Original Article - Evaluative Study

Healer Granules in Nonhealing Infected Wounds

Santosh Ashok Nandimath, Rajkumar Garudanahally Chickklingaiah, Viresh Ashok Nandimath[1], Adwait Madhav Godse[2], Bappaditya Mishra, S. Priya

Department of OMFS, Vokkaligara Sangha Dental College and Hospital, Bengaluru, Karnataka, [1]Department of Preventive and Community Medicine, V M Medical College and Hospital, Solapur, [2]Department of General and Physiology Biochemistry, Sinhgad Dental College and Hospital, Pune, Maharashtra, India

Abstract

Background: Head-and-neck infection is one of the most frequently encountered issues in the field of oral and maxillofacial surgery. Most of the cases with head-and-neck infections are managed by empirical antibiotic therapy and extraction of offending infected tooth/teeth. However, long-term systemic antibiotic therapy can have profound compromising effects on host immune defense and thereby hamper healing, which, in turn, may lead to life-threatening complications such as localized septic foci or widespread septicemia at times leading to death of an individual. In this study, we are reviewing management of 15 cases with space infection in the maxillofacial region by local drug delivery with the help of collagen particles combined with mupirocin 2% w/w and metronidazole 1% w/w (BioFil-AB). We intend to study its efficacy in managing the space infections associated with extraoral infected wound as well as in preventing hazards of long-term systemic antibiotic therapy. **Aims:** The aim of this study is to assess the efficacy of the topical use of BioFil-AB in infected maxillofacial wounds. **Materials and Methods:** A total of 15 patients with infected maxillofacial wounds reporting to the department of oral and maxillofacial surgery were categorized into three groups depending on the severity of infections. Of these 15 cases, 8 patients were suffering from infected extraoral wounds, 3 had traumatic infection, and remaining 4 had extraoral consolidated abscesses due to odontogenic infection. All patients had a history of prior antibiotic therapy. Incision and drainage of the septic focus/foci were performed in most of the cases, and healing of the site was assessed after application of topical BioFil-AB (mupirocin + metronidazole + collagen granules) dressing. **Results and Conclusion:** Dressing with BioFil-AB granules proved to be efficient in control of infection as well as in promoting uneventful wound healing, especially with good follow-up. Further studies with a large sample size may be necessary to corroborate the findings and provide substantial evidence. This novel local drug delivery therapy will definitely help in maintenance of good host immune response as well as in preventing or minimizing occurrence of antibiotic resistance.

Keywords: Cellulitis, collagen granules, facial space infection, fasciitis, metronidazole, minimal bactericidal concentration, minimal inhibitory concentration, mupirocin

Introduction

The various layers of fascia are normally filled with loose connective tissue and bounded by anatomical barriers such as bone, muscle, or fascial layers. These fascial spaces in the head and neck are potential spaces for odontogenic infections. The buccal, canine, submandibular, pterygomandibular, and masseteric spaces are few of the most commonly affected spaces.[1] The risk of infection of these spaces increases many fold, especially in older patients in the presence of an underlying systemic condition.[2,3] Odontogenic infections are usually mixed infections demonstrating isolates of aerobic bacteria such as *Streptococcus viridans* (36.4%), followed by Klebsiella (27.3%), *Pseudomonas aeruginosa* (18.2%), coagulase-negative staphylococci (9.1%), Neisseria (4.54%), and *Enterobacter* spp. (4.54%), whereas peptococci (58.9%) and peptostreptococci (41.1%) are frequently isolated anaerobic bacteria.[2]

Various metabolites of these microorganisms such as superoxide dismutase, lipopolysaccharide endotoxins, methyl mercaptan, and the highly cytotoxic hydrogen sulfide are responsible for the complications of fascial space infections of the head and neck such as facial cellulitis, mediastinitis, brain abscess, septicemia, and thromboembolism and in severe cases death from sequelae

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Address for correspondence: Dr. Santosh Ashok Nandimath, Department of OMFS, Vokkaligara Sangha Dental College and Hospital, K R Road, V V Puram, Bengaluru - 560 004, Karnataka, India.
E-mail: drsantu111@gmail.com

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such as necrotizing fasciitis, brain abscess, and disseminated intravascular coagulation.[2]

