ORIGINAL ARTICLE

CLINICAL EVALUATION OF THE INDIGENOUSLY MANUFACTURED REJUVENATE® BARE METAL STENT SYSTEM IN PAKISTANI PATIENTS WITH CORONARY ARTERY DISEASE

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Objectives: The aim of this pilot study was the first-in-man evaluation of the safety, feasibility, deliverability, and efficiency of the newly developed REJUVENATE® bare metal stent system in coronary artery disease.

Methodology: Current study was a pilot non-randomized, multi-centric and prospective study which was intended to study the safety of the REJUVENATE® bare metal stent in Pakistani population over 10 months. Study endpoints included target vessel related myocardial infarction, stent thrombosis, in-stent restenosis, stroke and death. The diameter of the target lesions selected was between 3-4mm with length no more than 22mm. Only one BMS was implanted per patient. These patients had well defined regular clinical follow-ups and CT scan coronary angiography at the end of 10 months.

Results: 20 patients suffering from coronary artery disease (CAD) including15 male subjects and 5 female subjects were enrolled in this study and were treated with REJUVENATE® BMS. 65% patients were hypertensive, 25% diabetics and 25% were active smokers. Out of the 20 stents implanted, 14 stents were implanted in the right coronary artery and 6 were implanted in the left circumflex artery. During this 10-month study period there was 10.65% of cases in which late lumen loss (lumen stenosis <70%) was observed, however no cases of in stent restenosis and stent thrombosis were observed. There was no target vessel related myocardial infarction or stroke as well. One patient died of pneumonia during the follow up period.

Conclusion: The current study demonstrated the deliverability and clinical safety of REJUVENATE® bare metal stent over a period of 10 months.

Keywords: percutaneous coronary intervention, first in man evaluation, stents, angioplasty, Pakistani population

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INTRODUCTION

Swiss radiologist Andreas Gruentzig changed the history of percutaneous intervention (PCI) by introducing percutaneous transluminal coronary angioplasty in 1977 for the treatment of the coronary artery disease (CAD). Before that, coronary artery bypass surgery was considered the standard procedure.[1]

First BMS was introduced by Ulrich Sigwart in 1986 and first DES was introduced in 2002 in European markets. Historic clinical trials of BMS BENESTENT[2] and STRESS[3] in 1993 proved the superiority of BMS over PTCA.[4] BMS ruled the stent market for two decades because of its lower restenosis rate and reduced elastic recoil as compared to PTCA.[5]

According to an estimation, CVD was the cause of 31% deaths globally (roughly 17.7 million people) in 2015.[6] Three quarters of these deaths were in low to middle income countries. The cost of performing a PCI is variable since a large number of materials and human resources are involved, with the stent cost being a significant factor. In developing countries, the cost of stent technology becomes burdensome for the patient and the health system. Nowadays more and more countries have started their own research and development of novel devices for cardiac diseases in order to reduce cost.

Pakistan is among countries with high incidence of coronary artery disease. According to the latest data published by World Health Organization (WHO) in 2018, the mortality rate because of CAD has reached more than 20% of total deaths in Pakistan.[7] Even at this age of science and technology, Pakistan

is considerably lagging in science and technology investments as compared to the rest of the world. The lack of in-house development of modern technology resulted in expensive and delayed treatments. According to the market analysis of Pakistan, around 40,000 cardiac stents are being implanted in patients annually which are all imported from foreign countries.[8] Low life standards, poverty and unavailability of the resources deprived a major portion (approx. 80%) of the Pakistani CAD patients from the treatment. This hopeless and dire healthcare condition made the government of Pakistan to consider and improve the situation. This is first time in the history of Pakistan that the government has taken an initiative and established a dedicated medical device manufacturing facility named as N-ovative Health Technologies (NHT) at National University of Sciences and Technology (NUST) keeping in view the university's rich research-oriented focus. NHT is a certified production set up from European Commission licensed notified body and Drug Regulatory Authority at Pakistan (DRAP). The design of the stent system and entire production technology was acquired from German stent manufacturing facility. Currently, NHT is producing a variety of cardiovascular devices such as Bare Metal Stents, Angioplasty Balloon Catheters and Drug Eluting Stents.

