SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY. THIRUVANANTHAPURAM.

PROJECT REPORT

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PROGRAMME : **DM CARDIOLOGY**

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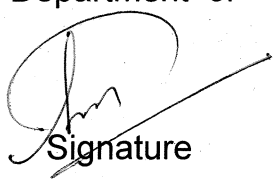
CERTIFICATE

I, *Dr.Anees, T,* hereby declare that the projects in this book were undertaken by me under the supervision of the faculty, Department of Cardiology, SCTIMST.



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EFFECTIVENESS OF HIGHER DOSE OF CLOPIDOGREL AFTER PERCUTANEOUS CORONARY INTERVENTION: A RANDOMIZED CONTROLLED STUDY

Abstract

Objectives : The main objective was to assess the antiplatelet effect of 150mg/day of clopidogrel versus the standard 75mg/day when used as maintenance dose after percutaneous coronary intervention .

Methods and Results : We randomized 50 patients after an elective percutaneous coronary intervention with bare metal stent into two groups , one which received the standard 75mg/day and the other 150mg/day of clopidogrel in addition to other standard drugs. Platelet function was evaluated at 3 months with Optical Aggregometry with 2 agonist : 5 micromol ADP and Collagen. The higher maintenance dose produced 30% more inhibition of aggregation that tended to statistical significance (22.14 +- 16.6 Vs 15.41 +- 10 , p = 0.1 ; control (mean) - 52.4). The slope or velocity of aggregation was significantly different between the groups (43.41+- 18 in group A Vs 32.82 +- 10 in group B, p= 0.023). The ratio of aggregation in each subject to the extent of aggregation of the corresponding controls were analyzed and compared between groups; there was significant difference between the groups (0.41 +- 0.28 for Group A Vs 0.26 +-0.14 for Group B ,p = 0.03) . At 3 months the higher dose of clopidogrel was well tolerated with no added side effects.

Conclusions : Higher maintenance dose of clopidogrel produces added antiplatelet effect without any adverse effects , which may translate to reduction in ischemic complications after percutaneous coronary intervention .

Key Words : Clopidogrel , Angioplasty , Platelet , Aggregometry , Stent thrombosis

Effectiveness Of Higher Dose Of Clopidogrel After Percutaneous Coronary Intervention : A Randomized Controlled Study

Introduction

The activation of platelets and formation of platelet thrombi are crucial to the pathogenesis of acute coronary syndromes and the antiplatelet agents have important role to play in prevention of progression of CAD and occurrence of coronary events. Early studies in balloon angioplasty demonstrated reduction of acute ischemic complications with aspirin use. With the widespread use of coronary stenting it also became clear that the platelet thrombus has an important role to play in ischemic complications after stenting. Ticlopidine which was shown to produce greater inhibition of platelet activation than aspirin was found to decrease acute occlusion further and also to reduce sub acute Stent thrombosis.

In 1998 there was a switch to use of clopidogrel instead of ticlopidine, because of its greater safety profile and indirect evidence for its efficacy based on equivalence in trials of vascular disease . Subsequent trials and registry data indicated that

clopidogrel is superior to ticlopidine in terms of side effects and reduction in cardiac events. The all cause mortality was also lower with clopidogrel compared to ticlopidine in a meta analysis comparing clopidogrel versus ticlopidine[1]. The anti platelet agent clopidogrel has been shown to substantially reduce ischemic complication in the peri-procedural period after percutaneous coronary intervention as evidenced by the numerous trials evaluating various loading doses of clopidogrel in combination with aspirin. Long term continuation of clopidogrel was also shown to give added benefit.

Ischemic complications after stenting

Stent thrombosis is a rare but catastrophic complication after coronary stenting, because of the high risk of death and myocardial infarction associated with it. Stent thrombosis can be acute, i.e. during the procedure or within 24 hrs of the procedure, sub acute (between 1 to 30 days) , late (between 30 days to 1 year) or very late (after one year). The cornerstone of the strategy to prevent sub acute or late Stent thrombosis is the use of dual antiplatelet agents – aspirin and clopidogrel . Although non compliance with dual anti platelet treatment is considered a major risk factor for stent thrombosis , more than 50% of the time stent thrombosis cannot be attributed to drug non compliance[2] . Various other factors may be implicated – patient factors like diabetes , renal failure, Left ventricular dysfunction ; lesion characteristics like use of long stent or bifurcation lesion;

procedural characteristics like under deployment of stent and non responsiveness to clopidogrel have been implicated .

Variable response to aspirin and clopidogrel

The response of an individual patient to a standard dose of drug cannot be predicted accurately because of variability in response. In any population the this variability in response can be attributed to the individual variation affecting the drugs metabolism or action. However estimation of such a variable response to anti platelet agents are not standardized and depending on the method of estimation different values for prevalence of anti platelet resistance is obtained .

Anti platelet resistance and hypo responsiveness

Aspirin does not prevent the majority of cardiovascular events. This is not surprising because aspirin blocks only one of several pathways of platelet activation and aggregation. In some cases however, failure to respond to aspirin may be caused by an inadequate primary pharmacological effect. This has sometimes been referred to as "aspirin resistance." Depending on the population studied, the assay used, and the definition applied, prevalence of aspirin resistance is estimated to be between 5% and 65%[3,6] . Incomplete inhibition of arachidonic acid–induced platelet aggregation, or failure to prevent the TX (Thromboxane A_2)-

dependent second wave of platelet aggregation in response to weak agonists, indicates incomplete platelet COX inhibition. The primary pharmacological effect of aspirin is almost complete inactivation of platelet COX-1 and consequent inhibition of TX biosynthesis. In spite of the demonstration of prevalence of aspirin resistance in various populations, the clinical implications of such hyporesponsiveness have not been proven conclusively[6]. Wenaweser et al reported the higher incidence of aspirin resistance in patients who had stent thrombosis compared with patients who did not. Eighty-two patients were included in the study: 23 patients with previous ST, 50 matched controls (coronary stenting without ST), and 9 healthy volunteers. Platelet aggregation (PA) was studied (optical aggregometry) under monotherapy with acetylsalicylic acid (ASA) 100 mg daily for one month, followed by dual therapy with ASA 100 mg and clopidogrel 75 mg daily (loading dose 300 mg) for another month . Patients who had stent thrombosis previously had higher incidence of aspirin resistance. . However addition of clopidogrel decreased platelet aggregation further in both groups , the stent thrombosis group still had higher degree of residual activity[5] . Dose dependent variability in aspirin response has been demonstrated with biochemical assays . Secondary prevention studies in large populations, however, fail to show additional clinical benefit of higher aspirin doses. The various formulations of aspirin used and the low dose often used for fear of side effects may critically affect the bio availability and pharmacodynamic effect of aspirin in a population which shows variability in response to the drug.

Several other studies have shown that aspirin hyporesponsiveness to be associated with risk for adverse cardiac events. The clinical relevance of aspirin resistance was demonstrated in a study of stable patients with cardiovascular disease who were found to have a greater than threefold increase in the risk of major adverse events during long-term follow-up compared with those on aspirin who exhibited normal inhibition of platelets[4].

Consistent levels of platelet inhibition are required to deliver effective therapy. Adverse consequences of variable response are particularly apparent when antiplatelet drugs are used as an adjunct to coronary revascularization. During percutaneous coronary intervention (PCI), atherosclerotic plaque is invariably disrupted, thrombosis occurs, and endothelial healing is delayed. Intensive periprocedural platelet inhibition minimizes morbidity and mortality, whereas persistence of a prothrombotic environment necessitates chronic antiplatelet therapy. Failure to provide adequate platelet inhibition in all individuals can result in stent thrombosis, myocardial infarction, and death[6]. Platelet inhibition with aspirin at the time of coronary artery bypass graft surgery also provides benefit.

