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Adverse events of intra-articular temporomandibular joint injections: a systematic search and review

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ABSTRACT
Temporomandibular joint (TMJ) disorders manifest as joint pain and limited mobility of the mandible. Treatment options include arthrocentesis and intra-articular drug administration. Adverse events associated with such interventions are rarely described in separate articles and may be overlooked when presented in clinical trial reports. Their identification in the medical literature is difficult due to the need to develop a rich set of keywords. This systematic search and review aims to identify and map adverse events associated with injections into the TMJ. Primary clinical trials of TMJ disorders treated with joint irrigation and/or drug administration were included. Data were extracted using a predesigned form and presented in text, tables, and graphs. A total of 58 adverse events were identified, more than half of which were pain and/or swelling. Overall, 14 types of events were classified into 3 categories (distant, local, and articular), none of which were fatal or life-threatening. These were, in order of most frequently diagnosed: pain and/or swelling (52%), ear pressure (5%), eyelid paresthesia (5%), periarticular tissue atrophy (5%), generalized rash (4%), hypoesthesia (4%), open bite (4%), skin hypopigmentation (4%), headache (3%), local rash (3%), malocclusion (3%), mandibular hypomobility (3%), TMJ noises (3%), and fever (2%).
Keywords: temporomandibular joint; intra-articular injections; temporomandibular joint arthrocentesis; adverse events; postoperative complications; corticosteroids.

INTRODUCTION

Background

The skin of the preauricular area covers the temporomandibular joint (TMJ). Bilateral TMJs are used to move the lower jaw in relation to the immobile temporal bones. Temporomandibular disorders (TMDs) are a complex group of abnormalities in the functioning of the TMJ. The main treatments for TMD are: pharmacotherapy, physiotherapy, splint therapy, and intra-articular injections [1, 2, 3, 4, 5, 6, 7, 8]. Temporomandibular joint surgery ranges from various open approaches, through arthroscopy, to minimally invasive single injection techniques [5, 8, 9, 10]. Injection techniques include lavage of the TMJ and intra-articular administration of medications [2, 5]. Irrigation may reduce the concentration of inflammatory mediators and is performed using saline or Ringer's solution [5, 11, 12]. Commonly used drugs include hyaluronic acid and steroids [2, 5, 6, 7, 13]. Autologous blood preparations are also administered [2, 12, 14, 15].

Rationale

Identifying adverse events in the medical literature is difficult because it requires extensive searches without prior knowledge of the correct keywords. Preliminary searches did not reveal any reviews that adequately described the potential complications of TMJ intra-articular injections. Adverse events that have been reported include increased joint pain and preauricular swelling [16]. In the course of preliminary research, more troubling side effects have also been identified, such as lipoatrophy and joint dysfunction [16, 17]. The importance of the appearance of the preauricular area for the aesthetics of the entire face is undisputed [9, 10, 18]. Therefore, it is natural to take steps to identify possible adverse events of intra-articular TMJ injections, to establish an indicative frequency of their occurrence and methods of their prevention, and, at a later stage, to develop repair treatment protocols.

Objectives

The aim of this systematic search and review is to identify and map therapeutic adverse events resulting from injecting articular cavities of the TMJs.

MATERIALS AND METHODS

Protocol and registration

In the absence of guidelines for systematic search and review article type, this study was conducted in accordance with the

Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) [19].

Eligibility criteria

The review inclusion and exclusion criteria are based on the PICOS scheme [20, 21]. No timeframe limits were applied. The individual criteria are presented in Table 1.

TABLE 1. Criteria for including and excluding studies from the review

	Inclusion criteria	Exclusion criteria
Problem	TMJ disorders	animal studies
Intervention	TMJ rinsing or intra-articular drug administration	more invasive interventions, e.g.: arthroscopy, open surgery
Comparators	any or none	none
Outcome	intraoperative or postoperative adverse event	no adverse event data available
Settings	primary studies	non-English reports

TMJ – temporomandibular joint

Information sources

The final searches performed on September 12, 2023, involved medical databases covered by the PubMed search engine [22].

