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REVIEW

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The use of corticosteroids in the lateral sinus augmentation surgical procedure: A systematic review and meta-analysis

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Abstract

Background: The lateral maxillary sinus augmentation (MSA) procedure has good predictability in terms of the success of bone regeneration with a low incidence of postoperative infections, estimated between 2% and 5.6%. Although the use of antibiotics is an established and standardized prophylactic measure for MSA procedures, the addition of corticosteroids still varies among clinician preference and clinical judgment.

Purpose: The aim of this systematic review was to identify whether the administration of corticosteroids during the MSA surgical procedure affects postoperative symptoms including swelling, pain, and infection rate.

Materials and methods: A literature search through PubMed, EMBASE, Ovid MEDLINE, and Web of Science indices, according to PICO criteria, was conducted to identify whether MSA peri-operative use of corticosteroids reduces the incidence of complications and patient morbidity. A single arm meta-analysis was performed due to the lack of randomized controlled trials (RCTs) comparing groups treated with or without peri-operative corticosteroids. The intracluster correlation co-efficient (ICC) and design effect were calculated to adjust for the clustering design.

Results: In the 37 studies included, a total of 1599 patients (378 Cort, 1221 No-Cort) were analyzed. Before and after taking account of clustering, there was statistically significant effect of corticosteroids on swelling, pain, wound dehiscence, trismus, and hematoma. The complication rates postoperatively were comparable between the two study groups, however slight differences existed in the incidence of active suppuration (1.7% [95% CI 0.7–3.9] Cort vs. 3.2% [2.2–4.5] No-Cort), wound dehiscence (3.9% [1.3–11.2] Cort vs. 2.1% [1.0–4.1] No-Cort) and trismus (2.7% [0.8–8.4] Cort vs. 1.4% [0.8–2.5] No-Cort).

Conclusions: Although the event rate of the 1-to-2-week postoperative complications did not differ between the two groups, the lack of conclusive data and research

comparing peri-operative corticosteroid use makes it impossible to draw definitive conclusions and more evidence and studies designed for this specific purpose are needed.

KEYWORDS
antibiotics, corticosteroids, maxillary sinus augmentation

What is known

- The frequency of reported postoperative infections after maxillary sinus augmentation (MSA) is between 2% and 5.6%.
- Pre- and postoperative prophylaxis regimens for MSA procedures include the use of antibiotics.
- Corticosteroids have both an anti-inflammatory and an analgesic effect.

What this study adds

- There are no studies directly comparing patients treated with or without peri-operative corticosteroids for the MSA procedure.
- Similar complication rates are reported in the literature between MSA performed with or without corticosteroids prescription.

1 | INTRODUCTION

The maxillary sinus is a pyramidal-shaped cavity and is the largest of the paranasal cavities. The maxillary sinus borders are comprised of (1) the nasal cavity medially, (2) the floor of the ocular orbit superiorly, (3) the maxillary tuberosity posteriorly, (4) the canine fossa anteriorly, and (5) the apical portion of the alveolar process inferiorly. During the aging process, and to a greater degree, after the loss of posterior teeth, the maxillary sinuses progressively increase their volume at the expenses of the superior–posterior alveolar ridge, which can complicate or impede dental implant placement. To overcome this problem, the bone augmentation technique known as sinus lift or maxillary sinus augmentation (MSA) was introduced in 1970.[1,2] This surgical procedure, and in particular, the lateral approach, has remained essentially unchanged in its execution protocol since it was first described. However, the procedure now exists as a one or two stage variant depending on whether the implants are placed simultaneously or consecutively to augmentation.

The MSA, although rather invasive, appears to be the most successful among the intra-oral bone augmentation techniques, with an implant survival rate comparable to implants placed in native bone.[3] The low frequency of reported postoperative infections, which is reported to be between 2% and 5.6%, contributes to safety and effectiveness of the procedure.[4] However, sinus infections can still occur. An infection of the maxillary sinus can remain localized or spread to neighboring structures, leading to life threatening scenarios if not properly treated. For this reason, it is recommended to follow specific pharmacological protocols to prevent such consequences.

Currently, pre- and postoperative prophylaxis regimens for MSA procedures include the use of antibiotics. However, corticosteroids are less commonly used, and if so, are generally administered only pre- or peri-operatively via oral or intramuscular route. This decision is operator-dependent and is not as standardized as antibiotics.

The use of corticosteroid drugs in oral surgery is much debated; those who use them aim to reduce the direct effects of inflammation on postoperative symptoms such as edema.[5–7] This is because corticosteroids decrease the activity and migration of inflammatory cells (T helper lymphocytes, monocytes, and macrophages) on the site of trauma and their production of pro-inflammatory substances (histamine, leukotrienes, prostaglandins, and cytokines).[8,9] Furthermore, the inhibition of enzyme phospholipase A_2 and prostaglandin production makes corticosteroids a potent analgesic substance, which reduces postoperative pain.[10,11]

A challenging factor regarding MSA-related complications is that the postoperative infections can be either true sinus infections (i.e., acute sinusitis) or bone graft-related infections (i.e., bacterial contamination of graft). A sinus infection is distinguished from a bone graft infection in that it occurs within the sinus space surrounded by the Schneiderian membrane (SM) versus a bone graft infection which is found between the inferior aspect of the SM and the apical portion of alveolar process.[12]

In light of these considerations, the purpose of this systematic review is to identify whether the administration of corticosteroids during the MSA surgical procedure operative phase affects postoperative symptoms, including swelling, pain, and infection rate.

2 | MATERIALS AND METHODS

This review has been registered at the National Institute for Health Research PROSPERO, International Prospective Register of Systematic Reviews and has been assigned the number CRD42020190884.

2.1 | PICO criteria definitions

Population: Partially or fully edentulous atrophic posterior maxillae.

Intervention: MSA surgery with lateral approach with peri-operative prescription of corticosteroids.

Comparison: MSA surgery with lateral approach without peri-operative prescription of corticosteroids.

Outcome: Presence of postoperative inflammatory symptoms (edema, pain, infection, symptoms of acute sinusitis, trismus, and wound dehiscence) within 1 week post-intervention.

2.2 | Focused question

Does the prescribed post- or peri-operative corticosteroids reduce the occurrence of complications and patient morbidity after the lateral MSA procedure?

2.3 | Search strategy

The data for this systematic review and meta-analysis were obtained and processed following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) principles.[13]

Relevant articles, published up to December 30, 2020, were searched using the relevant keywords and respective Boolean logic operators (AND, OR, and NOT) in the above-mentioned databases: PubMed, EMBASE, Ovid MEDLINE, and Web of Science. The relevant keywords were combined as follow for the search: ([jaw, edentulous, partially] OR [partially edentulous] OR [partial edentulism] OR [full edentulism] OR [fully edentulous] OR [atrophic maxilla] OR [posterior maxilla]) OR (lateral AND ["maxillary sinus lift" OR "sinus lift" OR "maxillary sinus floor elevation" OR "sinus floor elevation" OR "maxillary sinus floor augmentation" OR "sinus floor augmentation" OR steroids OR steroid OR corticosteroids OR corticosteroid]) OR (lateral AND ["maxillary sinus lift" OR "sinus lift" OR "maxillary sinus floor elevation" OR "sinus floor elevation" OR "maxillary sinus floor augmentation" OR "sinus floor augmentation"]) AND (pain OR pain reduction OR trismus OR swelling OR complications OR inflammation OR outcome).

