

# Intra-Lesional Medicaments for the Management of Intra-Osseous Lesions of Maxilla and Mandible - Systematic Review

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## ABSTRACT

**Aims and Objectives:** This study aimed to review the success or remission of intralesional medicaments in the management of intraosseous lesions in the oral cavity. **Materials and Methods:** A comprehensive search was performed in two databases (PubMed and Scopus). Research articles, case reports, case series, and clinical trials were included. Review articles, lesions not involving the bone, incomplete reporting, any other treatment other than intralesional medicaments to treat intraosseous bone lesions, publications without any treatment, and letter to editor were excluded. Data on remission (complete, partial, or no remission), details and regimen of the intervention, number of participants, and follow-up in months were recorded. **Results:** A total of 653 publications were available for title and abstract screening after the removal of duplicates. Seven articles were excluded, which were not in English. After title and abstract screening, a total of 88 publications were available for full-text screening. Fifty-five articles were included in qualitative synthesis. A total of 168 patients from 55 publications were evaluated. Minimum follow-up was 1 month and maximum was 264 months. More than two-third ( $n = 38$ ) of the publications were case reports on single patient. More than two-third ( $n = 38$ ) of the publications had complete remission. **Conclusion:** Intralesional medications have shown variable success rates. Extensive lesions may undergo intralesional medications followed by surgical management.

**KEYWORDS:** Aneurysmal bone cysts, giant cell granuloma, intralesional injections, langerhans cell histiocytosis, vascular malformation osseous

## INTRODUCTION

The myriad pathological entities involving the mandible can be odontogenic or non-odontogenic in origin. Most of these lesions are treated surgically by curettage, resection, and so on, along with chemotherapy, radiation, or pharmaceutical management. In most cases, surgical intervention has proven to be a complete cure; however, recurrences have been reported by multiple authors for various diseases.

Moreover, for large lesions, surgical intervention may result in detrimental postoperative functional, aesthetic, or neurological outcomes. Hence, health-care professionals have tried pharmacological aids such as

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intralesional medications. Intralesional injections (ILIs) mean those injections with standard dosage, which are injected directly into a lesion on or immediately below the skin or mucosa.<sup>[1]</sup>

Reports in the past have used intralesional steroids for the treatment of intraosseous lesions with different regimens. For example, central giant cell granuloma (CGCG) have been treated with intralesional steroids with different regimens viz., weekly<sup>[2,3]</sup> or biweekly,<sup>[4,5]</sup> different doses viz., 10mg/mL,<sup>[6,7]</sup> 20mg/mL,<sup>[4,5]</sup> or 40mg/mL;<sup>[8,9]</sup> and different durations viz., 5 weeks,<sup>[2]</sup> 6 weeks,<sup>[10,11]</sup> 9 weeks,<sup>[2]</sup> and 11 weeks.<sup>[3]</sup> There is no lack of consensus and mostly dictated by the clinician judgment and or radiological improvement in the subjects. Similarly, langerhans cell histiocytosis (LCH) of jaws has been treated with intralesional steroids with different regimens.<sup>[12,13]</sup> However, these conditions have been predominantly treated by ILI of steroids.

There is lack of consensus with respect to the duration, frequency, dosage, criteria, or guideline for improvement for these intraosseous conditions. Also, majority of these publications are case reports and case series. With this background, we aimed to systematically review the existing literature on intralesional treatment of intraosseous lesion of the jaws and provide summary on remission, dosage, regimen, and follow-up.

## MATERIALS AND METHODS

A comprehensive search was performed in two databases (PubMed and Scopus) up to August 31, 2019 separately for each condition. The keywords included in the search strategy for all the databases are listed in Table 1. The studies from these databases were imported to Rayyan website for the removal of duplicate titles. The remaining articles had their title and abstracts screened (GS and KS) for inclusion in the full text review. Articles were subjected to full-text screening by two reviewers (PKC and GS). Discrepancies if any were resolved by third reviewer (MB). Research articles, case reports, case series, and clinical trials were included. The inclusion criteria were subjects of any age group and those treated with any of the established intralesional treatment protocols. The exclusion criteria were only review articles, lesions not involving the

bone, incomplete reporting, any other treatment other than intralesional medicaments to treat intraosseous bone lesions, publications without any treatment, and letter to editor. Data on remission (complete, partial, or no remission), details and regimen of the intervention, number of participants, and maximal follow-up in months were recorded independently by two reviewers. No attempt was made to contact the authors for any additional data.

