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ORIGINAL ARTICLE

Comparison of Outcome of Surgical Treatment of Odontogenic Keratocyst Using 5-Fluorouracil and Liquid Nitrogen: A Randomized Clinical Trial

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Abstract

Introduction Conservative management of OKC through enucleation followed by adjunctive therapy is widely advocated to minimize recurrence while preserving anatomical structures. The present study aimed to compare the clinical and radiological outcomes of topical 5-fluorouracil versus liquid nitrogen cryotherapy used after enucleation of OKC.

Methods A prospective randomized clinical trial was conducted on 24 patients diagnosed with OKC. Patients were allocated into two equal groups: Group I received 5% fluorouracil applied on ribbon gauze post-enucleation for 24 h, while Group II underwent cryotherapy with liquid nitrogen spray in two 1-minute freeze cycles separated by 5-minute thaw interval. Clinical parameters such as pain, swelling, wound sloughing, gaping, and paresthesia were assessed postoperatively, and radiographic outcomes, including bone regeneration and bone density, were evaluated at six months using standardized imaging protocols.

Results Both groups showed comparable recurrence rates (8.3%) and bone regeneration (>50% in 92% of cases). However, the cryotherapy group showed statistically significant advantages in terms of lower postoperative swelling, sloughing, wound gaping, and higher bone density at six months ($p<0.05$). Pain and paresthesia outcomes did not significantly differ between the two groups.

Conclusion Both 5-fluorouracil and liquid nitrogen cryotherapy are effective adjuncts in the conservative management of OKCs. While both promote favourable bone healing and comparable recurrence rates, cryotherapy demonstrates superior outcomes in early soft tissue healing and radiographic bone density, suggesting its potential advantage in select clinical situations.

Keywords Odontogenic keratocyst · 5-fluorouracil · Cryotherapy · Bone regeneration · Conservative management

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Introduction

Odontogenic keratocyst (OKC) is a distinct odontogenic lesion with aggressive behavior, potential for local destruction, and high recurrence rates [1]. It occurs predominantly in the posterior mandible but may arise throughout the maxillofacial skeleton [2]. Its anteroposterior expansion with minimal cortical expansion often delays diagnosis and permits substantial bone loss [3]. Histologically, OKC presents a thin, friable parakeratinized epithelial lining prone to detachment; satellite/daughter cysts further contribute to recurrence after surgery [1, 4, 5].

Simple enucleation alone carries recurrence rates of about 25–60% [4, 5]. To reduce residual epithelial remnants, adjuncts such as Carnoy's solution, marsupialization, liquid nitrogen cryotherapy, peripheral ostectomy, and topical 5-fluorouracil (5-FU) have been explored [6–9]. Cryotherapy is effective in destroying remnant epithelium via intracellular ice formation and necrosis [10–12] but may pose risks of bone necrosis, delayed healing, and nerve injury, and requires specialized equipment and expertise [13–16]. Conversely, 5-FU inhibits thymidylate synthase and disrupts DNA/RNA synthesis in rapidly proliferating epithelial cells [17, 18]; its rationale in OKC is supported by parallels with basal cell carcinoma biology (PTCH1/Sonic Hedgehog pathway dysregulation) [19, 20] and by its ability to act without extensive tissue destruction, potentially preserving bone and limiting complications such as nerve injury or infection [17, 21].

Both modalities, however, have limitations: cryotherapy can compromise surrounding bone integrity [22], whereas 5-FU lacks the deep tissue penetration of cryotherapy and has relatively limited long-term clinical data in OKC [13, 16, 17]. These contrasting profiles underscore the need for comparative clinical evidence to guide adjunct selection. In this context, the present randomized clinical trial aimed to compare the clinical outcomes of OKC treatment following enucleation using either liquid nitrogen cryotherapy or topical 5-FU as adjunctive modalities. The objective of the study was to evaluate and contrast their efficacy in preventing recurrence, promoting bone healing, minimizing postoperative complications, and improving patient-reported outcomes.

Materials and Methodology

Study Design and Setting

This prospective, randomized clinical trial was conducted in the Department of Oral and Maxillofacial Surgery from April 2024 to March 2025. The primary objective was to compare the clinical outcomes of 5% 5-Fluorouracil (5-FU) cream (Efudex®, Valeant Pharmaceuticals) and liquid nitrogen cryotherapy in the surgical management of histologically confirmed OKC. The study protocol was approved by the institutional ethical review board [GDC&HMUMBAI/ETHICALCOMMITTEE/1374/2023, dated 28/03/2023] and was prospectively registered in the clinical trial registry of India [Ref: CTRI/2024/07/071123 on 23/07/2024]. The study was conducted in accordance with the Helsinki Declaration, and informed consent was obtained from all patients before enrolling them in the trial.