The REJUVENATE® is cobalt chromium (MP35 NLT) BMS and optimized for cardiac vessels for the treatment of CAD. This stent system has been developed to maintain radio-opacity and radial strength without compromising long-term results. This stent passed all the physico-chemical, biocompatibility and animal testing. The physico-chemical trials were conducted in Germany (Heinze Shade Testing Lab) and animal studies were conducted at the Center for Cardiovascular Research and Development American Heart Poland (CCRD AHP) and REJUVENATE® performed brilliantly in all the trials. This paper reports the results of first clinical experience of REJUVENATE® stent system in Pakistani population.

METHODOLOGY

This study was initiated by N-ovative Health Technologies Pakistan for the investigation of the clinical outcome of REJUVENATE®, a cobalt chromium coronary bare metal stent. This trial was conducted at two leading cardiovascular centers as single-arm prospective study. The target population was native people of Pakistan. Baseline clinical data of patients along with procedural outcomes were obtained from medical records and follow up data was recorded at specific intervals. The study was designed and approved by the Institutional Review Board of Rawalpindi Institute of Cardiology, Rawalpindi and Ethical committee of National Institute of Cardiovascular Diseases, Karachi, Pakistan (NICVD) (Study # RIC/RERC/05/2019). The protocols for the trial were developed by the combined efforts of experts from Emory University, Atlanta, USA and cardiologists of RIC and NICVD in consultation with American Herat Poland and KIWA Turkish notified body (KIWA certification services Inc.). The trial took place at RIC and NICVD, Pakistan, and the entire study was evaluated and analyzed by a cardiologist of Emory University as per ISO-25539 and ISO-14155 standards.

Between July 2019 and August 2020, twenty consecutive patients were enrolled at RIC and NICVD. This study was complied with the rules of the Declaration of Helsinki with regards to investigation in humans. Written informed consent was obtained from the patients before the start of their treatment. The inclusion criteria for study were patients aged ≥18 years with stable ischemic heart disease; able to come for check-up for follow-up period of 10 months; have given informed consent to participate in the trial; suffering from single coronary artery disease with a single coronary lesion; the percentage stenosis > 70% with target lesions less than 22 mm long; reference lumen diameter of the vessel was between 3 and 4 mm and each lesion was covered by a single stent only. Patients with left main disease; having any non-dilatable lesion with conventional balloons or any contraindication to DAPT (dual antiplatelet therapy) were excluded from this study. The patients who had creatinine clearance level less than 45ml / min and moderate to severe calcification were not included in this study. In addition, patients suffering from cardiogenic shock, multivessel CAD, hemodynamic instability, chronic total occlusion, less than 30% left ventricular ejection were also excluded.

The REJUVENATE® coronary stent system is made of MP35 NLT cobalt chromium metallic platform and has strut thickness of 90 µm. It is first ever stent that is indigenously manufactured in Pakistan. The manufacturing company of the REJUVENATE® is NHT at NUST, Islamabad.

This stent is fine mesh like tubular metallic structure which expands with the help of a balloon catheter. It has an open cell design. Upon deployment and balloon expansion, the stent applies

an outward radial force on the luminal surface of the vessel to establish its patency. The catheter has radio-opaque markers which makes it visible under X-ray imaging. The REJUVENATE® stent is available in different lengths 8, 12, 16, 18, 22, 26 and 30mm and different diameters2, 2.5, 3.0, 3.5, and 4.0mm.

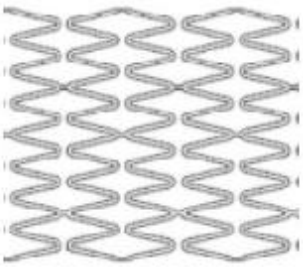

Figure 1: REJUVENATE® stent design

Hemodynamically significant lesions were those lesions which had diameter stenosis more than 50% in the proximal and left main segment of the LAD (left anterior descending) coronary arteries and more than 70% in other segments of the coronary arteries.

