COMPARISON OF EVEROLIMUS-ELUTING AND SIROLIMUS-ELUTING CORONARY STENTS IN 1 YEAR CLINICAL AND ANGIOGRAPHIC FOLLOW UP: A RETROSPECTIVE COHORT STUDY.

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ABSTRACT

Background:
Everolimus and sirolimus releasing new-generation coronary stents have been shown to reduce the risk of restenosis. However, efficacy and safety between the two types of stents in terms of end points is unclear.
Similar outcomes have been reported in several recent randomized trials comparing everolimus-eluting stent (EES) and sirolimus-eluting stent (SES).

Methods and results:
In this study, a retrospective cohort study was done in the patients who underwent stent implantation using SES or EES. Comparison between SES and EES was done in patients who presented for follow up in our cardiology department over one year after their angioplasty. The study was carried out for evaluating non-inferiority of EES as compared to SES in terms of late ST and ISR requiring TRL. Out of the total 136 patients, 60 had SES implantation and 76 had EES implantation. All of these patients were subjected to coronary angiography after 1 year to look for patency of the stent. In-stent restenosis (outcome) was found in 3 patients in SES group and 4 patients in EES group respectively. All 7 patients who had ISR were suffering from diabetes and hypertension. Association between diabetes & ISR (Chi square= 5.488; p= 0.01; considering 95% CI) and hypertension & ISR (Chi square= 6.756; p= 0.00) is significant. While comparing the two stents: Everolimus-Eluting and Sirolimus-Eluting Coronary Stents with the outcome i.e., in-stent restenosis and target lesion revascularisation (Chi square= 0.005; p= 0.94) with 95% CI, no significant difference between the two stents was found. Hence the null hypothesis, that there is no significant difference between use of Everolimus-Eluting and Sirolimus-Eluting Coronary Stents on clinical and angiographic follow up is accepted.

Conclusions:
At the end of 12 months, everolimus-eluting stent was non-inferior to and had similar results to SES implantation in terms of clinical and angiographic outcome in a population of patients who had minimalexclusion criteria.

Key words: Everolimus. Sirolimus. Stent. Restenosis. Thrombosis.

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INTRODUCTION

As currently used in clinical practice, "drug-eluting" stents (DES) refers to metal stents that elute a drug designed to limit the growth of neointimal scar tissue, thus reducing the likelihood of stent restenosis.[1]Percutaneous coronary revascularization is a mainstay in the management of coronary artery disease.[2] The issue of restenosis has been the focus of intensive research since the introduction of PTCA, and DES have come a long way in inhibiting in-stent neointimal hyperplasia while exploiting the mechanical scaffolding properties of the metallic stent platform. On the other hand, DES are not immune from adverse effects. The most fearsome is stent thrombosis, which if often due to improper stent implantation[3]and/or incomplete endothelialization of stent struts.[4] To minimize this risk, prolonged dual antiplatelet therapy with aspirin and a thienopyridine (either clopidogrel or ticlopidine) is routinely recommended after DES implantation, from a minimum of 2 months (in the RAVEL trial)[5] to a maximum of 12 months as currently enforced by international guidelines.[6]SES was the first-generation DES that had been most widely used and most extensively studied in the past decade.[7] Although SES has substantially reduced restenosis after coronary stent implantation, late adverse events such as very late stent thrombosis (ST) and late target-lesion revascularization (TLR) occurring beyond 1 year emerged as new problems associated with use of SES.[8,9]Everolimus-eluting stent (EES), a second-generation DES, is a cobalt chromium alloy stent releasing a reduced dose of everolimus in comparison with the dose used in SES.[2] Clinical efficacy data of DES are to date quite satisfactory, whereas clinical safety data are promising but yet incomplete as limited only to early and mid-term follow-up (≤12 months).

