

Article

Aminogam[®] Gel Allows Faster Wound Healing after Oral Surgery by Formation of Mature Connective Tissue with Low Vascular Density and Reducing Inflammatory Infiltration. A Retrospective Study on 580 Cases with Histological and Confocal Laser Investigation

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Received: 12 December 2019; Accepted: 3 February 2020; Published: 7 February 2020



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Abstract: Reduction of the wound healing time after surgical procedures along with good hemostasis, and the reduction of post-surgical edema, pain and infective complications are generally desirable to both clinicians and patients. Recently, a gel compound containing sodium hyaluronate and four synthetic aminoacids (glycine, leucine, proline, lysine) and marketed as Aminogam[®] (Errekappa Euroterapici, Italy), has been proposed as a medical device promoting faster wound healing after oral surgery procedures. To assess its achievable clinical benefits, we studied retrospectively 580 cases (290 study cases and 290 control cases) undergoing oral surgery and receiving Aminogam[®] gel application. More precisely, cases were divided into 7 groups on the bases of the kind of surgery (teeth extraction, oral surgery in patients taking bisphosphonates, surgical treatment of jaw osteonecrosis related to bisphosphonates therapy, placement of endosseous implants, diode laser surgery of oral mucosa lesions with second intention healing without stitches, diode laser photocoagulation of slow flow vascular malformations and bone surgery). In all instances, Aminogam[®] gel was applied at least five times a day until the wound healed completely. We compared the elapsed time between surgery and complete healing with Aminogam[®] application compared to control cases receiving no other drug treatment. Our results confirmed that the overall time of healing is certainly reduced in cases receiving Aminogam[®] gel regardless of the kind of oral surgery.

Keywords: wound healing; faster healing; oral cavity; sodium hyaluronate; aminoacids

1. Introduction

The reduction of the wound healing time along with reduction of infective complications, good hemostasis and the reduction of the post-surgical edema and pain are certainly desirable to both

clinicians and patients. Wound healing is a specific and crucial biological process characterized by consecutive phases starting with angiogenesis and followed by fibroblast proliferation and differentiation, deposition of the extracellular matrix (ECM) and final re-epithelialization [1–3]. Fibroblasts and macrophages are both involved in the healing process. Fibroblasts promote neo-angiogenesis, secrete all ECM components (glycosaminoglycans, proteoglycans, glycoproteins and collagens) and produce several cytokines and growth factors [4]. Macrophages digest and kill bacterial pathogens, clean tissue debris and secrete a variety of chemotactic and growth factors [5,6]. Hyaluronic acid is a glycosaminoglycan composed of repeating disaccharide units of D-glucuronate and N-acetylglucosamine, which is one of the most abundant constituents of the ECM, and is also involved in developmental processes such as cell proliferation, differentiation and motility [7–9]. Its effectiveness in favoring wound repair has been previously described in literature [1,7]. Moreover, it is generally accepted that because of the increased metabolic activity, a large availability of aminoacids is necessary on site during the wound repair process [10]. On such bases, Aminogam[®] gel has been formulated as containing sodium hyaluronate with the addition of four synthetic aminoacids (glycine, leucine, proline, lysine) to increase their availability in the surgical site. In previously published studies, authors have already demonstrated that Aminogam[®] gel promotes a faster healing of oral soft tissues after surgery and reduces post-surgical complications [1,11] by neo-angiogenesis and fibroblasts' activity stimulation, thus inducing neo-collagenogenesis and ECM deposition.

On these bases, we performed the current retrospective study on 580 cases in order to confirm on a larger sample the effectiveness of Aminogam[®] to promote faster healing of oral soft tissues after different surgical procedures in the oral cavity.

2. Material and Methods

This study was performed on patients treated at the Complex Operating Unit of Oral Surgery, University of Bari “Aldo Moro” in the period 2006–2015. We studied retrospectively 580 cases in total, subdivided into 7 groups of different surgical treatments. For each group, cases showing similarities for site and dimensions were casually and equally divided into experimental and control cases. After the surgical treatment, cases of each experimental subgroup, 290 in total, were treated by Aminogam[®] gel application at least five times a day over the surgical wound until the complete closure of the covering mucosa. Control group patients received no treatment.