Four independent reviewers (NAV, GLD, GP, and LM) first screened all study titles, then read abstracts, and lastly assessed the full texts of included articles. Disagreements were resolved by discussion among reviewers. The final selections according to the inclusion and exclusion criteria were made by the same authors, as some articles were excluded only after the full text analysis.

2.4 | Inclusion criteria

Studies were included if the following criteria were met:

- Studies specifically referring to lateral sinus lift
- RCTs

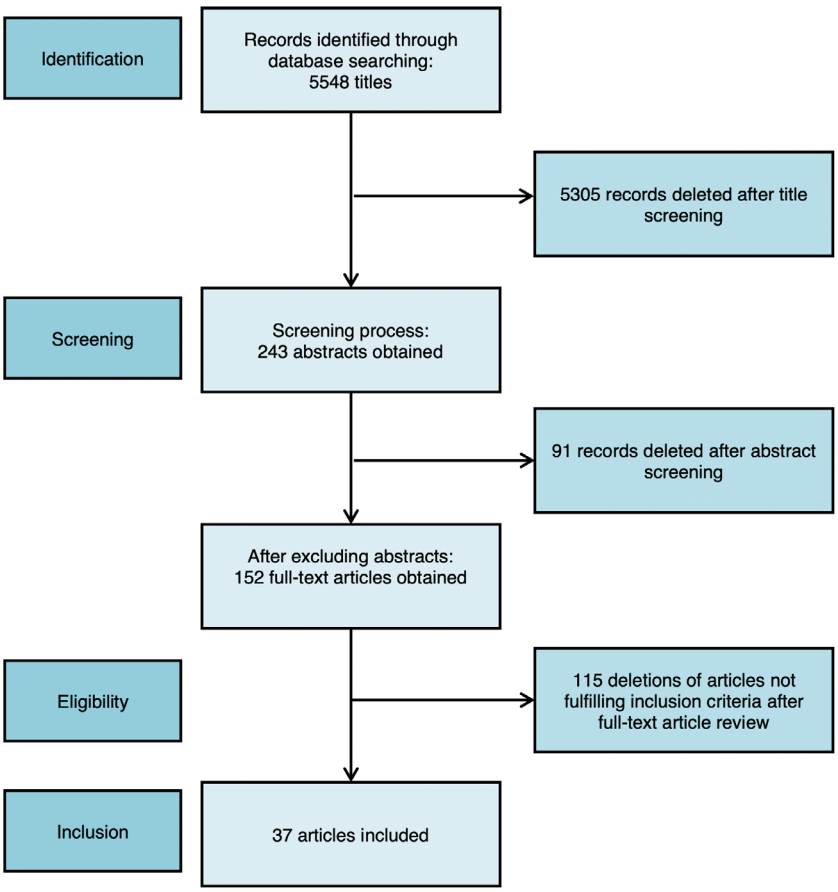


FIGURE 1 PRISMA flow diagram of the study selection process

TABLE 1 Effect of corticosteroids on the number of participants in the lateral sinus augmentation surgical procedure

		Unadjusted for clustering[b]			Design	Adjusted for clustering[c]		
Complication	*N*[a]	Cort	No-Cort	Relative risk odds ratio (95% CI)	Effect	Cort	No-Cort	Relative risk odds ratio (95% CI)
Early implant loss	3513	835(6)	2678(18)	1.07(0.43–2.68) 1.07(0.42–2.70)	4.483	186(1)	597(4)	0.80(0.09–7.14) 0.80(0.09–7.22)
Number of infected sinuses	2096	459(7)	1637(36)	0.67(0.30–1.50) 0.67(0.30–1.51)	2.767	166(3)	592(14)	0.76(0.22–2.63) 0.76(0.22–2.68)
Swelling	1421	356(29)	1065(41)	2.07(1.31–3.26)* 2.16(1.32-3.52)*	2.260	158(13)	471(19)	2.03(1.03–4.03)* 2.13(1.04–4.43)*
Active suppuration	1525	345(0)	1180(20)	0.17(0.02–1.27) 0.17(0.02–1.26)	2.317	149(0)	509(9)	0.38(0.05–2.95) 0.38(0.05–3.02)
Pain	1207	253(25)	954(23)	4.10(2.37–7.10)* 4.44(2.47-7.96)*	2.263	112(11)	422(10)	4.14(1.81–9.51)* 4.49(1.85–10.86)*
Bleeding	1399	317(2)	1082(7)	0.98(0.20–4.67) 0.98(0.20–4.72)	2.242	141(1)	483(3)	1.14(0.12–10.89) 1.14(0.12–11.07)
Wound dehiscence	1905	389(24)	1516(29)	3.11(1.84–5.27)* 3.26(1.88–5.64)*	2.702	144(9)	561(11)	3.18(1.35–7.55)* 3.33(1.35–8.21)*
Trismus	1408	345(8)	1063(0)	24.74(3.11–197.14)* 25.23(3.14–202.49)*	2.251	153(4)	472(0)	12.37(1.39–109.80)* 12.67(1.41–114.25)*
Hematoma	1397	334(23)	1063(23)	3.18(1.81–5.60)* 3.34(1.85–6.04)*	2.239	149(10)	475(10)	3.19(1.35–7.51)* 3.35(1.36–8.20)*
Other complications	1446	334(5)	1112(31)	0.52(0.20–1.32) 0.51(0.19–1.33)	2.209	151(2)	503(14)	0.48(0.11–2.11) 0.48(0.11–2.12)

[a]The number of participants at study end.
[b]Analyses performed on summary data ignoring the effect of cluster design. Both relative risk (top line) and odds ratio (bottom line) are presented for each group.
[c]Analyses performed on summary data accounting for clustering. Summary data were obtained by calculating the $1 + (M - 1)$ ICC where M was the average cluster size and ICC was 0.03. The adjusted analysis where performed by dividing all the numbers on the design effect and repeating analyses.
*p value <0.05.

