SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY THIRUVANANTHAPURAM – 695011

PROJECT REPORT

Name: Dr. Mukundan.C

Programme: DM Cardiology

Month &Year of Submission: November 2005

Certificate

I, Dr.Mukundan.C, hereby declare that I have undertaken the work necessary for the project, under the guidance of the Faculty, Department of Cardiology.

Signature

Name: Dr.Mukundan.C

Place: Trivandrum

Date: 03/11/2005

Forwarded. He has carried out the minimum required procedures.

Signature

Head Of the Department

LIST OF PROJECTS

1. **Clinical and angiographic comparison of two different types of paclitaxel eluting stents**
2. **Long term follow up of ventricular function and other parameters after trans catheter closure of secundum type of atrial septal defects with ASD device.**

Name: **Dr. Mukundan.C**

Programme: **DM Cardiology**

Month &Year of Submission: **November 2005**

CLINICAL AND ANGIOGRAPHIC COMPARISON OF TWO DIFFERENT TYPES OF PACLITAXEL ELUTING STENTS

ABBREVIATIONS

ACEI	Angiotensin converting enzyme inhibitor
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CAG	Coronary angiogram
CK MB	Creatine kinase MB isoenzyme
GP IIb IIIa	Glycoprotien II B III a
LAD	Left anterior descending artery
LCX	Left circumflex artery
MACE	Major adverse cardiac events
MLD	Minimal luminal diameter
NSTEMI	Non ST elevation Myocardial infarction
NYHA	New York heart association
% DS	Percentage diameter stenosis
PTCA	Percutaneous transluminal coronary angioplasty
QCA	Quantitative coronary angiogram
RCA	Right coronary artery
RVD	Reference vessel diameter
STEMI	ST elevation Myocardial infarction
TLR	Target lesion revascularisation
TMT	Treadmill test

BACKGROUND

The use of stents has significantly improved the outcome of percutaneous coronary intervention. However, despite major advances in angioplasty and stenting, instent restenosis has remained a major limitation until recently. The use of drug eluting stents that deliver site specific controlled release of therapeutic agents has significantly reduced the problem of restenosis inherent to bare metal stents. Since 2000, drug-eluting stents have emerged as a very promising approach in preventing restenosis, and several different compounds have been shown to have a major impact on both angiographic & clinical outcome (1-7).

As compared with a bare metal stent, a polymer encapsulated stent releasing sirolimus reduced the rate of angiographic & clinical restenosis in several randomized trials. Similarly polymer based, paclitaxel eluting stent consistently reduced the rate of extension & the need for repeated revascularization procedures as compared with bare metal stents (6,8-11). A recent metaanalysis of drug eluting stents confirmed that sirolimus & paclitaxel eluting stents reduced the rate of restenosis (12). The rates of death & MI were similar to those with bare metal stents, attesting to safety of these devices. Different trials recently published, have shown conflicting

results in comparing sirolimus & paclitaxel eluting stents (13-17).

In a recent metaanalysis by Adnan et al comparing sirolimus & paclitaxel stents showed significantly lower risk of restenosis & target vessel revascularisation for sirolimus eluting stents compared with those receiving paclitaxel eluting stents (12). Rate of death, death or MI and stent thrombosis were similar. The paclitaxel eluting stents compared with in these trials were of TAXUS stents (Boston Scientific), which is coated on stainless steel stents with a non-biodegradable polymer as drug delivery vehicles.

Another type of paclitaxel eluting stent INFINNIUM (sahejanand medicals) uses biodegradable polymer as the drug eluting vehicle. In two studies published recently this stent has shown comparable MACE, target lesion revascularisation and death as the other drug eluting stents (18-19). But to date no trial has compared the two different types of paclitaxel eluting stents. This study compares the safety of efficiency of the two different types of paclitaxel eluting stents.

AIM OF THE STUDY

Aim of the study in to assess safety & efficacy two different types of paclitaxel drug eluting stents in a prospective single center non randomized matched case control clinical study.

MATERIALS AND METHODS

Patient population

Between April 2003 & July 2004 more than 122 patients underwent implantation of drug eluting stents. These patients were prospectively followed up for a period of nine months from stent implantation.

Inclusion criteria

1. Patients between 18-85 yrs.
2. Angina pectoris
   - ✓ CCS Class I, II, III, IV (stable)
   - ✓ Braunwalds class A, B&C I, II, III (Unstable)
   - ✓ Documented silent ischemia.
3. Target vessel diameter of lesions between 2.5 to 4mm.
4. Lesion length >10mm
5. Target lesion extension for both lesion >50%
6. At least TIMI I coronary blood flow for both lesions.
7. Number of lesions >/=1

Exclusion criteria

1. Acute MI with in 1 week.
2. Ostial lesions
3. Unprotected left main disease
4. Documented LVEF </= 25%; cardiogenic shock.
5. Totally occluded vessel (TIMI 0 or I)
6. In stent restenosis.
7. Allergy to antiplatelet drugs, heparin, stainless steel, contrast agents, or paclitaxel.
8. Terminal illness

The stent designs

The Taxus stent is the NIR stent (made of 316 L surgical grade stainless steel) coated with paclitaxel [1μg/mm2 paclitaxel per unit of stent surface area] in a slow release formulation of a proprietary polymer (hydrocarbon based elastomer). The TAXUS stent uses Translute™ Polymer, a proprietary polymer carrier technology (non-biodegradable coating), to control the drug release. The stents were available in lengths ranging from 8 mm to 32 mm

and diameter ranging from 2.5 to 3.5mm.

The Infinnium stent has paclitaxel coating over millennium stent (made of surgical grade stainless steel slotted tube design) with a biodegradable coating. The dose of the drug in Infinnium was 18μgm over 16mm with 3μgm/mm^2. The drug release was >90% completed within first 11 days. There are four different layers of the polymer in Infinnium stents. The stents were available in lengths ranging from 11 mm to 33 mm and diameter ranging from 2.5 to 4.0mm.

Procedural details

The procedure was performed via right femoral artery through 7F sheath. Revascularisation was done in same sitting on angiogram or in another sitting.

All the patients received 150mg of aspirin daily before the procedure, 75mg clopidogrel >36 hrs before the procedure, with an initial 300mg loading dose of clopidogrel. Those patients receiving Infinnium stents received 300mg day of aspirin from day 1 to day 3 followed by 150mg daily aspirin indefinitely and 150mg twice daily dose of clopidogrel for 3 days from day 1 to day 3 followed by 75mg twice daily of clopidogrel till the end of one month. All patients receiving Taxus stents received 150mg aspirin daily and

75mg clopidogrel daily till the end of follow up. All patients received unfractionated heparin in 70 to 100 units per kg body weight to keep an ACT between 300-350. GPIIbIIIa antagonists were used at operator's discretion.

Creatinine kinase and the CK MB isoenzyme were measured immediately after the procedure and eighth hourly for three times and twelve lead ECG were obtained after the procedure and serially till discharge.

All interventions are performed according to current standard procedures, routine balloon inflation angiographic success was defined as residual stenosis less than 30% by quantitative coronary angiography or by visual analysis in the presence of TIMI grade 3 flow.

Clinical follow up was obtained at 2 weeks, 1 month, 3 months and nine months. Information was collected on vital status, occurrence of myocardial infraction, clinical angina status and current medication. The follow up coronary angiogram was obtained at 9 months or more if consent for angiogram was given by the patient.

STUDY END POINTS AND DEFINITIONS

Primary end point

The prespecified primary end point was a composite of major adverse cardiac events (MACE) i.e., death from cardiac causes myocardial infraction and Ischemia driven revascularization of target lesion by nine months.

Secondary end points

1. Occurrence of stent thrombosis
2. In stent & in segment late loss in internal luminal diameter by quantitative coronary angiography (QCA) at 9 months post procedure.
3. Instent and insegment angiographic binary restenosis of >/=50%stenosis by QCA at 9 months post procedure

Definitions

Target vessel revascularisation was considered to be driven by ischemia if the stenosis of the target vessel was at least 50% of luminal diameter on the basis of a quantitative analysis with either electrocardiographic changes while the patient was at rest or a functional study indicating ischemia in the distribution of the target

vessel or if there was stenosis of at least 70% conjunction with recurrent symptoms alone. Target vessel revascularisation was defined as repeated revascularisation for ischemia owing to stenosis of at least 50% of luminal diameter anywhere with in the stent or with in the 5mm borders proximal or distal to stent.

Angiographic stent thrombosis was defined as angiographically documented complete occlusion. (Thrombolysis in Myocardial infarction grade O or 1 flow) or a flow limiting thrombus (thrombolysis in myocardial infarction grade 1 or 2 flow) in a previously successfully stented artery or in the absence of angiographic confirmation, acute MI in the distribution of the of the target vessel. The diagnosis of myocardial infraction was based on the presence of new Q waves lasting at least 0.04 sec in at least two contiguous leads and an elevated creatine kinase MB fraction. In the absence of pathologic Q waves, the diagnosis of myocardial infarction was based on as increase in the creative kinase level to more than twice the upper limit of the normal range with an elevated level of creatine kinase MB or Troponin T.

Quantitative coronary angiographic examination was done in multiple views. Quantitative coronary angiographic end points included binary restenosis, defined as >50% diameter stenosis, the reference vessel diameter (RVD), minimum lumen diameter (MLD),

percent diameter stenosis (%DS) and late lumen loss. Late lumen loss was measured as the difference between post intervention MLD and MLD at follow up. RVD, MLD and %DS were measured before the procedure, after the procedure, & at follow up.

The principal secondary end point of the angiographic sub study was late luminal loss with in the stent as well as with in 5mm margins proximal and distal to the stent (insegment). Other angiographic endpoints were late luminal loss with in the stent (in stent) and in segment stenosis and in stent and in segment binary re stenosis.

Angiographic analysis

Procedural and follow up angiograms were reviewed by an independent observer and quantitative angiographic analysis were performed for standard qualitative and quantitative characteristics such an luminal dimensions, including proximal & distal reference diameters and the minimal luminal diameter before and after the procedure and at follow up. Angiograms were evaluated quantitatively for morphological features of the lesion, flow grade, dissection grade, side branches larger than 2mm.

Statistical analysis

Continuous variables are presented as mean (SD) and were compared by students unpaired t test. Categorical variables are presented as counts and percentages and compared by Fishers exact test. All statistical tests were two tailed. The cumulative incidence of adverse events was estimated by Kaplan Meier method. Results were expressed on mean +/- standard deviations. Analysis done by using independent t test for comparing continuous variables and paired samples of t test for comparison between groups. Discrete variables were compared using chi square test. Correlative analysis was performed between variables in paired groups using Spearman's and Pearson co-efficient. A p-value of <0.05 was considered statistically significant.

RESULTS

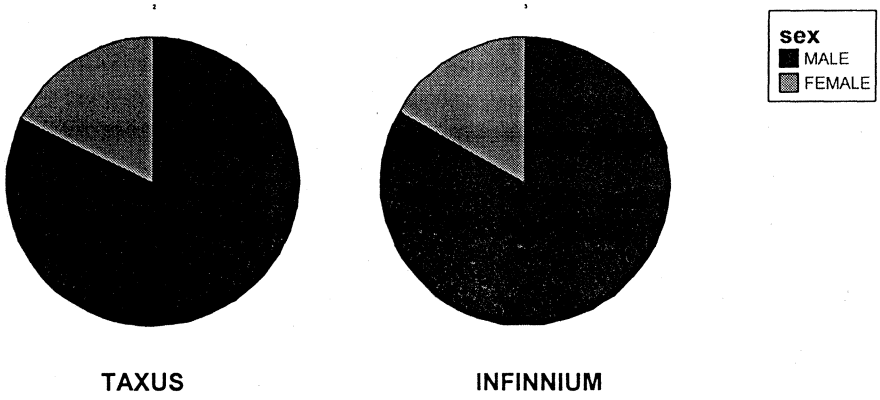
Between April 2003 and September 2004, 118 patients who have received Taxus or Infinnium stents were enrolled into the study who received 121 stents for 121 lesions. All the lesions were of native coronary arteries. 60 patients received 62 Taxus stents and 58 patients received 59 Infinnium stents.

Age

Mean age of the patients in the study was 57.1+/-9.4 years and 56.7+/-6.67 years in the two groups respectively.

Gender

The study group included women 10 (17.7%) and men 51(82.3%) in Taxus group and women 10(16.9%) and men 49(83.1%) in Infinnium group.



Clinical features

20 patients in Taxus group and 26 patients Infinnium group had chronic stable angina. 2 patients in Taxus group of 2 patients of Infinnium group had severe chronic stable angina of NYHA class III. 15 patients in Taxus group and 19 patients in Infinnium group had unstable angina. 6 patients in each group had tropT positive unstable angina. 17 patients in Taxus group and 10 patients in Infinnium group had MI within 7-30 days of the stenting and 16 patients in Taxus group and 18 patients in Infinnium group had MI more than 30 days prior to stenting. 24 patients in Taxus group and 27 patients in Infinnium group had positive TMT prior to the procedure. 18 patients in Taxus group and 16 patients in Infinnium group had anterior wall MI. 9 patients in Taxus group and 4 patients in Infinnium group had IW and RV MI. The infarct related artery was stented in 32 patients in Taxus and 21 patients in Infinnium. One patient in Taxus group and 2 patients in Infinnium group had previous CABG/PTCA.

