Clinical Oral Investigations (2021) 25:2511–2536
https://doi.org/10.1007/s00784-021-03859-y

REVIEW

Post-operative pain management in dental implant surgery: a systematic review and meta-analysis of randomized clinical trials

Ismael Khouly[1] · Rosalie Salus Braun[2] · Michelle Ordway[3] · Mashal Alrajhi[4] · Sana Fatima[2] · Bhupesh Kiran[4] · Analia Veitz-Keenan[5]

Received: 18 November 2020 / Accepted: 22 February 2021 / Published online: 10 April 2021

Abstract

Purpose To evaluate the clinical efficacy of various analgesic medications in mitigating orofacial pain following dental implant surgery.

Materials and methods A systematic search was conducted to identify randomized controlled clinical trials (RCTs). The primary outcomes examined were post-operative pain (POP) and consumption of rescue analgesics following implant placement; secondary outcomes included adverse effects, post-operative inflammation, infection, swelling, bleeding, patient satisfaction, and quality of life. Random effects meta-analysis was conducted for risk ratios of dichotomous data.

Results Nine RCTs fulfilled the eligibility criteria. Individual studies and meta-analysis of two studies indicated that nonsteroidal anti-inflammatory drugs (NSAIDs) significantly reduced POP and consumption of rescue analgesics after dental implant placement compared to placebo. Transdermal administration of NSAIDs may be superior to the oral route as it was similarly effective for POP control and resulted in fewer side effects. Glucocorticoids administered as primary analgesics or NSAID adjuvants resulted in comparable pain sensation compared to NSAIDs alone. Caffeine-containing analgesics were reported as acceptable and effective for the treatment of POP and swelling when compared to codeine adjuvants. With regard to analgesic dosing schedules, pain modulation may be most critical during the first 72 h following dental implant placement. Risk of bias assessment indicated an overall low risk of bias across the included trials.

Conclusion Within the limitations of this review, POP following implant surgery may be effectively treated with the short-term use of analgesic medications. However, given the heterogeneity in the available RCTs, there is insufficient evidence to recommend an analgesic regimen following dental implant surgery.

Clinical relevance Short-term use of analgesic medications may be sufficient for post-operative pain management in dental implant surgery. Ultimately, the clinician's analgesic prescription should be directed by a patient's medical history, in order to increase the success of pain management in a short period of time and decrease potential adverse effects.

Trial registration CRD42018099324

Keywords Analgesics · Dental implant · Nonsteroidal anti-inflammatory drugs · Pain · Surgery

Introduction

Post-operative pain (POP) management following surgical implant placement is critical for optimal dental care. In light of the opioid epidemic, healthcare providers have been compelled to prescribe non-opioid pharmacologic agents to reduce pain (Center for Disease Control, National Center for Health Statistics, 2017) [1]. A recent overview of systematic reviews,

✉ Ismael Khouly
dr.ismaelkhouly@gmail.com

[1] Department of Oral and Maxillofacial Surgery, New York University College of Dentistry, 421 First Avenue – BCCR 2W, New York, NY 10010, USA

[2] Department of Cariology and Comprehensive Care, New York University College of Dentistry, New York, NY, USA

[3] Department of Periodontics, University of Pennsylvania, School of Dental Medicine, Philadelphia, PA, USA

[4] Department of Periodontology and Implant Dentistry, New York University College of Dentistry, New York, NY, USA

[5] Department of Oral and Maxillofacial Pathology, Radiology & Medicine, New York University College of Dentistry, New York, NY, USA

summarizing the available evidence on the benefits and harms of analgesic agents, concluded that nonsteroidal anti-inflammatory drugs (NSAIDs), with or without acetaminophen, are equally effective or better than opioid medications for post-operative dental pain relief [2].

Post-operative pain in dental implant surgery is the result of a surgical insult to the tissue and the subsequent inflammatory process [3]. Prostaglandins, among other inflammatory factors, sensitize peripheral nerve endings and produce electrophysiological changes that result in the pain sensation [4]. The initial insult causes a firing of fast speed myelinated A-delta fibers that ultimately transmit the pain signal to the central nervous system (CNS) where the pain signal is interpreted; inflammatory pain then results from the activation of slow unmyelinated C-fibers and reaches its peak 48–72 h following the completion of the surgery [3]. Theoretically, if these firing pathways were inhibited, the sensation of pain following implant surgery should be relieved. However, pain modulation is complex as pain signaling pathways are influenced by patient-specific physiological and psychological factors, such as gender, age, predisposition to feeling pain, anxiety levels, and pain expectations [5, 6]. Thus, variable dosing and non-pharmacological techniques may be required for effective control of POP in some cases.

Considering the urgency of the opioid epidemic, the prescription of non-opioid medications has been supported when appropriate. Analgesic medications, such as NSAIDs, are being used to reduce pain following implant surgery. However, the most effective analgesic medication for the management of POP after dental implant placement procedures has not yet been identified. Thus, the aim of the present systematic review of the literature and meta-analysis is to determine if there is a difference in mitigating orofacial pain following dental implant surgery for the administration of analgesic medications versus no medications and, more specifically, for various analgesic regimens with regards to medication compound, dosage, and dosing schedule.

Methods

Standardized criteria and type of study

A detailed protocol was designed according to the guidelines of the Cochrane Handbook [7] as well as the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) [8] criteria in order to appropriately select and critically appraise the clinical studies included in the present review.

Registry protocol

The review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42018099324).

Criteria for considering studies for this review

The focus question for the present systematic review was as follows: For patients undergoing surgical dental implant placement (*Population*), is there a difference using an analgesic medication (*Intervention*) versus comparative pain therapy/placebo (*Comparison*) in the efficacy of mitigating POP (*Outcome*), as reported in randomized controlled trials (RCTs)?

Eligibility criteria

Inclusion criteria

For inclusion, the studies were required to meet the following criteria:

1. Randomized controlled trials (RCTs).
2. Overall healthy human adult patients (≥18 years) undergoing surgical dental implant placement and receiving analgesic treatment for POP management.
3. Presence of a comparative analgesic treatment group or no analgesic/placebo control.
4. Analgesic treatment with the specification of the analgesic compound, dose, and duration.
5. Subjects, $N \geq 10$ in each group.
6. Perception of pain and/or rescue analgesic consumption reported for a minimum of 12 hours (h) following completion of surgery and up to 14 days following the procedure.

Exclusion criteria

The exclusion criteria were as follows:

1. Prospective cohort studies, controlled clinical trials, case reports, retrospective studies, systematic reviews, animal trials, and in vivo and in vitro studies.
2. Studies that were not published as full reports, such as conference abstracts and letters to editors.
3. Incomplete data.
4. Studies that involved any additional therapy that could have affected the outcomes (e.g., simultaneous ridge augmentation, maxillary sinus augmentation procedures, implant placement into the infected site).
5. Studies in children.

Types of interventions

Included studies had at least one treatment arm using an analgesic treatment, and a comparison arm using either a placebo and/or a comparative analgesic treatment.

Types of outcome measures

Primary outcomes

The primary outcomes included the following: patient-reported pain outcomes (including pain relief scale (PRS), pain intensity scale (PIS), visual analog scale (VAS), numeric rate scale (NRS), and verbal rating scale (VRS)) and the need for rescue analgesics (total number of doses, type of analgesic, time to first rescue analgesic, and duration).

Secondary outcomes

Secondary outcomes included the following: adverse effects related to analgesic therapy, post-operative inflammation, infection, swelling, bleeding, and complications (e.g., wound dehiscence), and patient satisfaction and/or quality of life.

Search methods for identification of studies

With the help of a medical and dental librarian (RM), literature searches were performed in the following electronic databases: PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, and Dentistry & Oral Sciences Source (DOSS). Articles published up to November 1, 2020, were included. Primary and secondary subject headings were selected specifically for each database. Concepts and subject headings were combined for each of the database searches (Appendix 1). The search was not limited by any restrictions on language or date of publication.

In addition, a hand search in dental journals, published between January 1990 and November 1, 2020, was performed. The list of journals included is presented in Appendix 2. The reference lists of the identified studies and relevant reviews were also scanned for possible additional studies.

Finally, online databases providing information about ongoing clinical trials were included in the search (clinicaltrials.gov; www.centerwatch.com/clinicaltrials; www.clinicalconnection.com).

Data collection and analysis

Selection of studies

Eligibility assessment was performed through title and abstract analysis and subsequent full-text analysis. Titles and abstracts for studies identified through the electronic database search were scanned independently by three reviewers (M.A., B.M., S.F.) for possible inclusion in the review, according to pre-determined eligibility criteria. After selection, the full-text papers were read in detail, independently by two reviewers (M.A., B.M.), to determine if the articles met all inclusion criteria. Disagreements were solved by discussion and consensus and moderated by a fourth reviewer (I.K.). Reasons for study exclusion were recorded.

Data extraction and management

Data extraction was independently completed by two review authors (M.A., B.M.) using a standardized data extraction form (Appendix 3) that was specifically designed for the present systematic review. The final extracted data was double checked by the same two reviewers (M.A., B.M.) as well as a third reviewer (S.F.); following data collection, data extraction forms from each of the two independent reviewers (M.A., B.M.) were compared by the third reviewer (S.F.) to ensure data extraction accuracy. Disagreements were resolved through discussion and consensus and moderated by a fourth party (I.K.). In case of incomplete data reported in the included studies, the corresponding authors were contacted for clarification.

Assessment of risk of bias in included studies

The Cochrane Handbook was applied to assess the risk of bias and evaluate the methodological quality of all included studies [8].

Risk of bias assessment was independently completed by three reviewers (A.K., I.K., M.M.) by application of the Cochrane Risk of Bias tool within the RevMan 5.3 software. The following seven domains were included in the risk of bias assessment: selection bias (random sequence generation and allocation concealment), performance bias, detection bias, attrition bias, reporting bias, and other bias. Corresponding authors of the included studies were contacted via email for detailed information on study methodology, when key domains were assessed as *unclear* risk of bias by the three reviewers. Any disagreements were resolved by discussion.

Statistical analysis

If studies assessed the same intervention and reported similar outcome measures, a meta-analysis was attempted; in cases of insufficient data for statistical analysis, a narrative synthesis was planned. The meta-analysis was conducted using RevMan statistical software version 5.3 (The Cochrane Collaboration, Manchester, UK). For dichotomous outcomes, treatment effects were expressed as risk ratios together with 95% confidence intervals. For continuous outcomes, such as

visual analog scale (VAS) scores, mean differences, and 95% confidence intervals were calculated using random effects. The variation in treatment effects was assessed by means of Cochran's test for heterogeneity and I^2 statistics (Higgins 2011); heterogeneity was considered statistically significant if the P value was < 0.05.

Results

Results of search

The electronic search yielded a total of 990 results and 787 articles when duplicates were removed. The hand search yielded one additional relevant article. A total of 788 abstracts were screened; 769 articles were excluded following the abstract screening process and nineteen articles were included in the full-text analysis. Ten of the nineteen articles were excluded as they did not meet eligibility criteria [9–18]. Reasons for study exclusion are summarized in e-Table 1. The remaining nine articles were included in the present systematic review. The results for the study selection process are shown in e-Figure 1.

Description of included studies

General characteristics of included studies

A total of nine RCTs [19–27] were included in the systematic review on the basis of the pre-determined eligibility criteria. The nine trials included a total of 560 patients with 829 implants.

Eight of the nine studies examined the efficacy of using NSAIDs to reduce POP and consumption of rescue analgesics following implant surgery [19–21, 23–27]. Additionally, two of these studies attempted to determine the efficacy of corticosteroids as a primary or adjuvant analgesic [19, 27]. One of the nine included studies evaluated the efficacy of using analgesics containing opioid versus caffeine adjuvants for managing POP and swelling [22].

Study characteristics, including study design, treatment groups, study site, and surgical protocol, are shown in Table 1.

Effects of interventions

Table 2 and e-table 2 summarize the primary and secondary outcomes of the included studies, respectively.

