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Comparison of the effectiveness of 5-Fluorouracil and modified Carnoy's solution in reducing the recurrence of odontogenic keratocyst

Sandip A. Wanve *, Neelam N. Andrade, Lakshmi Venkatakrishnan, Harsh Desai

Nair Hospital Dental College, Mumbai, Maharashtra, India

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ABSTRACT

Introduction: Odontogenic keratocysts (OKC) has a high potential for recurrence. Resection is currently the only fool-proof method to ensure that recurrence does not occur; however, it drastically affects the patient's function and aesthetics. Application of modified Carnoy's solution (MCS) as an adjunct to reduce the recurrence rate is currently in vogue. 5- Flurouracil (5-FU) is an anti-metabolite that has been used in the treatment of basal cell carcinoma and is relatively safer than MCS. The present study aims to compare the effectiveness of 5-UC and MCS in reducing the recurrence rate in OKC..

Material and methods: A total of 42 OKCs were enucleated followed by application of MCS (control group, n = 21) or 5-FU dressing (study group, n = 21) following enucleation. Pain, swelling, temporary and permanent paresthesia paresthesia, bone sequestrum formation, osteomyelitis and recurrence in both groups were evaluated at periodic intervals up to 12 months post-surgery.

Results: There was no significant difference in terms of pain, or swelling in both groups. Permanent paresthesia and recurrence rates were higher in patients treated with MC but the difference was not statistically significant.

Conclusion: 5-FU is an easy-to-use, feasible, biocompatible and cost-effective alternative for MCS in the management of OKCs. Treatment with 5-FU, therefore, reduces the risk of recurrence and also the post-surgical morbidity associated with other treatment procedures.

1. Introduction

Odontogenic keratocyst (OKC) is the second most frequently occurring odontogenic cyst accounting for about 10% of all odontogenic cysts.[1] The classification of this cyst has always remained a matter of controversy owing to its aggressive nature and high recurrent potential.[2] The cysts tend to expand in an anteroposterior direction without any associated symptoms and attain a large size by the time they are discovered.

There is no standard treatment protocol for the treatment of OKCs and the selection from various options including enucleation, marsupialization, peripheral ostectomy, application of Carnoy's solution, cryotherapy and resection have been adopted by clinicians as per their clinical judgement. The highest rate of recurrence (56%) has been reported after enucleation whereas surgical resection has near-zero chances of recurrences.[3] However, the price to pay for resection is impairment of aesthetics and function which drastically affects the patient's quality of life. It is, therefore, important to look into more conservative methods of treatment that have minimal risk of recurrence.

Carnoy's solution, which comprises ferric chloride, absolute alcohol, chloroform, and glacial acetic acid, is considered an adjunct with other methods for treating OKCs that can reduce the risk of recurrence. One concern associated with the use of Carnoy's solution is the potential carcinogenicity of its chloroform component. Subsequently, a modified Carnoy's solution (MCS) was formulated which retained all the original chemicals except for chloroform.[4]

5-Flurouracil (5-FU) is an antimetabolite drug that has been used with a high rate of success in the treatment of basal cell carcinoma (BCC).[5] It acts by inhibiting the enzyme thymidylate synthetase which is essential for DNA synthesis. Because of the similar genetic mutation in the PTCH-1 gene and the fact that multiple OKCs and BCC are together noted in patients with Nevoid basal cell carcinoma syndrome (NBCCS), it can be hypothesized that the drugs used for the treatment of BCC will also be effective in case of OKC. Leddergof et al., 2016 found that cases treated with 5-FU exhibited fewer instances of recurrence.[6]

A recent systematic review identified only three studies that evaluated the effectiveness of 5-FU in reducing the risk of recurrence of OKC.[7] Although these studies provided supportive results, there is yet a need to

* Corresponding author. 55,Dr.Anandrao Nair Marg, Mumbai Central, Mumbai, Maharashtra, 40008, India.
E-mail addresses: sandipwanve3@gmail.com (S.A. Wanve), drnnandrade@gmail.com (N.N. Andrade), lakshmi1994@gmail.com (L. Venkatakrishnan).