Study Population and Randomization

Patients between 18 and 60 years of age, irrespective of gender or socioeconomic background, were included based on clinical, radiographic, and histopathological diagnosis of OKC. Patients were required to be fit for surgery under the American Society of Anesthesiologists (ASA) physical status I or II classification and willing to undergo either adjunctive treatment [23]. Exclusion criteria included systemic illnesses uncontrolled by medication, pregnancy, lactation, and refusal to consent.

Randomization and Allocation Concealment

Eligible patients were randomized (1:1) to receive either 5-fluorouracil (Group I) or liquid nitrogen cryotherapy (Group II). A computer-generated block randomization sequence (block size = 4) was prepared by an independent investigator (SSS) using an online platform (http://www.randomization.com). Allocation was concealed in sequentially numbered, opaque, sealed envelopes which were opened by the investigator (KW) only after patient enrolment to ensure allocation concealment. Potential confounders such as lesion size, jaw location, and patient age were balanced between groups at baseline The randomization minimized allocation bias which was confirmed statistically.

Preoperative Assessment and Preparation

All participants underwent a comprehensive preoperative evaluation, including detailed medical and dental history, clinical examination, and radiographic imaging (panoramic radiograph and cone-beam computed tomography as needed). Incisional biopsy was performed for histopathological confirmation of OKC. Blood investigations and physician fitness clearance were obtained before scheduling surgery.

Surgical Protocol

Surgical procedures for both groups were carried out under local or general anesthesia. In both groups, after sterile draping and antiseptic preparation, incision placement and reflection of a full-thickness mucoperiosteal flap, along with bony access to the lesion, were established. Complete enucleation of the cystic lining was performed, ensuring minimal disruption to adjacent structures. Wound debridement was performed with sterile normal saline and povidone-iodine solution. All procedures were carried out by the same operator (HS) under the supervision of a senior investigator (SK) to eliminate procedural confounding.

Group I: 5-Fluorouracil Protocol

Following complete enucleation and irrigation, a sterile ¼ inch ribbon gauze was thoroughly coated with 5% 5-FU cream (Efudex®) and carefully packed into the osseous defect. The gauze was left in situ for 24 h, with a small tail end exposed intraorally to allow for retrieval. The flap was sutured primarily around the gauze. After 24 h, under local anesthesia, the gauze was removed and the site was re-irrigated. The flap was then primarily sutured using 3−0 Vicryl sutures. The surgical procedures for a representative case in the 5-Fluorouracil group are depicted in Fig. 1.

Group II: Liquid Nitrogen Cryotherapy Protocol

In Group II, following enucleation and irrigation, cryotherapy was applied using a cryogun (Brymill® Cry-Ac®). The surrounding soft tissues were retracted using wooden spatulas to avoid cold contact injury. The bony cavity was sprayed with liquid nitrogen in two cycles of one minute each, with a thaw interval of five minutes between cycles. Frosting of the tissue was visually confirmed as a clinical endpoint. After completion of cryotherapy, the site was re-irrigated and primarily sutured using 3−0 Vicryl sutures. The surgical procedures for a representative case in the Liquid Nitrogen group are depicted in Fig. 2.

Outcome Assessment and Follow-Up

Postoperative assessment was carried out at predetermined intervals to monitor healing, evaluate complications, and assess treatment outcomes in both study groups. Each patient was followed up clinically and radiographically, with documentation of all the primary outcomes including pain levels, swelling, neurosensory changes, wound healing, and bone regeneration.