Clopidogrel

Mechanism of action

The mechanism of action of clopidogrel centers around its ability to bind to the receptors for ADP on platelet surface, the purinergic receptor $P2Y_{12}$. ADP also binds to $P2Y_1$ receptor and leads to early activation of platelets. Clopidogrel does not bind to this receptor. These G protein coupled receptors ultimately leads to increased expression of active forms of GpIIb/IIIa on the platelet surface. These agents not only prevent aggregation but also produce disaggregation of the platelets. By inhibiting action of ADP it producers greater inhibition of platelet function as ADP can act together with other agonists to stimulate the platelets. Antagonism to P2Y12 may also attenuate CD40L and P-selectin expression, inhibit platelet – leukocyte aggregate formation and inhibit periprocedural rise of CRP in patients who undergo coronary revascularization[7]. Thus clopidogrel may modulate coagulation and vascular inflammation also. Both agents aspirin and clopidogrel inhibit platelet aggregation induced by ADP, TX analogs, collagen, low-dose thrombin, and shear, but strong agonists such as high-dose thrombin can overcome inhibition[8] . Recent evidence indicates that $P2Y_{12}$ receptors exist in homo-oligomeric complexes associated with platelet cell membrane lipid rafts and that the active metabolite of clopidogrel partitions the receptor out of the rafts to disrupt these oligomers, which thereby prevents signal transduction[9] .

Variable response to clopidogrel

Currently the evidence in favor of clopidogrel for different clinical settings is remarkable. The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial found that dual antiplatelet therapy with clopidogrel and aspirin in acute coronary syndromes (ACS) reduced adverse coronary events by 20% when compared with aspirin monotherapy[10]. The PCI-CURE sub study and the Clopidogrel for the Reduction of Events During Observation (CREDO) trial investigated the use of pretreatment and long-term treatment with clopidogrel following stenting. PCI-CURE showed a 30% relative risk reduction in the primary endpoint of MI, urgent revascularization, or cardiovascular mortality at 30 days and showed further benefit from prolonged administration[11]. CREDO demonstrated a 26.9% relative risk reduction in cardiovascular risk at 1 year and also showed the efficacy of clopidogrel pretreatment in certain patients undergoing PCI[12] .The Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY-TIMI-28) study evaluated clopidogrel in conjunction with aspirin, anticoagulation, and thrombolytics in ST-elevation myocardial infarction. This study revealed a 20% relative risk reduction in death, recurrent myocardial infarction, and recurrent ischemia in patients who received clopidogrel as opposed to placebo[13]. The Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study (COMMIT/CCS-2) enrolled nearly 46 000 patients receiving aspirin and compared the use of 75 mg of clopidogrel to placebo in patients with an ST-elevation myocardial infarction. The results complemented that of CLARITY-

TIMI-28 by showing a 9% relative risk reduction of death, myocardial infarction or stroke; the reduction in mortality alone was 7% . However addition of clopidogrel to aspirin was not found to be useful in stable coronary artery disease in the CHARISMA trial[14].

Serebruany et al in their study reported the variation in platelet response to clopidogrel[15]. Platelet functions before and after clopidogrel therapy was analyzed in 544 individuals by conventional aggregometry. Using light-transmittance aggregometry and analyzing the change in maximal platelet aggregation with 5 μmol of ADP as the agonist, they discovered that the mean change in aggregation from baseline after the initiation of clopidogrel therapy was 41.9%, with a SD of 20.8% .The histogram of the study population is consistent with a normal, bell-shaped distribution. There were 23 subjects (4.2%) with a change in ADP-induced platelet aggregation greater than two standard deviations above the mean (>83.5%); they were considered to be hyper-responders. Similarly, 26 subjects (4.8%) experienced almost no measurable change in aggregation (<2 standard deviation reductions in aggregation from the mean); they were considered to be hyporesponders. They had used 300mg loading dose of clopidogrel before PCI in this study.

Muller et al defined nonresponders as those with <10% reduction in platelet aggregation to ADP and semi responders as those with 10% to 29% reduction 4 hours after 600-mg clopidogrel load, as no additional effect was seen with this

treatment regimen at 24 hours[16] . This study found that to 5 μmol/L ADP, 5% were nonresponders and 9% were semi responders, and to 20 μmol/L ADP, 11% were nonresponders and 26% were semi responders.

However, despite the recognition for several decades of wide inter patient variability in the measured response to antiplatelet therapy, a true relationship between any test of platelet inhibition and clinical outcomes was not evident for a long time. The term "clopidogrel resistance" (as opposed to clopidogrel response variability) can only be accurately used when there is documentation that administration of clopidogrel not only results in a lack of platelet inhibition but also yields less clinical benefit than in patients achieving greater levels of platelet inhibition[6] . Some investigators argue that platelet response is a continuous variable like blood pressure and , it would be reasonable to classify patients who have recurrent events on therapy as having failure of therapy, while limiting the term resistance to those patients for whom the agent does not achieve its pharmacological effect[3,6] . In most studies resistance have been defined arbitrarily either based on specific cut off values of platelet aggregation to an agonist like ADP or by percentage reduction in aggregation after clopidogrel or using values above one or 2 standard deviations of the aggregation response after clopidogrel. This has lead to much confusion. Recent studies indicate that rather than estimating the platelet response in comparison to basal platelet activity estimation

of post treatment platelet reactivity alone is associated with more significant clinical implications[17,20] .

Mechanism of variable response after clopidogrel

Individual heterogeneity in responsiveness to antiplatelet agents may be due to either inherited or acquired factors. These potential variables include genetic polymorphisms in platelet proteins targeted by the drugs, differences in their pharmacokinetics, drug or other environmental interactions, and the baseline state of platelet function before initiation of treatment. Although intrinsic platelet hyper reactivity may be due to acquired factors, such as accelerated vascular disease (eg, acute coronary syndrome), hypertension, diabetes, or smoking, it can also be caused by genetic factors[6]. The molecular basis for inter individual variability is less well understood than for aspirin. Polymorphisms affecting the CYP3A4 enzyme that converts clopidogrel to its active metabolite may have a part in determining the variable response. Large clinical trials have shown that interaction with some statins which are also metabolized by CYP3A4 is not a major determinant of hypo responsiveness to clopidogrel.

Clinical implications of variable response to clopidogrel.

Many small non randomized studies have described higher residual platelet aggregation response while on dual antiplatelet treatment in patients who had

developed stent thrombosis post PCI. Because ischemic events are strongly influenced by platelet-mediated events, it is logical to hypothesize that patients suffering these events will have greater ex vivo platelet reactivity than those without events despite the use of antiplatelet drugs .A major reason for the lack of data correlating individual platelet function to the occurrence of ischemic events is the tedious nature, labor, and expense of serial testing with conventional laboratory assays. There are only few studies prospectively evaluating patients with low response to clopidogrel. Gurbel et al in 2004 reported the high prevalence of platelet reactivity above the baseline in patients who underwent percutaneous intervention which was persistent even 30 days after stenting. In the PREPARE POST STENTING study Gurbel et al studied the pre and post treatment platelet reactivity after 300 mg loading dose followed by 75mg/day of clopidogrel. On follow up it was found that those patients who had ischemic events had higher post treatment platelet reactivity as assessed by LTA and measurement of clot strength using thromboelastography[17]. The change in mean platelet aggregation between pre- and post procedure for the event group was 8% versus 17% for the group without events ($p < 0.001$). More importantly, ~50% of the events occurred in patients with 25th to 75th percentile post treatment platelet reactivity to ADP. This observation may suggest that agonists other than ADP play a dominant role in the genesis of ischemic events and that antiplatelet therapy directed against $P2Y_{12}$ and cyclooxygenase-1 in the current dosages is not sufficient to overcome thrombosis in selected patients. In this trial, however patients were not stratified before

clinical events to different degrees of platelet reactivity or clot strength and data on drug compliance is not provided.