I. *Individual study results*

a. NSAIDs only comparison:

Ibuprofen (NSAID) vs. placebo Alissa et al. (2009) reported that rescue analgesic consumption mirrored pain perception and the controls consistently consumed significantly higher numbers of analgesic tablets for pain relief as compared with the group that received post-op ibuprofen (P < 0.001). The placebo patients took 2.5 tablets daily on average compared to 1 tablet for the ibuprofen patients resulting in a total of 533 tablets and 186 tablets, respectively. Two of 31 patients in the ibuprofen group were unable to complete the prescribed course of ibuprofen due to self-reported minor stomach upset and dropped out of the study [25].

Pereira et al. (2020) reported significantly lower VAS scores overall in the pre-op ibuprofen group compared to the placebo group overall (P < 0.001) and at 1 (P = 0.01), 6, 12, and 24 h (P < 0.001) post-op. The overall VAS scores in the ibuprofen group were 0.30 ± 0.57 compared to 1.14 ± 1.07 in the placebo group. The group also reported significantly lower use of rescue medications and longer post-operative time elapsed from the first rescue event in the ibuprofen group compared to placebo (P = 0.002). None of the patients in either of the study groups reported major adverse effects and/or drug side effects.

Lornoxicam (NSAID) vs. placebo Bölükbaşı et al. (2012) reported a reduction in pain intensity at all time points for patients who received quick-release lornoxicam (NSAID) following implant surgery compared to those who received a placebo (P = 0.000) [21]. Patients who were given lornoxicam did not report severe pain at 60 min, 90 min, or 2 h post-op. Conversely, of the patients given a placebo, 12.2%, 9.8%, and 17.1% reported severe pain at 60 min, 90 min, and 2 h post-op, respectively. The number of patients requiring rescue analgesics was significantly greater in the placebo group, while the level of patient satisfaction was significantly higher in the LNX-treated patients (P = 0.007). None of the patients in either of the study groups reported adverse events [21].

Dexketoprofen trometamol (NSAID) vs. placebo Sanchez-Perez et al. (2018) reported that pre-op administration of DKT (NSAID) significantly reduced pain severity immediately post-op (P < 0.023) as compared to placebo; the average pain VAS reported immediately post-op by the DKT group was 3.75 (CI, 2.0–5.41) compared to average pain of 8.52 (CI, 4.74–12.3) reported by the placebo group. However, there was no statistically significant difference between the groups in pain scores reported during the late follow-up period, 3–7 days post-op. The DKT group also experienced a lower degree of inflammation and swelling as compared to the placebo group. The authors reported the absence of adverse events, post-operative infections, and wound dehiscence in both study groups [20].

Table 1 Detailed data of included studies

Author and year	Design/study period	Study period	Setting, location, funding, and COI	Study groups	*N* patients/*n* implants	Sex/mean age (years), SD, range	*N* implants per patient/implant location
NSAID							
Alissa et al. (2009)	Double-blind, parallel, RCT 2000–2007	7 days	University, UK Funding: NR COI: none	2 groups: NSAID post-op vs. placebo post-op	58 (61 onset)/132	37/58 NR	1–4 implants per pt Mandible and maxilla
				Ibuprofen 600 mg (NSAID) 4 times/d for 7 d post-op	29 (31 onset)/67	20/9 48.3 (17–87)	1 implant: 6 pts 2 implants: 15 pts 3 implants: 4 pts 4 implants: 2 pts
				Placebo tablets (lactose 350 mg) 4 times/d for 7 d post-op	29 (30 onset)/65	17/12 39.5 (18–76)	1 implant: 11 pts 2 implants: 10 pts 3 implants: 1 pts 4 implants: 7 pts
Bölükbaşı et al. 2012)	Triple-blind, parallel, RCT 2007-2011	12 h	University, Turkey Funding: Private COI: none	2 groups: NSAID pre-op vs. Placebo pre-op	83/142	47/36 NR	NR
				Lornoxicam 8 mg (NSAID) 1 h pre-op	42/73	21/21 46.7 ± 12.7	
				Placebo 1 h pre-op	41/69	26/15 45.0 ± 12.0	
Sanchez-Perez et al. (2018)	Double-blind, parallel, RCT 2013–2015	7 days	University, Spain Funding: None COI: none	2 groups: NSAID pre-op vs. placebo pre-op *Ibuprofen (NSAID) post-op for both groups	83/83	54/29 52.7 (50–55.4)	10 maxillary anterior, 6 mandibular anterior, 26 maxillary premolar, 5 mandibular premolar, 13 maxillary molar, and 23 mandibular molar
				Dexketoprofen trometamol (DKT) 25 mg (NSAID) 15 min pre-op + ibuprofen 600 mg (NSAID) 2 h post-op and 3 times per day for 2 days post-op	41/41	31/10 51.8 (48.0–55.6)	
				Placebo vitamin C 500 mg 15 min pre-op + ibuprofen 600 mg (NSAID) 2 h post-op and 3 times per day for 2 days post-op	42/42	23/19 53.6 (49.5–57.7)	
Bhutani et al. (2019)	Triple-blind, parallel, RCT	5 days	University, India Funding: NR COI: none	2 groups: NSAID pre-op and post-op vs. placebo pre-op and NSAID post-op	40/40	Gender: NR Age: 16–40	Maxillary posterior
				Piroxicam 40 mg (sublingual) 1 h per-op + Piroxicam 20 mg 2/d days 1 and 2 and 1/d day 3	20/20		
				Placebo 1 h per-op + Piroxicam 20 mg 2/d days 1 and 2 and 1/d day 3	20/20		
Rajeswari et al. 2017)	Double-blind, split-mouth, RCT Study period: NR	3 days	University, India Funding: NR COI: NR	2 groups: Oral NSAID vs transdermal NSAID	20/40	9/11 45 (30–65)	Bilateral mandibular first molars
				Oral diclofenac sodium 50 mg, 2/d for 3 d	20/40		
				Transdermal (patch) diclofenac diethylamine 100 mg for 3 d	20/40		
Pereira et al. (2020)	Triple-blind, parallel, RCT 2018–2019	3 days	Private office, Brazil Funding: NR COI: none	2 groups: NSAID pre-op vs. placebo pre-op	54/54	Gender: NR 37–74	1 implant/patient Maxillary/mandibular-anterior/posterior
				Ibuprofen 600 mg (NSAID) 1 h pre-op	27/27	61.07 ± 8.01	
				Placebo 1 h pre-op	27/27	55.63 ± 9.36	
NSAID and corticosteroid							
Bahammam et al. (2017)	Double-blind, parallel, RCT 2014–2016	7 days	University, Kingdom of Saudi Arabia Funding: Academic COI: none	3 groups: NSAID peri-op vs. corticosteroid peri-op vs. placebo peri-op	117/117	46/71 38.4 ± 10.5	NR
				Ibuprofen 600 mg (NSAID) 1 h pre-op + 600 mg 6 h after 1st dosage	39/39	11/28 33.0 (32.0–37.0	

Table 1 (continued)

Author and year	Design/study period	Study period	Setting, location, funding, and COI	Study groups	*N* patients/*n* implants	Sex/mean age (years), SD, range	*N* implants per patient/implant location
				Dexamethasone 4 mg (corticosteroid) 1 h pre-op + 4 mg 6 h after 1st dosage	43/43	20/23 35.0 (33.0–44.0)	
				Placebo 1 h pre-op + 6 h after the first dosage	35/ 35	15/20 41.0 (34.0–50.0	
Meta et al. (2017)	Double-blind, parallel, RCT Study period: NR	14 days	University, El Salvador/Argentine-an Funding: Academic COI: none	2 groups: NSAID vs. NSAID + corticosteroid Ketorolac tromethamine 10 mg (NSAID) 1 h pre-op and twice a d for 2 d post-op Ketorolac tromethamine 10 mg (NSAID) 1 h pre-op and twice a d for 2 days post-op + betamethasone 2 mL (corticosteroid) within 2 h pre-op	29/145 14/70 15/75	19/11 (43–81) NR 66.36 (± 10.7 NR 64.47 (± 8.1)	5 implants/patient Mandibular interforaminal region
Narcotics							
Samieirad et al. (2017)	Triple-blind, parallel, RCT Study period: NR	7 days	University, Iran Funding: none COI: none	2 groups: acetaminophen + opioid vs. acetaminophen + caffeine Acetaminophen 300 mg + codeine 20 mg (opioid) 1 h per-op and 4 times per day for 2 d Acetaminophen 300 mg + caffeine 20mg 1 h per-op and 4 times per d for 2 d	76/76 38/38 38/38	38/38 41.06 ± 5 19/19 41.5 ± 5.3 19/19 40.50 ± 4.80	Mandibular posterior

Author and year	Duration of surgery (min)	Type and amount of anesthesia	Additional measures (microbial control, use of antibiotics, etc.)	Who carried out procedures	One/two-stage approach & flap design	Implant brand
NSAID						
Alissa et al. (2009)	NR	NR	AB: No prophylactic antibiotic given; MW: Chlorhexidine gluconate 0.12% for 2 min prior to surgery	2 oral surgeons	Two-stage Full-thickness flap	Astra dental implants (Astra Tech, Mölndal, Sweden)
Bölükbaşı et al. 2012)	< 60 min = 71 pts 60–120 min = 12 pts	47/36 NR	NR	4 experienced surgeons	Staging: NR Full-thickness flap	NR
	< 60 min = 34pt 60–120 min = 8 pts	21/21 46.7 ± 12.7				
	< 60 min = 37 pts 60–120 min = 4 pts	26/15 45.0 ± 12.0				
Sanchez-Perez et al. (2018)	40–60	54/29 52.7 (50–55.4) 31/10 51.8 (48.0–55.6) 23/19 53.6 (49.5–57.7)	AB: 500 mg of amoxicillin or 300 mg of clindamycin 3 times/d for 7 d	1 surgeon	Staging: NR Full-thickness flap	TiCare Inhex, Mozo Grau, Valladolid, Spain)
Bhutani et al. (2019)	NR	NR	AB: amoxicillin 500 mg 3 times/d for 5 d	Single operator	Staging: NR Flap design: NR	NR
Rajeswari et al. 2017)	NR	NR	AB: None MW: NR	Single implantologist	Staging: NR Full-thickness flap	NR

Table 1 (continued)

Author and year	Duration of surgery (min)	Type and amount of anesthesia	Additional measures (microbial control, use of antibiotics, etc.)	Who carried out procedures	One/two-stage approach & flap design	Implant brand
Pereira et al. (2020)	*P* = 0.328	Prilocaine hydrochloride (30 mg/ml) 2 to 4 tubes at most	NR	Single operator	Staging: NR Flap design: NR	Titamax, external hexagon, Neodent, Paraná, Brazil
	49 ± 5.1	NR				
	51 ± 4.2	NR				
NSAID and corticosteroid						
Bahammam et al. (2017)	*P* value < 0.001	46/71	AB: 500 mg amoxicillin 3 times/d for 5 d; or 300 mg clindamycin 4 times/d for 5 d	6 postdoctoral periodontal residents specializing in periodontology	Staging: NR Flap design: NR	NR
	40.0 (25.0–45.0	38.4 ± 10.5 11/28				
		33.0 (32.0–37.0				
	45.0 (35.0–45.0	20/23				
		35.0 (33.0–44.0)				
	30.0 (25.0–30.0	15/20				
		41.0 (34.0–50.0				
Meta et al. (2017)	NR	19/11 (43–81)	AB: Amoxicillin 500 mg 3 times/d for 7 d starting 24 h before surgery MW: Chlorhexidine gluconate 0.12% 2 times/d for 14 d	2 periodontists	Two staged Full-thickness flap	MEI; B&W, Buenos Aires, Argentina
		NR				
		66.36 (± 10.7				
		NR				
		64.47 (± 8.1)				
Narcotics						
Samieirad et al. (2017)	No SS (*p* = 0.76)	38/38	AB: Amoxicillin 500 mg 3 times/d for 4 d starting 30 min before surgery	Carried out or supervised by a surgeon	Staging: NR Flap design: NR	Implantinum implant, Dentium, South Korea
		41.06 ± 5				
	14.2 ± 0.69	19/19				
		41.5 ± 5.3				
	14.27 ± 0.71	19/19				
		40.50 ± 4.80				