Systemic antibiotic therapy affects not only the causative target pathogens but also nontarget commensal microflora. The extent of the impact on nontarget microbial populations depends on the antibiotic used, its mode of action, and the degree of resistance for antibiotic group in the community. Sometimes, an imbalance in the commensal gut microflora due to antibiotic administration can result in intestinal problems, such as antibiotic-associated diarrhea (McFarland, 1998). An additional concern is the *increasing incidence of* antibiotic resistance and the potential spread of resistance genes to pathogenic bacteria. Recently, it has been shown that even short term antibiotic administration can lead to stabilization of resistant bacterial populations in the human intestine that may persist for years (Jakobsson *et al*., 2010; Jernberg *et al*., 2007; and Lofmark *et al*., 2006.[4,5] However, only a few recent studies have investigated the long-term impacts of antibiotic administration, including development of resistance (Jakobsson *et al*., 2007; Jernberg *et al*., 2007., Lindgren *et al*., 2009; Lofmark *et al*., 2006; Nyberg *et al*., 2007; and Sjolund *et al*., 2003).[5] When empirical antibiotic therapy has failed, local application of various therapeutic agents has been found to produce excellent results in limiting the spread of infection and promoting wound healing. The local therapeutic agent BioFil-AB is basically a composition of mupirocin 2%, metronidazole 1%, and type I collagen particles (fish derived).

The aim of this study is to assess the efficacy of BioFil-AB in the management of infected wounds in maxillofacial region and to minimize long-term use of systemic antibiotic therapy which may lead to deleterious effect on host immune response and may contribute to antibiotic resistance.

Materials and Methods

This study was conducted in the department of oral and maxillofacial surgery of an academic dental hospital located in Bengaluru over a period of 6 months from June 2017 to December 2017.

BioFil-AB as novel material for dressing of the wounds was used in the current study, and time-tested chemicals such as hydrogen peroxide and povidone-iodine were used for irrigation of wound before dressing of the wound.

BioFil-AB

Mupirocin

Mupirocin is a natural crotonic acid derivative extracted from *Pseudomonas fluorescens* which acts by reversible inhibition of isoleucyl-tRNA synthetase[2,6] and is a novel agent that differs from most of the available antibiotic agents. Mupirocin was first developed by Beecham. It is bacteriostatic in low concentration and bactericidal in high concentration. It is a new nonsystemic antibiotic and is used for the treatment of small areas of skin infection and has been found to be effective, especially against methicillin-resistant *Staphylococcus aureus*.[1,7] In *in vitro* studies, mupirocin exhibits a high level of activity against Gram-positive cocci which are causative organism for primary and secondary skin infections such as *S. aureus*, *Staphylococcus epidermidis*, *Streptococcus pyogenes*, and other beta-hemolytic streptococci.

Metronidazole

Metronidazole is a synthetic antibacterial and antiprotozoal agent belonging to *nitroimidazole group* which covalently binds to DNA and disrupts its helical structure inhibiting bacterial nucleic acid synthesis leading to its cytotoxic effect, especially on facultative anaerobic bacteria such as *Fusobacterium* spp., *Bacteroides fragilis,* peptococci*,* and anaerobic streptococci. It is reported in literature that metronidazole dressing has potential effect in reduction of wound odor (wound odor is a frequent complaint in most of the anaerobic infections), decrease in wound drainage, and improvement in wound appearance.

Collagen

Collagen is an extracellular matrix (ECM) protein playing a major role in formation of supporting connective tissue. It is made up of three polypeptide chains that are rich in amino acid –hydroxyproline – and are twisted together into a triple-helical structure.[8] Collagen plays a key role in each phase of wound healing. Collagen-based dressings have the ability to absorb wound exudates and maintain a moist wound environment and address the issue of elevated levels of matrix metalloproteinases (MMPs) by acting as a "sacrificial substrate" in the wound.[9] It has also been demonstrated that collagen breakdown products are chemotactic for cells in immune system responsible for the formation of granulation tissue.[7]

Hydrogen peroxide

It is used due to its effervescent and presumed antimicrobial effects. This effervescent action is the result of oxygen bubbles created by the breakdown of hydrogen peroxide to water and oxygen by tissue catalase. This "bubbling" action may enhance mechanical cleansing.