Recurrence of the lesion was assessed at the 6-month follow-up through clinical examination and radiographic imaging, with statistical comparisons between groups analyzed using Chi-square and non-parametric tests. Neurosensory integrity was evaluated using the brush direction test as described by Costa et al., wherein five vertical and five

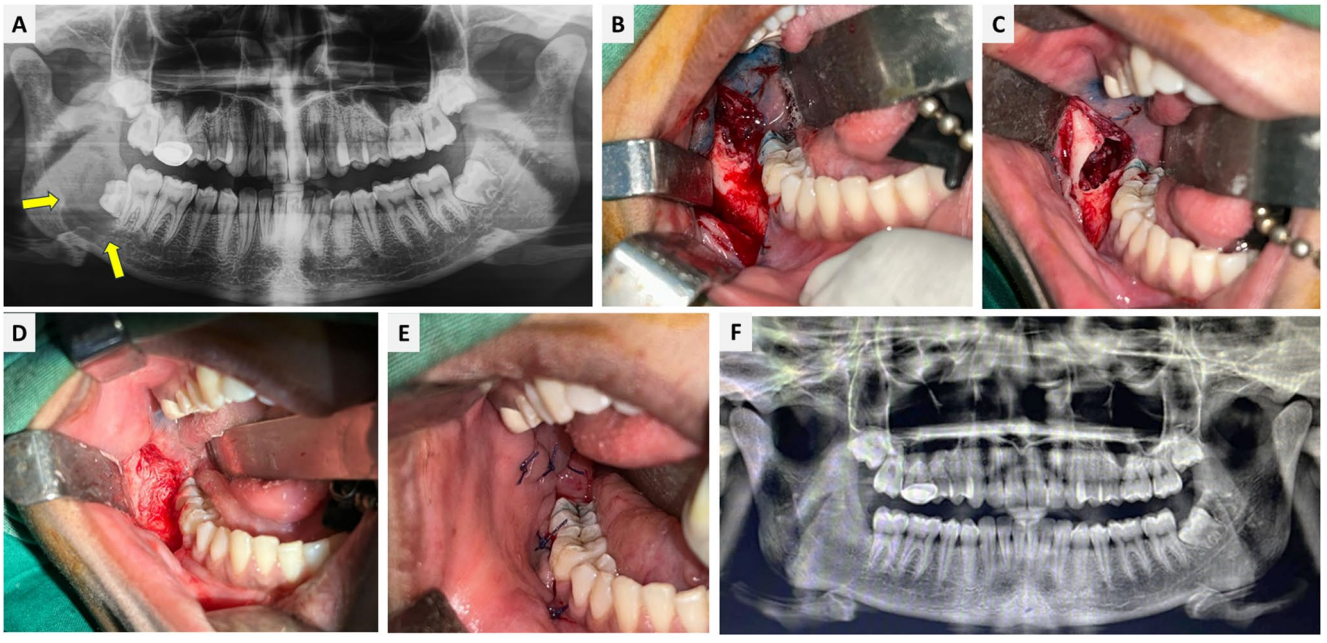

Fig. 1 **A** Orthopantomogram showing odontogenic keratocyst indicated by arrows; **B** Incision and flap reflection; **C** Surgical cavity after cyst enucleation; **D** Packing of 5-Fluorouracil gauze in the cystic cavity; **E** Suturing of the flap using vicryl sutures; **F** 6-month post-operative radiograph showing adequate bone healing