AB, antibiotics; *COI*, conflict of interest; *d*, day; *MW*, mouthwash; *NR*, Not reported; *NSAID*, nonsteroidal anti-inflammatory drugs; *PRN*, pro re nata (as needed); *RCT*: randomized clinical trial

Table 2 Detailed primary outcome data of included studies

Author and year	Study groups	Post-operative pain				Within-group difference (SS or not SS) (p value)	Intergroup difference (SS or not SS) (p value)	Rescue analgesic consumption	Author's main conclusions
		Mean and SD							
NSAID									
Alissa et al. (2009)	2 groups: NSAID post-op vs. Placebo post-op	NR				NR	NR	Tablets of codeine phosphate 30 mg and acetaminophen 500 mg up to 7 d Less RAC in ibuprofen group ($P < 0.001$)	RAC was significantly lower in the ibuprofen group compared to placebo and sufficiently effective for pain management
	Ibuprofen 600 mg (NSAID) 4 times/d for 7 d post-op							Average per pt: 1 tablet/d Overall: 186 tablets	
	Placebo tablets (lactose 350mg) 4 times/d for 7 d post-op							Average per pt: 2.5 tablets/d Overall: 533 tablets	
Bölükbaşı et al. (2012)	2 groups: NSAID vs. placebo within 120 min post-op PRN	- Pain intensity scale (PIS) (0 = none, 1 = mild, 2 = moderate, 3 = severe) at baseline (pre-dosing), 15 min, 30 min, 60 min, 90 min, 2 h, 4 h, and 12 h post-dosing. - Pain relief scale (PRS) (0 = none, 1 = a little, 2 = some, 3 = a lot, 4 = complete) at the same time points except the baseline (pre-dosing).				NR	Patient satisfaction higher in the lornoxicam group ($P = 0.007$) PIS: 15 min: $P = 0.387$ not SS 30 min: $P = 0.002$ SS 60 min: $P = 0.000$ SS 90 min: $P = 0.000$ SS 2 h $P = 0.000$ SS 4 h: $P = 0.002$ SS 12h: $P = 0387$ not SS PRS: 15 min: $P = 0.002$ SS 30 min: $P = 0.000$ SS 60 min: $P = 0.000$ SS 90 min: $P = 0.000$ SS 2 h: $P = 0.011$ SS 4 h: $P = 0.205$ not SS 12 h: $P = 0.009$ SS	Up to 3 × 500 mg of acetaminophen in total $P = 0.000$ Odds ratio, 0.069; 95% confidence interval, 2.07–9.22.	Post-operative pain was significantly lower in the lornoxicam-treated group compared to the placebo group. Patients in the lornoxicam group reported significantly higher pain relief scores than the placebo group. None of the lornoxicam-treated patients experienced a low satisfaction level (scores 6 and 7), while 6 (14.7%) patients in the placebo-treated
	Lornoxicam 8 mg (NSAID) post-op PRN	PIS: - 15 min 0 = 4 (9.5%) 1 = 22 (52.4%) 2 = 11 (26%) 3 = 5 (11.9%)	- 2h 0 = 29 (69%) 1 = 10 (22.8%) 2 = 3 (7.1%) 3= 0 (0%) - 4 h	PRS: - 15 min 0 = 10 (23.8%) 1 = 13 (31.0%) 2 = 8 (19.0%) 3 = 7 (16.7%)	- 2h 0 = 8 (19.0%) 1 = 6 (14.3%) 2 = 4 (9.5%) 3 = 6 (14.3%) 4 = 18 (42.9%)			LNX: 6 pts (17.1%) = 0.167 ± 0.43	

Table 2 (continued)

Author and year	Study groups	Post-operative pain				Within-group difference (SS or not SS) (p value)	Intergroup difference (SS or not SS) (p value)	Rescue analgesic consumption	Author's main conclusions
		Mean and SD							
		- 30 min 0 = 13 (31%) 1 = 24 (57.1%) 2 = 4 (9.5%) 3 = 1 (2.4%) - 60 min 0 = 24 (57.1%) 1 = 15 (35.7%) 2 = 3 (7.1%) 3 = 0 (0%) - 90 min 0 = 28 (66.7%) 1 = 13 (31%) 2 = 1 (2.4%) 3 = 0 (0%)	0 = 27 (64.3%) 1 = 9 (21.4%) 2 = 5 (11.9%) 3 = 1 (2.4%) - 12h 0 = 18 (42.9%) 1 = 10 (23.8%) 2 = 8 (19%) 3 = 6 (14.3%)	4 = 4 (9.5%) − 30 min 0 = 8 (19.0%) 1 = 11 (26.2%) 2 = 7 (16.7%) 3 = 5 (11.9%) 4 = 11 (26.2%) − 60 min 0 = 5 (11.9%) 1 = 10 (23.8%) 2 = 3 (7.1%) 3 = 11 (26.2%) 4 = 13 (31%) − 90 min 0 = 7 (16.7%) 1 = 7 (16.7%) 2 = 3 (7.1%) 3 = 7 (16.7%) 4 = 18 (42.9%)	- 4h 0 = 8 (19.0%) 1 = 6 (14.3%) 2 = 5 (11.9%) 3 = 3 (7.1%) 4 = 20 (47.6%) - 12h 0 = 7 (16.7%) 1 = 4 (9.5%) 2 = 8 (19.0%) 3 = 5 (11.9%) 4 = 18 (42.9%)				group reported low satisfaction.
	Placebo post-op PRN	PIS: - 15 min 0 = 1 (2.4%) 1 = 21 (51.2%) 2 = 15 (36.6%) 3 = 4 (9.8%) - 30 min 0 = 5 (12.2%) 1 = 19 (46.3%) 2 = 13 (31.7%)) 3 = 4 (9.8%) - 60 min 0 = 7 (17.1%) 1 = 16 (39%) 2 = 13 (31.7%) 3 = 5 (12.2%) - 90 min 0 = 9 (22%) 1 = 15 (36.6%) 2 = 13 (31.7%) 3 = 4 (9.8%)	- 2h 0 = 9 (22%) 1 = 15 (36.6%) 2 = 10 (24.4%) 3 = 7 (17.1%) - 4h 0 = 13 (31.7%) 1 = 13 (31.7%) 2 = 11(26.4%) 3 = 4 (9.8%) - 12h 0 = 11 (26.8%) 1 = 15 (36.6%) 2 = 11 (26.8%) 3 = 4 (9.8%)	PRS: - 15 min 0 = 20 (48.8%) 1 = 14 (34.1%) 2 = 4 (9.8%) 3 = 3 (7.3%) 4 = 0 (0%) - 30 min 0 = 19 (46.3%) 1 = 13 (31.7%) 2 = 8 (19.5%) 3 = 1 (2.4%) 4 = 0 (0%) - 60 min 0 = 15 (36.6%) 1 = 11 (26.8%) 2 = 9 (22.0%) 3 = 3 (7.3%) 4 = 3 (7.3%)	- 90 min 0 = 14 (34.1%) 1 = 12 (29.3%) 2 = 9 (22%) 3 = 2 (4.9%) 4 = 4 (9.8%) - 2 h 0 = 12 (29.3%) 1 = 8 (19.5%) 2 = 12 (29.3%) 3 = 3 (7.3%) 4 = 6 (14.6%) - 4 h 0 = 10 (24.4%) 1 = 12 (29.3%) 2 = 6 (14.6%) 3 = 8 (19.5%) 4 = 5 (12.2%) - 12 h 0 = 12 (29.3%) 1 = 9 (22.0%) 2 = 8 (19.5%) 3 = 5 (12.2%) 4 = 17 (17.1%)			Placebo: 29 pts (82.9%) = 1.024 ± 0.79	

Table 2 (continued)

Author and year	Study groups	Post-operative pain			Within-group difference (SS or not SS) (p value)	Intergroup difference (SS or not SS) (p value)		Rescue analgesic consumption	Author's main conclusions
		Mean and SD							
Rajeswari et al. (2017)	2 groups: Oral NSAID vs. transdermal NSAID	Pain by NRS, VRS, and PRS				NRS: 2 H: No SS (p = 0.400) 4 H: No SS (p = 1.000) 8 H: No SS (p = 0.553) 12 H: No SS (p = 1.000) 24 H: No SS (p = 1.000) 48 H: No SS (p = 1.000) 3 D: No SS (p = 1.000)	PRS: 2 H: No SS (p = 1.000) 4 H: No SS (p = 0.681) 8 H: No SS (p = 0.553) 12 H: No SS (p = 0.553) 24 H: No SS (p = 1.000) 48 H: No SS (p = 1.000) 3 D: No SS (p = 1.000)	Acetaminophen 500 mg up to 3 days	Efficacy of oral and transdermal diclofenac was similar.
	Oral diclofenac sodium 50 mg, 2/d for 3 d	NRS 2 H: 0.50 (± 0.61) 4 H: 0.35 (± 0.49 8 H: 0.05 (± 0.22) 12H: 0.00 (± 0.00) 24 H: 0.00 (± 0.00) 48 H: 0.00 (± 0.00) 3 D: 0.00 (± 0.00)	VRS 2 H: 0.55 (± 0.69) 4 H: 0.10 (± 0.31) 8 H: 0.05 (± 0.22) 12 H: 0.00 (± 0.00) 24 H: 0.00 (± 0.00) 48 H: 0.00 (± 0.00) 3 D: 0.00 (± 0.00)	PRS 2 H: 0.60 (± 0.68) 4 H: 0.15 (± 0.37) 8 H: 0.10 (± 0.31) 12 H: 0.00 (± 0.00) 24 H: 0.00 (± 0.00) 48 H: 0.00 (± 0.00) 3 D: 0.00 (± 0.00)				NR	Less adverse events found on transdermal diclofenac compared to oral.
	Transdermal (patch) diclofenac diethylamine 100 mg for 3 d	NRS 2 H: 0.70 (± 0.73 4 H: 0.35 (± 0.49 8 H: 0.10 (± 0.31) 12 H: 0.00 (± 0.00) 24 H: 0.00 (± 0.00) 48 H: 0.05 (± 0.22) 3 D: 0.00 (± 0.00)	VRS 2 H: 0.70 (± 0.73) 4 H: 0.15 (± 0.37) 8 H: 0.00 (± 0.00) 12 H: 0.00 (± 0.00) 24 H: 0.00 (± 0.00) 48 H: 0.00 (± 0.00) 3 D: 0.00 (± 0.00)	PRS 2 H: 0.60 (± 0.68) 4 H: 0.20 (± 0.41) 8 H: 0.05 (± 0.22) 12 H: 0.00 (± 0.00) 24 H: 0.00 (± 0.00) 48 H: 0.00 (± 0.00) 3 D: 0.00 (± 0.00)		VRS: 2 H: No SS (p = 0.502) 4 H: No SS (p = 0.637) 8 H: No SS (p = 0.317) 12 H: No SS (p = 1.000) 24 H: No SS (p = 1.000) 48 H: No SS (p = 1.000) 3 D: No SS (p = 1.000)		0/20 patients	
Sanchez-Perez et al. (2018)	2 groups: NSAID pre-op vs. placebo pre-op + NSAID post-op for both groups Dexketoprofen trometamol (DKT) 25 mg (NSAID)	Pain intensity (VAS) (0–100) VAS Before anesthesia: 2.03 (± 2.92) After anesthesia: 4.45 (± 6.17) Immediately post-operatively: 3.76 (± 5.32) 2 H: 12.39 (± 21.16)			NR	- Time (F(d.f.); P value (m^2)) F(10.800) = 9.273; p < 0.001 (0.104) - Group × time (F(d.f.); P value (m^2)) F(10.800) = 2.186; P = 0.003 (0.092) VAS Before anesthesia: No SS After anesthesia: No SS Immediately post-operatively: SS (P < 0.023) 2 H: No SS 8 H: No SS 12 H: No SS 24 H: No SS 36 H: No SS		NR	The prescription of ibuprofen 600 mg as a post-operative analgesic certainly masked the effect of DKT on pain perception. Ibuprofen was taken 2 h after the surgery but does not explain the differences in the immediate