CAD Risk factors

28 patients [45.2%] in Taxus group and 20 patients [33.9%] in Infinnium group were diabetics (P value 0.265) of which 2 patients in Taxus group required insulin.28 patients [45.2%] in

Taxus groups and 36 patients (61%) in Infinnium group were current smokers (P value 0.102). 28 patients [45.2%] in Taxus groups and 21 patients [45.8%] in Infinnium group were having hypertension [P value 1.000]. 21 patients Taxus groups and 19 patients in Infinnium groups had family history of CAD [P value 1.000].

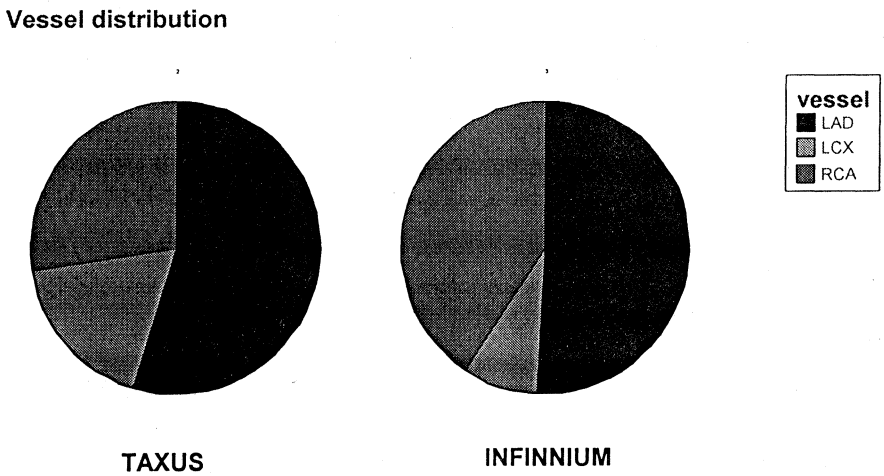
Treatment before the procedure

60 patients [96.8%] in Taxus groups and 59 [100%] patients in Infinnium group had received beta-blockers (P value 0.496). Two [3.2%] patients in Taxus group and none in Infinnium group received calcium channel blockers. 14 patients (22.6%) in Taxus group and 12 patients (20.3%) in Infinnium group received ACEI. All the patients in both groups received statins, aspirin and clopidogrel. All the patients in Infinnium and 6 patients (9.7%) in Taxus group received high dose clopidogrel. All the patients received clopidogrel more than 36 hours before the procedure.

Procedural characteristics

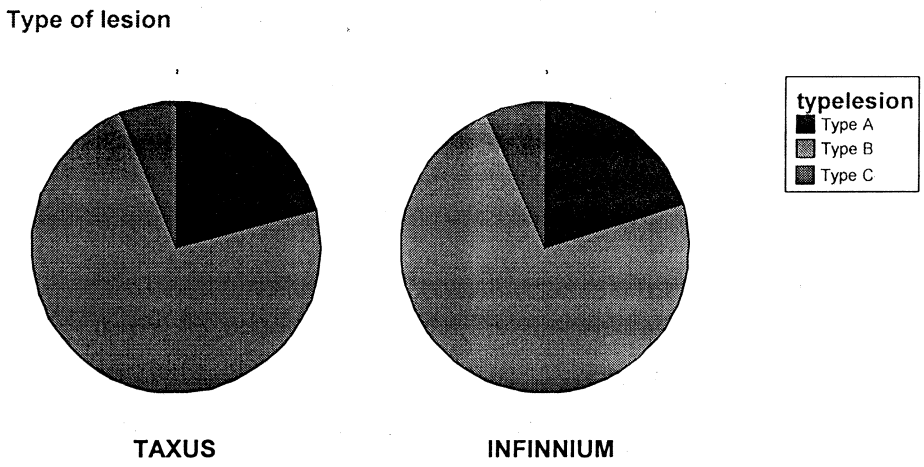
All patients received unfractionated heparin during the procedure. 2 patients (3.2%) in Taxus group and 3 patients (5.1%) in Infinnium group had received GP II b IIIa inhibitors during the procedure (P value 0.674). All patients underwent the procedure

through right femoral artery access through 7F sheath. 10 patients (16.1%) in Taxus group and 10 patients in Infinnium group (16.9%) had either 2 vessel disease or 3 vessel disease (p value-0.54). 52 patients (83.1%) in Taxus group and 49 patients (83.1%) in Infinnium group had single vessel disease (P value 1.000). 34 patients 50.8% in Taxus group and 34 patients (50.8%) in Infinnium group had stent to LAD, 11patients (17.7%) in Taxus group and 5 patients (8.5%) in Infinnium groups had stent to LCX and 17 patients (27.4%) in Taxus group and 24 patients (40.7%) in Infinnium group had stent to RCA.



45 patients (72.6%) in Taxus group and 43 patients (72.9%) in Infinnium group had type B lesion. 13 patients (21%) in Taxus group and 12patients and 4 patients in Infinnium group had type A

and type C lesion respectively (P value 0.994).



7 patients (11.3%) in Taxus group and 3 patients (5.1%) in Infinnium group had thrombosis seen in the angiogram at the site of lesion. 2 patients (3.2%) in Taxus group and 2 patients (3.4%) in Infinnium group had calcific lesion. The mean length of lesion was 13.9 +/- 3.73 in Taxus group and 13.1 +/- 2.94 in Infinnium group (P value 0.184). Mean diameter of the vessel was 3.083 +/- 2.202 in Taxus groups and 2.74 +/- 1.253 in Infinnium group (P value 0.238). Mean percentage of stenosis was 89.7 +/- 5.38 in Taxus group and 87.32+/- 7.25 in Infinnium (p value 0.141). The mean balloon length was 16.96 +/- 4.05 and 15.68 +/- 2.59 in Taxus and Infinnium groups respectively. The sizes of the balloon used were 2.508 +/- 0.207 and 2.466 +/- 0.127 respectively in the two groups. The mean stent length was 19.79 +/- 4.79 and 19.47 +/- 4.38 in

Taxus and Infinnium group respectively (P value 0.706). Mean stent size was 2.903 +/- 0.269 and 2.890 +/- 0.302 in the two groups (P=0.797). Small stents defined as stent size of less than or equal to 2.75 mm was used in 26 patients (41.9%) in Taxus group and 26 patients (44.1%) in Infinnium group (P value 0.856). Stents were inflated at pressures >/= 12 atmospheres (bars) in 55 patients (88.7%) in Taxus group and 46 patients (78%) in Infinnium group. (P value 0.144). No patients had local complications.

VARIABLE	TAXUS	INFINNIUM	P VALUE
Age	57.1+/-9.4	56.7+/-6.67	0.856
Male	51(82.39)	49(83.1%)	0.908
Diabetes under treatment	28(45.2)	20(33.9%)	0.266
Diabetes requiring insulin	2(7.7%)	0	0.256
Current smoker	28(45.2%)	30(61%)	0.08
Hypertension	28(45.2%)	27(45.8%)	0.547
Previous PCI/CABG	1(1.6%)	2(3.4%)	0.530
Prior MI	33(52.8%)	24(40.8%)	0.107
Chronic stable angina	20(32%)	26(44.2%)	0.181
UA	20(32%)	18(32.3%)	0.836
Single vessel disease	52(83.9%)	49(83.1%)	0.926
Double vessel disease	10(16.1%)	9(15.3%)	0.82
Three vessel disease	1(1.6%)	0	0.512
LAD	34(54.8%)	30(50.8%)	0.66
LCX	11(17.7%)	5(8.5%)	0.133
RCA	17(27.4)	24(40.7)	0.124
GPIIbIIIa use	2(3.3%)	3(5.1%)	0.608
Type A lesion	13(21%)	12(20.3%)	0.994
Type B lesion	45(72.6%)	43(72.9%)	0.994
Type C lesion	4(6.5%)	4(6.8%)	0.917
Mean RD pre	2.82+/-0.26	2.82+/-0.24	0.97
Mean stent length	19.79+/-4.79	19.47+/-4.38	0.706
Mean stent diameter	2.9+/-0.269	2.88+/-0.3	0.797

Follow up parameters

4 patients (6.5%) in Taxus group and 6 patients (10.2%) Infinnium group had NYHA 2 Angina on follow up (P value =NS). 61 patients (98.4%) in Taxus group and 58 patients (98.3%) in Infinnium group had received beta blockers on follow up (P=0.74). 48 patients in Taxus group and 44 patients in Infinnium group had underwent TMT. 8 patients in each groups had positive TMT (P value 0.137) at 8.85 +/- 2.27 mets in Taxus groups and 9 +/- 2.34 mets in Infinnium group (P value 0.797). There was no in hospital deaths in both the groups. One patient (1.7%) in Infinnium group had in hospital ST elevation MI and none in Taxus group had the same (p value 0.488).One patient in Infinnium group had in hospital target vessel revascularisation as opposed to none in Taxus group.(P value 0.488).In hospital stent thrombosis was seen in same patient on angiogram. Thus total in hospital complications occurred in one patient in Infinnium group and did not occur in any patients in Taxus group.

28 patients in Taxus group & 33 patients in Infinnium group had undergone Re CAG. (P value 0.156). Re CAG was done at 10.1 +/- 3.56 month in Taxus group and 9.9 +/- 3.5 months in Infinnium group (P value 0.142). 2 patients (3.2%) were hospitalized against for reasons other than Re CAG. 8 patients (13.6%) in Infinnium

group got hospitalized again for reasons other than Re CAG.

There was no out of hospital mortality in both the groups. Comparing Taxus and Infinnium groups there was significant difference in the event of myocardial infraction with four patients in Infinnium groups (6.8%) developing myocardial infraction compared to none in Taxus group (P value 0.037). There was trend towards significance in the event of ST elevation MI out of hospital. 3 patients in Infinnium group (5.1%) developing ST elevation MI compared to none in Taxus group. (p-0.072). There was no significant difference in non-ST elevation MI. (one patient in Infinnium group (1.7%) Vs none in Taxus group). There was trend towards significance in post discharge stent thrombosis, 3 patients [5.1%] developing stent thrombosis in Infinnium group Vs none in Taxus group. (P=0.072). There was no significant difference in post discharge CABG with one patient in each group undergoing the same. There was trend towards significance in post discharge re PTCA with three patients (5.1%) in Infinnium group as opposed to none in Taxus group (0.072). There was no significance difference in target lesion revascularisation after discharge with one patient in Taxus group (1.6%) and 4 patients in Infinnium group (6.8%) undergoing the same (P value-0.153). Thus in comparing post discharge total major acute coronary events, there

was significant difference between the 2 groups [1patient (1.6%)in Taxus group Vs 6 pts (10.2%) in Infinnium group] (P=0.044).

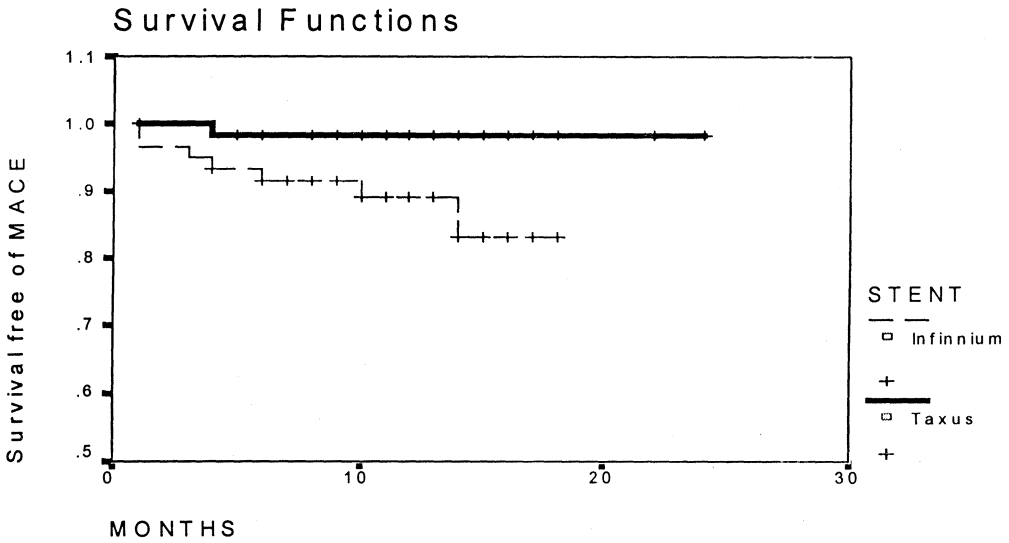
Thus comparing the cumulative events there was no death in either group either in hospital or out of hospital. There was significant difference in the incidence of cumulative myocardial infarction [5 patients (8.5%) in Infinnium Vs none in Taxus](p value-0.019), Cumulative ST elevation MI [4 patients (6.8%) in Infinnium Vs none in Taxus] (p value-0.037), cumulative stent thrombosis [4 patients (6.8%) in Infinnium Vs none in Taxus] (p value-0.037) and cumulative PTCA [4 patients (6.8%) Vs none in Taxus] (p value-0.037) between the two groups. There was a trend towards significance in comparing the incidence of cumulative target vessel revascularisation 1 patient (1.6%) in Taxus group and 5 patients (8.5%) in Infinnium group undergoing the same (P value 0.08). There was no significant difference in NSTEMI (P value=0.303) and in incidence of cumulative CABG (P value= 0.972).In comparing Taxus & Infinnium groups there was significant difference in cumulative MACE. 1 patient [1.6%] in Taxus group Vs 7 patients [11.9%] in Infinnium groups [P value 0.023]

