Role of surgery and antimicrobials in refractory skull base osteomyelitis- a prospective study.

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Abstract

Abstract Objective: To analyse the role of surgery along with antimicrobials to improve clinical outcomes in treating refractory cases of skull base osteomyelitis (SBO). Study design and setting: A prospective comparative study in a tertiary care centre with 70 SBO patients meeting eligibility criteria. Participants: The study population comprised 35 patients refractory to systemic antimicrobials of at least four weeks duration who later underwent surgery in addition to medication (surgical group). They were compared with a medical group that responded to medications alone. Main outcome measures: The outcome variables studied were the resolution of clinical features (pain, discharge, radiology, and inflammatory markers), culture yield, and total duration of treatment. Results: According to our study, relief of pain was faster in the surgical group(1.66 against 4.57 months) with statistical significance (p< 0. 001). Relief of symptoms (p< 0.001), radiological improvement (p= 0.001), and normalizing of inflammatory markers (p<0.001) were better in the surgical group than in the medical group. The duration of treatment was an average of 9. 2 months in the surgical group compared to 11.3 months in the medical group (p= 0.019). Microbial culture from deep tissue sampling was positive in 24 surgical patients (68.57%). Conclusion: The treatment response to surgery and antimicrobials in treating refractory cases of SBO was better than the group who responded to antimicrobials alone. Surgery provided higher microbial yield resulting in culture-specific antimicrobials. The surgical group observed faster relief of symptoms, reduced hospital stay, and total treatment duration.

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Keywords:

Malignant otitis externa, Skull base Osteomyelitis, Temporal Bone, Necrotising otitis externa

Keypoints:

- Surgery along with antimicrobials were found to be effective in all cases of refractory SBO
- Faster relief of symptoms and lesser duration of antimicrobials and hospital stay was seen in the surgical group
- Culture yield was better for the surgical group
- Surgical intervention did not aggravate the existing clinical scenario
- Surgery may be considered in patients when they are unresponsive after 4 weeks of IV antibiotics.

Introduction:

Skull base osteomyelitis (SBO) is an invasive infection in which pathogens spread to the periosteum of the temporal bone and tissue planes, causing necrosis. Chandler coined the term malignant otitis externa (MOE) in 1968.[1] Synonyms like necrotizing otitis externa, temporal bone osteomyelitis, and SBO also are used. SBO accurately describes the pathophysiology of the disease.[2] In atypical or central SBO, sphenoid and occipital bones are affected.[3] The disease commonly affects people with diabetes with poor chemotaxis, phagocytosis, and humoral immunity.[4] Diagnosis is from clinical features, culture, histopathology, and imaging modalities like CT and MRI scans. PET CT and PET MRI having a superior spatial resolution, less radioactivity, and higher sensitivity and specificity, have been preferred lately over other nuclear scans to diagnose and determine the resolution of SBO. [5- 8]

When initially described by Chandler, the treatment was mainly surgical, along with antibiotics like Colistin or Polymixin, with a mortality of 46%.[1] With broad-spectrum antibiotics, surgical interventions have become a rarity, and mortality has reduced to 10%. With the emergence of refractory cases probably due to multidrug-resistant strains, fungal pathogen, and lack of positive culture, the role of surgery is being considered by many centres to shorten the hospital stay and duration of treatment.[9]While antimicrobials and polypharmacy pose problems in treating these elderly immunocompromised patients, surgery may increase morbidity further. The role of surgery in the treatment of refractory SBO forms the study's objective.

Materials and Methods:

The Institutional Ethics Committee approved this prospective observational study on 70 patients of SBO of our institute (IRB-AIMS 2018-029). The ethical standards in the Declaration of Helsinki have been adhered to. All investigations and interventions were performed with the informed consent of the patient. The study and reporting followed the guidelines of ICMJE (International Committee of Medical Journal Editors-http://www.icmje.org) and COPE (Committee on Publication Ethics).

Inclusion criteria:

(Medical group) Patients of SBO who responded to antimicrobial therapy alone.

(Surgical group) All patients of refractory SBO who did not respond to at least four weeks of systemic antibiotic therapy and were fit to undergo surgery.