Table 2 (continued)

Author and year	Study groups	Post-operative pain			Rescue analgesic consumption	Author's main conclusions
		Mean and SD	Within-group difference (SS or not SS) (p value)	Intergroup difference (SS or not SS) (p value)		
	15 min pre-op + ibuprofen 600 mg (NSAID) 2 h post-op and 3 times per d for 2 d post-op	8 H: 11.14 (± 15.26) 12 H: 11.76 (± 16.01) 24 H: 7.86 (± 13.29) 36 H: 8.69 (± 14.64) 48 H: 7.76 (± 14.15) 3 D: 7.61 (± 13.48) 7 D: 4.83 (± 12.27)		48 H: No SS 3 D: No SS 7 D: No SS		post-operative period. The use of 25 mg DKT administered 15 min before implant placement had statistically significant effects on immediate post-operative pain compared to placebo.
	Placebo vitamin C 500 mg 15 min pre-op + ibuprofen 600 mg (NSAID) 2 h post-op and 3 times per d for 2 d post-op	VAS Before anesthesia: 3.65 (± 8.95) After anesthesia: 6.08 (± 10.38) Immediately post-operatively: 9.52 (± 12.14) 2 H: 15.44 (± 17.80) 8 H: 9.95 (± 13.83) 12 H: 7.08 (± 10.76) 24 H: 6.56 (± 11.60) 36 H: 7.05 (± 12.53) 48 H: 7.24 (± 13.27) 3 D: 6.89 (± 12.16) 7 D: 4.77 (± 6.74)				
Bhutani et al. (2019)	2 groups: NSAID peri-op vs. placebo pre-op and NSAID post-op	Pain (VAS) (0–10)	Comparison between consecutive two follow-ups (Wilcoxon-signed-rank test)	VAS (0–10) 1 H: No SS ($p = 0.0767$ 6 H: SS ($p < 0.00001$) 1 D: SS ($p = 0.0117$) 3 D: SS ($p = 0.0434$) 5 D: SS ($p = 0.0168$)	NR	The use of piroxicam 40 mg (sublingual) pre-operatively was more effective for pain control than placebo
	Piroxicam 40 mg (sublingual) 1 h per-op + piroxicam 20 mg 2/d days 1 and 2 and 1/d day 3	1 H:0.4 ± 0.6633 6 H: 0.95 ± 0.2179 1 D: 2.7525 ± 0.8437 3 D: 1.325 ± 0.6759 5 D: 0.8 ± 0.5099	1 H–6 H: SS ($Z = -2.4990$; $p = 0.0124$) 6 H–1 D: SS ($Z = -3.7236$; $p = 0.0002$) 1 D–3 D: SS ($Z = 3.4557$; $p = .0005$) 3 D–5 D: SS ($Z = -2.2749$; $p = 0.0232$)			
	Placebo 1 h per-op + piroxicam 20 mg 2/d days 1 and 2 and 1/d day 3	1 H: 0.8 ± 0.6782 6 H: 4.25 ± 0.7665 1 D: 3.4 ± 0.5612 3 D: 1.925 ± 0.8258 5 D: 1.275 ± 0.5356	1 H–6 H: SS ($Z = -3.9199$; $p < 0.0001$) 6 H–1 D: SS ($Z = -3.1284$; $p = 0.0017$) 1 D–3 D: SS ($Z = -3.6620$; $p = 0.0003$)			

Table 2 (continued)

Author and year	Study groups	Post-operative pain			Rescue analgesic consumption	Author's main conclusions
		Mean and SD	Within-group difference (SS or not SS) (p value)	Intergroup difference (SS or not SS) (p value)		
			3 D–5 D: SS ($Z = -2.2752$; $p = 0.0226$)			
Pereira et al. (2020)	2 groups: NSAID pre-op vs. placebo pre-op	Pain intensity (VAS) (0–10)	NR	Comparison groups SS ($p < 0.001$) Comparison times SS ($p < 0.001$) Group vs time SS ($p < 0.001$) Global SS ($p < 0.001$) 1 H: SS ($p = 0.011$) 6 H: SS ($p < 0.001$) 12 H: SS ($p < 0.001$) 24 H: SS ($p < 0.001$) 48 H: No SS ($p = 0.05$) 72 H: No ($p = 0.735$)	Acetaminophen 750mg Intergroup comparison SS (p=0.002) Mean: 0.81 (± 1.27)	Ibuprofen group with significant effect in reducing pain and RAC
	Ibuprofen 600 mg (NSAID) 1 h pre-op	VAS Global: 0.30 (± 0.57) 1 H: 0.15 (± 0.36) 6 H: 0.41 (± 057) 12 H: 0.44 (± 0.57) 24 H: 0.44 (± 0.69) 48 H: 0.19 (± 0.80) 72 H: 0.16 (± 0.47)				
	Placebo 1 h pre-op	VAS Global: 1.14 (± 1.07) 1 H: 0.74 (± 1.05) 6 H: 1.56 (± 1.36) 12 H: 2.22 (± 1.34) 24 H: 1.56 (± 1.12) 48 H: 0.48 (± 0.84) 72 H: 0.26 (± 0.71)			Mean: 1.59 (± 1.11)	
NSAID and corticosteroid						
Bahammam et al. (2017)	3 groups: NSAID peri-op vs. corticosteroid peri-op vs. placebo peri-op	Pain assessed by VAS and NRS-101 VAS (0–10) 101-point rate numeric scale (NRS-101), ranging from 0 to 100 Discomfort assessed by a four-point verbal rating scale (VRS-4): (1) no discomfort; (2) some discomfort; (3) considerable discomfort; or (4) sever discomfort	NR	Intergroup difference between the ibuprofen and dexamethasone	Rescue (1000 mg acetaminophen) - All pts in the placebo group required RAC. - There was no significant difference in the number of RAC taken by pts in the ibuprofen and dexamethasone groups, and numbers taken by both groups were lower than numbers taken by the placebo group.	Patients in the ibuprofen and dexamethasone groups reported less pain in the morning compared to the placebo group on days 1 to 4 via VAS ($P < 0.01$), but on the afternoon of day 3, there were no significant differences. There were no statistically significant differences between ibuprofen and

Table 2 (continued)

Author and year	Study groups	Post-operative pain					Rescue analgesic consumption	Author's main conclusions
		Mean and SD	Within-group difference (SS or not SS) (p value)	Intergroup difference (SS or not SS) (p value)				
				VAS	NRS-4	VSR		dexamethasone at any time point. Dexamethasone was similar to placebo at the 4-h time point on day 1. The placebo group had the highest median discomfort scores at all time points investigated, and these scores were significantly higher than those of test groups ($P < 0.05$). Ibuprofen before and after surgery was as effective as dexamethasone for preventing and controlling post-operative pain after implant placement surgery.
				D1H1 $P < 0.001$ D1H2 $P < 0.001$ D1H3 $P < 0.001$ D1H4 $P < 0.001$ D1H5 $P < 0.001$ D1H6 $P < 0.001$ D1H7 $P < 0.001$ D1H8 $P < 0.001$ D2 morning $P < 0.001$ D2 noon $P < 0.001$ D2 afternoon $P < 0.001$ D3 morning $P < 0.001$ D3 noon P < 0.001 D3 afternoon $P < 0.001$ D4 morning $P < 0.001$ D4 noon N/A D4 afternoon N/A D7 morning N/A D7 noon N/A D7 afternoon N/A	D1H1 $P < 0.001$ D1H2 $P < 0.001$ D1H3 $P < 0.001$ D1H4 P 0.02 D1H5 $P < 0.001$ D1H6 $P < 0.001$ D1H7 $P < 0.001$ D1H8 $P < 0.001$ D2 morning $P < 0.001$ D2 noon $P < 0.001$ D2 afternoon $P < 0.001$ D3 morning $P < 0.001$ D3 noon $P < 0.001$ D3 afternoon P 0.16 D4 morning $P < 0.001$ D4 noon N/A D4 afternoon P 0.44 D7 morning N/A D7 noon N/A D7 afternoon N/A	D1H1 $P < 0.001$ D1H2 $P < 0.001$ D1H3 $P < 0.001$ D1H4 $P < 0.001$ D1H5 P 0.67 D1H6 $P < 0.001$ D1H7 $P < 0.001$ D1H8 $P < 0.001$ D2 morning $P < 0.001$ D2 noon $P < 0.001$ D2 afternoon $P < 0.001$ D3 morning $P < 0.001$ D3 noon N/A D3 afternoon N/A D4 morning N/A D4 noon N/A D4 afternoon P 0.44 D7 morning N/A D7 noon N/A D7 afternoon N/A		

Table 2 (continued)

Author and year	Study groups	Post-operative pain					Rescue analgesic consumption	Author's main conclusions
		Mean and SD			Within-group difference (SS or not SS) (p value)	Intergroup difference (SS or not SS) (p value)		
	Ibuprofen 600 mg (NSAID) 1 h pre-op + 600 mg 6 h after 1st dosage	Median VAS D1H1: 4 (2.06 to 5.49) D1H2: 5 (2.82 to 6.92) D1H3: 4 (3.98 to 7.67) D1H4: 4 (3.93 to 7.50) D1H5: 6 (4.74 to 9.19) D1H6: 3 (3.99 to 7.55) D1H7: 3 (1.77 to 5.18) D1H8: 2 (1.08 to 4.40) D2 morning 7: (4.03 to 8.28) D2 noon: 3.3 (2.59 to 4.27) D2 afternoon: 3.5 (2.22 to 3.49) D3 morning: 3 (0.80 to 2.14) D3 noon: 0 (0.31 to 0.96) D3 afternoon: 0 (0.33 to 1.03) D4 morning: 0 (0 to 0) D4 noon: 0 (0 to 0) D4 afternoon: 0 (0 to 0) D7 morning: 0 (0 to 0) D7 noon 0 (0 to 0) D7 afternoon: 0 (0 to 0)	Median NRS-101 D1H1: 5 (2.41 to 6.00) D1H2: 5 (3.42 to 7.45) D1H3: 5 (4.62 to 8.15) D1H4: 7 (5.62 to 9.10) D1H5: 8 (6.74 to 10.55) D1H6: 5 (4.20 to 7.80) D1H7: 5 (2.20 to 5.60) D1H8: 3 (1.76 to 5.06) D2 morning: 6 (4.45 to 8.53) D2 noon: 5 (3.65 to 5.68) D2 afternoon: 5 (2.65 to 4.38) D3 morning: 0 (1.15 to 2.80) D3 noon: 0 (0.69 to 2.08) D3 afternoon: 0 (0.65 to 2.02) D4 morning: 0 (0 to 0) D4 noon: 0 (0 to 0) D4 afternoon: 0 (− 0.03 to 0.08) D7 morning: 0 (0 to 0) D7 noon: 0 (0 to 0) D7 afternoon: 0 (0 to 0)	Median VRS-4 D1H1: 1 (1 to 2) D1H2: 1 (1 to 2) D1H3: 1 (1 to 2) D1H4: 1 (1 to 2) D1H5: 1 (1 to 2) D1H6: 1 (1 to 2) D1H7: 1 (1 to 1) D1H8: 1 (1 to 1) D2 morning: 1 (1 to 3) D2 noon: 1 (1 to 2) D2 afternoon: 1 (1 to 2) D3 morning: 1 (1 to 1) D3 noon: 1 (1 to 1) D3 afternoon: 1 (1 to 1) D4 morning: 1 (1 to 1) D4 noon: 1 (1 to 1) D4 afternoon: 1 (0 to 1) D7 morning 1 (1 to 1) D7 noon: 1 (1 to 1) D7 afternoon: 1 (1 to 1)	NR		0/39 implants 0/39 pts	

