Original Article

Opioid-free anesthesia and opioid-based anesthesia in oral and maxillofacial surgery: a systematic review and meta-analysis of randomized controlled trials

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Background: The use of opioid-free anesthesia (OFA) versus conventional opioid-based anesthesia (OBA) for oral and maxillofacial surgery (OMS) procedures remains controversial due to uncertainty regarding the safety and efficacy of OFA.

Methods: PubMed, Embase, Cochrane Library, and Web of Science were systematically searched, from database inception to January 25, 2022, for studies concerning efficacy of OBA and OFA in OMS. The primary outcomes were postoperative pain 1 and 2 hours postoperatively, and overall postoperative pain assessment. Secondary outcomes included incidence of postoperative nausea, as well as duration of operative and anesthesia time. Cochrane Risk of Bias Tool was used for quality assessment.

Results: In total, four eligible global studies with 161 patients underwent OMS were included in this systematic review. Patients in OBA group had less postoperative pain at both 1 and 2 h than OFA group [1 h: standard mean difference (SMD) –1.13, 95% CI: –1.71 to –0.55, P<0.01; 2 h: SMD –1.17, 95% CI: –1.73 to –0.61, P<0.01]; but there was no difference in overall postoperative pain assessment (SMD –1.00, 95% CI: –1.52 to –0.49, P=0.81). Besides, the add-up of opioid agents did not increase the incidence of nausea [relative risk (RR) 0.36, 95% CI: 0.11–1.17, P=0.64].

Conclusions: While there are relatively few studies comparing the use of OBA and OFA in OMS, the data suggests that OFA and OBA may have similar outcomes in terms of safety and efficacy. Nevertheless, OBA has superior early-stage pain control and no increase in nausea. Further studies are needed to evaluate the potential of using OFA for OMS procedures.

Keywords: Efficacy; opioid free anesthesia; opioid sparing anesthesia; oral and maxillofacial surgery; randomized controlled trial (RCT)

Received: 22 June 2022; Accepted: 02 June 2023; Published online: 26 June 2023.

doi: 10.21037/joma-22-20

View this article at: https://dx.doi.org/10.21037/joma-22-20

Introduction

Background

Oral and maxillofacial surgery (OMS) spans a wide scope of surgical treatments for the mouth, face, head, and neck region. The extensive scope of procedures in turn necessitates diverse and nuanced anesthesia approaches.

A multitude of anesthetic options, including benzodiazepines, propofol, ketamine, dexmedetomidine, and opioids agonists, enable OMS to conducted in an office-based environment (1). Commonly used opioid anesthetic options include morphine, hydromorphone, and fentanyl (2). Opioids are often used in combination with other hypnotic or sedative agents to achieve a balanced anesthetic strategy. These strategies are named opioid-based anesthesia (OBA).

Rationale and knowledge gap

Due to increasing awareness regarding the risks of using opioids, such as the development of hyperalgesia, as well as addiction and misuse, discussion regarding opioid-free anesthesia (OFA) strategies have increased in recent years (3-5). However, it remains unclear whether OFA can serve as a safe and effective anesthetic option to replace OBA (2,3,6).

Objective

In this study, we aimed to compare the safety and efficacy of OFA versus OBA for oral and maxillofacial surgical procedures, with specific outcomes including postoperative pain, duration of anesthesia, and incidence of pos-operative nausea. We present this article in accordance with the PRISMA reporting checklist (available at https://joma.amegroups.org/article/view/10.21037/joma-22-20/rc).

Highlight box

Key findings

- OBA had better early-stage postoperative pain control than OFA, but there was no difference in overall postoperative pain assessment.
- OBA and OFA had similar incidence of post-operative nausea.
- OBA had shorter duration of anesthesia than OFA, but both groups had the same total duration of operation.

What is known and what is new?

- OFA is increasingly discussed as an alternative to OBA, in order to avoid risks of opioid-use.
- From limited existing studies, OFA and OBA may have comparable outcomes regarding safety and efficacy.