Matetzky et al in 2004 reported the incidence of post stenting ischemic events in 60 patients after percutaneous intervention for STEMI. Almost all patients who had an event in the next 6 months were low responders to clopidogrel (inhibition of platelet aggregation below 25 percentile) [18] .

Recently several new study data are available that point to the clinical implications of response variability. Hochholzer et al showed that after 600mg loading dose of clopidogrel in 802 consecutive patients, platelet reactivity immediately before PCI significantly influenced the incidence of ischemic events at 30 days[19]. Post treatment aggregation values above the median were associated with 6.7 fold increased risk for ischemic events. In this study, the 2 quartiles showing more platelet aggregation had more diabetics and body mass index was also higher in these groups. There was trend towards greater prevalence of smoking and LV dysfunction in the high platelet reactivity quartiles. Similar studies with varying loading doses of clopidogrel has shown that higher loading doses are associated with lower platelet reactivity early after PTCA and that such dosing decreases ischemic clinical events post PCI. Buonamici et al published his data on 804 patients in whom platelet reactivity was tested after PCI. At 6 months, impaired platelet reactivity, more than 70% aggregation with ADP, was independently associated with subsequent risk of stent thrombosis after 6 months. This study

however had larger proportion of high risk patients compared to other studies using DES[20]. Stent thrombosis (definite and probable) rates in the whole population were 3.1% at 6 months; all were sub acute stent thrombosis. By multivariate analysis, in addition to non responsiveness to clopidogrel; LV dysfunction , longer stent length and acute myocardial infarction correlated with future risk for stent thrombosis . The cardiac mortality rate was 8.6% in the nonresponders and 1.4% in responders to clopidogrel.

Thus it has become clearer that platelet non responsiveness do play a role in the future risk of ischemic events. However most of the studies to date have only evaluated the effect of higher loading dose of clopidogrel to attain optimal level of platelet inhibition during the procedure of PCI or for few days after the procedure. But stent thrombosis and other ischemic complications continue to occur for several months after the index procedure. The exact reasons for such events are not clear. For drug eluting stents incomplete endothelialisation and persistent fibrin on the stent are considered risk factors. In most cases of late stent thrombosis drug non compliance is thought be an important factor .However, other factors may be important. In most series, at least 50% of cases of late stent thrombosis occurred while the patients were on adequate dual antiplatelet treatment.

Maintenance dose of clopidogrel.

A clopidogrel dose of 75 mg/d is commonly used during chronic therapy. This dose has been selected because it leads to antiplatelet effects equivalent to those of 500 mg/d ticlopidine, the first of the thienopyridine drugs used clinically. Nevertheless, it is still not known whether further suppression of platelet function can be achieved with clopidogrel in addition to that provided by the currently recommended maintenance dose of 75 mg/d. In a study published in 2004 by Kastrati et al a loading dose of 600 mg when given to patients already on chronic treatment of 75mg/day achieved significantly more platelet inhibition compared to 600mg loading for patients who were not on chronic treatment[22]. This means that higher platelet suppression is possible for patients on chronic treatment. This is not surprising as earlier dose ranging studies of clopidogrel did not conclusively show that 75mg/day is the ceiling dose for clopidogrel. At the same time there is significant lose of efficacy with dose of 60 mg/day. It is in this context that the biochemical and clinical effect of higher maintenance dose of clopidogrel should be sought.

Aims

The aim of the study was to assess the utility of higher dose (150 mg/day) of clopidogrel as maintenance dose after coronary intervention to suppress platelet reactivity as assessed by a standard platelet function test, compared to the standard maintenance dose of 75 mg/day of clopidogrel. The study also aimed to analyze the safety profile and tolerability as well as clinical benefits if any, of the higher dose of clopidogrel.

Patients

Consecutive patients who underwent non emergent PTCA with bare metal stent implantation were randomized into the study. All these patients were on aspirin 150 mg and most of them on clopidogrel 75 mg /day for a variable duration prior to PTCA. On the day of PTCA a further loading dose of 300 mg of clopidogrel and 300 mg of enteric coated aspirin was also given more than 4 hours prior the PTCA. Patients who had drug eluting stents implanted were excluded from the study as it was the usual practice to continue 150 mg/day of clopidogrel in these patients empirically for at least one month. Patients who underwent percutaneous coronary intervention for complex coronary lesions were like wise excluded.

Inclusion Criteria

Non emergent PTCA

Use of Bare metal stent

Exclusion Criteria

Primary angioplasty

Emergency PTCA for unstable syndromes

Use of Upstream Gp IIb/IIIa Inhibitors

Ostial lesions

Lesions requiring Bifurcation strategy

Angiographic thrombus

Known bleeding/ platelet disorders

Platelet count < 1.2 Lakhs/cmm

Severe LV dysfunction

Hepatic disease

Renal Dysfunction, Creatinine > 2 mg/ dl

Allergy to clopidogrel or aspirin.

Methods

Study Design and randomization

This was a Randomized controlled study. Patients were included in the study if they satisfied the inclusion and exclusion criteria. Randomization was done pre discharge. Computer generated randomization sequence was used to randomize the patients. 50 consecutive patients who met the inclusion and exclusion criteria were randomized to the 2 arms of the study .Group A received the standard maintenance dose, 75mg/d of clopidogrel while group B received the higher maintenance dose, 150 mg/d of clopidogrel. Both group of patients also received 150 mg of aspirin (enteric coated) and 10 or 20 mg /day of atorvastatin. Any patient who developed in hospital complications were not included .Platelet aggregation was also studied in a group of controls.

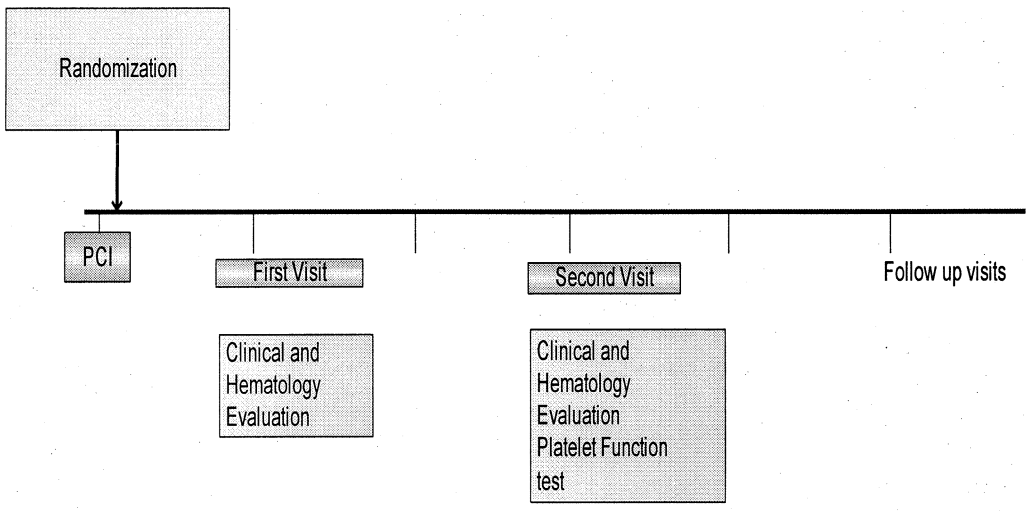


Figure 1 . Randomization and Follow up

Methods

Follow up evaluation was done for cardiac events, side effects and hematology parameters . Platelet aggregation study was done during second visit (at 3 months) after PTCA. Drug compliance was ascertained by interview. The study medication of higher dose of clopidogrel was maintained till 6 months. After the second visit follow up was at 6^{th} month and then six monthly.

