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Vascular brachytherapy: a landmark chapter in the field of interventional cardiology

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Primum non nocere is one of the fundamental principles in medical ethics, which also applies whenever a new therapeutic modality is introduced into clinical practice. When vascular brachytherapy (VBT) became available for patient care there were legitimate concerns about the potential late effects of intracoronary radiation. Two decades after conceiving the novel concept of delivering intracoronary radiation for the prevention and treatment of restenosis, we are pleased to learn that there were no late adverse effects related to the technology and that the principle of "do no harm" was upheld.

VBT was the first technology proven to be effective in the prevention of restenosis as adjunct therapy to balloon angioplasty and for the treatment of in-stent restenosis (ISR). The technology was based on intervening in the cell cycle in the mitosis phase, which resulted in delayed healing following vessel injury.[1] The effectiveness of VBT was supported by a series of preclinical trials utilising the rabbit and the porcine models of restenosis, which demonstrated robust reduction of neointima formation following balloon or stent injury and minimised late vessel recoil when applied as adjunct to balloon angioplasty.[2-4]

Delivery of radiation in the form of radioisotopes into the coronary arteries was technically challenging. Two major platforms were developed to achieve this goal: radioactive stents using a low activity of P32 source and catheter-based systems using gamma and beta isotopes. Radioactive stents were tested clinically for the treatment of *de novo* lesions and were associated with high rate of edge effect and target lesion revascularisation, and therefore never commercialised.[5] In contrast, catheter-based systems were tested both for *de novo* lesions and for the treatment of ISR.[6,7] The initial clinical trials using VBT for *de novo* lesions had mixed results in regards to efficacy and safety. VBT when used as adjunct therapy to balloon angioplasty alone resulted in lower restenosis rates, but when used in combination with bare metal stents (BMS), restenosis and late thrombosis rates were higher when compared to conventional BMS.[8]

In contrast, when tested clinically for the treatment of ISR, application VBT (both with gamma and beta isotopes) demonstrated superiority when compared to conventional therapy in numerous clinical trials with up to three years' post intervention.[9] These results have led to the global approval of both gamma and beta catheter-based systems with an indication for the treatment of ISR of BMS, and transformed VBT as the gold standard for the treatment of ISR.

Despite being the most effective therapy for the treatment of ISR, the adoption of VBT was slow due to the logistic limitations associated with handling the radioactive isotopes in the catheterisation laboratory and the requirement that the radiation oncologist, physicist, and radiation safety officer are present during the procedure.

In addition, the idea of delivering radiation into the coronary arteries was not well received due to concerns regarding the potential of late adverse radiation effects and the fear of aneurysm formation, late atherosclerosis, etc. The sceptics asked for five years' follow-up and questioned the feasibility and safely aspects of treating patients who failed VBT with conventional modalities.

In this issue of EuroIntervention are three manuscripts detailing the late outcome following radioactive stent implantation in *de novo* lesions and beta brachytherapy for *de novo* and ISR lesions.[10-12]

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A high incidence of major adverse cardiac events and re-intervention was seen during the first year following radioactive stent implantation mainly related to target lesion revascularisation for edge restenosis. However, from year one to year eight, the clinical outcome of radioactive stent patients was similar to the control group, indicating that there are no late adverse effects related to low dose-rate intracoronary radiation therapy delivered with a radioactive stent.[10] For the catheter-based system patients, through 10 years of clinical follow-up, there was a differential in the outcome based on the type of lesion. In *de novo* lesions there was a higher rate of recurrences with VBT compared to the matched-propensity control group, while in ISR lesions there were similar rates of target lesion revascularisation. Importantly, for the entire cohort there was similar event rates after two years and no very late adverse effects related to VBT up to 10 years' follow-up for both *de novo* and ISR lesions, including in those who required repeat revascularisation. This is good news for all the patients and physicians who were involved with VBT.

