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Systematic review

Safety and efficacy of adjunctive therapy in the treatment of odontogenic keratocyst: a systematic review

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Abstract

The odontogenic keratocyst (OKC) is a common cystic lesion in the jaw. Its management, however, is highly debated with no consensus on the best treatment option. Clinicians base their approach on treatment efficacy and associated morbidity. Management often consists of enucleation with peripheral ostectomy and adjunctive therapy to prevent recurrence. The aim of our systematic review was to evaluate the safety and efficacy of these different modalities. Embase, Medline, and Cochrane were searched according to the PRISMA guidelines for articles that presented non-syndromic patients with histopathologically confirmed OKC treated with 5-fluorouracil (5FU), Carnoy's solution (CS), or modified Carnoy's solution (MCS) as adjunctive therapy after enucleation and peripheral ostectomy. The outcomes of interest were safety (measured as adverse events) and efficacy (expressed as recurrence). Risk of bias was evaluated using the Newcastle-Ottawa scale. Four studies were included and 62 patients were evaluated. The results show that recurrence occurred only in patients treated with MCS. Reported adverse events were mostly limited to paraesthesia that could be permanent (in the CS and MCS treatment groups) or transient (across all adjunctive therapies). With the prohibition of CS, both MCS and 5FU are promising replacement adjunctive therapies. From a safety and efficacy perspective we consider 5FU, which was associated with the lowest recurrence and fewest adverse events, to be the most viable option. More high-evidence prospective studies, such as randomised controlled trials, with a longer follow-up period are necessary to draw definite conclusions.

Keywords: Odontogenic keratocyst; Recurrence; Safety; Treatment; Review

Introduction

The odontogenic keratocyst (OKC) is the most common cystic lesion in the jaw and has been defined by the World Health Organization (WHO) as an odontogenic cyst characterised by a thin, regular lining of parakeratinised, stratified, squamous epithelium with palisading hyperchromatic basal cells.[1] The cyst arises from the dental lamina, and in most cases presents itself in the posterior body of the ramus of the mandible.[1,2] When found in other locations it is more likely to be part of a naevoid basal cell carcinoma syndrome (NBCCS). Clinical presentation varies widely and is habitually associated with a painless swelling of the soft tissues. The cyst is often an incidental finding on a routine orthopantomogram and presents as a unilocular or multilocular radiolucency. Lesions present with aggressive growth through bony resorption, and lead to possible facial deformity, tooth displacement, and expansion into adjacent structures.[1–3]

There is no consensus on the best method to remove these cysts. With a broad spectrum of treatment modalities, clinicians base their choice on the treatment's efficacy in comparison with its morbidity in a patient-specific manner.[4] Complete or partial resection has the lowest recurrence (less than 2%) but is associated with major morbidity.[5] Thus clinicians often opt for a less invasive approach preferably with the lowest recurrence rate. Enucleation is associated with the

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lowest morbidity, but also with the highest recurrence (up to 25%).[4,6–8]

To lower this recurrence rate, multiple adjuvant therapies can be applied to the remaining defect after enucleation with peripheral ostectomy. Several adjunctive therapies have been investigated to act on the peripheral lining and chemically cauterise it. Carnoy's solution (CS) (1 g of ferric chloride ($FeCl_3$) dissolved in 6 ml of alcohol, 3 ml of chloroform, and 1 ml of glacial acetic acid) has been widely used as adjunctive treatment with a resulting recurrence rate of approximately 11%, after application for three minutes to minimise side effects.[9–11] Since 2013, however, its use has been prohibited by the US Food and Drug Administration (USFDA) after banning chloroform, which was shown to be carcinogenic.[10,12] Modified Carnoy's solution (MCS) was therefore introduced with a composition comparable to CS without the chloroform.[13,14] More recently, 5-fluorouracil (5FU) was introduced for topical application because of its antimetabolic effect that leads to cell apoptosis.[10,15,16]

When comparing studies, there was a lack of systemic evidence on the efficacy, and especially on the safety, of these adjuvant therapies. The objective of the present systematic review was to assess the efficacy and safety of CS, MCS, and 5FU after enucleation with peripheral ostectomy in patients with OKC. This will help clinicians to make evidence-based decisions regarding suitable adjuvant treatment after enucleation to reduce recurrence and adverse events.

Methods

Protocol and search strategy

The PIO of the search was defined as (p) non-syndromic patients diagnosed with histologically confirmed OKC; (i) usage of 5FU, CS, or MCS as an adjunctive therapy after surgical enucleation with peripheral ostectomy of the cyst; and (o) efficacy and safety of the different treatment options. The primary outcome was the risk of recurrence after at least 12 months of follow up. Safety was evaluated through adverse events and defined as the secondary outcome. These events were taken into account at any time after surgery and were assessed using the common terminology for adverse events (CTCAE).[17] Furthermore, we included only adverse events that were possibly, probably, or definitely related to the study drug. As there is no official gold standard for adjunctive therapy, no comparator was used.