Table 2: Major Adverse Cardiac Events

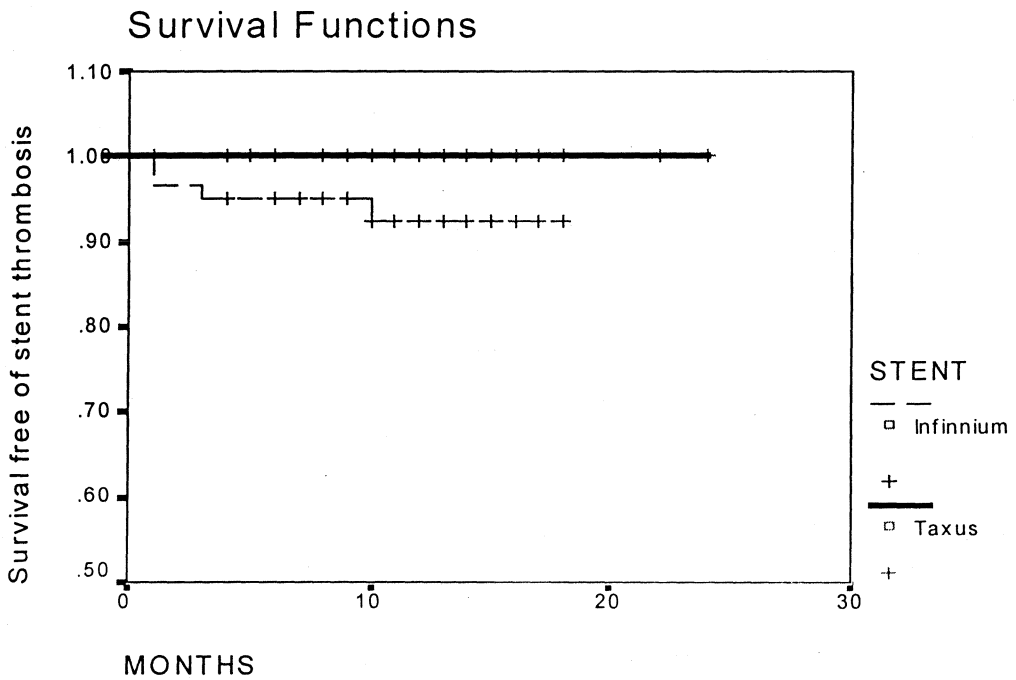
	TAXUS	INFINNIUM	P value
IN HOSPITAL			
Death	0	0	-
MI	0	1(1.7%)	-
STEMI	0	1(1.7%)	0.488
NSTEMI	0	0	-
Stent thrombosis	0	1(1.7%)	0.488
TLR	0	1(1.7%)	0.488
PTCA	0	1(1.7%)	0.488
CABG	0	0	-
TOTAL	0	1(1.7%)	0.488
OUT OF HOSPITAL			
Death	0	0	-
MI	0	4(6.8%)	0.037
STEMI	0	3(5.1%)	0.072
NSTEMI	0	1(1.7%)	0.303
Stent thrombosis	0	3(5.1%)	0.072
TLR	1(1.6%)	4(6.8%)	0.153
PTCA	0	3(5.1%)	0.072
CABG	1(1.6%)	1(1.7%)	0.972
TOTAL	1(1.6%)	6(10.2%)	0.044
CUMULATIVE			
Death	0	0	-
MI	0	5(8.5%)	<0.02
STEMI	0	4(6.8%)	<0.04
NSTEMI	0	1(1.7%)	0.303
Stent thrombosis	0	4(6.8%)	<0.04
TLR	1(1.6%)	5(8.5%)	0.082
PTCA	0	4(6.8%)	<0.04
CABG	1(1.6%)	1(1.7%)	0.972
TOTAL	1(1.6%)	7(11.9%)	0.02

There was no significant difference in angiographic sub study binary restenosis between the two groups [1 patient (3.6%) in Taxus group Vs 5 pts (15.6%) in Infinnium group] (P value 0.131).

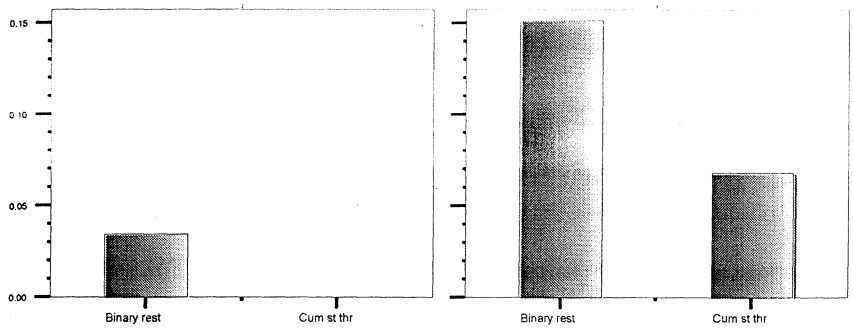
Kaplan-Meier cumulative-event curves for the primary end point of cardiac death, myocardial infarction and Ischemia driven target vessel revascularization



Kaplan-Meier cumulative-event curves for cumulative stent thrombosis



Binary restenosis and cumulative stent thrombosis in the two groups

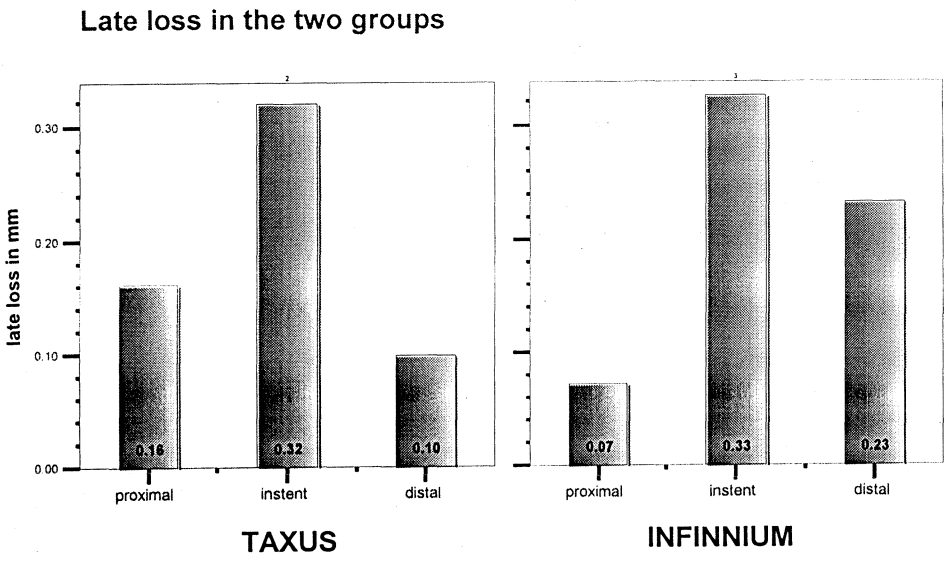


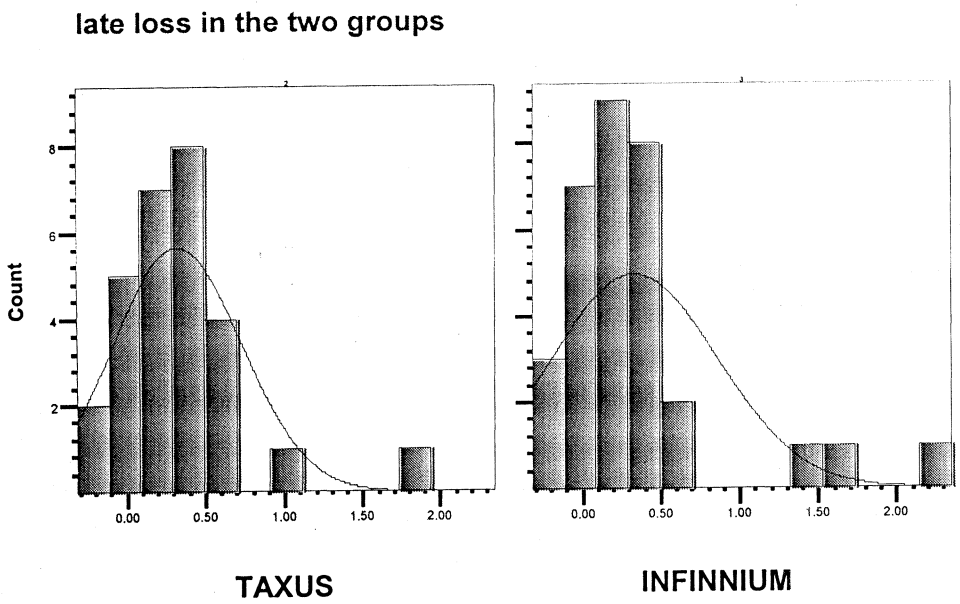
There was no significant difference in the pre reference vessel diameter [RD], minimum luminal diameter [MLD], immediate post stent RD, MLD and MLD on follow up between the two groups (See table 3).

Table 3: Angiographic characteristics

	TAXUS	INFINNIUM	p VALUE
Before procedure			
Reference diameter	2.83+/-0.26	2.082+/-0.25	0.972
MLD	0.73+/-0.30	0.78+/-0.26	0.436
After procedure			
IN STENT			
Immediate MLD	2.6+/-0.29	2.7+/-0.29	0.673
Follow up MLD	2.34+/-0.47	2.3+/-0.60	0.833
Late loss	0.32+/-0.41	0.32+/-0.53	0.957
PROXIMAL			
Immediate MLD	2.48+/-0.28	2.83+/-0.35	0.851
Follow up MLD	2.68+/-0.38	2.75+/-0.39	0.473
Late loss	0.16+/-0.24	0.07+/-0.26	0.171
DISTAL			
Immediate MLD	2.6+/-0.26	2.66+/-0.35	0.484
Follow up MLD	2.5+/-0.35	2.4+/-0.57	0.514
Late loss	0.11+/-0.29	0.23+/-0.45	0.189
IN SEGMENT			
Immediate MLD	2.6+/-0.26	2.6+/-0.34	0.832
Follow up MLD	2.3+/-0.47	2.3+/-0.10	0.833
Late loss	0.3+/-0.22	0.3+/-0.16	0.852
Binary restenosis	1(3.6%)	5(15.6%)	0.121

There was no significant difference in the late loss i.e. in stent region or in segment region both proximal and distal.





DISCUSSION

Drug eluting stents have changed the course of coronary artery disease by reducing restenosis rates to minimum (1-5). Predominantly 2 types of drugs have been used, Sirolimus and Paclitaxel as the drugs coating the stents and several studies have confirmed low restenosis rates & safety of drug eluting stents. Two types of drug eluting stents have been compared in different clinical trials and in the recent meta analysis of the comparison between Sirolimus & paclitaxel stents it was shown that sirolimus stents (Cypher) had significantly lower risk of restenosis & target vessel revascularisation compared with those receiving paclitaxel eluting stents (12). The rates of death, MI & stent thrombosis were similar in the two groups. A different type of paclitaxel eluting stent Infinnium with a biodegradable polymer coating has been shown in different trails to have low restenosis rate comparable to other drug eluting stents (18-19).

The present study, compares two different Paclitaxel eluting stents differing in stent design, polymer coating etc. This study is the first of its kind in comparing two Paclitaxel eluting stents.

The main findings from the study was a significant increase incidence of myocardial infraction especially STEMI and stent

thrombosis in patients treated with Infinnium stents. There was significant difference in target vessel revascularisation by repeat PTCA more in Infinnium stent group thus producing a higher cumulative MACE (the primary end point). There was no significant difference between the two groups in the parameters of binary restenosis and late luminal loss. The minimal lumen diameter in the two groups were similar in angiographic sub study on follow up.

Incidence of MI

Incidence of MI in this study showed that in the Taxus group it was less than earlier reported trials of 2.6 to 3.5% (10). In this trial no patient in Taxus group had myocardial infarction where as in the Infinnium group this was much higher (8.5%). In a previous trial comparing Sirolimus & Paclitaxel stents The SIRTAX trial Stephan Windecker et al (13) found that acute myocardial infarction incidence was similar between two stent groups (2.4 Vs 2.6%, P value 0.86). In another trial TAXI trial by Goy et al (15) the incidence of MI was similar between paclitaxel & sirolimus stents (3% Vs 2%, P value 0.6). In another randomized control trial Adnan Kastarati et al (ISARDESIRE trial) (16) found that cumulative myocardial infraction was similar between the two groups (1% Vs 2%, P value >0.5). In an earlier trial of Infinnium stents, Gambhir

DS et al (18) six months follow up of Infinnium stents showed an incidence of MI of 1.06% and 1.42% at twelve months (19). In a study from Iran, Ostovan MA et al (20) found a myocardial infarction incidence of 3.92%. In this study the myocardial infraction was found to be more than previous trials in Infinnium group. To our knowledge there is no prior study comparing incidence of MI between Taxus and Infinnium stents.