Diagnosis of SBO requires the presence of clinical features and imaging (CECT- Contrast Enhanced Computed Tomography or MRI- Magnetic Resonance Imaging)as per Cohen and Friedman criteria.[10]Clinical

features like pain, edema of the canal wall, ear discharge, and granulations were documented. Ear discharge and granulation tissue from the ear and nasopharynx were sent for culture and biopsy. Weekly checking of inflammatory markers [C- Reactive Protein(CRP) and erythrocyte sedimentation rate(ESR)] was done till the patient became asymptomatic. Later, markers were checked at an interval of two weeks till they became standard value, resulting in the stoppage of antimicrobials. Antibiotics were administered through a PICC line (peripherally inserted central catheter). Relief from pain was considered an initial indicator of response to antibiotics. Patients who completed treatment with medications alone were categorized as the medical group. Those who continued to have pain despite four weeks of systemic antibiotic treatment were considered refractory and were offered surgical debridement (surgical group).

Medical group: All patients were treated with culture-directed antibiotics whenever possible. Culture included direct biopsy and culture of granulations from the ear canal and nasopharynx performed in the outpatient section. All culture-negative patients were empirically started either on intravenous (IV) Ceftazidime (2g per dose 12th hourly) or Piperacillin-Tazobactum (4.5g 8th hourly) combined with IV or oral Ciprofloxacin (IV - 400 milligrams [mg] 12th hourly, oral- 750mg 12th hourly). Antibiotics were changed after one week if the patient continued to have pain. Antifungal therapy was initiated when the patient did not respond after changing antibiotics twice or thrice. Intravenous Voriconazole at a loading dose of 6 mg/kg 12th hourly for two doses was followed by intravenous at 3 mg/kg or oral 200 mg 12th hourly as a maintenance dose.

Surgical group: Surgical option was given to patients with no pain relief after a minimum of four weeks of IV antimicrobial therapy. The surgery aimed to obtain deep tissue for culture and to reduce the microbial load as much as possible. All consenting patients underwent complete or partial debridement under general anaesthesia based on CT or MR imaging. Antimicrobials were changed if the surgery yielded culture. Otherwise, advice from the infectious diseases department was followed. The extent of debridement could be a mastoidectomy; subtotal petrosectomy with disease clearance from the tympanic ring, anterior canal wall, facial canal, jugular foramen, carotid canal, eustachian tube or petrous apex. The temporomandibular joint; parotid; parapharyngeal space, infratemporal fossa, nasopharynx, sphenoid, clivus or greater wing of the sphenoid were debrided in some cases. In some patients, only partial debridement was possible due to difficult access. Histopathology and cultures for fungus, bacteria, and acid-fast bacillus were done. In those already on multidrug therapy, a DNA-PCR with gene sequencing improved the yield.[11]

In both groups, treatment ended when the inflammatory markers remained normalized for six weeks in a symptom-free patient. After the initial scan, CT or MRI scans were done only for new symptoms. Radiological follow-up was with 32 FDG - PET CT (Fluorodeoxyglucose- Positron Emission Tomography) scans in all cases. Usually, it confirmed disease clearance at the end of 6 to 8 weeks of treatment if the patient was asymptomatic. If possible, the PET scan was repeated every 8 to 12 weeks when the treatment became prolonged. At the end of the study period of 26 months, there were 35 patients in the surgical group. First, 35 patients who completed medical treatment comprised the medical group. We used absent activity in PET scans as an indicator of cure in our patients.[7] The rapidity of relief from pain, ear discharge, edema of the ear canal, granulations, and duration of treatment in both groups were evaluated. For the medical group, the entire duration of antimicrobial treatment was taken. For the surgical group, the duration of treatment included the initial antimicrobial therapy, the surgery, and postoperative therapy. The antimicrobial treatment before surgery ranged from 4 weeks to 36 weeks. Follow-up ranged from 12 weeks to 26 months.