The systematic review was performed according to the Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[18] Data were gathered from Embase, Medline, and Cochrane, and the search was concluded in October 2022. The search strategy combined database thesaurus terms (MeSH and EMTREE) and free terms in abstract and title (Supplemental Appendix A).

Study selection

Only full-length articles in English published from 1994 until October 2022 were considered because the standard practice of a maximum application duration of three minutes was introduced for Carnoy's solution in 1994.[19] Inclusion criteria were: histopathologically confirmed diagnosis of OKC, use of adjunctive therapy in combination with enucleation and peripheral ostectomy, and mention of recurrence or adverse events after treatment. Exclusion criteria were: patients with NBCCS, the inclusion of other cysts, surgical enucleation as monotherapy (without adjunctive therapy), or no mention of recurrence or adverse events in the study outcomes, review articles, letters to the editor, animal studies, poster abstracts, articles that included patients treated before 1994, non-primary OKC, no peripheral ostectomy or a surgical approach in two stages, an application time of more than three minutes for CS and MCS, and studies that did not focus on recurrence and adverse events or adverse events alone, or those with a follow-up period for recurrence of less than 12 months.

First, all titles and abstracts were assessed according to the eligibility criteria using Rayyan software.[20] Secondly, full-text articles were screened and those fitting our criteria were included.

Data extraction

A data checklist was used to ensure similar extraction between the different studies. The following data were included in the checklist: author and year of publication, country in which the study was performed, study design, data collection period, population and treatment groups, inclusion and exclusion criteria, mean age, gender, location of the OKC (mandible or maxilla), lesion characteristics, type of adjunctive therapy, recurrence, adverse events, follow up, and funding or competing interests.

Risk of bias and applicability

Risk of bias and concerns of applicability in the individual studies were evaluated using the Newcastle-Ottawa scale.[21]

Results

Study selection and study characteristics

The search found 192 results and after the removal of duplicates, 140 articles were screened for title and abstract. A total of 17 articles were screened on full-text, and four studies were included: an ambispective cohort study by Ledderhof et al,[22] a retrospective cohort study by Ribeiro-Junior et al,[23] a case report study by Matijevi et al,[24] and a prospective cohort study by Akhter Lone et al.[25] The PRISMA flow diagram is shown in Figure 1.