## RESULTS

A total of 233, 71, 149, and 37 publications were reported from PubMed for CGCG, central hemangioma, central vascular malformations (CVMs), aneurysmal bone cyst, and langerhan cell histiocytosis, respectively. Similarly, 226, 17, 147, and 5 publications were reported from Scopus for CGCG, central hemangioma or CVMs, aneurysmal bone cyst, and langerhan cell histiocytosis, respectively. Reference lists of articles were further searched to identify other articles that may have been missed during the respective database searches with the keywords ( $n = 17$ ). A total of 653 publications were available for title and abstract screening after the removal of duplicates. Seven articles were excluded, which were not in English. After title and abstract screening, a total of 88 publications were available for full-text screening. Fifty-five articles were included in qualitative synthesis [Figure 1].

A total of 168 patients from 55 publications were evaluated. Minimum follow-up was 1 month and maximum was 264 months. The age ranged from 3 to 84 years. More than two-third ( $n = 38$ ) of the publications were case reports on single patient. More than two-third ( $n = 38$ ) of the publications had complete remission.

## DISCUSSION

CGCG was first introduced by Jaffe<sup>[14]</sup> and described by WHO<sup>[15]</sup> as an aggressive idiopathic benign intraosseous lesion that occurs almost exclusively in the jaws. Generally, this lesion is classified as either a nonaggressive and an aggressive form; the aggressive form is characterized by a size larger than 5cm, rapid growth, high recurrence, thinning and/or perforation

**Table 1: List of keyword lesions used for the building search strategy**

Pathology	Intervention	AND	Site
Central giant cell granuloma (CGCG) Langerhan cell histiocytosis (LCH) Hemangioma and central vascular malformations (CVM) Aneurysmal bone cyst (ABC)	“Management” OR “treatment”	AND	“Maxilla” and “mandible” OR “jaws”