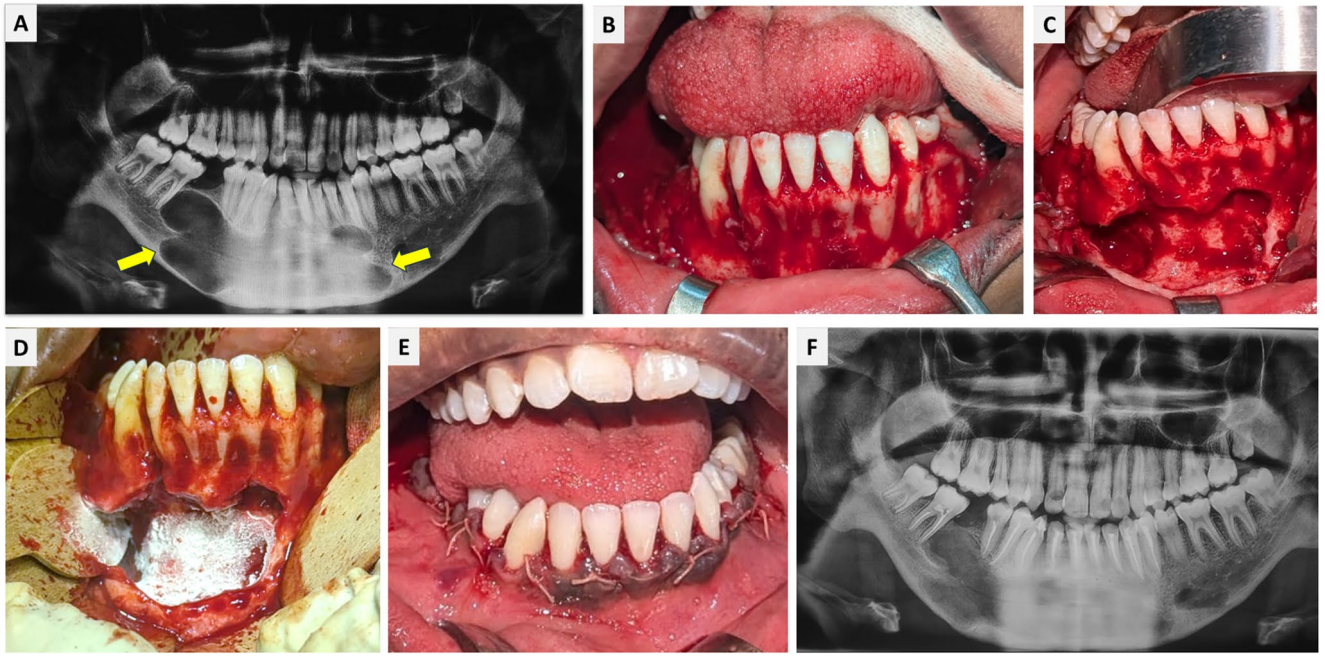

Fig. 2 **A** Orthopantomogram showing odontogenic keratocyst indicated by arrows; **B** Incision and flap reflection; **C** Surgical cavity after cyst enucleation; **D** Liquid Nitrogen applied to the cystic cavity; **E** Suturing of the flap using vicryl sutures; **F** 6-month post-operative radiograph showing adequate bone healing

horizontal strokes were applied across the operated region [24].

Wound healing was examined at the end of the first postoperative week for any evidence of wound dehiscence or gaping. Postoperative pain was assessed using the Visual Analog Scale (VAS), where patients marked their pain intensity on a scale of 0 to 10 [25]. Facial swelling was evaluated on the third postoperative day and graded using a standardized ordinal scale ranging from 0 (no swelling) to 5 (extremely severe swelling). The presence of mucosal sloughing was also noted at the end of the first postoperative week.

Bone regeneration within the surgical cavity was assessed radiographically at 6 months and categorized based on the percentage of defect fill, as either greater than or less than 50%. In addition to this, bone quality was analyzed using computed tomography (CT) to measure Hounsfield Units (HU), with values >160 indicating normal mineral density and values < 160 suggestive of osteopenia [26].

All perioperative data, including subjective symptoms and objective findings such as paraesthesia, pain, swelling, and healing, were meticulously recorded at each review.

Statistical Analysis

Sample size was calculated to detect a clinically relevant difference of 20% in the primary outcome with 80% power and $\alpha = 0.05$. Data distribution was tested using Kolmogorov–Smirnov and Shapiro–Wilk tests. Continuous variables were expressed as mean ± standard deviation (SD). Between-group comparisons of normally distributed data were performed using unpaired t-tests, while non-parametric data were analyzed with the Mann–Whitney U test. Categorical variables were compared using Chi-square or Fisher's exact tests as appropriate. All tests were two-tailed with $p < 0.05$ considered statistically significant. Analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Pain scores on the third postoperative day were marginally higher in the 5-FU group (mean: 4.66) compared to the liquid nitrogen group (mean: 4.33), with a mean difference of 0.33. However, this difference was not statistically significant ($p > 0.05$), suggesting that both treatment modalities offered comparable levels of postoperative pain control (Table 1).

In contrast, swelling was significantly more prominent in the fluorouracil group (mean: 3.25 ± 1.36) than in the liquid nitrogen group (mean: 2.16 ± 0.79), yielding a statistically significant mean difference of 1.09 ($p < 0.05$). This indicates that cryotherapy was associated with reduced tissue inflammation during the acute postoperative phase, likely due to its anti-inflammatory cryogenic effect.

