Intracoronary Radiation

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Abstract

With in-stent restenosis remaining major limitation of coronary stenting and adjunctive pharmacologic therapy and re-stenting having failed to reduce the rates of in-stent restenosis, a new treatment alternative is warranted. Vascular brachytherapy - the intracoronary delivery of radiation has been proposed as one such therapy. Thus far it is an important break-through in combating re-stenosis. To date, 5 years of clinical data has been generated and further studies are underway to perfect the technology.

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Key Words : Coronary artery; Ionising radiation; Re-stenosis

Introduction

Re-narrowing of a coronary artery after dilatation (re-stenosis) is the principal limitation of Percutaneous Transluminal Coronary Angioplasty (PTCA)[1]. Re-stenosis typically affects between 25% to 45% of patients within six months after PTCA, resulting in the need for a repeat interventional procedure. Re-stenosis can be considered as an exaggeration of 'vascular healing' and 'remodelling' - the probability that occurs to some degrees in all cases. Pharmacologic and mechanical adjuvants have made little impact on this refractory problem of post-PTCA re-stenosis. The field of 'Vascular Brachytherapy' is a new treatment alternative. It has shown promising results and is a team work of multiple disciplines. The catheter based procedure is performed by the

interventional cardiologist, dosing is determined by medical physicist and the administration of radiation is performed by the radiation oncologist.

The effects of ionizing radiation on proliferating tissues are well known [2]. The main effect of clinical doses of ionizing radiation is to impair the reproductive integrity of cells, especially in the rapidly proliferating tissues. As a consequence of this DNA damage, the cell dies when it attempts to divide. The effect of radiation on proliferating tissues has been clinically exploited to treat a variety of benign conditions characterized by uncontrolled proliferation, including keloids, heterotopic bone formation etc.

Extensive animal studies and early clinical data have consistently shown that vascular brachytherapy can reduce post-angioplasty neointimal hyperplasia and

Table 1

Trials in intracoronary brachytherapy beta-radiation

Acronym	investigator	Design	Radiation system	Isotope and dose	Remarks
Geneva	Verin	Open label feasibility study in 15 patients after PTCA in de novo lesions	(Schneider) hand loaded 0.014" 29 mm fixed 90 Y source wire centering balloon (segmented) with no perfusion capability	18 Gy to surface of balloon	Although safety and feasibility demonstrated there was no clinical efficacy. Re-stenosis rate of 40%. Subsequent analysis showed that radiation dose to adventitia was lower than desired
BERT	King, Bonan and Serruys	Open label in 23 patients in US arm+ 30 patients in Canadian arm and 30 patients in European BERT trial. No control group	(Novoste) Hydraulic manual delivery of a train of 12 radioactive seeds of 90 Sr/Y (30 mm) in a non-centered 5 Fr catheter (The Betacath System)	12,14,16 Gy to 2 mm from the source	Result of the combined groups show a low re-stenosis rate in the treated segment.
BRIE		European Registry with Novoste system.	The Betacath system	12,14,16 Gy to 2 mm from the source.	27% recurrence rate at 6 months
BETACHATH	Kuntz	Multicentre randomized blinded study in 1100 patients after PTCA and provisional stenting.	The Betacath system	14 and 18 Gy to 2 mm from balloon surface	Enrollment started in Jul 97, 25 participating sites.
PREVENT	Raizner	Multicentre, randomized, blinded study in 72 patients including stented lesions	The Guidant Brachy-therapy system consists of remote controlled after loader, 32P source Wire (0.0014") and spiral centering balloon catheter	16,20 and 24 Gy delivered to a depth of 1 mm from balloon vessel interface	Results from 72 patients low rates of re-stenosis in target lesions (6%) with adjacent segments included

