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Original Research Paper

Plastic Surgery

HOLISTIC STUDY OF FACIAL REHABILITATION OF MUCORMYCOSIS IN PATIENTS INFECTED WITH COVID- 19

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ABSTRACT

Background: Mucormycosis is a deep fungal infection which witnessed a steep rise in India following the covid 19 pandemic. Extensive involvement with sinonasal and sinonasocerebral variants were seen. Involvement of various structures of sinus orbit and nose along with soft tissues put the patients into threat of losing the supporting and covering structures for survival. Post debridement there was composite defects of face. Addressing these disfigurement and planning a suitable reconstruction based on there general health condition with multiple comorbidities is a challenge. **Aim:** this study aims at evaluating the factors associated with poor outcome in flap reconstruction and selection of the types of flaps , timing of reconstruction and type of reconstruction associated with favourable outcome. **Material And Methods:** Prospective observational study conducted from Apr 2021 to Apr 2022 of 20 patients for reconstruction of post mucormycosis debridement facial defects. The factors like d- dimer, ferritin, LDH, timing of surgery, type of reconstruction, types of flaps and the condition of the debrided residual tissues were assessed for its association with the flap outcome. Follow up at regular intervals were done to look for complications upto 6 months. **Results:** Out of 20 patients, 13 had good clinical outcome for flaps in terms of its survival, lack of dehiscence, but still had functional deficit. Whereas, 7 patients had complications of flaps like flap failure, flap dehiscence and underwent secondary surgery. All these patients had increased comorbidities, increase in the acute phase proteins suggesting the persistence of inflammatory state post covid. **Conclusion:** Best outcome in facial rehabilitation in post mucormycosis defects can be brought by optimizing the risk factors, deciding on the time of intervention, giving enough time for the residual tissue to improve and the acute phase proteins to normalize and selection of suitable flaps for reconstruction.

KEYWORDS : Covid- 19 Infection, Mucormycosis, Facial Reconstruction.

INTRODUCTION

The COVID- 19 infection caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS- CoV- 2) may be associated with a wide range of disease patterns, ranging from mild to life- threatening pneumonia. Due to the pre-existing morbidities like diabetes mellitus and lung diseases, a wide range of bacterial and opportunistic fungal infections may occur in infected patients.[1]

Mucormycosis is one amomg such serious but rare opportunistic fungal infection, mainly affecting elderly patients, diabetics, immunocompromised individuals. The infection is known to spread rapidly causing infarction and necrosis in the host tissue.[2]

Mucormyosis has varied presentations, typical being rhino-orbito- cerebral typical presentation, wherein the fungal elements invade paranasal sinuses, orbit and brain. Orbital apex syndrome, a rare manifestation of invasive mucormycosis is often fatal leading to complete ophthalmoplegia, rapid vision loss, involving cranial nerves II, III, IV, V, and VI. Prompt and early initiation with oral anti-fungals, surgical intervention and control of risk factors is advised to prevent morbidity and mortality.[2]

In India, the prevalence of mucormycosis is 0.14 per 1000population, which is 80 times higher than developed countries. During the second wave of Covid- 19 pandemic, India showed an alarming rise in mucormycosis infection also referred to as black fungus.[3]

Mucormysis causes osteomyelitis, which is an inflammatory condition encroaching the medullary cavity, Haversian systems and extending to the periosteum of the bone. The invasion of fungus in the bone marrow leads to growth of the fungus, affecting the endothelial lining of vessels inturn causing vascular insufficiency, eventually leading to bone necrosis developing into fungal osteomyelitis. [4,5]

Craniofacial mucormycosis is most commonly an acute manifestation often imitating symptoms of sinusitis or periorbital cellulitis. The patients present with unilateral facial swelling and pain. The hallmark is black necrotic eschar of the nasal mucosa or palate. The necrotic eschars are formed due to local disease progression, tissue infarction and blood vessel thrombosis. There is ulceration of the hard palate which indicates extension of disease outside the maxillary sinus.6 Hosseini et al. reported in their study that the pterygopalatine fossa is the pool of the disease, from where the infection spreads to surrounding structures, such as the infratemporal fossa and retro- orbital space[7].