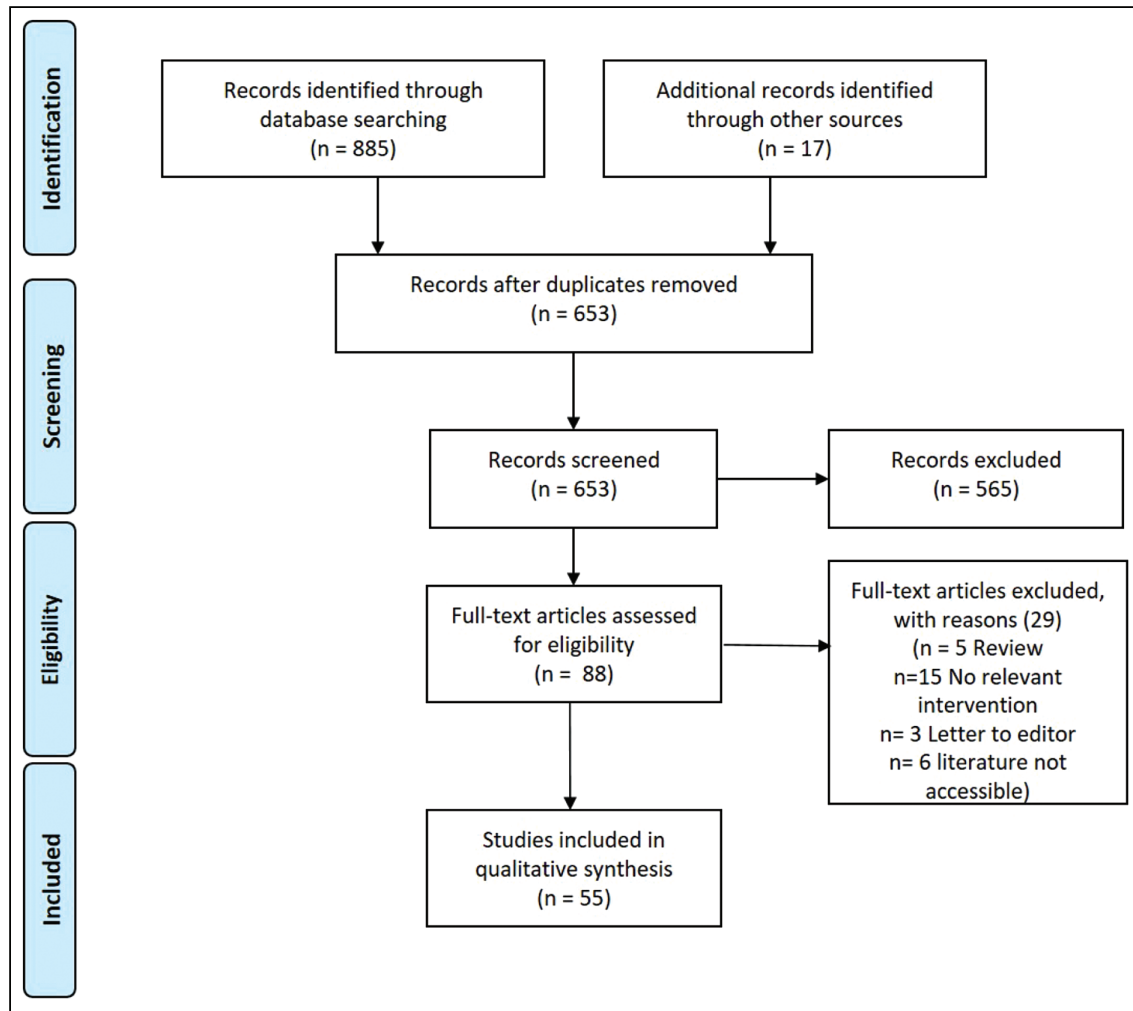


Figure 1: PRISMA flow chart of articles for review

of the bone, tooth mobility, rotation, and/or root resorption.<sup>[16]</sup> Medical management of CGCG includes intralesional steroids, calcitonin, interferon- $\alpha$ , and bisphosphonates. However, only corticosteroids have been used as ILI.

ILI was first reported by Jacoway *et al.*;<sup>[17]</sup> the rationale for its use was based on its histological similarity to sarcoid and with proven effect of corticosteroids on the treatment of the latter.<sup>[9]</sup> Corticosteroids act by suppressing angiogenesis of the lesion and inhibiting bone resorption by inhibiting protease production from multinucleated giant cell and apoptosis of osteoclastic cells.<sup>[18]</sup> The success of the ILI for the management of CGCG of various reports is listed in Table 2. A total of 34 publications have used intralesional steroids for the treatment of CGCG. Of which 22 publications have reported complete remission. Two complications with the use of ILI of corticosteroids have been reported such as central retinal artery occlusion resulting in blindness<sup>[19]</sup> and cushinoid appearance of the patient.<sup>[6]</sup>

Studies in the past have used calcitonin in the treatment of CGCG through subcutaneous or intranasal routes.<sup>[41-47]</sup> However, till date no studies have reported the treatment of CGCG with ILI of calcitonin. Limited case reports have been published on the use of subcutaneous injections of interferon- $\alpha$  as a treatment for aggressive CGCG with variable success rates.<sup>[48-52]</sup> However, no studies have used ILI of interferon- $\alpha$  in the treatment of CGCG.

LCH is a disease characterized by cell proliferation with three clinical forms such as Letter–Siwe disease (acute disseminated form), Hand–Schüller–Christian syndrome (chronic disseminated form), and localized LCH (localized form) also known as eosinophilic granuloma.<sup>[53-55]</sup> Treatment options include resection, curettage, chemotherapy, radiotherapy, or a combination of them. The principal modality is surgical curettage but is limited by the extent of the lesion, which, in the case of extensive lesions, may result in a loss of function and disfigurement.<sup>[56]</sup>