Stent thrombosis

In this study incidence of stent thrombosis was found to be significantly higher in Infinnium groups [6.8% in Infinnium Vs none in Taxus group]. In earlier trial (Sirtax trial) comparing paclitaxel and sirolimus stents, incidence of stent thrombosis was 1.6% & 2% respectively in the two groups and was not different between the two groups (13). In TAXI trial, no increase in incidence of stent thrombosis in either of the groups (15). In a meta analysis of six trials comparing paclitaxel & sirolimus eluting stents, they found that no definite conclusion could be made on the issue of stent thrombosis between paclitaxel & sirolimus stents (12). In REALITY trial there was a trend towards higher incidence of stent thrombosis in patients with paclitaxel stent implantation. Another trial by Lacovou et al also found a higher incidence of stent thrombosis with paclitaxel eluting stents. Incidence of acute

stent thrombosis was 2.1% in simple 1 trial (18). In a trial from Iran Ostovan et al found 3.92% incidence of stent thrombosis (20). In our study one patient had stent thrombosis at nine month of implantation and one patient had stent thrombosis after 6 hrs of the procedure. The other two had stent thrombosis between first to 30th day. In a trial by Andrew et al the incidence of late stent thrombosis defined as stent thrombosis occurring after 1 month of stent implantation was found to be 0.35% and it occurred in 7 patients out of 2006 patients (21). In a meta analysis by Raul Moreno et al (22) no increase in stent thrombosis after drug eluting stents were found under appropriate antiplatelet therapy (0.54 % Vs 0.58 % for bare metal stents and drug eluting stents). They also found higher stent length in patients with stent thrombosis (23.4 +/- 8.1mm Vs 21.3mm +/- 4.1mm, P value 0.025).

In this trial none of the patients had stopped Clopidogrel and Aspirin till the final follow up. The cumulative incidence of stent thrombosis was also higher 6.8% compared to other trials. The incidence of subacute stent thrombosis in 2 patients and late stent thrombosis in one patient raises the issue of safety of this stent on long term follow up.

Binary restenosis

There was no significant difference in the incidence of angiographic binary restenosis between the two groups (3.6% Vs 15.6%, P value 0.131). The incidence of binary restenosis for Infinnium group is 15.6% compared to 6.3% at 6 months and 8.9% at 12 months in Simple 2 trail. In the previous trials of drug eluting stents it ranged from 0% - 8% for paclitaxel and sirolimus eluting stents. In meta analysis of 6 trials (12) it was shown that Sirolimus eluting stents were more effective in reducing angiographic restenosis (9.3% Vs 13.6%, P value 0.001).

Target lesion revascularisation

There was no significant increase in the incidence TLR in the two groups even through there was a trend towards higher rates of TLR in Infinnium group (8.5% Vs 1.6%, P value 0.08). There was no significant difference the CABG done for target lesion failure although the incidence of PTCA for Target Lesion Failure (TLF) was higher in Infinnium group (6.8% Vs 0.0%, P value 0.037). The cumulative incidence of TLR in simple 2 trial was 6.7% at 12 months comparable to the present trial (19). The incidence of CABG was 1.4% in the simple 2 trial (19). In the other drug eluting stent trials comparing paclitaxel and sirolimus the incidence of TLR

significantly differed between the two groups. In Sirtax trial (13) had higher TLR for paclitaxel eluting stents (6% Vs 9.2%, P value 0.05). In REALITY trial the incidence was 1.6% Vs 1.2% with out any significant difference b/w the two groups (P value 0.65). In TAXI trial (15) it was 1% Vs 2% (P value 0.9). In ISARDESIRE trial it was 8% Vs 19% (P value >0.5). In a meta analysis of six trials it was seen that TLR was needed the 5.1% of sirolimus eluting stent group and 7.8% in paclitaxel stent group (P value 0.001) with significant increase in the paclitaxel stent group (12).

Late luminal loss by quantitative coronary angiography

The Drug eluting stent platforms elicit a biologic response with respect to angiographic late coronary lumen loss that differs in its distribution from the late loss distribution previously observed in response to bare metal stent deployment. The precedent statistical methodology used to describe this response and its relationship to restenosis no longer accurate. Late loss retains a close correlation with late outcomes when appropriate statistical methodology is applied. Thus the importance of late loss remains the same in the era of drug eluting stents only the statistical methodology has changed. Therefore we might predict that in a randomized comparative trial of two drug eluting stents with differing levels of late loss, if reference vessel diameter and post

procedural gains are equivalent, late loss will remain a valuable and ordinal variable related directly to adverse late clinical events including restenosis (23). This underscores the importance of measuring the MLD and late luminal loss.

Late luminal loss by QCA did not differ between the groups in the instent region and in segment region. Late loss at 12 months in simple 2 trial was 0.2 +/- 0.5 mm comparable to the other drug eluting stent trials. In the SIRTAX trial the late luminal loss in segment was 0.19 +/- 0.45 Vs 0.32 +/- 0.55 mm with a higher incidence of late loss in patients with Taxus stents (p value= 0.001) and the maximum difference in the late loss was more in the stented segment compared to proximal or distal margins. In ISAR DESIRE study it was significantly higher in both instent and in segment region in paclitaxel eluting stents 0.28 Vs 0.1 mm (P value 0.004) and 0.55 Vs 0.32 mm (P value 0.2) respectively. In a study of paclitaxel stents Vs Sirolimus eluting stents in diabetics the late loss was 0.67 +/- 0.62 Vs 0.43 +/- 0.45 (P value 0.002) in insegment region and was 0.46 +/- 0.64 Vs 0.19 +/- 0.44 (P value< 0.001) in the instent region.

The fact that the incidence of restenosis and late luminal loss is not different between the two groups shows that the two stents are comparable.

In the primary end point of MACE at 9 months it was seen that the cumulative MACE (death, acute MI, and TLR) was significantly different between the two groups with higher incidence in the Infinnium group 11.9% Vs 1.6% (P value 0.023). The MACE was higher due to the higher incidence of TLR and acute myocardial infarction in the Infinnium group. There were no deaths in either of the groups. The fact that the MACE is higher due to higher incidence of ACS implicates that the culprit was stent thrombosis either acute [<1 day] sub acute [1-30days] or late stent thrombosis [>30days].

The incidence of higher stent thrombosis could not be explained clearly even though some hypothesis can be driven out of this

1. Nature of the polymer coating of the two stents were different. In Taxus it was a non-biodegradable polymer and Infinnium it is a biodegradable polymer.

2. The dose of the drug in Infinnium was 18μgm over 16mm with 3 μgm/mm^2. The drug release was >90% completed within 1st 11 days. There are four different layers of the polymer in Infinnium stents. The Taxus uses Translute™ Polymer, a proprietary polymer carrier technology, to control

drug release. Taxus has a paclitaxel concentration of 1μg/mm2 paclitaxel per unit of stent surface area

These features are different between the stents and this could result in more drug released producing decreased endothelisation and thus stent thrombosis

Limitation

This trial is non-randomized matched trial and has fewer number of patients. A larger randomized trial may be needed to confirm the results in the present trial.

CONCLUSION

The incidence of stent thrombosis is higher in patients receiving Infinnium stent. The incidence of binary restenosis and late luminal loss is similar between the Taxus and Infinnium stent groups. However larger randomized controlled trials are necessary to confirm these results.

REFERENCES

1. Hiatt BL, Ikeno F, Yeung AC, Carter AJ. Drug-eluting stents for the prevention of restenosis: in quest for the Holy Grail. Catheter Cardiovasc Interv. 2002 Mar; 55(3): 409-17.

2. Lemos PA, Regar E, Serruys PW. Drug-eluting stents in the treatment of atherosclerotic coronary heart disease. Indian Heart J 2002 Mar-Apr; 54(2): 212-6.

3. Oberhoff M, Herdeg C, Baumbach A, Karsch KR. Stent based Anti restenotic Coatings (Sirolimus/Paclitaxel) Catheter Cardiovasc Interv. 2002; 55(3): 404-408.

4. Sousa JE, Abizaid A, Popma J, et. Al. Late (2-year) follow-up from the first-in-man (FIM) experience after implantation of sirolimus eluting stents. Presented at American College of Cardiology Annual Scientific Session, Atlanta, GA; March 2002.

5. Carter AJ. Drug-eluting stents for the prevention of restenosis: Standing the test of time. Catheter Cardiovasc Interv. 2002 Sep; 57(1): 69-71.

6. Morice MC, Serruys PW, Sousa JE et. al. The RAVEL study (RAndomized study with the sirolimus-eluting VElocity

balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions trial. N Engl J Med 2002 Jun 6;346(23):1773-80.

7. PW Serruys, E.Regar, AJ Carter. Rapamycin eluting stents: The onset of a new era in interventional cardiology.(Editorial)Heart 85 ;307-308.:2002.

8. Jeffry W.Moses, Martin B.Leon, Jeffry J.Popma, Siralimus eluting stents Versus standard stents in patients with stenosis in a native coronary artery. New England Journal of Medicine 2003; 349: 1315-23.

9. Erich Schampaert, Erick A Cohan, Michad Schluter. The Canadian study of Sirolimus eluting stents in the treatment of patients with long denovo lesion in small native coronary arteries J Am Coll Candiol 2004; 43: 1110-25.

10. Seung- Jung Park, Won Harm Schin, David S Ho. A paclitaxel eluting stent for prevention of coronary stenosis. New England Journal of Medicine 2003; 348: 1537-45.

11. Joachin Schofa, Michael Schuter, Authony H.G, Sirolimus eluting stents for the treatment of patients with long atherosclerotic lesions in small coronary arteries; double

blind randomized controlled trial (E-SIRIUS). Lancet 2003; 362: 1093-99.

12. Adnan Kastrati, Alban Dibra, Sonja Eberle, Julinda mehilli. Sirolimus- Eluting stents Vs Paclitaxel eluting stents in patients with coronary artery disease, Metaanalysis of randomized trials. JAMA 2005; 294: 819-825.

13. Stephan Windacker, Andria Remondino, France R Eberle. Sirolimus eluting and paclitaxel eluting stents for coronary revascularisation. New England Journal of Medicine 2005; 353: 653-662.

14. Andrew T.L Ong, Jiro Aoki, Karlos AJ. Comparison of short and long term outcomes of Sirolimus vs Paclitaxel eluting stents in 293 consecutive patients with diabetes mellitus Am. J Cardiol: 2005; 96:358-362.

15. Jacques Goy, Jean Cristophile Stopher Manon.S. A prospective randomized comparison between paclitaxel and sirolimus eluting stents in the real world of Interventional Cardiology J. Am Coll Cardiol 2005; 45: 308-311.

16. Adrian Kastrati, JulindaMehith, Nicolas V.B. Sirolimus eluting stents or Paclitaxel eluting stents Versus balloon angioplasty for prevention of recurrences in patients with

coronary instent restenosis. J AMA 2005; 293: 165-171.

17. Alban dibra, Adrian Kastrati, Julinda Mahelli Paclitaxel eluting or sirolimus eluting stents to prevent restenosis in diabetic patients. New Engl J Med 2005; 353:663-70.

18. D.S. Gambhir et al. Infinnium A paclitaxel eluting stents from India simple I trial results. Drug eluting stents Shunt II, September 19, 2003.

19. D.S Gambhir et al. The Infinnium polymer based paclitaxel eluting stent, result from real world clinical trials. Sample I & sample II. Drug eluting stents unit III October I 2004.

20. Ostovan M.A, kojuri J. Single Carter Registry of Infinnium stent for complex coronary lesion in shiraz, Iran.

21. Andrew TL Ong, Eugene P Mac Fadden, Evelya Regar Late angiographic stent thrombosis (LAST). Events with eluting stents. J Am Coll Cardiol 2005; 45: 2088-2092.

22. Roaul Morrlno Cristina F, Rosenna hernandex Drug eluting stent thrombosis results for pooled including 10 randomized trials. J Am Coll cardiol 2005; 45: 954-959.

23. Dean J Keriakes, Loura Mauri. Surrogates, sub studies and real clinical and patients trials of drug eluting stents. J Am Coll cardiol 2005; 45: 1062-1212.

LONG TERM FOLLOW UP OF VENTRICULAR FUNCTION AND OTHER PARAMETERS AFTER TRANSCATHETER CLOSURE OF SECUNDUM TYPE OF ATRIAL SEPTAL DEFECTS WITH ASD DEVICE.