- Prospective cohort studies
- Case series
- Studies published in the English language
- Explicit reference to the peri-operative (pre and/or post) pharmacological prescriptions (antibiotics, anti-inflammatories, and analgesics)
- Details of at least one of the postoperative inflammatory parameters reported (swelling, suppuration, symptoms of acute sinusitis, trismus, pain, and wound dehiscence)

2.5 | Exclusion criteria

- Crestal/vertical sinus lift
- Less than 20 patients or 20 sinus lift surgeries
- Case reports
- Retrospective studies
- In vitro studies
- Animal studies
- Articles with same cohort of patients
- Postoperative inflammatory parameters not considered in the analysis (not mentioned in the materials and methods, or the analysis of the parameters were not clearly identifiable in the results)
- Inflammatory parameters not discernable as values for a meta-analysis

2.6 | Quality assessment

Two authors (NAV and LM) independently assessed the studies in terms of the inclusion, relevance, eligibility, and risk of bias following the Cochrane Collaboration tool[14] for RCTs and the Newcastle-Ottawa tool for prospective cohort studies[15]; any disagreement was resolved by consensus of reviewers and statistics researcher (ZN).

2.7 | Data extraction and collection process

Following the screening process, four reviewers (NAV, GLD, GP, and LM) independently extracted the data of the selected articles using data tables. All extracted data were reviewed, and any conflict was resolved among the authors and confirmed by the statistician. The following information was extracted from each included trial: year of publication, study design, number of patients, number of patients at the end of the study, number of implants, dropouts, mean age of patients, age range, mean initial bone height, type of biomaterial used, type of membrane used, single or bilateral sinus augmentation, dosage and timing of antibiotics prescribed, type of antibiotic, timing and dosage of corticosteroids prescribed, other anti-inflammatory medications prescribed, type and number of intra-operative complications, and type and number of postoperative symptoms at 1 and 2 weeks.

The primary (swelling, pain, and infection) and secondary outcomes (active suppuration, bleeding, wound dehiscence, trismus, hematoma, and early implant failure) were classified as present or absent, as clearly reported and numbered by the authors of the selected articles. If an article did not directly provided the number of outcome occurrences, they were extrapolated from the specific scales or tables, by counting the number of patients that still reported that outcome during the first 2 weeks post-op; as an example, we counted the number of patients that still reported pain in a visual analog scale (VAS) pain scale after 7 days. In this case, the pain was considered to be medium-high or high.

2.8 | Statistical analysis

A single arm meta-analysis was performed using the CMA software (Comprehensive Meta Analysis Version 2.0) for each group separate. A random effects model was performed to estimate the event rate. Heterogeneity was checked based on methods, design, and type of complications. These analyses were based on patients who received only sinus elevation procedure. Some studies reported their results based on unilateral sinus augmentation, other studies reported on bilateral sinus augmentation, or based on both. Some studies did not use the appropriate statistical analyses with bilateral sinus augmentation. However, in this report, we are using the absolute numbers of complications as reported in these studies.

To account for clustering effect, we estimated the intracluster "intraclass" correlation (ICC), and the design effect for the study using the formula $1 + (M - 1)$ * ICC where M is the average cluster size.[16] Using the summary data and design effect, we calculated the relative risk (RR) and odds ratio (OR) for both group.

3 | RESULTS

3.1 | Study selection

The article selection process, summarized in the PRISMA flow diagram (Figure 1), resulted in 5584 items which, after screening of the titles, was reduced to 243 abstracts. After evaluating the latter, 91 articles were excluded. Out of the remaining 152, 37 fulfilled the inclusion and exclusion criteria and were used for data extraction.[4,17–52] Twelve[20,21,25,31,34,36,37,39,40,42,50,52] out of the 37 included studies clearly reported the administration of pre- or peri-operative corticosteroids. None of the included articles specifically compared lateral MSA procedure outcomes with or without the use of corticosteroids. However, all the selected studies explicitly mentioned the pharmacological prophylaxis adopted for the surgical procedure.

3.1.1 | Risk of bias

According to the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2),[14] regarding the RCTs included, only some concern was found in some studies. No study reported another risk of bias for our outcome variables (Figure 1S in supplementary online materials).

Regarding the non-RCT studies, according to the Newcastle-Ottawa Scale (NOS)[15] for Assessing the Quality of Nonrandomized Studies in Meta-Analysis, no high risk of bias was found for any study, especially for the parameters relating to outcomes (Table 1S in supplementary online materials).

3.1.2 | Corticosteroid use

Among the studies initially included in the "corticosteroid group" (Cort), five used dexamethasone, five used betamethasone, one used methylprednisolone, and one used deflazacort. In seven studies corticosteroids were administered postoperatively, in three studies preoperatively, in one study both pre- and postoperatively, and in one study they were administered intra- and postoperatively. Corticosteroids were administered orally (seven studies), intramuscularly (three studies), intravenously (three studies), and both orally and intramuscularly (one study).

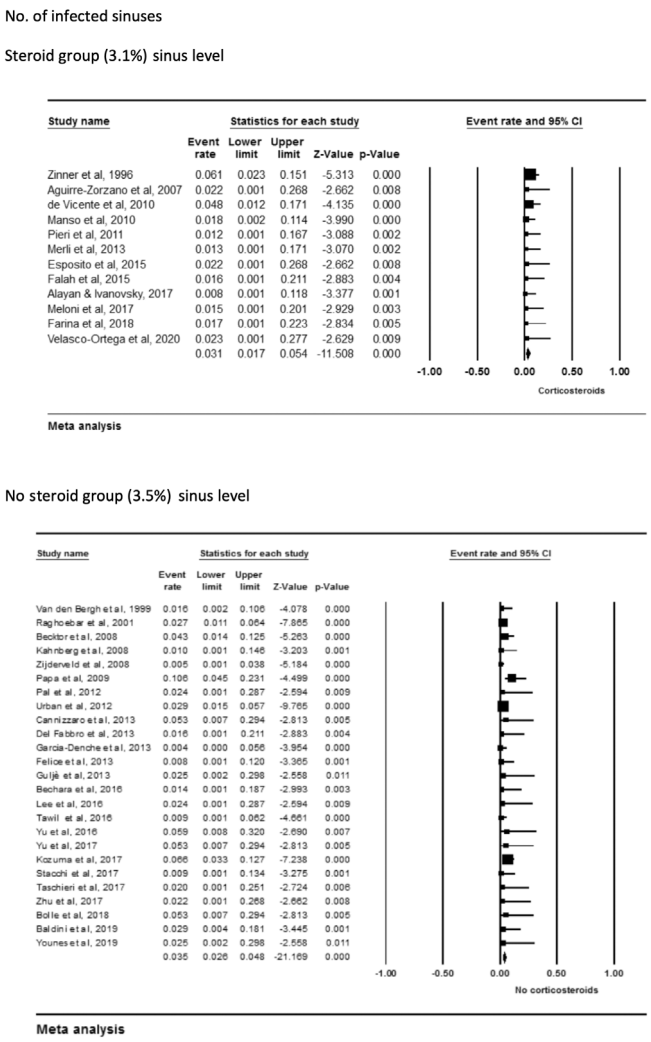
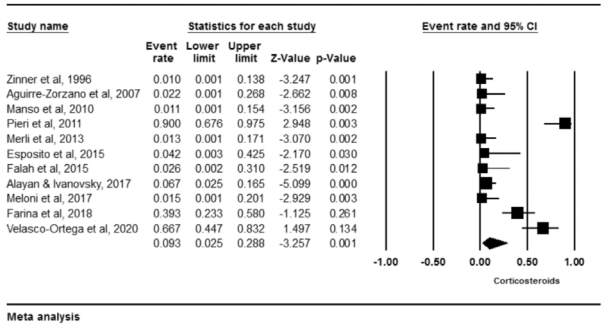


