Vitamin A Acid, Vitamin E and Vitamin C Injectable for the Treatment of Tissue Necrosis

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ABSTRACT

Experimental studies reckoning vitamin A acid (all trans retinoic acid 0.1%) with the antioxidant action of vitamin E (tocopherol acetate 0.2%) and vitamin C (coated ascorbic acid 0.2%) diluted 1:4 to vitamin A 0.02%, vitamin E 0.05% and vitamin C 0.05%, with efficacy in the vascular neoformation induction and in the cellular membrane stabilization, has been clinically used by us for the improvement of the skin and the skin necrosis regression after routine plastic surgeries.

Patients after rhytidectomy, breast reduction and abdominoplasty with localized skin flap necrosis were submitted to daily intradermic injections for a period of 15 days, had their skin healed by these vitamin effects.

INTRODUCTION

Very often skin necrosis by traumatism and after routine plastic surgeries are reported in the literature and in scientific meetings. In the same patient, the skin react diversely even after safe surgical manipulation, from region to region, in different or the same decade of their lives by unknown biochemical behavior and stimulation.

Several examples illustrate these occurrences. In the same scar line there are keloids segments alternated with unconspicuos scars. In the rhytidectomy there are scars with aesthetic variations in the same patient, in which hypertrophic reactions, keloids, scar broadness, skin flap necrosis, etc. are present.

The skin texture, undermined extension, local suture tension, smokers, age and even the surgeons qualification are some of the countless factors, used to explain these secondary unpleasant problems, where some are predictable and others unexpected. Isolated or in combined situations, not extended to extensive, deep or superficial skin necrosis are always a problem for the

doctors and for the patients, based on the emotional involvements and unaesthetic effects.

Laboratory researches proved the capacity of vascular neo-formation induced by vitamin A (all trans retinoic acid 0.1%), with the anti-oxidant action of the vitamin E (tocopherol acetate 0.2%) and vitamin C (coated ascorbic acid 0.2%) "ACE pool" diluted 1:4 to vitamin A 0.02%, vitamin E 0.05%, vitamin C 0.05%, and their ability of stabilizing the skin necrosis when intradermically injected.

Based on preliminary studies with ACE pool, we have been using this product for increasing of the collagen and the elastic fibers of the skin face for aesthetic purposes especially 24 hours after rhytidectomy, and in extension in cases of abdominoplasty and breast reduction, up to 15 days post-operative period, with the scope to obtain better scars aspects and the reduction of eventual mild skin necrosis.

VITAMIN A

It was already described that vitamin A (retinoic acid) has the ability of intra-nucleous activation in the retinoic cycle, resulting in a better cellular function with the increase of collagen and elastic fibers production. Its anti-oxidant action and immune regulation effects, may be used in different pathologies [2, 6, 11, 12, 15, 17, 18, 20, 21].

Vitamin A relationship to the hyperkeratotic syndrome was first clinically diagnosed by STTUTGEN[20] in 1962. RW Johnson Pharmaceutical Research Institute, supported Sttutgen's experiments with retin A for ortho diagnosis[15]. KLIGMAN[11], in 1969, was the first to clinically associate vitamin A with the problem of acne. He began vitamin A treatment for skin alterations, mainly in the photo aged skin.

Recently ELLIS[5], in 1990, demonstrated the positive effect of Tretinoin based cream (all trans retinoic acid 0.1% = 1000 mm/ml) in the treatment of the photo aged skin. He observed the reduction of the epidermic corneal layer and the increase of granular layer, an advanced number of mitosis in the keratocytes, the presence of glicosaminoglicans, a growth of the anchoring fibers in the intersection of the dermal layers and a higher thickness of the epidermis. This first evaluation was done 4 months after the treatment and repeated 22 months later.

The final result showed a significant decrease of the

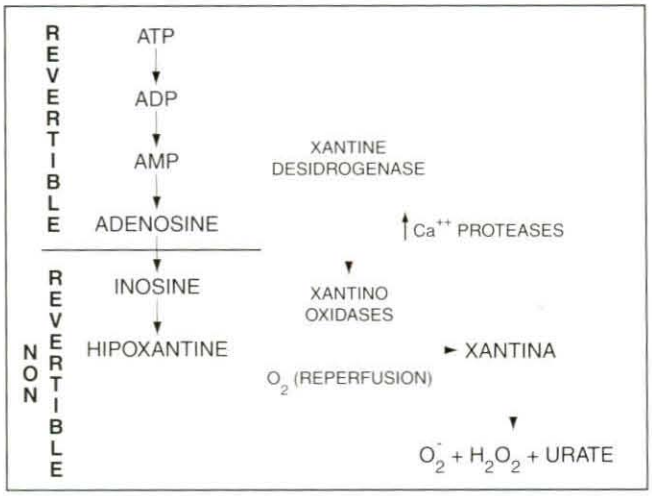


Fig. 1 - Ischemia by re-perfusion.