Management is complex as it involves multistaged intervention probably by mutispecialist team. Both medical and surgical intervention should be promptly delivered with timely decision and reconstruction contemplated as early as the disease is stable. No prior data on the management protocol exists as not only the covid is new, but mucormycosis is relatively uncommon. the timing for secondary reconstruction is another challenge as immediate may be burdened with residual disease and incomplete general recovery of the patient to undergo long standing or reconstructive surgery.

Considering delayed reconstruction, few believe in dessication of the bones and injuries or infection to vital structures around the face[8], while others believe in decreasing morbidity and mortality when reconstruction is delayed until recovery of infection and optimization of general condition.[9] Type of reconstruction also matters as most of the patients have multiple comorbidities contraindicating them for microvascular reconstruction. Simple local flaps to complex reconstruction are demanded in these patients. Hence a thorough study of these variables to stratagise treatment

guide is necessary.

METHODOLOGY

All cases of facial defects uni/multilamellar post debridement and post completion of antifungal for covid associated mucormycosis attending the Out- patient department and in-patients of Plastic and reconstructive surgery were included in this prospective observational study.

Inclusion And Exclusion Criteria

All cases of facial defects due to covid associated mucormycosis irrespective of age and gender were included in the study. Mucormycosis in other regions were excluded.

1. All pre- operative investigations for operation was done with special investigations like d- dimer, ferritin and LDH .
2. CECT head and face with 3D reconstruction was obtained.
3. MRI was obtained for patients with dilemmatic CT findings and suspected cerebral and angio- invasion.
4. All patients fungal culture was sent from the involved tissue.

ETHICS-

The ethical clearance was obtained from Institution Ethics committee.

RESULTS

The study comprised of 17 males and 3 females with mean age of males 48.03 and mean age of females 52 years.

There were a total of 13 orbital defects with 7 on right and 6 on left. Other defects were cheek defects (4), palatal defects (4) and a nasal defect.

Sixty percent of study population had sino- naso- orbital and forty percent had sino- naso- orbito- cerebral involvement. These patients had increased morbidity and complications owing to the persistence of infection/post infection inflammatory state.

Majority of patients had orbital involvement which led to orbital excentration with residual orbital defects, where 9 csese underwent medial maxillectomy and turbinectomy, 4 cases underwent suprastructutal maxillectomy (Figure.1) with loss of inferior skeletal support of orbit leading to flap retraction and dehiscence.

We considered all the available factors in accessing the association with the outcome and considered the optimum time for surgery and found that 13 patients who were operated later than 3 months had better flap survival and were devoid of local and systemic complications. Seven patients who underwent surgery soon after resolution of infection or within 3 months were the ones who had flap complications, probably due to persistent infection or post- infection inflammatory state (Figure 2).

Likewise, nutrition, comorbidities like uncontrolled diabetes, had more impact on flap failure or mortality compared to hypertension, ischaemic heart disease. Five patients had uncontrolled diabetes and all had complications of flap and post- op flap infection and respiratory infections (Figure 2).

The inflammatory indicators showed positive relationship with the flap failure and mortality or wound healing. All 7 cases with raised d- dimer(p- value 0.000) and 5 out of 7 raised ferritin and LDH(p- value0.002) had flap complete loss and dehiscence contributing to wide defects (Figure. 2)

Even the surrounding tissue condition played important role in the outcome of the flap. Friable inflamed tissues contributed to wound dehiscence and wide defects.

The extent of the secondary contraction (Table/ Figure. 3) was another contributing factor to the flap dehiscence. Here the width of the defect was measured in each cases. More than one- third of previous defect was considered maximum and less than 1/3rd of previous defect was termed minimal.

Among the local flaps reconstructed, 7 were paramedian forehead flaps, among which 4 of them sustained dehiscence and 1 out of 6 mustarde flaps had dehiscence. All three temporalis flaps showed no complications. Paramedian flap had higher dehiscence due to lack of support and retraction and there was recurrence of defect (Figure. 4).