FIGURE 2 Forest plot for number of infected sinuses outcome

Swelling

Steroid group (9.3%) patients level



Steroid group (10.8%) patients level

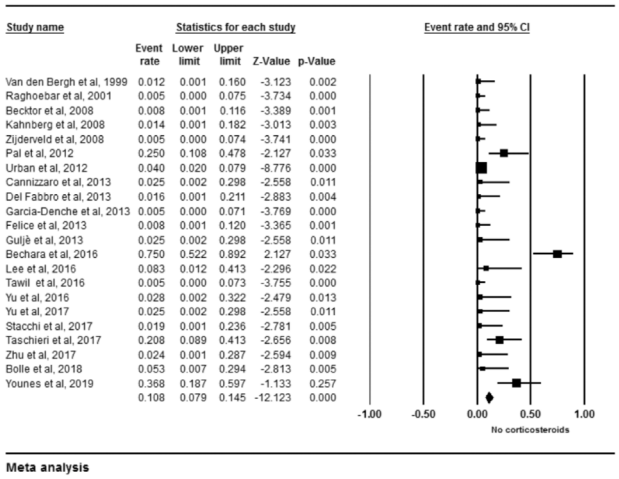


FIGURE 3 Forest plot for swelling outcome

3.1.3 | Antibiotic use

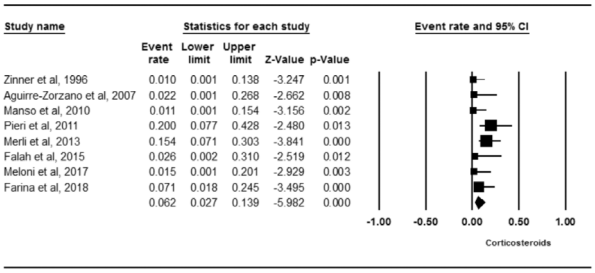
Amoxicillin was used in 3 studies of the Cort group and in 12 studies of the no corticosteroid group (No-Cort). Amoxicillin plus clavulanate was used in five Cort and four No-Cort studies. Antibiotic choice was unreported in four studies, including one study of the Cort group. In most studies, clindamycin was used for patients who were intolerant to amoxicillin, however one Cort group study[40] used Clindamycin as the first line of antibiotics and amoxicillin as the second. Ceftriaxone, phenoxymethylpenicillin, and penicillin V were used in only one study each.[41,42,46] In the majority of the studies, antibiotics were prescribed for a total of 7 days.

3.1.4 | Sinus lift procedures

In five studies of the Cort group and in seven of the No-Cort group, unilateral sinus lifts were performed. In two Cort and two No-Cort studies, bilateral sinus lifts were executed. In the remaining studies,

Pain

Steroid group (6.2%) patients level



No steroid group (4.9%) patients level

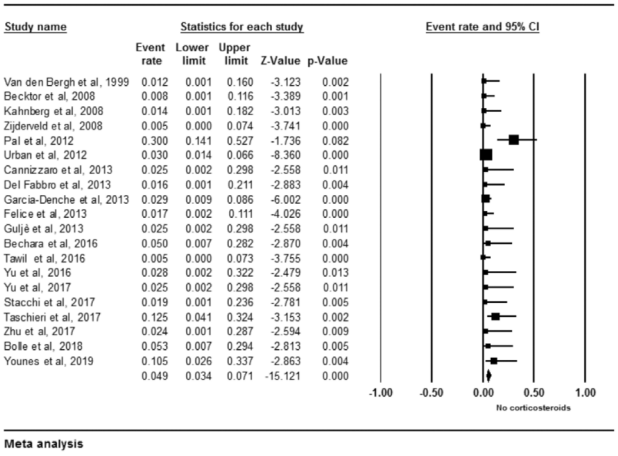


FIGURE 4 Forest plot for pain outcome

the authors did not specify whether they performed uni- or bilateral MSA on the participating subjects.

The most commonly used biomaterial was bovine xenograft and it was most often combined with other autologous or synthetic biomaterials. In six studies of the Cort group and in seven of the No-Cort group, the implants were placed at the same time as the MSA. In six No-Cort studies and in one Cort study the implants were placed simultaneously or in two stages depending on the clinical scenario. In all other studies, only the MSA was performed.

3.1.5 | Analyses using summary data

Table 1 shows the effect of this adjustment of corticosteroids on the participants with lateral sinus augmentation surgical procedure. The mean number of participants per cluster for each outcome was varied. The ICC estimated was 0.03 (95% CI 0.01–0.05). Therefore, the design effect was presented in Table 1. The RR and OR remain unchanged. However, the confidence intervals (CIs) are much wider because the sample size is effectively much smaller. Before taking account of clustering, there was statistically significant effect of corticosteroids on swelling, pain, wound dehiscence, trismus, and