Aggregometry: Platelet aggregation was done with optical Aggregometry, which is considered the gold standard for assessing platelet reactivity. The tests were done at the Thrombosis Research Unit of the Biotechnology division of the Institute. Blood was collected in acid citrate dextrose in a ratio 8.5:1.5. Control blood was also collected. All samples were processed within 60 min of collection. For the aggregation test we used the Optical Aggregometer (Whole blood lumi-ionized calcium aggregometer, Chrono- Log Corporation; USA) using 2 reagents - ADP and Collagen . Both early and late response to ADP reflective of the inhibition $P2Y_{12}$ clopidogrel receptor on the platelet was analyzed.

In the Lab, blood was centrifuged at 2500 rpm for 5 minutes to get Platelet rich plasma (PRP) and further centrifuged at 4000 rpm for 15 minutes to get platelet poor plasma (PPP). PRP was diluted with PPP to get 2×10^8 to 2.5×10^8 platelets per ml. Aggregation was tested with addition of two agonists— 5micro mol ADP and Collagen. As platelets aggregate the PRP becomes less turbid and transmits more light which is measured. Extent of aggregation is expressed as percentage of

light transmission. The PRP is considered as 0% light transmission and PPP as 100% light transmission. The Change in light transmission is continuously recorded and plotted. As aggregation proceeds the light transmission of the sample PRP approaches that of PPP. Both the velocity (slope) of aggregation and the extent (% change in light transmittance, at maximum aggregation) of aggregation were measured.

Results

The final analysis included data from 44 patients whose platelet function test was available as planned, 22 patients in each group.

Statistical analysis

All data are reported as means ± SD. No confirmatory statistical purposes were pre-specified. Categorical values were tested using the chi-square test. Continuous variables were compared using independent t test. Comparison between groups was done using paired sample t test. **p** value of <0.05 was considered to indicate statistical significance .Analysis was performed with the SPSS 14.0 statistical software.

The baselines characteristics and procedural characteristics were similar between the two groups. Nine patients (41%) in group A and 11 patients (50%) in group B were diabetics. Fifty percent of patients in both groups received Glycoprotein IIb/IIIa inhibitors during the procedure. Patients with significant procedural or peri procedural complications were not included for randomization.

The patients were followed up for mean of 12.3 months (range 6 months to 19 months) .

	Group A	Group B	
Age	55.95+-8	51.4 +-9	NS
Sex , n of males	20	19	NS
BMI	25.06 +-3.06	23.87 +-3.7	NS
Diabetes ,n (%)	9(41%)	11(50%)	NS
Hypertension (%)	14(63%)	9(41%)	NS
LV dysfunction ,n (%)	3(13%)	6(26%)	NS
Multivessel disease ,n (%)	10(45%)	8(36%)	NS

Table 1. Baseline characteristics

	Group A	Group B	
Type of lesion , n			
A	**4**	**2**	**NS**
B	**16**	**17**	**NS**
C	**2**	**3**	**NS**
Multi vessel PTCA, n	**2**	**3**	**NS**
Stent length ,mm	**19.4+-6**	**22.3+-8**	**NS**
Stent size ,mm	**2.85+-0.47**	**2.63+-0.28**	**NS**
Adjuvant IIb/IIIa use ,n	**12**	**12**	**NS**
Post Procedure CPK	**110+-77**	**99+-30**	**NS**

Table 2. Procedural characteristics

Platelet Aggregation response

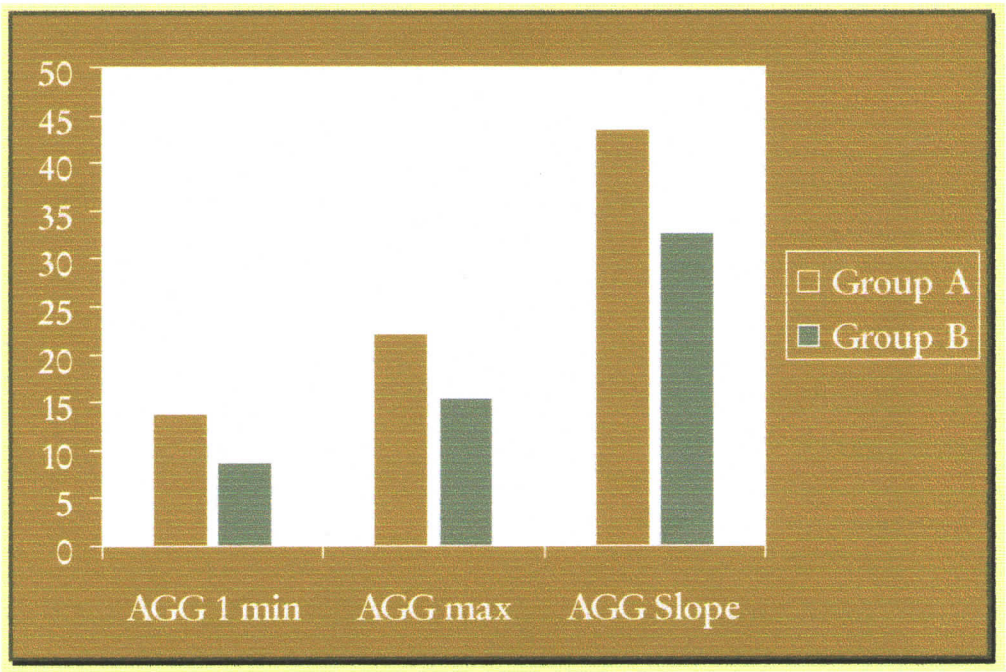
Platelet aggregation was tested with two reagents – 5 micro mol ADP and Collagen.

With 5 micro mol ADP both the study groups showed considerably less aggregation than the controls. The extent of aggregation was greater in Group A(75mg/day) compared to group B(150 mg/day). The higher maintenance dose produced 30% more inhibition of aggregation but failed to reach statistical significance (22.14 +- 16.6 Vs 15.41 +- 10 , p = 0.1 ; control (mean) - 52.4). The dual antiplatelet treatment with aspirin and 75mg/day of clopidogrel produced more than 50% inhibition of platelet aggregation to ADP, when compared to the controls.

The slope or velocity of aggregation was significantly different between the groups (43.41+- 18 in group A Vs 32.82 +- 10 in group B, p= 0.023), showing the enhanced platelet inhibition with 150mg/day of clopidogrel.

The ratio of aggregation in each subject to the extent of aggregation of the corresponding controls were analyzed and compared between groups; there was significant difference between the groups (0.41 +- 0.28 for Group A Vs 0.26 +- 0.14 for Group B ,p = 0.03) .