Table 1 Intergroup comparison of clinical parameters

Clinical Parameter (Time-point)	5-Fluorouracil Group (Mean ± SD)	Liquid Nitrogen Group (Mean ± SD)	Mean Difference	*p*-value
Post-operative pain (3rd day)	4.66 ± 0.94	4.33 ± 1.37	0.33	> 0.05
Post-operative swelling (3rd day)	3.25 ± 1.36	2.16 ± 0.79	1.09	< 0.05*
Sloughing present (1 week)	6 / 12 (50%)	4 / 12 (33%)	—	< 0.05*
Wound gaping present (1 week)	9 / 12 (75%)	4 / 12 (33%)	—	< 0.05*
Nerve paraesthesia score (6 months)	6.66 ± 3.29	7.00 ± 3.41	0.33	> 0.05

*Statistically significant ($p < 0.05$)

Table 2 Intergroup comparison of radiographic parameters at 6 months

Radiographic Parameter	5-Fluorouracil Group	Liquid Nitrogen Group	*p*-value
Bone regeneration > 50%	11 / 12 (92%)	11 / 12 (92%)	0.05
Bone regeneration < 50%	1 / 12 (8%)	1 / 12 (8%)	0.05
Bone density > 160 HU (Normal bone)	10 / 12 (90%)	11 / 12 (92%)	< 0.05*
Bone density < 160 HU (Osteopenic bone)	2 / 12 (10%)	1 / 12 (8%)	< 0.05*
Recurrence present	1 / 12 (9%)	1 / 12 (9%)	0.05
Recurrence absent	11 / 12 (91%)	11 / 12 (91%)	

*Statistically significant ($p < 0.05$); HU = Hounsfield Units

Regarding wound-related complications, the incidence of sloughing at one week was higher in the 5-FU group (50%) compared to 33% in the cryotherapy group. Similarly, wound dehiscence or gaping was observed in 75% of cases in the 5-FU arm, while only 33% of the cryotherapy group exhibited gaping. Both of these differences were statistically significant ($p < 0.05$), implying better epithelial healing and mucosal integrity in the cryotherapy-treated cohort.

Nerve paraesthesia assessed at the six-month interval showed nearly identical outcomes between the groups, with mean scores of 6.66 and 7.00, respectively. The negligible mean difference of 0.33 and non-significant p-value (> 0.05) reflect that neither adjunctive treatment had a deleterious effect on long-term neurosensory function.

The data regarding all clinical parameters is collectively summarized in Table 1.

Radiographic Outcomes

Radiographic assessment at six months postoperatively provided insights into the regenerative and recurrence-related outcomes (Table 2).

Bone regeneration, evaluated radiographically by estimating the percentage of defect fill, revealed that in both groups, 92% of patients exhibited more than 50% bone fill. The intergroup distribution was identical and the difference was not statistically significant ($p = 0.05$), indicating that both modalities supported comparable rates of osseous healing in terms of defect volume.

Bone quality was further assessed by measuring Hounsfield Units (HU) on CT scans [27]. A threshold of 160 HU was used to differentiate normal mineral density from osteopenic bone. In the fluorouracil group, 90% of patients achieved normal bone density (> 160 HU), whereas the figure was slightly higher in the liquid nitrogen group at 92%. Although the numerical difference was marginal, it was statistically significant ($p < 0.05$), suggesting that cryotherapy may have a slight advantage in promoting more mineral-dense bone regeneration.

Recurrence was minimal and equal in both groups, with only one case of recurrence (9%) documented per arm at six months. The absence of a statistically significant difference ($p = 0.05$) confirms that both adjuncts were similarly effective in suppressing early cystic recurrence within the follow-up period.

Discussion

The present study was undertaken to evaluate and compare the clinical and radiographic outcomes following enucleation of odontogenic keratocysts (OKCs) when supplemented with either topical 5-fluorouracil or liquid nitrogen cryotherapy. Recognizing the aggressive biological behavior of OKCs and their tendency to recur due to the presence of residual epithelial islands and satellite cysts, the addition of adjunctive chemical or cryogenic treatment has been widely recommended to enhance surgical efficacy and minimize recurrence [1, 5, 27]. This study aimed to explore which of these two commonly used conservative modalities offers a better recurrence control, healing outcomes, and postoperative morbidity.

Cryotherapy induces localized necrosis via intracellular ice crystal formation, while 5-fluorouracil acts by inhibiting DNA synthesis in epithelial cells without diffusing extensively into adjacent tissues [7, 9]. These controlled actions spare nociceptive structures, resulting in equivalent pain responses. These findings are consistent with those of Schmidt and Pogrel (2001), who reported minimal pain

following cryotherapy, and Ledderhof et al. (2016), who highlighted the targeted cytotoxicity of 5-FU [7, 28].