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further validate these findings. In this context, the present study was conducted to compare the effectiveness of 5-FU and MCS in reducing the recurrence rate in OKC to establish the most effective chemical agent to treat Odontogenic keratocyst after surgical enucleation.

2. Materials and methods

The present randomized control trial had a parallel-arm study design and the study protocol was approved by the institutional ethical review board. The study was conducted from 2018 to 2020 in the department of Oral and Maxillo-facial surgery at Nair hospital dental college, Mumbai. Patients of age 15 years or above with histologically proven OKCs (multi-locular and unilocular) were considered eligible for the study (Fig. 1). Patients with no systemic medical issues and were willing to participate were included. Informed consent was obtained from the patients following which their medical history was elicited in brief. Cases of recurrent OKC and patients with other systemic conditions, trigeminal nerve injury or discontinuity in the inferior border of the mandible were excluded. The overall selection process is delineated in Fig. 2. Appropriate radiographs in the form of an orthopantomogram (OPG) or cone beam computed tomography (CBCT) scan were obtained for each patient to determine the exact extent of the lesion. Two investigators participated in this study.

A total sample size of n = 42 was calculated and the patients were equally divided into two groups the study group (treated with 5-FU) or the control group (treated with MCS). Randomization of the patients was performed by means of an online randomization tool; depending on the code generated the patients were assigned to either group. At the time of surgery, the patients were scrubbed with 7.5% povidone-iodine and preliminary surgical preparation were made as per standard protocol for treatment under general anaesthesia.

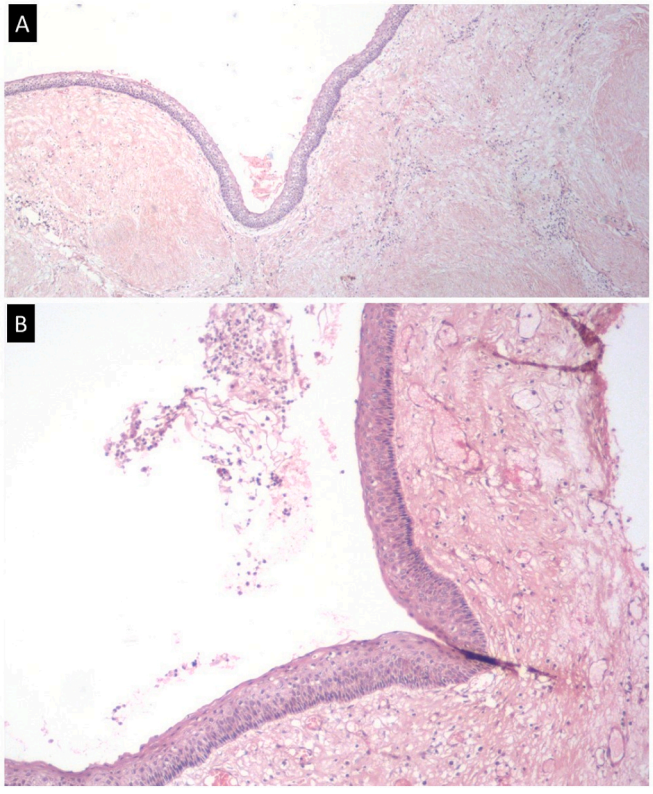

Fig. 1. A) Cystic lumen lined by a uniform in folded epithelial lining which has a flat interface with the capsule (H and E, Original magnification x100); B) Epithelial lining of 6–12 layers of odontogenic epithelial cells with palisaded appearance of nuclei in the basal layer (H and E, Original magnification x400).

Incisions were made to raise a full-thickness mucoperiosteal flap. Enucleation of the cystic lining was done in toto followed by mechanical curettage using a round bur. Petroleum jelly was applied to protect the inferior alveolar canal in cases where it was visible. The empty bony cavity was then packed with a roller gauze piece coated with 5-FU (FLONIDA 5%) cream for patients in the study group (Fig. 3). For the control group, MCS solution was applied to the bone cavity for 3 minutesfollowing which it was washed off by normal saline. The wound was sutured with a 3-0 Vicryl suture and the patient was re-called for follow-up after 24.hours The patients were given intravenous antibiotics Augmentin (1.2 gm) BD, Metronidazole (500 mg) TDS, Diclofenac (75 mg) BD and Pantaprazole (40 mg) OD post-operatively for 5 days. Follow up was done at1,3,5,7 days after surgery and antibiotics course was started.

