ORIGINAL RESEARCH PAPER
Volume - 9 | Issue - 7 | July - 2020 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

"CONSERVATIVE TREATMENT MODALITIES IN THE MANAGEMENT OF ODONTOGENIC KERATOCYST (OKC): AN 8 YEAR RETROSPECTIVE STUDY"

Dental Science

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ABSTRACT

The purpose of this study was to collect and analyse retrospective data of 30 patients diagnosed with Odontogenic Keratocyst. The study evaluated surgical outcomes and recurrence rates of various conservative surgical treatment modalities such as Enucleation, Peripheral Ostectomy, use of Carnoy's solution and topical 5-Fluorouracil. The follow-up period ranged from 1.5 to 8 years. Post-surgical complications included 5 cases of transient neurosensory deficit, 5 cases of wound dehiscence and 1 case of pathological fracture. In subsequent follow-up, 2 cases showed recurrence. All the complications were managed successfully and the patients with recurrence were retreated by Enucleation with Peripheral Ostectomy followed by chemical cauterization using Carnoy's solution, with no further recurrence. Hence, we suggest that the conservative treatment modalities should be considered due to its associated merits, before electing for radical surgery.

KEYWORDS

Odontogenic Keratocyst; Conservative Treatment Modalities; 5-fluorouracil; Enucleation And Peripheral Ostectomy; Carnoy's Solution

INTRODUCTION

Odontogenic Keratocyst (OKC) is an aggressive odontogenic cystic lesion containing keratin accumulation in the cystic cavity [1]. The term OKC was first coined by Philipsen in 1957 whereas Toller in 1976 suggested OKC to be considered as a neoplasm [2, 3]. Since then it has been a matter of controversy whether to call it a cystic lesion or a neoplasm. In 2005, it was termed as Keracystic Odontogenic Tumor (KCOT) by World Health Organization [4]. However, it has been reclassified as Odontogenic Keratocyst (OKC) by WHO Classification of Head and Neck Tumours 2017 [5]. Immunohistochemical studies have greatly contributed in the understanding of the proliferative activity and DNA damage based on the positive staining for Ki-67 and p53 respectively [6]. PTCH gene mutation also plays a vital role in the etiopathogenesis of OKC [7].

Its aggressive behaviour is characterized by rapid anterio-posterior medullary spread with minimal cortical involvement and perforations [8]. This spread and expansion may be due to collagenase activity and enzymatic degradation [4]. Histopathologically, it was categorized into Parakeratinized and Orthokeratinized forms; the latter being considered a separate entity nowadays [4]. Parakeratinized variant of OKC shows more recurrence rate in contrast to Orthokeratinized variant which has an excellent prognosis even after enucleation alone [9]. Propensity of OKC to recur can be attributed to multiple reasons.

Multiple treatment options have been proposed till date according to the size, extension and clinical and radiographic appearance [10]. It includes conservative as well as radical surgeries. Surgical treatment alternatives are marsupialization, enucleation and resection. With enucleation, various adjunctive remedies can be considered such as peripheral ostectomy, use of carnoy's solution, liquid nitrogen therapy and topical 5-fluorouracil [1, 7]. The current study evaluates cases of OKC treated by using different conservative surgical treatment modalities and reserves the option of surgical resection for cases of multiple recurrences and large lesions.

The present study aims at the following:

1) Collection of demographic data regarding occurrence of OKC in Gujarat
2) To analyse the occurrence of post-surgical consequences including wound dehiscence, infection, neurosensory deficits and pathological fracture and their successful post-surgical management.
3) Evaluation of the recurrence rate for various conservative surgical treatment modalities to treat OKC.

MATERIALS AND METHODS

This study was based on collection and analysis of documented medical records and radiographs. Institutional Ethics Committee approval has been taken for conducting the study. Total of 422 patients having benign cystic lesions of jaws were treated in the Department of Oral and Maxillofacial Surgery at Ahmedabad Municipal Corporation Dental College and Hospital, Ahmedabad, Gujarat, India, in a period of 7 years from 2012 to 2018. Out of which, 30 cases were clinico-histologically diagnosed as Odontogenic Keratocyst and treated by various conservative surgical approaches like enucleation followed by peripheral ostectomy (EPO), enucleation with peripheral ostectomy followed by chemical cauterisation using Carnoy's solution (EPOC), enucleation with peripheral ostectomy followed by application of topical 5-Fluorouracil (EPOF).