The 5-FU group demonstrated a greater degree of facial edema on the third postoperative day. This could be attributed to the 24-hour in-situ application of medicated gauze, which may have triggered a prolonged inflammatory response [17, 20]. In contrast, cryotherapy induces vasoconstriction and transient ischemia, limiting inflammatory exudation and tissue swelling [6]. Tonietto et al. (2011) similarly reported reduced soft tissue edema with cryotherapy due to its vascular effects [12]. Although 5-FU is broadly accepted as biocompatible, variability in application technique and individual inflammatory responses may account for the increased edema [17].

Wound sloughing and mucosal dehiscence were more frequently encountered in the 5-FU group. This is likely due to unintentional contact of the 5-FU-soaked gauze with adjacent mucosal tissues, leading to cytotoxicity of the basal epithelial layers and delayed epithelial turnover [17]. Although designed to act within the cystic cavity, diffusion into healing soft tissues can impair keratinocyte viability and fibroblast-mediated healing. Cryotherapy, when administered with adequate tissue retraction, primarily affects the bone and underlying tissues, sparing the mucosa and thereby reducing sloughing and promoting better tissue integrity [29, 30]. The increased incidence of wound dehiscence in the 5-FU group may also be linked to its inhibitory effect on fibroblast activity, collagen synthesis, and angiogenesis, all of which critical for primary closure [17, 20]. These observations partially contrast with Caminiti et al. (2021), who reported favorable healing with 5-FU, possibly due to differing flap designs and gauze positioning [30].

Nerve paraesthesia, evaluated at six months, showed no statistically significant difference between the groups, although cryotherapy showed a slightly better mean score. Controlled application of cryotherapy ensures that freezing does not extend to nerve bundles, as validated by Schmidt and Pogrel (2001), who observed no long-term neural deficits after cryotherapy near the inferior alveolar nerve [7]. Similarly, the local application of 5-FU, when placed away from major neural structures, poses minimal risk of neurotoxicity [26].

Radiographic assessment at six months revealed that both groups exhibited excellent bone fill, with over 50% regeneration in 92% of cases. This supports the bone-healing potential of conservative approaches, aided by either cytotoxic or cryogenic adjuncts [13, 16]. Cryotherapy likely enhances bone healing through an initial inflammatory response that facilitates osteoblastic activity, while 5-FU eradicates residual epithelial cells without disrupting osteogenic potential [13, 18]. These outcomes are consistent with studies by Casino et al. (2023) and Tonietto et al. (2011), who documented favorable regeneration with both methods [12, 31].

Interestingly, CT-based evaluation of bone density showed significantly higher Hounsfield units in the cryotherapy group [26]. This may reflect better mineral quality of newly formed bone due to cryogenic stimulation of angiogenesis and osteoblastic differentiation [32]. While the 5-FU group also exhibited substantial mineralization, slightly lower density scores suggest a delayed maturation pattern despite adequate volume regeneration [33].

Recurrence was noted in only one case in each group over the six-month follow-up. While these results are promising, the short follow-up duration necessitates caution, as OKCs are known for late recurrences. Nevertheless, the comparable recurrence rate aligns with previous studies supporting both adjuncts as effective in reducing residual epithelial viability [7, 34].

Despite these promising findings, the study has several limitations. The sample size was relatively small, which may limit the generalizability of results. Additionally, the follow-up period was restricted to six months, which may be insufficient to capture late recurrences. The study was also limited by the absence of histological evaluation of regenerated bone. Future research should aim for multicentric trials with larger cohorts and extended follow-up to validate these findings. Incorporating histomorphometric analysis and long-term radiographic monitoring could provide deeper insights into the biological behavior of treated lesions. Furthermore, studies exploring modifications in 5-FU delivery, such as sustained-release carriers or controlled irrigation systems, may help overcome its soft tissue cytotoxicity while preserving its epithelial specificity. These findings serve as a foundation for refining conservative treatment protocols and optimizing outcomes for patients with OKCs.

Conclusion

Within the limitations of this study, both 5-FU and liquid nitrogen cryotherapy were effective adjuncts to OKC enucleation, showing similar results in recurrence prevention and bone regeneration. Liquid nitrogen offered better outcomes in soft tissue healing and bone density, while both treatments were well tolerated with minimal pain or neurosensory issues. Although 5-FU is easier to apply and cost-effective, careful technique is essential to avoid soft tissue complications.

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Declarations

Conflict of interest The authors have no conflicts of interest to declare. The authors are entirely responsible for the content of the manuscript.

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