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Role of adenosine based tissue restorative in oral surgery

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The paper describes the study on the action of an Adenosine based product in the tissue regenerative process and postoperative healing of the wound in oral surgery. The study was conducted on a sample of 30 subjects, which proved to be healing more quickly and efficiently than subjects who were not treated with the Adenosine based product.

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1. Introduction

Healing of surgery wound is part of the general mechanism of body defence, of "self" keeping, a differentiated mechanism, organized, fixed by genotype and transmitted by phenotype. It is a non-specific process, because the reactions that characterize it such as the order of their occurrence are identical, in all tissues and organs, irrespective of the vulnerant agent. Generally, the healing process consists of the replacement of the destroyed, necrotic or devitalised tissues, with the partial or as a whole restoration of the affected structures and functions.

In case of wounds, healing achieved by the mechanisms of reparatory histogenesis is produced by regeneration and organising-repairing [1]. The regeneration represents the process of replacement of a tissue destroyed by the proliferation of the neighbouring cells, which have structural and functional qualities with those of the altered cells.

Normal cicatrisation is the result of a complex of events where cells, proteins, proteases, increasing factors and matrix components interact. The platelet influx induced by injury is followed by degranulation and delivery of chemical mediators, which initiate and maintain the fall of healing. This is carried on in a predictable manner: coagulation, inflammation, angiogenesis, fibroplasia, collagen deposition, epithelization, and contraction-reshuffle [2]. As concerns the method of postoperative healing, a primary healing is desirable, which presumes remaking without incidents of the parietal continuity, after incision and suture.

The therapeutic procedures that may facilitate healing are multiple, starting with the wound dressing until the use of chemical mediators of inflammation, nitric oxide, genetic engineering, mini invasive surgery techniques etc.

The treatment with chemical mediators –cytokines and increasing factors. The cytokines (tumour necrosis factor TNF-beta, interleukins 1-18, the neutrophil-activating protein NAP-2, Granulocyte-macrophage colony-stimulating factor GM-CSF etc.), released from lymphocytes and mononuclear phagocytes, act as intracrine, autocrine or paracrine signalling, being involved in the immune control response [3]. The increasing factors (fibroblast growth factor FGF, vascular endothelial growth factor VEGF, FC endothelial EGF, FC derived from PDGF-B platelet, epidermal growth factor EGF etc.) act on nonhematopoietic cells and on the connective tissue, respectively having a strictly local effect [3].

Therapy with nitric oxide produced in cells under the action of the nitric oxide synthase (NOS) occurs in all stages of healing, by: antimicrobial effect, antiplatelet effect, vasodilator, modulator of cell chemotaxis, cells proliferation and differentiation, collagen deposition, angiogenesis and contraction of the wound. The capacity to regulate cell proliferation depends of NO level and of the cell sensitivity to its antiproliferative action [4].

Genetic therapy occurs on somatic cells. Experiments on gametes are accepted in terms of only uncertain countries, and their therapeutic use on humans is forbidden(5).

2. Rationale of the study

The presence of an oral and dental pathological condition, in a subject who will undergo oral surgery to improve tissue healing (or after surgery), has always negatively affected the final result, therefore imposing the need for different strategies in order to increase the

possibility of success, such as the use of restoratives or treatment with various drugs.

The Adenosine based products are classified as a tissue restorative and their main components are as follows: DNA nucleotides, methylsilanol mannuronate, nisin, nucleotides and lactic acid [6,7].

3. Assumption of the study

We believe that the subjects to undergo oral surgery will show better healing compared to the group of subjects who do not undergo treatment.

4. Primary objective

The primary objective of this study is to assess the effectiveness of an Adenosine based product improving the healing of odontostomatologic conditions and after oral surgery.

This objective will be assessed by means of direct feedback from periodical visits at 24 -48 - 120 hours after surgery, photographs, and, if necessary, X-Ray exams.

5. Conception and design of the study

This pilot study will enrol 30 subjects, both male and female, affected by odontostomatologic conditions; they will be divided into two groups:

- Group "A" 15 subjects to be treated using an Adenosine based product;
- Group"B" 15 non-treated subjects

The subjects of the first group shall be administered with Adenosine based product the first time by the Doctor of Dental Surgery/ Doctor of Dental Medicine, and then shall self-administer it daily for a total treatment period of 5 days.

The other non-treated subjects shall instead be treated using a product devoid of adenosine and shall constitute the control group.