Angiographic success was defined as less than 30% residual stenosis after studied device placement in the presence of TIMI flow 3.

Device success was defined as successful delivery and deployment and retraction of REJUVENATE® Stent delivery system.

Procedural success was defined as the satisfactory angiographic outcome without the occurrence of any pre-procedural major adverse cardiac events (MACE). According to the definitions of the ARC (Academic Research Consortium), MACE is defined as an amalgam of cardiac death, MI (myocardial infarction) and clinically indicated TLR (target lesion revascularization). TLR was defined as any repeat PCI of target lesion because of any complication i.e. restenosis, unstable angina.

Target vessel failure (TVF) was defined as the combined endpoint of restenosis and TLR.

Late lumen loss was defined as defined as mean luminal diameter (MLD) at post-procedure minus MLD at follow-up.[8,9]

In-stent restenosis was defined as >70% narrowing down of the coronary artery after the implantation of the stent within the specific time period (10 months) and resulting in angina needing intervention.[10]

Quantitative variables of the study were presented as median ± standard deviation (SD). The categorical variables of the study were presented as numbers and percentages.

RESULTS

Total 20 patients including 15 male subjects and 5 female subjects suffering from CAD were enrolled in this study and were treated with REJUVENATE® BMS. The age of patients ranged from 41 to 71 years. 65% patients were hypertensive, 25% diabetics and 25% were active smokers. Single REJUVENATE® stent was implanted in each patient. All the stents were post dilated with a non-compliant balloon at appropriate pressures. Out of the 20 stents implanted, 14 stents were implanted in the right coronary artery and 6 were implanted in the left circumflex artery. During this 10-month study period there was 10.65% of cases in which late lumen loss (lumen stenosis <70%) was observed, however no cases of in stent restenosis (with minimum of 70% stenosis) and stent thrombosis were observed. There was no target vessel related myocardial infarction or stroke as well. One patient died of pneumonia during the follow up period.

Table 1: Baseline demographics characteristics of patients

Characteristics	Percentage
Patient Details	
Age	>40
Men	75%
Women	25%
Active smokers	25%
Diabetes Mellitus	25%
Hypertension	65%
Hypertension + Diabetes	10%
Target Coronary Artery	
Right coronary artery	70%
Left circumflex	25%
Left anterior descending artery	0%
Obtuse marginal	5%
Clinical Presentation	
Unstable angina	10%
Stable angina	90%
Number of diseased vessels	
Single vessel disease	100%
Number of stents per patient	1

In this study, 20 stents were implanted for the treatment of CAD. The stent diameter was 3.5 - 4.00 mm and stent length was 12 – 22 mm. The average nominal inflation pressure for stent deployment was 12±2 atm. The success rate of stent deployment was 100%. All the stents were post dilated after the insertion of stent. The stents showed good trackability and deliverability. There was no report

of stent migration or distortion. Overall late lumen loss at the end of 10 months was 10.65%.

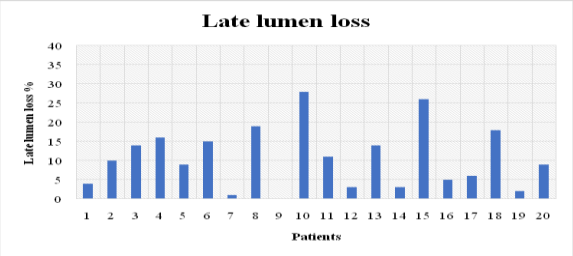

Figure 2: Rate of LLL after 10 months follow up
Patient #9 died because of pneumonia (age 71 years)

The clinical follow-up did not record any event of TLR, TVF and cardiac death for 10 months. Also no ISR (defined as in stent restenosis >70%) was recorded on CT angiography done at 10 months; thus, the patient-oriented and device-oriented MACE rate was 0%. During the 10 months, an elderly patient died (71 years old) because of pneumonia. Remaining 19 patients did not develop any complications and consented to 10 months angiogram re-study. The angiograms of patients are given in figure 2 which exhibit successful stenting after 10 months.