- Group A patients

Group A included 120 post-extractive surgical sites of mandibular molars, two for each patient, one on each side of the jaw, to obtain an in-patient comparison among case (receiving gel) and control (not receiving gel).

- Group B patients

Group B included 60 post-extractive sites of molars in oncologic patients receiving intravenous bisphosphonates (BPs) and considered at high risk for medication-related osteonecrosis of the jaw (MRONJ); teeth extractions were performed after a drug-free period of 3 months with suspension of all antiresorptive therapies [12]. Thirty post-extractive sockets were inserted in the experimental subgroup and treated with Aminogam[®] (five applications per day) until the complete gingival closure.

- Group C patients

Group C included 100 cases of MRONJ who underwent surgical resection of necrotic bone; of these, 50 belonged to the experimental subgroup which received Aminogam[®] gel (five applications per a day) after surgery until the full thickness closure of the mucosal flaps.

- Group D patients

Group D included 80 cases of endosseous dental implants with gingival flap elevation; of these, 40 were inserted into the experimental subgroup, which was treated with Aminogam[®] (five applications per day) until the gingival healing.

- Group E patients

Group E included 140 cases of diode laser excisions of proliferating oral mucosa lesions (neoplastic and not) without direct closure of surgical margins by stitches (wound diameter had an average size of 30 mm); the 70 cases of the experimental subgroup were treated with Aminogam[®] gel (five applications per day) until the complete reconstruction of a normally colored covering mucosa.

- Group F patients

Group F included 40 cases of diode laser photocoagulation of slow flow vascular malformations (lesion diameter ranging from 20 to 40 mm); the 20 cases of the experimental subgroup received application of Aminogam[®] gel (five applications per day) until the complete healing of the irradiated area.

- Group G patients

Group G included 40 cases of bone lesions (benign and/or malignant odontogenic or not odontogenic tumors, and odontogenic cysts) radiographically appearing as radiolucent areas larger than 50 mm in diameter, and all surgically removed. The 20 cases of the experimental subgroup received Aminogam[®] gel directly within bone cavity immediately after lesion removal and also upon receiving stitches until the complete gingival closure.

- Healing time evaluation after oral surgery

To assess the effectiveness of Aminogam[®] in terms of reducing of the healing time (HT), we compared the average time elapsed between the oral surgical procedure and the clinical healing of the covering soft tissue among control and experimental subgroups, and compared using the t-test or the Mann–Whitney U test when the normality test failed. A P value of less than 0.05 was considered to indicate statistical significance. Analyses were carried out with the use of SPSS 23 for Windows.

Furthermore, three months after implant insertion in Group D patients, gingival tissues were removed during fixture exposition, collected and then sent for histological examination (conventional and confocal laser scanning microscopic analysis) to histologically compare soft tissues treated with Aminogam[®] gel and those which were not, approximately 4–6 months after surgery.

The surgical samples were formalin-fixed, paraffin embedded, cut at 4 µm thickness and stained with two different methods: hematoxylin–eosin for conventional optical microscopy and picosirius red for Confocal Scanning Laser Microscopy (CSLM) analysis performed by a Nikon Eclipse E600 microscope (Nikon Corporation, Tokyo—Japan), equipped with Argon-ion and Helio–Neon lasers, which allows both optical and confocal laser scanning analyses.

This study was performed in accordance with the principles of the Declaration of Helsinki and has been approved by our institution's ethical committee (Study n°3134, Prot. 21/C.E.); patients released informed consent on diagnostic and therapeutic procedures and the possible use of biologic samples for research purposes.