The protocol followed was aspiration of fluid during clinical examination and history taking. Aspiration of white cheesy fluid helped in the diagnosis of OKC. For smaller unilocular lesions, excisional biopsy was performed and for large unilocular / multilocular lesions, incisional biopsy was considered. Non-restorable, carious, mobile, non-vital or impacted teeth associated with OKC were removed.

Enucleation was done by removal of cystic lining from the bony cavity without leaving any macroscopic remnants of the lesion. Following enucleation, peripheral ostectomy was performed using micromotor handpiece and rotary burs under copious irrigation to reduce the peripheral bony margins [11]. In case of suspicion regarding remnants of fragile cystic lining in difficult anatomical site, chemical cauterization was carried out using either Carnoy's solution (3 ml chloroform + 6 ml 95% absolute alcohol + 1 ml glacial acetic acid + 1 g ferric chloride) or topical 5-Fluorouracil [7, 12]. Freshly prepared Carnoy's solution was applied to the bony defect for 3 minutes with predictive measures taken to prevent the nerve damage. Then the cavity was irrigated with Normal Saline and proceeded for primary closure [10]. In cases where topical 5-FU was used, a ribbon gauze coated with 5-Fluorouracil ointment was packed into the residual cavity and closure was done in such a manner that one end of the gauze remains free into oral cavity for easy retrieval. After 24 hours, the ribbon gauze was retrieved and primary closure was performed [7].

Patients with minimum follow-up period of 1.5 years were included in the study. Retrospective data for all 30 patients was studied and analysed to obtain data regarding age, sex, anatomical site, histological variant, clinical and radiographic features, treatment performed, follow up, recurrence and complications encountered.

Results

The present study reveals data regarding 30 non-syndromic patients of OKC (7.11%) out of total of 422 patients with odontogenic cysts. Amongst these, 21 were male and 9 were female, giving Male: Female ratio of 2.33:1. In terms of ethnicity, all the patients were Indians. The patient's age ranged from 11 to 63 years with the mean age of 32.83 years and the maximum incidence during 3rd decade of life. **[Table 1]**

Table 1: Age distribution in 30 patients of OKC

AGE GROUP (in years)	NUMBER OF PATIENTS
1-10	**0**
11-20	**5**
21-30	**12**
31-40	**5**
41-50	**3**
51-60	**4**
61-70	**1**

Out of 30 cases, 21 (70%) patients showed occurrence of OKC in mandible whereas 9 (30%) were present in maxilla. 37.14% lesions were found on left side of jaw, 31.43% on the right side and 31.43% in the midline. While determining distribution of lesion according to the anatomical site, higher incidence was found in posterior mandible (50%), followed by anterior mandible (25%), anterior maxilla (13.89%) and posterior maxilla (11.11%).

Data showed that the common chief complaints were pain, swelling and fluid discharge. However, in 5 cases (16.67%) it was an accidental finding. **[Table 2]** Pre-operative clinical findings showed presence of nerve paresthesia in only one patient (3.33%), association of impacted tooth in 16 patients (53.33%) and root resorption in 5 patients (20.83%). Radiographic evaluation also revealed pattern of locularity of the lesion. 18 cases (60%) were multilocular and 12 lesions (40%) were unilocular.

Table 2: Clinical examination revealed following symptoms in 30 patients of OKC

PRESENTING SYMPTOMS	NUMBER OF PATIENTS
Pain	**9**
Swelling	**6**
Pus discharge	**3**
Pain + Swelling	**4**
Pain + Swelling + Pus discharge	**3**
Asymptomatic	**5**

The diagnosis was confirmed based on thorough clinical examination, radiological investigations and final histopathological report. Clinical, histological and treatment data for all 30 patients have been tabulated in **[Table 3]**. Surgical procedure carried out can be grouped into three categories: EPO (8 cases), EPOC (13 cases) and EPOF (9 cases). Tooth associated with the lesion were either treated by endodontic treatment or extracted during surgery based on the tooth vitality, mobility and root resorption. Associated impacted tooth were removed in all the cases of impaction.