What is the implication, and what should change now?

- Further studies are needed to evaluate the potential of using OFA for OMS procedures.

Methods

Literature searches

Bibliographic databases including PubMed, Embase, Cochrane Library, and Web of Science were searched comprehensively from the inception of each database to January 25, 2022 to identify all relevant articles. Moreover, abstracts and presentations of all major conference proceedings were also reviewed. The results were combined using the Boolean operator "OR" with the search terms with Mesh and text words including Tramadol, Tapentadol, Sufentanil, Remifentanil, Promedol, Pirinitramide, Phenoperidine, Phenazocine, Pentazocine, Oxymorphone, Oxycodone, Opium, Opiate Alkaloids, Nalbuphine, Morphine, Methadyl Acetate, Methadone, Meptazinol, Meperidine, Levorphanol, Hydromorphone, Hydrocodone, Heroin, Fentanyl, Etorphine, Ethylmorphine, Ethylketocyclazocine, Enkephalin, Enkephalin, Diphenoxylate, Dihydromorphine, Dextropropoxyphene, Dextromoramide, Codeine, Butorphanol, Buprenorphine, Alphaprodine, Alfentanil, Anesthesia, AND Oral Surgery, Maxillofacial Surgery, Exodontics. All words available for Medical Subject Headings (MeSH) were searched by MeSH. Reference lists were also reviewed in a snowball sampling technique to identify additional studies. Two investigators (Y Qi and H Dong) independently screened the titles and abstracts of identified articles. Major conflicts were resolved by another researcher (X Kong). The full texts of identified studies were further reviewed by two independent reviewers (Jingping Wang and Jing Wang). The search was again extended by review of references of articles included in the final selection. Additionally, this review prepared no protocol and it was not registered.

Selection criteria and data extraction

Eligibility criteria were as follows: (I) studies reporting data regarding efficacy and safety between OBA and OFA applied among patients undergoing OMS; (II) randomized controlled trials (RCTs); (III) the intervention under study

was OBA procedure compared with OFA procedure; (IV) studies limited to humans; (V) reports available in English. Exclusion criteria were as follows: (I) non-RCTs studies, letters, reviews, guidelines, conference proceedings, commentaries and publications in which the relevant data could not be ascertained; (II) studies done in other than the OMS; (III) study designed lack of OFA or OBA group; (IV) opioid agents applied post-operations; (V) studies with no efficacy or safety information; (VI) duplicate studies from the same population or database. Two investigators (Y Qi and H Dong) independently reviewed the list of retrieved articles to choose potentially relevant articles; disagreements were discussed and resolved by consensus with another investigator (X Kong). Both reviewers also independently extracted data from all studies; discrepancies were resolved by consensus with another investigator (X Kong). The following information was extracted from each publication: country, study design, data type, surgery type, participants randomly allocated, follow-up time, participants followed up (%), intervention design, comparator design, mean age (range) (years), female (%), duration of operation (min), pain measurement at 1 h post-operation, duration of anesthesia (min), area under the curve of pain assessment, nausea event.

Data synthesis and analysis

Y Qi and H Dong independently viewed titles, abstracts and full texts according to the selection criteria, and then extracted relevant data (as listed above) using a standardized data sheet. Statistical heterogeneity among studies was evaluated using Cochran's Q test and the I^2 statistic; I^2 (% residual variation due to heterogeneity) values of 25%, 50%, and 75% were considered to represent low, moderate, and high heterogeneity, respectively (7). Forest plots were created to illustrate heterogeneity for outcomes of safety and efficacy. Incidence and relative risk (RR) were calculated. Heterogeneity between studies was assessed by Q test and I^2 statistics. If the I^2 value was less than 50%, the meta-analysis was performed using the fixed effects model. Otherwise, the random-effects model was selected. An alpha of $P<0.05$ was considered statistically significant. Analyses were performed using R software version 4.1.2.