ABBREVIATIONS

ASD – Atrial Septal Defect

ASO – Amplatzer Septal Occluder

BSA-Body Surface Area

LVfnInd- Change in LV dimension over the total follow up period per BSA

LVdiff1Ind- Change in LV dimension immediate post procedure per BSA

LVdiff2Ind- Change in LV dimension over first three months per BSA

LVdiff3Ind- Change in LV dimn over 3 months to final follow up per BSA

RVfnInd- Change in RV dimension over the total follow up period per BSA

RVdiff1Ind- Change in RV dimension immediate post procedure per BSA

RVdiff2Ind- Change in RV dimension over first three months per BSA

RVdiff3Ind- Change in RV dimn over 3 months to final follow up per BSA

RVSP-Right Ventricular Systolic Pressure

TEE- Trans esophageal Echocardiography

TR- Tricuspid Regurgitation

TTE- Trans thoracic Echocardiography

INTRODUCTION

Transcatheter closure has emerged as an effective alternative to surgery in patients with secundum type of Atrial Septal Defects (ASD). King and Mills first successfully performed transcatheter closure of ASD in 1974. Since then several devices were introduced for this purpose like the Rashkind ASD Occluder, Clamshell Devices, Angelwing Device, ASDOS device, Sideris Buttoned device and the Cardio Seal device (1). These devices did not find wide spread clinical application in view of problems like need for large delivery sheaths, complex implantation procedures, inability in repositioning, high degree of residual shunts, arm fractures and embolization (1).

The Amplatzer Septal Occluder (ASO) has become the most widely used device for trans-catheter closure of secundum ASD, overcoming the disadvantages of its predecessors (2). The main advantages of the ASO device are the relatively simple technique of implantation, ability to be successfully retrieved and repositioned even after opening and the very low incidence of residual shunts on follow-up. This is particularly the case in patients with large defects with deficient rims.

A recent study by Podnar et al had shown that 80% of secundum ASDs could be successfully closed using the ASO (3). This device can

be successfully deployed in all patients with defect size of up to 30mm on trans-thoracic echo (TTE) or trans-esophageal Echo (TEE) provided there are adequate margins (at least 5mm) from surrounding structures (3). A deficient antero-superior (aortic) rim does not preclude use of the ASO device. Worldwide experience with the use of ASO has shown excellent results in both short term as well as intermediate term (up to 2 years) follow-up (4 – 8). The overall procedural success has been around 95% in the various reported studies. Recent studies have shown that with modification of techniques of deployment, the ASO device can be successfully used to close larger defects of up to 35mm (9).

Most of the studies of ASD closure using the ASO have reported that intra-procedural use of TEE greatly facilitates the successful implantation of the device and significantly lowers failure rates. (10–12). Many authors recommend peri-procedural TEE as an essential pre-requisite for trans-catheter closure of ASD, especially large defects (2). There have been very few reports of ASD device closure using the ASD device without the use of intra-procedure TEE.

Procedural complications have been described in 3-10% of cases (8 13). The most common of these include device embolization (3.5%), arrhythmias (2.6%), pericardial effusion, transient ST segment elevation in inferior leads (air embolism), groin complications and

rupture of sizing balloon (10). There has been no reported morality during the procedure (8).

The incidence of long term complications after ASD closure using the ASO device has been relatively few in most of the studies. Late device embolisation, thromboembolic complications, atrial tachyarrhythmias, stroke, nickel toxicity, RA-Aorta Fistula and sudden cardiac death (1 report) are among the various long term complications reported in various studies (4-7,19,28). Studies reporting on 24 hour Holter monitoring after ASO implantation have shown higher prevalence of Atrial Premature Complexes, Supraventricular tachycardias and occasional instances of AV conduction blocks (16,17). Higher incidence of conduction abnormalities are more common in patients with older age at device implantation and a larger Qp/Qs ratio before procedure (16).

AIMS OF THE STUDY

I To assess the long term results of ASD closure in the following parameters

1. LV dimension by echo
2. RV dimension by echo
3. P wave dispersion in ECG
4. Regression of intra ventricular conduction defect in ECG
5. Change in QRS axis in ECG
6. Development of atrial fibrillation on follow up.

II To assess for left atrial / device thrombus formation in transesophageal echo on follow up.

III To assess the frequency of migraine developing after device closure on immediate & long term follow up.

IV To see the device remodeling on long term follow-up by fluoroscopy.

MATERIALS AND METHODS

Patient Population

The present retrospective study was conducted in a tertiary referral center in South India. All patients who had undergone device closure between Nov 1998 and March 2005 are included in the study. All patients with a defect size of less than 30mm on TEE and a septal rim of at least 5mm from right pulmonary vein, coronary sinus, superior and inferior vena cavae and mitral value were considered potentially suitable for device closure if the patients were financially willing for the procedure. Patients with only deficient aortic rim were also considered for device closure. Patients with multiple defects, inadequate rim other than aortic rim, defects in Primum or sinus venosus location and those with significant associated cardiac defects, which merited surgery were excluded.

Pre-implantation assessment

All patients were clinically assessed for the magnitude of shunt. Chest X-ray and ECG were performed in all. Trans-thoracic echocardiogram (TTE) was performed to assess the size and position of defect, number of defects, adequacy of rim, septal motion, RA, RV size and RV systolic pressure (RVSP) by tricuspid regurgitation (TR)

jet. Any associated cardiac defects were also looked for. Subsequently, a trans-esophageal echocardiogram was performed in transverse and longitudinal planes to confirm the findings of TTE and also to check the adequacy of septal rims. The maximum measured diameter of the ASD in any given plane was taken as the size of the defect.

The Device

The Amplatzer septal Occluder (ASO; AGA Medical Corporation; Golden Valley, Minnesota, USA) and Blockaid device (Shanghai Shape Memory Alloy Corp. Ltd, Shanghai) was used for transcatheter closure of the ASD in all patients. The prototype of the devices has been described previously (4).

Technique of implantation

The procedure was performed under local anesthesia in adults. In children the procedure was done under sedation or ketamine without need for intubation. BSA was found out according to height, weight and sex from nomogram. A complete oximetry and haemodynamic study was performed initially. The shunt (Qp / Qs ratio), PA pressures and PVR were noted in all patients. Normal pulmonary vein drainage was ensured either by entering individual pulmonary veins or by using levophase of pulmonary artery angiography. After that balloon sizing of the defect was performed using the Meditech sizing balloon and

Amplatzer/Numed balloon catheter by standard methods. The stretched diameter of the ASD was defined as the diameter of a balloon that can be withdrawn across the ASD with mild resistance and slight deformity. In those patients, in whom the Amplatzer / Numed balloon was used for sizing of the defect, the waist is measured as the size of the defect The selected ASO device was either the same size as the stretched diameter or up to 2mm larger.

Standard techniques as previously described were used for implantation of the device.

The implantation was carried out under fluoroscopy and TTE & TEE guidance under local anesthesia. The selected ASD device was attached to the delivery wire by the screw mechanism and was withdrawn in to the loader by traction on the delivery wire. The collapsed ASD device was then advanced through the long sheath that had been previously placed in the left atrium. Under fluoroscopic control, the left atrial disc and the waist was extruded either by advancing the delivery wire or withdrawing the sheath. The sheath and the delivery wire were withdrawn in unison until the extruded left atrial disc was apposed to the atrial septum. The ASD device was when then fully deployed by withdrawing the sheath over the delivery wire to extrude the right atrial disc.

The position and stability of the ASD device were confirmed by fluoroscopy and TTE & TEE. Its position was deemed optimal if the device was stable and did not obstruct the pulmonary veins, coronary sinus, caval veins or the mitral valve. Any residual shunt was documented by TTE. A right atrial angiogram was done through the sheath to confirm the position of the Right atrial disc. Once the position and stability of the device was confirmed, it was released by anticlockwise rotation of the delivery wire. A final assessment of the position of the device was performed by TTE & TEE after its release.

Post procedure management

The patients were observed in ICU overnight and then transferred to the general ward the next day. A repeat TTE was performed prior to discharge. Patients were discharged 2 days after the procedure if their clinical status was stable. Aspirin 5 mg/kg was continued for 6 months after the procedure while Clopidogrel / Ticlopedine was given for 6 months.

Follow up

All patients were followed up at 1,3,6 and 12 months and then every 12 months after the procedure and then yearly afterwards. The patients were clinically assessed for development of new migraine after the device closure.

During the follow up visits, a TTE was performed to assess any residual shunt, position and stability of the device and obstruction to surrounding structures. The RA, RV size and RVSP by TR jet were also noticed in TTE every visit

ECG was taken at 1yr and a measurement of p wave dispersion (calculated by difference between maximum p wave duration and minimum p wave duration) was taken and was compared with preprocedural p wave dispersion. QRS axis and QRS duration in V_1 and V6 were also measured and compared with preprocedural ECG. On follow up ECG the rhythm was also noted.

In adult patients a follow up TEE was performed after getting consent, minimum 9 months after implantation. In the follow up TEE residual shunt, obstruction to surrounding structures, profile of the device [length of RA & LA discs and thickness of the discs were noted]. The device was visualized in 0, 45 and 90 degrees and all measurements were taken in the best profiled view. Occurrence of clot over the device or left atrium was also looked for.

On follow up a fluoroscopic assessment of the device was taken minimum of 9 months after implantation. During fluoroscopy, the length of the waist and breadth of the waist was measured in the angle in which the device was well profiled.

Statistical analysis

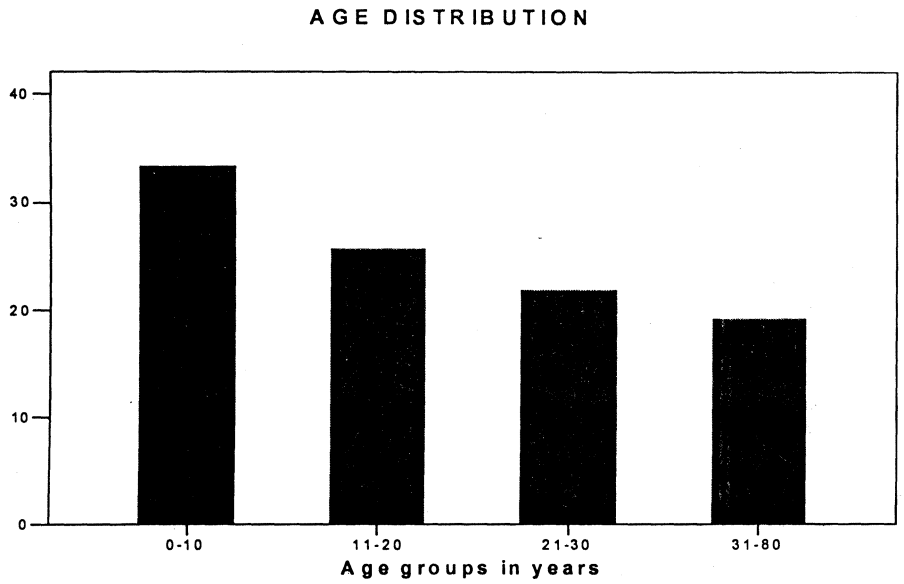
Numeric variables were expressed as mean ± SD and categorical variables as percentage. Following dimensions were indexed to BSA: device size, RV and LV size. The measured variables were divided into categories based on mean age (22 years), median age (14 years), mean ASD size 22mm, mean ASD size indexed to BSA (18 mm/ m2) mean shunt (shunt 2.2) and analysed to find significant differences between these groups. The change in the ventricular dimension over the basal was also calculated as percentages and the percentage change during specified times of follow up also examined. Stepwise multiple regression analysis was done to identify variables independently associated with change in ventricular dimension. The following were entered into the univariate model: age, Qp/Qs and ASD size. Student's *t* for continuous variables and Chi square tests for categorical variables were used. p value <0.05 was considered statistically significant.

RESULTS

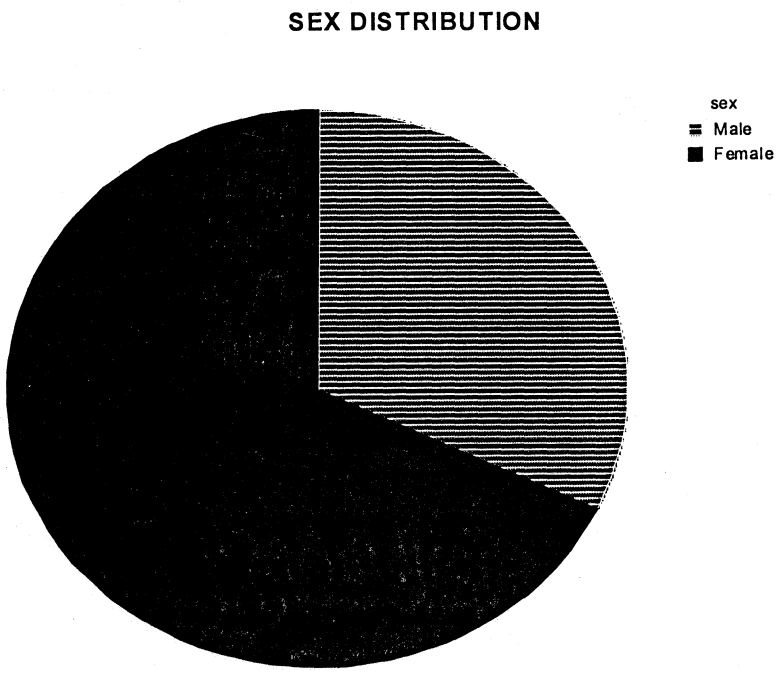
All patients who were diagnosed to have secundum ASDs that merited closure (Clinically significant shunt, RA, RV volume overload on Echo) were evaluated for feasibility for trans-catheter closure. After evaluation with TTE and TEE using the selection criteria mentioned earlier device closure was performed in patients found to have a suitable defect. From November 1998 to March 2005 a total of 83 patients had undergone ASD device closure of which one patient expired during the procedure and was excluded. In another three patients the device was not stable and so a total of 79 were included in the study.