**Table 2: Characteristics of the reports that used ILI for the management of CGCG**

Author	N	Regimen	Result	Follow-up in months
Terry and Jacoway <sup>[17]</sup>	4	Triamcinolone 10 mg/mL and marcaine 0.5%, 1:1; 2 mL per 2 cm of the lesion, once a week for 6 weeks.	Complete remission	16–36
Kermer <i>et al.</i> <sup>[20]</sup>	1	Triamcinolone 10 mg/mL and lidocaine 0.5%, 1:1; 3 mL, once a week for 5 weeks.	Complete remission	36
Rajeevan and Soumithran <sup>[11]</sup>	1	Triamcinolone 10 mg/mL and lidocaine 0.5%, 1:1; 2 mL per 2 cm of the lesion, once a week for 6 weeks.	Complete remission	10
Khafif <i>et al.</i> <sup>[10]</sup>	1	Triamcinolone 40 mg/mL and marcaine 0.5%, 1:1, once a week for 6 weeks.	Complete calcification of the lesion.	24
Kurtz <i>et al.</i> <sup>[21]</sup>	1	Triamcinolone 10 mg/mL and marcaine 0.5%, 1:1; 2 mL per 2 cm of the lesion, once a week for 6 weeks.	Complete remission after two treatment sessions.	18
Adornato and Paticoff <sup>[22]</sup>	1	Triamcinolone 10 mg/mL and marcaine 0.5%, 1:1; 2 mL per 2 cm of the lesion, once a week for 6 weeks.	Complete remission	7
Carlos and Sedano <sup>[23]</sup>	4	Triamcinolone 10 mg/mL and marcaine 0.5%, 1:1; 6 mL, variable number of injections (3–20). Additional surgery in two patients.	Variable from considerable regression to complete remission.	48–84
Abdo <i>et al.</i> <sup>[24]</sup>	1	Weekly, three weeks	Complete remission	18
Sezer <i>et al.</i> <sup>[25]</sup>	1	5 mL injection of triamcinolone acetate 10 mg/mL, and lidocaine solution 2% with epinephrine 1:200,000, 1:1; once a week for 6 weeks.	Complete remission	36
Mohanty and Jhamb <sup>[2]</sup>	2	Triamcinolone 10 mg/mL and lidocaine, 1:1; weekly for five weeks in one case and 9 weeks in the other.	Complete remission	13–18
Wendt <i>et al.</i> <sup>[3]</sup>	1	Triamcinolone 10 mg/mL and 0.5% bupivacaine, 1:1; weekly for 11 weeks	Complete remission	72
Al-Ahmad <i>et al.</i> <sup>[26]</sup>	1	Surgery followed by ILI (triamcinolone acetate) once a week for 6 weeks.	Complete Remission	36
Nogueira <i>et al.</i> <sup>[5]</sup>	21 Cohort Study	Triamcinolone hexacetate (20 mg/mL) twice weekly for three weeks. Superadded with osteoplasty in 8 cases, curettage in three cases and surgical resection in two cases.	15 good responses, four moderate, and two negative response.	48–84
Shirani <i>et al.</i> <sup>[18]</sup>	1	40 mg/mL triamcinolone acetate mixed with 5 cc lidocaine 1% with 1:200,000 epinephrine, weekly for six weeks.	Minimal response and presence of side effects.	10
Ferretti <i>et al.</i> <sup>[9]</sup>	1	Triamcinolone acetate (40 mg/mL) twice weekly; three injections.	Complete remission	48
Rachmiel <i>et al.</i> <sup>[7]</sup>	1	Triamcinolone aqueous suspension (10 mg/mL) six weeks along with calcitonin nasal spray 200 IU/day for three months. After which curettage and osteotomy were done.	Complete remission	60
Da Silva <i>et al.</i> <sup>[27]</sup>	1	Triamcinolone acetate (40 mg/mL) 10 injections, seven of which were given over a period of approximately 15 days and the remaining three injections over the course of one month. Alendronate sodium (70 mg) and weekly oral calcium carbonate (500 mg).	Complete remission	24
da Silva Sampieri <i>et al.</i> <sup>[28]</sup>	1	Calcitonin 60-mg thrice weekly but changed to corticosteroid because of side effects of calcitonin. Treatment continued with triamcinolone	Complete remission	24
Fonseca <i>et al.</i> <sup>[29]</sup>	1	Triamcinolone (40 mg/mL)	Partial remission	24
El Hadidi <i>et al.</i> <sup>[6]</sup>	1	Triamcinolone (10 mg/mL) twice weekly for three months	Complete remission	12