The patient's swelling status was graded subjectively as mild, moderate or severe, and the pain levels were evaluated by Visual Analog Scale (VAS) after 1, 3, 5, and 7 postoperative days respectively. The patients were also assessed for any nerve injury, wound dehiscence, osteomyelitis and recurrence at 3-month, 6-month and 1-year post-surgical follow-up visits. Radiographs were also obtained at these visits to confirm whether there was any evidence of disease (Fig. 4).

The recorded data were subjected to statistical analysis using the Statistical package for social sciences (SPSS v 26.0, IBM). Descriptive statistics like frequencies for age, gender, and locularity of both groups. Inter-group comparisons of mean numerical values such as age and pain levels (2 groups) were performed using an unpaired *t*-test. Comparison of frequencies of categories of variables such as gender, swelling status and site of the lesion within groups was done using the chi-square test or one-way ANOVA. For all the statistical tests, $p < 0.05$ was considered to be statistically significant, keeping α error at 5% and β error at 20%, thus giving power to the study as 80%.

3. Results

The age of the patients ranged from 17 to 75 years with a mean age of 32.81 ± 12.84 years. There was a statistically non-significant difference ($p > 0.05$) between the mean age, number of individuals of each gender, and site of the lesions of both groups. This implies that the randomization was adequate and both groups had similar clinicodemographic baseline characteristics. The chief complaint was swelling in 15 out of all the 42 patients. Multilocularity was noted radiographically in eight cases of the 5-FU group and six cases of the MCS group. Location of the individual cysts is mentioned in Table-3.

The mean VAS score for both groups at all the follow-up visits is listed in Table 1. The differences between the means at all the follow-up visits was found to be statistically non-significant ($p > 0.05$) when tested by unpaired *t*-test. No recurrence was seen at the end of six months in either of the groups. At the end of one year, two recurrences were seen in the control group while none occurred in the 5-FU groups; however, the difference was not statistically significant.

Moderate swelling was seen in all cases on the day following the surgery. The grade of the swelling gradually reduced to mild on the 3rd day and 1-week post-surgical follow-up visits. No swelling was evident at the end of two weeks in both groups. Temporary paresthesia paresthesia was seen in n = 5 patients in the control group and n = 3 in the 5-FU group after three months post-surgery. Permanent paresthesia paresthesia rates for the control and the study groups were 4.5% and 0% respectively, although the difference was statistically non-significant ($p > 0.05$).

Wound dehiscence was seen in 3 cases in the control and 2 cases in 5-FU group, while all of them healed satisfactorily at the end of 6 months after adequate debridement measures. Localized sequestrum formation was seen in one case in the 5-FU group at the end of six months and persisted in 2 cases in the control group even a year after the surgery. Findings relevant to all the outcome parameters analyzed are summarized in Table 2. 5-FU appeared to be superior to Modified Carnoy's

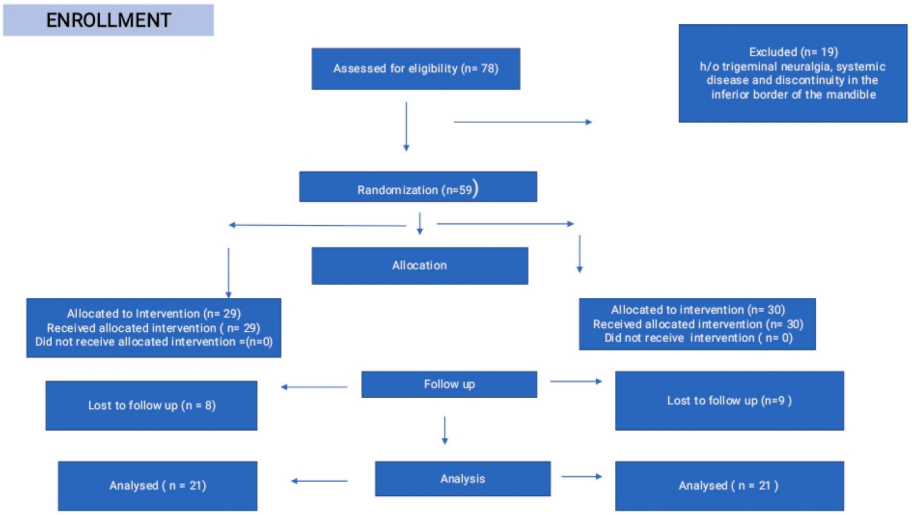

Fig. 2. Selection process of the participants in the study.