Fig. 1a - Isquemia por reperfusão.

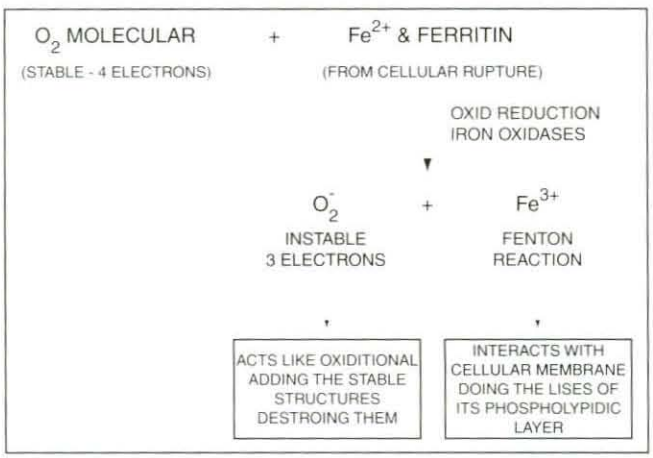


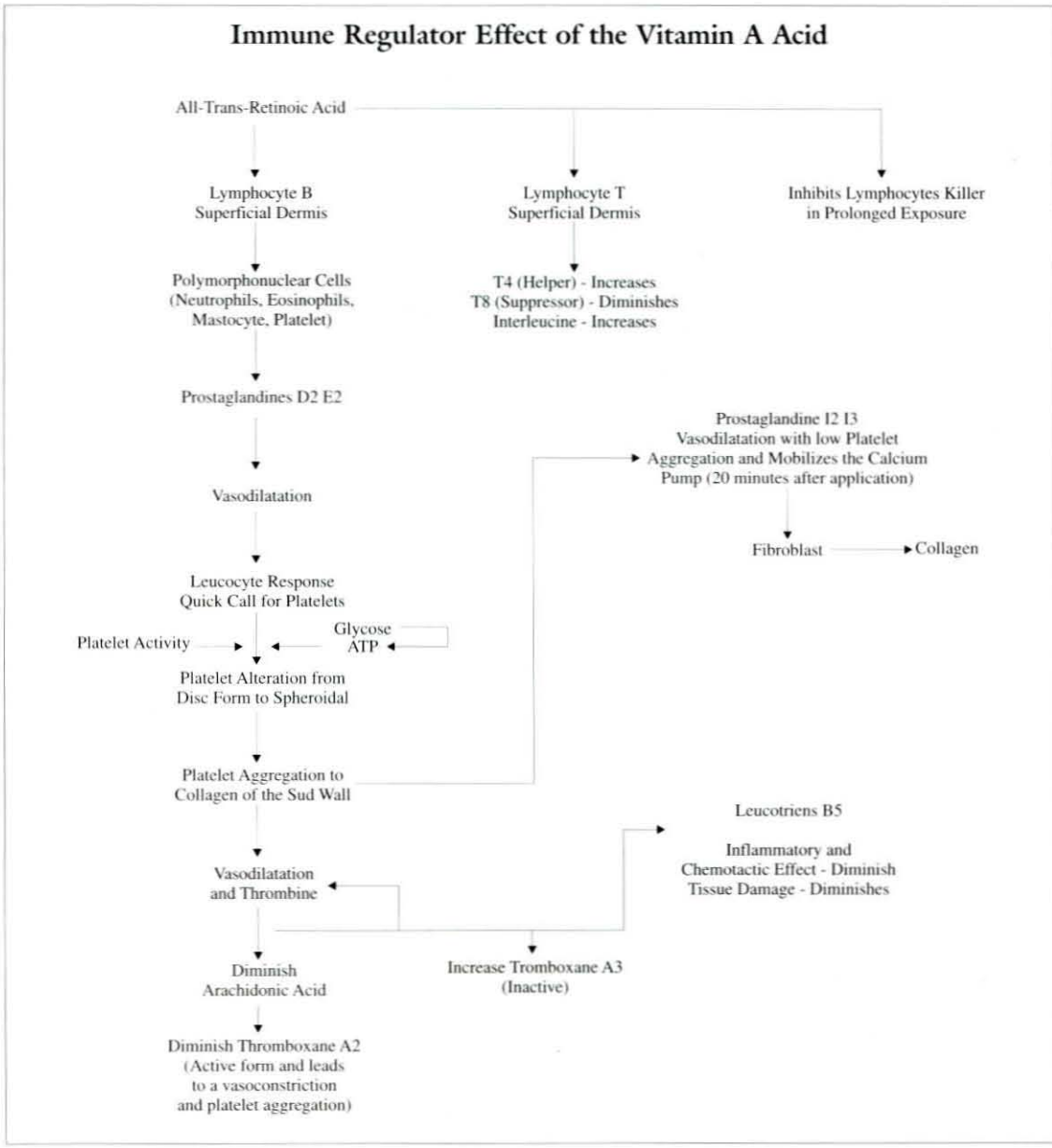
Fig. 1b - Haber-Weiss reaction.