Statistical analysis:

Statistical analysis was done using the IBM SPSS Statistics 20 Windows (SPSS Inc., Chicago, USA). The results are given in mean ± SD for all the continuous variables and frequency (percentage) for categorical variables. To test the normality of the data, the Kolmogorov-Smirnov test was applied. Independent sample t-test and Mann-Whitney U test were applied to compare the two groups' mean/ average of continuous parameters. A p-value < 0.05 was considered statistically significant. All tests of statistical significance were two-tailed.

Results:

Of 70 patients, 35 were managed surgically with antibiotic coverage and 35 medically. All patients were known cases of Type II Diabetes Mellitus (Table- 1). Twenty-five patients from the medical group and 13 from the surgical group could adhere to the planned antibiotic protocol (Table- 2).

In the surgical group, the pain was relieved at a mean value of 1.66 months(range:0.5 - 5). Symptoms like canal edema and granulations resolved within 3.11 months (range:1- 13 months)(Table- 3). ESR and CRP values returned to normalcy at a mean value of 6.91 months(range: 2-22 months). Radiological resolution occurred in 8.29 months(range: 3- 22 months). The total duration of treatment was 9.2 months (range: 3-24 months). There were no complications related to surgery. In 22 patients, who had complete clearance of disease, resolution of pain, edema, discharge, markers, imaging and total duration of treatment were 1.55, 2.41, 2.59, 5.95, 7.23 and 8.18 months respectively(Table- 4).

In the medically treated group, the pain was relieved at a mean value of 4.57 months(range: 1- 12 months) which was statistically significant ($p< 0.\ 001$)(Table- 3). Canal wall edema and granulations resolved in a mean of 6 months (range: 2-13 months)($p< 0.001$). Markers took 9.69 months to normalise (range: 4- 20 months) ($p< 0.\ 001$). Radiological resolution with PET CT scan took 11.23 months in the medical group, which was statistically significant(range: 5- 26 months) ($p= 0.\ 001$). Total treatment duration was 11.24 months which was statistically significant(range: 5- 26 months) ($p= 0.\ 019$)(Table- 3).

Discussion:

SBO refractory to medications result in multiple antibiotics, prolonged symptoms and loss of quality of life for the patient. The aim of the study was to evaluate the role of surgery in such cases. In our study, the surgical group showed better clinical outcome in terms of relief of pain, canal wall edema, granulations, ear discharge, duration of treatment and hospital stay compared to the medical group. Patients usually received empirical treatment with dual anti- pseudomonals like quinolones and Ceftazidime, monotherapy with Ceftazidime, or Piperacillin with Fluoroquinolones.[12] Antimicrobials were changed when indicated by culture (Table- 1). Pseudomonas aeruginosa was the usual organism cultured (34%), followed by fungus (21%). The number of fungal pathogens and negative cultures were more in the surgical group, which might explain the refractoriness to medical treatment (Table- 1).

Besides, some patients developed transaminitis, changes in renal parameters, and exfoliative dermatitis during the course, which resulted in a change of antibiotics (Table- 2).

Oral antibiotics given included those with good bone penetration, like Quinolones, Cloxacillin, Linezolid, and Minocycline. Injection to oral switch therapy was possible with culture-specific oral antibiotics, given after six weeks of systemic antibiotics.[13]

Patients generally became asymptomatic after a few weeks of antibiotic therapy, but it might be ideal to continue medications till inflammatory markers and or PET CT became normal.[7, 8] We observed a sequence, of symptom resolution followed by stabilization of inflammatory markers and later radiological stability. After the initial diagnosis, we did not repeat imaging unless there were new symptoms. The decreasing values and normalization of inflammatory markers would guide in determining the timing of the PET CT scan.[7] Using radiological resolution by PET CT as the criteria for cure in our study, 28 patients in the medical group and 33 patients from the surgical group were cured. Another clinical criteria for cure described is an asymptomatic patient for 18 months after cessation of treatment.[9]

It was difficult to predict who might need surgical intervention at the initial presentation. Clinical variables like nerve palsy, relapse, fungal disease, and extensive radiological involvement were associated with severe disease.[14] However, we observed various combinations of these variables in both groups, some successfully treated with medicines alone (Table- 2). The surgical group had rapid symptomatic improvement with clinical and radiological resolution compared to the medical group, which was statistically significant across all variables(Table- 3). In both groups, the mean duration of treatment was more with antifungal therapy and negative culture. Antifungal therapy was for a minimum of three months.