Povidone-iodine

About 1% povidone-iodine solution has been recommended for wound irrigation as this solution provides an optimal therapeutic balance between bactericidal capacity and tissue toxicity associated with iodine-containing formulations.[10]

Rationale for using BioFil-AB

The chronic wounds are characterized by an elevated level of MMPs which degrade not only nonviable collagen but also viable collagen. In addition, fibroblasts in a chronic wound may not secrete tissue inhibitors of MMPs at an adequate level to control the activity of MMPs. These events prevent the formation of the scaffold needed for cell migration and ultimately prevent the formation of the ECM and granulation tissue.[9] A synergistic effect on wound healing has been noted when mupirocin was added to the collagen granules which form the rationale behind using BioFil-AB. Thus, the current

study is trying to propose that it can be an ideal biomaterial as compared to existent modalities of treatment of surface wounds, burns, and foot ulcer.[9]

Subjects and methods

Fifteen patients (10 males and 5 females) who reported to the department of oral and maxillofacial surgery suffering from maxillofacial space infection were included in this study on voluntary basis. The prospects and consequences of participation in the study was explained to them in a local language understood by them (Kannada) as well as in English (as per necessity). An informed consent was obtained from all participants before inclusion in the study. Most of the participants belonged to the age group between 40 and 70 years, except for 1 participant who was 21 years old. Seven out of 15 patients were known cases of Type II diabetes mellitus (4 males and 3 females) and were on medications for the same. All patients with odontogenic infection gave a history of receiving antibiotic therapy and analgesic therapy from health-care facilities outside our institution.

Eight patients among 15 patients participating in the study showed deleteriously managed extraoral wounds at health facilities outside the place of conduct of study that had led to complications; 3 patients had developed fasciitis and 5 patients had developed cellulitis. These patients were included in Group I [Table 1]. Four patients participating in the study had extraoral consolidated abscesses of odontogenic infectious etiology and they were included in Group II [Table 1]. Three patients participating in the study with posttraumatic infection were included in Group III [Table 1].

The patients in Group I were administered intravenous empirical antimicrobial therapy (1.2 g co-amoxiclav [amoxicillin + clavulanic acid] and metronidazole (0.5 g w/w)) for 48 h before surgical treatment (incision and drainage). No postoperative antimicrobial therapy was administered to patients in Group I. Patients in Group II were administered oral antimicrobial therapy (co-amoxiclav [amoxicillin + clavulanic acid] 625 mg and metronidazole 400 mg) 1 h before surgical treatment (incision and drainage) and the same was continued during postoperative period up to 36 h, after which it was discontinued.

No antibiotic therapy was administered to patients in Group III and they were not subjected to any surgical treatment (incision and drainage).

All the surgical procedures (incision and drainage) were performed under local anesthesia following utmost standards of aseptic protocols. In cases of odontogenic etiology, the offending teeth were also extracted along with incision and drainage. The pus samples collected during surgical procedures were immediately sent for culture and sensitivity.

All groups received dressing with topical drug BioFil-AB (collagen granules, mupirocin 2% w/w, and metronidazole 1% w/w) as treatment modality. The total duration of dressing with BioFil-AB was planned as follows [Tables 2-4]:

1. Group I – 2 weeks: 1 week on inpatient basis and 1 week on day-care basis
2. Group II – 10 days: Day-care basis
3. Group III – 5-6 days: Day-care basis.

Irrigation for intraoral wounds was performed with povidone-iodine and normal saline solution. Irrigation for extraoral wounds was done with hydrogen peroxide diluted with normal saline. This was then followed by dressing with topical drug BioFil-AB. Extraoral wounds received irrigation with povidone-iodine before dressing with topical drug BioFil-AB. The irrigation protocols were strictly followed every time before dressing.