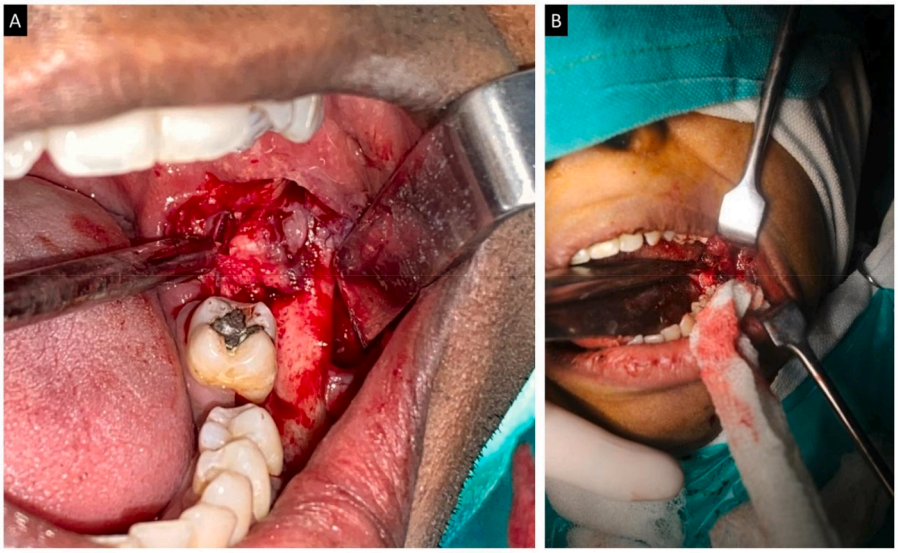

Fig. 3. A) Enucleation of the cyst in the left angle and ramus region B) Placement of 5-Fluorouracil pack in the cystic cavity in the left angle and ramus region of mandible.

solution in terms of preventing recurrence of OKC. Lesser incidence of paresthesia was also seen in the group treated with 5-FU.

4. Discussion

OKC exhibits a pronounced frequency of occurring in the second and third decades, which is usually noted in about 40–60% of cases. A mean age of occurrence of 32.1 years has been described in earlier extensive studies on the clinicodemographic profile of OKC.[8] These facts are corroborated by the characteristics of the current study population wherein two-thirds of the patients were of 20–40 years of age with a mean age of 32.81 years.

Because the cyst lining tends to infiltrate between the bony trabeculae, the cyst grows to a significant proportion in the anteroposterior direction before giving rise to any clinical symptoms. This accounts for the extensive involvement of the jaws by OKCs. The cyst then expands the cortical plates by an active proliferation of the lining, and resorption of surrounding bone by components of the extracellular matrix such as matrix metalloproteinases, and hydrostatic pressure.[8] Noticeable swelling was the chief complaint of 37% of the patients in the present study. The swelling was reduced by the third postoperative day and completely subsided for all the patients by the end of two weeks.

In addition to proliferation between the bony medullae, the thin friable lining and daughter cells in the cyst wall add to the challenge of removing the entire lesion completely. The leading component of the cyst may be present in the advancing front and may be retained following enucleation.[9,10] The basal cells of the overlying surface epithelium may also serve as a source for the odontogenic cells leading to recurrence. Therefore, the removal of at least 1 cm of marginal bone as well as soft tissues is recommended for OKC.[3,11]

Treatment of the surrounding bone by chemical agents such as 5-FU or Carnoy's solution aids in destroying the odontogenic cells infiltrated between the trabeculae while preserving the surrounding bone.[7] MCS acts by cauterization and fixation of tissue resulting in cell death. 5-FU, on the other hand, inhibits thymidylate synthetase an enzyme required for DNA synthesis causing cell death.[12] In the present study it was found that there was no statistically significant difference in the reduction of the number of recurrences by MCS and 5-FU. This implies that 5-FU is equally effective as the currently widely used MCS and also does not have adverse effects on the surrounding tissues produced by the latter.

