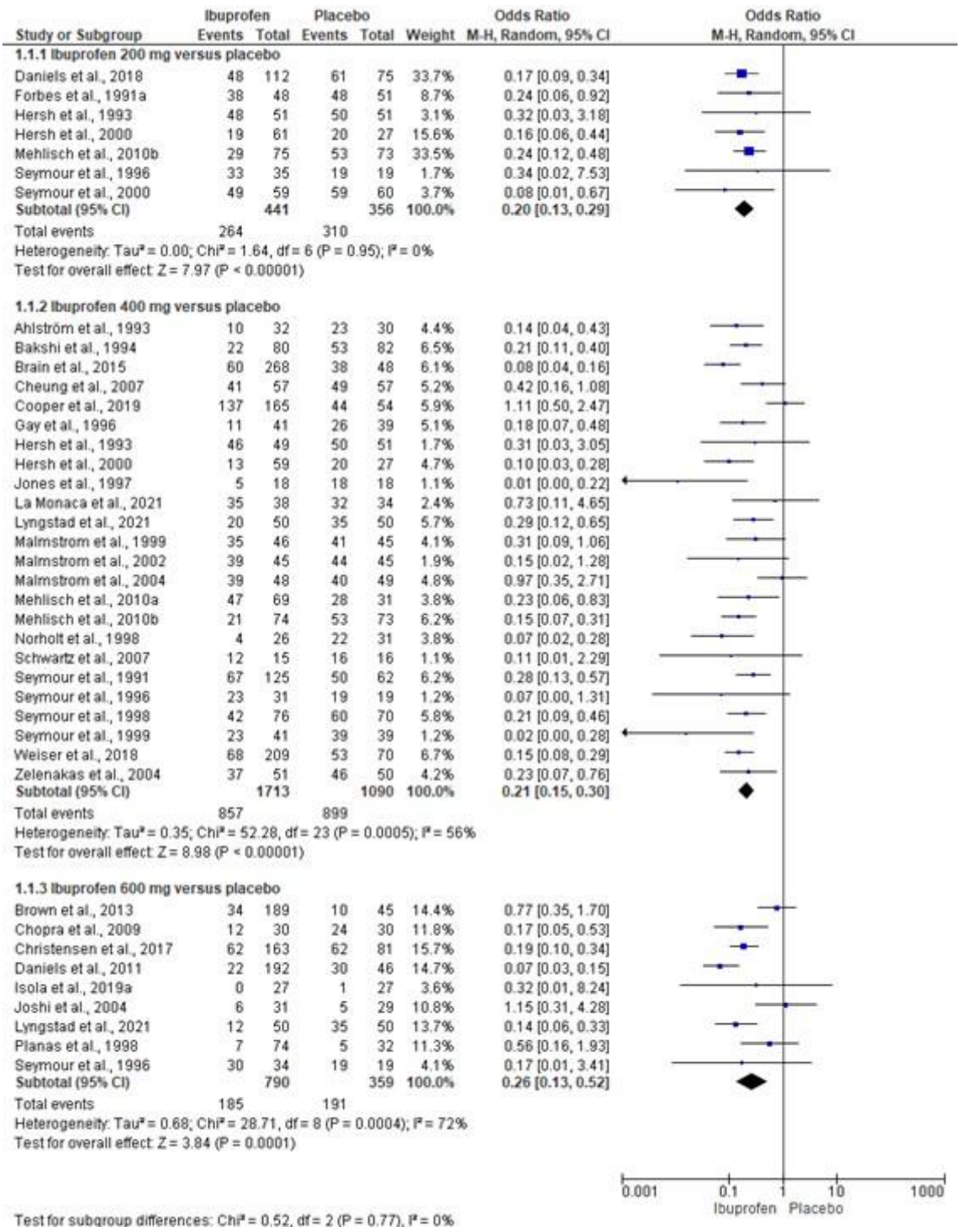

Figure 3. Number of patients who took rescue analgesics [38,39,41–45,47–49,53,57,59,60,62,64,65,68–72,76,77,79,82,84–89,93,94].

