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Postagressional Arterial Remodeling: An Experimental Study

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ABSTRACT

AIM: The unprecedented development of cardiac surgery and interventional cardiology we have witnessed these past years, has led to an increassing need to find solutions for the post-traumatic modifications of the arterial wall: stenosis and neo-intimal proliferation. The aim od this study is to asses the effect of diltiazem on reactive prolifferation of the intima after lesion in an experimental model (rabbit) and to quantify these modiffications from a qualitative and quantitavive point of view.
MEANS AND METHOD: We used 20 male rabbits, weighing between 2,5-3kg, to which a lesions was made using the baloon of a Fogarty catheter on the left internal carotid artery. The lot was dividen into two groups: one group (A) to which we only administered fractioned heparin post-operatively, the other group (B) to which we administered 3g of diltiazem two times a day in addition to fractioned heparin. The subjects were examined clinicaly and with doppler ultrasound 24h, 7days, 14 days and 30 days after surgery. Upon sacrification, the carotid artery was examined under optical microscopy.
RESULTS: The site of the lesions induced were mainly on the intimal level as follows: mural hematoma, clivation of the supperficial layer or intimo-medial dilaceration. On succesive sections one can asses intimal prolifferation, with either concentrical of excentrical disposition, the healing the the lesions with a tendency to oclusion in deep lesions.
CONCLUSION: Intimal hiperplasia appears as a healing reaction after a surgicaly induced intimal lesion. Diltiazem appears to inhibit intimal proliferration.

KEYWORDS baloon angioplasty, intimal lesion, intimal hiperplasia, diltiazem

INTRODUCTION

Although there have been net developments in interventional cardiology procedures in coronary and peripheral angioplasty techniques, restenosism remaains still an issue. This is caused mainly by complex healing reactions after the lesions induced during the angioplasty procedure on the vessel. Sistematicaly we can present the the mechanism as follows: dissection, elastic rebound of the aterial wall, thrombosys, leukocyte infiltration, reactive cellular prolipheration, arterial remodelling. Of these, cellular prolipheration is among the most difficult cu contain, even though there are therapeutic agent aveilable to counter this phenomenon. The anti-prolipherative effect of diltiazem was shown in in-vitro studies but in-vivo studies have not confirmed this action widely because it is hard to accomplish the plasmatic concentration with oral administration. We aim to show the in-vivo results of diltiazem in an experimental study on rabbits.

MEANS AND METHOD

We made an experimantal model using white Belgian and cincilla rabits, weighing 2,5 to 3 kg, on a superffical artery (left internal carotid artery), using 0,2ml Fogary catheter baloon tip. We used ketalar 0,5% solution for antesthesia, administerd intra-muscular, with a 1ml/kg dosage toghether with local instilation on 1% lidocain, 5ml administered subcutaneously. The rabbits were then contentioned, with the exposure of the left carotid traingle. We isolated the carotid bifurcation through an incission made paralel to the lateral neck muscle. The atery is easy to palpate, it is about 2mm thick and bifurcates into two branches: internal and external. After isolation of the internal carotid artery, we administered 1ml of sodium heparin in the jugular vein. We then clamped the the carotid artery, made a small 1 mm incision in the internal carotid artery and passed the Fogarty catheter in the carotid artery, gomflating the baloon and maintaing it for 5 minutes. The catheter was then extracted and the incision was sutured with 8/0 polypropilene sutures. All animals received fractioned heparin begining day 2 after the procedure (fragmine 100IU/KG avery 12 hours, or Clexane 1mg/Kg every 12 hours). We divided the lot into two subgroups. Group A (10 rabits) were sacrificed as follows: 2 after 24 hours after surgery, 2 after 7 days, 3 after 14 days and 3 after 30 days. Group B also received 3mg of diltiazem twice a day and were sacricifec according to the same pattern. We examined the carotid artery after the procedure using an ultrasound doppler in days 7, 14 and 30 before scariffication and we followed the occurace of stenosys or oclusion. The histologycal study was made using an Olympus BH2 optical microscope. The examination comprised 5-6 blocks fron different levels of the carotid: from the lesions site, above and below the site. The sections were 5micrometer thick and were collored with haematoxilin-eosyn and Masson's tricorme stains. The examinations searched for modifications the arterial wall, stenosys, oclusion and intimal hiperplasia.

RESULTS

The ultrasound examination showed the occurance of stenosys on days 3-4 after the preocedure. We concluded that the degree of stenosys was higher in group A than in group B. We found mural hematoma, dilaceration of deeper wall structures and clivation of the intima's superficial layer. 7 days after the procedure we found important arterial wall modifications in group A, with mural thrombosys and intimal hyperplasia, with minor stenosys. 14 days after the procedure the mural thrombosys persists, the degree of intimal hyperplasia is higher and stenosys is signifficant. In group B we observed reduced stenosys, with higher repair mechanisms in the intima and in cases were the lesion was deep, large thrombus formation with suboclusive stenosys. 30 days after the intervention, group A shows less significant modiffications in the arterial wall mainly as a result of healing. The histological assay also showed concentrical or excentrical neo-intimal prolifferation. The deeper lesions were more prone to cause oclusive throm-

bosis of the vessel. The administration of heparin slowed the process of thrombosys. In group B the intimal prolifferation was weeker, as a result with lower degree of stenosys. Also in this group deep lesions were prone to develop oclusive stenosys.

DISSCUTION

In the modern age of surgery and interventional cardiology lesions of restenoys are frequent. It is present 30-40% of the cases in the first year after percutaneous coronary interventions, 10-50% of the cases 5 years after venous or prostehtic graft use and 40-80% 10 years after coronay artery by-pass with graft. The lesions that appear after these interventions are similar to atherosclerosys. In 1973, Glomset and Ross, sugested that lesions of the arterial wall heal the same no matter the pathogenic phenomenon, and are similar to the progressions of atherosclerosys. The lesion generates a speciffic response: cronical, inflamatory and of fibroprolifferation. Generaly the response is protective but degenerates in certain cases of exagerated response. The migration and prolifferation of smooth muscle cells are important in the appearance of restenosys. Injury to the arterial wall leads to the prolifferation of smooth muscle cells. Heparin inhibits this process and also the accumulation of extracelular matrix. Sugested mechanisms of this process are atrituted to the inhibition of c-myb, the supression of C proteinkinase on the c-fos pathway and the negation of the growth factor receptors of smooth muscle cells. The response of the vascular wall is complex, but what causes multiplication of smooth muscle cells is yet unknown. The intimal replication of smooth muscle cells is in conection with the vascular endothelial growth factor (VEGF/VPF) and with HB-EGF, a growth factor with a powerful mytogenic effect. The effect of diltiazem was shown in-vitro and prooves the reduction of stenosys with arround 50% in high dosys administration. Further clinical studies are in progress and have not yet been comunicated. In conclusion, intimal prolifferation appears as a result of baloon induces vascular lesions. It is at it's highest between days 7 and 14. The more complex and deep the lesion is the more ample the response is. Diltiazem administered oraly diminishes the cellular response and the degree of stenosys.

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