The dressing with BioFil-AB was changed every 8 hourly and the dressing was applied at 8.00 am, at 4.00 pm, and at 11.00 pm, respectively. The treatment procedures were conducted on day-care basis for 7 patients, while for 8 patients, already receiving inpatient care, inpatient care continued with the same level of care. Thus, 7 patients being treated on day-care basis were instructed and trained to change BioFil-AB dressing at home at around 11.00 pm with all irrigation protocols. These patients in Group II and III were discharged after application of the second dressing with BioFil-AB at 4.00 pm. Group I received the dressing with BioFil-AB on inpatient basis for 1 week and l was later discharged with a specific instruction about 1-week treatment on day-care basis. The type of discharge, condition of granulation tissue, and extent of healing were assessed as well as monitored during day-care procedure as per the treatment plan during the study [Tables 2-4].

Results and Discussion

In our study, we divided patients into three groups as follows: Group I, II, and III [Table 1]. In Group I cases, we assessed wound healing up to 14 days with periodical follow-up [Table 2 and Figures 1, 2]; in Group II cases, we have assessed healing up to 10 days [Table 3 and Figure 3]; and in Group III cases, we achieved immediate healing within 6 days [Table 4 and Figure 4].

Table 1: Group wise patients distribution

Group I	Group II	Group III
8 patients (3 fasciitis and 5 cellulitis). Badly managed extraoral wounds	4 patients with extraoral consolidated abscess	3 patients - traumatic infection
Empirical IV antibiotic therapy given for 48 h. All cases were followed up for 2 weeks to assess wound healing	Oral empirical antibiotics were given 1 h before I and D. Cases were followed up for 10 days	No antibiotics were prescribed. Follow-up for 5-6 days

IV=Intravenous

In our study, where we did topical drug delivery with collagen granules (i.e. Biofil- AB consisting of sterile collagen particles with Mupirocin 2% w/w and Metronidazole 1% w/w), treatment had a promising outcome; leading to the formation of healthy granulation tissue without any discharge and without necessitating any long term systemic antimicrobial therapy.

The ideal property of a local therapeutic agent should be to have a sufficiently broad spectrum of activity, should not promote cross resistance or multiple resistances, should be unrelated to systemically administered agents, should be least toxic to tissue, should have prolonged action, should be easy to apply, and should enhance the formation of healthy granulation tissue.[2] A foul odour is one of the most frequent and worrisome concerns for patient as well as relatives, suggesting that something is wrong with the body and may be associated with infection, presence of necrotic material, devitalized tissue, fungating malignant tumors and poor wound care practices. It is reported in literature that metronidazole dressing has a positive effect in reduction of wound odor, decrease in wound drainage, improvement in wound appearance, decreasing in surrounding cellulitis, halting of tissue necrosis and treatment of topical as well as systemic metronidazole may reduce the possibility of antibiotic resistance.[6] The combination of sterile collagen particles with mupirocin 2% w/w and metronidazole 1% w/w is close to ideal. A foul odour is one of the most frequent and worrisome concerns for patient as well as relatives, suggesting that something is wrong with the body and may be associated with infection, presence of necrotic material, devitalized tissue, fungating malignant tumors and poor wound care practices. It is reported in literature that metronidazole dressing have impending effect in reduction of wound odor, decrease in wound drainage, improvement in wound appearance, decreasing in surrounding cellulitis, halting of tissue necrosis and treatment of topical as well as systemic metronidazole may reduce the possibility of antibiotic resistance.[11] Collagen helps in wound debridement by enticing monocytes, provides a matrix for tissue and vascular progression, attracts fibroblasts, binds with fibronectin, supports differentiation and migration of keratinocytes and helps in deposition of organized fibers. It has also been demonstrated that collagen can inactivate potentially detrimental factors such as proteases, oxygen free radicals and excess metal ions present in chronic wound fluid, whilst simultaneously protecting positive factors such as growth factors and delivering them back to wound.[3,10] The combination of sterile collagen particles with mupirocin 2%

Table 2: Group I

Day	Discharge	Granulation tissue	Healing
Day 1-3	Purulent	Absent	Not seen
Day 4	Purulent and serosanguinous	Absent	Not seen
Day 6	Purulent and serous	Reddish pink	Not significant
Day 8	Serous mild purulent	Pinkish red	Not significant
Day 10	Serous	Pinkish	Significant
Day 14	Minimal serous	Pinkish	Complete healing