The overall evaluation of ibuprofen 200 mg was performed with data from 6 clinical trials [49,59,60,77,86,89] while that of ibuprofen 400 mg was conducted with 20 studies [39,41,47,57,59,60,66,69–72,76,77,80,84–88,94], and ibuprofen 600 mg was made using 2 clinical trials [42,86]. The pooled results show that ibuprofen 200 (n = 694), 400 (n = 2407), and 600 mg (n = 291) resulted in better patient scores when compared to the placebo group (Figure 4). The NNT and CIs can be seen in Table 1.

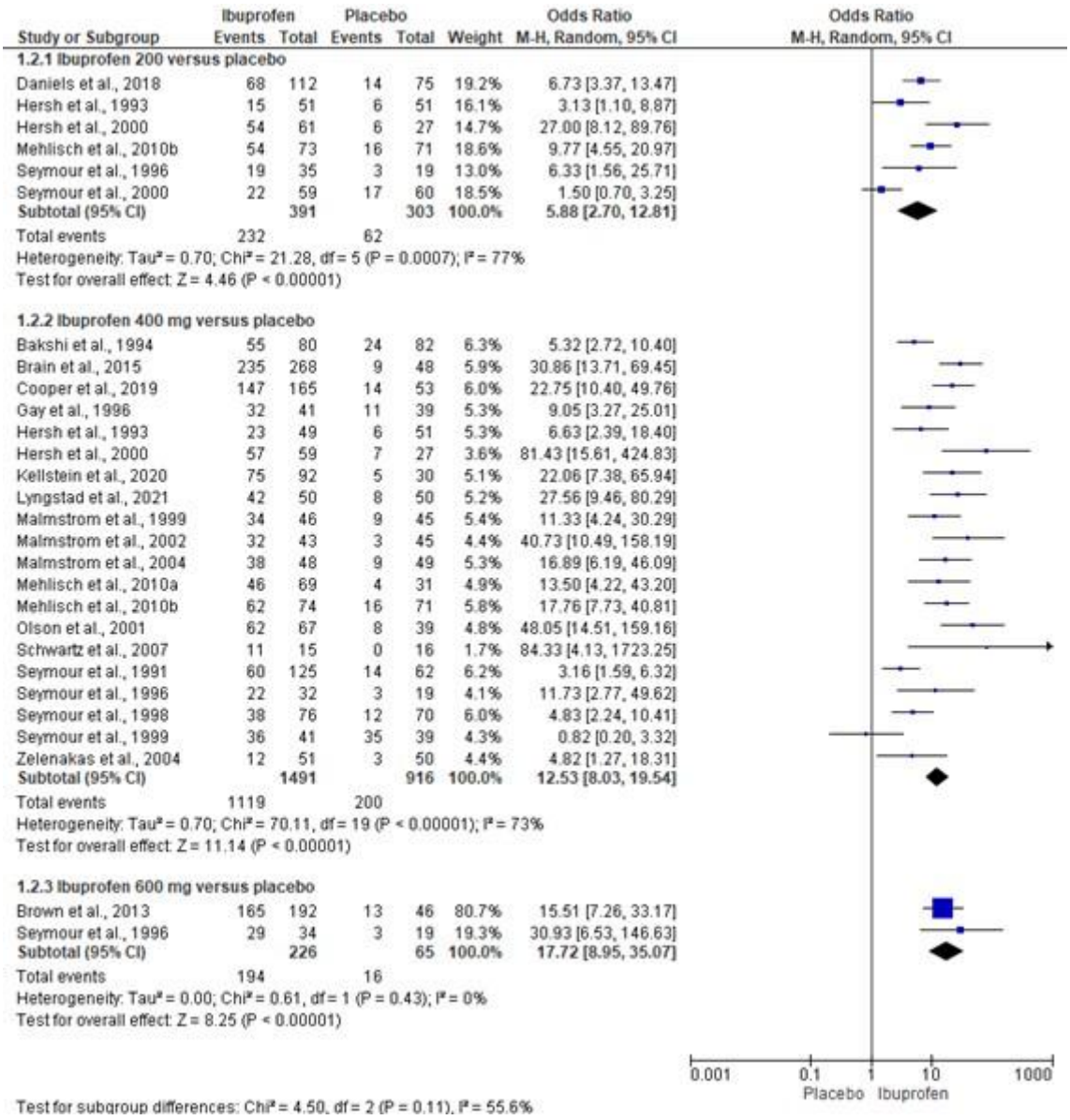

Figure 4. Global evaluation of study medications [39,41,42,47,49,57,59,60,66,69–72,76,77,80,84–89,94].

3.5. Adverse Effects

Data from 13 articles were used to evaluate the adverse effects of ibuprofen 200 mg and placebo [40,46,49,51,53,59,60,73,75,77,83,89,90]. The pooled analysis shows that ibuprofen caused a decrease in nausea (n = 1461, I^2 = 0%, Z = 3.14, OR = 0.48, 95% CIs = 0.31 to 0.76, p = 0.002; Figure 5) [40,46,49,51,53,59,60,75,77,83,89,90], vomiting (n = 1319, I^2 = 0%, Z = 2.24, OR = 0.51, 95% CIs = 0.29 to 0.92, p = 0.02; Figure 5) [40,46,49,53,59,60,73,75,77,89,90], and headache (n = 1342, I^2 = 0%, Z = 2.72, OR = 0.53, 95% CIs = 0.34 to 0.84, p = 0.007; Figure 5) [40,46,49,51,53,59,60,75,77,83,90] when compared to placebo. The NNH and CIs can be seen in Table 1.

