



Topical 5-fluorouracil application in management of odontogenic keratocysts



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ABSTRACT

Aim & objectives: The aim of this study was to evaluate the efficacy of topical application of 5-fluorouracil (5-FU) after peripheral ostectomy, and compare it with other treatment modalities in the management of odontogenic keratocyst (OKC).

Materials & methods: This prospective study was conducted in the OMFS department for last seven years, wherein twenty seven patients of OKC were included and randomly allocated to the three treatment groups. Nine were treated by enucleation followed by application of modified carnoy solution (CS), eleven by peripheral ostectomy followed by application of 5-FU and eleven by segmental resection (SR). Follow-up ranged from 2 to 4 years to assess bone healing and record any recurrence of lesion.

Results: Amongst twenty seven patients, eighteen were males and nine females, age range 20–66 years. The most common location of OKC was posterior mandible. Complications included nerve injury, swelling, infection, and recurrence (66.6% after modified CS). Functional and aesthetic compromise was seen in resection patients whereas application of 5-FU had minimal nerve injuries, infection, swelling, no recurrence with no compromise in aesthetics and function.

Conclusion: Management of OKC by 5-FU is a novel surgical method having less morbidity, minimal recurrence, low cost, no functional or cosmetic deformity.

1. Introduction

Odontogenic keratocysts (OKC) is an aggressive cystic lesion of jaw arising from dental lamina, with high growth and recurrence rates.¹ It was first described by Philipson in 1956.² OKCs constitute between 1.8 and 21.5% of odontogenic cysts³ and most frequently occur in the ramus or angle of mandible, and the third molar is commonly seen involved. The age of these patient ranges from 7 to 83, years with peak incidence between 10 and 30 years. Male to female ratio is 16:1, with a mild predominance to males. Patients are usually asymptomatic and are accidentally detected during routine radiographic examination. Swelling, pain, facial asymmetry, infection, paraesthesia are seen in symptomatic patients.⁴ OKC radiographically presents as multilocular or unilocular radiolucent lesion.²

Management of OKC varies from conservative procedures like simple enucleation, peripheral ostectomy to aggressive resection.⁵ Attention has been given to new treatment procedures in OKC to make it

simple and successful.

5-FU is an antimetabolite drug, used in treatment Basal cell carcinoma (BCC), and various other cancers. It is an established treatment for actinic keratosis. It inhibits thymidylate synthetase an enzyme required for DNA synthesis causing cell death. Although the mechanism of action is not fully known but is being attributed to a decrease in the formation of arachnoid metabolite, to inhibit apoptosis and immune surveillance, increase angiogenesis and the invasive ability of tumour cells. It acts in several ways but principally as a thymidylate synthetase (TS) inhibitor, interrupting the action of enzyme blocks the synthesis of pyrimidine thymidine required for DNA replication. Thymidylate synthase methylates deoxyuridine monophosphate (dUMP) to form thymidine monophosphate (dTMP) Administration of 5-FU causes scarcity in (dTMP), so rapidly dividing cancer cells undergo cell death via thymine less death.⁶

This prospective study was planned to determine the efficacy of 5-FU in OKC because of its similarities to BCC in molecular

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etiopathogenesis.

2. Material & methods

This prospective study was conducted in OMFS department after ethical clearance from the Institutional ethical committee, for last seven years. The procedures, risks & benefits with each procedure were discussed with the patients, and were enrolled in the study if their consent was obtained. Twenty seven patients were enrolled in this study and randomly allocated to three treatment groups; nine were treated by enucleation followed by application of modified carnoy solution (CS), eleven by application of 5-fluorouracil (5-FU) after peripheral osteotomy, and eleven by segmental resection (SR). Follow-up ranged from two to nine years, mean being 3.5 years to assess bony healing and check for any recurrence.

A detailed history and examination was done to rule out any medical conditions. Demographic information like age, sex, lesion size, location, paraesthesia, pain, and radiographic appearance was recorded. Incisional biopsy was performed to confirm the diagnosis.

