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Original Research

USE OF TOPICAL 5-FLUOROURACIL IN THE MANAGEMENT OF ODONTOGENIC KERATOCYSTS: A COMPARATIVE STUDY

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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 modified carnoys solution in the management of Odontogenic Keratocysts (OKC). **Materials & methods**: This comparative study was conducted in the OMFS department for last 5 years, wherein 32 cases of OKC were included and randomly allocated to the two treatment groups. 14 were treated by enucleation followed by application of modified carnoy solution (CS), 18 by peripheral ostectomy followed by application of 5-FU and. Follow-up ranged from 2 to 4 years to assess bone healing and record any recurrence of lesion. **Results:** Amongst thirty two patients, nineteen were males and thirteen were females, age range 20–66 years. The most common location of OKC was posterior mandible. Complications included nerve injury, swelling, infection, and recurrence (22.2% after modified CS). 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.

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INTRODUCTION

WHO defined OKC as ‘‘a benign uni- or multi-cystic, intraosseous tumor of odontogenic origin, with a characteristic lining of parakeratinized stratified squamous epithelium and potential for aggressive, infiltrative behavior (Barnes et al., 2005).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 cysts 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 1.6:1, with a mild predominance to males. Patients are usually asymptomatic and are accidently detected during routine radiographic examination. Swelling, pain, facial asymmetry, infection, paraesthesia are seen in symptomatic patients.[3] 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.[4] 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 Basel 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 acid metabolite, to inhibit apoptosis and immune surveillance, increase angiogenesis and the invasive ability of tumour cells[5,6]. 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.[7] The purpose of this study was to determine the efficacy of topical 5% 5-FU in the treatment of KOTs.

MATERIAL & METHODOLOGY

This study has been designed and implemented as an ambispective study of patients treated with topical application of 5-FU, or MC, following enucleation and peripheral ostectomy of KOTs. The study population was composed of all patients presenting for evaluation and management of KOTs from 2015 to 2020 at the department of oral and maxillofacial surgery government dental college and hospital Srinagar

To be included in the study sample, patients had:

(1) A biopsy-proven KOT/OKC,

(2) A complete history and clinical examination prior to definitive surgical intervention, and

(3) Completed surgical intervention for KOT

Patients were excluded as study subjects if they had:

(1) A diagnosed psychiatric condition,

(2) Multiple KOTs or diagnosed Gorlin-Goltz syndrome,

(3) A recurrent KOT,

(4) A prior trigeminal nerve injury or existing paresthesia, and/or

(5) A diagnosis of orthokeratinizing odontogenic cyst or odontogenic keratocyst orthokeratinized variant

The independent variables for this study were KOT treatment with topical 5% 5-FU or MC solution. Primary outcome variables include: (1) time to KOT recurrence (months) and (2) incidence of inferior alveolar nerve injury. Other study variables included age (years), sex, tumor location (mandible or maxilla), and tumor size (mm).

Ethics approval was obtained from the ethical committee of government dental college Srinagar

A comprehensive history and examination was performed on all patients to rule out a history of medical conditions or disorders that may alter their trigeminal sensory perception.

Oral biopsy specimens of all patients meeting the inclusion criteria were evaluated by department of oral pathology to confirm the diagnosis of KOT.

Demographic information was collected for each patient including age, sex, lesion location, radiographic appearance and tumor size. The procedure, risks, alternatives and benefits of treatment with 5-FU or MC were reviewed with the patient and informed consent was obtained

Topical application of 5-FU

Following enucleation and peripheral ostectomy of the KOT lesion, sterile quarter-inch ribbon gauze was coated with 5% 5-FU (5% flonida) and packed into the surgical wound.

The wound was then closed per usual manner, leaving a small distal end (approx. 1 cm) of gauze exposed to allow gauze removal at 24 hours post-operatively

Topical application of Modified carnoy's solution

- Following intraoperative enucleation and peripheral ostectomy of the OKC lesion, the surrounding soft tissues were protected with multiple sterile petroleum jelly-coated neuro patties.
- MC solution-saturated neuro patties were then carefully placed in the surgical wound so that every discernable surface of the lesional cavity was exposed to MC for 3minutes followed by thorough normal saline irrigation.
- All instruments exposed to MC were then removed from the operative field, and the surgical team re-gowned and gloved in order to prevent possible injury to healthy tissues by the caustic MC solution during wound closure. Data were reported as mean ± SE; Fishers exact tests and Kaplan-Meier analysis were used as appropriate ($p<0.05$ considered to reflect statistical significance) using SPSS version 22.0 software for analysis.