Search strategy

The following search strategy was used: '(temporomandibular OR tmj) AND (complication OR complications OR failure OR failures) AND "intra-articular" AND (injection OR administration OR disposition OR supplementation)'.

Selection of sources of evidence and data extraction

Screening was performed manually MC using the Rayyan tool (Qatar Computing Research Institute, Doha, Qatar and Rayyan Systems, Cambridge, Massachusetts, USA) [23]. If a record met the PICOS criteria or was in doubt, it was advanced to the next stage of selection. Full-text analysis was performed without the use of automated tools (NT and MC). The selection process was visualized using the PRISMA 2020 flowchart [24]. All data items were manually collected (NT and MC) and tabulated using Google Docs Editors software (Google LLC, Mountain View, California, USA).

Data charting process and data items

The following data items were extracted: (1) total number of patients; (2) number of complicated cases; (3) injected substance; (4) name of adverse event; (5) complication severity according to the CLASSIC scale: I – no need for treatment; II need for treatment; III – life-threatening; IV – death [25]. In the absence of data, this fact was noted in the collective data sheet.

Critical appraisal of individual sources of evidence and synthesis methods

Sources were assessed for study type: (1) controlled; (2) uncontrolled; and (3) case report. Case reports and reports with incomplete data were excluded from the syntheses. The results of each synthesis were presented graphically and described in the text. The percentage of individual adverse events in the pool of identified events was determined. Microsoft Excel software (Microsoft Corporation, Redmond, Washington, USA) was used for visualization.

RESULTS

Selection of sources of evidence

A search of medical databases yielded 72 records. No duplicates were found among these records. During the screening phase, 62 reports were rejected on the basis of their abstracts. Ten full-text articles were analyzed, of which 2 did not meet the inclusion criteria. Thus, 8 studies with 289 patients reporting 59 adverse events were included in the review. The subsequent stages of the selection process are shown in Figure 1.

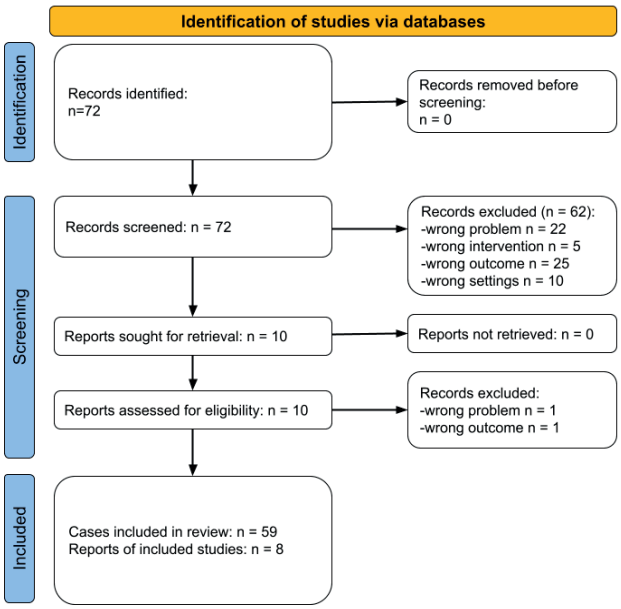

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension flow diagram

Characteristics and results of individual sources of evidence

The study characteristics are presented collectively in Table 2. Data on intracavity TMJ intra-articular injection adverse events extracted from individual studies are listed in Table 3.