3. Results

The statistical analysis showed that HT was consistently shorter in all cases treated with Aminogam gel ($p < 0.001$) regardless the kind of surgery. More precisely, the HT was found to be at least 3 days less (approximately the 21%) in Group A patients (teeth extractions—only mandibular molars), at least 4 days less (approximately the 28%) in Group B patients (teeth extractions in patients taking BPs), at least 7 days less (approximately the 25%) in Group C patients (MRONJs with surgical resection of the

necrotic bone), at least 3 days less (approximately the 33%) in Group D patients (endosseous implants), at least 6 days less (approximately the 28%) in Group E patients (diode laser excisions), at least 4 days less (approximately the 25%) in Group F patients (diode laser photocoagulations) and at least 6 days less (approximately the 26%) in Group G patients (bone surgery). Overall, the average value of time reduction was at least 26% regardless of the type of surgical procedure. All the results are summarized in Table 1.

Table 1. Statistical analysis of results for each group with controls.

	N	HT (Means \pm SD)	<i>p</i> Value
GROUP A: 120 teeth extractions (only inferior molars)			
CASE	60	10.10 \pm 0.75	<0.001
CONTROL	60	14.20 \pm 1.04	
GROUP B: 60 teeth extractions in patients taking BPs			
CASE	30	9.60 \pm 1.38	<0.001
CONTROL	30	14.67 \pm 0.48	
GROUP C: 100 MRONJs with surgical resection of the necrotic bone			
CASE	50	17.90 \pm 1.31	<0.001
CONTROL	50	25.30 \pm 0.46	
GROUP D: 80 endosseous implants			
CASE	40	6.93 \pm 0.73	<0.001
CONTROL	40	10.58 \pm 1.06	
GROUP E: 140 diode laser excisions			
CASE	70	14.14 \pm 1.00	<0.001
CONTROL	70	21.21 \pm 1.43	
GROUP F: 40 diode laser photocoagulations			
CASE	20	11.95 \pm 0.69	<0.001
CONTROL	20	16.30 \pm 0.86	
GROUP G: 40 bone surgery			
CASE	20	16.60 \pm 1.05	<0.001
CONTROL	20	23.05 \pm 0.76	

Moreover, all the experimental subgroups showed complete healing of surgical sites without complications; In contrast, several complications such as inflammatory reaction, wound dehiscence and delayed HT were recognized among control cases (18%–20% of cases). Careful descriptions of different clinical cases of different groups have been reported in Figure 1a–h, Figures 2a–h and 3a–h.

Histological analysis of the surgical specimens, obtained from patients of the experimental D group, highlighted the prevalence of abundant old collagen in sites treated with Aminogam[®] gel; such data were confirmed by contextual CLSM analysis showing a higher fluorescence of collagen along with less vascular density (Figure 4a,b). In opposition, histological examination of samples obtained from control cases of D group showed a less mature connective tissue with abundant inflammatory infiltrate, young collagen with fibroblasts characterized by round nuclei and high vascular density, all confirmed by CLSM analysis (Figure 4c,d).

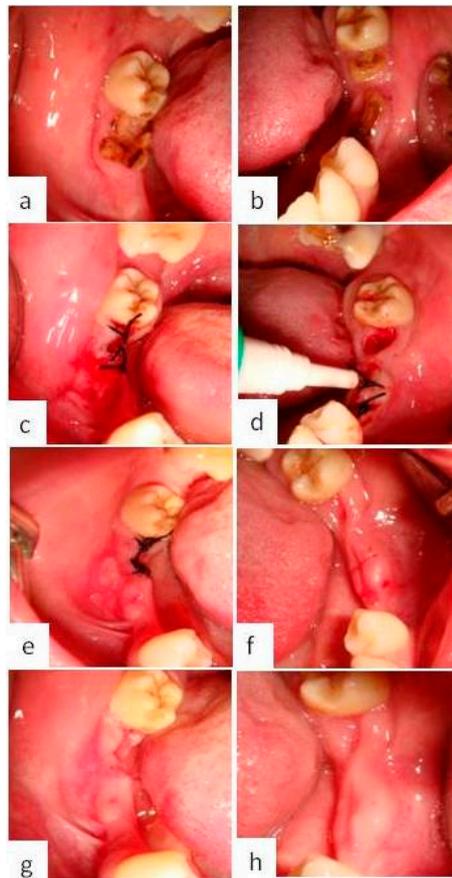


Figure 1. GROUP A: necrotic roots of 4.7 (a) and 3.6 (b) removed with margins closure by stitches (c,d). Aminogam[®] gel was applied within the alveolar socket and upon stitches only on the left side (d) After 5 days, stitches were removed exclusively on the left side (f), while the right one showed signs of flogosis and uncompleted healing (e). After 8 days, 3.6 site showed sockets closure and gingival healing (h), while stitches were removed by 4.7 socket which still appeared to be not completely healed (g).