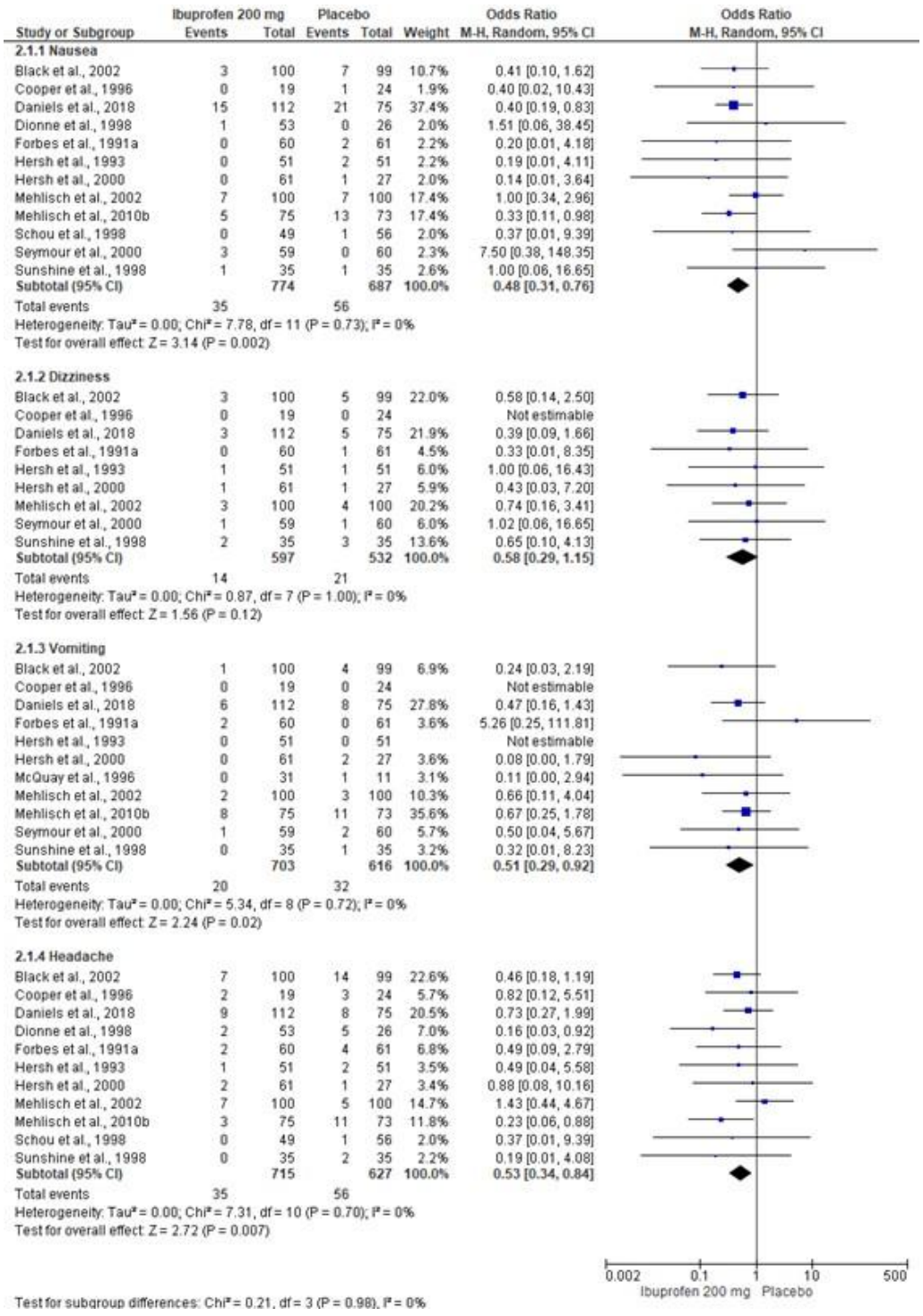

Figure 5. Adverse effects of ibuprofen 200 mg and placebo [40,46,49,51,53,59,60,73,75,77,83,89,90].

Data from 28 clinical trials were used to assess the adverse effects of ibuprofen 400 mg and placebo [39–41,43,47,51,54,55,57,59,60,66,70–77,80,81,83–85,87,92,93]. The results showed that ibuprofen significantly decreased the number of patients reporting nausea (n = 3917, I^2 = 0%, Z = 3.51, OR = 0.65, 95% CIs = 0.51 to 0.83, p = 0.0004; Figure 6) [39–41,43,47,51,54,55,57,59,60,66,70–72,74–77,80,81,83–85,92,93], vomiting (n = 3124, I^2 = 0%, Z = 3.14, OR = 0.61, 95% CIs = 0.45 to 0.83, p = 0.002; Figure 6) [40,41,43,47,59,60,66,70–72,74–77,81,84,87,92,93], and headache (n = 2477, I^2 = 0%, Z = 2.95,

OR = 0.58, 95% CIs = 0.41 to 0.84, $p = 0.003$; Figure 6) when compared to placebo [40,41,43,47,51,54,55,57,59,60,70,72,75,77,81,83–85,87]. The NNH and CIs can be seen in Table 1.