Inclusion Criteria

Subjects meeting the following criteria will be enrolled in the study:

- Men/Women affected by Angular Cheilitis - Herpes - Mouth Aphtha;
- Subjects who should undergo oral surgery or dental implant

Exclusion Criteria

- Men and Women who are heavy smokers;
- Men and Women suffering of Diabetes;
- Men and Women suffering systemic disease;
- The subjects who have received steroids based treatment 13 days before surgery,
- Subjects with acute or chronic affections of oral mucosa that may negatively influence healing of wound.

6. Materials and methods

Subjects belonging to group "A" will be treated with Adenosine based product thus:

- oral surgery and implantology: 2-3 puffs, at the end of intervention depending on the area following to be treated, 2-3 puffs after 24 hours, 2-3 puffs after 48 hours.
- cheilitis, herpes: 1-2 spraying at the beginning of treatment, 1-2 puffs after 24 hours, 1-2 spraying after 48 hours, 1-2 puffs after 72 hours, 1-2 puffs after 96 hours, 1-2 spraying after 120 hours.

Subjects who belong to group "B" shall be treated with a batch of product devoid of Adenosine and will be part of the control group. The control group must be submitted to the same criteria of medicine administration as the subjects who belong to group "A". The subjects potentially eligible for the study will undergo the following:

- A full orthopantomography of the dental arches for the subjects who will undergo oral surgery or dental implant surgery;
- Photographic pre-treatment assessment for all subjects.

Assessment of Results

- Monitoring the subjects through periodical visits;
- A full orthopantomography of the dental arches for the subjects who have undergone oral surgery or dental implant surgery;
- Photographic post-treatment assessment for all subjects;
- All within 120 days from the start of the tests.

The 30 subjects have been treated for the following lesions:

4 subjects were diagnosed with labial herpes

3 subjects had aphta in the oral mucosa

3 subjects had angular cheilitis

4 subjects had fibroma of the jugal wall and lip fibroma

2 subjects had mucocele of the lip

7 subjects had apical lesions and radicular cysts

3 subjects had severe bone atrophy treated by bone augmentation procedures

4 subjects who needed treatment with prosthetic implant

In case of subjects whose diagnosis does not impose a surgical treatment, the therapeutic protocol consisted of topical substance spraying on the surface of lesions during 5 successive days, 1-2 puffs. The subject have been monitored and clinically examined until their complete healing. Further they were examined on weekly basis during 30 days and then on monthly basis another 90 days.

In case of the subjects whose diagnosis imposed surgical treatment, the therapeutic protocol a protocol consisted of spraying the substance on the surgical wound surface immediately after surgery and another two successive days with 2-3 puffs. Further they have been examined after 5 days, 7 days and then on weekly basis during 30 days and then on monthly basis during 90 days.

The graphic expression of the healing of the lesions, which did not benefit of surgical treatment, has been carried out by measuring the time needed until complete healing.

The graphical expression of clinical signalling of postoperative healing and tissue regeneration has been accomplished by the analysis of the postoperative pain symptoms; postoperative oedema, postoperative ecchymosa and the time elapsed until the surgical healing with suppressing the suture wires. For the assessment of postoperative pain intensity a scoring system from 0-7 was used, 0 being similar with the absence of pain and 7 with unbearable pain: 0 – without pain, 1- painful discomfort, 2- pain with reduced intensity, 3- moderate pain, 5- pain with increased intensity, 6- vivid, strong pain, 7- unbearable pain (Fig. 2). For the assessment of postoperative oedema a scoring system from 0 to 5 was used, has been used: 0- absence of postoperative oedema, 1- small, localised oedema, 2- moderate oral oedema, 3- intensive oral and cutaneous oedema 4- large cutaneous oedema, 5- neighbouring large oedema both oral and coetaneous (Fig. 3). For the assessment of postoperative ecchymosis sites a scoring system from 0-5: 0- without ecchymosed, 1- small local ecchymose, 2- local moderate ecchymose, 3- extensive oral ecchymose and small cutaneous ecchymose, 4- large facial cutaneous ecchymose, 5- cervical ecchymose (Fig. 4).

7. Results

The subjects with lesions of labial herpes type, aphta in the oral mucosa aphta and angular cheilitis who did not required surgery interventions and were treated with adenosine based products had a favourable response to the treatment, with complete healing of the lesions after three or four days. In comparison, the subjects treated with a product without adenosine had a healing time longer with 7-10 days.

Monitoring the group of subjects that suffered surgical interventions, the presence of postoperative oedema (Fig. 2) and local pain (Fig. 1) is noticed in case of the subjects treated with a product without adenosine, 3-5 days after surgery and sometimes ecchymose persistent at 7-10 days after surgery (Fig. 3). Healing of the wound and suture wire suppressing is made after 7-10 days after surgery.

