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Original Article

A Comparative Assessment of Topical 5-Fluorouracil and Modified Carnoy's Solution for the Treatment of Odontogenic Keratocyst

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ABSTRACT

This study sought to investigate the potential of 5-fluorouracil (5-FU) as an alternative treatment for odontogenic keratocysts (OKC) in the mandible. A total of 17 patients, diagnosed with non-syndromic and non-recurrent OKC, participated in this prospective and comparative clinical trial. All patients underwent enucleation and peripheral osteotomy of the cyst. Following this procedure, group A (n = 9) was treated with 5-FU, while group B (n = 8) received modified Carnoy's solution (MC). The primary outcomes assessed included recurrence, nerve paresthesia, and bone healing. Statistical analysis for age, lesion size, gender, and location was performed using analysis of variance and the chi-square test. Kaplan-Meier analysis was used to use recurrence, and an unpaired t-test was used to compare bone healing. The patients' ages ranged from 26 to 61 years, with a male-to-female ratio of 1.8:1. The follow-up period was 43.7 months for group A, and 47.5 months for group B. The 5-FU group showed no recurrence, while 25% of the MC group (n = 2) experienced recurrence. Kaplan-Meier survival analysis showed a 90% disease-free survival rate at 30 months for the MC group, which decreased to 70% at 60 months. Temporary nerve paresthesia was observed in 28.5% (n = 2) of the 5-FU group and 42.8% (n = 3) of the MC group, with all cases resolving completely. Bone healing, measured by changes in grey-level score, showed a mean increase of 36.52 ± 2.96 for the 5-FU group and 34.064 ± 6.52 for the MC group, with no significant difference between the groups (P = 0.225184). In summary, 5-FU proved to be a promising treatment for OKC, showing lower recurrence and nerve paresthesia rates compared to MC.

Keywords: 5-Fluorouracil, Odontogenic cyst, Keratocystic odontogenic tumor, Enucleation.

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Introduction

Odontogenic keratocyst (OKC) is a commonly occurring jaw cyst known for its tendency to recur. Traditionally, treatment approaches vary from conservative methods, such as cyst lining enucleation, to more invasive procedures like jaw resection. Enucleation is associated with minimal postoperative complications, but the recurrence rate can be as high as 56% [1, 2]. In contrast, jaw resection with adequate bone margin clearance can significantly reduce the risk of recurrence, though it comes with higher morbidity and often requires extensive reconstructive surgeries. To minimize recurrence, adjuvant therapies such as chemical cauterization using Carnoy's solution (CS),

peripheral ostectomy, and cryosurgery are sometimes combined with enucleation [3]. CS, which contains absolute alcohol, glacial acetic acid, chloroform, and ferric chloride, has been found effective in reducing OKC recurrence after enucleation [4]. However, its use near nerves carries the risk of peripheral nerve damage, with 18% of patients experiencing inferior alveolar nerve paresthesia after using CS for mandibular OKC [5].

In 1992, the FDA classified chloroform as a carcinogen, which led to its removal from therapeutic products [6]. As a result, a modified Carnoy's solution (MC) was developed, which excludes chloroform. Research by Dashow et al. revealed a higher recurrence rate of 35% with MC, compared to a 10% recurrence rate with the original CS [7]. These issues, along with the morbidity from more invasive procedures like resection, have led to the search for alternative treatments to prevent recurrence while maintaining a more conservative approach. Both OKC and basal cell carcinoma share genetic similarities, notably mutations in the patched homolog (PTCH) gene [8]. These mutations activate the smoothened receptor and the sonic hedgehog signaling pathway, which contribute to abnormal cell growth [9, 10].

5-fluorouracil (5-FU), a drug that inhibits the sonic hedgehog gene and induces cell death, has been used topically in the treatment of basal cell carcinoma and other cancers such as hepatocellular and colorectal carcinomas [11, 12]. Although the use of 5-FU in OKC treatment has not been extensively studied, initial research by Ledderhof *et al.* [13] and Lone *et al.* [14] suggests it could reduce recurrence and nerve damage risks. This prospective study aimed to assess the effectiveness of 5-FU as an adjunct to enucleation for the treatment of non-syndromic, non-recurrent OKC in the mandible. It was hypothesized that the topical application of 5-FU after OKC enucleation would result in comparable or better outcomes in terms of recurrence and nerve paresthesia than the conventional MC solution.