TABLE 2 Basic characteristics of the studies

First author	Year	Study design	Planned no. of pat. (all Pat.)	Actual no. of pat at the end of study	Drop-out %	Drop-out number	Mean age	Age range	Gender M/F	Operators (setting)	Mean initial bone height	Implants placed contextually Y/N	No. of implants	No. of treated sinuses	Biomaterial used (type)	Membrane used (Y, N, NR)	Membrane used (type)	MSA/Pt (single–bilateral–NR)
Corticosteroids																		
Zinner et al.	1996	Case series	50	50	0	0	NR	30/71	17/33	University	NR	Y	215	57	HA + DFDBA + autogenous	y	Collagen	Single, bilateral
Aguirre-Zorzano et al.	2007	Prospective	22	22	0	0	47	36/69	9/13	NR	NR	Y	36	22	β-TCP + AB	NR	NR	Single
de Vicente et al.	2010	Prospective	34	33	2.9	1	NR	34/69	14/21	University	NR	Both	90	42	ABBM+AB	Y	Collagen	Single, bilateral
Manso et al.	2010	Prospective	45	44	2.2	1	54	26/80	16/29	University	NR	Y	160	57	BCP + AB	Y	Collagen	Single, bilateral
Pieri et al.	2012	Prospective	20	20	0	0	54.6	47/69	9/11	University	2.37	N	155	40	ABBM + AB	Y	Collagen	Bilateral
Merli et al.	2013	RCT	40	39	2.5	1	50.6	38/66	19/21	Private Practice	2.15	Y	59	39	ABBM or AB	Y	Collagen	Single, bilateral[a]
Esposito et al.	2015	RCT	13	11	15.4	2	52	29/65	5/8	Hospital	NR	N	92	22	AB	Y	Synthetic co-polymer	Bilateral
Falah et al.	2016	Prospective	18	18	0	0	52	38/60	8/10	University	5.61	Y	72	30	none	Y	Collagen	Single, bilateral
Alayan and Ivanovsky	2018	Prospective	60	60	0	0	59.2	NR	17/43	University, private practice	3.09	N	60	60	ABBM + AB, ABBM-C	Y	Collagen	Single
Meloni et al.	2017	RCT	32	32	0	0	48	22/76	13/19	Private practice	2.5	N	46	32	ABBM or ABBM + AB	Y	Collagen	Single
Farina et al.	2018	RCT	28	28	0	0	53.0	48/59	11/17	University	4.1	Y	33	28	ABBM	Y	Collagen	Single
Velasco-Ortega et al.	2020	RCT	24	21	12.5	3	55.9	38/77	8/16	University	2.6	N	44	21	ABBM or BCP or BCP + HyA	Y	Collagen	Single
No corticosteroids																		
Van den Bergh et al.	1998	Case series	42	42	0	0	44	22/64	dic-30	University	NR	N	161	62	AB	Y/N	Demineralized laminar bone membranes	Single, bilateral
Raghoebar et al.	2001	Prospective	105	99	5.7	6	48	17/73	41/58	University	3	Both	392	182	Abintra or Abextra	NR	N/A	Single, bilateral
Becktor et al.	2008	Prospective	61	61	0	0	55.7	17/78	23/38	NR	2.6–3.5–3.8–6.5[b]	N	146	70	AB Block/particulate	N	N/A	Single, bilateral
Kahnberg et al.	2008	Prospective	36	36	0	0	59.8	NR	14/22	NR	5.8	N	153	47	AB or AB + DBBM	N	N/A	Single, bilateral
Zijderveld et al.	2008	Case series	100	100	0	0	50	17/73	36/64	University	NR	N	243	118	No	Y/N	Collagen	Single, bilateral
Papa et al.	2009	Prospective	34	30	11.8	4	NR	32/61	NR	University	3.4	Both	108	47	ACC + PRP	NR	NR	Single, bilateral
Pal et al.	2012	RCT	20	20	0	0	NR	20/55	NR	University	4.5	Y	25	NR	ABBM	Y	Collagen	NR

(Continues)

TABLE 2 (Continued)

First author	Year	Study design	Planned no. of pat. (all Pat.)	Actual no. of pat at the end of study	Drop-out %	Drop-out number	Mean age	Age range	Gender M/F	Operators (setting)	Mean initial bone height	Implants placed contextually Y/N	No. of implants	No. of treated sinuses	Biomaterial used (type)	Membrane used (Y, N, NR)	Membrane used (type)	MSA/Pt (single–bilateral–NR)
Urban et al.	2012	Case series	198	198	0	0	53	30/80	93/105	University	NR	N	NR	274	ABB	Y	Collagen	Single, Bilateral
Cannizzaro et al.	2013	RCT	20	19	5	1	53.3	30/72	6/14	Private practice	NR	Y	44	19	ABBM + AB	Y	Collagen	Single
Del Fabbro et al.	2013	RCT	30	30	0	0	52.3	37/66	12/18	Dental clinic	4.0	N	NR	NR	DBBM vs. DBBM + P-PRP	Y/N	PRP in test	NR
Garcia-Denche et al.	2013	RCT	104	104	0	0	64.9	39/81	46/59	Private practice	NR	Both	278	135	DBBM	Y/N	Collagen	Single, bilateral
Felice et al.	2014	RCT	60	59	1.7	1	55	30/68	31/29	Private practice	NR	Both	137	59	DBBM	Y	Collagen	Single
Guljè et al.	2014	RCT	20	19	5	1	48	29/72	13/7	Private practice	NR	Y	21	19	AB + DBBM	N	N/A	Single
Bechara et al.	2016	RCT	20	20	0	0	49.2	28/75	9/11	University	NR	Y	45	NR	CPG	Y	Collagen	Single, bilateral
Lee et al.	2016	RCT	16	12	25	4	45.2	NR	13/3	University	1.9	N	NR	20	ABBM or APBM	Y	Collagen	Single, bilateral
Tawil et al.	2016	Case series	102	102	0	0	60.6	43/78	46/56	Private practice	5.01	Both	206	109	ABBM	Y/N	Collagen	Single, bilateral
Yu et al.	2017	RCT	18	17	5.5	1	50.9	34/60	10/8	University	4.35	N	41	17	DBBM + AUTOGENOUS	N	N/A	Single
Yu et al.	2017	RCT	21	19	9.5	2	50.3	NR	10/9	University	2.43	N	52	23	DBBM + AUTOGENOUS	Y	Collagen	Single, bilateral
Kozuma et al.	2017	Prospective	109	109	0	0	58.3	32/76	47/74	University	NR	Both	252	121	β-TCP–HA–ABintra–ABextra–ABBM (mixed in different combinations)	Y	Collagen or PRF	Single, bilateral
Stacchi et al.	2017	RCT	28	26	7.1	2	60.1	39/79	18/10	Private practice	2.0	N	107	52	SNHA or ABBM	Y	Collagen	Bilateral
Taschieri et al.	2017	RCT	25	24	4	1	51	36/68	14/11	University	5.39	N	58	24	DBBM	Y	Collagen	Single
Zhu et al.	2017	Case series	20	20	0	0	46.1	19/78	10/10	University	3.0	Y	46	22	DBBM + AUTOGENOUS	Y	Collagen	Single, Bilateral
Bolle et al.	2018	RCT	20	19	5	1	56.4	36/71	9/11	University, hospital, private practice	NR	Y	41	19	CPG	Y	Collagen	Single
Baldini et al.	2019	RCT	17	17	0	0	55.6	NR	9/8	University	3.03	Y	72	34	ABBM	Y	Collagen	Bilateral
Younes et al.	2019	prospective	22	19	13.6	3	59	38/73	7/15	University	NR	N	50	19	DBBM	Y	Collagen	Single

Abbreviations: β-TCP, beta tricalcium phosphate; AB, autogenous bone; ABBM, anorganic bovine bone mineral; ABBM-C, collagenated block of ABBM; ABextra, extraoral autologous bone;ABintra, intraoral autologous bone; APBM, anorganic porcine bone mineral; ACC, aragonitic calcium carbonate (Coral); BCP, biphasic calcium phosphate; BHA, anorganic bovine-derived hydroxyapatite; BHp, bone hydroxypatite w cell binding peptide; CPG, collagenated porcine graft; FDBA, freeze dried bone allograft; HA, hydroxyapatite; HyA, hyaluronic acid; PRP, platelet-rich plasma; SNHA, sintered nanohydroxyapatite; SRBGs, synthetic bioactive resorbable graft.