DISCUSSION

Development of bare metal stent was a colossal step in the history of cardiac diseases which was further revolutionized by the introduction of Drug Eluting Stents (DES). Despite the benefits of dramatic decrease in restenosis and superior results by DES, BMS has still occupied some part of stent market. Many studies have reported that results of BMS and DES are comparable in term of increased risk for stent thrombosis[9,11] but the major benefit BMS offers is, firstly, it allows 1 month duration of dual antiplatelet therapy which is 6 to 12 months in the case of DES.[12] The issues of DES made BMS to stay in the market till the date encouraging the stent manufacturing companies to develop better and more efficient BMS.

Pakistan being one of the densely populated countries of the world has been associated with higher rates of cardiovascular diseases, obesity and diabetes. Demographic studies have been conducted to observe the different risk factors, variables, causes and behaviors of CAD on Pakistani population. A local study was conducted at Agha Khan University Hospital to determine the different risk factors of CAD.[10]

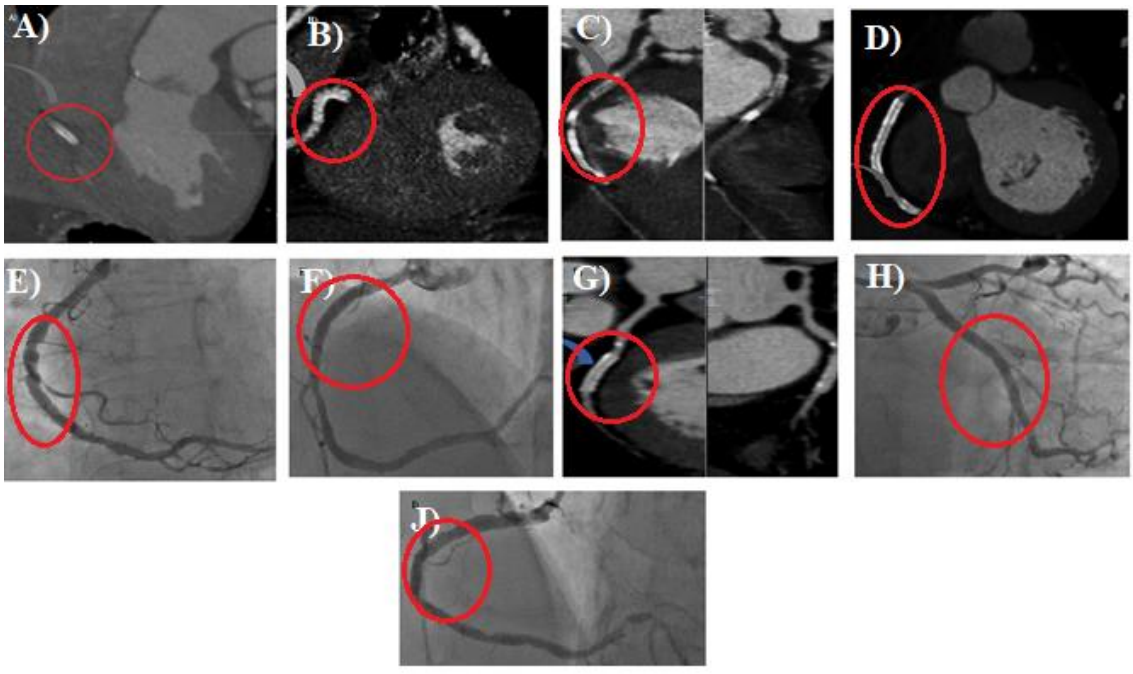

Figure 2A: Angiograms of patient 1 to 10 from RIC (Patient # 9 died (age = 71 y/o) because of pneumonia)