Both groups of patients showed equal inhibition of aggregation with the agonist collagen. The diabetic patients in each group showed greater aggregation (ie less inhibition of platelet reactivity). The diabetic patients on 150 mg/day of clopidogrel showed a greater inhibition of platelet reactivity but this was not statistically significant (24.5 +- 16.9 Vs 17 +- 9.4, p = 0.22).The aggregation values were not influenced by Body Mass Index.



	Group A n = 22	Group B n =22	p
Amplitude of Aggregation at 1 min	13.8+-9	8.95+-7.5	0.06
Aggregation Max	22.14+-16.6	15.41+-10	0.11
Slope of aggregation	43.41+-18	32.82+-10	0.023

Fig 1 and Table 3. Aggregation values for both groups at 1 min and maximum aggregation and the slope of aggregation.

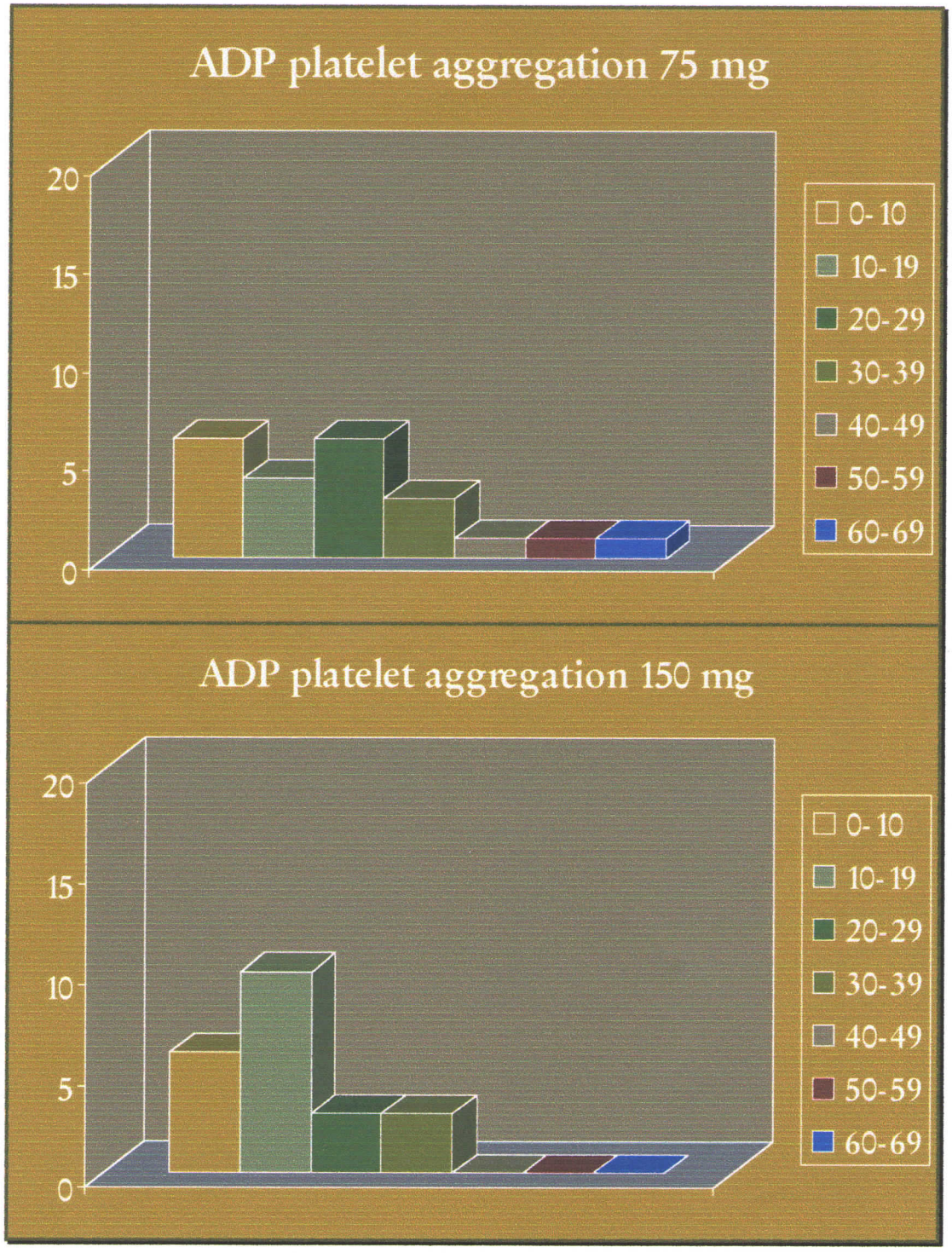
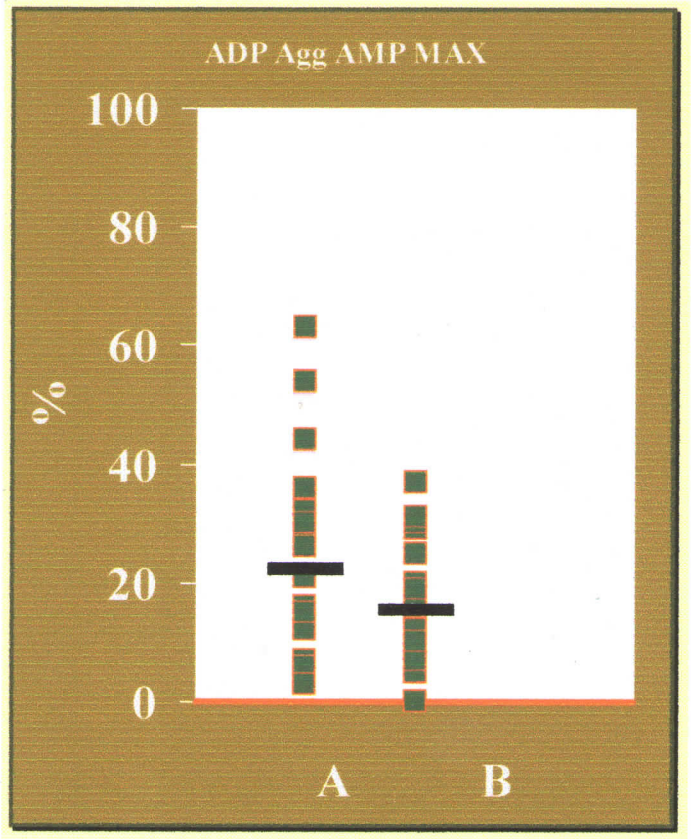
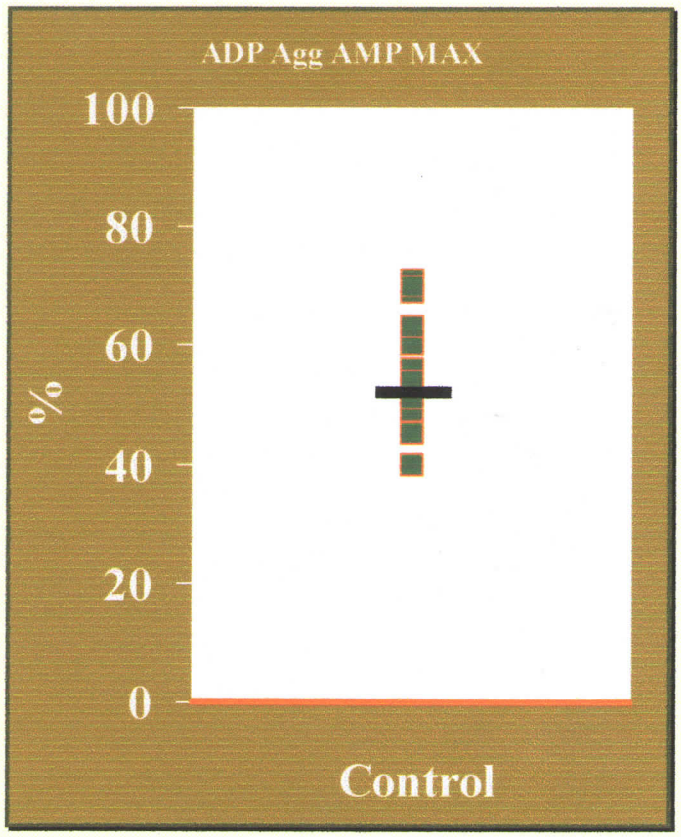