Qualitative assessment and risk of publication bias assessment

The risk of bias for the studies included was also assessed by two independent investigators according to the Cochrane Risk of Bias Tool version 2.0 (https://training.cochrane.org/handbook/current/chapter-08#section-8-2). This tool measured the key aspects of the methodology in selected studies with regard to design quality and risk of bias estimates based on three design criteria: (A) bias arising from the randomization process; (B) bias due to deviations from intended interventions; (C) bias due to missing outcome data; (D) bias in measurement of the outcome; (E) bias in selection of the reported results; (F) overall bias. Issues with "L" valuation represented low risk of bias; with "S" valuation represented some concerns; with "S" valuation represented high risk of bias. Any scoring differences were resolved by group discussion. Egger's test and Begg's funnel plots to examine publication bias were unable to be performed because only four studies were included in the analyses (8).

Results

Literature search

Figure 1 shows the study selection flowchart. After screening and eligibility assessment, we included a total of four studies which reported the data regarding efficacy and safety between OBA and OFA applied among patients undergoing OMS (9-12). Near-misses studies were excluded because these randomized studies were designed differently from included studies (13-17). The PICOS were: population: patients who required anesthesia for OMS; intervention: OBA; comparison: OFA; outcome: duration of anesthesia, duration of operation time, AUC of pain assessment, postoperative pain assessment at the first 1 and 2 h; study design: RCTs. The included studies totally contained information regarding 161 patients. Summary of basic characteristics and information of included studies were shown in *Table 1*.

Efficacy analysis

There was no statistically difference of duration of operation time between OBA group and OFA group [standard mean difference (SMD) –0.21, 95% CI: –0.54 to 0.12, P=0.73, I^2=0%]. The duration of anesthesia time of OBA group was statistically shorter than OFA group (SMD 0.73, 95% CI: 0.29–1.16, P<0.01) (*Figure 2*). There was no statistically difference of AUC of postoperative pain assessment between OBA group and OFA group (SMD