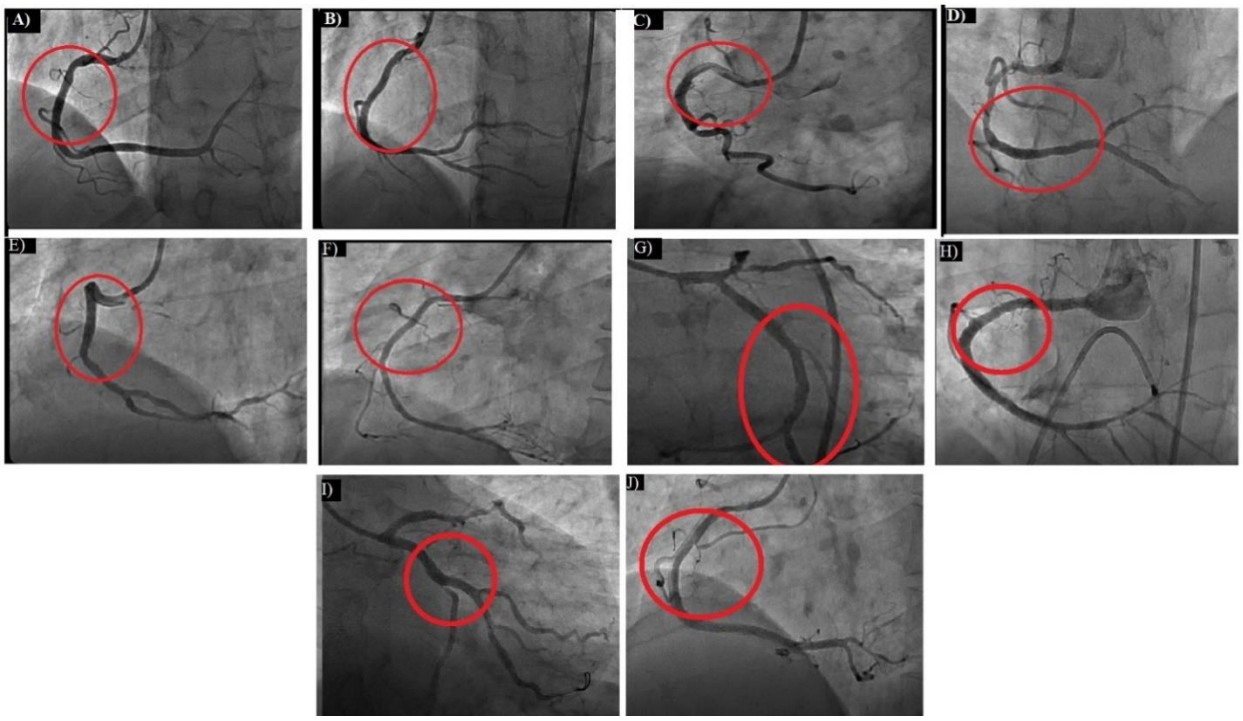

Figure 2B: Angiograms of different patients (Patient # 11 to 20) from NICVD

The effects of different drug eluting stents on Pakistani population were studied in 2002 and results demonstrated 4.6% TLR and 6.8% MACE.[11] Another study was conducted in 2011 to observe the effects of different stent length on 376 patients and results proved that stent diameter and length does not effect the rate clinical outcomes for short period of time.[12] Till date, no study has been reported to study the effects of a specific stent in Pakistani population.

The current study was a first-in-man evaluation of REJUVENATE® stent. The study was a single arm clinical trial similar to the studies done for commercially available stents i.e. SYNERGY [Boston Scientific Corporation, USA,[13] ULTIMASTER [Terumo Corporation, Japan],[14] XIENCE V [Abbott Laboratories, USA][15] and many more. This pilot study required less than 100 patients. The success of this study has led towards the larger scale study which will be done in future.