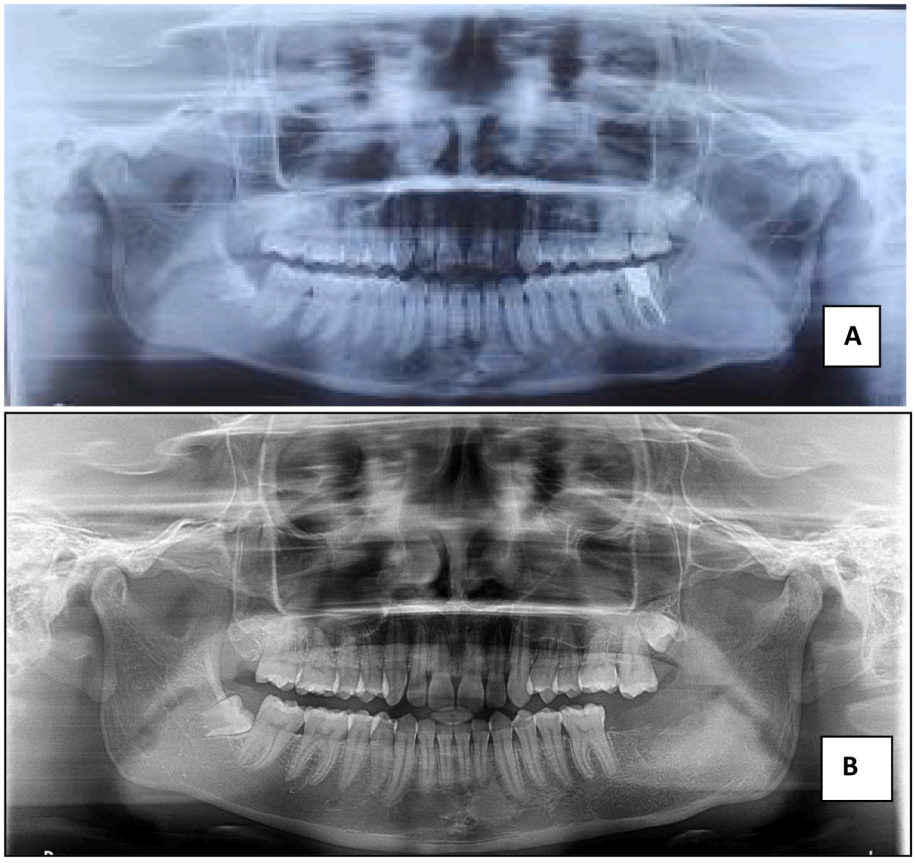

Fig. 4. A) pre-operative radiograph showing cystic lesion in the left angle and ramus region of mandible B) Post-operative radiograph showing adequate bone fill post-treatment with 5-fluorouracil in the left angle and ramus region of mandible.

Table 1
Inter-group comparison of mean score for pain and swelling status.

Follow-up period	Pain level (Visual analog scale)		Swelling	
	Modified Carnoy's solution	5-Fluorouracil	Modified Carnoy's solution	5-Fluorouracil
Day 1	5.5	5.4	Moderate	Moderate
Day 3	4.6	4.3	Mild	Mild
Day 7	2.5	0.7	Mild	Mild
Day 14	0.7	0.5	No	No

Ledderhoff et al.[6] had found a recurrence rate of 6% in patients treated with MCS similar to findings in the present study wherein recurrence had occurred in about 4% of patients treated with MCS after one-year post-treatment but none in the patients treated with 5-FU.Lone et al. saw a much higher recurrence rate with MCS -66% and no recurrence in the 5-FU group. The higher recurrence rate in the 5-FU group could be due to the longer follow up period of 7 years.[16]

Transient paresthesia was noted post-treatment in 22.7% of patients treated by MCS and 15% by 5-FU.Lone et all in their study saw higher rates of temporary paresthesia is the MCS group ie.55% and only 9% in the 5-FU group.[16] Although not statistically significant, post-operative paresthesia occurred less frequently in the patients treated by 5-FU. Permanent nerve injury and paresthesia occurred only in two control group patients. Similarly, localized sequestrum formation also occurred in two patients treated by MCS, but in none of the patients treated by 5-FU. The nerve damage and sinus necrosis can particularly occur in maxillary OKCs close to the sinus or the orbit that are treated with MCS.[6] No such local caustic effects are noted when treated with 5-FU. Therefore, the use of MCS is contra-indicated in cases in which the cortical plate is on the verge of perforation or has already been perforated.