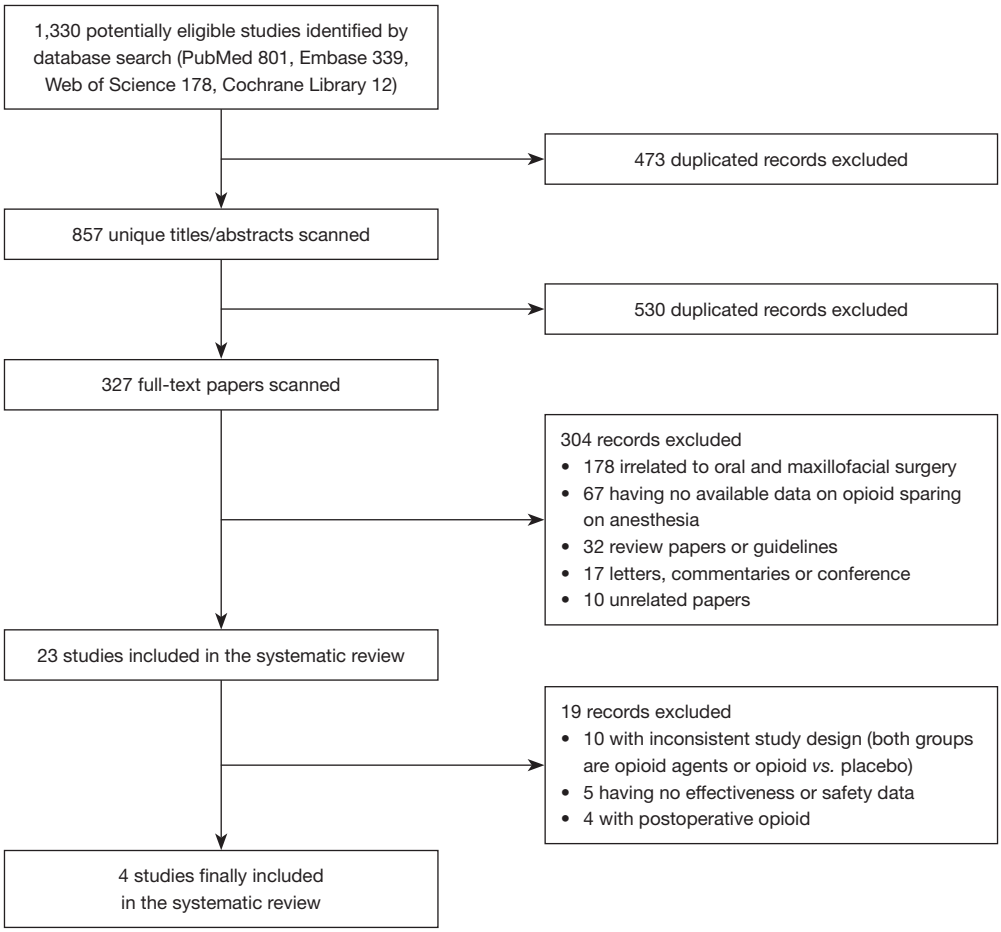

Figure 1 Study eligibility flowchart.

–1.00, 95% CI: –1.52 to –0.49, P=0.81). Patients in OBA group had slighter postoperative pain at both 1 and 2 h than OFA group (1 h: SMD –1.13, 95% CI: –1.71 to –0.55, P<0.01; 2 h: SMD –1.17, 95% CI: –1.73 to –0.61, P<0.01) (*Figure 3*).

Safety analysis

There totally 161 patients from four studies enrolled in safety analysis: 81 patients from intervention group and 80 patients from comparator group, respectively. There was no statistically difference between OBA and OFA group concerning about nausea event incidence (RR 0.36, 95% CI: 0.11–1.17, P=0.64) (*Figure 4*).

Heterogeneity, meta-regression, and qualitative assessment

Forest plots of safety analysis showed low heterogeneity, while efficacy analysis forest plots revealed high heterogeneity. However, since only four studies were included in some analysis, the meta-regressions of those analysis were difficult to perform. The risk of bias tool was used to conduct a qualitative assessment of the selected studies to review their quality and detect possible bias. As shown in Table S1, all of the four RCTs studies exhibited a low risk of bias.

Discussion

Key findings and explanation

We conducted this meta-analysis to evaluate the efficacy and safety of OBA versus OFA strategies during OMS procedures. Four studies with 161 subjects were included, and the overall risk of bias valuation was low. Subjects were randomized into two groups: one with OFA strategies such