RESULTS

A total of 32 subjects with 32 KOTs were reviewed, with 41% in women and 59% in men ($p>0.05$). The mean age at diagnosis was 42 years, 2 months ± 2.9 years ($P>0.05$). Mandibular lesions accounted for 27/32 KOTs with the remaining 5/32 found in the maxilla ($p>0.05$). A total of 18 KOTs were treated with enucleation, peripheral ostectomy and topical application of MC, and 14 KOTs were treated by enucleation, peripheral ostectomy and topical application of 5% 5-FU cream There were no significant differences in patient demographics between the two treatment groups ($p>0.05$). OKCs measured a mean of 34.8 x 44.5 ± (3.9 x 4.8) mm in the MC group and 28.4 x 30.1 ± (4.1 x 6.1) mm in the 5-FU group (*$p>0.05$).*(Table 1). *In the MC group (n=18), there were 4* (22.2%) recurrences with a mean recurrence time of 26.3 ± 1.8 months and a mean follow up time of 41.3 ± 3.8 months. In contrast, there were no recurrences in the 5-FU group (n=14) with a mean follow up time of 35.0 ± 8.5 months (*$p=0.19,$).*(Table 2). *All 5-FU treated* cases demonstrated normal bony healing. A Kaplan-Meier analysis was performed to illustrate differences in the time to recurrence between the two treatment groups *($p>0.05$).* There were no adverse local or systemic events in response to 5-FU or MC application. In 14/18 mandibular cases (77.8%) treated with MC, post-operative inferior alveolar nerve paresthesia was noted with a mean recovery time of 29.0±10.6 weeks. Four of these cases (22.2%) resulted in permanent paresthesia. In contrast, only 3 cases (33.3%) of 5-FUtreated patients had transient paresthesia that

resolved in a mean time of 42.0±10.0 weeks (*p=0.039,).* (Table 3)

TABLE 1	MC	5-FU	Total
Number of Cases	18	14	32
Age (+/- SE years)	42y 3m (3.7)	42y 1m (4.8)	42y 2m (2.9)
Sex Female	8	5	13
Male	10	9	19
Location **Mandible**	15	12	27
Maxilla	3	2	5
Radiographic Appearance Unilocular	12	9	21
multilocular	7	4	11
Mean lesion size (width x height mm)(+/- SE width x height)	34.8 x 44.5 (3.9 x 4.8)	28.4 x 30.1 (4.1 x 6.1	31.6 x 37.3 (2.9 x 3.9)

Table 2	**MC (n=18)**	**5-FU (n=14)**
Recurrences	4	0
Mean time to recurrence in months (±SE)	26.25 (1.8)	n/a
Follow up time in months (±SE)	41.3 (3.8)	35.0 (8.5)

Table 3	MC	5-FU
Total Cases	18	14
Post-operative nerve injury cases	14	3
Average neurosensory recovery time in weeks (±SE)	29.0(10.6)	42.0(10.0)
Permanent nerve injury cases	4	0