Table 3: Group II

Day	Discharge	Granulation tissue	Healing
Day 1-3	Purulent and sanguineous	Absent	Not significant
Day 4	Serosanguinous	Reddish pink	Not significant
Day 6	Serous	Pinkish red	Significant
Day 8	Minimal serous	Pinkish	Significant
Day 10	No discharge	Pinkish	Healed

Table 4: Group III

Day	Discharge	Granulation tissue	Healing
Day 1-2	Purulent and serosanguinous	Absent	Not significant
Day 3-4	Serous	Pinkish red	Significant
Day 5-6	Minimal serous	Healed tissue	Complete healing

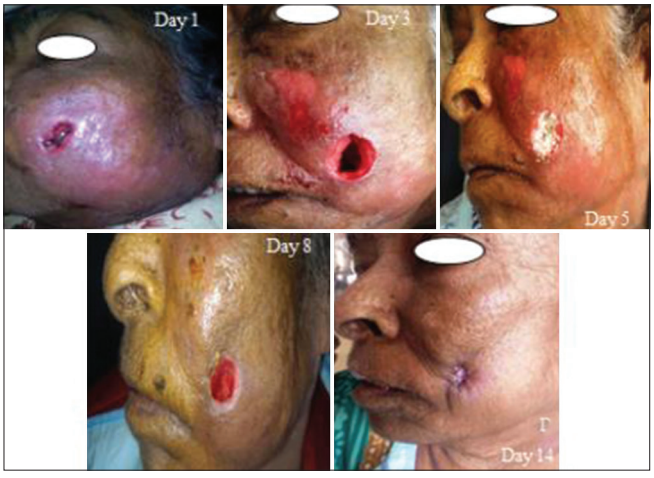

Figure 1: Infra-orbital & buccal space infection

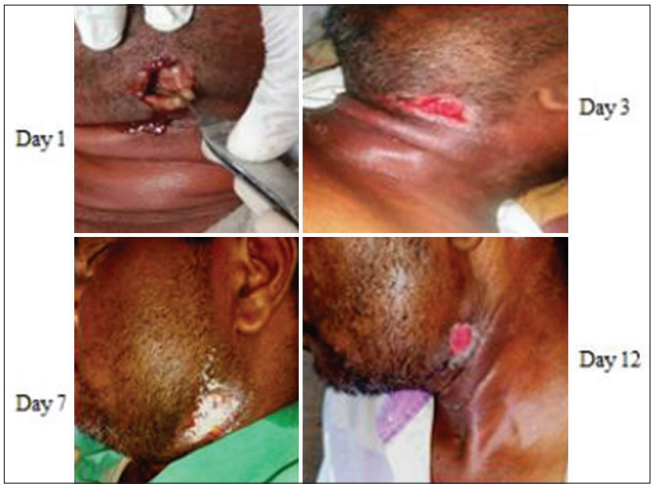

Figure 2: Buccal & submandibular space infection

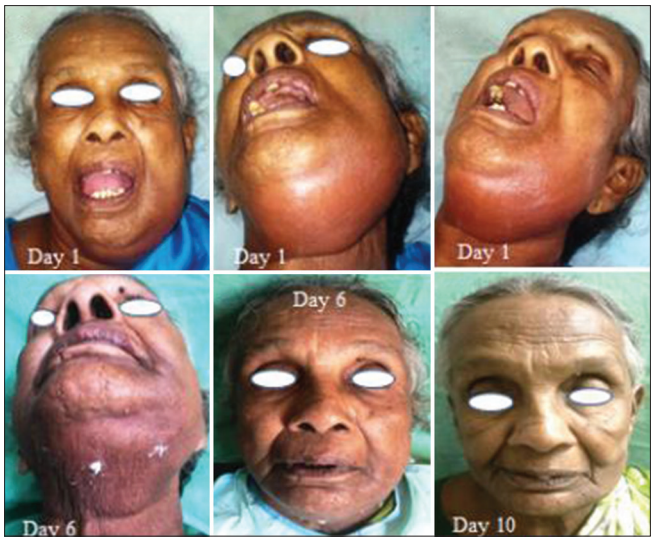

Figure 3: Ludwig's Angina

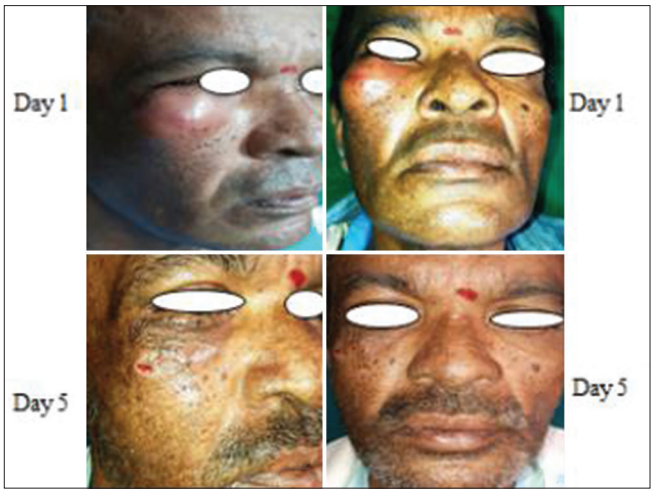

Figure 4: Infra-orbital space infection

w/w and metronidazole 1% w/w is closer to ideal. Moreover, it avoids all the deleterious effects of long-term systemic antimicrobial therapy employed during treatment of most of the space infections in oral and maxillofacial region.

Important adverse effects of systemic antimicrobial therapy include disturbance of the metabolism and absorption of vitamins (Levy, 2000) and alteration of susceptibility to infections (Levy, 2000) and overgrowth of yeast (Sullivan *et al*., 2001), and/or clostridium difficile (Edlund and Nord, 1993, and Sullivan *et al*., 2001).[5] Different antimicrobial agents can influence the normal gut microbiota in many different ways which is directly or indirectly a predisposing factor for most of the aforementioned adverse effects. The extent of the antibiotic-induced alterations in the microbiota depends on several factors: (a) the spectrum of the agent, (b) dose and duration of the treatment, (c) route of administration, and (d) the pharmacokinetic and pharmacodynamic properties of the agent.

In a study conducted by Shah *et al*, where randomized controlled trial was done comparing collagen granules dressing with COMUPIMET consisting of sterile collagen particles with (Mupirocin 2% w/w and Metronidazole 1% w/w) versus EUSOL (12.5 mg of sodium hypochlorite bleaching power and 12.5 mg of Boric acid in 1 litre of Luke-warm water) used within 15 minutes of preparation, and results were found to be superior in COMUPIMET when compared with EUSOL.[4] Ermolov *et al*. found that Type 1 collagen-based dressing showed accelerated wound epithelialization. Perumal *et al*. found that wound closure analysis revealed complete epithelialization in 14.2 ± 0.44 days for mupirocin–Silica-Microspheres loaded collagen.[9]