Table 1 Summary of characteristics of included studies

Author	Year	Country	Study design	Data type	Surgery type	Participants randomly allocated	Follow-up	Participants followed up (%)	Intervention		Comparator		Duration of operation (E/C) (min)	Post-operative pain measurement (E/C)			Duration of anesthesia (E/C) (min)	AUC of pain (E/C) (%)
									Treatment	Population/mean age [range] (years)/female (%)	Treatment	Population/mean age [range] (years)/female (%)		1 h	2 h	3 h		
Kolacz (9)	2015	Poland	RCT	EHR	Odontogenic maxillary	48	24 h	100	Received regional anesthesia with 5 mL of a 2% solution of lidocaine with norepinephrine (lignocainum 2% c. Noradrenaline 0.00125% WZF, Polfa Warszawa SA) and 1 mg of morphine (Morphini Sulfas WZF, 10 mg/mL, Polfa Warszawa SA)	24/36.5/54.2	Received an identical solution but without morphine	24/44.9/54.20	41.7/44.4	1.1/0.2	1.6/0.6	2/0.9	56.3/59	NA
Isiordia-Espinoza (10)	2012	Mexico	RCT	EHR	Inferior alveolar nerve block surgery	20	4 h	100	2% mepivacaine with 1:100,000 epinephrine (Scandonest, Septodont, France) plus submucous tramadol 50 mg (1 mL of saline; Tradol, Grünenthal, Aachen, Germany)	10/[18–25]/NA	2% mepivacaine with 1:100,000 epinephrine plus submucous placebo (1 mL of saline)	10/[18–25]/NA	NA	5.3/7.4	2.5/3.7	0.1/0.1	174/162	10.8/4.4
Pozos (11)	2006	Mexico	RCT	EHR	Removal of an impacted mandibular third molar	48	6 h	100	Articaine 4%, 1:100,000 epinephrine, 1.5 cartridges (2.7 mL) and tramadol (Tradol; Grünenthal, Aachen, Germany), 50 mg (1 mL) into the surgical site	24/20.5 [19–26]/54.17	Articaine 4%, 1:100,000 epinephrine, 1.5 cartridges (2.7 mL) and saline (1 mL) into surgical site	24/21.5 [19–26]/58.33	7.0/8.0	NA	NA	NA	246/124.5	NA
Shipton (12)	2003	New Zealand	RCT	EHR	Removal of an impacted third molar tooth	45	10 h	100	Received intravenous tramadol 1.5 mg/kg injected over 2 minutes, followed by a bolus dose of intravenous propofol 0.4 mg/kg	22/29/63.64	Received no tramadol but instead a saline placebo solution and an identical amount of propofol	23/29/73.91	42.0/43.0	0.36/1.91	1.86/3.89	3.5/5.5	NA	15.91/29.52

E/C, experimental group/control group; AUC, area under the curve; RCT, randomized clinical trial; EHR, electronic health record; NA, not applicable.

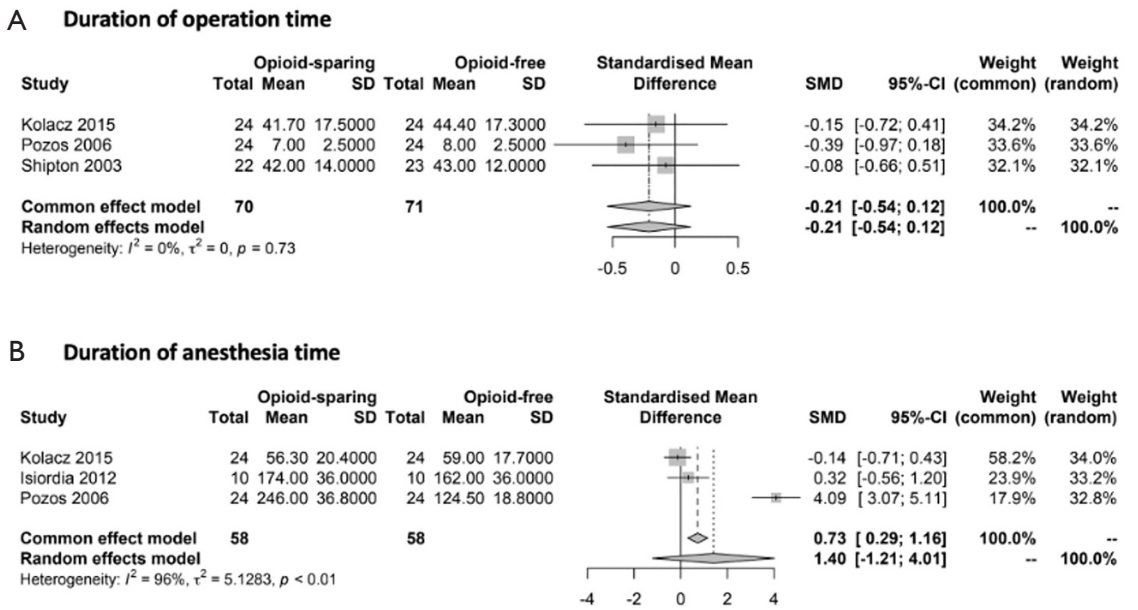

Figure 2 Duration of operation and anesthesia time between OBA and OFA groups. (A) Duration of operation time: there was no statistically difference of duration of operation time between OBA group and OFA group (SMD –0.21, 95% CI: –0.54 to 0.12, P=0.73). (B) Duration of anesthesia time: the duration of anesthesia time of OBA group was statistically shorter than OFA group (SMD 0.73, 95% CI: 0.29–1.16, P<0.01). SD, standard deviation; SMD, standard mean difference; CI, confidence interval; OBA, opioid-based anesthesia; OFA, opioid-free anesthesia.