[a]In patients with bilateral MSA only one sinus was included in the trial.

[b]Second molar-first molar-second premolar-first premolar regions.

TABLE 3A Pharmacological prophylaxis (corticosteroids group)

First author	Year	Corticosteroids (type)	Corticosteroids (dosage)	Pre, post, or both	Corticosteroids (length in days)	Corticosteroids (route of administration—OS, IM)
Corticosteroids						
Zinner et al.	1996	Hospitalized patients: metilprednisolone, IV 125 mg (one intra-operatory and two doses post + 40–80 on discharge); Nonhospitalized patient: 8 mg dexamethasone before and 0.75 every 12 h (5 tablets total)				
Aguirre-Zorzano et al.	2007	Betamethasone	6 mg	Post	1	IM
de Vicente et al.	2010	Deflazacort	60 mg	Both	2	OS
Manso et al.	2010	Dexamethasone	NR	Post	3	OS
Pieri et al.	2012	Betamethasone	1 mg (4 mg immediately after)	Post	5	OS (IM)
Merli et al.	2013	Betamethasone	4 mg	Pre	1	IV
Esposito et al.	2015	Betamethasone	4 mg	Post	3	IV
Falah et al.	2016	Dexamethasone	6 mg	Pre	1	OS
Alayan and Ivanovsky	2018	Dexamethasone	8 mg	Pre	1	OS
Meloni et al.	2017	Betamethasone	4 mg	Post	2	OS
Farina et al.	2018	Dexamethasone	8 mg	Post	1	IM
Velasco-Ortega et al.	2020	Dexamethasone	4 mg (8 mg immediately after)	Post	5	OS

hematoma. The results was not changed after accounting of clustering, RR = 2.03 (1.03–4.03), 4.14 (1.81–9.51), 3.18 (1.35–7.55), 12.37 (1.39–109.80), and 3.19 (1.35–7.51), respectively.

3.1.6 | Postoperative complication rates

The cumulative rates of events related to the immediate postoperative phase and the results for each type of event in the two groups are described by the forest plots in Figures 2–4 and 2S–8S in supplementary online materials.

The basic characteristics of the studies, the descriptive factors of the MSA procedures, the pharmacological therapies, and the outcomes are illustrated in Tables 2, 3A, 3B, and 4.

In the absence of studies comparing the outcomes of MSA with prescribed corticosteroids versus MSA without corticosteroids, a comparative meta-analysis could not be carried out.

In the 37 studies included, a total of 1599 patients (378 Cort, 1221 No-Cort) were analyzed.

Overall, the complication rates postoperatively were comparable between the two study groups, however slight differences existed in the incidence of active suppuration (1.7% [95% CI 0.7–3.9] Cort vs. 3.2% [2.2–4.5] No-Cort), wound dehiscence (3.9% [1.3–11.2] Cort vs. 2.1% [1.0–4.1] No-Cort) and trismus (2.7% [0.8–8.4] Cort vs. 1.4% [0.8–2.5] No-Cort). Trismus complications were surprisingly unfavorable to the Cort group, perhaps due to the fact that this complication occurred only in a single study.[31] Otherwise, the parameters of swelling (9.3% [2.5–28.8] Cort vs. 10.8% [7.9–14.5] No-Cort) and pain (6.2% [2.7–13.9] Cort vs. 4.9% [3.4–7.1] No-Cort), namely the two for which a corticosteroid effect could have been expected, showed no substantial differences.

The total number of complications could not be calculated or meta-analyzed because different types of complications occurred at varying levels (patient level, sinus level, and implant level). For each complication, it was explained on which level the analysis was conducted. For example, steroid group 5.8% hematoma at patient level and early implant failure 1.5% at implant level. It means 5.8% of the patients developed hematoma and 1.5% of the implants had early failure among steroid group.

4 | DISCUSSION

The scientific literature lacks clinical studies directly comparing the use of corticosteroids and the outcomes of lateral MSA procedures. To the best of authors' knowledge, this is the first systematic review providing data with the use of corticosteroids during MSA procedures to help clinicians to reduce MSA postoperative sequelae.

The scientific literature provides extensive data on lateral MSA procedures, which is a well-documented and predictable procedure. Unfortunately, the effect of corticosteroids use with MSA procedures is scarcely highlighted or described. The majority of studies on MSA mainly focus on quantitative (radiographic) or qualitative (histological) outcomes, to prove effectiveness of biomaterials. Only a few studies accurately report and describe the occurrence and features of postoperative complications. Even less describe the immediate or short-term events post-MSA procedures. Although there are no studies investigating the effects of corticosteroids on MSA procedures, it is common opinion that their use in oral and orthognathic surgery has beneficial effects in reduction of swelling, pain, and trismus. In a randomized split-mouth study, Graziani and colleagues[53] showed how perioperative use dexamethasone via 4 or 10 mg as endo-alveolar powder or 10 mg by submucosal injection was effective in significantly reducing the postoperative sequelae of surgical third molar extractions. Most of the studies that investigated the use of corticosteroids in oral

TABLE 3B Pharmacological prophylaxis (both groups)

First author	Year	Antibiotics treatment (type)	Antibiotics treatment (daily dosage in mg)	Pre, post, or both	Antibiotics treatment (length in days)	Other anti-inflammatory/analgesic medications (Y/N)	Other anti-inflammatory medications (type and dosage)	Other anti-inflammatory medications (length in days)
Corticosteroids								
Zinner et al.	1996	Ampicillin + sulbactam (pre) − amoxicillin + clavulanate (post)	3000 IV (pre) 500 × 3 (post)	Both	10	y	Flurbiprofen (dosage NR)	NR
Aguirre-Zorzano et al.	2007	Amoxycillin + clavulanic acid	500 × 3	Post	7	Y	Piroxicam 40 mg	NR
de Vicente et al.	2010	Amoxicillin	1000 (pre) − 500 × 3 (post)	Both	7	N	N/A	N/A
Manso et al.	2010	Clindamycin (amoxicillin + clavulanate for intolerants)	300 × 3	Both	14	Y	Paracetamol or ibuprofen (dosage NR)	3
Pieri et al.	2012	Amoxicillin + clavulanate (clarithromycin for allergic)	1000 × 2	Both	7	Y	Ibuprofen 600 mg × 3	5
Merli et al.	2013	Ceftriaxone	1000 IV	Pre	1	Y	Tramadol 100 mg and ketorolac 30 mg (IV pre), Ibuprofen 600 mg (per OS post)	3–4 (ibuprofen)
Esposito et al.	2015	Amoxicillin + clavulanate	2200 × 2	Post (at the hospital)	3	Y	Ibuprofen, 600 mg 4/D	7
Falah et al.	2016	Amoxicillin + clavulanate (clindamycin for allergic)	1000 × 2 (300 × 3)	Both	10	N	N/A	N/A
Alayan and Ivanovsky	2018	Amoxicillin (clindamycin for allergic)	500 (300) × 3	Both	7	Y	Paracetamol 500 mg, ibuprofen 200 mg	7
Meloni et al.	2017	Amoxicillin (clindamycin for allergic)	1000 (300) × 2	Both	7	Y	Ketoprofen 80 mg××2/3	As needed
Farina et al.	2018	Yes, type NR	NR	Both	7	Y	Ibuprofen 600 mg	As needed
Velasco-Ortega et al.	2020	Amoxicillin + clavulanate (clindamycin for allergic)	1000 × 2 (300 × 3)	Both	7	Y	Paracetamol 1000 mg × 3	As needed
No corticosteroids								
Van den Bergh et al.	1998	Amoxicillin	500 × 3 (IV before)	Both	7	N	N/A	N/A
Raghoebar et al.	2001	Yes, type NR	NR	Both	7	N	N/A	N/A
Becktor et al.	2008	Phenoxymethylpenicillin	1000 × 2	Post	7	NR	N/A	N/A
Kahnberg et al.	2008	Penicillin V	NR	Post	7	Y	Ibuprofen 400 mg	NR
Zijderveld et al.	2008	NR	NR	NR	NR	NR	NR	NR
Papa et al.	2009	Amoxicillin	1000 × 2	Post	7	N	N/A	N/A