Patients were operated under general anaesthesia. Antibiotics, anti-inflammatory and analgesics were prescribed. Sutures were removed after seven days. Any complication occurring in the postop phase was recorded.

Group 1: After enucleation, mucosa was covered with modified Carnoy solution (60% ethanol, and 10% glacial acetic acid, 1 g of ferric chloride) for 3 min, followed by thorough irrigation and wound was sutured.

Group 2: After peripheral osteotomy sterile ribbon gauze was coated with 5-FU and packed into the surgical cavity. Wound was closed in usual manner leaving a small end exposed into oral cavity, and removed after 24 h postoperatively.

Group 3: After segmental resection, reconstruction was done using reconstruction plate.

3. Results

Out of the 27 enrolled OKC patients, eighteen were males and 9 females. Their age ranged from 20 to 66 years. As per location of the lesion, 44% of lesion involved Parasynphysis, body, angle region; 25.92% involved Parasynphysis to condyle-coronoid, 18.5% involved ramus and condyle, only 3.7% were seen in maxilla (Table 1).

In Group 1, paraesthesia was seen in 55%, which recovered in all except one case with recurrence of lesion in 66.6%. In Group 2, 9% patients had temporary paraesthesia which was eventually resolved, no recurrence with no functional & aesthetic deformity. In group 3 there were 100% functional & cosmetic deformity, paraesthesia was seen in all cases, but no recurrence (Table 2).

Table 1
Demographics of OKC.

Cases	27	N (%)
Gender	Males	18 (66)
	Females	9 (33)
Age	20–66 years	
Location	Maxilla Anterior region	1 (3.7)
	Body ramus & Parasynphysis	12 (44.4)
	Ramus, body condyle & coronoid region	5 (18.5)
Signs & Symptoms	Parasynphysis to condyle & coronoid	7 (25.92)
	Swelling & facial asymmetry	5 (18.5)
	Pain & Swelling	11 (40.7)
	Paraesthesia	4 (20)
Radiographic appearance	Asymptomatic, detection on routine radiographic examination	7 (25.9)
	Multilocular	19 (70.37)
	Unilocular	8 (29.62)

Table 2
Comparative postoperative results.

Total cases	Modified CS	5%FU	Segmental Resection
N = 27	N = 9	N = 11	N = 7
Post-operative nerve injury	Temporary 5 (55)	Temporary %	Permanent 7 (100)
Recovery	4 (44.44)	0	0
Recurrence	6 (66.6)	0	0
Disadvantages	2nd surgery	–	Aesthetic & functional problems
Mean follow-up 3.5 years	3–7years	2–4years	4–9years

4. Discussion

The name keratocysts was first introduced in 1950. The classification underwent many changes from 1950 to 2017, and as per WHO organization in 2005, it was renamed from OKC to keratocystic odontogenic tumour (KCOT) due to its aggressive potential.⁷ According to these classification there are two subtypes of OKC, the orthokeratinized and the parakeratinized. In 2005 both were classified as independent types depending upon their tendency to occur under the category of epithelial tumour of odontogenic origin. In 2007, KCOT was again reclassified as odontogenic keratocysts (OKC).⁸

The treatment goal is to develop a method of treatment that will minimize morbidity, maintain vitality of surrounding structures and reduce the possible chances of recurrence. Literature has reported different surgical treatment methods which include enucleation, marsupialization, curettage, peripheral osteotomy, adjunctive solution application and segmental resection. The treatment modality depends upon the size of lesion, location, proximity of lesion to vital structures like inferior alveolar nerve, maxillary sinus & nasal cavity.⁹

Enucleation can be performed with or without adjunctive procedures. According to literature there is 56% recurrence rate when enucleation alone as a definitive treatment option.^{3,5,10} Adjunctive therapies include treatments like cryotherapy, osteotomy, CS, modified CS. Studies have reported that CS, a chemical fixative (chloroform, glacial acetic acid absolute alcohol, ferric acid), decreases the rate of recurrence however, due to the carcinogenicity chloroform was removed and a modified CS is used instead. Recent studies have shown markedly high recurrence rate with modified CS than original CS.^{11,12} Our study also reported a high recurrence rate (66.6%) of OKC after modified CS.