TABLE 2. Study characteristics

Authors (publication date)	Diagnosis	Total number of patients (administered substance)	Number of adverse event cases (administered substance)	Study type
Arabshahi et al. (2005) [26]	juvenile idiopathic arthritis	16 (CS)	2 (CS)	controlled
Bjørnland et al. (2007) [27]	osteoarthritis	40 (20 HA, 20 CS)	11 (6 HA, 5 CS)	controlled
Fritz et al. (2009) [28]	various diagnoses	31 (N/S)	1 (CS)	controlled
Parra et al. (2010) [17]	juvenile idiopathic arthritis	83 (CS)	11 (CS)	uncontrolled
Stoll et al. (2012) [29]	juvenile idiopathic arthritis	63 (CS)	3 (CS)	uncontrolled
Skármeta et al. (2017) [30]	degenerative joint disease	1 (CS)	2 (CS)	case report
Isacsson et al. (2019) [31]	temporomandibular joint arthralgia	54 (27 CS, 27 saline)	28 (22 CS, 6 saline)	controlled
Memis and Can (2022) [32]	bilateral disc displacement with reduction	1 (HA)	1 (HA)	case report

HA – hyaluronic acid; CS – corticosteroids; N/S – not specified

TABLE 3. Results of individual studies

Case number	Authors (publication date)	Adverse event name	Adverse event severity	Substance
1	Arabshahi et al. (2005) [26]	swelling/pain	I or II	CS
2	Arabshahi et al. (2005) [26]	swelling/pain	I or II	CS
3	Bjørnland et al. (2007) [27]	swelling/pain	I or II	HA
4	Bjørnland et al. (2007) [27]	swelling/pain	I or II	HA
5	Bjørnland et al. (2007) [27]	swelling/pain	I or II	HA
6	Bjørnland et al. (2007) [27]	swelling/pain	I or II	HA
7	Bjørnland et al. (2007) [27]	ear pressure	I or II	HA
8	Bjørnland et al. (2007) [27]	ear pressure	I or II	CS
9	Bjørnland et al. (2007) [27]	ear pressure	I or II	CS
10	Bjørnland et al. (2007) [27]	open bite	I or II	HA
11	Bjørnland et al. (2007) [27]	open bite	I or II	CS
12	Bjørnland et al. (2007) [27]	generalized rash	I or II	CS
13	Bjørnland et al. (2007) [27]	generalized rash	I or II	CS
14	Fritz et al. (2009) [28]	periarticular atrophy	I or II	CS
15	Parra et al. (2010) [17]	periarticular atrophy	I or II	CS
16	Parra et al. (2010) [17]	swelling/pain	I	CS
17	Parra et al. (2010) [17]	swelling/pain	I	CS
18	Parra et al. (2010) [17]	swelling/pain	I	CS
19	Parra et al. (2010) [17]	swelling/pain	I	CS
20	Parra et al. (2010) [17]	swelling/pain	I	CS
21	Parra et al. (2010) [17]	swelling/pain	I	CS
22	Parra et al. (2010) [17]	swelling/pain	I	CS
23	Parra et al. (2010) [17]	swelling/pain	I	CS
24	Parra et al. (2010) [17]	swelling/pain	I	CS
25	Parra et al. (2010) [17]	swelling/pain	I	CS
26	Stoll et al. (2012) [29]	swelling/pain	I or II	CS
27	Stoll et al. (2012) [29]	fever	I or II	CS
28	Stoll et al. (2012) [29]	skin hypopigmentation	I or II	CS