as lidocaine, mepivacaine, articaine and propofol, and the other group with OBA strategies such as the addition of tramadol or morphine. Our analysis demonstrated that the duration of anesthesia time of the OBA group was statistically shorter than OFA group, while the duration of operation showed no statistical difference.

While OBA had superior pain control 1 and 2 h post-operatively, there was no difference in total pain assessment between OBA and OFA. The difference in short-term pain control may be due to the fact that some opioids used may have rapid onset to peak effects within minutes. Nevertheless, these results suggest that OFA strategy is a promising analgesic alternative to OBA.

Strengths and limitations

This meta-analysis has several limitations. Firstly, there were only four RCT studies included in this meta-analysis with only 161 patients, in which there were discrepancies in population age, operation types, anesthesia agents, follow-up time, assessment tools and valuation items, further leading to substantial variation in several of the outcomes. Secondly, the evaluation of the data and sample was considered to be too small for statistical and/or visual examination of publication bias, subsequently the probable existence of such bias could not be well-determined. Therefore, the results were generalizable only to population eligible for included clinical trials.

Comparison with similar research

Perioperative high-dose use of opioids may cause continuously postoperative use and increase the risk of dependence, addiction and overdose. With these concerns increasing, OFA was introduced by some clinicians to avoid hyperalgesia and tolerance (3-5). In 2019, a systematic review conducted by Frauenknecht *et al.* investigated 1,304 patients from 23 randomized trials, which demonstrated that pain scores were not statistically different between OFA and OBA groups, but the OFA group had lower incidence of vomiting and nausea (RR 0.78, 95% CI: 0.61–0.97) (18). In 2020, King *et al.* studied 48 women receiving mastectomy, and reported that the pain scores were not significantly different between OFA and OBA groups, while OFA had