MATERIAL AND METHODS

Study design

This is a retrospective cohort study. It consists of all cases that underwent PTCA and were implanted with Sirolimus or Everolimus Eluting stents in Dhiraj General Hospital, Vadodara, Gujarat without any exclusion criteria. Comparison between SES and EES was done in patients who presented for follow up in our cardiology department over one year i.e. May 2014 to May 2015 after their PCI. Based on angiographic and clinical outcome in terms of late ST and ISR requiring TRL, outcome variables were set. The study was carried out for evaluating non-inferiority of EES as compared to SES in terms of late ST and ISR requiring TRL. A total of 136 patients who underwent stent implantation using SES or EES one to one and half year back agreed to be part of our study and constituted our cohort. Out of these 136 patients, 60 had SES implantation and 76 had EES implantation. The study protocol was approved by the institutional review board. Written informed consent was obtained from all the study patients.

Study Procedures

EES was available in diameters of 2.50, 2.75, 3.00, and 3.50 mm with each available in lengths of 12, 15, 18, 23 and 28 mm. SES was available in diameters of 2.50, 2.75, 3.00, and 3.50 mm, and in lengths of 13, 16, 19, 24, 29, 32, 37, 40. All of these patients were subjected to coronary angiography after 1 year to look for patency of the stent. Patients were assessed clinically and evaluated at the end of 12 months. They were asked specific questions about the interim development of angina, according to the Canadian Cardiovascular Society classification of stable angina and the Braunwald classification of unstable angina. Coronary angiography was done for all patients who came for

follow up after one year of angioplasty. Baseline, post procedure and 1 year follow up angiograms were assessed in these patients for analysis. The target segment was defined as the entire segment involving the implanted stent and the 5-mm proximal and distal edges adjacent to the stent. A segment treated with multiple overlapping stents was regarded as a single target segment. Information on the technical details for the index PCI procedure was recorded during or immediately after the procedure by the dedicated technicians in the cardiac catheterization laboratory.

Antithrombotic Therapy

Unfractionated heparin was used during the procedure for anticoagulation. The antiplatelet regimen used in our institution was aspirin **(150 mg daily) indefinitely and 75 mg clopidogrel or 10 mg prasugrel once a day for 1 year.**

Quantitative Coronary Angiography

Baseline and postprocedure angiograms were assessed in all patients. Coronary angiography evaluation was done using Cardiovascular Angiography Analysis System – XceleraR3.1L1**.** The entire segment involving the implanted stent and the 5-mm proximal and distal edges adjacent to the stent was defined as the target segment. A segment treated with multiple overlapping stents was regarded as a single target segment. The patients who were enrolled for the study, follow-up angiographieswere performed 365 days after the index PCI procedure.

In-segment late lumen loss was taken as the primary end point for the angiographic substudy. In-stent late loss, percentage of diameter stenosis at follow-up, and binary restenosis was included as the secondary angiographic end points. Diameter stenosis of ≥50% was defined as the binary restenosis.

Statistical Analyses

Continuous variables were expressed as mean value ± SD or median with interquartile range. Data was analysed using statistical variant analysis or SPSS after applying tests like chi square test.Categorical variables were compared with the χ^2 test or Fisher exact test. All statistical analyses were performed by a statistician. All reported probability values were2-sided and probability values of <0.05 were regarded as statistically significant.

RESULTS

Revascularization Procedures and Patient Characteristics

Retrospective cohort study was done in the patients who underwent stent implantation using SES or EES in Dhiraj Hospital, Vadodara. Comparison between SES and EES was done in patients who presented for follow up in our cardiology department over one to one and half years after their index PCI. The analysis was carried out for a total of 136 patients who were enrolled in the trial. Out of these 136 patients, 60 had SES implantation and 76 had EES implantation. All of these patients were subjected to coronary angiography on their follow-up visit i.e., after 1 year to look for patency of the stent. The study population included patients with advanced age, diabetes mellitus, smoking and multivessel coronary artery disease, heart failure, small-vessel disease, chronic total occlusion, and bifurcation lesions. Baseline clinical and lesion characteristics were well balanced in both the groups taken up for study.