With complete debridement, all 22 patients in our series responded immediately though medications were continued as per protocol (Table- 4). Wide debridement till viable tissue was the key to successful treatment.[15] The debridement may expose the healthy bone to the pathogen worsening disease.[16] Among our surgical patients, only one patient with partial debridement continued to have pain after surgery, and none showed worsening. There was one recurrence in our series. Early debridement may prevent the emergence of biofilms and resistant bacteria. According to Spellberg and Benjamin, there was no solid evidence for support therapy beyond 4- 6 weeks after surgical debridement.[17] Apart from removing poorly vascularized (infected) bone, surgery brought well-vascularized tissue to the area, thus facilitating the healing process and allowing antibiotics to reach the target area.[18] The abundant vascularity of the flat bones compared to the long bones and mandible may account for the excellent response to antibiotics alone in most cases of SBO. But, flat skull bones of more than 4 mm essentially behaved like long bones in microvasculature and hence may resemble chronic osteomyelitis elsewhere in the body.[19]Treatment of chronic osteomyelitis of the long bones includes surgery and antibiotics for 3 to 6 months.[15]

According to Chen et al., the role of surgery may be limited to abscess drainage, sequestrum debridement, and specimen acquisition for microbiological and pathologic examination and play a complementary role to antibiotics.[20] In their study of 20 patients, Peled et al. suggested the role of surgery in prolonged treatment, readmissions, and facial nerve palsy. The minimum surgery should be a canal wall-up mastoidectomy, and further treatment should be based on radiological findings.[21, 22] He suggested deep tissue sampling for culture in SBO since the concordance with the local swab and bone culture was less than 50%. [23] In our observation surgery itself was sufficient when debridement was complete. However, in incomplete debridement our observations were similar to Chen et al..

Hyperbaric oxygen (HBO) has been advocated for refractory cases though not supported by definite evidence.[24] We had three patients for HBO, but poor compliance due to bilateral earache was a drawback. Gruber et al. observed that surgery promoted the cure of fungal osteomyelitis.[25] In our series, there were 15 proven cases of fungal SBO, of which ten underwent surgery. Empirical administration of Voriconazole should be restricted as far as possible.

Since surgery was neither done at the first visit nor antibiotics stopped, the role of surgery alone in SBO could not be studied. Partial response by antibiotics could not be ruled out. Surgery would alter inflammatory markers and imaging, parameters on which termination of treatment was decided. All asymptomatic patients after complete debridement were also given antimicrobials as per protocol till the markers and imaging normalized. A longer duration of antimicrobial therapy than necessary might have been given for them. Though early termination by as early as two to four weeks was possible after complete debridement, study protocol was adhered to . In all such cases, patients could resume normal life faster. At the same time, partial surgery also bettered clinical response through improved culture yield and targeted therapy. So, it was observed that surgery had both curative and faciliatory roles depending on surgical access. A large number of patients added to the strength of the study. However, heterogeneous factors like comorbidities, polypharmacy, and the various antimicrobials administered may have acted as confounding variables.

Conclusion:

Our study indicated a definite role for surgery and antibiotics in refractory cases of SBO. Debridement hastened recovery with a reduced total duration of treatment. The improved culture yield resulted in targeted antimicrobial therapy. There was no worsening of the disease after surgery.

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Conflict of interest: None to declare.

Data Availability Statement:

The data supporting this study's findings is available from the corresponding author at reasonable request.

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Legends for tables:

Table- 1 shows the cultural characteristics and antimicrobials used.

Table- 2 shows the radiological extent of the disease, microbial profile and antimicrobials during the course of the study.

Table- 3 shows statistically significant early response to treatment in the surgical group in terms of resolution of pain, resolution of canal edema and granulation and normal inflammatory markers and radiological resolution of disease. * indicates statistically significant p-value.