Baseline Clinical Characteristics

The mean age, at device closure was 22.12 +/- 16.8yrs [median of 14yrs, range = 3-70yrs]. Majority of patients were in the age group of 0-10yrs [33%]. In the range of 11-20yrs there were 20pts [25.6%]. Above the age of 20yrs there were 32 patients [41%].



Gender: There were 53 females [67.9%] and 25 males [32.1%]



Clinical characteristics

All patients were in NYHA class I/II. The mean body surface area was 1.26 +/- 0.37 [0.5-2m^2].

Baseline Echocardiography:

All the patients had ostium secundum type atrial septal defects. There was evidence of RA / RV volume overload in all patients. The septal motion in parasternal long axis view by M mode echocardiography were paradoxic in all the patients.

The mean LV internal dimension prior to the procedure was 35.49mm+/- 5.99 mm (24-50). The mean LV dimension after indexing to body surface area was 30.50 +/- 9.87 mm/m^2.

The RV internal dimension prior to the procedure was 28.76 +/- 7.66 mm [14-46mm] The RV internal dimension indexed to body surface area was 25.03 +/- 10.89 mm per m^2. One patient had PAPVC of left upper pulmonary vein to right atrium.

ECG:

The p dispersion prior to the procedure in ECG was 0.0178 +/- 0.009 seconds (Range 0.00-0.04). The baseline QRS duration in V_1 and V6 were 0.083+/-0.01 sec [Range-0.06-0.12 sec] and 0.07 +/-0.014 sec (Range 0.04-0.12sec) respectively. The mean QRS axis prior to the

procedure was + 78.3 +/- 41(range- 75 to +160).

Baseline Cardiac Catheterization findings:

The average size of the defect by balloon sizing 21.9 +/- 4.84mm [10 mm-32mm]. The mean Qp/Qs was 2.186+/- 0.79 (range 1.2- 5.9). One patient had isolated PAPVC of LUPV to RA

Device Implantation:

The average size of the device deployed was 22.92 +/- 4.88mm (range 11-32 mm). 26mm device was used in 11 patients and 18, 22 & 24mm devices were used in 10pts each.

The device size employed was 1.03+/- 1.2mm (Range 0-4mm) above the balloon stretched diameter of the defect.

All patients had device closure successfully. Post procedure the device position was found optimal by TTE and fluoroscopy in all patients.

Table 1: baseline characteristics

Mean age	**22.12+/- 16.8 yrs**
Females	53(67.9 %)
Males	25(32.1 %)
BSA	1.26 +/- 0.37 m2
Basal LV dimension	35.49+/-5.49 mm

LV dimension indexed to BSA	30.5+/-9.87 mm/m2
Basal RV dimension	28.76+/-7.66 mm
RV dimension indexed to BSA	25.03+/-10.89 mm/m2
P wave dispersion	0.0178+/-0.009 secs
QRS duration in V1	0.083+/-0.01 secs
QRS duration in V6	0.07 +/-0.014 secs
QRS axis	+78.3 +/- 41
Size of ASD	21.9 +/- 4.8 mm
Qp/Qs	2.186 +/- 0.79
Device size	22.92 +/- 4.88 mm

Follow up results

Left ventricular dimension

Left ventricular dimension indexed to body surface area assessed by M-mode echocardiogram was found to be increased at the final follow up echocardiographic examination compared to LV dimension prior to the procedure [35.33 +/- 11.62 mm/m2 Vs 30.45 +/- 9.96 mm/m2]. The mean increase in LV dimension in whole group was 10.38 +/- 11.46 mm/m2. This increase was found to by statistically significant (p value <0.0001). This was found to be more in patients with ASD size > 22mm compared to ASD size < 22mm (P value < 0.0001){15.26 +/- 8.56 mm/m2 in the group with ASD size > 22mm Vs 5.23 +/- 11.96 mm/m2 in the group less than 22mm}. This increase was found to be more in patients aged more than 22yrs (mean age)

compared to patients younger (18.06+/- 7.06 mm/m2 Vs 5.49 +/- 11.08 mm/m2, P<0.0001). This increase in LV dimension was not found to be significantly different between patients with smaller shunt [Qp/Qs<2.2] compared to patients with larger shunt.

The increase in LV size over the basal value was found to be significant immediately following the procedure (P value<0.0001), over 1st three months compared to post procedure LV dimension (P value<0.0001) and between the third month of follow up to the final follow up (P value < 0.0001). This increase was found to be maximum between the 3rd month of follow up and the final follow up (P value<0.0001).

The percentage increase in LV dimension above the baseline was not different in the immediate post procedure echo or at 3 month follow up or final follow up, showing that the percentage increase was steady over the follow up period.

LV increase immediately following the procedure

The LV dimension in immediate post procedure period increased by 1.52 +/- 3mm / m^2 (range 3.75mm/m^2 to 19.5mm/m^2). The LV dimension increase immediately following the procedure was found to be significantly different in younger age group [<14yrs] compared to older age group [2.29+/- 3.87 mm/m2 Vs 0.76 +/- 1.4 mm/m2 (P value

<0.03)]. This was also found to be significantly different between smaller ASDs [<22mm] and larger ASDs. [2.25 +/- 4.08 mm/ m2 Vs 0.77 +/- 1.52-mm/ m2 (P value <0.01)]. This increase was not found to be significantly different between those patients with higher Qp/Qs and lower Qp/Qs.

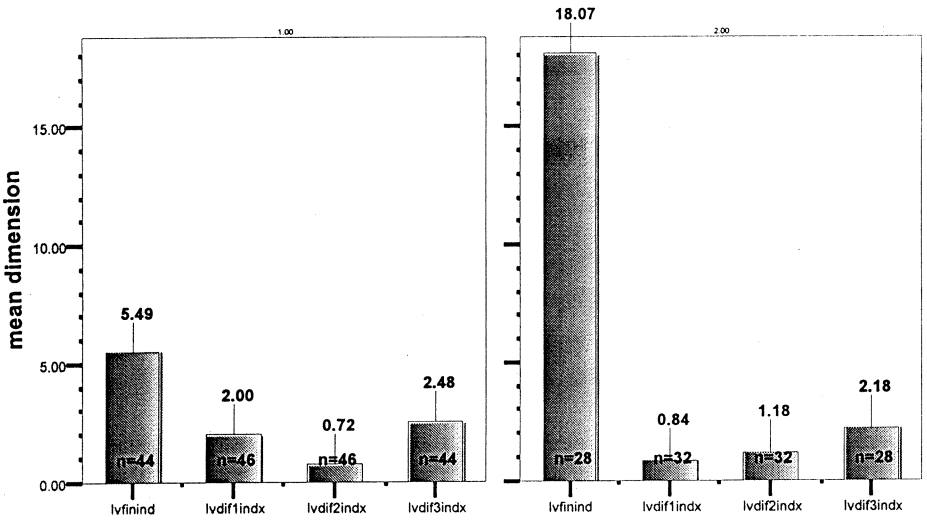
Increase in LV dimension over first 3 months

Increase in LV dimension over first 3 months after the procedure was 0.91 +/- 1.91 mm/ m2 [Range - $^{-}4$ to $^{+}5$ mm/m^2]. This increase was not significantly different between younger & older age groups, smaller & larger ASDs, higher & lower Qp/Qs.

Increase in LV dimension after 3 months of procedure

The maximum increase in LV dimension occurred during this period i.e., 2.36 +/- 4.76 mm/m^2 [Range- 8.75mm/m^2 to 22 mm/m^2]. The increase during this period was found to be significantly different between smaller ASDs [<22mm] & larger ASDs with smaller ASDs having higher increase in LV dimension compared to larger ASDs [3.75 +/- 6.4 mm/ m2 Vs 1.38 +/- 2.78 mm/ m2 (P value <0.04)]. This was not found to be significantly different between younger & older age and lower & higher Qp/Qs.

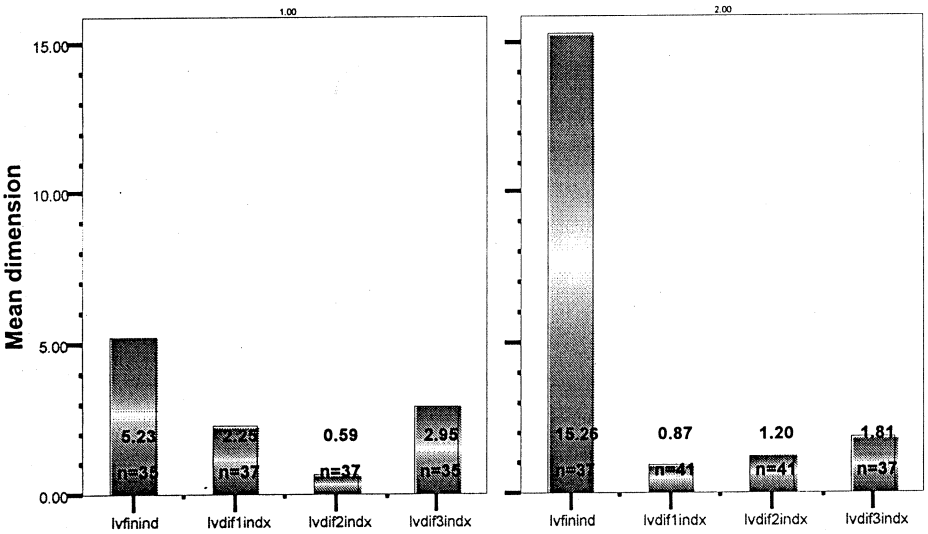
LV dimension according to age



age < 22 years

age > 22 years

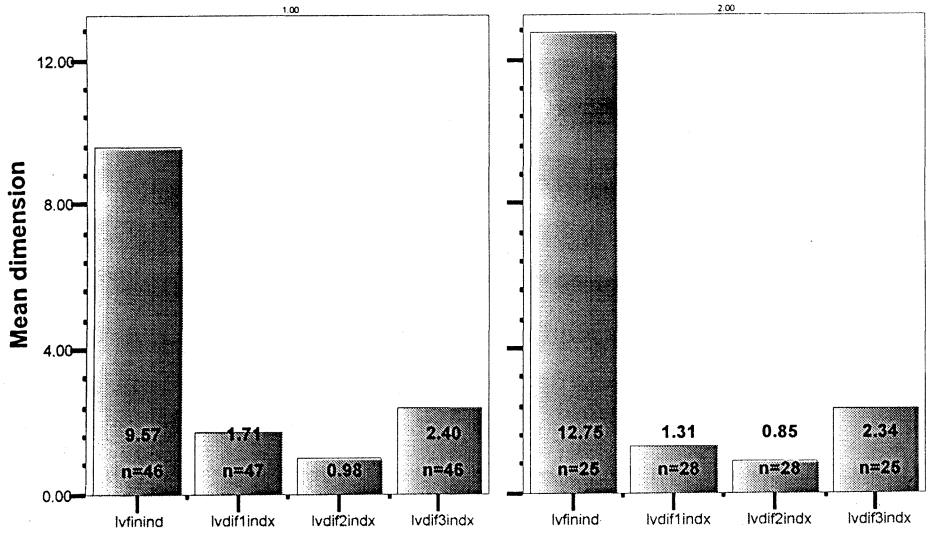
LV dimension according to ASD size



ASD size < 22 mm

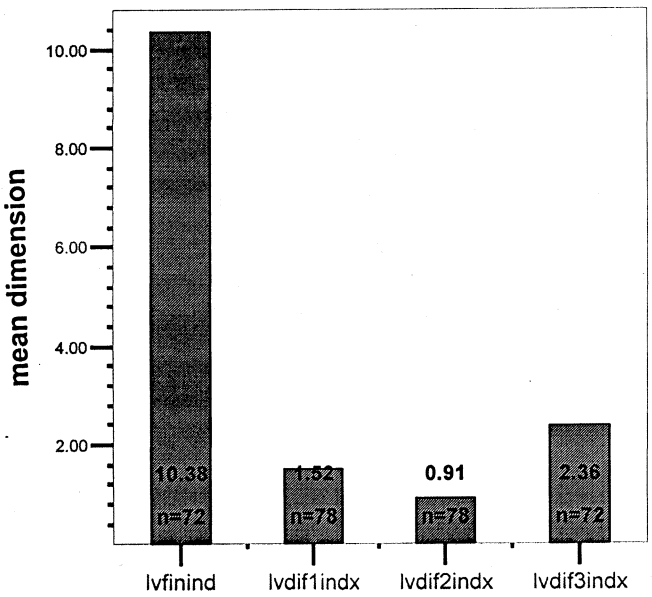
ASD size > 22 mm

LV dimension according to shunt magnitude



Qp/Qs < 2.2 **Qp/Qs > 2.2**

LV dimension change over the follow up



Right Ventricular dimension

Right ventricular dimension indexed to body surface area by M mode echocardiogram was found to be decreased in the final follow up echocardiographic examination compared to RV dimension prior to the procedure [15.95 +/- 5.5 mm/m2 Vs 25.11 +/- 11.1 mm/m2]. The mean decrease in RV dimension in the whole group was 6.6 +/- 11.8mm/m^2. This decrease was found to be statistically significant (P<0.0001). This decrease was found to be significantly different between patients with smaller ASDs and larger ASDs with larger ASDs having better reduction in RV size (P value <0.0001). The mean decrease in patients with larger ASDs [>18mm/m2] were 14.2 +/- 14.1-mm/ m2 where as in patients with smaller ASDs, 1.78 +/- 6.70 mm/m2. This decrease in RV dimension was seen in patients who are young (<14yr) compared to older patients (P value <0.0001). Younger patients had 10.4 +/- 14.45mm/m^2 reduction in RV size compared to 0.62 +/- 7.9mm/m^2 decrease in RV dimension in older patients. This decrease in RV dimension was not found to be different in patients with low or high Qp/Qs. The decrease in RV size over the basal value was found to be significant immediately following the procedure compared to the basal value and over 1st 3 months compared to post procedure RV dimension (P value <0.0001). This was also significantly different between 3rd month of follow up to final follow up (P value <0.0001).