Clinical Outcome

Out of these 136 patients in-stent restenosis (outcome) was found in 3 patients in SES group and 4 patients in EES group respectively. The back records at the time of their angioplasty (at time of presentation), around one to one and half year back, were tracked and referred. Certain exposure variables like age, sex, diabetes and hypertension status etc were considered for analysis. Average age of the study population was 58.7 years (SD: 9.2 years, ranging 29-79 years). The study population comprised of 97 males and 39 females, out of them 5 males and 2 females showed signs of ISR. In 57.4% patients gave history of diabetes and 52.2% were suffering from hypertention, while 55.9 of them were chronic smokers. 39.7% of these patients presented on their first visit with MI and while 30.1% presented Unstable and Stable angina each. Mean age of patient with restenosis is 61.8 years and without restenosis is 58.3 years. All 7 patients of restenosis were suffering from diabetes and hypertension. Association between Diabetes & In-stent restenosis (*Chi square= 5.488; p= 0.01; considering 95% CI)* and Hypertension & In-stent restenosis (*Chi square= 6.756; p= 0.00)* is significant. Although 5 out of 7 restenosis patients were chronic smokers, the association is found to be insignificant (*Chi square= 0.723; p= 0.39).* Sirolimus-Eluting Coronary Stents were used in 24 patients with MI, 17 with Stable angina and 19 with Unstable angina whereas Everolimus-Eluting Coronary Stents were used in 30 patients with MI, 24 with Stable angina and 22 with Unstable angina. No significant association between presenting disease (MI and Angina) and outcome (In-stent restenosis) was found; for instance h/o MI and in-stent restenosis (*Chi square= 0.382; p= 0.53),* h/o Stable angina and in-stent restenosis (*Chi square= 0.009; p= 0.92),* h/o Unstable and in-stent restenosis (*Chi square= 0.382; p= 0.53).* Post stent placement patients were either put on Prasugrel or Clopidogrel and that too seem to have no significant association with outcome, restenosis *(Chi square= 0.007; p= 0.93)*

DISCUSSION

The primary clinical end point was met in this study byshowing the noninferiority of the EES, as compared with the SES. The study population has the minimal exclusion criteria. In this study, no significant difference was found between the two stents used. Hence the null hypothesis, that there is no significant difference between use of Everolimus-Eluting and Sirolimus-Eluting Coronary Stents on clinical and angiographic follow up is accepted.A similar efficacy and safety outcome has been suggested in previously reported randomized trials comparing EES with SES.[10-16] The biohazard of late stent thrombosis was recognized by a Food and Drug Administration panel in 2006.[17,18]A broad, unselected patient population, which would be more representative of everyday clinical practice was recommended that future trials should address to. Our study had the minimal exclusion criteria which resulted in enrollement of a large proportion of patients. This lack of stringent exclusion criteria led to enrollement of patients with acute myocardial infarction, multivessel intervention, small-vessel disease, long lesions. These are the types of cases that are encountered in contemporary practice. Thus, the results were consistent across all predefined subgroups.Overall in our study, we observed no significant between-group difference in overall rates of stent thrombosis. Likewise, rates of stent thrombosis were low and similar to those in previous studies involving all comers or patients with acute coronary syndromes.[19-23] In regards to the use of antiplatelet theraphy, no significant difference was observed between the two groups in our study.

A recent observational study was done comparing EES with a historical control group of SES. This study suggested a lower 3-year risk for TVR in the EES group.[24] We could not exclude the possibility of superior antirestenostic efficacy of EES in our study group because of the limited duration of follow up. Future long term follow up is required in such studies to establish a more concrete difference if any between the two groups with a possibility of superior antirestenostic effects of EES. Furthermore, we would like to continue follow up of our study population for a period of 3 years.

CONCLUSION

In conclusion, the new-generation everolimus-eluting stent was found to be as safe and effective as the
sirolimus-eluting stent. EES implantation was non-inferior to and had similar results to SESimplantation after one year in terms of clinical and angiographic outcome. Both the SES and EES groups showed a similarefficacy and excellent outcome after one year with a very low rate of in-stent restenosis, stent thrombosis and target-lesion revascularization.

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