In case of the group who suffered surgical interventions and who has been treated after surgery with Adenosine based product, in majority of the cases 24 hours after surgical intervention, the postoperative oedema is minimum, the subject having no pain or a slight painful discomfort, the antialgic and anti-inflammatory treatment being needed about 1-2 days after the surgical intervention. 72 hours as of the intervention the oedema is remitted almost entirely, the subject accusing no local pain, small local ecchymose is possibly present.

After 5 days fast tissue regeneration is noticed in the majority of the cases, the wounds are surgically healed and the suture wire are suppressed.

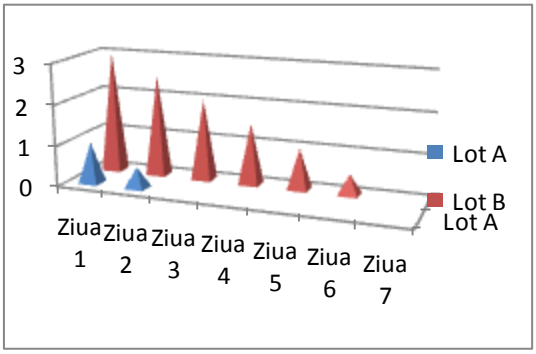

Fig. 1. Postoperative pain intensity for "A" and "B" group.

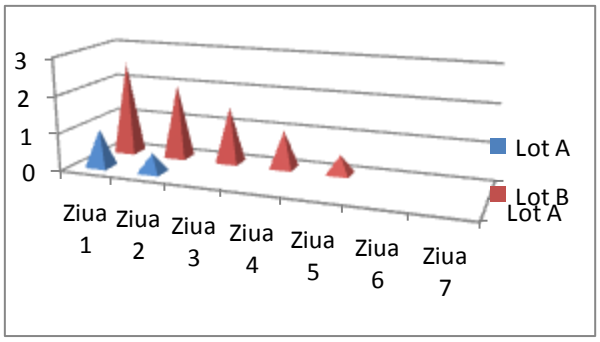

Fig. 2. Ilustrating postoperative oedema for "A" and "B" group.

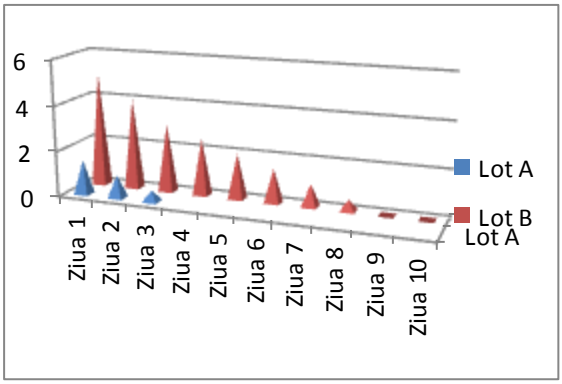

Fig. 3. Ilustrating postoperative ecchymosis for "A" and "B" group.

We have chosen three clinical cases of the subjects belonging to group "A" and who suffered surgical intervention.

Case 1 a subject diagnosed with fibroma of the lower lip (Fig. 4), who benefited of benign tumour extirpation. Healing of the postoperative wound is emphasized 24 hours (Fig. 5), three days (Fig. 6) and 5 days (Fig. 7) after surgery.

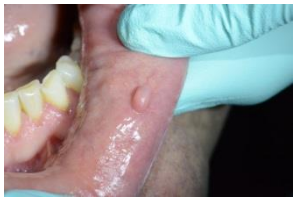

Fig. 4. Mucocele of the lip.

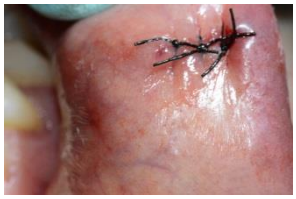

Fig. 5. Postoperative wound aspect after 24 hours.

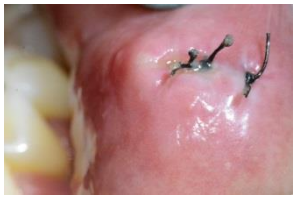

Fig. 6. Postoperative wound aspect after 72 hours.

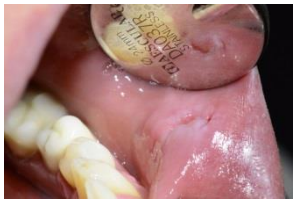

Fig. 7. Postoperative wound aspect after 5 days.