Fig 2 : The distribution of patients according to Agg max for the two groups





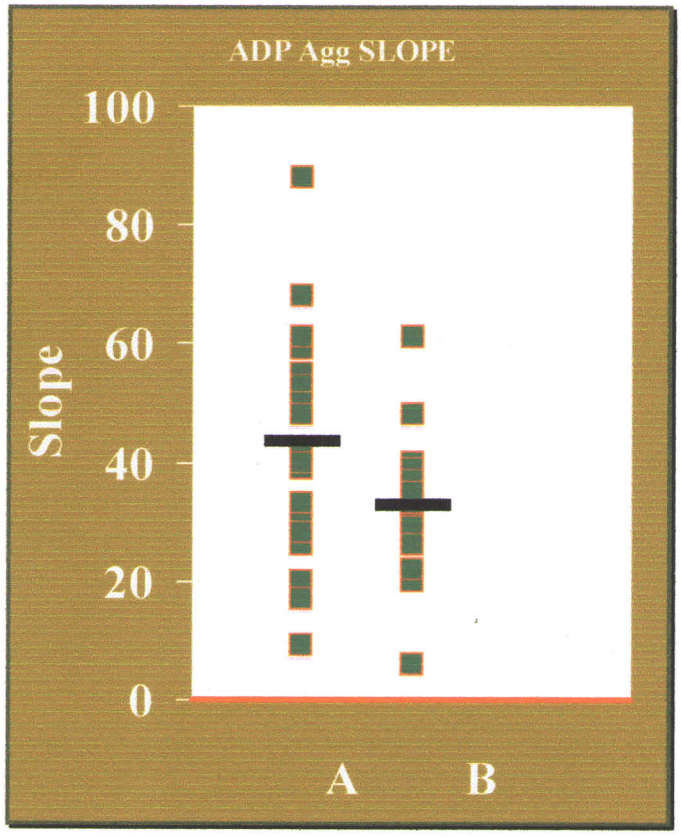


Fig 3 (Above) : The distribution for the aggregation values in each group and controls

Fig 4 (Left) : The distribution of slope of aggregation

	Group A n = 22	Group B n =22	p
Ratio of Amplitude of aggregation (Subject/Control)	0.41+-0.28	0.26+-0.14	0.03
Ratio of Slope of aggregation (Subject/Control)	0.95+-0.66	0.65+-0.26	0.06

Table 4 . Ratio of aggregation value and slope of aggregation to the corresponding control values for patients in each group.

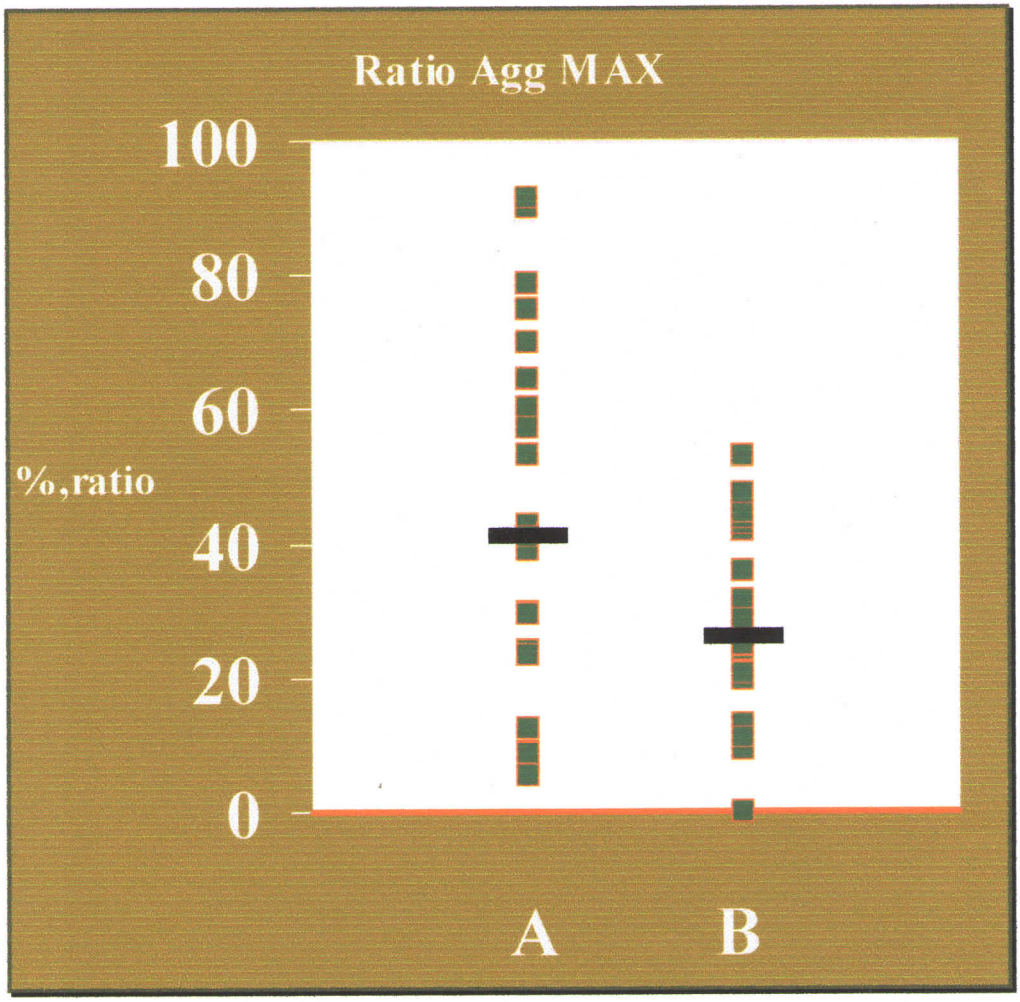


Fig 5. Ratio of aggregation values of patients to aggregation values of the controls , for Group A and Group B

On follow up, two patients in each group had an acute coronary event. One patient in Group A underwent coronary angiography for clinical restenosis. He subsequently presented again with an acute coronary syndrome and underwent percutaneous coronary intervention for in stent restenosis. Another patient, from Group B, presented with sub acute stent thrombosis 6 months after randomization which was attributed to drug non compliance. Two other patients presented with Troponin negative unstable angina. No patient developed a serious adverse effect necessitating withdrawal of the drugs. Four patients in Group B (150 mg/day of clopidogrel) developed gastric intolerance while 2 patients in group A had that adverse effect. Only one patient in group A transiently discontinued the drug during study period. At no point in follow up did any of the patients develop anemia, leucopenia or thrombocytopenia.

Discussion

The initial few dose ranging studies of clopidogrel resulted in the selection of 75mg/day as the standard dose for clopidogrel. The volunteer studies had at that time showed that 150 mg/day of clopidogrel was superior to 75 mg in terms of inhibition of platelet aggregation with more prolonged bleeding time[21]. The equivalency to ticlopidine was the more important concern and as clopidogrel at 75 mg/day was shown to be better than ticlopidine, clopidogrel continued to be used in the same dose.