Table- 4 shows faster resolution of pain, canal edema and inflammatory markers and imaging in the surgical group with complete debridement. No observations were statistically significant except for the resolution of canal edema and granulation (p= 0.015). * shows statistically significant p- value

Table- 1. Demographics of the study population

	Surgical group(n=35) (%)	Medical group(n=35) (%)
Male	29(82.86%)	27(77.14%)
Female	6(17.14%)	8(22.86%)
Diabetes	35(100%)	35(100%)
Central SBO	10(28.57%)	9(25.71%)
No growth in culture	11(31.43%)	9(25.71%)
Pseudomonas	10(28.57%)	14(40%)
Fungal	10(28.57%)	5(14.29%)
Mixed flora	2(5.71%)	5(14.29%)
Klebsiella	1(2.86%)	2(5.71%)
Bacteroids	1(2.86%)	0(0%)

	Surgical group(n=35) (%)	Medical group(n=35) (%)
Antimicrobials given	Antimicrobials given	Antimicrobials given
Voriconazole	18(51.43%)	16(45.71%)
Piperacillin	17(48.57%)	19(54.29%)
Ciprofloxacin	12(34.29%)	11(31.43%)
Ceftazidime	9(25.71%)	7(20%)
Cefaperazone	8(22.86%)	7(20%)
Linezolid	4(11.43%)	1(2.86%)
Meropenem	4(11.43%)	2(5.71%)
Vancomycin	3(8.57%)	1(2.86%)
Minocycline	5(14.29%)	2(5.71%)
Fluconazole	4(11.43%)	0(0%)
Levofloxacin	2(5.71%)	2(5.71%)
Clindamycin	1(2.86%)	0(0%)

Table- 1 shows the cultural characteristics and antimicrobials used.

Table- 2: Imaging, culture and antimicrobial profile of surgical and medical groups

BS- basisphenoid, CRP- C- Reactive Protein, EAC- external auditory canal, ESR- Erythrocyte sedementation rate, FL- foramen lacerum, ICA- Internal carotid artery, IJV- internal jugular vein, ITF- infratemporal fossa, JB- jugular bulb, MCF- middle cranial fossa, ME- middle ear, na- not applicable, NP- nasopharynx, PA- petrous apex, PPS- parapharyngeal space, PV- prevertebral, RP- retropharyngeal, SMF- stylomastoid foramen, SSC- superior semi-circular canal, TMJ- temporomandibular joint

Table- 2 shows the radiological extent of the disease, microbial profile and antimicrobials during the course of the study.

Table- 3. Clinical and radiological response of both groups

Variables	Medical group (n= 35)	Medical group (n= 35)	Surgical group (n= 35)	Surgical group (n= 35)	p- value
	Mean(months)	SD	Mean(months)	SD	
Resolution of pain	4. 57	2.47	1.66	1.57	<0.001*
Resolution of ear discharge	5.69	2.069	2.66	1.93	<0.001*
Resolution of canal edema, granulation	6.00	2.210	3.11	2.763	<0.001*
Normal value of ESR, CRP	9.69	4.042	6.91	4.280	<0.001*
Radiological resolution	11.23	4.845	8.29	4.205	0.001*
Total duration of treatment	11.34	4.875	9.20	4.549	0.019*

Table- 3 showing statistically significant early response to treatment in the surgical group in terms of resolution of pain, resolution of canal edema and granulation and normal inflammatory markers and radiological resolution of disease. * indicates statistically significant p- value.

Table- 4. Resolution of disease among the surgical group

Variables	Incomplete (n= 13)	Incomplete (n= 13)	Complete (n= 22)	Complete (n= 22)	p-value
	Mean	SD	Mean	SD	
Resolution of pain	1.85	1.463	1.55	1.654	0.365
Resolution of ear discharge	3.08	1.754	2.41	2.039	0.066
Resolution of canal edema and granulation	4.00	3.055	2.59	2.501	0.015*
Normal follow up value of ESR, CRP	8.54	4.701	5.95	3.798	0.084
Resolution of disease by imaging	10.08	4.387	7.23	3.804	0.051
Total duration of treatment	10.92	4.991	8.18	4.043	0.085

Table- 4 showing faster resolution of pain, canal edema and inflammatory markers and imaging in the surgical group with complete debridement. No observations were statistically significant except for the resolution of canal edema and granulation (p= 0.015). * shows statistically significant p- value.

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