This decrease was found to be maximum in the 1st 3 months after the procedure. The percentage decrease in RV dimension below the base line was not different in the immediate post procedure echo, at 3months follow up or final follow up showing that the percentage decrease was steady over the follow up period.

RV decrease immediately following the procedure

RV dimension significantly reduced over the baseline immediately following the procedure (P value <0.0001). The RV dimension immediate post procedure period decreased by 3.06 +/- 2.56mmm2 [Range – 12.22mm/m^2 to 8.71mm/m^2]. This reduction in RV dimension in immediate post procedure period was found to be significantly more in younger age group <14 yrs compared to older patients [3,73 +/- 2.7mm/m^2 Vs 2.38 +/- 2.14mm/m^2 (P value <0.02)]. This is also significantly different between patients with higher Qp/Qs (>2.2) and smaller Qp/Qs with better reduction in RV size in patients with higher Qp/Qs [3 +/- 2.58 mm/m^2 Vs 2.96 +/- 2.57 mm/m^2 (P value <0.04)]. This difference was not significantly different between smaller and larger ASDs.

Decrease in RV dimension over first 3 months

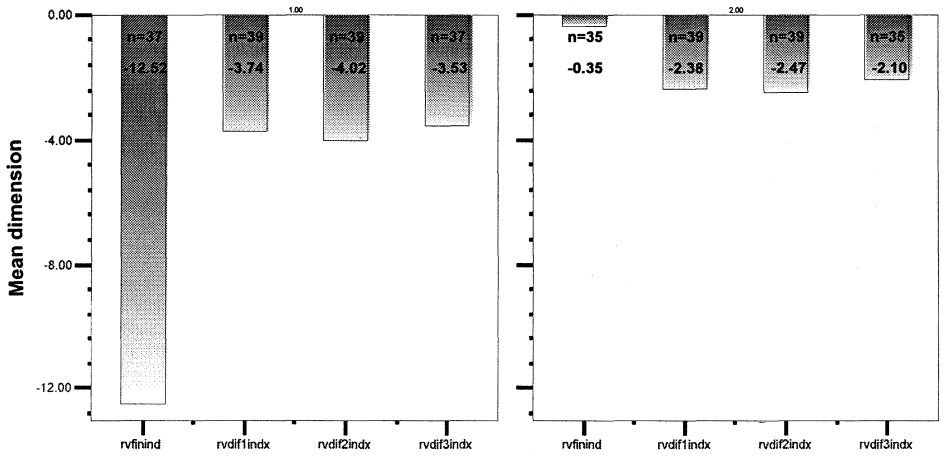
The maximum change in RV dimension after the procedure was found during this period. Decrease in RV dimension over first 3

months after procedure was 3.25 +/- 3.29mm/m^2 [Range $^{-}$18.33 to $^{+}$1.88mm/m^2]. This decrease was more in the younger age group <14yrs compared to alder age group (P value <0.04). [Younger patients having a reduction of 4.02 +/- 3,8mm/m^2 versus 2.47 +/- 2.46mm/m^2 in older age group]. This difference was also significant between smaller ASDs [<18mm/ mm2] and larger ASDs (P value <0.009). [Larger ASDs having a reduction in RV size of 4.45 +/- 3.9mm/m^2 Vs 2.45 +/- 2.5mm/m^2 reduction patients with smaller ASDs]. This reduction was not found to be significantly different between higher & lower Qp/Qs.

The increase in RV dimension after 3 months of procedure

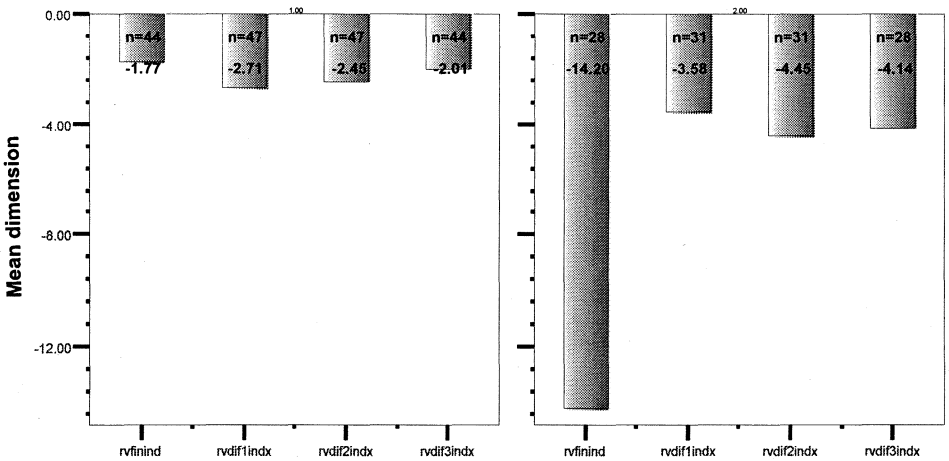
The increase in RV dimension after 3 months of procedure was 2.84 +/- 4.71mm/m^2 range [$^{-}$21.67 to $^{+}$ 8mm/m2]. This decrease in RV dimension after 1st 3 months of procedure was not significantly different between younger & older age groups, smaller and larger ASDs & higher & lower Qp/Qs.

RV dimension accoding to age



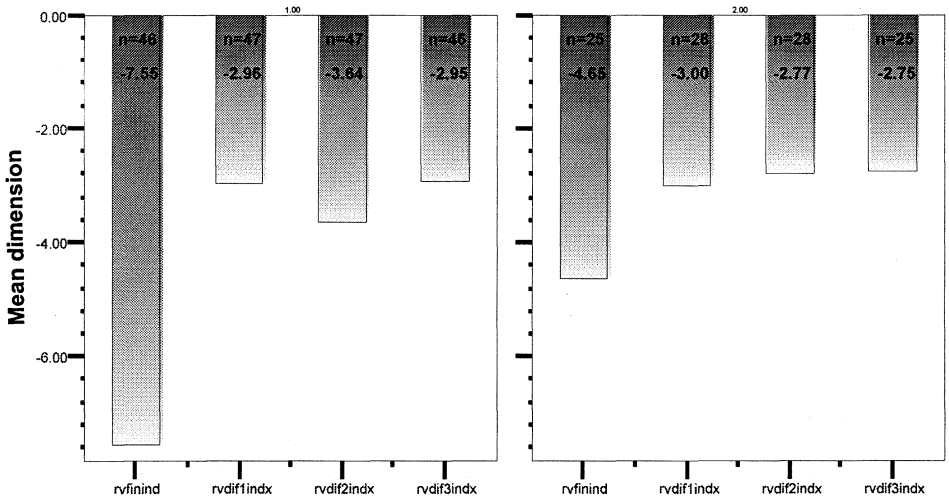
Age < 14 years **Age > 14 years**

RV dimension accoding to indexed ASD size



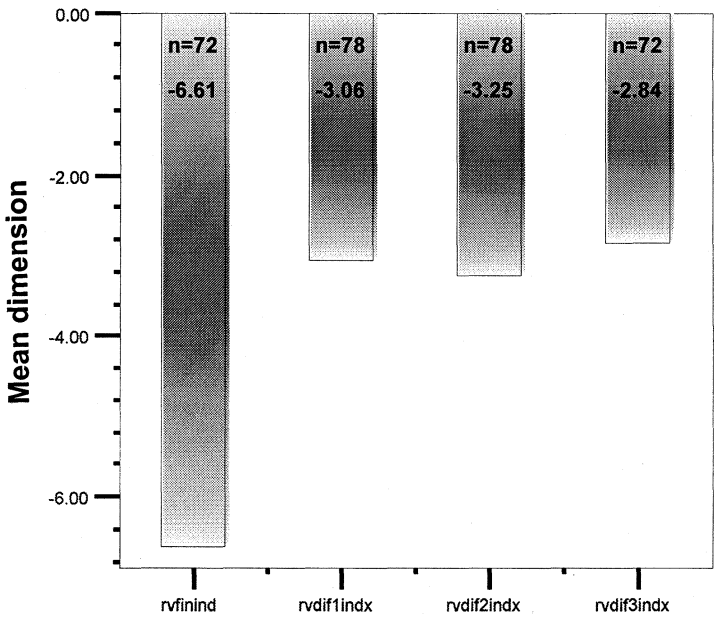
ASD size < 18 mm **ASD size > 18 mm**

RV dimension according to shunt magnitude



Qp/Qs < 2.2 **Qp/Qs > 2.2**

RV dimension change over the folow up period



ECG Characteristics

P dispersion

Mean P dispersion pre procedure was 0.0178 +/- 0.009 sec [Range 0.00 – 0.04 sec] and the post procedure p dispersion was 0.02 +/- 0.009 sec [0.00-0.04sec]. There is no significant difference between P dispersion in ECG prior to the procedure or following procedure [P value 0.08].

QRS axis

Mean QRS axis prior to the procedure was 78.3 +/- 41 [Range $^{-}$75 to $^{+}$160] and following the procedure was 57.22 +/- 34.9 [Range $^{-}$50 to $^{+}$110]. There was significant reduction in mean QRS axis post procedure (P value 0.0001).

This reduction in QRS axis was more in patients with larger ASDs (>22mm) compared to smaller ASDs (P value = 0.011) with larger ASDs having more reduction in QRS axis of 21.03 +/- 27.2 Vs 17.4 +/- 27.9 in patients with smaller ASDs. This reduction in QRS axis was not significantly different between older & younger age groups, between higher & lower Qp/Qs and between higher body surface area >1.26 m^2 and lower body surface area.

QRS duration in V1

QRS duration in V_1 prior to the procedure was 0.0835 +/- 0.01 sec [range 0.06-0.12 sec] and on follow up was 0.0756 +/- 0.014 sec [range 0.05 – 0.13 sec]. The QRS duration in V_1 reduced significantly after the procedure over the follow up period (P value <0.0001). This reduction in QRS duration in V_1 was not significantly different between younger & older age group, lower & higher Qp/Qs and smaller and larger body surface area. There was a trend towards higher reduction in QRS duration in V_1 in patients with ASD size >16mm with patients with larger ASDs having a reduction of 0.0089 +/- 0.01 seconds Vs 0.002 +/- 0.009 seconds reduction in patients smaller ASDs (P value = 0.054).

QRS duration in V_6

Mean QRS duration in V_6 prior to procedure was 0.0758 +/- 0.14 sec [Range-0.04-0.12 sec] & on follow up was 0.065 +/- 0.015 sec [Range 0.04 to 0.12 sec]. This reduction in QRS duration in V_6 was statistically significant (P value 0.0001). This reduction QRS duration in V_6 was not significantly different between higher & lower age group, higher or lower qp/qs, larger & smaller ASDS and larger and smaller body surface area.

The decrease in QRS duration in V_6 was found to be more

compared to V_1 [0.01 +/- .01 sec Vs 0.008 +/- 0.01 sec (P value <0.02)].

All the patients were in sinus rhythm prior to the procedure and all patients except one was in sinus rhythm on follow up. This patient was an old aged lady having AF after 3 months of procedure

The fluoroscopic size of ASD device on follow up

The fluoroscopic size of the device measured on final follow up was found to be smaller than the device size chosen during the procedure [22 +/- 4.69 mm (device size chosen) Vs 19.24 +/- 4.65 mm (follow up fluoroscopic dimension) (P value <0.001)]. The fluoroscopic size of the device measured on follow up was also found to be smaller than ASD size measured by balloon sizing during catheterization [balloon size of ASD 20.93 +/- 4.71] Vs [fluoroscopic device size 19.24 +/- 4.6] (P value <0.0001).

This reduction in size measured on follow up was found to be having a non significant trend of having more reduction in patients with ASD size >22mm [mean ASD size] compared to ASD size <22mm [3.17 +/- 2.22 mm] Vs {2.42 +/- 1.06mm] (P value 0.092). The reduction in measured size was not significantly different between higher lower age groups, lower & higher Qp/Qs & higher & lower BSA.

Trans esophageal Echo examination

One third of the patients in the whole group under went TEE on follow up & on TEE there was no evidence of left atrial thrombus or thrombus on device in any of the patients. There was no residual ASD in the follow up TEE at one year after the procedure. There was no evidence of residual ASD in trans thoracic echo on final follow up of any of these patients.