At the same time , it was recognized that the high risk groups such as after PCI and after ACS would benefit with higher degrees of platelet inhibition , Patients with Type 2 Diabetes may also show higher platelet reactivity and less response to the platelet antagonists like aspirin and clopidogrel [23]. Thus subsequent studies mainly concentrated on various loading doses of clopidogrel before percutaneous intervention. But the benefit of a loading dose wanes of and during the subsequent phase of treatment after percutaneous coronary intervention the patient continues to be at risk of thrombotic complications depending on the individual's response to the platelet inhibiting drugs.

Over the last 2 years more evidence has come in regarding the variability of response to clopidogrel and the adverse clinical outcome in those patients who continued to show significant platelet aggregation in spite of being on dual

antiplatelet treatment. At the same time, the current treatment guidelines have been shown to significantly reduce the acute and sub acute thrombotic complications after percutaneous coronary intervention. Further, acute and sub acute stent thrombosis is caused by various demographic and procedural factors and not only by the non compliance to drugs or hypo responsiveness to anti platelets.

The present study is a single institution randomized study to evaluate the effectiveness of a higher maintenance dose of clopidogrel to achieve further platelet inhibition in a group of patients after percutaneous coronary intervention. At the time of randomization for the study there was no data regarding the effectiveness of this higher dose , either biological or clinical , in patients with CAD. The study demonstrated that higher dose of clopidogrel produces more intense platelet inhibition. Even though the difference in primary end point of maximal platelet aggregation was not statistically significant the slope of aggregation was significantly reduced in the higher dose group. The ratio of maximal aggregation in patients to that of corresponding controls was also significantly reduced in the patients on 150mg/day of clopidogrel compared to those on 75mg/day of clopidogrel. Further, even though the higher dose was maintained for a minimum of 3 months there was no difference in adverse effects or drug intolerance.

Recently two controlled trials have been reported regarding the laboratory effectiveness of 150 mg/day of clopidogrel after percutaneous coronary intervention compared to standard dose of 75mg/day. The OPTIMUS study randomized 40 sub optimal responders to clopidogrel from a group of diabetic patients followed up after percutaneous coronary intervention into two arms of the study – 150 mg/d or 75m/day of clopidogrel for 30 days[24]. At 30 days platelet function tests were done using light transmission Aggregometry and flow cytometry for vasodilator-stimulated phosphoprotein (VASP). They showed that higher dose resulted in a further 15% inhibition of aggregation which returned to baseline after reverting back to the standard dose. The VASP phosphorylation a measure of $P2Y_{12}$ reactivity was also significantly reduced with the higher dose.

The ISAR CHOICE 2 investigators randomized 60 patients who underwent elective percutaneous coronary intervention after a loading dose of 600mg of clopidogrel[25]. The group which received 150mg/day of clopidogrel had greater inhibition of platelet aggregation at 30 days. Maximal 5 mM ADP-induced platelet aggregation 30 days after PCI was significantly lower in the group treated with 150 mg/day (45.1+20.9%) than in the group treated with 75 mg/day (65.3+12.1%; P , 0.001). They also used *The Verify now* P2Y12 assay and demonstrated greater inhibition with higher maintenance dose.

Both the above studies maintained patients on higher dose of clopidogrel only for 30 days. No clinical benefit of higher dose was demonstrated. In our study the

dose difference was maintained for at least 3 months. This may help in ruling out any effect of the variability in dose response to the loading dose at the time of percutaneous coronary intervention. The tolerability of higher dose of clopidogrel also is more clearly demonstrated.

By reducing the incidence of stent thrombosis a higher dose of clopidogrel during maintenance may decrease morbidity and mortality. But any clinical benefit of a higher dose is yet to be demonstrated and hence it will be premature to advice routine use of this higher dose. However, in high risk groups like type 2 diabetics and patients who already had stent thrombosis or in those patients whom enhanced platelet aggregation has been demonstrated by in vitro tests it may be prudent to prescribe 150 mg/day of clopidogrel as the maintenance dose after percutaneous coronary intervention.

Conclusion

There is significant individual variation in dose response to clopidogrel with the standard dose. Higher maintenance dose of clopidogrel showed significant in vitro efficacy in inhibiting platelet reactivity compared with the standard dose of 75mg/day. The higher dose appeared to be well tolerated and had no added side effects. Further larger randomized studies may demonstrate

translation of this greater inhibition of platelet activity into greater clinical benefit with higher dose clopidogrel.

Limitations of the study

The study was planned as a pilot study. Some end points did not reach statistical significance because of the smaller number of patients randomized. The baseline values of platelet reactivity were not assessed and hence the actual drug effect could not be measured. But the study clearly demonstrated difference in post treatment platelet reactivity with the 2 doses used, and previous studies have shown increased platelet reactivity post treatment is associated with increased events. Only the Lab personnel doing the platelet function test were blinded to the randomization sequence. Drug compliance was ascertained by patient interview only. Even though the study shows the in vitro efficacy of higher dose of clopidogrel over the standard dose, it is a small study and hence the effect of the higher dose on clinical events and adverse effects cannot be assessed.

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PAEDIATRIC PACEMAKER IMPLANTATION : SHORT AND LONG TERM OUTCOMES .

Abstract

Introduction : Permanent pacemaker implantation is a niche area accounting for less than one percent of all implantations . The indications , the pacemaker system and the pacemaker modes are different from that used in adults. The natural history of the patient with implanted device is important not only to define the use of such pacemakers but also for introducing new and technologically advanced devices and implantation techniques. However such data is limited , especially from developing countries like India

Aims : To define the natural history of children and adults with an implanted pacemaker

Materials and Methods: This is a retrospective study based on hospital data from inpatient and outpatient records. Systematic evaluation for indications for pacing , mode of pacing , presence of structural heart disease as well as early and late complications were assessed . Follow up records for obtaining lead survival and event free survival was assesses for the different patient groups

Results : A total of 71 permanent pacemaker implantation from 1982 to June 2007 were analyzed. This included 17 patients below age 6 years and 17 patients with epicardial pacemakers. 32 patients had structural heart disease with sixteen post operative cases (implantation within 30 days of surgery) and 9 late post operative cases. The follow was for mean of 7.9 years .Early complications within one month occurred in 14 cases (20%) , only age and postoperative nature of implantation tended to influence early complication . Survival free of major early

complication and re intervention was influenced by post operative status alone (p--059). Structural heart disease or epicardial implantation did not influence freedom from intervention. Lead survival at 5 years was influenced by epicardial placement of lead (p – 0.032) and date of implantation.

Conclusion: The long term experience of pacing in children less than 18 years showed acceptable short term results and good long term results with reasonable lead survival comparable to studies from developed countries.

Introduction

Pediatric cardiac pacing is a rapidly advancing field .Some advances are due to the improved technology and miniaturization. Perhaps the most important advances are due to our understanding of the mechanism of the arrhythmias and of their natural history and the natural history of the devices when implanted in children. In addition to pacing for atrio ventricular node and sinus node dysfunction devices are now available for treatment of atrial and ventricular tachyarrhythmias.

The number of children who need a pacemaker (PM) is small and negligible in relation to the number of adults being supplied with a PM. Only about one percent of all pacemakers are implanted into children. For this reason no hardware was specifically designed for this small cohort and up to this day all implantations in children are carried out with the hardware which was developed for the grown-up population [1].