Short- versus long-term outcome

The study of Cheng et al[11] included 301 patients treated with beta radiation and followed for 10 years. The poolability of the data is in question since it includes patients from nine clinical trials, including compassionate use, who received different radiation doses, some of whom underwent stent implantation found to be harmful and others had geographic miss in positioning the source. We can assume that when the lessons learned from these trials were implemented in clinical practice, physicians avoided the stent and VBT combination, minimised geographic miss, and prescribed the optimal dose, which ultimately improved the overall results of VBT. Therefore, this paper by Cheng et al provides assurance on the absence of radiation-related adverse events at 10 years, but does not compare the short-term results of VBT versus conventional therapy, which were found to be superior in favour of VBT in every randomised clinical trial for the treatment of ISR with a follow-up of six months to three years.

Drug-eluting stents versus vascular brachytherapy

With the introduction and dissemination of drug-eluting stents (DES) for *de novo* lesions, the use of VBT was limited to the treatment of BMS restenosis. However, edge effects, late restenosis in patients treated with VBT, and the logistical issues associated with the technology, led to head-to-head comparisons between DES and VBT for the treatment of BMS ISR. Two pivotal trials, Sirolimus-Eluting Stents Versus Vascular Brachytherapy for In-Stent Restenosis (SISR), which compared sirolimus-eluting stents (SES) to gamma radiation[13] and TAXUS V ISR, which compared paclitaxel-eluting stents (PES) to beta radiation,[14] demonstrated superiority of DES over VBT for the this indication.[13] Wiemer et al,[12] who compared SES with VBT to beta radiation for the treatment of BMS ISR, also demonstrated superiority of SES in terms of quantitative coronary angiography, intravascular ultrasound, and the need for repeat revascularisation at six months and at three years.

There are several limitations concerning these studies. First, it is not adequate to compare late loss post balloon angioplasty, which was performed in the majority of VBT patients, versus late loss in the DES patients, especially when the acute gain obtained with the stent is much higher compared to that obtained with the balloon. Secondly, VBT in combination with BMS was demonstrated to be deleterious and should not be used in head-to-head trials. In the series of Weimer et al[12], 10 % of the patients underwent stent implantation either prior to or post VBT, which could have contributed to the worse results in the VBT group. Further, it is possible that the angiographic follow-up performed in those studies prompted the ocular restenotic effect, which led to a revascularisation rate increase in the VBT group. Nevertheless, the totality of the data supports the current practice of treating BMS ISR with DES. The question remains as to which DES. Previous studies demonstrated differences in efficacy between SES and PES for this indication; no data is available for second-generation DES in the treatment of BMS ISR.

With DES use increasing to nearly 70-90% across practices and the differential selection of DES for patients and lesions at high risk for restenosis, the incidence of BMS ISR is declining and usually responds well to DES treatment. Is there still a role for VBT in the treatment of restenosis in 2011? Small registry data suggests that VBT is still effective and safe for the treatment of DES ISR when compared to repeat DES.[15] But this target population is small and given the other therapeutic alternatives, such as second-generation DES and drug-eluting balloons, the use of VBT may be limited to niche indications as a last resort for patients who failed all other modalities. A few centres in the US currently treating DES failure with VBT for this complex population utilise the Beta-Cath™ system (Novoste Corporation, Norcross, GA, USA) with good results.

Perhaps the major contribution of VBT to the interventional cardiology field was that it identified the pathway by which restenosis can be prevented and treated, and the knowledge learned regarding the consequences of delayed healing, which has led to stent thrombosis and the need for prolonged dual antiplatelet therapy.

In medicine we are experiencing a transformation of treatment strategies, drugs and devices. Old is replaced with new and each technology has its own clinical lifespan. Some drugs and devices may last for decades and some may trigger and facilitate the development of more effective and safer treatment modalities. VBT was a breakthrough in interventional cardiology and played a significant role at a time when there was an unmet need for ISR treatment. The technology was superior to the existing treatment at the time and contributed to the development and understanding of DES technology, which was found to be more efficacious and easier in use. DES technology, the leading technology for prevention of restenosis, has its own drawbacks; and we wait with baited breath for the next breakthrough to overcome the limitations of DES.

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