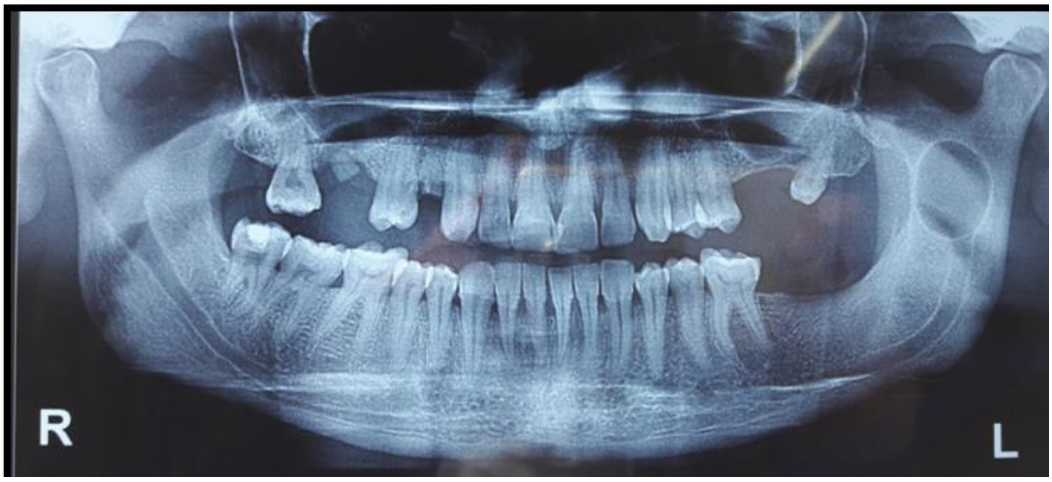

Figure 1: Preoperative radiograph

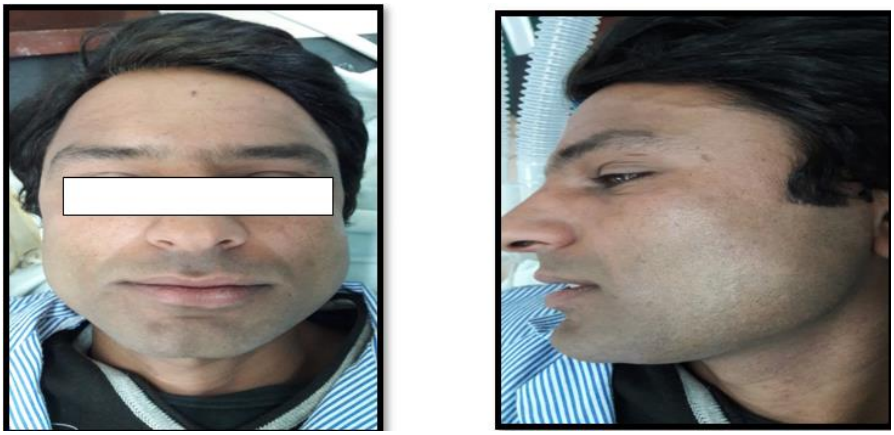

Figure 2: Preoperative patient image

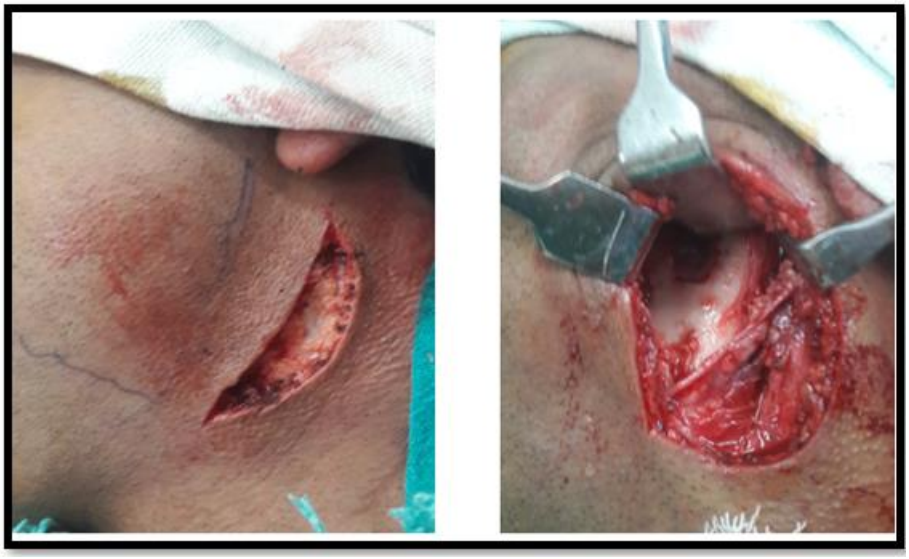

Figure 3: Intraoperative procedure

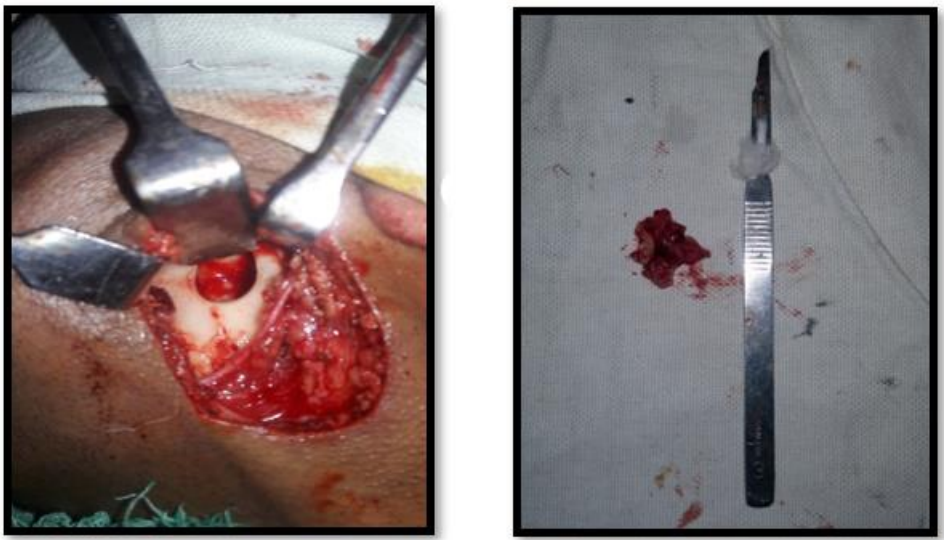

Figure 4: Enucleation and removal of cyst lining

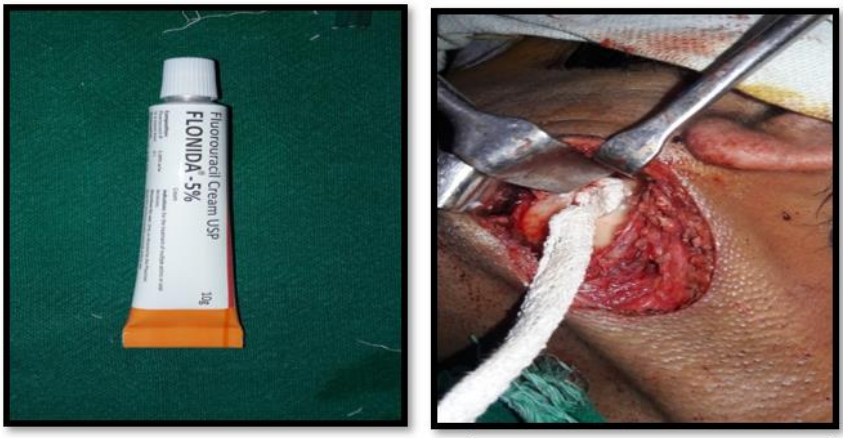

Figure 5: 5% 5 fluorouracil

Packing of 5-FU into cavity

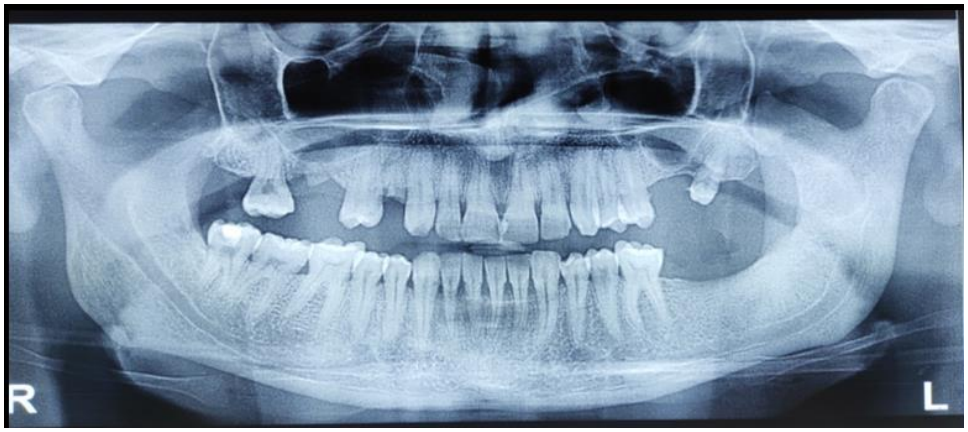

Figure 6: Postoperative 1-year OPG

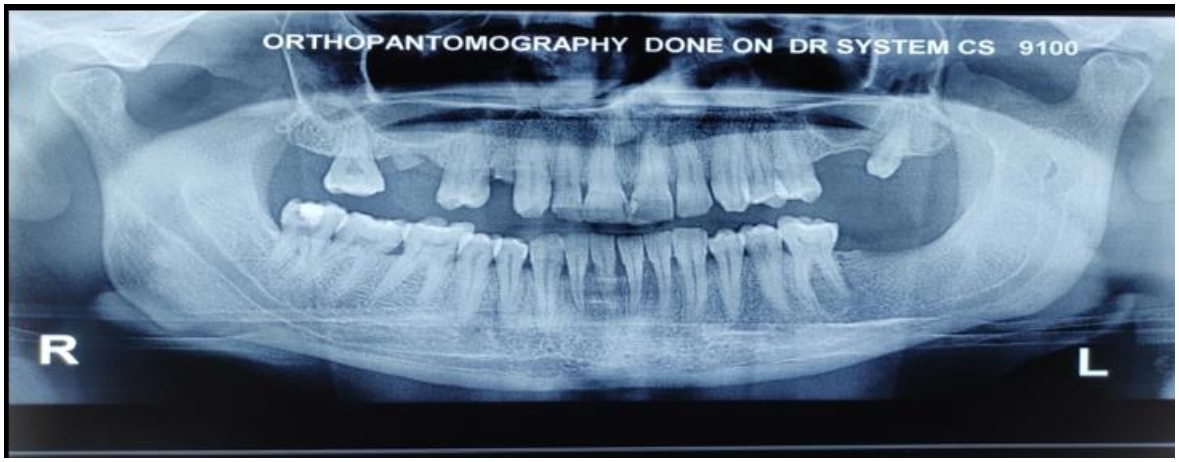

Figure 7: Postoperative 3-year OPG

DISCUSSION

The purpose of this study was to determine the efficacy of using topical 5% 5-FU for the treatment of OKCs.This study demonstrate for the first time that 5-FU is an effective and novel targeted treatment for OKCs. Topical application of 5-FU, following enucleation an peripheral ostectomy, effectively treats OKCs resulting in normal bony healing with no adverse local or systemic effects

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 ostectomy, 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[8]

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.[9] 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.[10] 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

5-FU may be more ideal than MC due to its ready availability, technical ease, shorter operating time, similar efficacy, and decreased morbidity compared to MC. 5-FU is simply coated onto ¼ inch ribbon gauze and packed into the residual bony cavity in a manner that allows for easy retrieval at 24 hours post-op. In contrast, there is substantially increased operating time when MC is used, due to the need for multiple precautions as described previously[11, 12].