Additional advantages of using 5-FU over MCS include its ease of availability, low cost and ease of application.[13] MCS cannot be stored over time and requires fresh preparation at the time of surgery. 5-FU, on the other hand, is available in ready-to-use forms and does not require a waiting period after its application, significantly reducing the operator's chair-side time.[14] The only drawback of using 5-FU dressing is that the pack has to be removed from the bone cavity after 24 h hours following which the wound has to be sutured again.

The limitations of the present study include the limited sample size and the shorter follow-up period. OKCs have been reported to recur even a decade later after removal and therefore, the follow-up period of one year in the present study may not be adequate to accurately infer results on the long-term recurrence rate.[15] Nevertheless, it was evident from our findings that 5-FU is equally effective or slightly better in reducing the number of recurrences as compared to MCS. It also eliminates the risk of permanent post-operative paresthesia paresthesia associated with the use of MCS for the treatment of OKC.

5. Conclusion

5-FU is an easy-to-use, feasible and cost-effective alternative for MCS in the management of OKCs. It is relatively more biocompatible than the latter which has detrimental effects on the surrounding nerves and bone. Treatment with 5-FU, therefore, reduces the risk of recurrence and also the post-surgical morbidity associated with other treatment procedures.

Support and funding

Nil.

Table 2
Inter-group comparison of the outcomes- Recurrence, Nerve injury, Wound dehiscence, Osteomyelitis.

Parameter	Follow-up period	Status	Modified Carnoy's solution	5-Fluorouracil	Chi-square value	P value
Recurrence	3 months	Yes	0	0	–	–
		No	22	20	–	–
	6 months	Yes	0	0	–	–
		No	22	20	–	–
	1 year	Yes	2	0	0.431	0.512
		No	20	20		
Nerve injury	3 months	Yes	5	3	0.431	0.512
		No	20	20		
	6 months	Yes	2	0	6.281	0.043
		No	20	20		
	1 year	Yes	2	0	1.241	0.265
		No	20	20		
Wound dehiscence	3 months	Yes	3	2	0.013	0.910
		No	19	18		
	6 months	Yes	0	0	–	–
		No	22	20		
	1 year	Yes	0	0	–	–
		No	22	20		
Sequestrum formation	3 months	Yes	0	0	–	–
		No	22	20		
	6 months	Yes	1	1	0.431	0.512
		No	21	19		
	1 year	Yes	2	0	0.431	0.512
		No	20	20		

Table 3
Location of cystic lesions.

1.		Group 1	Group 2	Chi square value	p value
site 1	Anterior mandible	2	0	9.813	0.366#
	Left angle	1	0		
	left angle ramus of mandible	0	1		
	Left body of mandible	3	7		
	Left ramus	2	2		
	Right angle	2	0		
	Right body of mandible	8	6		
	Right parasymphsis	1	0		
	Right ramus	3	3		
	symphysis of mandible	0	1		
site 2	0	8	11	7.061	0.423#
	Left angle	3	2		
	Left body of mandible	2	4		
	Left parasymphysis	1	0		
	Left ramus	1	0		
	Right angle	3	1		
	Right body of mandible	0	1		
	Right ramus	4	1		
site 3	0	21	19	2.009	0.366#
	Right ramus	1	0		
	symphysis of mandible	0	1		
site 4	0	22	20	–	–
site 5	0	22	20	–	–

Ethics committee approval

Ethical approval from Instituitional ethics committee was obtained before starting the study.

Consent to participate

Written informed consent was obtained from all the participants of the study.

Consent for publication

All authors consent to publish.

Competing interests and funding

The authors declare that there were no competing interests during the study and no funding was received.

Declaration of competing interest

There is no conflict of interest in this study.

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