Fig. 1b - Reação de Haber-Weiss.

thin facial wrinkles, creases, as well as the improvement of the skin texture and the skin elasticity. No side effects were observed, confirmed by KLIGMAN[12], LASNITZKI[13] and WILSON[22]. According to JADILLIER[9], the retinoic acid is more efficient than retinol because it doesn't need glycolization in order to generate glycosaminoglicans which are responsible for the presence of fibronectines. The fibronectines are reduced in the photo aged skin and with an uncontrolled growth in the malignant transformations. Based on these effects, vitamin A may possibly inhibit the skin carcinogenesis.

Immune Regulator Effect of the Vitamin A Acid.

According to PENN et col.[17] supplementary vitamins A, C and E, increase the functions of the im-



munologic cellular mediator, with significant absolute number increase of lymphocyte T, followed by an increase of lymphocyte T4 (Helper), and the stabilization of lymphocyte T8 in reply to the phytohemaglutinine, which is a chemical mediator increased with the presence of vitamins A, C and E.

Many articles reports that vitamin A maintain the intra-cellular communication with each other. They also described that the prostaglandines E2 synthesized by the epidermis in the presence of all trans retinoic acid induces blood stimulation increasing the leukocyte response. These reactions improve the skin defensive mechanism against virus, bacteria, parasites and non malignant or malignant tumoral processes. CONNOR[03].

Retinoic acid also stimulates the production of interleucin. Its presence in the integument actives the network of the Merckel cells and the free extremities neurons placed in the dermic-epidermic junction. These reactions are recognized as important elements in the release of prostaglandines D2, serotonin, leukotriens (chemical mediators) which stimulate vasodilatation with the subsequent increase of vascular permeability. Based on these, some possible chemical reactions can be described:

a) The platelets when adhered to the sub-endothelium become activated by their

Fig. 2a - Three of the skin flaps are mobilized in the dorsal aspects of the rats. Each flap presents 5 cm length and 1 cm in the base. The flaps vertex are placed cranially.

Fig. 2a - Desenho e confecção dos retalhos realizados em ratos. Os retalhos possuem 5 cm de lado e 1 cm de base, com ápice cefálico e base caudal.

Fig. 2b - The skin flaps after undermined are placed in their normal position. At the vertex "a" Gillis isolated type of stitch with 5-0 mono filament nylon is placed and an isolated stitch in each flap side complete the suture.

Fig. 2b - Nota-se o fechamento delicado dos retalhos, com preocupação em utilizar pontos de Guilles nos ápices, menos traumáticos, e com 2 pontos simples em cada lateral. Usou-se fios monofilamen-tares de nylon 5-0.

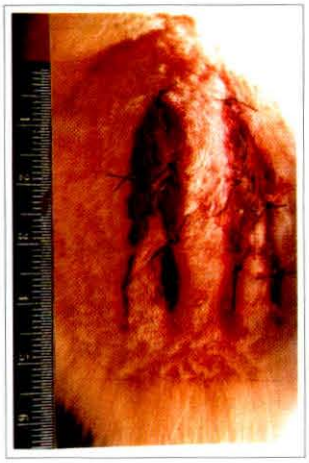


Fig. 2c - All the triangular flaps present 16% of necrosis of their distal portion, 24 hours after their mobilization.

Fig. 2c - Todos os retalhos triangulares apresentaram necrose de aproximadamente 16% da área, após 24 horas.

Fig. 2d - At the 8th postoperative day, the flap "A" treated with ACE Pool shows significant necrosis regression, while the flap "B" presents a necrotic scar.