Among the free flaps 3 were free radial forearm flaps and 1 was anterolateral thigh flap. One ALT flap sustained failure and one out of three free radial forearm flap sustained failure. A patient with antero- lateral thigh flap succumbed to death at 5th post - op day due to ARDS contributed by increased acute phase reactive proteins, multiple comorbidities - uncontrolled diabetes, IHD and hypertension and infection due to poor condition of tissues. Similarly in one patient with palatal reconstruction , there was raised d- dimer, LDH and ferritin and mutiple comorbidities which contributed to the flap failure due to coagulopathy .Secondary flaps reconstructed were 3 temporalis, 1 each paramedian, limberg and free radial forearm flaps (Table/ Figure 5).

The functional complications with these flaps were difficulty in mastication seen in 4 patients , among them 3 had underwent infrastructural maxillectomy with palatal loss and 1 had medial maxillectomy with alveolar loss. There were complaints of air leaks in 9 patients with 6 suprastructural maxillectomy and 3 medial maxillectomy due to communication of nasal cavity with the orbital and maxillary cavity(Figure. 6).

One complex nasal mucormycosis patient with loss of total nasal skeletal and soft tissue extending into upper lip and palate and associated medial maxillectomy (figure 8), posed a reconstructive challenge of the skeletal and soft tissue, in the background of multiple comorbidities. Other cases have been represented from figures 7 to 15.

DISCUSSION

Mucormycosis is a rare invasive fungal infection caused with an incidence of 0.43 to 1.7 cases per million per year. It is caused by various opportunistic fungi belonging to Mucoraceae family. Eighty percent of the cases are caused by Rhizopus, Mucor, and Lichtheimia. The infection usually affects patients with poorly controlled diabetis mellitus, malignancy, and solid organ transplant recipients.[4,10]

The risk factors for mucormycosis surge in India include COVID- 19 induced immune dysregulation, uncontrolled diabetes mellitus and indiscriminate use of steroids may be the risk factors. Clinical findings suggest that SARS- CoV- 2 infection targeted the integral immune system and altered it by suppressing the activity of immune cells, particularly T lymphocytes, CD4+ and CD8+ T cells, which are potential work force involved in the pathological process of Covid- 19 infection[11].

Based on invasion, mucormycosis is categorized as rhinocerebral (most common), pulmonary, cutaneous, gastrointestinal or disseminated.4 Rhinocerebral form is subdivided into rhinonasal, rhinoorbital or rhinoorbitocerebral based on tissue involvement.[12]

Rhino- orbital variant is an acute invasive variant and potentially fatal fungal infection of the nose, paranasal sinuses, and the orbit, often involving the intracranial compartment and the facial soft tissues of immunocompromised hosts. In severe cases, the survival rate of 36% - 42% is seen.[13]

The rapid filamentous growth due to angioinvasion, tissue necrosis, and thrombosis along with the failure of the human immune system to successfully clear the infection and the resistance or poor therapeutics currently employed accounts for very high mortality rate in more than 50% of cases.[14,15]

The localisation of infection determines the severity of infection. Specifically, the rhino- orbito- cerebral mucormycosis (ROCM) is more dangerous as it causes vision impairment and seizures in brain leading to death.16 In our study also, the ROCM patients faced flap failure and mortality more than the rhino- orbital mucormycosis (ROM) patients. Uncontrolled diabetes patients also had post- op infection , flap dehiscence and even mortality due to diabetic ketoacodosis.

Studies suggest role LDH, an intracellular enzyme as a predictor of mortality.LDH is found in cells in almost all organ systems, catalyzing the interconversion of pyruvate and lactate, with concomitant interconversion of NADH and NAD+. LDH is present in lung tissue (isozyme 3), heart, striated muscle and kidney. Severe infections may cause cytokine- mediated tissue damage and LDH release. In patients with severe COVID- 19 infection, release greater amounts of LDH in the circulation preedisposes to severe form of interstitial pneumonia, often evolving into acute respiratory distress syndrome. Hence, high serum LDH levels is a negative prognostic factor in such patients17. LDH is also elevated in thrombotic microangiopathy, which is in turn associated with renal failure and myocardial injury17,18,19. Elevated LDH was associated with flap failure or dehiscence and mortality like post- op pneumonia and distress.