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Table 2

Trials in intracoronary brachytherapy gamma radiation

Acronym investigator	Design	Radiation system	Isotope and dose	Remarks																				
ARREST David Faxon	Randommized trial N=800 (400+400)	Catheter based intracoronary radiotherapy	192 Ir 12 Gy @ 2 mm	Final results pending																				
ARTISTIC Ron Walks-Man, Washington DC, USA	Randomized trial N=290	Angiorad mechanical delivery system of 0.014" fixed wire 30 cm into a mono rail closed end lumen Balloon centering Catheter (3.2 Fr)	192 Ir 12 GY @ 2 mm	26 patients completed major event-3 (Death, MI, TLR, CABG) PTCA to TLR-1 PTCA to NON TLR-1																				
GAMMA-I Martin B Washington DC, USA	Multicentre randomized trial N=252 (126+126)	Post PTCA IVUS guided	192 Ir 8-30 Gy to adventitia	Re-stenosis markedly reduced. Re-stenosis rate shorter lesions (6,10 seeds) 15.2% vs 48.4% longer lesions (14 seeds) 31.1% vs 7.9%																				
GAMMA-II GAMMA Wire Jose A Venezuela	N=125 Prospective registry adjunctive local Gamma radiation	do PTCA + 192 Ir	14 Gy @ 2 mm 192 Ir	Active Low rate of angiographic re-stenosis																				
SCRIPPS Pauls S Teirstein CA	Double blind randomized trial N=55 (26+29)	Catheter based intracoronary radiotherapy+Stenting	192 Ir 8-30 Gy	2 year follow up <table><tr><td>Ir</td><td>Palcebo</td><td>p Value</td><td></td></tr><tr><td>Death</td><td>2</td><td>2</td><td>NS</td></tr><tr><td>MI 1</td><td>2</td><td>NS</td><td></td></tr><tr><td>TLR</td><td>4</td><td>13</td><td>0.01</td></tr><tr><td>Pr endpt</td><td>6</td><td>15</td><td>0.03</td></tr></table>	Ir	Palcebo	p Value		Death	2	2	NS	MI 1	2	NS		TLR	4	13	0.01	Pr endpt	6	15	0.03
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SMARTS Ron Walksman Washington	Randomized Trial N + 180	Balloon centering catheter Mechanical delivery of 0.014' fixed wire	192 Ir 12 Gy @ 2 mm	Active																				
INDIRA AM Nissar Syed Collaboration India and USA	Prospective randomized trial N=48	Catheter based	192 Ir 11 Gy to adventitia	Active																				

reduce the risk of re-stenosis [3]. A large number of different isotopes and treatment devices are currently being evaluated in over 30 clinical trials in North America, Europe and elsewhere as is given in Table 1 & Table 2 using beta & gamma radiation respectively [4].

The radiation system used and the findings of some trials using beta and gamma radiation sources are as under :

BETA Vascular Brachytherapy - Clinical Trials

Beta emitters known for their unique qualities of high energies and low penetration make them attractive for use in trials in vascular brachytherapy involving multiple systems and isotopes [5]. The trials using beta radiation systems are as under :

- RENO (European Registry Novoste Trial) - The largest consecutive registry of patients, initiated in April 1999 and clinical data currently available for 1085 patients out of total 1098 patients from 46 hospitals throughout Europe and Middle East clearly demonstrates high procedural success and low rates of both in hospital events and 6 month major adverse cardiac effect (MACE) [6].
- START and START 40 Trials - Strontium 90/ Yttrium 90 source delivered by Beta-Cath system - a portable system that hydraulically delivers the

radiation to the coronary arteries. Interim results are shown in Table 3 [7]. The findings indicate that treating lesions with longer sources reduces the incidence of restenosis by 51%. Longer source wire reduces the incidence of edge effect and geographical miss.

- BRITE and BETTER Trials - 32P source delivered by the RDX system - a balloon system that incorporates solid 32P into balloon material using a trilayered, sealed source designed to ensure equal dose distribution to the vessel wall. Interim results are shown in Table 4 [7]. The findings indicate that intracoronary radiation with RDX system is safe since very low TVR and MACE rates have been reported.
- PREVENT AND INHIBIT TRIALS - P 32 source delivered by Galileo Intravascular Radiotherapy system which utilizes a P32 source wire delivered through a helical centering balloon that allows side branch and distal perfusion. The two trials, PREVENT (Proliferation Reduction and Vascular Energy Trial) and INHIBIT (Inhibit re-stenosis with beta radiation), initiated to evaluate the use of the Galileo system for the treatment of re-stenosis.