Fig. 2d -Retalhos 7 dias após sua confecção. Observa-se que o retalho "A" (tratado) apresenta uma regressão significativa da necrose, sem seqüelas cicatriciais. O retalho "B" ainda apresenta crosta em fase de destacamento.

contact with trombine and the collagen tissue. New platelets when connected with these activated platelets also become active, releasing platelet activating factor .

b) The trombine and the collagen have different receptors regarding the platelets. Biochemical reactions among them, determine the appearance of platelets granules secretion.
One of these reactions release prostaglandine IP3 which is the second most important platelet activator. IP3 prostaglandine plays the role of calcium ionophore increasing its concentration, and subsequently activates A2 like phospholipases enzymes, which by reactions release arachidonic acid.

c) Tromboxane A2, a potent vasoconstrictor and platelet aggregator is a subproduct of the arachidonic acid. Therefore it is necessary its inhibition, and stimulation of the cyclo-oxigenase enzyme in order to obtain a small quantity of tromboxane A3; which is physiologically inactivated and reduces platelets aggregation while maintaining vasodilatation.

d) The production of prostaglandin I2 (a potent vasodilator and anti-platelet aggregator) in the endothelium is not significant inhibited and the physiologic activity of a new prostaglandin I3 is added to prostaglandin I2. The resulting effect is a homeostatic equilibrium tending to an increased vasodilatation condition, with lower platelet aggregation. ABB[1].

e) Leukotriens are also sub products of arachidonic acid . Leukotriens B4 (L T B4) are present in diseases like rheumatoid arthritis and psoriasis. In the presence of lipoxigenase enzyme, the Arachidonic acid generates leukotriens B5 (L T B 5) with reduced effect over inflammatory and chemiostatic processes, improving the skin local conditions.

The prolonged use of retinoic acid even in non-toxic concentration will inhibit the T-killer lymphocyte.

VITAMIN C

Vitamin C (ascorbic acid) is essential for the collagen synthesis, OLZEWER[14] . It is required in the hydroxylation of proline in the collagen, STRYER[19]. The ascorbat removes the ferric ion from the enzyme which was inactive during the proline hydroxylation, becoming a specific anti-oxidant. The synthesis of collagen without the ascorbat will produce abnormal fibers and will contribute to the appearence of skin lesions and vascular fragility.

CLINICAL APPROACHES

Patients

Based on the experimental studies in rats and on the literature, 21 patients were treated with ACE pool injections in specific necrotic areas after routine plastic surgeries; 4 underwent rhytidectomy, 10 breast reduction (3 bilateral and 7 unilateral skin localized necrosis) and 7 abdominoplasties. Figs. 3, 4 & 5. The patient's ages averaged from 17 to 65 years old. Each necrotic area received daily 1 to 3 cc of ACE pool intradermically (diluted), injected daily for 15 days. The injections were performed with insulin type of needles adapted to 1 to 3 cc disposable syringe. The place of the injections were 5 mm behind the necrotic area at intradermic superficial level and towards the necrotic zone. The amount of infiltration reached the local epidermic saturation and the necrotic extension. The infiltrations were punctiform and 5 mm distant from each other.

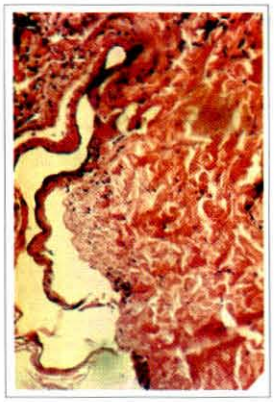


Fig. 2e - Microscopic aspect of the flap C (control) 24 hours after its mobilization, showing dermo epidermic necrosis with acute inflammatory reaction, with the presence of capillary network dilation, high neutrophil concentration around the vessels, necrotic phanerous and neutrophils surrounding the hair axis.

Fig. 2e - Avaliação microscópica do exame anátomo-patológico do retalho do grupo C (grupo controle - biópsia 24 horas após a confecção dos retalhos) mostrando necrose dermo-epidérmica e reação inflamatória. Nota-se a rede capilar dilatada, grande quantidade de neutrófilos ao redor dos vasos, anexos necróticos.

Fig. 2f - Microscopic aspects of the non treated flap (B) after 7 postoperatory days, showing the dissociation of the corneal stratus done by neutrophils and red cells, epidermic necrotic focus, neutrophils exudate below the dermal level dermo epidermic necrosis focus of tissue regeneration and inflammatory reactions.

Fig. 2f - Aspectos micrográficos do retalho "B" (não tratado), biópsia realizada após 7 dias da confecção dos retalhos. Observa-se a dissociação da camada córnea por neutrófilos e hemácias, focos de necrose na epiderme e a derme subjacente mostra presença de exsudação de neutrófilos, pele com necrose dermo-epidérmica, reação inflamatória aguda e focos de regeneração.