Elevated d- dimer levels is another prognostic indicator. D-dimer is a fibrin degradation product with its main utility is in the diagnosis and management of thrombotic disorders. The levels suggests a hypercoagulable state contributing to severity of illness and mortality.20,21,22Similarly 22. Before the 2019 COVID- 19 pandemic, D- dimer was not considered a useful biomarker for bacterial or viral pneumonia despite some evidence to the contrary.23 Elevated levels of D- dimer is associated with thrombotic complications and poor prognosis.[17,24]

All patients who had increased d- dimer, or had doubling or more increase in d- dimer and coagulopathy and were associated with flap edge necrosis or total flap necrosis. In this study , nearly all patients with post- op pneumonia , flap dehiscence , infection and complete flap necrosis had 5 to 10 times increase in the d- dimer levels.

The treatment of mucormycosis encompasses three important steps[10,25]

1. Prompt reversal of underlying predisposing conditions like uncontrolled diabetes or ketoacidosis.
2. Surgical debridment of necrotic tissues.
3. Systemic antifungals like Amphotericin B or, if contraindicated, posaconazole.

In patients with massive necrosis of bone and soft tissues in the central portion of the face, there is severe aesthetic and functional impairment, impacting the quality of life.10 In such cases, surgical measures like resection of involved tissues, including skin and muscle, nasal skin, maxillary and ethmoid sinuses, necrotic tissue of the temporal area and infratemporal fossa, and orbital exenteration can be considered.[26]

Block resections of the involved area exposes bone and mucosal structures. If these structures are not reconstructed immediately, there are chances of desiccation, and in some cases, even necrosis, leading to atrophy and contraction hindering any subsequent reconstructions.9 Covering these defects with a well- vascularized flap facilitates antifungal perfusion to the exposed tissue borders and avoids additional complications like fistulas, exposed dura, and secondary wound infections. The choice of flap is based on the size of the defect.8 Various flaps like pedicle flap, post tissue expansion, free flap or chimeric flap have been used for reconstruction.

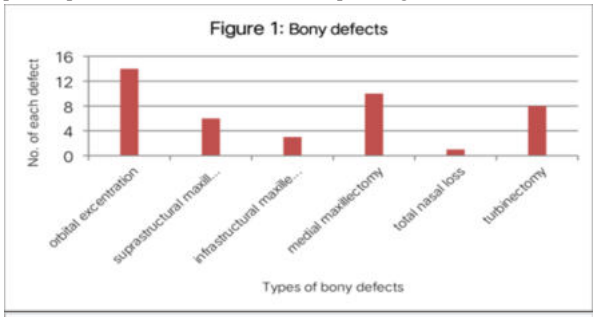
Local flaps of face like paramedian forehead flaps , mustarde flap, for orbital defect and radial free forearm flaps were used. Mustarde flap were more sustainable compared to forehead flaps which showed dehiscence and two stage procedure and more secondary contraction. Whereas free flaps were robust and aesthtically pleasing. But the coagulopathy, and thriving chronic infection hindered its survival in few patients.

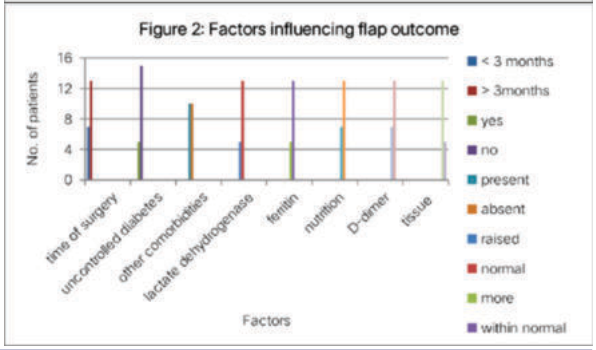
All patients would not be fit to undergo microvascular reconstruction due to comorbidities and poor cardiac condition owing to poor ejection fraction. Hence, local flaps are also required to take care of such patients. knowing which flap could do better in these conditions and best donor sites are a must to provide optimal surgical care to these already debilitated patients.