TABLE 3. Results of individual studies

Case number	Authors (publication date)	Adverse event name	Adverse event severity	Substance
29	Skármeta et al. (2017) [30]	periarticular atrophy	I	CS
30	Skármeta et al. (2017) [30]	skin hypopigmentation	I	CS
31	Isacsson et al. (2019) [31]	swelling/pain	I or II	CS
32	Isacsson et al. (2019) [31]	swelling/pain	I or II	CS
33	Isacsson et al. (2019) [31]	swelling/pain	I or II	CS
34	Isacsson et al. (2019) [31]	swelling/pain	I or II	CS
35	Isacsson et al. (2019) [31]	swelling/pain	I or II	CS
36	Isacsson et al. (2019) [31]	swelling/pain	I or II	CS
37	Isacsson et al. (2019) [31]	swelling/pain	I or II	CS
38	Isacsson et al. (2019) [31]	swelling/pain	I or II	CS
39	Isacsson et al. (2019) [31]	swelling/pain	I or II	CS
40	Isacsson et al. (2019) [31]	swelling/pain	I or II	saline
41	Isacsson et al. (2019) [31]	swelling/pain	I or II	saline
42	Isacsson et al. (2019) [31]	swelling/pain	I or II	saline
43	Isacsson et al. (2019) [31]	swelling/pain	I or II	saline
44	Isacsson et al. (2019) [31]	eyelid paraesthesia	I or II	CS
45	Isacsson et al. (2019) [31]	eyelid paraesthesia	I or II	CS
46	Isacsson et al. (2019) [31]	eyelid paraesthesia	I or II	CS
47	Isacsson et al. (2019) [31]	hypoaesthesia	I or II	CS
48	Isacsson et al. (2019) [31]	hypoaesthesia	I or II	CS
49	Isacsson et al. (2019) [31]	local rash	I or II	CS
50	Isacsson et al. (2019) [31]	local rash	I or II	CS
51	Isacsson et al. (2019) [31]	mandible hypomobility	I or II	CS
52	Isacsson et al. (2019) [31]	mandible hypomobility	I or II	CS
53	Isacsson et al. (2019) [31]	TMJ noises	I or II	CS
54	Isacsson et al. (2019) [31]	TMJ noises	I or II	CS
55	Isacsson et al. (2019) [31]	malocclusion	I or II	CS
56	Isacsson et al. (2019) [31]	malocclusion	I or II	saline
57	Isacsson et al. (2019) [31]	headache	I or II	CS
58	Isacsson et al. (2019) [31]	headache	I or II	saline
59	Memis and Can (2022) [32]	bilateral TMJ dislocation	II	HA

CS – corticosteroids; HA – hyaluronic acid; TMJ – temporomandibular joint

Synthesis of results

Two case reports and 1 study in which the substances administered were not specified were excluded from the syntheses due to lack of epidemiologic relevance [28, 30, 32].

Types of adverse events

In the included articles, 14 types of adverse events were identified. More than half of the reported events were swelling, pain, or swelling and pain at the injection site. The remaining events were reported at most 3 times each. We propose to divide them into the following categories: (1) distant, (2) local, and (3) articular. The "remote" adverse events were: (a) fever, (b) generalized rash, and (c) headache. The "local" category included: (a) ear pressure, (b) eyelid paresthesia, (c) hypoaesthesia, (d) local rash, (e) periarticular atrophy, and (f) skin hypopigmentation. The "articular" events were: (a) malocclusion, (b) mandibular hypomobility, (c) open bite, and (d) TMJ noises (Fig. 2). The proportion of each adverse event in the total number of events identified is shown in Figure 3.