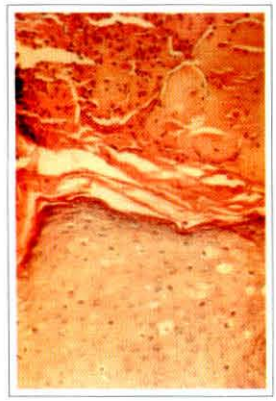


Fig. 2g - Microscopic aspects of the treated flap (A) after 7 days postoperative, showing a thick corneal stratum with regenerate epidermis, the dermis with presence of cutaneous annex, ectasia of capillary network with few surrounding neutrophils, fibroblast proliferation and histioid cells inside the fibrin network.

Fig. 2g - Avaliação microscópica do retalho "A" (tratado), biópsia realizada 7 dias após a confecção dos retalhos. Observa-se epiderme regenerada com camada córnea espessada, derme contendo vários anexos cutâneos, rede capilar ectásica, observa-se a proliferação de fibroblastos e células histióides em meio a malhas de fibrina.

DISCUSSION AND CONCLUSIONS

The clinic evidences of the healing processes and the necrotic remissions high level in rats and in the clinic patients allow the following conclusions:

1. The vitamin E in the ACE pool intradermic skin injection seems to be responsible for the cellular membrane stabilization based on the reduction level of phospholipolization in the membrane structures.

2. In combined reactions vitamin A determines the intranucleous activation and stimulates the collagen fibers formation

3. The vitamin C determines the collagen tissue stabilization induced by the

Fig. 3a - A 51 year-old white woman after a routine rhytidectomy, shows a retro-auricular skin necrosis behind the ear 24, hours after the surgery.

Fig. 3a - Paciente com 51 anos, submetida a ritidoplastia, sem intercorrências. Observa-se o sofrimento do retalho retroauricular 24 horas após a cirurgia.

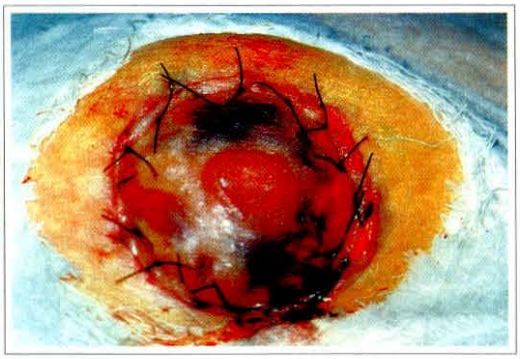


Fig. 3b - Same patient 14 days after daily injection of ACE pool. A complete skin regeneration is observed without evidence of scarring.

Fig. 3b - A mesma paciente após 14 dias de tratamento com ACE pool injetado diariamente. Observa-se a completa recuperação do retalho, sem a presença de seqüelas ou cicatrizes.

Fig. 4a - A 33 year-old woman, after breast reduction through vertical incision procedure, shows vascular deficiency at the areola-nipple complex 24 hours after surgery.

Fig. 4a - Paciente de 33 anos, submetida a mastoplastia redutora por técnica de incisão vertical. Observa-se o sofrimento do CAM 24 horas após a cirurgia. Visão da abertura do primeiro curativo.

Fig. 4b - Same patient 14 days after daily injection of ACE pool. A complete regeneration of the areola-nipple complex is observed, without suture dehiscence or scar deformity.

Fig. 4b - Memo paciente, após 14 dias de tratamento com ACE pool. Observa-se a completa recuperação do CAM, sem deiscências de sutura nem seqüelas cicatriciais.

Figs. 5a & 5b - A 50 year-old man 24 hours after rhytidectomy, shows a huge hematoma with skin vascular deficiency.

Figs. 5a e 5b - Paciente com 50 anos, sexo masculino, submetido a ritidoplastia. Observa-se o grande hematoma formado 24 horas após a cirurgia com sofrimento de pele.

Fig. 5c - 4 days after daily injection of ACE pool.

Fig. 5c - 4 dias após o tratamento com ACE pool.

Fig. 5d -15 days after daily injection of ACE pool.

Fig. 5d - 4 dias após o tratamento com ACE pool.

proli-hidroxilation.

4. The association of these vitamins, also determine the vitamin E potencialization that inhibit the cellular lipidic peroxidation.

5. The tissues treated with ACE pool presented a time reduction in the healing processes when compared to similar healing involvements in a non treated area.

6. Localized necrosis remission were evident in almost all treated cases. The final cicatrization macroscopic aspect were of a high acceptable aesthetic quality compared to scars after secondary intention healings.

7. In conclusion injectable ACE pool is a specific method for limited necrotic areas that determine a high percentage of necrosis remission with a better acceptable scar in a shorter period of time, compared to traditional methods.

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