As already mentioned, the acute phase markers like d- dimer , LDH, ferritin all were raised and strongly associated with the flap failure and mortality and post - op respiratory complications. Uncontrolled diabetics hypertensives, ischemic heart patients with low ejection fraction were also related with poor flap outcome.It was seen that, a minimum of 3 months was required post mucormycosis to operate on these patients for reconstruction because the surrounding tissue remained inflamed and friable and not healthy to affect healing of flap and itself. Hence the time of intervention, control of comorbidities and complete resolution of infection and chronic inflammation, indicated by the normal d- dimer LDH and ferritin are important to bring favourable and optimal surgical outcome.

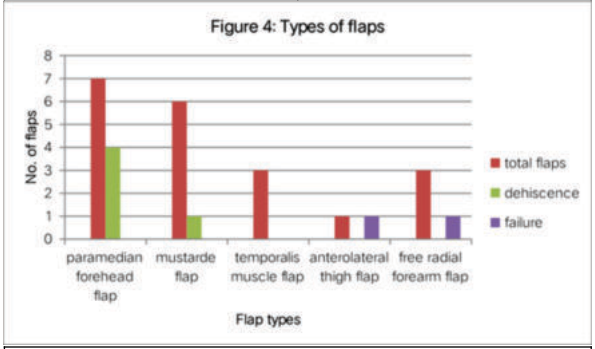
CONCLUSION

Best outcome in facial rehabilitation in post mucormycosis defects can be brought by optimizing the risk factors like uncontrolled diabetes hypertension and ischemic heart disease. Deciding on the time of intervention is equally important as patients who were operated 3 months post treatment of mucormycosis had better flap outcome giving enough time for the residual tissue to improve and the acute phase proteins to normalize and improving the nutrition.

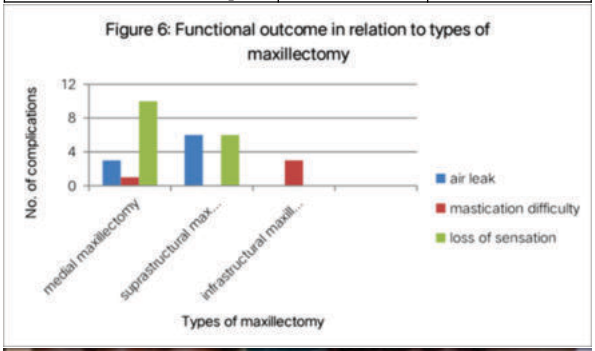




Table/ Figure 3. Secondary contraction of flaps	
Type of flap	Secondary contraction
Forehead flap	Maximum
Cheek rotation flap	Minimal



Table/ Figure 5. Second Flap Reconstructed Following First Flap Failure		
Flap types	Numbers	p- value
Temporalis	3	0.000
Paramedian	1	
Limberg	1	
Free radial forearm flap	1	