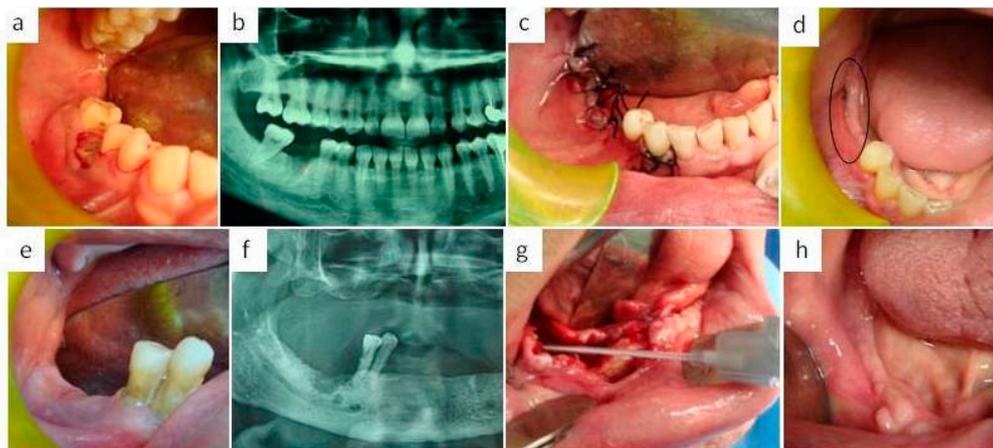


Figure 2. GROUP C: medication-related osteonecrosis of the jaw (MRONJ) of the right mandible in 2 oncologic patients receiving zoledronic acid infusions (a–f). Patients underwent surgical resection of necrotic bone, and Aminogam[®] gel was applied both within bone cavity and upon stitches only in one patient (g) After 20 days, uncompleted healing of the surgical wound with signs of inflammation was detectable in the patient not receiving Aminogam[®] gel (d), while complete wound healing was observable in the treated patient (h).

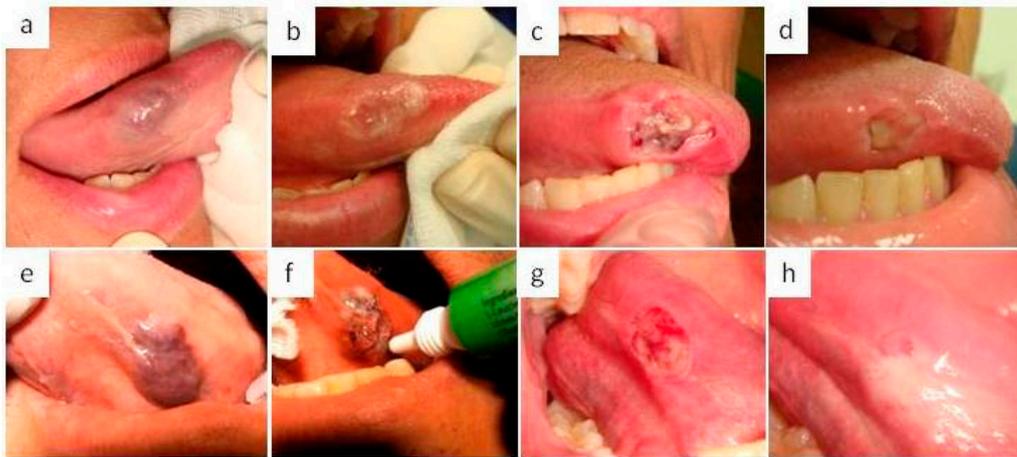


Figure 3. GROUP F: Slow-flow vascular malformations of the tongue in 2 patients (a,e) treated by diode laser photocoagulation (b,f). Patient receiving Aminogam[®] gel (f). After 5 days, uncompleted healing was observed in the untreated patient (c), still showing signs of flogosis and ulceration and following residual pain, all the latter undetectable in the treated patient (g). After 12 days, clinical examination showed uncompleted healing of surgical wound untreated by Aminogam[®] gel (d), while a complete resolution was detected in the treated one (h).