Initially, BMS were made of stainless steel and had thick struts which increased the risks of the vessel injury, inflammation, and less flexibility. REJUVENATE® is made of cobalt chromium alloy and has thin strut (90 µm). The stent has gone through many lab testing and pre-clinical evaluation, in which it exhibited excellent results which led towards the human trials. In this trial, 20 patients were studied, and results indicated no ISR as compared to other commercially available stents and no event of MACE. The reason might lie in the efficiency of the metal alloy and thinner struts. Another major reason was the inclusion criteria as the stent was used in vessels with mean diameter of >3mm thus stents with diameters (>3mm) were used. It has proven through ISAR STEREO II study that the thin struts give better results in term of restenosis when compared to thick strut stents (17.9% vs. 31.4%).[16] Replacement of 316L stainless steel (SS) with a cobalt-based alloy is advantageous in many aspects. Firstly, CoCr is stronger in term of yield strength (76% stronger) than SS which helps in establishment of thinner struts without decreasing radial strength. The second reason is that CoCr alloy is denser than 316L stainless steel which makes it possible to design a thin-strut stent with radiopacity as good as or even better than a stainless-steel stent. Because of the better properties of metal alloy, effective stent design and better stent surface led the REJUVENATE® towards bare minimum ISR which is huge thing for the success of a stent. Similarly, patient selection (using > 3mm stents) also had a role in the low ISR rates

The results of ISR of REJUVENATE® were lesser than many commercially available stents. In 12 months, follow-up, Multilink Vision and Mini Multilink Vision [Abbott Laboratories, USA] showed 29% and 49% respectively.[14] In KARE study, Kaname™ stent system [Terumo Corporation, Japan] (a cobalt chromium stent) showed 26.1% restenosis rate in small vessels up to 6

months follow up.[17] It is estimated that the rate of restenosis in BMS is between 17% and 41%[18] and REJUVENATE® demonstrated no restenosis due to the reasons cited above. The reason for selecting large caliber coronaries for stenting in the study was the novel nature of the stent and the reason to first test the stent in large caliber vessels.

Hypertension causes high blood pressures which increases the odds of major cardiac events and vessel revascularization.[19] A study was conducted to observe the effects of high blood pressure levels on ISR during PCI. The results indicated that high blood pressure increases the risk of ISR by 24%.[20] Diabetes as a major predictor of stent restenosis, is a conflicting matter. There are many studies which negate the idea that diabetes increases the risk of ISR. However, some studies have proven that diabetes in fact increases the risk of restenosis at the edges of the stents.[21] The efficiency and efficacy of REJUVENATE® can be estimated by the fact that around 80% patients were either diabetic or hypertensive or both and still it performed efficiently; and did not give rise to any major cardiac event. In Driver Registry, there were 68% hypertensive patients and 27% diabetic patients and Driver BMS [Medtronic, U.S.A] exhibited 3.4% of TLR and 5% TVF.[22] REJUVENATE® had similar ratio of hypertensive and diabetic patient (REJUVENATE® = 65% and 25%, Driver = 68% and 27%) but it exhibited 0% TLR and TVF. Like REJUVENATE®, Driver is a cobalt chromium MP35 NLT bare metal stent. The clinical and angiographic outcomes of REJUVENATE® stent deployment is comparable to the outcomes reported from the Driver Registry.

This study was a single arm first-in-man evaluation which was conducted on a small group of patients. For coronary stents, multiple trials are available which were conducted on larger group of patients for longer period of time. REJUVENATE® needs to be studied in randomized trials on larger group of patients, nevertheless, REJUVENATE® proved its efficiency and safety in real world practice. Another limitation of this trial was that the REJUVENATE® was not compared with any other commercially available stents; although data is available in literature and indirect comparisons have been made, there is absence of direct comparison.

CONCLUSION

REJUVENATE® showed favourable 10-month safety for the treatment of the de novo coronary lesions and it can further be studied in larger sample size and diverse population and also in medium to small sized vessels.

AUTHORS' CONTRIBUTION

AMK and SNHR designed and conducted the study, KAN supervised the study and analysed the data, MNA designed, conducted the study and prepared the manuscript for publication; MMA, MM and HA helped in literature review, study design, paper writing and experimentation.

Conflict of interest: Authors declared no conflict of interest.

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