Migraine

Four patients had new onset migraine after the procedure and the occurrence of migraine was not related to age, body surface area and size of ASD or Qp/Qs.

DISCUSSION

Transcatheter closure of ASD using the Amplatzer septal occluder has become a standard practice for closure of these defects in modern pediatric cardiology practice. A large number of studies reported in literature have confirmed the efficacy and safety of this device in the closure of secundum ASD .The results of our study confirms the observations of the previous reports.

LV and RV function

Right heart enlargement by echocardiographic imaging has shown to accurately estimate the degree of shunt in ASD. Following closure of ASD echocardiographic assessment suggests increase in LV volume and in one study LV function was normal one year after repair (Bjorkhem G etal). Persistence of RV dilatation after closure of ASD is commonly reported affecting 80% patients 5 years after repair especially after surgery. The impairment of RV function was thought to be due to cardiopulmonary bypass but an echocardiographic study comparing surgical repair of ASD with device closure failed to show any change in RV volume or function after closure by either technique (21). Another study by Dhillon R etal showed that RV systolic and diastolic function was preserved following device closure where as it was impaired on surgical repair on short term follow up (18). Similar

results were found by Yui-fai Cheung etal on longer follow up (23). By TDI and M mode K.C. Hanseus etal found that tricuspid annular and septal systolic amplitude and velocities reduced significantly after surgical closure compared to device closure concluding that device closure does not affect RV function (20). Judith et al also found similar effects. They found that the increase in LVEDD after ASD closure was similar in surgical and device closure groups. Walker etal saw a 17% increase in LVEDV immediately after the device closure of ASD (24). Similar to observation by Salehian etal of 16% increase in LVEDV after the device closure.

In our study we have seen similar findings with increase in LVEDD (35.33+/- 11.62 mm /m2 to 30.45+/-9.06 mm / m2) and decrease in RVEDD (25.11+/- 11.1 mm/m2 to 19.95 +/- 5.5 mm/m2) by M mode echocardiography. The rapidity of these changes were also analysed in our study and we have found that the change in LV dimension occurs immediately after the procedure and over a course of one year. But the maximum increase in LV dimension occurred after the 3rd month to one year period of follow up. This is different from the study by Walker et al in which they observed an immediate increase in the LV size of 17 %. But in this study the follow up period was for a very short period. In our study also there was an increase in LV dimension but maximum occurred after 3 months to one year

period.

In the case of improvement in RV dimensions we have seen that the decrease occurs in the first three months of the procedure. Studies have shown that after ASO implantation there is significant resolution of right heart enlargement (RA, RV volumes.), particularly in the first 3-6 months after the procedure. After 6 months, significant regression of RA, RV size does not occur. The resolution of right heart enlargement is significantly more in younger patients. In the case of RV dimension Zhong Dong et al a dramatic reduction in RV size within 24 hours (22) similar to our results.

In relation to the age of closure we have seen that smaller ASDs more than > 22 mm were found to have a larger increase in LV dimension. We also found that LV dimension increased more often in older patients over the mean age of the study group (that is 22 years).

The RV dimension improvement was better in patients with larger ASDs and was seen to be better in patients younger than 14 years. This is in contrast to study by Giuseppe et al in which they didn't see any difference between younger and older age group (19). This suggests that delayed ASD closure is less effective to restore RV function. It is seen in surgical and device closure series that longer the volume overload, the lesser the normalization of cardiac size.

Increased RV size was seen in patients who had surgery before 25 years. It has been noted that the surgery after 25 years is less effective to improve the secondary RV dysfunction. Patients operated less than 25 years had a comparable life expectancy to healthy individuals. The decrease in RV size after device closure is inversely related to age in a device series. Children with more dilated RV had a slower reversal of RV overload compared to younger patients with mildly dilated RV. Hence patients with larger ASDs may benefit from earlier intervention as seen in the present study.

The electrical characteristics

In the present study we have seen that the QRS axis and the QRS duration in the chest leads decreased significantly after the device closure. The decrease in QRS duration was constant over the whole of the follow up period and was not different according to age, ASD size or shunt even though there was a trend towards better reduction of QRS duration in V1 in patients with larger ASD > 18 mm even though statistically nonsignificant. We also noted that the QRS duration in V6 decreased more compared to that in V1. The QRS axis was found to be decreased more in patients with larger ASDs > 22 mm.

This confirms the concept that the changes in ECG are due to larger shunt, more RV overload and in patients with larger ASDs there

was better reduction in these parameters.

In measuring the p wave dispersion we have seen no significant difference between the p wave dispersion in patients after ASD closure over the follow up period. The p wave dispersion is found to be a predictor of atrial arrythmias by different studies and this may signify a future atrial fibrillation. A much larger study group with a longer follow up may show a significant reduction in p wave dispersion as this small study could not demonstrate the same.

Most of the studies reporting follow-up have shown excellent results on long term follow-up (4 – 7). Complete occlusion without residual shunts have been reported in 85%, 92% and 98.7% of patients at 24 hours, 1 month and 3 month after procedure (5). A meta-analysis by Omeish et al on the world wide experience with ASO device (3535 patients; 3580 implants) had shown 97% total occlusion rate at 1 month which became nearly 100% at 6 months (8). Most of the studies have analyzed residual shunts on follow-up using transthoracic echocardiography. Cao et al reported use of TEE for assessing residual shunt on follow-up and reported complete closure of the defect in 91.4% of patients at 6 months after implantation (14). In our study we did not find any residual ASD on the TEE after one year of the procedure

LA thrombus

One notable feature we have seen in our study is the absence of LA thrombus or thrombosis in the device after the closure on follow up by TEE. In earlier studies LA clot /device related thrombus have been found to cause CVA in patients after device closure (25-26).

Follow up device size

Another important finding that we have noted is a reduction in the device size measured by fluoroscopy on follow up. There was a significant reduction in the device size compared to the ASD size chosen during the procedure and the measured balloon size of the ASD. This may be because the device does not expand to its fully expanded size but is restricted by the septum.

Migraine

We also noted new onset migraine in 4 patients (5%) after the procedure. Earlier reports mention an incidence of upto 35% of migraine after ASD device closure (Machebourdager etal).

In our study we did not notice any evidence of CVA, residual shunt or embolic phenomenon in any of the patients.

Limitations

Potential limitations of this study should be mentioned. Our study did not have larger population size. A longer follow-up would be required to see any further age related changes in the ventricular dimensions. Surgery is still an important therapeutic option for ASD. Patients with larger defects were subjected to surgery and we have not compared our results with the surgical closure.

CONCLUSION

This study shows that ASD device closure results in a decreased RV dimension and increased LV dimension on follow up. This difference was more in younger patients and larger ASDs. The QRS duration and the QRS axis decreased on follow up. We did not find any change in the p wave dispersion that is a predictor of future atrial arrythmias in our study. The was no incidence of residual shunt or LA thrombus in our study. Some patients developed new onset migraine in our study after the device closure.

REFERENCES

1. Latson L.A Per-catheter ASD Closure. Pediatric Cardiology 1998; 19: 86-93.

2. Harper RW, Mottram PM, McGaw DJ. Closure of Seccundum Atrial Septal Defects with the Amplatzer Septal Occluder Device: Techniques and Problems. Catheterization and Cardiovascular Interventions 2002; 57: 508-524.

3. Podnar T, Martanovic P, Masura J Morphological variations of secundaum type atrial septal defects: feasibility for percutaneous closure using amplatzer septal occluders. Catheterization and Cardiovascular Interventions 2001; 53: 386-391.

4. Masura J, Gavora P, Formanek A, Hijazi ZM Transcatheter closure of secundum atrial defects using the new self centering Amplatzer septal occluder: Initial Human exoperience. Catheterization and cardiovascular diagnosis 1997; 42: 388-393.

5. Chan KC, Godman MJ, Walsh K, Wilson K, Wilson N, Redington A, Gibbs JL Transcatheter Closure of atrial defect and interatrial communications with a new self expanding nitinol double disc device (Amplatzer septal occluder): multicentre UK experience Heart 1999; 82: 300-306.

6. Arora R, Kalra GS, Singh S, Passey R, Sinha S, Nigam M. transcatheter closure of atrial septal defects using self expandable septal occluder Indian Heart Journal 1999; 51: 289-293.

7. Taeed R, Shim D, Kimball T, Michelfelder EC, Salaymeh KJ, Koons LM, Beekman RH III One year follow-up of the anplatzer device to close atrial septal defects American Journal of cardiology 2001; 87: 116-118.

8. Omeish A, Hijazi ZM. Transcatheter closure of atrial septal defects in children and adults using the Amplarzer Septal Occluder. J Interv Cardiol 2001; 14(1): 37-44.

9. Kannan BRJ, Francis E, Sivakumar K, Anil SR, Kumar RK. Trans-catheter Closure of Very Large (>25mm) Atrial Defects Using the Amplatzer Septal Occluder. Catheter and Cardiovascular Interventions 2003; 59: 522-527.

10. Mazic U, Gavora P, Masura J. The role of transesophageal echocardiography in Transcatheter closure of secundum atrial septal defects by the Amplatzer septal occluder. Am Heart J 2001; 142(3): 482-8

11. Salaymeh KJ, Taeed R, Michelfelder EC, Beekman RH III, Shim D, Kimball TR Unique echocardiographic features

associated with deployment of the amplatzer atrial septal defect device Journal of the American Society of Echocardiography 2001; 14: 128-137.

12. Cooke JC, Gelman JS, haroer RW Echocardiolosista' role in the deployment of the Ampltzer Atrial Septal Occluder device in adults. J Am Soc Echocardiogr 2001; 14: 588-94.

13. Chessa M, Carminati M, Butera G, Bini RG, Drago M, Rosti L et al. Early and late complications associated with Transcatheter occlusion of secundum atrial septal defect. Journal of American collegte of Cardiology 2002; 39: 1061-1065.

14. Cao QL, Du ZD, Joseph A, Koeing P, Heitschimdt M, Rhodes J, Hijazi ZM. Immediate and Six-month Results of the Profile of the Amplatzer Septal Occluder as assessed by Transoesophageal Echocardiography. American Journal of Cardilogy 2001; 88: 754-759.

15. Kort HW, Balzer DT, Johnson MC. Resolution of Right Heart Enlargement After Closure of Secundum Atrial septal Defect with Transcatheter Technique. Journal of American college of Cardiology 2001; 38: 1528-1532.

16. Hill SL, Berul CI, Patel HAT. Early ECG abnormalities

associated with transcatheter closure of atrial septal defects using the Amplatzer septal Occluder. J Interv Card Electrophysiology 2000; 4: 469-474.

17. Hessling G, Hyca S, Brockmeir K, Ulmer HE. Cardiac Dysarrhythmias in pediatric patients before and 1 year after transcatheter closure of atrial septal defects using the Amplatzer Septal Occluder. Pediatric Cardilogy 2003; 24: 259-262.

18. Dhillon R, Josen M, Henein M, Redington AN. Transcatheter closure of atrial septal defect preserves right ventricular function. Heart 2002; 87:461–465.

19. Giuseppe Santoro, MD, Marco Pascotto, MD, Berardo Sarubbi, MD, PhD, Maurizio Cappelli Bigazzi, MD. Early Electrical and Geometric Changes After Percutaneous Closure of Large Atrial Septal Defect. The American journal of cardiology, vol. 93 April 1, 2004

20. Hanseus KC, Bjorkhem GE, Brodin LA, Pesonen E. Analysis of atrioventricular plane movements by Doppler tissue imaging and M-mode in children with atrial septal defects before and after surgical and device closure. Pediatr Cardiol 2002; 23: 152-9.

21. Berger F, Jin Z, Ishihashi K, et al. Comparison of acute effects

on rightventricular haemodynamics of surgical versus interventional closure ofatrial septal defects. Cardiol Young 1999; 9:484 –7.

22. Zhong-Dhong Du, Qui Ling Cao, Peter Koenig. Speed of normalization of Rv volume overload after transcatheter closure of ASD in children and adults.The americal journal of cardiology 2001;88:1450-1453.

23. Yiu-Fai cheung, Kin –Shing Lun, Adolphus .K.T. Chau. Doppler tissue imaging analysis of ventricular function after surgical and transcather closure of ASD. The American journal of cardiology 2004; 93: 375-378.

24. Roxanne E walker, Adrian M Moran, Steven D Colan. Evidence of adhverse ventricular interdependence in patients with ASDs. American journal of cardiology 2004; 93:1374-1377.

25. Krumsdorf U, Ostermayer S, BillingerK, TrepelsT.Incidence and clinical course of thrombus formation on ASD and PFO closure devices in 1000 consecutive patients. J Am Coll cardiology 2004; 43: 302-309.

26. Ansari H, Child J, Naterson B, krivokapic J. Incidence of thrombus formation on the Cardio-SEAL and Amplatzer inter

atrial closure devices. Am J Cardiol 2004; 93: 426-431.

27. Chessa M, Carmibati M, Butera G. Early and late complications associated with transcatheter closure of secundum ASDs. J Am Coll Cardiol 2002; 39: 1061-1065.