TABLE 3B (Continued)

First author	Year	Antibiotics treatment (type)	Antibiotics treatment (daily dosage in mg)	Pre, post, or both	Antibiotics treatment (length in days)	Other anti-inflammatory/analgesic medications (Y/N)	Other anti-inflammatory medications (type and dosage)	Other anti-inflammatory medications (length in days)
Pal et al.	2012	Amoxicillin + clavulanate and metronidazole	625 and 300 × 3	Pre (amox+clav) and both	5	Y	Aceclofenac 100 mg, paracetamol 500 mg	5
Urban	2012	Amoxicillin	500 × 3 (2 g 1 h before)	Both	7	Y	Diclofenac 50 mg	As needed
Cannizzaro et al.	2013	Amoxicillin	1000 × 3	Both	7	Y	Nimesulide 100 mg ×2/4	As needed
Del Fabbro et al.	2013	Amoxicillin	1000 × 2	Post	6	Y	Ibuprofen 600 mg ×2	As needed
Garcia-Denche et al.	2013	Amoxicillin, clyndamicin	750, 300	Post	7, 10	Y	Ibuprofen, 600 mg	4
Felice et al.	2014	Amoxicillin, clyndamicin	2000 (pre) - 1000 × 3 (post), 600 (pre) - 300 × 2 (post)	Both	7, 7	Y	Ibuprofen, 400 mg 2–4/D	N/A
Guljè et al.	2014	Amoxicillin, clyndamicin	3000, 600	Pre	N/A	N	N/A	N/A
Bechara et al.	2016	Amoxicillin + clavulanate	800 × 3	Both	6	Y	Ibuprofen 600 mg ×2	2
Lee et al.	2016	Amoxicillin (or roxithromycin)	500 mg (150 mg)	Both	7	Y	Ibuprofen 200 mg	7
Tawil et al.	2016	Amoxicillin and clavulanic	1000 × 2	Both	7	Y	Ibuprofen 600 mg	As needed
Yu et al.	2017	Amoxicillin	750 × 3 (2 g 1 h before)	Both	7	Y	Ibuprofen 600 mg	4
Yu et al.	2017	Amoxicillin	750 × 3 (2 g 1 h before)	Both	7	Y	Ibuprofen 600 mg	4
Kozuma et al.	2017	Yes, type NR	NR	Post	NR	Y	NR	NR
Stacchi et al.	2017	Amoxicillin (or clarithromycin for allergic)	1000 × 2 (250 × 3)	Post	6	Y	Ibuprofen 600 mg	As needed
Taschieri et al.	2017	Amoxicillin and clavulanic	1000 × 2 (2 g 1 h before)	Both	7	Y	Yes, type NR	As needed
Zhu et al.	2017	Amoxicillin + metronidazole	500 × 3; 400 × 3	Post	7	N	N/A	N/A
Bolle et al.	2018	Amoxicillin (clindamycin for allergic)	1000 × 2 (300 × 3)	Both	7	Y	Ibuprofen 400 mg or paracetamol 1000 mg ×2–4	As needed
Baldini et al.	2019	Amoxicillin	1000 × 2	Both	5	Y	Ibuprofen 600 mg	As needed
Younes et al.	2019	Amoxicillin	500 × 3	Both	6	Y	Ibuprofen 600 mg, paracetamol 500	As needed

TABLE 4 Number of complications

		Intra-operatory			Postoperatory (1–2 weeks)										
First author	Year	Total	Membrane perforations	Other complications	No. of infected sinuses	Swelling	Active Suppuration	Pain	Bleeding	Wound dehiscence	Trismus	Hematoma	Early implant failure	Other complications	Total complications
Corticosteroids															
Zinner et al.	1996	0	0	0	4	0	0	0	0	0	0	0	3	0	7
Aguirre-Zorzano et al.	2007	1	1	0	0	0	0	0	0	0	0	0	0	0	0
de Vicente et al.	2010	5	5	0	2	NR	NR	NR	NR	NR	NR	NR	NR	NR	2
Manso et al.	2010	0	5	0	1	0	0	0	0	18	0	0	0	0	19
Pieri et al.	2012	6	6	0	0	18	0	4	0	0	0	0	0	0	22
Merli et al.	2013	2	2	0	0	0	0	6[a]	0	0	0	0	0	0	6
Esposito et al.	2015	NR	NR	NR	0	0	0	13	0	2	0	0	0	0	15
Falah et al.	2016	3	3	0	0	0	0	0	0	0	0	0	3	0	3
Alayan and Ivanovsky	2018	8	8	0	0	4	0	NR	1	4	0	6	N/A	1	16
Meloni et al.	2017	1	1	0	0	0	0	0	0	0	0	0	0	3	3
Farina et al.	2018	5	5	0	0	11[b]	0	2[c]	NR	NR	8[d]	11[e]	NR	1	33
Velasco-Ortega et al.	2020	6	6	0	0	14	0	NR	1	0	0	6	N/A	0	21
No corticosteroids															
Van den Bergh et al.	1998	3	3	0	1	0	0	0	0	1	0	0	0	1	3
Raghoebar et al.	2001	47	47	0	5	0	2	NR	0	11	0	1	0	2	21
Becktor et al.	2008	1	NR	1	3	0	0	0	0	0	0	0	0	0	3
Kahnberg et al.	2008	NR	NR	NR	0	0	0	0	0	0	0	0	0	0	12
Zijderveld et al.	2008	13	11	2	1	0	2	0	0	3	0	0	4	3	11
Papa et al.	2009	24	24	0	5	NR	0	NR	NR	13	NR	NR	0	0	18
Pal et al.	2012	0	0	0	0	5	0	6	0	0	0	0	0	0	11
Urban	2012	0	0	0	8	8	7	6	0	1	0	0	0	5	27
Cannizzaro et al.	2013	2	2	0	1	0	0	0	0	0	NR	NR	4	0	6
Del Fabbro et al.	2013	3	3	0	0	0	0	0	0	0	0	7	NR	0	7
Garcia-Denche et al.	2013	NR	NR	NR	0	0	0	3	0	0	0	0	0	0	3
Felice et al.	2014	2	1	1	0	0	0	1	0	0	0	0	0	0	1
Guljè et al.	2014	0	0	0	0	0	0	0	0	0	0	0	0	0	0