This study has derived sound scientific rationale from above-mentioned studies but is unique and novel in its approach since it uses Type 1 collagen-based BioFil-AB with mupirocin 2% w/w and metronidazole 1% w/w as its active pharmaceutical ingredients. The results achieved are very encouraging in terms of rate of wound healing (5–14 days depending on extent of involvement) and clinical outcome which is evident in Figures 1-4.

Limitation of the study

The current study is carried out on a group of 15 participants. A larger sample size will surely generate more robust data underlining clinical superiority of the technique employed in this study. Besides this, the financial aspects of the study were not taken into consideration. However, through clinical acumen and experience, we opine that the use of BioFil-AB outscores conventional systemic antimicrobial-based therapy not only in terms of economics of the treatment modality but also in terms of physical quality of life rendered through the treatment to the participating patients.

Conclusion

For all the participants of the study, application of dressing with BioFil-AB granules proved to be effective and led to uneventful wound healing. Thus, it can be definitely considered as an important treatment modality to manage infected wounds with proper follow-up. A study with a larger sample size may be necessary for a robust and statistically significant outcome. Therapy with this novel local drug delivery will definitely help in maintenance of good host immune response as well as in preventing or minimizing occurrence of antibiotic resistance. Badly handled infected wounds after proper wound care protocol managements and usage of BioFil-AB granules assisted us in controlling infection and its lethal effects on general status of patients and significantly promoted better wound healing.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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