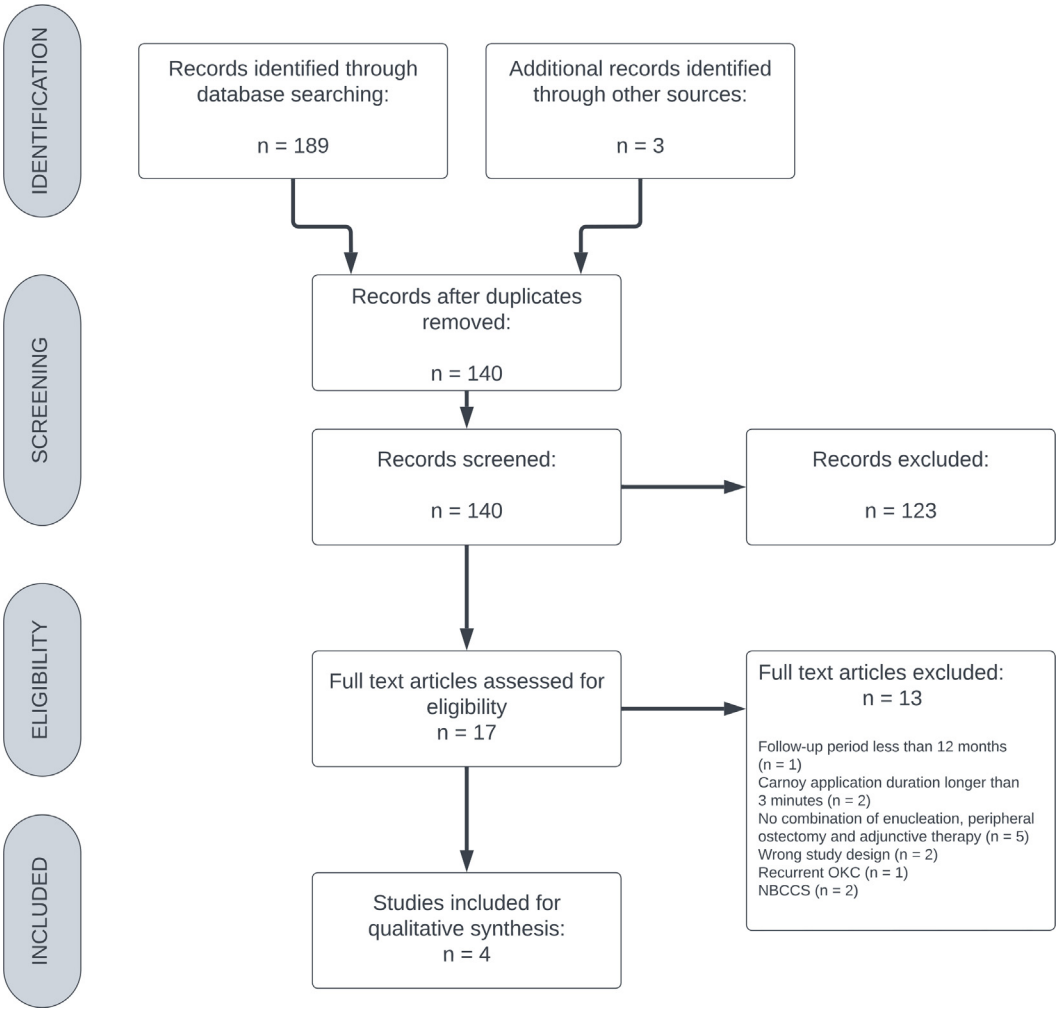

Fig. 1. PRISMA flowchart of the selection process.

Results of individual studies

All the information retrieved from the individual articles can be found in our data extraction table (Supplemental Appendix B). All the included study data were collected over a period of five to eight years.[22–25] A total of 62 patients were included, 22 treated with 5FU, 30 with MCS, and 10 with CS as adjunctive treatment to enucleation with peripheral ostectomy. Most lesions were located in the mandible.[22–25] Two studies included more unilocular lesions,[21,22] while one study had a multilocular predominance.[25]

The overall application and composition of CS and MCS were comparable throughout the studies. There were directives in clinical practice to minimise contact between the healthy tissue and the solutions, and also strict instructions for preparation of the solutions.[15,26]

The primary outcome of this study was risk of recurrence. Of the 62 patients included, the recurrence rates varied from 19% to 66%. Two studies only reported results for patients treated with CS. In these studies the follow-up period was 41.8 months and 60 months, and they showed no recurrence within this time period.[23,24] No recurrence was reported in patients treated with 5FU, with mean (SD) follow-up times of 35.0 (8.5)[22] and 42 months.[25] The recurrence rates in patients treated with MCS were 19% (n = 4) and 67% (n = 6) with respective mean (SD) follow-up periods of 41.3 (3.8) and 42 months.[22,25] One study disclosed a mean (SD) recurrence-free survival of 26.3 (1.8) months.[22]

The secondary outcome of the review, adverse events, was assessed according to the CTCAE. Mild symptoms of paraesthesia, a grade 1 adverse event, were predominant.[17,22–25] Patients treated with MCS across all studies reported paraesthesia. Transient paraesthesia was reported in 78% (n = 14)[22] and 56% (n = 5)[25] of these patients. In one study the mean (SD) recovery period was 29.0 (10.6) weeks.[22] Permanent paraesthesia was also reported in 22% (n = 4)[22] and 11% (n = 1).[25] Patients treated with 5FU presented with only transient paraesthesia as an adverse event. The complaints appeared in 33% (n = 3)[22] and 9% (n = 1)[25] of patients, with one study describing a mean (SD) recovery period of 42 (10) weeks.[22] Mild postoperative paraesthesia was diagnosed in 25% (n = 2) of patients treated with CS. In 50% (n = 1) it was transient with clinical recovery after 48 months, in the other 50% (n = 1) it was perma-

nent.[23] The included case report did not report any postoperative adverse events after the use of CS.[24] Further, in one study, wound dehiscence was described in 11% of patients treated with CS (n = 1).[23]

Risk of bias assessment

All studies included were assessed for bias concerning selection, comparability, and outcome using the Newcastle Ottawa Scale (Supplemental Appendix C).[21] Regarding selection bias, all studies ensured an ascertainment of exposure and showed that the outcome of interest was not present at the start of the study. High selection bias was due to low representativeness in the case report, and to a lack of exposure differentiation because of the retrospective approach.[23,24] A retrospective approach focuses on the treatment given to the patient, not on the initial clinical presentation. Patients with smaller lesions or milder symptoms might be involuntarily excluded. All studies presented with high comparability bias as there was only univariate analysis of study controls. The overall outcome bias was low as its criteria were based on follow up that was well assessed in all the studies.[22–25]

Discussion

Primarily, a notable finding in the overall assessment of the studies was that there were no direct comparisons between the use of CS (the previous gold standard) and 5FU (a promising new modality) as adjunctive therapies. This occurred because their use never overlapped in clinical practice,[12,15] and this made qualitative assessment of the adjunctive therapies difficult.