GAMMA Vascular Brachytherapy - Clinical Trials

- SCRIPPS WRIST AND GAMMA Trials - They

Table 3

Patient data from START TRIAL

Released at the 12th Annual Transcatheter Cardiovascular Therapeutics (TCT) meeting and XXIII Congress of European Society of Cardiology

	Control	START 30	START 40
Enrolled patients	232	244	207
Angiographic analysis (Interim)	188	198	137
Source train (Sr 90 wire)		30 mm	40 mm
Dose		16 Gy/20 Gy	16 Gy/20 Gy
6 month follow-up			
TLR	27.9%		11.4%
TVR	28.8%		14.3%
MACE	29.7%		16.5%
2 year follow-up			
TLR	34.9%		22.5%
TVR	37.9%		27%
MACE	39.7%		30%
Restenosis rate (%)			
Stent segment	41%	14%	16%
Total analysis segment	45%	29%	22%

START - 90 Sr treatment of angiographic restenosis

Table 4

Patient data from BRITE and BETTER trials

Released at 12th Annual TCT Meeting XXIII Congress of European Society of Cardiology

	BETTER	BRITE
Number of patients	N=82	N=94
Death	1 (1.39%)	0
MI	1 (1.39%)	1 (1.1%)
TLR	18 (22.5%)	10 (10.6%)
CABG	0	1 (1.1%)
Any MACE	20 (24%)	11 (11.7%)
Re-stenosis	-	8.4%

MI - Myocardial infarction; TLR - Target lesion revascularisation; CABG - Coronary artery bypass graft; MACE - Major adverse cardiac effects; BRITE - Beta radiation trial to reduce in-stent stenosis; BETTER - Beta radiation trial to eliminate restenosis

are all double blinded, randomized trials initiated to evaluate the safety, effectiveness, durability and simplicity of using ¹⁹²Ir gamma irradiation to treat in stent re-stenosis. All the three trials have had favourable results during all points of follow-up and have demonstrated a marked reduction in the rate of re-stenosis as compared with the placebo as seen in Table 5 [7].

- (b) **GAMMA II Trial** - A multicentre registry that compared the effects of a higher dose with the acute and long term outcomes of GAMMA I trial. The prescribed dose was 14 Gy at 2 mm from the source. Comparison is shown in Table 6 [7]. Compared with the GAMMA I trial, the results of GAMMA II suggest that higher the radiation dose, more effective the outcome. To test this theory, enrolment began recently for SCRIPPS IV trial which will use 17 Gy at 2 mm (22% increase in dose from previous

Table 5

Data from SCRIPPS, WRIST & GAMMA I trials

Released at 12th Annual TCT Meeting XXIII Congress of European Society of Cardiology

	SCRIPPS	WRIST	GAMMA I
Number of patients	N=55	N=130	N=252
Dose	8-30 Gy IVUS guided	15 Gy @ 2 mm	8-30 Gy, IVUS guided
Follow-up	3 years	2 years	1 year
TLR (%)	4 (15.4%)	21 (32.3%)	32 (24.4%)
Total MACE	10 (38.5%)	29 (44.6%)	37 (28.2%)

IVUS - Intra vascular ultra sound; TLR - Target lesion revascularisation; MACE - Major adverse cardiac effects; SCRIPPS - Scrips coronary radiation to inhibit proliferation post stenting; WRIST - Washington radiation for in-stent restenosis trial; GAMMA - Multicentre randomized trial of localized radiation therapy to inhibit restenosis after stenting.

Table 6

Comparative results of GAMMA I and II

Released at 12th Annual TCT Meeting XXIII Congress of European Society of Cardiology

	Placebo	GAMMA I	GAMMA II
Number of patients	N=121	N=131	N=125
TLR	44.6%	24.4%	23.2%
MACE	46.3%	28.2%	29.6%
Stent Closure @ 30-270 days	1 (0.8%)	8 (6.1%)	5 (4.0%)

TLR-Target lesion revascularisation; MACE-Major adverse cardiac effects

SCRIPPS studies) in 358 patients at 4 centers. The results indicate that intravascular radiation with Iridium-192 profoundly reduces in-stent re-stenosis with no apparent significant increase in the complications at three years.

Intravascular gamma radiation has also shown to improve in-stent re-stenosis in saphenous-vein bypass graft [7]. The results at 12 months of a randomized study - SVG WRIST [8] with 120 patients (60+60) has shown that the re-stenosis rate in the radiation arm was 70% lower.