Table 3: Clinical findings, treatment performed and its outcomes

Patients	Site of Lesion	Locularity	Histopathological variant	Treatment done	Complications	Follow up period (in months)	Notes
Patient 1	Posterior Mandible	Multilocular	Parakeratinized	EPOC	Transient Paresthesia	87	
Patient 2	Posterior Mandible	Multilocular	Parakeratinized	EPOC		92	
Patient 3	Anterior Maxilla	Unilocular	Parakeratinized	EPO	Transient Paresthesia	35	Platelet rich fibrin and perioglass bone graft were packed
Patient 4	Posterior Mandible	Unilocular	Parakeratinized	EPOC		94	
Patient 5	Posterior Mandible	Unilocular	Parakeratinized	EPOF		30	
Patient 6	Anterior Maxilla	Unilocular	Parakeratinized	EPOF		31	
Patient 7	Posterior Mandible	Multilocular	Parakeratinized & Orthokeratinized	EPOC	Transient Paresthesia	79	
Patient 8	Posterior Mandible	Multilocular	Parakeratinized	EPOC	Transient Paresthesia	81	
Patient 9	Anterior and Posterior Mandible	Multilocular	Parakeratinized	EPOC		89	
Patient 10	Anterior and Posterior Mandible	Multilocular	Parakeratinized	EPOC	Infection and wound dehiscence	30	Required extended period of IV antibiotics
Patient 11	Anterior and Posterior Mandible	Multilocular	Parakeratinized	EPO		96	
Patient 12	Anterior and Posterior Mandible	Multilocular	Parakeratinized	EPOC		79	
Patient 13	Anterior Mandible	Multilocular	Parakeratinized	EPOC		87	
Patient 14	Anterior Maxilla	Unilocular	Parakeratinized	EPOC	Watery discharge till 1 month post op	59	Got cured on its own
Patient 15	Posterior Maxilla	Unilocular	Parakeratinized	EPO	Recurrence at 42 months	83	Retreated by EPOC
Patient 16	Posterior Maxilla	Unilocular	Parakeratinized	EPOF		26	
Patient 17	Posterior Mandible	Multilocular	Parakeratinized	EPOC	Transient paresthesia +wound dehiscence	59	
Patient 18	Posterior Maxilla	Multilocular	Parakeratinized	EPOF	Wound dehiscence	27	
Patient 19	Posterior Mandible	Multilocular	Parakeratinized	EPO		90	
Patient 20	Anterior Maxilla	Unilocular	Parakeratinized	EPO		88	
Patient 21	Posterior Mandible	Multilocular	Parakeratinized	EPO	Recurrence at 24 months	79	Retreated by EPOC
Patient 22	Posterior Mandible	Unilocular	Parakeratinized	EPO		59	
Patient 23	Posterior Mandible	Multilocular	Parakeratinized	EPOC	Pathological fracture	79	Treated by Intermaxillary fixation for 6 weeks
Patient 24	Anterior Mandible	Multilocular	Parakeratinized	EPO	Wound dehiscence +infection	20	
Patient 25	Anterior Mandible	Unilocular	Parakeratinized	EPOF		18	
Patient 26	Posterior Mandible	Multilocular	Parakeratinized	EPOF	Wound dehiscence	36	
Patient 27	Posterior Maxilla	Unilocular	Parakeratinized	EPOC		29	
Patient 28	Anterior and Posterior Mandible	Multilocular	Parakeratinized	EPOF		32	

Patient 29	Anterior Maxilla	Unilocular	Parakeratinized	EPOF		21	
Patient 30	Posterior Mandible	Multilocular	Parakeratinized	EPOF		28	

Histopathological evaluation confirmed odontogenic keratocystic lesion in all 30 cases. All 30 cases were histologically characterized by parakeratinized odontogenic lining. We found one unique case (Patient 7) showing a combination of both parakeratinized as well as orthokeratinized cystic lining.

Surgical comorbities included post-operative IAN deficit in 4 cases (19.05%) of mandibular OKC, infraorbital nerve paresthesia in 1 case (11.11%) of maxillary OKC, wound dehiscence in 5 cases (16.67%), infection in 2 cases (6.67%) and pathological fracture in 1 case (3.33%). Neurosensory deficit recovered in all the cases with the mean time of recovery being 7.8 months. Wound dehiscence observed in 5 cases was treated individually. In Patient 17 & 26, wound healing was achieved by re-suturing. In Patient 18, a customized acrylic stent with a small extention into the cavity was used to allow it to heal by secondary intention. In Patient 10, resuturing was attempted but the surgical site got infected. Culture and sensitivity reporting suggested infection caused by *Pseudomonas Aeruginosa & Eschericia coli*, for which adequate intravenous antibiotic therapy was initiated and the wound was allowed to heal secondarily. Similarly, patient 24 was treated by resuturing the wound and extended IV antibiotics. In patient 23, pathological fracture at right mandibular angle region was managed by intermaxillary fixation for 6 weeks and it healed uneventfully.