Table 2 (continued)

Author and year	Study groups	Post-operative pain					Rescue analgesic consumption	Author's main conclusions
		Mean and SD			Within-group difference (SS or not SS) (p value)	Intergroup difference (SS or not SS) (p value)		
	Dexamethasone 4 mg (corticosteroid) 1 h pre-op + 4 mg 6 h after 1st dosage	Median VAS D1H1: 5 (3.05 to 4.87) D1H2: 6 (3.63 to 6.40) D1H3: 6 (4.25 to 6.45) D1H4: 6 (4.76 to 6.76) D1H5: 8.6 (5.66 to 8.37) D1H6: 5 (3.87 to 5.95) D1H7: 3 (2.43 to 4.01) D1H8: 2 (1.57 to 3.00) D2 morning 3: (2.87 to 5.36) D2 noon: 3 (2.28 to 3.39) D2 afternoon: 2 (1.45 to 2.33) D3 morning: 3 (2.3 (0.57 to 1.45) D3 noon: 0 (0.16 to 0.69) D3 afternoon: 0 (0.17 to 0.72) D4 morning: 0 (0 to 0) D4 noon: 0 (0 to 0) D4 afternoon: 0 (0 to 0) D7 morning: 0 (0 to 0) D7 noon: 0 (0 to 0) D7 afternoon: 0 (0 to 0)	Median NRS-101 D1H1: 7 (4.33 to 6.83) D1H2: 8 (5.23 to 8.26) D1H3: 9 (5.81 to 8.47) D1H4: 10 (7.04 to 9.47) D1H5: 11 (7.77 to 10.70) D1H6: 5 (3.83 to 5.98) D1H7: 5 (3.10 to 4.77) D1H8: 3 (2.05 to 3.58) D2 morning: 4 (3.96 to 6.37) D2 noon: 3 (2.96 to 4.30) D2 afternoon: 2 (1.82 to 2.88) D3 morning: 0 (0.62 to 1.61) D3 noon: 0 (0.43 to 1.34) D3 afternoon: 0 (0.26 to 1.18) D4 morning: 0 (0 to 0) D4 noon: 0 (0 to 0) D4 afternoon: 0 (− 0.02 to 0.11) D7 morning: 0 (0 to 0) D7 noon: 0 (0 to 0) D7 afternoon: 0 (0 to 0)	Median VRS-4 D1H1: 1 (1 to 2) D1H2: 1 (1 to 2) D1H3: 1 (1 to 2) D1H4: 1 (1 to 2) D1H5: 1 (1 to 2) D1H6: 1 (1 to 2) D1H7: 1 (1 to 1) D1H8: 1 (1 to 1) D2 morning: 1 (1 to 3) D2 noon: 1 (1 to 1) D2 afternoon: 1 (1 to 1) D3 morning: 1 (1 to 1) D3 noon: 1 (1 to 1) D3 afternoon: 1 (1 to 1) D4 morning: 1 (1 to 1) D4 noon: 1 (1 to 1) D4 afternoon: 1 (0 to 1) D7 morning: 1 (1 to 1) D7 noon: 1 (1 to 1) D7 afternoon: 1 (1 to 1)	NR		0/43 implants 0/43 pts	

Table 2 (continued)

Author and year	Study groups	Post-operative pain					Rescue analgesic consumption	Author's main conclusions
		Mean and SD			Within-group difference (SS or not SS) (p value)	Intergroup difference (SS or not SS) (p value)		
	Placebo 1 h pre-op + 6 h after the first dosage	Median VAS D1H1: 28 (26.70 to 32.80) D1H2: 39 (33.56 to 42.15) D1H3: 16 (16.72 to 24.36) D1H4: 15 (15.97 to 22.20) D1H5: 17 (19.41 to 26.76) D1H6: 26 (26.50 to 32.75) D1H7: 29 (28.50 to 33.50) D1H8: 44 (33.65 to 45.06) D2 morning: 34 (34.96 to 41.56) D2 noon: 20 (18.37 to 29.29) D2 afternoon: 36 (19.83 to 31.83) D3 morning: 15 (7.50 to 15.47) D3 noon: 5 (3.96 to 7.01) D3 afternoon: 0 (0.24 to 1.82) D4 morning: 0 (0.12 to 0.91) D4 noon: 0 (0 to 0) D4 afternoon: 0 (0 to 0) D7 morning: 0 (0 to 0) D7 noon: 0 (0 to 0) D7 afternoon: 0 (0 to 0)	Median NRS-101 D1H1: 30 (24.31 to 34.95) D1H2: 30 (29.03 to 39.82) D1H3: 15 (12.08 to 19.86) D1H4: 10 (10.07 to 17.36) D1H5: 15 (15.10 to 22.78) D1H6: 24 (23.51 to 28.09) D1H7: 30 (27.72 to 30.00) D1H8: 40 (32.52 to 39.02) D2 morning: 30 (30.27 to 35.67 D2 noon: 30 (17.38 to 27.53) D2 afternoon: 30 (17.69 to 27.23) D3 morning: 5 (5.82 to 12.70) D3 noon 3 (2.65 to 6.21) D3 afternoon: 0 (0.08 to 0.61) D4 morning: 0 (0.08 to 0.61) D4 noon: 0 (0 to 0) D4 afternoon: 0 (0 to 0) D7 morning 0: (0 to 0) D7 noon: 0 (0 to 0) D7 afternoon: 0 (0 to 0)	Median VRS-4 D1H1: 2 (2 to 3) D1H2: 2 (2 to 3) D1H3: 1 (1 to 3) D1H4: 1 (1 to 3) D1H5: 1 (1 to 3) D1H6: 2 (1 to 3) D1H7: 2 (1 to 3) D1H8: 2 (1 to 3) D2 morning: 2 (2 to 3) D2 noon: 2 (1 to 3) D2 afternoon: 2 (1 to 3) D3 morning: 1 (1 to 2) D3 noon: 1 (1 to 1) D3 afternoon: 1 (1 to 1) D4 morning: 1 (1 to 1) D4 noon: 1 (1 to 1) D4 afternoon: 1 (1 to 1) D7 morning 1: (1 to 1) D7 noon: 1 (1 to 1) D7 afternoon: 1 (1 to 1)	NR		35/35 implants 35/35 pts	

Table 2 (continued)

Author and year	Study groups	Post-operative pain			Rescue analgesic consumption	Author's main conclusions
		Mean and SD	Within-group difference (SS or not SS) (p value)	Intergroup difference (SS or not SS) (p value)		
Meta et al. (2017)	2 groups: NSAID vs. NSAID + corticosteroid	Pain assessed by VAS (0–10)	Pain perception, InIn, and ExIn: patient distribution: 0 indicates no pain/inflammation, 10–30 indicates moderate pain/inflammation, and 40–70 indicates intense pain/inflammation Pain perception, InIn, and ExIn: No SS ($P > 0.05$) between 3 and 7 days within control and experimental groups	Pain perception, InIn, and ExIn: No SS ($P > 0.05$) between control and experimental groups at the 3 times at 3, 7, and 14 days	NR	There was no significant difference in pain perception between ketorolac betamethasone versus ketorolac alone at 3, 7, and, 14 days Limitation: low power RCT; RCTs with higher statistical power would be necessary for a definitive conclusion
	Ketorolac tromethamine 10 mg (NSAID) 1 h pre-op and twice a d for 2 d post-op	VAS 3D: 1.71 (± 1.49) 7D: 0.57 (± 0.76) 14D: 0.07 (± 0.27)	3 D: SS 0 = 4 10–30 = 9 40–70 = 1 7D: SS 0 = 8 10–30 = 6 40–70 = 0 14 D 0 = 13 10–30 = 1 40–70 = 0			
	Ketorolac tromethamine 10 mg (NSAID) 1 h pre-op and twice a d for 2 days post-op + betamethasone 2 mL (corticosteroid) within 2 h pre-op	VAS 3 D: 2.47 (± 2.10) 7 D: 1.13 (± 2.26) 14 D: 0.00 (± 0.00)	3 D: SS 0 = 5 10–30 = 5 40–70 = 5 7 D: SS 0 = 10 10–30 = 3 40–70 = 2 14 D 0 = 15 10–30 = 0 40–70 = 0			

Table 2 (continued)

Author and year	Study groups	Post-operative pain			Rescue analgesic consumption	Author's main conclusions
		Mean and SD	Within-group difference (SS or not SS) (*p* value)	Intergroup difference (SS or not SS) (*p* value)		
Narcotics						
Samieirad et al. (2017)	2 groups: acetaminophen + opioid vs. acetaminophen + caffeine	Pain assessed by VAS (0–10) at 30 min, 3 h, 6 h, 12 h, 21 days, 2 days, and 1 week	NR	VAS 30 min: *p* value 0.592 not SS 3 H: *p* value 0.001 SS 6 H: *p* value 0.001 SS 12 H: *p* value 0.001 SS 24 H: p value 0.071 not SS 48 H: *p* value 0.188 not SS 72 H: p value 0.074 not SS 1 W: *p* value 0.083 not SS	NR	Codeine-containing analgesics were significantly more effective than caffeine-containing ones in reducing post-operative pain. Caffeine-containing analgesics were significantly more effective than codeine-containing ones in reducing post-operative swelling. Non-opioid pain medications can be used effectively in pain management. There was no implant failure/peri--implantitis reported in either group up to 6 months post-op.
	Acetaminophen 300 mg + codeine 20 mg (opioid) 1 h per-op and 4 times per day for 2 d	VAS 30 min: 0.56 (± 0.616) 3 H: 4.00 (± 1.572) 6 H: 4.39 (± 1.614) 12 H: 3.22 (± 1.003) 24 H: 2.39 (± 1.037) 48 H: 0.78 (± 1.166) 72 H: 0.28 (± 0.575) 1 W: 0.00 (± 0.000)				
	Acetaminophen 300 mg + caffeine 20mg 1 h per-op and 4 times per d for 2 d	VAS 30 min: 0.44(± 0.616) 3 H: 5.61 (± 1.243) 6 H: 6.06 (± 1.259) 12 H: 5.17 (± 1.757) 24 H: 2.94 (± 0.735) 48 H: 0.94 (± 0.416) 72 H: 0.67 (± 0686) 1 W: 0.17 (± 0.383)				

D, day; *H*, hour; *NRS*, numeric rating scale; *NSAIDs*, nonsteroidal anti-inflammatory; *PIS*, pain intensity scale; *PRS*, pain relief scale; *SS*, statistically significant; *VAS*, visual analog scale; *VRS*, verbal rating scale

Piroxicam (NSAID) vs. placebo Bhutani et al. (2019) reported that the VAS pain intensity was significantly lower in the piroxicam (peri-operative sublingual administration) group overall and at all self-reported time intervals (6 h, days 1, 3, and 5) except for 1 h post-op, compared to the placebo group (placebo pre-op and NSAID for 3 days post-op). Mean swelling scores were also significantly lower in the piroxicam group. Neither side effects nor adverse events were included in the study [24].

Oral and transdermal NSAID comparison Rajeswari et al. (2017) found in their split-mouth design trial that there were no statistically significant differences in pain outcomes between the oral and transdermal routes of diclofenac delivery. However, the safety of the transdermal route was superior, as three patients reported gastric irritation and a mild burning sensation when taking oral diclofenac and none of the patients developed any adverse effects when using the transdermal patch [26].

b. NSAIDs and corticosteroids (primary or adjuvant analgesic) comparison:

Ibuprofen (NSAID) vs. dexamethasone (corticosteroid) vs. placebo Bahammam et al. (2017) found that both dexamethasone (corticosteroid) and ibuprofen (NSAID) significantly reduced pain up to 3 days after surgery and discomfort up to 2 days after surgery compared with placebo treatment [19]. Ibuprofen and dexamethasone were equally effective in reducing POP and swelling following surgical implant placement; no statistical difference between these two analgesic medications was reported at any time point. However, all patients in the placebo group required rescue analgesics compared to lower numbers of rescue analgesics taken by patients in the ibuprofen and dexamethasone groups; there was no significant difference in the number of rescue analgesics taken by patients in either of the analgesic therapy groups. The time to first rescue analgesic was also lower in patients in the placebo group compared to the analgesic therapy groups. The authors reported the absence of adverse events in any of the groups [19].