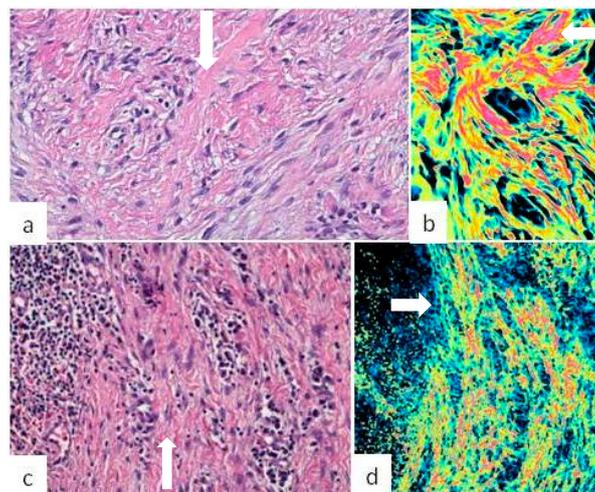


Figure 4. Histological analysis of the samples obtained from patients of experimental group D (a,b) highlights the presence of mature connective tissue, with low vascular density, abundant old collagen without inflammatory cells (a) (arrow), as confirmed by the high fluorescence seen by Confocal Laser Scanning Microscopy (b) (arrow). In opposition, the histological analysis of the surgical specimens obtained from patients of the control group D shows the presence of young connective tissue (c) (arrow), with abundant inflammatory infiltrate, high vascular density, immature collagen and fibroblast characterized by round nuclei, as confirmed by the low auto-fluorescence observable via the Confocal Laser Scanning Microscope (d) (arrow).

4. Discussion

In the past, several agents including topical liquid and semi-liquid formulations as well as dry traditional dressings have been employed to promote faster wound healing, thus also reducing the risk of complications and increasing the surgical success rate. Aminogam[®] gel has been proposed for the same purpose with an innovative formulation as containing sodium hyaluronate with the addition of four synthetic aminoacids (glycine, leucine, proline, lysine) [1,11].

In fact, although it is well documented that during the wound healing process, the hyaluronic acid promotes cell proliferation, differentiation and motility, and moreover that a large availability of aminoacids is necessary because of increased metabolic activity [13,14], at present, few medical devices exists which contain all of them [11].

These aminoacids are directly involved in tissue repair; in fact, glycine constitutes one-third of collagen molecules, proline/hydroxyproline or lysine/hydroxylysine represent approximately 23% of collagen chains [15], while leucine residues are important constituents of small leucine-rich repeat proteoglycans and proteins that participate in ECM organization and influence cell behavior [16].

Preliminary in vivo and in vitro studies demonstrated that Aminogam[®] gel promotes angiogenesis and macrophages activity, induces fibroblasts proliferation and the production of fibronectin and collagen I and III. In addition, it stimulates the expression of several cytokines and growth factors, such as vascular endothelial growth factor, interleukin-6 and -8 and transforming growth factor-beta, thus resulting in the acceleration of the wound healing process [1,11].

Beyond the investigations on the effects of Aminogam[®] on tissue components, clinical studies have been conducted to investigate effectiveness of this gel compound on humans [17,18]. In 2008, the authors themselves conducted a preliminary clinical study [1] on 120 cases (60 study cases treated with Aminogam[®] and 60 control cases) who underwent oral surgical procedures. The 60 experimental cases were divided into three groups of 20 cases each based on the kind of surgical procedure. Subgroup A patients underwent extraction of molars on both sides of the mandible, but only one side was treated with Aminogam[®] (three applications per day). Subgroup B patients received endosseous implants with flap elevation and were treated with Aminogam[®] (three applications per day) until the complete healing of the gingiva. Subgroup C patients underwent diode laser excision of oral benign neoplasms without stitches (average diameter of the surgical areas was 20 mm) and were treated with Aminogam[®] (three applications per day) until the complete healing of the covering mucosa. With the exclusion of subgroup A patients who had an in-patient comparison, an equivalent number of patients were selected as control cases for B and C experimental subgroups. Overall, a reduction of the elapsed time between surgery and stitches removal and between surgery and healing time were obtained in all experimental groups.