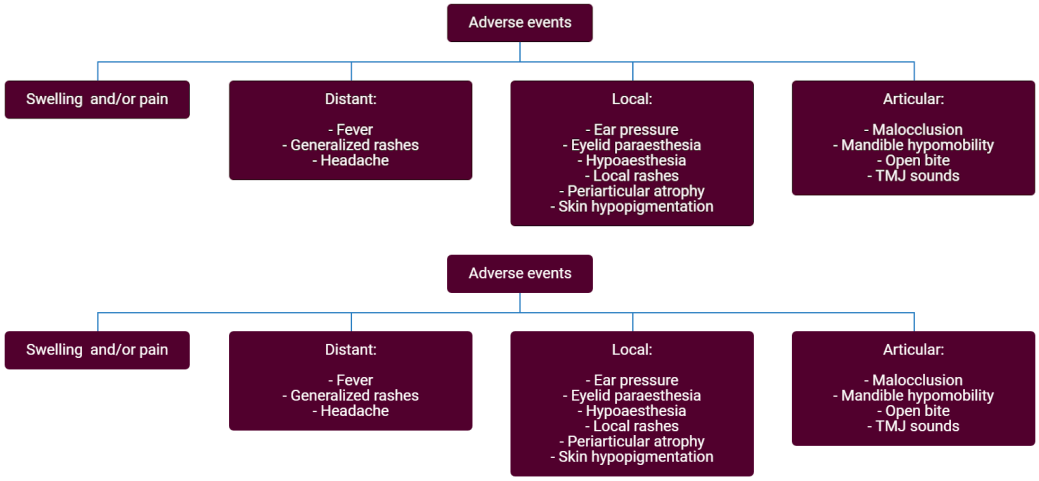

FIGURE 2. Adverse events division proposal

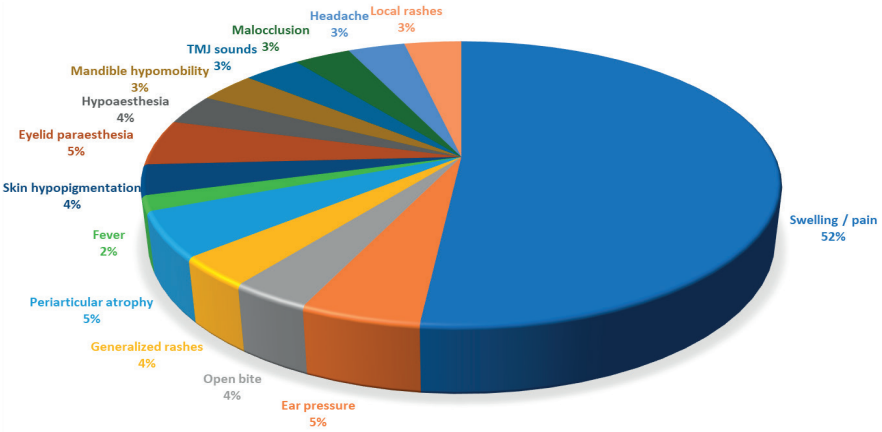

FIGURE 3. The share of individual adverse events in their total number

Substance dependence of adverse events

Adverse events related to steroid administration were reported in all reviewed studies [17, 26, 27, 28, 29, 30, 31]. Two single articles reported adverse effects of intra-articular administration of hyaluronic acid and saline [27, 31]. In the group of 209 patients receiving corticosteroids, 43 cases (21%) of adverse events were reported [17, 26, 27, 28, 29, 30, 31]. The small groups receiving hyaluronic acid and placebo saline included 20 and 27 patients, respectively, with 6 adverse event reports each (30% and 22%, respectively) [27, 31].

The severity of adverse events

There were no known complications that were fatal or life-threatening [17, 26, 27, 28, 29, 30, 31]. Of the adverse events reported, some were treated, but there is no evidence that any of them required treatment [17, 26, 27, 28, 29, 30, 31].

DISCUSSION

Summary of evidence

Fourteen types of adverse events associated with TMJ injections have been identified [17, 26, 27, 28, 29, 30, 31]. The method of reporting adverse events related to intra-articular TMJ injections is not uniform, and searching for information on them in the content of study reports is demanding [17, 26, 27, 28, 29, 30, 31]. Most of the events identified were difficult to evaluate objectively and were easily underestimated by patients and investigators due to their mild nature [17, 26, 27, 28, 29, 30, 31]. Therefore, it should be assumed with caution that many of the adverse effects of the described therapies may not be reported.

Intra-articular injections of various joints are commonly used to treat patients, especially those who cannot tolerate the side effects of long-term drug therapy. Commonly injected joints include the knee, ankle, and small joints of the hands and feet [33, 34, 35, 36]. Intra-articular injection of hyaluronan-derived products and steroids is a common method of treating knee osteoarthritis [34, 37, 38]. This minimally invasive procedure can cause complications that vary depending on the joint and injectable [34, 39, 40]. Similar to TMJ injections, the most common side effects of intra-articular injections in the knee are swelling or mild pain at the injection site [41]. Swelling and pain may be a reaction to the needle, the injected medication, or both [33, 42]. They can start immediately after the injection or a few hours later. In less common cases, it may be