Ketorolac (NSAID) vs. ketorolac and betamethasone (NSAID + corticosteroid) Meta et al. (2017) found no significant difference ($P > 0.05$) in pain sensation and swelling between subject groups treated with peri-operative ketorolac (NSAID) alone versus ketorolac in conjunction with betamethasone (corticosteroid). While pain sensation was rated approximately 0.76 higher in the group that received both ketorolac and betamethasone compared to ketorolac alone 3 days post-op, this difference was not statistically significant. Extra- and intra-oral inflammations were not different between the groups at each time point. Neither side effects nor adverse events were included in the study [27].

c. Opioid vs. caffeine analgesic adjuvants comparison:

Acetaminophen containing codeine vs. acetaminophen-containing caffeine Samieirad et al. (2017) determined that the post-operative combination of acetaminophen with codeine was significantly more effective in reducing pain than acetaminophen combined with caffeine ($p = 0.001$) at 3-, 6-, and 12-h intervals; average pain VAS 12 h post-op was 5.17 ± 1.757 for caffeine and 3.22 ±1.003 for codeine [22]. Conversely, acetaminophen combined with caffeine was more effective in reducing post-operative swelling ($p = 0.018$); average swelling levels (VAS) for the first day post-op were 1.11 ± 0.583 for caffeine and 1.39 ± 0.916 for codeine. Neither side effects nor adverse events were included in the study [22].

II. *Qualitative comparison of primary outcomes reported in included studies*

Table 2 summarizes the primary outcomes of the included studies.

a. Changes in pain over time

The included studies reported patients' pain scores during their respective follow-up periods. One trial monitored POP for 2 weeks following surgery [27]; four trials for 7 days post-op [19, 20, 22, 25, 27]; one trial for 5 days post-op [24]; two studies for 3 days post-op [23, 26]; and one trial for up to 12 h after surgery [21].

The highest levels of pain in analgesic and comparative/placebo study groups were reported in the 1 day post-op [19–24, 26] or 2 days post-op [19]. The general trend of post-operative pain in all study groups was low to moderate for the first 3 days post-op, followed by a gradual decline over the subsequent fourth day post-op; from the fourth day post-op onward, the pain was reported as low to no pain across the studies [19, 20, 22, 24, 27].

Intergroup comparisons that examined differences in pre-op NSAID and placebo (pre- or peri-op NSAID versus pre-op placebo only or pre-op placebo and post-op NSAID) indicated variable results in relation to time. Sanchez et al. 2018 found statistically significant differences in pain VAS outcomes immediately post-op but not at 2 h post-op and during subsequent follow-up times through 7 days post-op [20]. Bhutani et al. (2019) found statistically significant differences in pain intensity VAS from 6 h post-op through 5 days post-op but not at 1 h post-op [24]. Periera (2020) found statistically significant differences in pain intensity VAS from 1 to 24 h post-op but not 48–72 h post-op [23]. In the intergroup comparison of post-op NSAID and

placebo, Bolukbasi et al. (2019) found statistically significant differences in the pain intensity scale (PIS) from 30 min through 4 h post-op but not at 15 min and 12 h post-op [21].

b. Qualitative comparison of rescue analgesic consumption

All three studies that included rescue analgesic consumption as an outcome in the comparison of NSAID and placebo study groups found that a significantly greater number of rescue analgesics were consumed in the placebo group [21, 23, 25]. Similarly, the study that included rescue analgesic consumption as an outcome in the comparison of NSAIDs, corticosteroids, and placebo found that all patients in the placebo group required rescue analgesics compared to lower numbers of rescue analgesics taken by patients in the NSAID and corticosteroid groups, while no significant difference was found between the two analgesic groups [19]. In regard to the time elapsed to the first rescue analgesic, the two studies that reported on this outcome found that significantly less time elapsed to first rescue analgesic in the placebo group compared to the NSAID [23] and NSAID and corticosteroid groups [19].

III. *Qualitative comparison of secondary outcomes reported in included studies*

e-Table 2 summarizes the secondary outcomes of the included studies.

a. Adverse events

Five [19–21, 23, 25, 26] of the eight studies comparing oral administration of analgesics and comparative analgesic/placebo [19–27] reported adverse effects and/or drug side effects. Only one of these studies [25] reported gastric side effects in the ibuprofen group and not the placebo group. The other four studies reported the absence of adverse effects and/or drug side effects in the comparison of NSAIDs and placebo [20, 21, 23, 25] as well as corticosteroids as a third study group comparison [19]. Furthermore, one study [26] comparing the transdermal and oral routes of NSAID administration reported that three patients taking the oral NSAID reported gastric side effects and none of the patients using the transdermal patch developed any adverse effects; the authors concluded that the safety of the transdermal route is superior to the oral administration [26].

b. Post-operative inflammation, infections, swelling, and dehiscence

Three studies included post-operative inflammation as a study outcome [20, 22, 27]. A higher degree of inflammation was found in the placebo compared to the NSAID group [20, 22, 27]; in the NSAID group compared to NSAID plus corticosteroid group [27]; and in the codeine compared to the caffeine group [20, 22, 27]. The difference in inflammation between study groups was greatest in the first 3 days post-op [22, 27].

Four studies included post-operatives swelling as a study outcome [20, 22–25]. Two of the studies reported that swelling was lower in the NSAID compared to the placebo group [20, 24] with statistical significance through 5 days post-op [24]; one of the studies reported absence of swelling in both the NSAID and placebo groups [23]. The study examining acetaminophen with codeine compared to acetaminophen with caffeine reported that the swelling peaked in both groups at 2-days follow-up; the swelling was lower in the caffeine compared to the codeine group throughout the 7-day study period and the difference was significantly different through 3-days follow-up [22].

Three of the included studies included soft tissue dehiscence as a study outcome [19, 20, 25]. One study reported that 2 of 29 patients in the placebo group and 0 patients in the NSAID group experienced soft tissue wound dehiscence and subsequent exposure of the implant cover screw, but the dehiscence in the placebo group was caused by inadequate relief of the denture [25]. The other two studies observed 0 cases of wound dehiscence in the NSAID and placebo groups [20] as well as the corticosteroid group [19].

c. Patient satisfaction

One of the included studies reported levels of patient satisfaction as a study outcome and found significantly higher levels of patient satisfaction in the NSAID group compared to the placebo group [21].

Pooled data

Meta-analysis was conducted for two studies that examined pain VAS in peri-operative NSAIDs compared to pre-op placebo with post-op NSAIDs [20, 24]. Pooled results indicated significantly lower and more favorable pain scores in the peri-operative NSAID group at 1 to 2 h post-op (MD, − 0.38 [%95 CI, − 0.75, − 0.01]; p = 0.04). However, the pain VAS was not significantly different between the two groups at the 6–8-h follow-up, 1-day follow-up, and 3-day follow-up intervals, as well as for the 3-day study period overall (MD, − 0.63 [%95 CI, − 1.62, 0.36]; P = 0.89) (Fig. 1). Analysis of pooled data could not be conducted for other analgesic regimens and any secondary outcomes as no other two trials examining comparative study groups and/or reporting on comparable outcomes have been published to the best of the authors' knowledge.

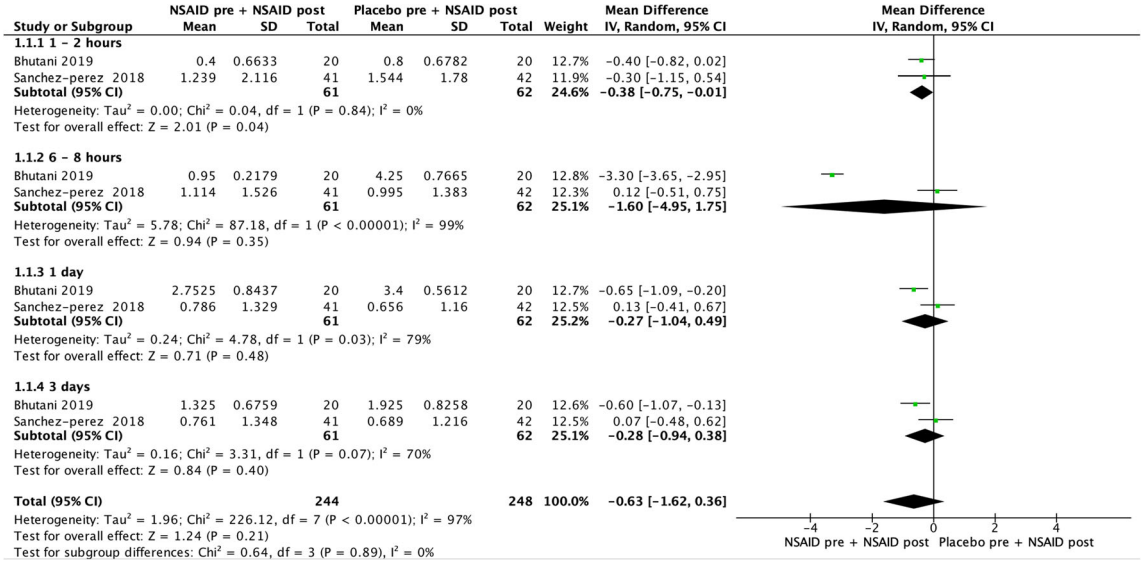

Fig. 1 Forest plot of VAS scores comparing NSAID pre-op and NSAID post-op versus placebo pre-op and NSAID post-op at 1–2 h, 6–8 h, 1, and 3 days after implant surgery

Risk of bias of included studies

All of the included studies are RCTs; risk of bias assessment determined that all 9 included studies have a low risk of bias [19–27]. While initially, one study had high-risk bias [26] and three of the studies had an unclear risk of bias in one to two of the seven domains assessed [20, 24, 27], the risk of bias was ultimately determined as low-risk following clarification by corresponding authors. A risk of bias graph and summary are shown in Fig. 2.

Discussion

Summary of key findings

Reducing post-operative dental pain is a fundamental component in the success of any surgery. To the best of the authors' knowledge, the present paper is the first to systematically review the current literature reporting on POP pharmacological management. An extensive literature search identified nine RCTs on the topic.

Five RCTs concluded that the administration of NSAIDs pre-op and/or post-op compared to placebo significantly reduces POP and the need for rescue analgesics following dental implant placement [20, 21, 23–25]. In regard to the administration route of the NSAIDs, a split-mouth design RCT determined that while oral and transdermal NSAID administration has similar efficacy for controlling POP, the transdermal NSAID group has fewer side effects compared to the oral administration route and may be a safer analgesic option following dental implant placement [26]. Two RCTs suggested that the administration of NSAIDs and glucocorticoids results in comparable POP sensation following dental implant surgery [19, 27] and reduced POP and rescue analgesics compared to placebo [19]. One study comparing acetaminophen combined with codeine versus caffeine found that while the codeine more effectively controlled POP throughout the first 12 h following implant surgery, caffeine resulted in significantly less swelling during the first 3 days post-op [22]; the authors determined that the use of caffeine-containing analgesics is an acceptable and effective treatment for POP and swelling [22].

Intra-group comparisons of pain over time suggested the highest pain levels in the first day post-op, followed by a gradual decline over the subsequent fourth day post-op and low to no pain from the fourth day onward.

Given the significant differences in pain outcomes found between the NSAIDs and placebo groups for all included studies, intergroup comparisons of pain outcomes over time were qualitatively examined for these studies. Statistically significant differences in pain outcomes varied for intergroup comparisons as individual studies reported differences immediately post-op [20], 1 to 24 h post-op [23], 30 min to 4 h post-op [21], and 6 h to 5 days post-op [24]. Furthermore, a meta-analysis of two studies that examined pain VAS in peri-operative NSAIDs compared to pre-op placebo and post-op NSAIDs [20, 24] indicated significantly lower and more favorable pain scores in the peri-operative NSAID group at 1 to 2 h post-op.