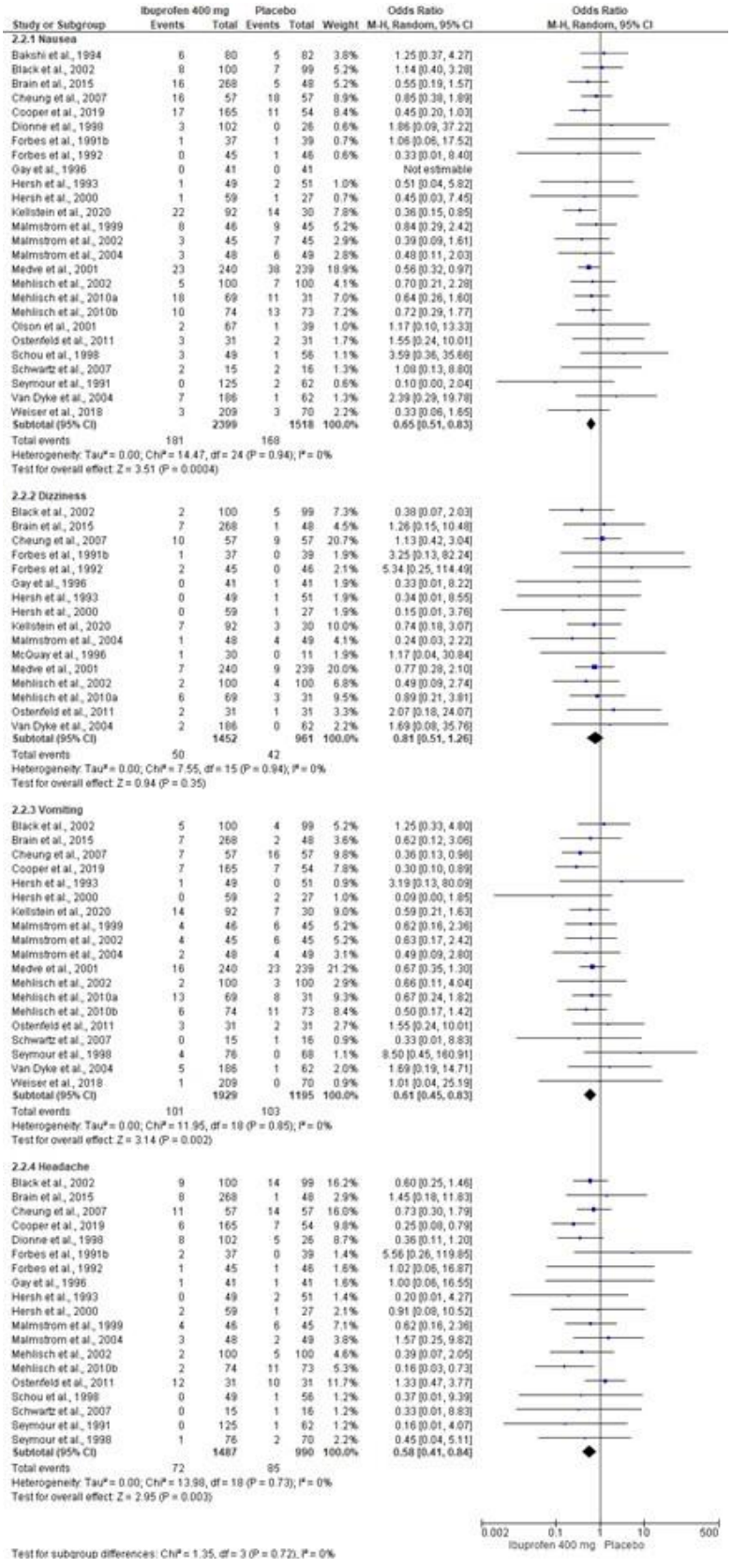

Figure 6. Adverse effects of ibuprofen 400 mg and placebo [39–41,43,47,51,54,55,57,59,60,66,70–77,80,81,83–85,87,92,93].

Data from 4 clinical trials were used to assess the adverse effects of ibuprofen 600 mg and placebo (n = 822) [42,45,48,82]. A pooled analysis shows that vomiting and headache were decreased in the ibuprofen group compared with placebo (n = 716, I^2 = 0%, Z = 2.98, OR = 0.19, 95% CIs = 0.07 to 0.57, p = 0.003, and n = 716, I^2 = 0%, Z = 3.65, OR = 0.27, 95% CIs = 0.13 to 0.54, p = 0.0003, respectively; Figure 7) [42,45,48].