Materials and Methods

A prospective, randomized, comparative clinical study was carried out at the Department of Oral and Maxillofacial Surgery, Krishna Hospital, Karad, India, after obtaining approval from the Institutional Ethics Committee. The study included patients diagnosed with odontogenic keratocysts (OKC) in the mandible, confirmed through histopathological biopsy reports, who were willing to participate and comply with follow-up visits. Enrollment took place between August 2012 and July 2018. Exclusion criteria involved patients with recurrent OKC, multiple OKCs associated with Gorlin-Goltz syndrome, lesions in the maxilla, lesions with significant cortical perforation or mucosal involvement, and those with pre-existing neurological conditions or nerve paresthesia.

Patients who met the inclusion criteria and completed at least two years of follow-up were part of the study. Participants were randomly assigned to two groups: group A (receiving 5-fluorouracil (5-FU)), and group B (receiving modified Carnoy's solution (MC)). Randomization was done using a computer-based software program (Clinstat, MS-DOS program, Bland M). The study compared the two treatment methods, with the primary outcome variables being recurrence (presence or absence), time to recurrence, incidence of inferior alveolar nerve paresthesia, and bone healing two years after surgery. Additional variables assessed included age, gender, lesion location (anterior mandible, body, body-ramus, ramus), and tumor size (measured by the largest dimension on computed tomography). The diagnosis of Odontogenic keratocyst was confirmed through the biopsy report.

All participants underwent initial screening with orthopantomograms, followed by detailed imaging using computed tomography (with contrast when necessary). Patients with large cortical perforations, important involvement of the mandible's lower border, or oral mucosal involvement were excluded. Before proceeding with cyst enucleation under general anesthesia, the potential risks, surgical procedure, potential risks, and benefits of 5-FU and MC treatment were explained to the patients, and informed consent was obtained.

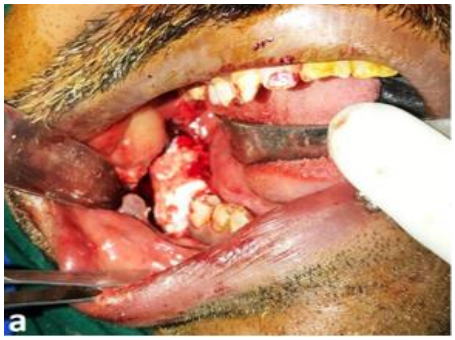
Protocol for enucleation and topical 5-FU application (group A)

All lesions were accessed via an intraoral incision. A bone window was created on the buccal cortex, and the cyst lining was carefully enucleated. Peripheral ostectomy was performed using a round motorized bur, with extra caution taken to avoid osteotomy near the inferior alveolar canal if the lesion was nearby. Afterward, the bone cavity was prepared for treatment with 5-fluorouracil (5-FU, 5% w/w cream). A sterile ribbon gauze soaked in 5-FU was placed in the cavity (**Figure 1a**). The oral mucosa was primarily closed, with the end of the ribbon gauze left exposed in the oral cavity. It was removed on the first postoperative day, 24 hours after placement.

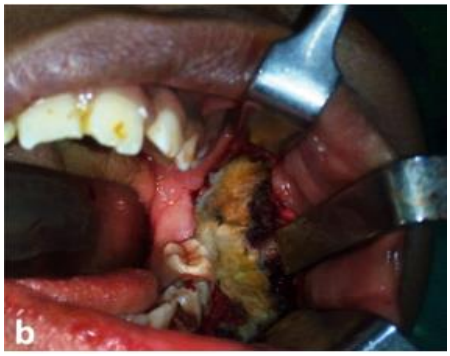
Protocol for enucleation and topical MC application (group B)

The cyst was accessed and enucleated following the same protocol as in group A. After completing

peripheral ostectomy, the cyst cavity was prepared for the application of modified Carnoy's solution (MC). If the inferior alveolar nerve was exposed during the surgical procedure, the nerve was isolated with paraffin-impregnated gauze (Bactigras dressing, Smith & Nephew Pvt Ltd) before applying the MC. Cotton applicators soaked in MC (composed of 60% ethanol, 10% glacial acetic acid, and one g of ferric chloride) were carefully placed into the bone cavity and left for 3 minutes, following the method outlined by Abdoola *et al.* [15] (**Figure 1b**). After the MC-soaked cotton was removed, the surgical site was closed with sutures for primary closure of the overlying mucosa.