All the patients were kept on regular follow up for first 2 years, followed by annual follow up. Patients included in the study had minimum 1.5 years of follow up. Minimum follow up time was 18 months and maximum was 96 months with an average follow up period of 61 months (5.07 years).

Recurrence was found in 2 cases (6.66%) at 2 years and 3.5 years follow up. In patient 21, a multilocular lesion was present in the right ramus region with parakeratinized cystic lining treated by EPO. The second case (Patient 15) of recurrence was in the region of left posterior maxilla with multilocular pattern and parakeratinized lining epithelium that was treated by EPO. In both the cases, re-surgery was done by EPOC and no recurrence was detected at an average follow up of 48 months.

Discussion

The term 'Odontogenic Keratocyst' has always been a topic of debate since many years and such controversies has also extended to its treatment. Treatment option for OKC is highly influenced by its aggressive nature and recurrence rate. Due to its association with Nevoid Basal Cell Carcinoma Syndrome (NBCCS) and mutation of PTCH tumor suppressor gene, it was categorized as Keratocystic Odontogenic Tumor (KCOT) in 2005 [5, 10]. However, it has been reclassified as OKC in 2017 due to 3 reasons: (a) the mutations in PTCH gene was also found in non-neoplastic lesions such as dentigerous cyst (b) the lesion doesn't depict neoplastic nature in terms of growth autonomy but merely shows the aggressive behavior (c) resolution of the cyst occurring after marsupialization is not compatible with a neoplastic process [5].

OKCs are known to occur in two forms: solitary and as a part of the Nevoid Basal Cell Carcinoma Syndrome (NBCCS) [13]. Multiple Odontogenic Keratocyst (OKCs) are a well-recognized feature of NBCCS [14]. Major and Minor criterias to diagnose NBCC syndrome have been framed by Evan et al and Kimonis et al [15, 16]. Woolgar et al compared syndromic and sporadic OKCs and summarized that 'daughter' cysts, epithelial remnants and mitotic activity in basal layer are significantly higher in syndromic patients which increases its potency to recur in such patients [17].

The demographic data obtained through our study is similar to that of many other studies [10, 18] In our study, the mean age of occurrence of OKC is found to be 32.83 years, which is identical to mean age of 38.55 years in a systematic review article. Most of the studies show male predilection which is true for our study also [10]. Maximum patients in our study presented with pain near the site of lesion which is in contradiction to the study presented by Kiran et al in which 20 out of 32 cases were asymptomatic [19]. Our study showed that 60% lesions were multilocular which is in line with the data collected by Leung et al that showed 58.1% multilocular OKCs[18].

Recurrence rates after different surgical procedures range from 0 – 62.5% [20]. The higher recurrence rates can be attributed to multiple factors. It may be due to presence of 'daughter' cysts, fragile cystic lining, local spread to surrounding mucosa from perforated bony cortex, multilocularity, incomplete removal of cystic lining (most common cause), inadequate access to the surgical site, association with NBCCS, histological variant, presence of remnants of dental lamina and so on [21]. However, Myoung et al suggested that recurrence within initial span of 3 years is most often due to residual disease rather than true recurrence [22].

Crowley et al [23] meticulously studied 449 cases of OKC and classified them into 3 types: parakeratinized (86.2%), orthokeratinized (12.2%) and a combination of the two types (1.6%). He highlighted the importance of histological variants. Moreover, their study showed recurrence of parakeratinized OKCs in 42.6% cases in contrast to orthokeratinized type with only 2.2% of recurrence. In our study, we have included only parakeratinized variant; amongst which two cases showed recurrence on subsequent follow-ups. Additionally, we have documented one case of OKC with a mixed histological variety (Patient 7) treated with EPOC, showing no recurrence at 19 months follow up.

Myriad treatment options have been proposed for treating OKC but no ideal algorithm has been agreed upon. Every surgeon makes an individual decision to treat OKC based on one's clinical experience as well as analysis of reported cases. In the present study, different combinations of conservative approaches such as Enucleation, Peripheral Ostectomy, chemical cauterization with Carnoy's solution and application of topical 5-Fluorouracil were used.