Table 2: Continued

Author	N	Regimen	Result	Follow-up in months
Özlem Filiz and Gülsüm <sup>[30]</sup>	1	Triamcinolone (40mg) weekly for six weeks.	Complete remission	12
Gupta et al. <sup>[31]</sup>	1	Triamcinolone (weekly 20mg for six weeks). Followed by triamcinolone (40mg) weekly.	No remission	12
Bhushan et al. <sup>[19]</sup>	1	Triamcinolone acetamide 10 mg	No remission	1
Badr <sup>[19]</sup>	1	Weekly triamcinolone acetamide (40mg) for six weeks. Postsurgery nine injections over a period of 12 weeks	No remission with ILI. Postsurgery + ILI resulted in complete remission	60
Pakla et al. <sup>[32]</sup>	1	20 injections of triamcinolone hexacetamide at weekly intervals	Partial remission	5
Maia Nogueira <sup>[33]</sup>	1	Biweekly application of triamcinolone hexacetamide (20 mg/mL) for 6 weeks	No remission	4
Dolanmaz et al. <sup>[34]</sup>	7	Weekly triamcinolone injections for six weeks.	Partial remissions	39
Chandna et al. <sup>[35]</sup>	2	Weekly injections triamcinolone acetamide (kenalog 10; 10mg/mL) for six weeks	Partial remission	12
de Oliveira et al. <sup>[36]</sup>	1	Nine injections with a gap of 15 days (triamcinolone hexacetamide)	Complete remission	6
Batista Severo et al. <sup>[4]</sup>	15	Six biweekly ILI of triamcinolone hexacetamide (20mg/mL).	Nine complete remission four partial response	52.80 ±44.72
Pinheiro da Rosa et al. <sup>[37]</sup>	1	Weekly ILI of triamcinolone (10mg/mL) for 6 weeks.	Complete remission	48
Moura et al. <sup>[38]</sup>	1	Triamcinolone (10mg/mL) for 8 session	Complete remission	36
Cavalcante et al. <sup>[39]</sup>	16	6 ILI of triamcinolone hexacetamide in biweekly intervals	Partial remission	12
de Mendonca et al. <sup>[40]</sup>	1	Triamcinolone actinide (20mg/mL (total 40 doses with once a week alendronate sodium and calcium carbonate.	Partial remission	72

A total of eight publications reported the treatment of LCH in 11 patients with intralesional steroids injections [Table 3]. All the publications showed complete remission with a minimum of 4 and maximum of 108 months' follow-up.

CVMs are categorized into low-flow lesions (such as lymphatic, venous, and capillary malformations) and high-flow lesions (such as AV malformations and AV fistula). Arterial vascular malformations (AVMs) are the most common malformations, and its occurrence in the maxillofacial region is frequently devoid of any signs or symptoms until they are extensive enough to cause pain, facial asymmetry, pressure on adjacent structures, auditory and visual problems, mandibular destruction, mobility of the tooth, and bleeding gums. They have a high propensity to bleed, which may be life-threatening.<sup>[63-66]</sup>

Treatment for such options is nonsurgical or surgical, with the former including intravascular embolization with/without sclerosants. Surgical correction is reserved because of its high propensity to bleed and is used for extensive lesions. Selective angiographic embolization

is considered first-line treatment with/without surgical approach to contain the bleeding.

A total of nine publications reported the treatment of CVM in 54 patients [Table 4]. Majority of the publications showed complete remission ( $n = 7$ ) with a minimum of 6 and maximum of 144 months' follow-up.

ABC is a benign cystic lesion of the bone comprising blood-filled spaces separated by connective tissue. It has a rapid growth pattern, which results in bony expansion and facial asymmetry. Treatment of an ABC is usually complete surgical removal of the lesion, along with surgical curettage or block resection. Because of its multilocular appearance and multiple bony septae, the chance of recurrence is high postsurgery. Surgical management, along with medical management, has been advised to reduce the risk of recurrence.

A total of four publications reported the treatment of ABC in 13 patients [Table 5]. Majority of the publications showed partial remission ( $n = 3$ ) with a minimum of 4 and maximum of 108 months' follow-up.