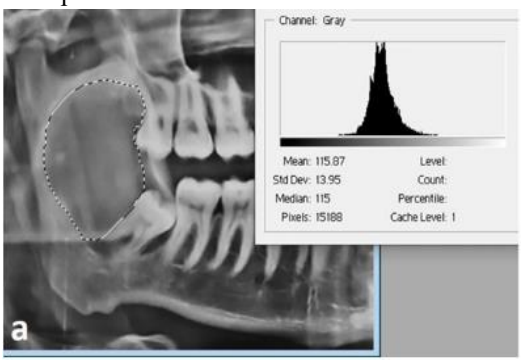
a)



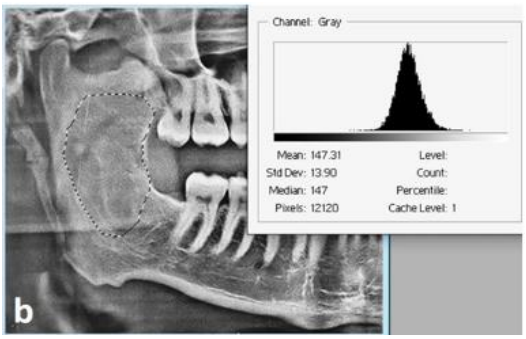
b)

Figure 1. Intraoperative images depicting the application of 5-FU in a patient from group A (a), and modified Carnoy's solution (MC) in a patient from group B (b).

The same postoperative care protocol was followed for both groups, with long-term monitoring through regular follow-ups. Inferior alveolar nerve paresthesia was assessed in patients with lesions located in the body and ramus of the mandible. Patients with anterior mandibular lesions or those whose nerve was exposed during surgery were excluded from this evaluation to prevent bias caused by direct nerve manipulation. Every six months, clinical exams and radiographic screening (orthopantomogram) were performed to assess bone healing and detect any signs of recurrence. Bone healing was evaluated by analyzing the radiographs using grey-level histogram scoring. Radiographs taken at baseline (preoperative) and the 2-year follow-up were processed with Adobe Photoshop software (version 7). The cyst area on the baseline radiograph was outlined using the selection tool, and the grey-level score was recorded. Areas with impacted teeth within the lesion were excluded from the selection. The same outline was applied to the follow-up radiograph, and the grey-level score was recorded again (**Figure 2**). The differences in mean grey-level scores between the two groups were then calculated and compared.



a)



b)

Figure 2. Assessment of bone healing through gray-level histogram scoring at baseline (a), and after a 2-year follow-up (b).

Statistical analysis

All data were recorded in Microsoft Excel 2010. Descriptive statistics, including mean ± standard deviation (SD), were calculated for age, location, gender, and lesion size for each group. Demographic details were presented as frequency distributions and percentages. To compare age and lesion size between groups, an analysis of variance (ANOVA) was conducted, while the Chi-square test was used to assess the relationship between gender and location. Disease recurrence in both groups was evaluated, and survival analysis was performed using Kaplan-Meier. Bone healing between the groups was compared with an unpaired t-test. A P-value of < 0.05 was considered statistically important. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS version 19).

Results and Discussion

Seventeen patients who met the inclusion criteria were randomly assigned to two groups: group A, which received 5-FU (n = 9), and group B, which was treated with MC (n = 8). In group A, patient ages ranged from 28 to 56 years, with a mean of 36.88 years (SD = 8.66), while in group B, ages varied from 26 to 61 years, with a mean of 37.75 years (SD = 11.58). The age difference between the 2 groups was not statistically significant (P-value = 0.863515). Group A consisted of 6 males and 3 females, whereas group B included five males and three females, yielding an overall male-to-female ratio of 1.8:1. Statistical analysis showed no important difference in gender distribution between the groups (P-value = 0.857596).