Enucleation of the cystic lining is considered as the gold standard treatment for all odontogenic cysts. It is an effective method for removal of the cystic lining and it possesses high success rates. On the other hand, marsupialization requires special hygiene measures and regular short interval follow ups [24]. However, for OKC, enucleation alone has unacceptable recurrence rate ranging from 25% to 50% [25]. In case of OKC, which is known to possess thin and fragile cystic lining, it is difficult to enucleate cyst in toto with absolute reliability; almost always epithelial remnants are left behind which need to be inspected and curetted to prevent recurrence. Adjunctive measures mentioned previously can aid in reducing the recurrence rate to 10% by eliminating possible viable epithelial cells remaining in the bony cavity [11].

Peripheral Ostectomy along with Enucleation yields into decreased rate of recurrence (18.2 %) [12]. In our study, combining enucleation with peripheral ostectomy was the basic procedure performed in all the cases. Demerits of this additional technique is that it is nearly impossible to measure the exact amount of bone removed by peripheral ostectomy. Methylene blue and other dyes have been used to detect the cystic remnants with questionable success[10].

Carnoy's solution is a caustic chemical agent which fixes the tissue that comes in its direct contact. Hence, it is used to eradicate the cystic remnants or satellite cysts after EPO. According to Morgan et al, in 25 years of retrospective study of 40 patients, 0 recurrence was found with patients treated by EPOC, in contrast to 54.5% for enucleation alone, 50% with EC and 18.2% with EPO [12]. Carnoy's solution penetrates the bony tissue till the depth of 1.54 mm [19]. It requires cautious handling in order to prevent injury to the surrounding vital structures.

Topical 5-Fluorouracil is a targeted approach therapy based on the understanding of the molecular genetics of OKC. Mutations in PTCH-1 causes smoothened (SMO) activation and sonic hedgehog (SHH) signalling, resulting in neoplastic growth. The antimetabolite drug, 5-fluorouracil (5-FU) induces apoptosis by inhibiting SHH pathway. Nicholas et al concluded 0 recurrence with EPOF at 35.0 ± 8.5 months follow up compared to 19% recurrence rate with average recurrence time of 26.3 ± 1.8 months in the opposite group treated with Enucleation followed by Modified Carnoy's solution [7]. Very little clinical data is available on use of topical 5-FU for the treatment of OKC. Our study documents 9 cases treated with EPOF that does not show any recurrence on average follow up of 28 months. Use of topical 5-fluorouracil is considered more acceptable due to its easy

availability, shorter operating time, good success rate, ease of handling and low morbidity of surrounding tissues compared to the use of Carnoy's solution [12]. Moreover, this technique can be used for areas of cortical perforation as well as in areas of concern where neurovascular injuries, sinus necrosis and injury to orbital or sinus content relatively contraindicate the use of Carnoy's solution [7].

After surgical intervention, our mean follow up time was 5.077 years. In our study, temporary nerve paresthesia was observed in 5 cases (16.67%). A review by Wakolbinger et al concluded chances of transient paraesthesia in 8 to 35% patients after enucleation and 7 to 18% chances of permanent neurosensory deficit after enucleation of odontogenic cysts[24]. Patient 23, in whom pathological fracture took place near right mandibular angle region, could have been prevented if first marsupilization was attempted to shrink the size of cystic lesion followed by enucleation of the cyst[21].

Many authors believe that odontogenic cysts have minimal potential for malignant transformation (0.12%) [26]. However, literature review carried out by Yasuoka et al revealed that amongst 50 cases of carcinoma arising from odontogenic cysts, 13 of them were OKCs [27]. Therefore, careful attention should be given to the lesions showing abnormal aggressive spread, ulceration, neurological changes or cervical lymphadenopathy [21]; and a thoughtful treatment plan should be framed.

This study concludes that if proper surgical techniques are followed then conservative surgical approaches can result into good prognosis for Odontogenic Keratocyst inspite of its aggressive behaviour and known recurrence pattern. Adjunctive treatment modalities can reduce the chances of recurrence and eliminate to a large extent the need of resection. Very few clinical studies for 5-FU have been documented, so our study may shed some light on the usefulness of this adjunct. More methods based on molecular genetics need to be researched. Early and accurate diagnosis based on clinical findings, radiological investigations and distinct histopathological features followed by appropriate treatment can result in management of OKC with minimal morbidity. Hence, conservative surgical techniques should always be evaluated as an initial treatment modality and the option of resection should be preserved for the cases of multiple recurrences and abnormally large lesions.

ACKNOWLEDGEMENT: Not applicable

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