Radioisotope Stents

Stents which serve as an internal scaffolding, have lowered the incidence of re-stenosis in short lesions; however, the typical patient with multiple or diffuse lesions still has a significant risk of post-PTCA re-stenosis. Radioisotope Stents (BENESTENT and STENT Trials) have shown statistically significant reduction in angiographic and clinical re-stenosis. It combines the two technologies in one mechanism viz stent to reduce recoil and radiation to reduce intimal hyperplasia. The phase - I, Isostent for Re-stenosis Intervention Study (IRIS), a non-randomised trial with beta particle emitting stent showed promising results and was followed by IRIS - IB which has been designed to test safety of higher activity upto 1.5 micro Ci stents.

Preliminary results have been encouraging and final results will have to be assessed.

The Indian Experience - INDIRA Trial

The incidence of coronary artery disease is increasing in India. Approximately 400,000 angioplasties are performed in USA each year with <1% mortality and initial success rate of 90%. However, re-stenosis occurs in 30 to 40% of these patients.

A prospective randomized trial in India [9]; Intracoronary irradiation in prevention of coronary re-stenosis (INDIRA), in collaboration with the Long Beach Memorial Medical Centre, Long Beach California, USA has been started in four major medical centres i.e. MediCiti Hospital, Care Hospital, Apollo Hospital and Bibi Cancer Centre. Intracoronary irradiation is delivered with Iridium-192 sources following angioplasty and stenting of the stenotic segment. The protocol requires 1100 cGy dose to the adventitia. The study was approved by the Atomic Energy Regulatory Board (AERB) and the trial was started in December 1998 under the supervision of Dr B.C. Bhatt, Director of Radiation Protection, Bhabha Atomic Research Centre (BARC) and member of AERB. The trial is currently progressing with approximately 800 patients already enrolled and the preliminary results as indicated by the angiography have been encouraging. The experience of doing radioactive stent implantation in India is from June 98. The stent used is PS153 (Palmaz-Shatz Stent, the most commonly used stent in different trials). There is an ongoing multicenter trial with P32 stents in India (3 micro Ci) and Dr MJ Gandhi of Bombay is the principal investigator for this trial.

The associated complications of vascular brachytherapy include edge-effect (re-stenosis at the edges of target length which is believed to be due to inadequate coverage with radiation), geographical miss (missing the target length of the vessel while giving radiation) and the most problematic, late thrombosis which appears to be in the 1-3% range. The target volume is always planned greater than the stenotic length and includes the length of the vessel with barotraumas from balloon angioplasty and stent deployment balloons. It is currently recommended to give 5-8 mm margin (both distal and proximal) to the traumatized area of the vessel while planning the target volume. A prolonged antiplatelet therapy (clopidogrel for 6 months) has shown to significantly decrease the late thrombosis.

Other Modalities and Trials

Besides Intracoronary Brachytherapy drug-eluting Stents [10] have entered clinical trials in combating re-stenosis. The preliminary data of RAVEL Trial with

Cypher device (Sirolimus-eluting stent Bx velocity) has shown 95% reduction of 1 year lumen loss due to re-stenosis, as measured by IVUS (Intravascular ultrasound). A second trial SIRIUS, with 1103 patients registered and randomized with 550 cases in the sirolimus arm is under progress. Some other drugs being used are Paclitaxel (ASPECT Trial), Actinomycin - D (ACTION Trial) with results expected in near future.

Intracoronary Sonotherapy is also undergoing clinical trials - Sonotherapy for In-stent Elimination of Neointimal Tissue (SILENT) and Compassionate Use Study [6], after observational and feasibility study conducted in limited number of patients showed that late lumen loss is comparable to conventional approaches in the prevention of re-stenosis.

Conclusion

The technology for Intracoronary Brachytherapy is simple and is currently the most effective treatment for in-stent restenosis. The procedure is safe, providing low environmental exposure to both patient and operator (with proper protection). There is dose dependent effect with higher doses increasing effectiveness and long term outcome. Although the findings confirm the efficacy of this modality, substantially longer follow-up will confirm whether this treatment can be sustained without long term side effects.

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