The included studies also suggested that the use of analgesics may be favorable compared to placebo for reducing inflammation [20, 22, 27] and swelling [20, 22, 24], and improving patient satisfaction overall [21].

On the basis of the results for individual and pooled studies, and in light of the adverse analgesic effects, analgesic

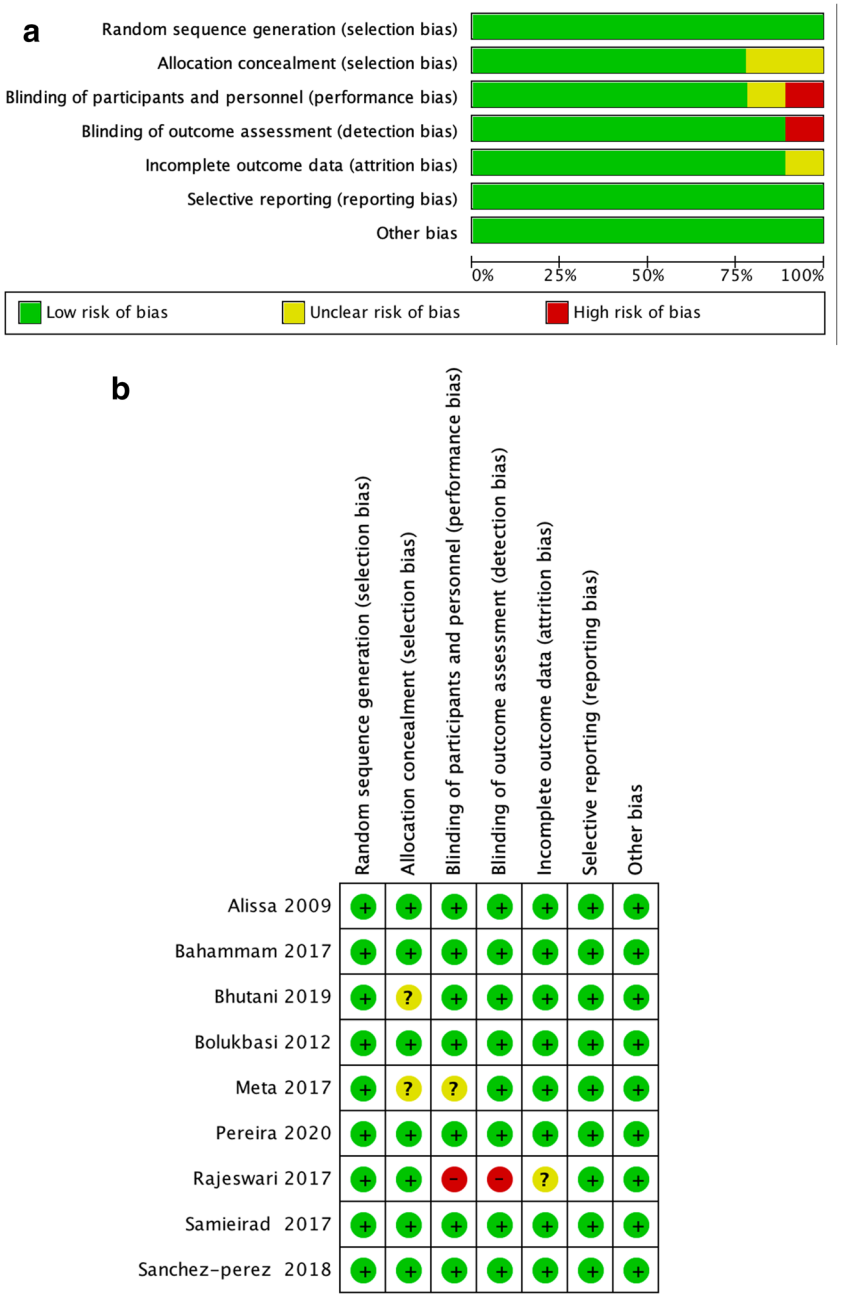

Fig. 2 Review of authors' judgments about each risk of bias item presented as **a** percentage in a graph and **b** summary for each included study

medications for more than 3 days following implant surgery may not add additional benefits in POP management. In addition, transdermal rather than oral administration of NSAIDs should be considered on an individual patient basis and especially for patients at risk for gastrointestinal adverse effects.

Quality of evidence

The risk of bias assessment indicated a low risk of bias for all included studies [19–27] meaning that the plausible bias was unlikely to seriously alter the results. However, it should be noted that one of the included studies was underpowered for reporting a statistically significant difference between groups [27]; all other included studies attained the statistical power calculated prior to enrollment.

Agreements and disagreements with previously published articles

While this is the first review to focus on analgesic POP management in dental implant surgery, effective therapies for modulating acute POP have been addressed in other fields [2, 28, 29].

Analgesic compound Recent literature on the benefits of glucocorticoids for pain modulation supports the results of two studies included in the present review on the benefits of dexamethasone for reducing pain following implant surgery [19, 27]. Glucocorticoids, such as dexamethasone, have been implicated in the treatment of both acute and chronic inflammatory conditions, albeit, more frequently for the treatment of chronic inflammation [30]. Historically, glucocorticoids have not been regularly prescribed to treat acute pain and inflammation because of their immunosuppressive properties. Nevertheless, in a prospective, RCT, Steffens et al. (2011) found that administration of dexamethasone prior to periodontal surgery reduces POP and patients' need for rescue analgesics [31]. The administration of dexamethasone to reduce POP has also been shown in the context of endodontic therapy [32–34]. Pochapski et al. reported that the pre-emptive use of dexamethasone resulted in a statistically significant reduction in POP during the first 12 h following the completion of endodontic therapy [33]. Aminoshariae et al. (2016) found in a systematic review that the pre-operative oral administration of dexamethasone effectively reduced POP following endodontic therapy [34].

The administration of caffeine in combination with analgesics has also become an area of research interest. A trial included in the present review determined that caffeine-containing analgesics are effective and acceptable in reducing POP and swelling [22]. Similarly, in a small prospective clinical trial, Rashwan et al. (2009) reported superior pain reduction following periodontal surgery in patients receiving acetaminophen combined with caffeine adjuvants as compared to those receiving ibuprofen alone ($p < 0.001$) and suggested that a combination of acetaminophen with caffeine may be an alternative treatment option for patients who are unable to take NSAIDs [35]. Consistent with these findings, Baratloo et al. (2016) reported in a recent literature review the potential role of caffeine in pain modulation [36] and suggested that the addition of caffeine to analgesic medications, such as ibuprofen, may improve pain relief by acting on adenosine receptors [37]. In contrast, a RCT that examined the efficacy of various analgesics for the treatment of POP following surgical removal of impacted third molars found no clinical difference in acute POP perception reported by patients who received ibuprofen alone to the combination of ibuprofen, acetaminophen, and caffeine [38].

Various other combinations of analgesic medications, in addition to those examined by included studies, have been suggested for POP modulation. Moore et al. (2018) concluded in a review of systematic reviews that the combination of acetaminophen and ibuprofen delivers a high degree of pain relief to adult patients with acute dental pain [2]. For the treatment of endodontic pain, Aminoshariae and colleagues (2016) recommended in a systematic review of RCTs the use of NSAIDs, and NSAIDs with acetaminophen or opioid adjuvants for effective pain modulation, when NSAIDs alone did not suffice [34]. For the treatment of POP following third molar extractions, a review published in 2013 suggested that the combination of acetaminophen and ibuprofen is an effective mode of treating acute POP [39]. More recently, Best et al. (2017) determined in a RCT that the addition of codeine to a cocktail of acetaminophen and ibuprofen did not improve POP following the extraction of impacted third molars [40].

For decades, dentists have prescribed opioids to treat acute POP following invasive surgical procedures [41]. In a recently published study examining the trends in opioid analgesic prescriptions by dental professionals, Steinmetz et al. (2017) found that oral implant surgeries had the highest rates of opioid prescriptions and the greatest increase in rates during the study period from 1996 to 2013 [42]. Nevertheless, the authors discouraged the use of opioids based on risk-benefit analysis and referenced other studies [43, 44] that demonstrated the efficacy of non-opioid analgesics in modulating acute POP. These findings are consistent with the trials included in the present review and ultimately support the use of non-opioid analgesics to treat POP following implant surgery.

Analgesic dosage In regard to the dosing schedule of analgesic medications for the treatment of POP, Sanchez-Perez et al. suggested in the included trial that pre-procedural analgesics may be considered potentially useful in reducing acute POP immediately following surgery [20]. However, clinical evidence on the use of analgesics before oral implant surgery for pain management is limited. A systematic review published in 2002 concluded that there is a lack of clinical evidence to support pre-emptive analgesia for improved POP relief [45]. However, the authors discussed the inherent complexity of the topic, such as the variations in surgical procedures and outcome measurements across included studies.

Route of administration In regard to the administration route, Rajeswari et al. (2017) found that oral and transdermal diclofenac (NSAID) administration have similar pain outcomes following dental implant placements, but the transdermal administration results in fewer gastric side effects compared to the oral route [26]. The results are supported by previous studies evaluating the efficacy and safety of diclofenac in general surgery [46, 47].

Clinical considerations for analgesic medications

The use of opioids for pain management has been scrutinized due to the highly addictive property that has given rise to a widespread drug abuse epidemic [48]. The chief clinical concerns associated with opioids include physical dependence and addiction, as well as serious adverse effects. While tolerance develops to the analgesic property of opioids, patients do not develop tolerance to the adverse effects, which may

compel the prescriber to reduce the prescription dose ultimately leading to inadequate analgesic effects [49]. As a result of the complex management, and in light of the opioid epidemic, the American Dental Association recently announced a policy supporting statutory limits on opioid dosage and duration [50]. Therefore, based on the results of the present review and literature discussed, opioids may not be warranted for pain management following oral implant surgeries and other non-opioid analgesics should be considered when clinically appropriate.

Nevertheless, the risks associated with NSAIDs must not be overlooked. Oral NSAIDs may cause numerous adverse effects including prolonged bleeding and gastrointestinal upset [25, 26, 51]. NSAIDs can impair platelet function and the coagulation cascade and are contraindicated for patients who have gastrointestinal ulcerations and/or erosive gastrointestinal diseases [51]. NSAIDs also increase the risk for thrombotic events, such as stroke and heart attack, and the risk of these vascular events increases with the duration of NSAID use [52]; NSAIDs should be used with caution in patients on blood pressure medications or with a history of cardiovascular disease [52]. However, when used appropriately and for a short 2–3-day period of time, adverse effects may be reduced [19].

As POP and swelling following oral implant procedures typically subsides following the third post-operative day [53], pain management is most critical for 3 days following surgery. Thus, NSAIDs may be appropriate.

Review limitations

The primary limitation of the available evidence is the small number of RCTs assessing pain management in dental implant surgery and the heterogeneity in the interventions implemented, outcomes assessed, and follow-up times. As a result, the present systematic review is largely qualitative in its synthesis of the available data. A meta-analysis of two studies was also conducted, but further results could not be pooled due to the limitations of the available evidence.

Conclusions

Implications for clinical practice

Within the limitations of this systematic review and meta-analysis, findings from the included RCTs suggest that POP following implant surgery may be effectively treated with the short-term use of analgesic medications. However, due to the limited number of comparable clinical trials, the most effective analgesic medication for dental implant surgery could not be determined. Thus, there is insufficient evidence to either recommend or discourage an analgesic regimen for pain management following dental implant surgery in clinical practices. Ultimately, the clinician's analgesic prescription should be directed by a patient's medical history, in order to increase the success of pain management in a short period of time and decrease potential adverse effects.