There were no KOT recurrences in the patients treated with 5-FU. Conversely, the 19.0% recurrence rate observed with MC in this study. The mean recurrence

time of 26.3 months is also in line with prior studies. MC may result in significant local tissue destruction if not carefully handled[13]. Contact of MC with peripheral nerves causes damage to the perineural tissues when following the 3-minute application protocol defined by Frerich and colleagues In agreement with prior studies large majority of the patients with mandibular KOTs treated with MC in this study developed post-operative paresthesia and a substantial number had permanent neurosensory deficits[14,15].

All KOTs in this study demonstrated a moderate proliferation index, which is in agreement with previous studies and suggests that KOTs are amenable to treatment by inhibition of DNA synthesis with an antimetabolite agent such as 5-FU. The overall low expression of TS in KOTs is suggestive of susceptibility to 5-FU treatment[16, 17].This study that demonstrates the efficacy and versatility of topical 5-FU application by packing the surgical site with 5-FU-impregnated ribbon gauze. This technique can be used for hard-to-treat areas of cortical perforation, in contrast to the relative contraindications for MC use in areas of cortical perforation. Similarly, 5-FU may be more amenable than MC for lesions in the posterior maxilla in close proximity to major vessels of the head and neck, orbital contents and the maxillary sinus, where there are concerns of vascular injury, neurovascular injury and sinus necrosis[18, 19, 20]. Peri-orbital connective tissues also seem to be unaffected by twice daily application of topical 