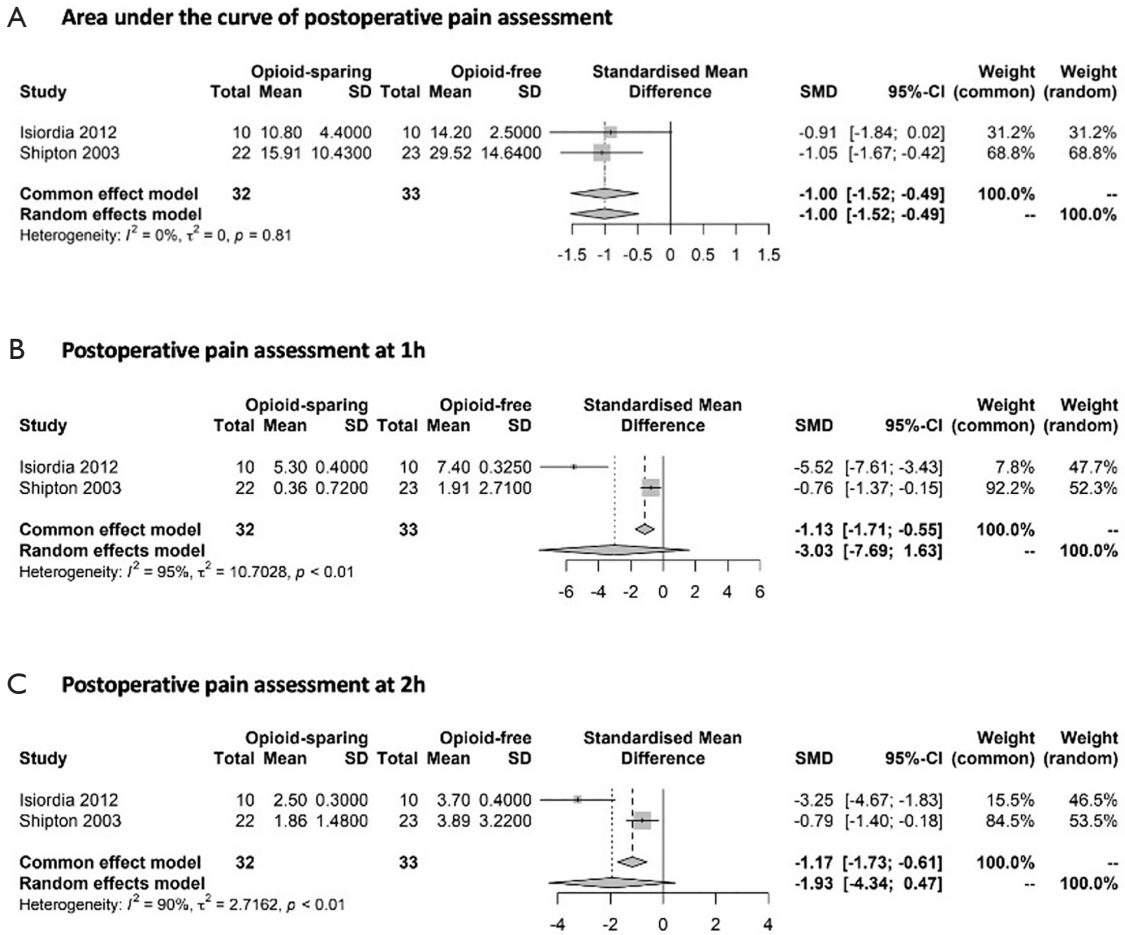

Figure 3 Anesthesia efficacy between OBA group and OFA group. (A) Area under the curve of postoperative pain assessment. There was no statistically difference between OBA group and OFA group (SMD −1.00, 95% CI: −1.52 to −0.49, P=0.81). (B) Postoperative pain assessment at 1 h. OBA group had slighter postoperative pain at 1 h than OFA group (SMD −1.13, 95% CI: −1.71 to −0.55, P<0.01). (C) Postoperative pain assessment at 2 h. OBA group had slighter postoperative pain at 2 h than OFA group (SMD −1.17, 95% CI: −1.73 to −0.61, P<0.01). SD, standard deviation; SMD, standard mean difference; CI, confidence interval; OBA, opioid-based anesthesia; OFA, opioid-free anesthesia.

decreased rate of postoperative nausea and vomiting events (P=0.02), which was consistent to previous studies (19).

However, scholars such as Lirk *et al.* (6) held the view that it might be too early to adopt OFA today. Concerns about tolerance and hyperalgesia are the leading cause of the acknowledged fact that opioids serve as sub-optimal analgesics, and the management of opioids is becoming time-dependently difficult. Poor-controlled pain, high-doses and long-periods postoperative use were reported as associated factors of persistent opioid use (20). Therefore, multimodal management that under the premise of adequate pain control, opioids administration with minimum doses for a short term is feasible and effective to help minify long-term opioid use, which subsequently improve the tolerance (21-24). The opioid-related hyperalgesia is most induced by remifentanil, which is dose-dependent and especially appears in procedures with strong pain or long period (25). This can be attenuated by low-dose ketamine, especially in acute post-operation occasion (26). Additionally, Chia *et al.* proposed the limitations and challenges of OFA (5). The challenge lies in the efficacy of pain control, the unexpected adverse events or drugs interactions arising from multimodal analgesics and insufficient management of cancer pain (27-29), and further persuasive studies should