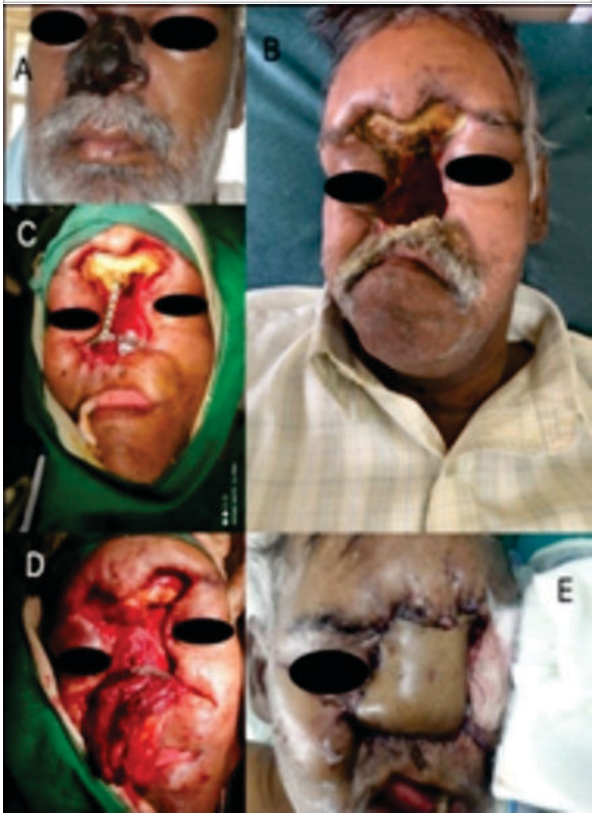


Figure 7. A 75 year old male, diabetic and ischemic heart disease patient sustained sinoorbitocerebral mucormycosis, underwent total nasectomy and bilateral medial maxillectomy with associated tissue debridement and free anterolateral thigh flap was reconstructed with titanium implant for nasal support.

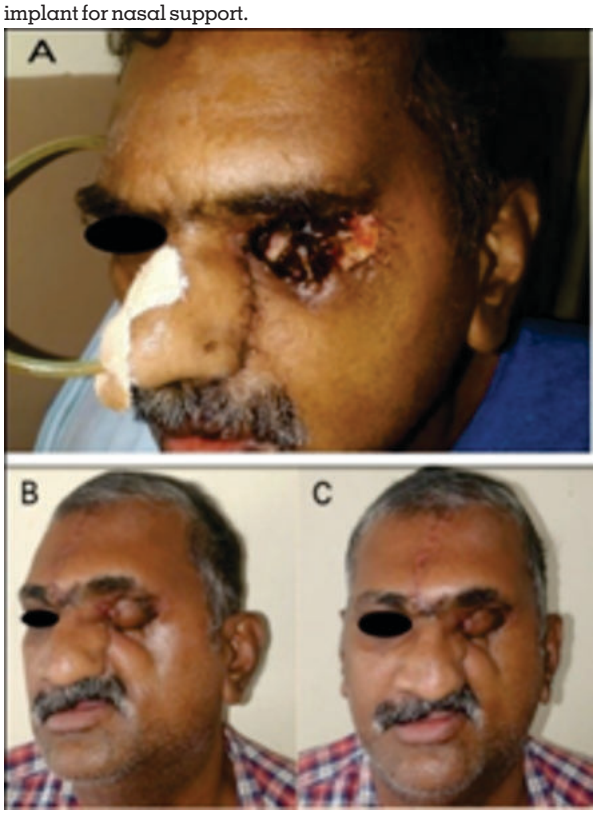


Figure 8. A 60 year old male with orbital exenteration was planned for paramedian forehead flap and the above picture 8b and 8c shows the flap at 6 months.

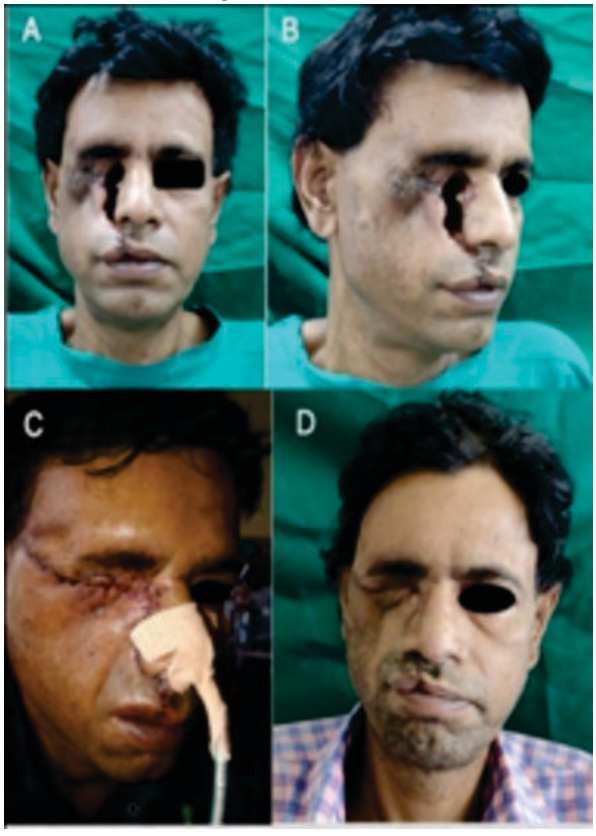


Figure 9. A 45 year old male patient had orbital excenteration and underwent cheek rotation flap reconstruction.