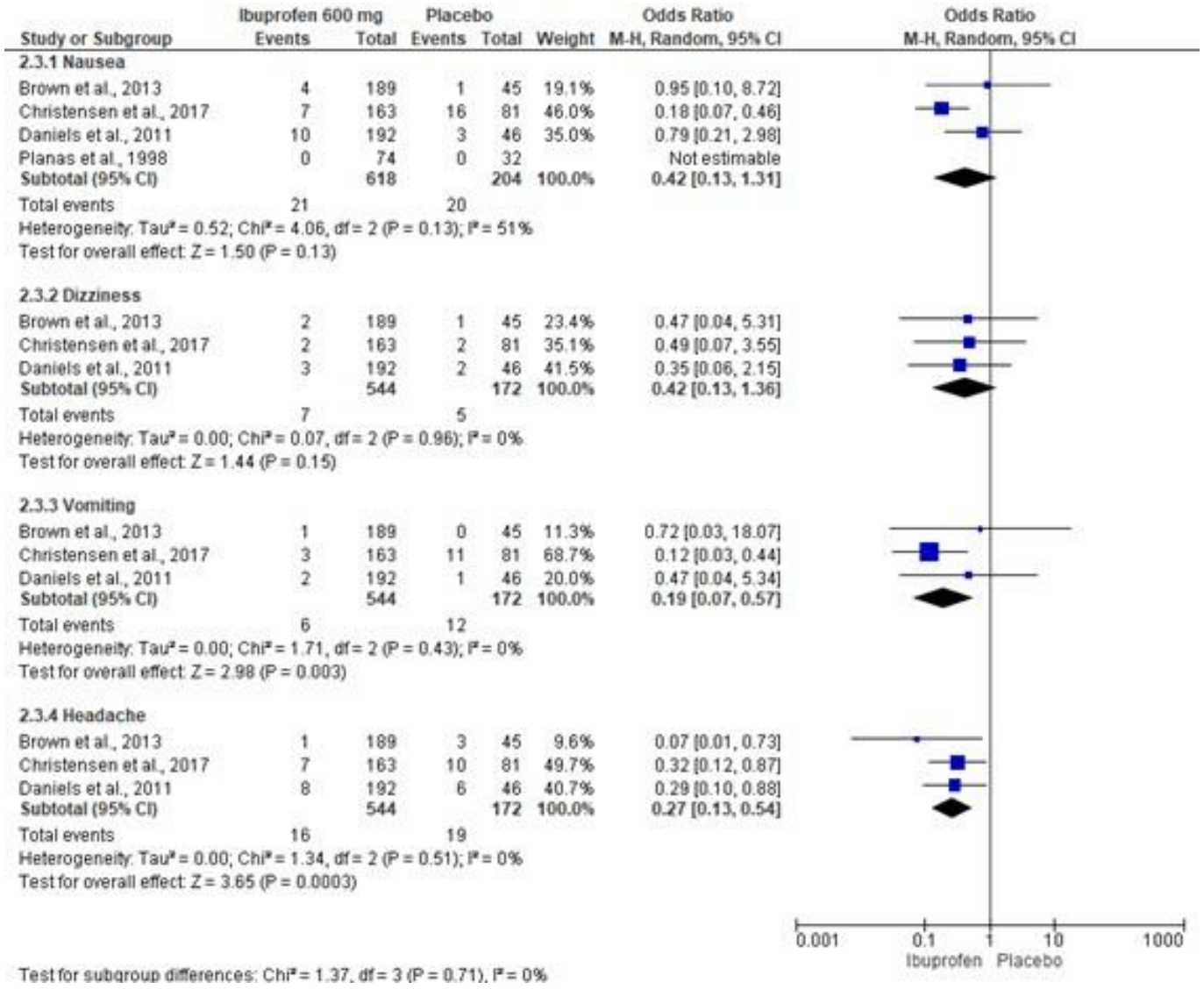

Figure 7. Adverse effects of ibuprofen 600 mg and placebo [42,45,48,82].

3.6. Assessment of Publication Bias

The funnel plot for rescue analgesic use shows slight asymmetry, suggesting potential publication bias. The OR close to 0.1 indicates that the treatment results in a significant reduction in rescue analgesic use (a). On the other hand, the funnel plot for the overall treatment assessment shows that the studies are dispersed, but center on an OR of 10. This OR demonstrates that ibuprofen has significant and robust efficacy (b) (Figure 8).