Case 2 a subject diagnosed with chronic apical periodontitis and apical granule (Fig. 8) who does not respond to enzootic therapy, suffered an apical resection and retrograde obturation. Healing of the postoperative wound is emphasized 24 hours (Fig. 9), 3 days (Fig. 10) and 5 days (Fig. 11) after surgery.

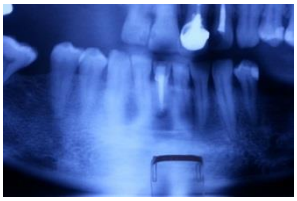

Fig. 8. Chronic apical periodontitis (tooth 3.1).

Fig. 9. Postoperative wound aspect after 24 hours.

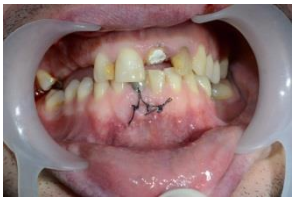

Fig. 10. Postoperative wound aspect after 72 hours.

Fig. 11. Postoperative wound aspect after 5 days.

Case 3 subject diagnosed with severe maxillary bone atrophy (Fig. 9) who suffered a surgical intervention of maxillary sinus floor augmentation followed by bone augmentation. Healing of the postoperative wound is emphasized 24 hours (Fig. 10), three days (Fig. 11) and 7 days (Fig. 12) after surgery.

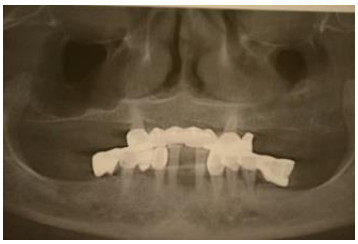

Fig. 12. Severe bilateral maxillary bone atrophy.

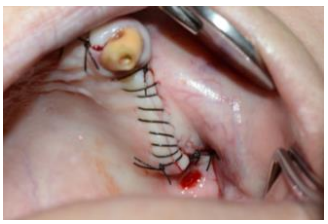

Fig. 13. Postoperative wound aspect after 24 hours.

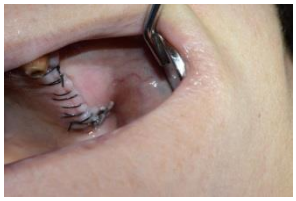

Fig. 14. Postoperative wound aspect after 72 hours.

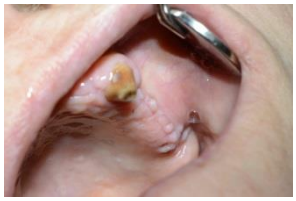

Fig. 15. Postoperative wound aspect after 7 days.

The graphical expression of postoperative pain is emphasized in Fig. 2. The results have been obtained from the subjects, by completing a questionnaire using the above-mentioned grading system.

The graphical expression of postoperative oedema and ecchymose are in the same manner emphasized in Figs. 3 and 4. The results have been obtained by the doctor using also the grading system described for each symptom.

It is obvious to recognize that already one day after the surgery the group of subjects where diode laser has been used within the treatment, benefited of a faster postoperative wound healing, without pain in the majority of the cases (75%). The superiority is continuing during the therapy period.

8. Discussions

Adenosine is the main active principle of adenosine based product and it allows tissue restoration through a reparative action with physiological cicatrisation by mitotic and angiogenic stimulation; this leads, therefore, to a proliferation of fibroblasts and osteoblasts, and allows a more rapid reconstruction of bone and mucosal tissues [8-10]. An adenosine based product is a fluid spray product with high regenerating, proliferative, antioedema**,** antinflammatory properties which acts as painkiller [11].

DNA-Na is an active molecule, which has shown to be effective on traumatic injuries of the mucous membranes and on diabetic wounds and bed-wounds [12]. Its action also allows severely burnt and damaged skin to restore. It allows optimal tissue restructuring, fast and effective, clinically detectable even to feedback made the day after surgery. The effect is explained through an effective tissue cleansing and a powerful restorative action and by physiological healing, allowing prevention and therefore formation of keloids and / or anomalous tissues [14].

By mitotic (mitosis is cell splitting keeping the same features of the original cell) and angiogenic (angiogenesis consists of developing new blood vessels) stimulation, re-normalisation of microcirculation is allowed and the development of contractures and / or mitochondrial and reticular contractures and / or ruptures is prevented, restoring normal homeostatic energy cellular balance, showing a strong anti-ischemic tissue and anti-degenerative activity [15,16].