an allergic reaction to the drug/disinfectant used to clean the skin or as a result of infection at the injection site. This reaction is usually not serious and resolves spontaneously. Cold packs and non-steroidal anti-inflammatory drugs are helpful in reducing the mild symptoms of post-injection inflammation. Sterile preparation before injection is necessary to prevent infection. If infection occurs, antibiotics may be needed [42]. Neurological complications may result from the administration of the anesthetic prior to intra-articular injection and not from the TMJ puncture itself. Therefore, it is important to obtain a detailed patient history, including allergies to anesthetics, prior to any procedure. Failure to obtain a history of anticoagulant treatment may lead to hemorrhagic complications of intra-articular injections [33, 40].

Another potential complication of minimally invasive procedures in the TMJ is bacterial infection. In iatrogenic cases, the possibility of microorganisms entering the joint structures from the skin surface as a result of inadequate disinfection should be considered. In recent years, 2 systematic reviews on septic arthritis of the TMJ have been published [43, 44]. Both studies agree that *Staphylococcus aureus* is the most commonly identified pathogen. As empirical therapy was predominant in the included studies, the duration of antibiotic treatment was usually prolonged to more than 30 days. Cephalosporin and metronidazole were the most commonly prescribed antibiotics, whereas staphylococci and streptococci require glycopeptide antibiotics or penicillins/cephalosporins that are resistant to beta-lactamases [44]. It is therefore advisable to check the susceptibility of the microorganism to antibiotics and to use a 2-week course of targeted antibiotic therapy. The most commonly used drugs in the treatment of septic arthritis of the TMJ are listed in Table 4. In particularly advanced cases, surgery should be considered [43, 44].

Adverse events may vary depending on the substance administered. Some side effects of corticosteroid therapy, such as sensory disturbances and skin atrophy, can be classified as treatment-emergent [16, 17, 28, 31]. In the group of patients treated with hyaluronic acid and saline placebo, only transient pain, swelling at the injection site, and transient dysfunction of the TMJ were observed [27, 31]. The results of this systematic search and review do not prove the safety of TMJ injection treatment protocols that are currently being developed for sequential injectables [15, 45]. It is important that clinicians always consider potential complications and minor inconveniences and thus seek the right balance between the benefits and potential risks of injection therapies [16].

Limitations

Due to the difficulty of creating a query that would identify adverse events unknown to the researchers, some may not have been identified. The searches were limited to 1 engine and therefore did not include reports indexed in other ways.

CONCLUSIONS

There are at least 14 types of adverse events associated with therapeutic injections into the TMJ. In the material reviewed, approximately half of these were temporary pain and/or swelling. Collectively, the 14 types of adverse events were divided into 3 categories (distant, local, and articular), none of which were fatal or life-threatening. These were, in order of most common: pain and/or swelling (52%), ear pressure (5%), eyelid paresthesia (5%), periarticular tissue atrophy (5%), generalized rash (4%), hypoesthesia (4%), open bite (4%), skin hypopigmentation (4%), headache (3%), local rash (3%), malocclusion (3%), mandibular hypomobility (3%), TMJ noises (3%), and fever (2%).

TABLE 4. Antibiotics used in septic arthritis of the temporomandibular joint

Authors (publication date)	Antibiotics
Jovanović et al. (2022) [44]	• third generation cephalosporin + metronidazole, • amoxicillin with clavulanic acid, • clindamycin + (optional) ciprofloxacin/ third generation cephalosporin, • meropenem + (optional) levofloxacin, • penicillinase-resistant penicillins (flucloxacillin, nafcillin), • penicillin G + (optional) gentamycin, • erythromycin + (optional) third generation cephalosporin, • ciprofloxacin, • voriconazole + (optional) metronidazole
Omiunu et al. (2021) [43]	• cephalosporin, • metronidazole, • penicillin-derived antibiotics, • clindamycin, • fluoroquinolones, • vancomycin

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