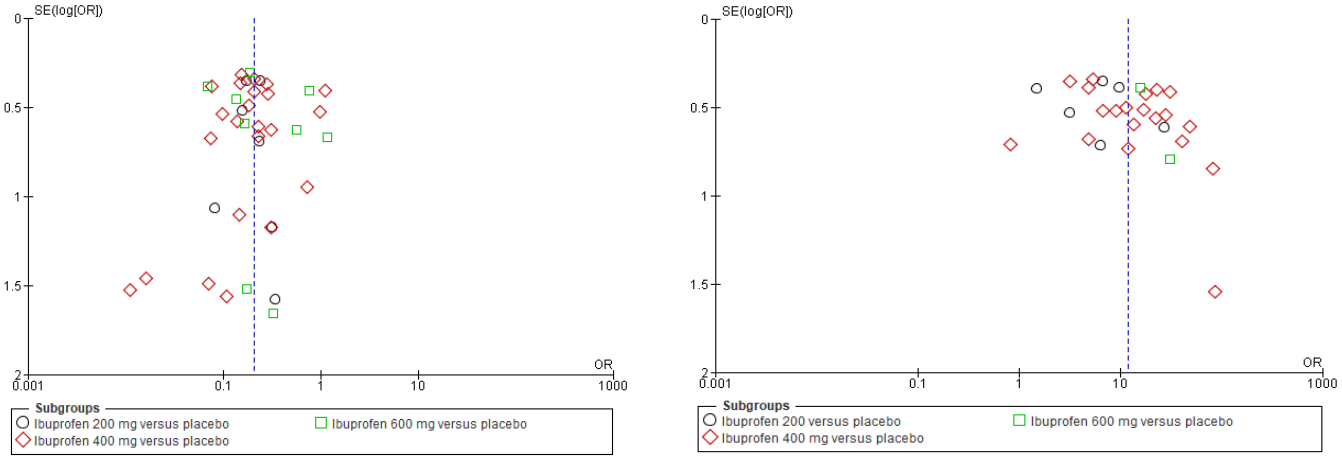

Figure 8. Publication risk assessment using the variables analgesic consumption (**a**) [38,39,41–45,47–49,53,57,59,60,62,64,65,68–72,76,77,79,82,84–89,93,94] and overall evaluation of treatments (**b**) [39,41,42,47,49,57,59,60,66,69–72,76,77,80,84–89,94].

4. Discussion

This systematic review analyzed the qualitative data from 57 studies and quantitative data from 49 clinical trials to determine the size of the analgesic effect of three doses of ibuprofen in comparison to placebo. The qualitative analysis showed that ibuprofen 400 mg was the most commonly used in the trials included in this systematic review [38–41,43,47,50–52,54–57,59–61,63,64,66,68–81,83–88,92–94], followed by ibuprofen 200 mg [40,46,49–51,53,58–60,67,73,75,77,83,86,89,90] and, finally, ibuprofen 600 mg [42,44,45,48,62,65,69,82,86,91]. Moreover, the pooled results show that ibuprofen substantially reduced the number of patients requiring rescue analgesia postoperatively compared with placebo. The overall assessment of the treatments showed that a greater number of patients rated ibuprofen as good, very good, and excellent compared to placebo. Both indicators of analgesic efficacy had high heterogeneity, so the statistical analysis was performed with a conservative approach using the random effects model. In this regard, the NNTs for the number of patients requiring rescue analgesics and global evaluation of the study drugs were low, close to NNT = 3, indicating that ibuprofen could be a highly efficient treatment with important clinical value after third molar surgery [95,96].

Franco-de la Torre et al., 2021 [20] conducted a systematic review and meta-analysis to compare the analgesic effect of ibuprofen in comparison with other analgesic treatments following third molar surgery. Although it was possible to compare ibuprofen with aspirin, bromfenac, and low doses of diclofenac, the sample size was small. In addition, analysis using pooled data of ibuprofen compared to other drugs was not feasible for the most part [20]. Due to these challenges, it was impossible to determine the NNT, NNH, or CIs in the systematic review by Franco-de la Torre et al., 2021 [20]. We decided to carry out this study to achieve larger sample sizes, which would allow for the calculation of these clinically important analgesic efficacy indicators, as well as to summarize existing information on the analgesic efficacy and adverse effects of ibuprofen 200, 400, and 600 mg following third molar surgery, so that the expert clinicians can have it available for implementation in clinical practice and/or to avoid its use.