In the current study, we enrolled a total of 580 cases (290 for experimental subgroups, 290 for control subgroups) subdivided according to the type of the surgical procedures as follows: teeth extractions—group A; teeth extraction in patients considered at risk of MRONJ development—group B; MRONJ treatment—group C; endosseous implants—group D; laser excision of soft tissues lesions—group E; laser photocoagulation of slow flow vascular malformations—group F; surgical removal of bone lesions—group G.

After surgery, cases of the experimental subgroups were treated with Aminogam[®] at least five times a day until the soft tissue healed completely.

In all the experimental subgroups we found a statistically significant reduction ($p < 0.05$) of the wound HT, evaluable as 26% less regardless of the kind of surgery, along with reduction of infective complications (infections and post-surgical pain). These data as obtained on a large sample confirm and improve our previously published results as showing an additional reduction of the HT, assuredly related to the increased number of Aminogam[®] applications used in the current study.

Furthermore, in the present study, we also introduced four new groups of patients which required additional considerations. Oncologic patients of B group receiving intravenous BPs were considered as at high risk of MRONJ in accordance with the well-recognized side effects of antiresorptive therapy both in oncologic and osteoporotic patients which is described in the literature [19]; for such reasons, faster wound healing without infective complications is certainly useful to avoid osteonecrosis development. Moreover, BPs are life-saving drugs for oncologic patients and, therefore, faster wound healing is also useful for reducing the drug suspension period.

Patients of C group were affected by MRONJ. In these cases, the reduction of wound HT is very important to reduce risk of infection and other complications, especially wound dehiscence

after large surgical incision, and to reduce the aforementioned life-saving drug suspension time in oncologic patients.

Patients of F group were affected by slow flow vascular malformations of oral mucosa and were treated by diode laser photocoagulation. In these cases, Aminogam[®] gel, by reducing the risk of ulceration and superinfection, provided a double effect both as mechanical protection for the wound and by accelerating the healing process.

Patients of G group were affected by bone lesions. In these cases, Aminogam[®] gel was applied both on the covering mucosa, to obtain a faster healing of surgical incision and to reduce the risk of wound dehiscence, and in the residual cavity in the jaw. As it has been postulated, if Aminogam[®] gel stimulates soft tissues healing, it could play a role in bone regeneration too [20]; the latter could be the object of future studies.

The effectiveness of Aminogam[®] gel in wound healing processes has been confirmed by histopathological analysis of specimens (gingival tissues) obtained during exposition of implants in D group patients. In fact, both traditional and CLSM examination highlighted the presence of abundant mature collagen and minor blood vessel density and inflammatory infiltrate in tissues receiving gel after surgery. Overall, these data confirm that Aminogam[®] can be considered a medical device able to accelerate wound repair processes, promoting the faster healing of oral soft tissues regardless of the kind of surgical procedure, and especially useful for patients needing oral surgery and affected by systemic disease requiring continuous life-saving therapy.

Author Contributions: Conceptualization: G.F., S.C.; methodology: G.F., E.M., L.L.; software: S.B.; validation: G.F., S.C.; formal analysis: S.B.; investigation: A.T., S.C., G.F.; resources: G.F.; data curation: S.B., A.T.; writing: S.C., A.T., L.; draft preparation: A.T.; writing—review and editing: S.C., E.M.; visualization: S.B.; supervision: G.F.; project administration: G.F. All authors have read and agreed to the published version of the manuscript.

Funding: No funds were obtained for the current study.

Conflicts of Interest: The authors declare no conflict of interest.

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