The most aggressive treatment of OKC is resection but is not accepted as a routine treatment considering that resection is aggressive and has high morbidity. Many clinicians argue that most severe cases should be treated with resection. There has been evidence of recurrence, despite resection and marginal resection, however majority of studies show 0% recurrence rate.¹³ Resection with an approximate 5 mm margin of healthy bone has the lowest recurrence rate. It is due to this high morbidity that it has not been accepted as a routine treatment modality. Many clinicians stress that resection should only be considered in most severe cases.¹⁴ The present study includes the cases who have undergone resection with follow-up of 4–9 years. There is no recurrence but patients remain functionally and aesthetically compromised, so resection should only be considered in most severe cases.

Over the past few years attention has been given to new procedures in treatment of OKC which should be as simple and successful as possible. One of the therapeutic agent considered in treatment of OKC is 5-FU. This antimetabolite induces apoptosis by inhibiting SHH in hepatocellular cancer, and is used in different malignant diseases, like BCC, for topical application. Leddehroff¹⁵ proposed a targeted approach based on the understanding of molecular genetics of OKC. OKC has been reported to develop through protein patched Homolog (PTCH) gene mutation like that in Basel cell carcinomas (BCC).¹⁶ PTCH causing

smoothened (SMO) activation and sonic Hedgehog (SHH) signals resulting in neoplastic changes. Study by Rui et al.¹⁷ shows that SHH signal pathway antagonism may be an effective way to target OKC molecularly through suppression of SHH transcription factor and SMO inhibition. This SMO gene alteration play an important role in OKC development. Balamurugan¹⁸ also reported 5-FU as a trend setter treatment modality in OKC.

Increase in TS mRNA is used as marker of resistance to 5-FU. Down regulation of TS results in increased efficacy 5-FU in colorectal cancer cell lines. DPD, an enzyme involved in thymidine and uracil catabolism, is responsible for breakdown of 5-FU to its excretory metabolites. Increased expression of TP suggests improved response to 5-FU because of increased fluorodeoxyuridine monophosphate (FDUMP), which is an active metabolite of FU. Low expression of DPD suggest an improved response to 5-FU treatment because DPD breakdowns 5-FU.^{19–21} A study by Leddehroff¹⁶ reported that recurrence after treatment with modified CS was 26.3 ± 1.8 months, 18% showed recurrence; whereas patients treated with 5FU showed no recurrence. Bone healing was normal in all patients treated with 5-FU than modified CS where 2% patient had delayed wound healing. No recurrence was seen in our study in 5-FU group of patients, similar to studies by Leddehroff.¹⁵

Majority of studies in literature report that patients of OKC treated with modified CS had neurosensory deficit^{11,12} even after following 3 min application protocol by Frerich et al.²² Similar to the present study the rate of peripheral nerve injury in our study was in 55%. 3% patients had temporary paraesthesia and showed remarkable improvement within 2–3 weeks, and complete in 6 postoperative weeks. Similarly 5-FU could be more amenable than MC in posterior maxilla in close proximity to major vessels to head & Neck, orbital contents & Maxillary sinus. Till date no study has shown adverse effects of direct application of 5-FU on major blood vessels However twice weekly application of topical 5% 5FU for 4 weeks after medial maxillectomy, sphenoidectomy for ethmoidal adenocarcinoma showed no adverse effects on infraorbital nerve or remaining sinus mucosa.^{23,24}

5. Conclusion

Since there are no universal protocol for management of OKC, the advantage of conservative management is low morbidity than resection. 5-FU has been considered more useful in treatment of OKC than carnoy solution due to its short operating time, availability, technical simplicity, reduced morbidity, low cost, with low or no recurrence, thereby decreasing the need for a second surgery. However, larger clinical trials are required to generate evidence on use of 5-FU, as a novel technique for management of OKC.

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