Without a doubt, ibuprofen 400 mg was the most used dose in the clinical trials included in this systematic review, followed by ibuprofen 200 mg and then ibuprofen 600 mg. According to some authors, ibuprofen 400 mg is considered the "gold standard" analgesic treatment for the treatment of pain after third molar surgery [94]. Considering

the above, clinicians must have highly relevant data such as NNT, NNH, and CIs at their disposal. This is one of several clinical studies our group is conducting to determine the indicators of the clinical utility—NNT, NNH, and CIs—of NSAIDs in third molar surgery so that physicians can become familiar with them and decide which one to use based on availability in their office or hospital or determine which drug they recommend in their private consultation.

Ibuprofen is considered the safest non-selective NSAID for the COX-2 enzyme [97]. Its main adverse effects occur in the gastrointestinal system and the kidneys [98,99]. Franco-de la Torre et al., 2021, in their systematic review and meta-analysis, evaluated the adverse effects of ibuprofen without distinguishing the type of adverse reaction, considering only the number of patients who reported adverse effects for each treatment [20]. In our systematic review, a statistical analysis was performed using pooled data of the most encountered adverse effects—nausea, dizziness, vomiting, and headache—in the included clinical trials. The results show that ibuprofen 200, 400, and 600 mg produced fewer adverse effects compared to placebo after the third molar extraction. Furthermore, in this systematic review, the NNH of ibuprofen was high, confirming the clinical safety of ibuprofen in oral surgery in relation to the severity of adverse effects found in the clinical trials included in the statistical analysis. It is important to note that none of the studies included in this systematic review reported serious adverse effects [38–94].

The main advantage of our study was the number of clinical trials included in both the qualitative and quantitative analyses. This entails a series of important points that we would like to highlight, such as the sample size achieved with all the included studies, which in turn provides greater robustness to the statistical analysis that demonstrated the NNT and NNH of ibuprofen 200, 400, and 600 mg, which had not been previously calculated specifically for third molar surgery. A bias assessment was performed, which revealed that most of the clinical trials included in this review exhibited high methodological rigor and yielded statistics that could be utilized by clinicians in their daily practice (NNT and NNH). The main disadvantage of this study was that some clinical trials did not provide data because they did not evaluate the variables of interest or presented the variable, but measured it on a measurement scale different from that established in our methodology. Another important limitation of this study is that a subgroup analysis was not performed considering the ibuprofen administration schedule (single-dose or multiple-doses), nor comparing the different pharmaceutical presentations of ibuprofen.

In conclusion, the statistical analysis in this systematic review and meta-analysis demonstrates that ibuprofen has high analgesic efficacy and a good safety profile when used after third molar surgery. Furthermore, the results of this meta-analysis could be considered a guide for the clinical use of ibuprofen 200, 400, and 600 mg after third molar surgery.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/oral5030072/s1, Table S1: Sociodemographic characteristics, treatments, and specifications of the surgical procedure.

Author Contributions: All authors made substantial contributions to the conception of this review. M.A.I.-E., S.L.-V. and O.H.A.-M. conceived and designed the study. M.A.I.-E., R.B.-M. and I.J.M.-F. analyzed the results, including the abstract and body of the article, figures, and tables. M.A.I.-E., I.A.A.-B., N.S.-H. and N.M.-F. helped with the statistical analysis and interpretation of the results. M.A.I.-E., R.B.-M. and N.M.-F. helped with the writing of the original draft. O.H.A.-M., S.L.-V. and M.A.I.-E. helped with the review and editing of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Borad Statement: This article does not contain studies with human participants or animals performed by any author.

Data Availability Statement: The database is under the protection of the corresponding author. Therefore, if you would like to obtain this database, please contact Mario Alberto Isiordia-Espinoza.

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