**Table 3: Characteristics of the reports that used intralesional medications for the management of LCH**

Authors	N	Regimen	Result	Follow-up in months
Cohen <i>et al.</i> <sup>[57]</sup>	1	150 mg intralesional methylprednisolone; two injections	Complete remission in 11 months.	11
Jones <i>et al.</i> <sup>[58]</sup>	1	Intralesional 164 mg methylprednisolone; one dose	Complete resolution in 8 months	8
Watzke <i>et al.</i> <sup>[59]</sup>	1	2 mL ILI of 25 mg/cc triamcinolone acetonide; weekly for six weeks.	Complete remission after 15 months.	108
Putters <i>et al.</i> <sup>[60]</sup>	3	Intralesional methylprednisolone 40 mg in one case and 80 mg in two	Complete remission in 3–6 months.	30–108
Moralis <i>et al.</i> <sup>[113]</sup>	1	200 mg intralesional methylprednisolone; one dose.	Complete remission in 17 months.	17
Esen <i>et al.</i> <sup>[112]</sup>	1	ILI methylprednisolone succinate 2 mL; 40 mg/mL; three injections(80–80–60 mg) over 8 months	Complete remission in 14 months.	36
Lee <i>et al.</i> <sup>[61]</sup>		One case received a 3 mL ILI of methylprednisolone 40 mg/mL; Other cases initial therapy with prednisolone and vinblastine followed by one year therapy using 6 mercaptopurine, prednisolone, and vinblastine	Complete remission in 6–7 months.	35 and 15
Hutchison <i>et al.</i> <sup>[62]</sup>	1	Methyl prednisolone	Complete remission	4

**Table 4: Characteristics of the reports that used intralesional medications for the management of CVM**

Authors	N	Regimen	Result	Follow-up in months
Thorn <i>et al.</i> <sup>[67]</sup>	2	Angiography using isopaqueamine 280, embolisation was performed with polyvinyl alcohol granules (ivalon) sized 100–150 µm, suspended in 0.8% sodium chloride and mixed with contrast medium (isopaqueamine 280).	Complete remission	8–10
Shultz <i>et al.</i> <sup>[68]</sup>	1	Cyanoacrylate (isobutyl-2-cyanoacrylate), 0.3 mL	Complete remission	48
Kaneko <i>et al.</i> <sup>[69]</sup>	1	Direct puncture embolization using <i>N</i> -butyl-2-cyanoacrylate	Complete remission	18
Giaoui <i>et al.</i> <sup>[26]</sup>	9	Gelfoam, spongel, ethibloc, and coils for arterial embolization and transcatheter transosseous embolization.	Complete remission in five local recurrence in four	6–144
Persky <i>et al.</i> <sup>[70]</sup>	31	Gelfoam, polyvinyl alcohol, isobutyl cyanoacrylate, <i>n</i> -butyl cyanoacrylate, and ethanol. Embolization only in 25 patients Embolization + surgical resection in 6 patients	Partial remission	12 - 264
Liu <i>et al.</i> <sup>[71]</sup>	8	The volume of the histoacryl glue ranged from 3 to 6 mL (NBCA diluted 30%–40% with iodized oil)	Complete remission in six and two required curettage	36- 102
Oliveira <i>et al.</i> <sup>[26]</sup>	1	Two sessions of embolization using <i>N</i> -butyl-2-cyanoacrylate (histoacryl)	Complete remission	19
Spreafico <i>et al.</i>	1	Direct injection of 3% sodium tetradecyl sulfate into the extraction socket. After 6 months methyl prednisolone acetate intraosseous injection for treatment of minor bleed.	Complete remission	6

Intraosseous lesions of the jaws were treated successfully by surgical intervention. However, conservative pharmaceutical therapies have been shown as successful as surgery with minimal complications.

ILIs have shown variable success rates with or without requirement of surgery. Extensive lesions may undergo medical management followed by surgical management. Hence, health-care providers should consider various

**Table 5: Characteristics of the reports that used intralesional medications for the management of aneurysmal bone cyst**