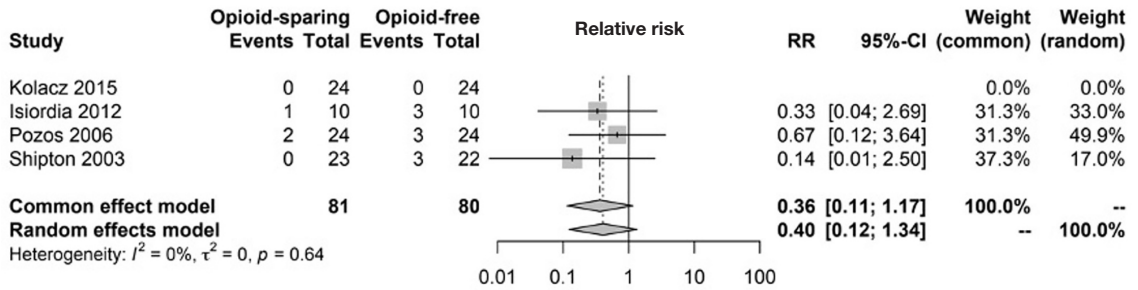

Figure 4 Nausea event incidence between OBA and OFA group. There was no statistically difference between OBA and OFA group concerning about nausea event incidence (RR 0.36, 95% CI: 0.11–1.17, P=0.64). RR, relative risk; CI, confidence interval; OBA, opioid-based anesthesia; OFA, opioid-free anesthesia.

be conducted to discovery and ascertain the long-term negative effects resulted from intraoperative opioids (2).

Implications and actions needed

While the results of this study are promising for the safety and efficacy of OFA, there is a current dearth of evidence comparing OBA and OFA. These results are in concordant with the current expert consensus that additional data are needed to formulate recommendations regarding whether OFA can be a suitable alternative for OBA (3,21,30,31). In the meantime, it remains critical that providers using opioid-based strategies remain vigilant and only use the minimal required dosage and duration.

Conclusions

While there are relatively few studies comparing the use of OBA and OFA in OMS, the data suggest that OFA and OBA may have similar outcomes in terms of safety and efficacy. Nevertheless, OBA has superior early-stage pain control and no increase in nausea. Further studies are needed to evaluate the potential of using OFA for OMS procedures.

Acknowledgments

We would like to thank our colleagues at Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA, and the Department of Breast Surgical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical and Peking Union Medical College.

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Oral and Maxillofacial Anesthesia*, for the series "Opioid-Free Anesthesia and Opioid-Sparing Anesthesia in OMF Surgery". The article has undergone external peer review.

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://joma.amegroups.org/article/view/10.21037/joma-22-20/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://joma.amegroups.org/article/view/10.21037/joma-22-20/coif). The series "Opioid-Free Anesthesia and Opioid-Sparing Anesthesia in OMF Surgery" was commissioned by the editorial office without any funding or sponsorship. Jingping W serves as the unpaid editorial board member of *Journal of Oral and Maxillofacial Anesthesia* from August 2021 to July 2023 and served as unpaid Guest Editor of the series. All authors declare the support by the Natural Science Foundation of China (Nos. 81872160, 82072940, 82103047, and 82102887). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/joma-22-20
Cite this article as: Qi Y, Wang TT, Dong H, Zhu N, Liu Y, Kong X, Wang J, Wang J. Opioid-free anesthesia and opioid-based anesthesia in oral and maxillofacial surgery: a systematic review and meta-analysis of randomized controlled trials. J Oral Maxillofac Anesth 2023;2:13.

Supplementary

Table S1 Assessment of risk of bias

Study	A	B	C	D	E	F
Kolacz, 2015	L	S	L	L	L	L
Isiordia, 2012	L	L	L	S	L	L
Pozos, 2006	L	L	S	S	L	L
Shipton, 2003	L	L	S	L	L	L

Risk of bias legend: (A) bias arising from the randomization process; (B) bias due to deviations from intended interventions; (C) bias due to missing outcome data; (D) bias in measurement of the outcome; (E) bias in selection of the reported results; (F) overall bias. L, low risk of bias; S, some concerns.

https://dx.doi.org/10.21037/joma-22-20