Adenosine is the main active principle, besides the basic nitrate quality constituent of NDA/RNA, it is a chemical bond between catabolism and anabolism by its triphosphate or, ATP produces immediately an efficient anti-inflammatory activity, antialgic and anti edematous [17,18]. Induces an efficient stimulation of fibronectin, presenting a strong proliferative activity both of fibroblast and osteoblast [19,20]. Fibronectin is a protein produced by many cells, which is present in the connective tissue also; the cicatrisation processes are characterized by an increased production of fibronectin [21].

Within this study the success of healing and of tissue regeneration have been assessed based on clinical aspects and in case of subjects who suffered a surgical intervention the clinical examination was accompanied by radiological examination also.

The clinical aspects monitored in case of the subjects who did not required surgical intervention, were represented by the period until the complete healing of the lesion. The response was favourable in case of 1-2 puffs local spraying with adenosine-based product on the lesion during 5 successive days. The subjects have been monitored and clinically examined during 7 days. The complete healing of the lesions occurs after three or maximum days (one case of labial herpes). Further they were examined on weekly basis during 30 days and than on monthly basis during another 90 days. The lesions treated this way did not recur during this time. In comparison, the subjects treated with a product without Adenosine had a longer healing time with 7-10 days, sometime even 10 days in case of labial herpes.

The clinical aspects monitored in case of the subjects who required surgical intervention were: postoperative pain, local oedema, ecchymose, infection or dehiscence of the wound, the time of healing of the postoperative wound. The therapeutic protocol consisted of spraying in the surface of the postoperative wound of the solution immediately after finalising the surgical intervention and another two days after surgery. The subjects have been clinically examined 5 days and 7days after the surgery. Further they were examined on de 30 days and then on monthly basis during another 90 days.

After the first treatment day, the group of subjects treated with adenosine-based product showed no postoperative pain in 86.6% of the cases (13 subjects), and after two days these disappeared completely in case of the rest of the subjects. In comparison, the subjects of the group treated in a conventional manner show no postoperative pain in 53.3% of the cases (8 subjects) and the rest showed local pain with moderate intensity during 3-4 days, sometimes 6 days after surgery in the absence of the treatment with adenosine based products (Table 1).

Table 1. Comparative postoperative pain intensity for "A" and "B" group.

Pain	Group A		Group B	
	n	%	n	%
0	13	86,6	8	53,8
1	2	14,4	3	20
2			2	13,3
3			2	13,3
4				
5				
6				
7				

As concerns the postoperative oedema in case of group "A", 8o% (12 cases) of the subjects showed no postoperative oedema the day after the surgery and three days after this was not present at any of the subjects. In comparison, the subjects of the group "B" show no postoperative oedema in 60% (9 cases) of the cases, 3 subjects (after two days, and 3 subjects (20%) showed oral and cutaneous oedema after three days (Table 2).

Table 2. Comparative postoperative oedema for "A" and "B" group.

Postoperative oedema	Group A		Group B	
	n	%	n	%
0	12	80	9	60
1	3	20	3	20
2			3	20
3			3	20
4				
5				

Ecchymose in the mucous membrane were present in 2 cases of the subjects in group "A" (13.3%) and persisted until two and three days, respectively after surgery. In comparison, in case of group "B" postoperative ecchymose has been present in case of 5 subjects (33%) until a maximum of 7 days after surgery, this case being a cervical ecchymose (Table 3).

Table 3. Comparative postoperative ecchymosis sites f or "A" and "B" group.

Postoperatrive Ecchymose	Group A		Group B	
	n	%	n	%
0	16	86,6	9	77,78
1	2	13,3	4	26,6
2			3	20
3			1	6,6
4				
5			1	6,6

The suture wires in case of group "A" were invariably removed within 5 days, considering postoperative wound surgically healed. In comparison, in case of group "B" the suture wires have been removed within 5 – 7 days, sometimes after 10 days from the surgical intervention, the postoperative wound having difficult healing in comparison with group "A".

As concerns dehiscence of the wound, this has been present in three cases only at the subjects belonging to group "B", with infection of the postoperative wound in one of the cases.

9. Conclusions

Due to all these specific characteristics the Adenosine based product is useful and excellent in the field of oral surgery because it induces a fast and correct of the bone tissues and of the buccal cavity mucous membrane, shortening very much the duration of healing.

The work hypothesis of this study has been confirmed: the subjects who followed a local treatment with adenosine based product benefited of a remarkable tissue regeneration and have been healed more quickly in comparison with the group of subjects who did not follow this treatment. The main objective of this study was also, reached: effectiveness of adenosine demonstrated fast healing of an oral lesion or of a postoperative wound after an oral surgical intervention.

Acknowledgements

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