Regarding lesion location, 2 cases were found in the anterior mandible (one in each group), 7 were in the body-ramus region (group A: 4, group B: 3), and 8 were confined to the ramus of the mandible (group A: 4, group B: 4). The lesion sizes ranged from 32 to 56 millimeters in group A, with a mean of 43.66 mm (SD = 7.71), and from 35 to 61 millimeters in group B, with a mean of 47.27 mm (SD = 10.43). No statistically significant differences were observed between the groups in terms of lesion location (P-value = 0.429546) or size (P-value = 0.958714).

Patients in group A were monitored for a duration of 24 to 64 months, with an average follow-up period of 43.7 months. During this time, no cases of recurrence were detected through clinical or radiological assessment. In contrast, two patients in group B (25%) experienced recurrence over a follow-up period of 26 to 68 months (mean 47.5 months), with an average recurrence time of 31 months. Kaplan-Meier survival analysis indicated that in group B, the probability of remaining disease-free was 0.9 at 30 months, which decreased to 0.7 by 60 months (**Figure 3**).

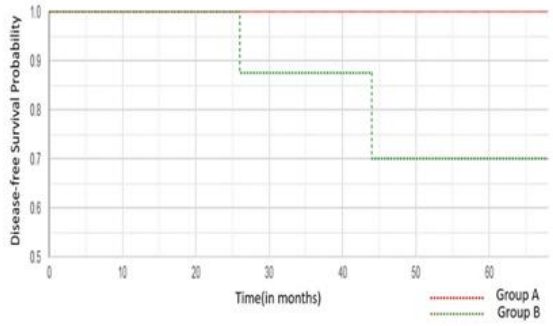


Figure 3. Evaluation of disease-free survival probability using Kaplan-Meier analysis.

Assessment of inferior alveolar nerve paresthesia was carried out in patients with OKC affecting the body and ramus regions. One case in group A was excluded due to direct nerve exposure within the surgical site (groups A and B: n = 7 each). Temporary sensory impairment was noted in two patients (28.5%) from group A and three patients (42.8%) from group B, all of whom recovered fully over an average follow-up period of 6.5 months and 11 months, respectively. No instances of permanent nerve dysfunction were observed in either group.

At the two-year follow-up, bone healing was evaluated using a grey-level score, which showed an average increase of 36.52 ± 2.96 (range: 32.37–39.72) in group A and 34.064 ± 6.52 (range: 23.63–41.22) in group B. The statistical comparison revealed no significant difference between the 2 groups (P-value = 0.225184).

OKC arises from the dental lamina of a developing tooth and has been recognized for its aggressive behavior and high recurrence rates following surgical removal. In 2005, the WHO classified it as an odontogenic keratocystic tumor, though this designation was reversed in 2007 [16]. Treatment approaches have ranged from extensive surgical resection to conservative enucleation. While resection effectively eliminates recurrence, it is associated with considerable morbidity, potential nerve damage, complex reconstructive needs, prolonged hospitalization, and increased treatment costs. Enucleation, though less invasive, carries a recurrence risk of 23% to 56% when performed alone [1, 17]. To mitigate this risk, adjunctive measures such as peripheral ostectomy, chemical cauterization, and cryotherapy have been commonly integrated into the treatment protocol [17].

CS functions as a tissue fixative composed of glacial acetic acid, chloroform, absolute alcohol, and ferric acid. When applied in conjunction with enucleation, it has been associated with a recurrence rate of less than 10% [7]. As outlined in the protocol by Abdoola et al. [15], CS is placed onto the bone surface lining the cyst cavity, leading to chemical necrosis that extends up to 1.5 millimeters into the cancellous bone. This process eradicates any residual cyst lining and microcysts, which, if left untreated, could contribute to recurrence [18]. To enhance clearance and further reduce recurrence, enucleation has traditionally been performed alongside peripheral ostectomy and CS application. However, due to the carcinogenic risks of chloroform, its removal from CS was deemed necessary. This modification resulted in a weaker formulation, leading to a recurrence rate as high as 35% [7]. Additionally, both CS and MC have been linked to an increased likelihood of nerve damage, ranging from temporary to permanent paresthesia of the inferior alveolar nerve, particularly in mandibular lesions.