Authors	N	Regimen	Result	Follow-up in months
Guibaud <i>et al.</i> <sup>[72]</sup>	1	Percutaneous embolization into the lesion with alcoholic zein	Partial remission	14
Dubois <i>et al.</i> <sup>[73]</sup>	5	Sclerotherapy with diluted ethibloc with 5 cm <sup>3</sup> 100% ethanol.	Complete remission	24–108
Kumar <i>et al.</i> <sup>[74]</sup>	6	Angiography and percutaneous embolotherapy with diluted <i>n</i> -butyl cyanoacrylate glue (19–20 cc)	No remission	4
Costa de Freitas <i>et al.</i> <sup>[75]</sup>	1	Sterile freeze-dried bone allograft (40 g) washed with 0.9% sodium chloride and manually crushed with an osseous press and a bone mill. Smaller particles (30 g) were mixed with 40-mL autologous bone marrow and 10-mL nonionic iodinated contrast medium.	Partial remission	36

factors such as patient characteristics, frequency, dose and type of ILI medications, requirement of conservative or surgical or both modalities of treatment, complications that might arise because of the ILI and their management, and presence of any comorbidities that may have a role in successful management of these lesions. Most of these factors are interlinked and may require modification or alternate strategies for effective management of these lesions.

### LIMITATIONS AND FUTURE SCOPE

Most of the publications included in this systematic review were case reports and case series, which limited us to perform meta-analysis. There was no consensus definition among the included publications about the remission or success of the treatment of various lesions using intralesional medications. The success or remission of these lesions was reported in these publications as anatomical cure, clinical cure, and radiological cure, which could create ambiguity to the researchers and clinicians. A uniform consensus on the definition of success or remission should be followed. Future reports should include the patient reported outcomes of the same as one of the parameters for success. Future reports should also include radiological assessment and quantification of the improvement with the treatment.

### CONCLUSION

Most intraosseous lesions of the jaws were treated successfully by surgical intervention. Several conservative pharmaceutical therapies have been shown as successful as surgery with minimal complications. For the above-discussed intraosseous lesions, ILIs have shown variable success rates with or without requirement of surgery. Extensive lesions may undergo medical management followed by surgical management.

### SEARCH STRATEGY FOR PubMed

((((central AND giant AND cell AND granuloma)) AND (Management OR Treatment))) AND (Maxilla OR Mandible OR Jaws)

(((((Central Hemangioma OR Central Vascular malformations)) AND (Management OR Treatment))) AND (Maxilla OR Mandible OR Jaws)))  
 (((((Aneurysmal bone cyst)) AND (Management OR Treatment))) AND (Maxilla OR Mandible OR Jaws)))  
 ((((((Langerhan cell histiocytosis)) AND (Management OR Treatment))) AND (Maxilla OR Mandible OR Jaws)))

Search strategy for Scopus:

(TITLE-ABS-KEY (central AND giant AND cell AND granuloma) AND TITLE-ABS-KEY (management OR treatment) AND TITLE-ABS-KEY (maxilla OR mandible OR jaws))

(TITLE-ABS-KEY (central AND hemangioma OR central AND vascular AND malformations) AND TITLE-ABS-KEY (management OR treatment) AND TITLE-ABS-KEY (maxilla OR mandible OR jaws))

(TITLE-ABS-KEY (aneurysmal AND bone AND cyst) AND TITLE-ABS-KEY (management OR treatment) AND TITLE-ABS-KEY (maxilla OR mandible OR jaws))

(TITLE-ABS-KEY (langerhan AND cell AND histiocytosis) AND TITLE-ABS-KEY (management OR treatment) AND TITLE-ABS-KEY (maxilla OR mandible OR jaws))

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Nil.

### CONFLICTS OF INTEREST

There are no conflicts of interest.

### AUTHOR CONTRIBUTIONS

*Komal Smriti*: study conception, data collection, initial draft

*Evit John*: study conception, data collection, data acquisition and analysis, initial draft

*Kalyana-Chakravarthy Pentapati*: Data acquisition and analysis, data interpretation, final draft

*Srikanth Gadicherla*: Study conception, Data acquisition and analysis, data interpretation, final draft

**Manish Bhagania:** Data collection, data acquisition and analysis, data interpretation, final draft

All the authors approved the final version of the manuscript for publication.

#### ETHICAL POLICY AND INSTITUTIONAL REVIEW BOARD STATEMENT

Not applicable.

#### PATIENT DECLARATION OF CONSENT

Not applicable.

#### DATA AVAILABILITY STATEMENT

Data set can be made available on request from (Dr Srikanth G, gadi\_mds@rediffmail.com).

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