The key findings of this systematic review can be summarised as follows. First, only three adjunctive therapies were assessed for safety and efficacy. It is important to mention that more are available and are being investigated. Secondly, the efficacy of the therapies across the studies showed that MCS was the only treatment with recurrence. No study mentioned patients with recurrence after treatment with CS or 5FU. Follow up, however, should be prolonged to ensure better assessment. Thirdly, when studies mentioned adverse events, they were mostly limited to paraesthesia. All the therapies mentioned transient paraesthesia, but only patients treated with CS and MCS reported permanent effects.

CS and MCS are cauterising agents. Their working mechanisms cause local coagulative fixation with consistent macroscopic and microscopic presentation.[11,26,27] Clinicians have also proposed cryotherapy, which causes cell death through extracellular and intracellular formation of ice crystals in combination with osmotic and electrolyte disturbances, as a fixative type of adjunctive therapy. Its use shows no bleeding and relatively low scarring, but it has imprecise tissue necrosis formation and a recurrence rate of 22%.[7,28] Its current safety and efficacy profile does not present it as a suitable replacement in clinical practice, but it could be improved with more research.[7] 5FU is a chemotherapeutic drug with an antimetabolite effect that disrupts the cell RNA and causes apoptosis.[16] As the understanding of genetics involved in the emergence of OKC grows, more hypotheses to target specific genes are under investigation. We found only in-vitro studies and theoretical speculation, but this type of treatment presents opportunities for the future.[29,30]

Efficacy

Across the different adjunctive therapies the overall recurrence rate in patients treated with MCS ranged from 19% to 67%.[22,25] Patients treated with CS and 5FU did not present any recurrence.[22,25] An important factor in the assessment of recurrence is the duration of follow up after surgery. The follow-up period of all included patients was longer than 12 months with a maximum of 60 months.[22–25] Only one study disclosed a mean (SD) recurrence-free survival of 26.3 (1.8) months before the patients treated with MCS presented with relapse.[22] OKC are cysts that can recur a long time after the initial treatment, and consistent, standardised follow up is important to ensure a quick diagnosis and prevent the appearance of symptoms. The included studies all had a follow up shorter than five years, but we advocate follow up of 25 years with varying degrees of intensity. We advise that patients are clinically examined postoperatively at one, three, and six months, and one year. At one year a radiographic orthopantomogram can be useful. This yearly clinical and radiological examination should be continued until five years after surgery, and afterwards it should be continued two-yearly. This plan should enable early diagnosis and ensure low invasive treatment in case of recurrence.[8,15,31,32]

Safety

The main adverse event assessed in the included studies was paraesthesia in the dermatome innervated by the inferior alveolar nerve. The results showed overall transient paraesthesia ranging from 9% (n = 1)[24] to 78% (n = 14),[22] and permanent paraesthesia ranging from 11% (n = 1)[25] to 22% (n = 4).[22] Paraesthesia presented as an adverse event in all three groups. Nevertheless, patients treated with 5FU did not experience permanent complaints, unlike those treated with CS and MCS. No unique explanation accounts for this variation in the gravity of neurological symptoms per treatment modality. However, CS and MCS have been found to reduce the number of axons conducting action potentials due to ion changes, which might cause permanent damage when intense enough.[19] It is important to mention that paraesthesia can also be linked to perioperative nerve manipulation.[33]

Only one study mentioned another adverse event, wound dehiscence. No further notion on the evolution was described.[23] Literature report that possible adverse events of OKC treatment are bone defects, infection, oronasal communication, and others.[34,35] Moreover, topical application of 5FU on the skin has been known to cause lesions such as

ulceration, erythema, and erosion.[36] Further research on local side effects is therefore advised to obtain a better risk assessment.

Limitations of the review method

When studies focused on the recurrence rate of adjunctive therapies as the primary outcome, adverse events were merely reported as additional findings. Furthermore, we noted imprecise data as well as a high risk of bias. The reported data should therefore be considered with care. Finally, comparison of the studies in this review was qualitative.

Conclusion

We conclude that MCS, CS, and 5FU are adjunctive therapies with differences in reported results on safety and efficacy. With the information retrieved from this review, it is plausible to consider 5FU instead of MCS as a replacement for CS given its reduced recurrence rates and its lower risk of permanent paraesthesia. Randomised controlled trials with broader evaluation of the adverse events of adjunctive therapies are encouraged to optimise clinical guidelines and prevent comorbidity and recurrence in patients with OKC.

Ethics statement/confirmation of patient permission

No ethics approval needed. No patient consent needed.

Conflict of interest

We have no conflicts of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bjoms.2023.04.006.

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