Future research

The review highlights the need for further large-scale long-term clinical trials examining the efficacy of analgesic medications in dental implant surgery. The clinical trials should be designed to assess the efficacy of various analgesics for pain management following dental implant placement. Research should also focus on the efficacy of glucocorticoids and analgesic-caffeine combinations as alternative therapies for POP modulation. In addition, the studies should include the number needed to treat (NNT) in order to demonstrate clinical relevance. Ultimately, risk-benefit assessments must be conducted to determine the analgesic regimen, including the compound, dosage, dosing schedule, and route, which provides the most effective pain management with the fewest adverse outcomes.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00784-021-03859-y.

Acknowledgments We are grateful to Mr. Richard McGowan (NYU Health Sciences Library liaison to the NYU College of Dentistry) for his assistance with the electronic database search process. We thank fellow researchers, Dr. Maha Bahammam (Bahammam 2017 group), Dr. Isaac Fernando Meta (Meta 2017 group), and Dr. Arturo Sanchez-Perez (Sanchez-Perez 2019 group), for kindly providing clarification with regards to study design and/or results.

Author contributions I. Khouly and M. Ordway conceived the idea and contributed to study conception and design, acquisition of data, analysis and interpretation, and drafted and critically revised the manuscript; A. Veitz-Keenan contributed to review conception and design, analysis and interpretation, and critically revised the manuscript; R. S. Braun contributed to review analysis and interpretation and drafted and critically revised the manuscript; M. Alrajhi, S. Fatima, and B. Kiran contributed to study design, acquisition of data, and analysis. All authors gave final approval and agree to be accountable for all aspects of the work.

Declarations

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors, ethical approval is not required.

Informed consent For this type of study, formal consent is not required.

Conflict of interest The authors declare no conflict of interest.

References

1. Rudd RA, Aleshire N, Zibbell JE, Gladden RM (2016) Increases in drug and opioid overdose deaths–United States, 2000-2014. MMWR Morb Mortal Wkly Rep 64(50-51):1378–1382
2. Moore PA et al (2018) Benefits and harms associated with analgesic medications used in the management of acute dental pain: an overview of systematic reviews. J Am Dent Assoc 149(4):256–265. e3
3. Bryce G, Bomfim DI, Bassi GS (2014) Pre- and post-operative management of dental implant placement. Part 1: management of post-operative pain. Br Dent J 217(3):123–127
4. Garg A (2011) Analgesia in implant dentistry. Dent Implantol Updat 22(6):41–45
5. Eli I, Schwartz-Arad D, Baht R, Ben-Tuvim H (2003) Effect of anxiety on the experience of pain in implant insertion. Clin Oral Implants Res 14(1):115–118
6. Beaudette JR, Fritz PC, Sullivan PJ, Piccini A, Ward WE (2018) Investigation of factors that influence pain experienced and the use of pain medication following periodontal surgery. J Clin Periodontol 45(5):578–585
7. Higgins JP et al (2019) Cochrane handbook for systematic reviews of interventions. Wiley
8. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6(7):e1000097
9. Keerthna M, Dhanraj M, Jain ARJDIT (2018) Analgesic effectiveness of opioid agonists in post-operative pain after endosseous dental implant placement–a split-mouth randomized control trial. 10(2)
10. Al-Khabbaz AK, Griffin TJ, Al-Shammari KF (2007) Assessment of pain associated with the surgical placement of dental implants. J Periodontol 78(2):239–246
11. Reddy MS, Jeffcoat MK, Richardson RC (1990) Assessment of adjunctive flurbiprofen therapy in root-form implant healing with digital subtraction radiography. J Oral Implantol 16(4):272–276
12. Winnett B, Tenenbaum HC, Ganss B, Jokstad A (2016) Perioperative use of non-steroidal anti-inflammatory drugs might impair dental implant osseointegration. Clin Oral Implants Res 27(2):e1–e7
13. Sakka S, Hanouneh SI (2013) Investigation of the effect of ibuprofen on the healing of osseointegrated oral implants. J Investig Clin Dent 4(2):113–119
14. Karabuda ZC, Bolukbasi N, Aral A, Basegmez-Zeren C, Ozdemir T (2007) Comparison of analgesic and anti-inflammatory efficacy of selective and non-selective cyclooxygenase-2 inhibitors in dental implant surgery. J Periodontol 78(12):2284–2288
15. Gonzalez-Santana H et al (2005) Pain and inflammation in 41 patients following the placement of 131 dental implants. Med Oral Patol Oral Cir Bucal 10(3):258–263
16. Li S et al (2015) Dexmedetomidine analgesia effects in patients undergoing dental implant surgery and its impact on postoperative inflammatory and oxidative stress. Oxidative Med Cell Longev 2015:186736
17. Jeffcoat MK et al (1995) The effect of systemic flurbiprofen on bone supporting dental implants. J Am Dent Assoc 126(3):305–311 quiz 346-7
18. Iero PT et al (2018) A prospective, randomized, open-label study comparing an opioid-sparing postsurgical pain management protocol with and without liposomal bupivacaine for full-arch implant surgery. Int J Oral Maxillofac Implants 33(5):1155–1164
19. Bahammam MA, Kayal RA, Alasmari DS, Attia MS, Bahammam LA, Hassan MH, Alzoman HA, Almas K, Steffens JP (2017) Comparison between dexamethasone and ibuprofen for postoperative pain prevention and control after surgical implant placement: a double-masked, parallel-group, placebo-controlled randomized clinical trial. J Periodontol 88(1):69–77
20. Sanchez-Perez A et al (2018) Effects of the preoperative administration of dexketoprofen trometamol on pain and swelling after implant surgery: a randomized, double-blind controlled trial. J Oral Implantol 44(2):122–129
21. Bolukbasi N et al (2012) Efficacy of quick-release lornoxicam versus placebo for acute pain management after dental implant surgery: a randomised placebo-controlled triple-blind trial. Eur J Oral Implantol 5(2):165–173
22. Samieirad S, Afrasiabi H, Tohidi E, Qolizade M, Shaban B, Hashemipour MA, Doaltian Shirvan I (2017) Evaluation of caffeine versus codeine for pain and swelling management after implant surgeries: a triple blind clinical trial. J Craniomaxillofac Surg 45(10):1614–1621
23. Pereira GM, Cota LO, Lima RP, Costa FO (2020) Effect of preemptive analgesia with ibuprofen in the control of postoperative pain in dental implant surgeries: a randomized, triple-blind controlled clinical trial. J Clin Exp Dent 12(1):e71–e78
24. Bhutani N, Sangolikar D, Bhutani S, Tapashetti R, Pushpalatha H (2019) Sublingual Piroxicam as Preemptive Analgesia in Single Implant Surgery. J Contemp Dent Pract 20(6):750–753
25. Alissa R, Sakka S, Oliver R, Horner K, Esposito M, Worthington HV, Coulthard P (2009) Influence of ibuprofen on bone healing around dental implants: a randomised double-blind placebo-controlled clinical study. Eur J Oral Implantol 2(3):185–199
26. Raja Rajeswari S, Gowda T, Kumar T, Mehta DS, Arya K (2017) Analgesic efficacy and safety of transdermal and oral diclofenac in postoperative pain management following dental implant placement. Gen Dent 65(4):69–74
27. Meta IF, Bermolen M, Macchi R, Aguilar J (2017) Randomized controlled trial comparing the effects of 2 analgesic drug protocols in patients who received 5 dental implants. Implant Dent 26(3):412–416
28. Moore RA et al (2011) Single dose oral analgesics for acute postoperative pain in adults. Cochrane Database Syst Rev (9):Cd008659
29. Moore RA et al (2014) Faster, higher, stronger? Evidence for formulation and efficacy for ibuprofen in acute pain. Pain 155(1):14–21
30. Coutinho AE, Chapman KE (2011) The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. Mol Cell Endocrinol 335(1):2–13
31. Steffens JP, Santos FA, Pilatti GL (2011) Postoperative periodontal pain prevention using two dexamethasone medication protocols: a double-blind, parallel-group, placebo-controlled randomized clinical trial. Am J Dent 24(6):354–356
32. Krasner P, Jackson E (1986) Management of posttreatment endodontic pain with oral dexamethasone: a double-blind study. Oral Surg Oral Med Oral Pathol 62(2):187–190
33. Pochapski MT, Santos FA, de Andrade ED, Sydney GB (2009) Effect of pretreatment dexamethasone on postendodontic pain. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 108(5):790–795
34. Aminoshariae A, Kulild JC, Donaldson M, Hersh EV (2016) Evidence-based recommendations for analgesic efficacy to treat pain of endodontic origin: a systematic review of randomized controlled trials. J Am Dent Assoc 147(10):826–839
35. Rashwan WA (2009) The efficacy of acetaminophen–caffeine compared to ibuprofen in the control of postoperative pain after periodontal surgery: a crossover pilot study. J Periodontol 80(6):945–952
36. Baratloo A et al (2016) The role of caffeine in pain management: a brief literature review. Anesthesiol Pain Med 6(3)
37. Sollevi A (1997) Adenosine for pain control. Acta Anaesthesiol Scand 41(S110):135–136
38. Raisian S, Fallahi HR, Badakhshan L, Zandian D (2012) A randomized double blind controlled trial comparing ibuprofen versus

ibuprofen plus acetaminophen plus caffeine for pain control after impacted third molar surgery. Open J Stomatol 2(02):110–115
39. Moore PA, Hersh EV (2013) Combining ibuprofen and acetaminophen for acute pain management after third-molar extractions: translating clinical research to dental practice. J Am Dent Assoc 144(8):898–908
40. Best AD, de Silva RK, Thomson WM, Tong DC, Cameron CM, de Silva HL (2017) Efficacy of codeine when added to paracetamol (acetaminophen) and ibuprofen for relief of postoperative pain after surgical removal of impacted third molars: a double-blinded randomized control trial. J Oral Maxillofac Surg 75(10):2063–2069
41. Koppen L et al (2018) Dentists' prescribing of antibiotics and opioids to Medicare Part D beneficiaries: Medications of high impact to public health. J Am Dent Assoc
42. Steinmetz C et al (2017) Opioid analgesic prescribing practices of dental professionals in the United States. JDR Clin Transl Res 2(3): 241–248
43. Huber MA, Terezhalmy GT (2006) The use of COX-2 inhibitors for acute dental pain: a second look. J Am Dent Assoc 137(4):480–487
44. Teater D (2015) Evidence for the efficacy of pain medications. National Safety Council, Washington, DC
45. Møiniche S, Kehlet H, Dahl JB (2002) A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: the role of timing of analgesia. Anesthesiology 96(3): 725–741
46. Banning M (2008) Topical diclofenac: clinical effectiveness and current uses in osteoarthritis of the knee and soft tissue injuries. Expert Opin Pharmacother 9(16):2921–2929
47. Gulcin Ural S, Yener O, Sahin H, Simsek T, Aydinli B, Ozgok A (2014) The comparison of analgesic effects of various administration methods of diclofenac sodium, transdermal, oral and intramuscular, in early postoperative period in laparoscopic cholecystectomy operations. Pak J Med Sci 30(1):96–100
48. Maxwell JC (2011) The prescription drug epidemic in the United States: a perfect storm. Drug Alcohol Rev 30(3):264–270
49. Ricardo Buenaventura M, Adlaka MR, Sehgal MN (2008) Opioid complications and side effects. Pain Physician 11:S105–S120
50. ADA, A.D.A (2018) Policy supports mandates on opioid prescribing and continuing education. Available from: https://www.ada.org/en/press-room/news-releases/2018-archives/march/american-dental-assoicaiton-announces-new-policy-to-combat-opioid-epidemic
51. Risser A, Donovan D, Heintzman J, Page T (2009) NSAID prescribing precautions. Am Fam Physician 80(12):1371–1378
52. Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger PM, Egger M, Juni P (2011) Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. Bmj 342:c7086
53. Urban T, Wenzel A (2010) Discomfort experienced after immediate implant placement associated with three different regenerative techniques. Clin Oral Implants Res 21(11):1271–1277