5-FU when used to treat ocular surface squamous neoplasia[21]. No studies to date have shown direct application of topical 5-FU to major blood vessels; however, twice weekly application of topical 5% 5-FU for 4 weeks following medial maxillectomy and sphenoethmoidectomy for ethmoidal adenocarcinoma had no mention of adverse effects on the infraorbital nerve nor the remaining sinus mucosa[22]

There were no adverse effects from topical application of 5-FU in this study. However, systemic administration of 5-FU may result in adverse responses including: mucositis, granulocytopenia, neuropathy, cardiac toxicities, nausea, vomiting, pallor, hypotension, general malaise and death[17]. Approximately 3-5% of the population is partially DPD deficient which can cause an intense systemic toxicity when 5-FU is used in any treatment. This is most prevalent in African-American females with up to 12% of this particular demographic reported to be DPD deficient; therefore, caution should be exercised when treating with 5-FU[23].

CONCLUSION

5-fluorouracil is a novel, effective, targeted treatment for KOTs with lower recurrence rates and less morbidity compared to modified Carnoy's solution. Inflamed KOTs may be more likely to respond to 5-FU treatment based on immunohistochemical findings. The advantages of topical 5-FU include decreased post-operative morbidity, lower risk of re-operation, lower cost, and simple technique. It is also a known, accessible and well studied drug. Further molecular characterization, prospective clinical trials and consideration of additional targeted medications such as SMO or SHH inhibitors are suggested for the treatment of KOTs

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