Given these drawbacks, the present study aimed to assess 5-FU as a potential alternative chemical adjunct to enucleation and peripheral ostectomy in OKC treatment.

The application of 5-FU in managing OKC remains a relatively unexplored approach. Ledderhof *et al.* [13] first reported its clinical use in 2017, demonstrating favorable outcomes, including an absence of recurrence and a lower risk of nerve impairment in OKC cases affecting both jaws. To maintain a standardized study sample and prevent treatment bias, this study exclusively included well-localized mandibular OKC without extensive cortical perforation or involvement of the overlying oral mucosa. Cases where the inferior alveolar nerve was exposed within the surgical defect were excluded from statistical analysis regarding nerve paresthesia.

The current study analyzed 17 cases of mandibular OKC, with a male-to-female ratio of 1.8:1 and an age range spanning 26 to 61 years. No recurrence was observed in the 5-FU group over an average follow-up of 43.7 months, whereas the MC group exhibited a recurrence rate of 25% with a mean follow-up period of 47.5 months. Similar findings were reported by Ledderhof *et al.* [13], who documented a 19% recurrence rate following MC application. In contrast, Lone *et al.* [14] noted a significantly higher recurrence rate of 66.6% among patients treated with MC, while those managed with 5-FU or resection remained recurrence-free. The comparatively lower recurrence in the MC group of this study could be attributed to the strict inclusion criteria, which focused on well-circumscribed, corticated lesions, and the incorporation of peripheral ostectomy alongside enucleation.

The method of administering 5-FU was straightforward and uncomplicated. A gauze strip soaked in 5-FU was placed over the bone surface at the surgical site following cyst removal and left in place for 24 hours. In contrast, the application of CS/MC required more careful handling to prevent any accidental contact with surrounding oral tissues, which could cause chemical burns and tissue injury. Additionally, exposure of CS/MC to nerve tissue could result in nerve damage. Abdoola *et al.* [15] observed that prolonged exposure (more than three minutes) of Carnoy's solution on a nerve led to axonal degeneration. In this study, temporary paresthesia of the inferior alveolar nerve (IAN) was more prevalent in the MC group (42.8%) than in the 5-FU group (28.5%). However, all patients fully recovered, with the MC group requiring an average recovery time of 11 months, while the 5-FU group recovered in about 6.5 months. The lower risk of nerve damage in this study might be attributed to the careful selection of localized lesions and the use of a protective paraffin gauze covering the inferior alveolar canal before applying the treatment. Furthermore, excluding cases where the IAN was directly exposed during the surgery helped eliminate bias due to direct nerve manipulation, likely reducing the occurrence of IAN paresthesia.

Topical 5-FU has been demonstrated to be safe in the treatment of ocular surface squamous neoplasms in the periorbital region and the sinus region following maxillectomy and sphenoid-ethmoidectomy, with no adverse effects on nerves or surrounding soft tissues [19, 20]. This supports the notion that 5-FU can be effectively applied not only to localized mandibular lesions but also in cases involving cortical perforations, maxillary lesions extending into the sinus, or OKCs near the orbit, where the use of CS/MC is contraindicated [14].

Although there is limited research on bone healing after 5-FU application [13, 14], grey-level histogram analysis in the current study showed promising results regarding bone regeneration. At the two-year follow-up, patients who received 5-FU demonstrated good bone fill, comparable to the results seen in those treated with MC.

Conclusion

5-FU presents a promising alternative to MC for treating OKC through enucleation and peripheral ostectomy. It demonstrated no recurrence and a reduced incidence of postoperative inferior alveolar nerve paresthesia. The simplicity of its application, cost-effectiveness, and accessibility make it an attractive option. However, the small sample size in this study limits its conclusiveness, and larger-scale, potentially multicentric studies are needed to further assess the effectiveness of 5-FU in OKC management.

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Conflict of Interest: None

Financial Support: None

Ethics Statement: None

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