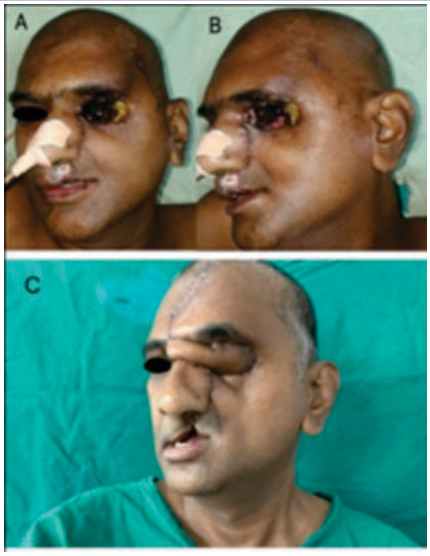


Figure 10. Above Picture Shows The Paramedian Forehead Flap Before The Division.

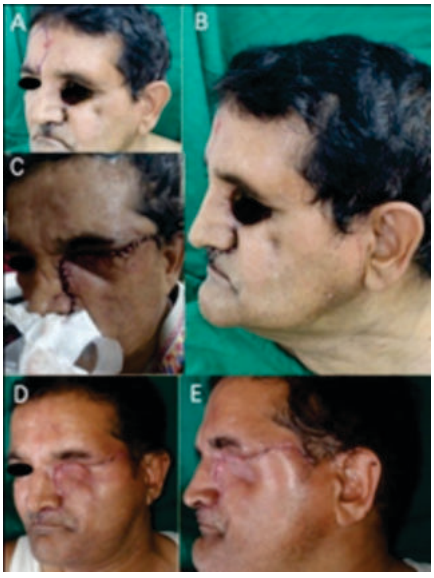


Figure 11. A 65 year old man with orbital excenteration underwent mustarde rotation and advancement flap cover.

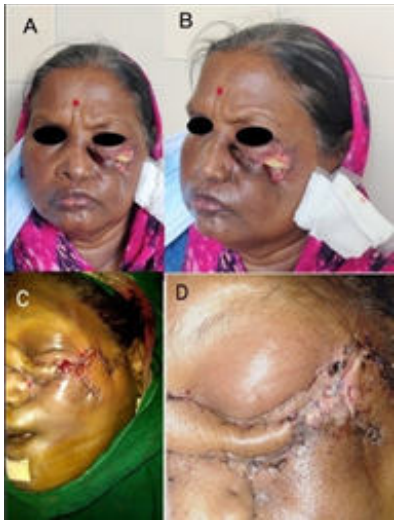


Figure 12. A 65 year old woman had to undergo multiple surgeries initially a forehead flap was reconstructed for suborbital defect with limberg flap for small adjacent defect, due to its retraction and bone exposure patient underwent temporalis flap secondarily .

Figure 13. A 49 year old male with right palatal defect reconstructed with free radial forearm flap.

Figure 14. A 45 year old male with orbital defect reconstructed with temporalis flap.

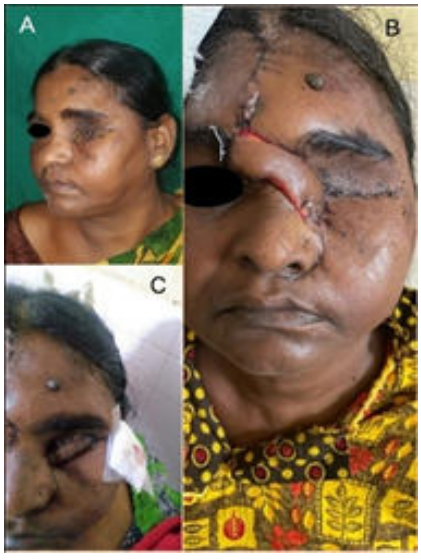


Figure 15. A 55 year old female with multiple comorbidities with medial orbital defect reconstructed with forehead flap.

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