TABLE 4 (Continued)

		Intra-operatory			Postoperatory (1–2 weeks)										
First author	Year	Total	Membrane perforations	Other complications	No. of infected sinuses	Swelling	Active Suppuration	Pain	Bleeding	Wound dehiscence	Trismus	Hematoma	Early implant failure	Other complications	Total complications
Bechara et al.	2016	3	0	3	0	15	0	1	0	0	0	0	0	0	16
Lee et al.	2016	1	1	0	0	1	0	NR	0	0	0	0	0	0	1
Tawil et al.	2016	14	14	0	1	0	0	0	0	0	0	0	1	0	2
Yu et al.	2017	1	1	0	1	0	1	0	3	0	0	0	1	6	11
Yu et al.	2017	1	1	0	1	0	0	0	0	0	0	0	0	9	10
Kozuma et al.	2017	18	18	0	8	NR	8	NR	NR	NR	NR	NR	8	NR	16
Stacchi et al.	2017	3	3		0	0	0	0	0	0	0	0	0	0	0
Taschieri et al.	2017	1	1	0	0	5	NR	3[a]	0	0	0	5	0	0	0
Zhu et al.	2017	2	2	0	0	0	0	0	0	0	0	0	0	0	0
Bolle et al.	2018	3	3	0	1	1	0	1	0	0	0	0	0	0	3
Baldini et al.	2019	10	6	4	1	NR	NR	NR	0	1	0	0	0	0	2
Younes et al.	2019	8	3	5	0	7[f]	0	2[f]	4	0	0	10[f]	0	6	10

[a]Obtained from the number of patients still taking analgesics at the end of the week.
[b]Obtained from the percentage of patients that had swelling at day 7.
[c]Since a VAS scale was used, decision was taken to consider the number of patients that still reported some degree of pain at day 7 and at day 14 according to the Supplementary Material of the article available on the journal's website.
[d]Obtained from the number of patients that had from "quite a bit" to "very much bleeding" during the first day of healing.
[e]Obtained from the percentage or number of patients that reported difficult to extremely difficult opening the mouth at day 3.
[f]Obtained from VAS percentages.
[g]Obtained from the percentage or number of patients that had bruising at day 7.

surgery confirmed their effectiveness in reducing edema and pain as confirmed by the systematic review by Dan and colleagues[54] Regarding postoperative pain following wisdom teeth extractions, some studies report more variable and inconsistent results. Skjelbred and Lokken[55] showed that corticosteroids use significantly reduced pain from a few hours to 2 days post-extraction only, compared to no use of corticosteroids. On the other hand, Buyukkurt and colleagues[56] showed how the analgesic efficacy of prednisolone, compared to the control group, was not statistically significant until after the sixth postoperative hour. It must be admitted that "pain" is a very challenging parameter to evaluate due to its subjective nature; individuals have different pain thresholds and definitions. Furthermore, as found in this systematic review and similarly by Dan and colleagues,[54] the variety of methods used by different studies for pain measurement (VASs, consumption of pain medication, and questionnaires) makes a meta-analysis difficult to obtain.

The most unfavorable side effects of corticosteroid use in oral surgery are avascular osteonecrosis, adrenal suppression, impaired healing, and increased risk of infections. Avascular osteonecrosis occurs more often when high doses of corticosteroids are taken for a long duration, which results in an inhibition of micro vascularity in the bone and necrosis.[57] There are no studies reporting avascular osteonecrosis after low dose and short terms use of corticosteroid use in oral surgery procedures.[54] Corticosteroid related adrenal suppression involves a reduced production of cortisol resulting from exposure of the hypothalamic–pituitary–adrenal axis to exogenous glucocorticoids and can have serious consequences including coma and death.[58] However, the dosage and time required to reach these serious consequences are beyond those used in oral surgery. To avoid these side effects, it would be advisable not to administer corticosteroids in patients who are concurrently taking steroid doses for other pathologies, moreover, the most recent evidence-based guidelines advise against this practice.[59,60]

Corticosteroids administration may also inhibit fibroblasts activity and proliferation[61,62] causing delayed wound healing and increased rate of infections. The current review gives data in favor of this hypothesis, reporting the highest number of wound dehiscences in the study with the longest duration of corticosteroid therapy.[40] Infections can be a side effect of corticosteroids as they limit the inflammatory response by decreasing lymphocytes, monocytes, and macrophages migration and activity. However, Dan and colleagues[54] support the use of corticosteroids in oral surgery, reporting a nonsignificant increase in the rate of infections compared to placebo. The authors mention that it is important to consider the combination of corticosteroids with antibiotics, which can lead to superinfections, when bacteria is not covered by the spectrum of action. It is not recommended, according to Dan and colleagues[54] that they be used in combination unless other indications are present. However, while for low or medium risk patients, antibiotics can be avoided or limited to a short preoperative prophylaxis,[63] pre- and postoperative prophylaxes are strongly recommended for guided bone regeneration procedures and especially for bone grafts in the maxillary sinus.[64] Finally, the current review showed that the two studies reporting the longest duration of corticosteroid therapy (5 days) showed the absolute highest rates of postoperative swelling.[20,21] This event was not confirmed by Dan and colleagues.[54]

The limitations of this systematic review are the absence of comparative studies specifically designed to investigate the use of corticosteroids in lateral MSA procedures, the extreme heterogeneity of reported complication outcomes, and the subjectivity of parameters such as pain.

5 | CONCLUSIONS

In general, the event rate of the 1-to-2-week postoperative complications analyzed in this systematic review did not differ between the two groups. In light of this observation, and within the limits of this analysis, we can conclude that the use of corticosteroids in the lateral sinus augmentation procedure needs further investigation in order to determine whether or not they have an impact on the postoperative course of lateral MSA. This can only be confirmed or denied through randomized clinical trials with the main purpose of investigating the use of corticosteroids in the lateral MSA procedure.

AUTHOR CONTRIBUTIONS

Lorenzo Mordini: Drafting article and approval of article. Giuseppe Pio Patianna: Concept/design and data collection. Giovanna Laura Di Domenico: Data collection. Zuhair Natto: Statistics. Nicola Alberto Valente: Drafting article, data collection, data analysis/interpretation, and approval of article.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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