Indications for cardiac pacing in children

Indications for pacing in newborns and infants are divided predominantly into three groups [1]: congenital abnormalities of the conduction system, acquired heart blocks after cardiac surgery for correction of congenital defects and sinus node diseases. Rare indications include the therapy of tachyarrhythmias, of hypertrophic obstructive cardiomyopathy and of the long-QT-syndrome .

The logic behind the decision to pace will be based on the patient's age and symptoms, the kind of disease and its natural history, and the possible coexistence of structural, congenital heart disease.

Congenital complete AV block

Congenital AV block is a relatively rare entity that is due to abnormal embryonic development of the AV node, or is the embryonic result of maternal lupus erythematosus. Congenital heart diseases, such as corrected transposition of the great arteries and ostium primum atrial and ventricular septal defects, may be associated with third-degree AV block. Isolated congenital AV block is mainly marked by an unusually slow heart rate, rather than by the symptoms it causes. The ECG usually reveals a third-degree AV block with a stable narrow QRS-complex escape rhythm. Nowadays, it is clear hat the child's symptomatology is not the main criterion for pacing: the prevailing view now recognizes that early

pacing based on a number of criteria (average heart rate, pauses in the intrinsic rate, exercise tolerance, presence of maternal antibodies mediated block, and heart structure) is the recommended treatment of choice. Although some patients can live into adulthood with congenital complete AV block , others become symptomatic and die suddenly in adolescence . Thus the indication for pacing is not based on symptoms alone[2].

The mortality in children with isolated CCAVB is estimated at 8 to 16% in infants and 4–8% in children and adults. With associated structural heart disease infant mortality is estimated at 29% and childhood mortality at 10%. The only effective treatment is permanent cardiac pacing [2]

Sinus node disease

Sinus node disease, although uncommon, is increasingly recognized in paediatric and adolescent patients, especially after atrial surgery for congenital heart diseases. In the young patient with sinus bradycardia, the criterion that carries most weight in the decision to pace is the symptoms (i.e. syncope or inappropriate weakness or dyspnoea), rather than absolute heart rate criteria. Bradycardia–tachycardia syndrome is often encountered in patients following surgery for congenital heart disease.

The syndrome is manifested by periods of bradycardia that are often associated with atrial tachycardia or atrial flutter. The mixed nature of the syndrome makes treatment difficult or ineffective and often requires a complex therapeutic

approach, combining antiarrhythmic medication, catheter ablation, or special anti-tachycardia pacing algorithms, with conventional ventricular pacing to treat episodes of excessive bradycardia .

Post operative atrioventricular block

AV heart block is one of the major complications of surgery for congenital heart disease and occurs in 1–3% of operations. Pacemaker implantation is recommended in patients with persistent post-operative heart block lasting for 7 days. Late recovery of AV conduction following pacemaker implantation for post-surgical block is found in a significant percentage of patients. However, it has not been possible to identify clinical predictors related to patient characteristics, type of block, or type of repair.

Other indications include pacing for haemodynamic benefit in HCM and for Long QT sysndrome [3]

Complications and risk in pediatric cardiac pacing

Permanently pacing in children is challenging due to anatomical abnormalities, difficult access to cardiac chambers, and small patient size

Traditionally children below 15 Kg were implanted with epicardial pacemakers whenever there was an indication for pacing. The problems

anticipated were difficult venous access and size of the pulse generator which could be better accommodated in the abdomen . Later the problems of vascular integrity became apparent. These patients require multiple lead replacements and generator changes and use of multiple leads increased the risk of venous thrombosis and AV valve damage . Furthermore, as the child grows it can lead to traction on the leads leading to rising thresholds and loss of capture. Children are also prone to produce injury to the lead resulting in lead fractures [4]. Use of bipolar leads is necessary to avoid pectoral muscle stimulation. This method is not ideal in case of right to left intracardiac shunts with the risk of systemic embolism. Furthermore venous access to cardiac chambers may not be possible in patients with abnormal cardiac anatomy or in some post operative patients eg post Fontan repair [1].

The problems with epicardial implantation is that it is more invasive and hence frequent pulse generator and lead changes becomes bothersome. Also the incidence of lead fractures is more. Pacing threshold is often higher with epicardial leads and it leads to more frequent pulse generator changes. But with newer steroid eluting leads and better follow up the longevity of epicardial pacing is nearly as good as endocardial pacing .[5]

Over the last one decade or so technological advancements and good technique have made endocardial placement the desired mode. New lead designs

allow for smaller size of leads for better venous access and decreased risk of venous thrombosis .Steroid eluting capability and active fixation techniques gave better long term stable pacing.

Pediatric pacing in clinical practice

The general policy in pediatric pacing is variable from one institution to another .Continuous evolution of pacing technology has made comparison between patients group difficult . The reported experience from various institutes have used different approaches in patient selection for endocardial and epicardial pacing, different lead architectures, different modes of pacing and different methods of follow up.

With availability of various new technologies and advanced surgical techniques the policy followed in developed countries is significantly different from that is used in developing countries like India. The indications for cardiac pacing are also different. A tertiary centre catering to congenital heart disease is for instance likely to have more post surgical patients with complete AV block and sinus node dysfunction. At the same time there is paucity of data regarding the natural history of children with bradyarrhythmia and the natural history of children undergoing pacing at a young age. Going through the literature we could find no large series or single centre experience pertaining to pediatric cardiac pacing from any developing country.

Aims

To analyze the short and long term out come of pediatric cardiac pacing in our institute , with emphasis on use of different modalities of pacing and their effect on lead related complications and long term survival.

Methods

We have retrospectively analyzed all the records of patients who have undergone pacemaker implantation till the age of eighteen years from the Sree Chitra Tirunal Institute of Medical Sciences and Technology from the year 1982 till middle of 2007. The data analyzed include the hospital in patient records , the procedure records , pacemaker implantation register from catheterization lab ,operation records of patients who underwent surgery and epicardial lead placements , out patient records of follow up and pacemaker interrogation .

The age of eighteen years for selection to the study is based on previous studies which show that indication for pacing as well as presence of structural heart disease is a common feature in many of these patients and hence is significantly different from the larger adult population.

Age was taken as a continuous and nominal variable for comparison .The period of pacemaker implantation was recorded. Indication for cardiac pacing, the presenting symptom of the patient, physical examination and ECG and cardiothoracic ratio from chest X-ray was recorded. For patients undergoing

pacemaker implantation after surgery , the rhythm immediately after surgery and time to pacemaker implantation was noted .

The implantation procedure was analyzed for the use of general anesthesia , prophylactic antibiotic treatment , the route of intravenous access and the surgical procedure for epicardial permanent pacemaker implantation. The location of the pulse generator and the electrode were sought from the records. The fixation mechanism used as well as additional mechanism used for longer survival of the leads eg loop of the lead in right arium wherever applicable was also noted down[6]. The acute stimulation thresholds were also noted.

The complications after procedure were divided into early, occurring within one month, and late which occurred after one month. Time to the complication was sought to be analyzed separately as the majority of lead and pacemaker site related complications are known to occur till 3 months after procedure[7].

Definition of complications

The classification of the complications were based on previous short and long term studies[7,8] .The hospital records were not always adequately informative about the nature of these complications . However all records pertaining to re procedures could be obtained .

Long term follow up

Specifically, the lead related complications were looked for. Lead related was defined as re operation due to early battery depletion (< 4 years), chronic

stimulation threshold increase, lead fracture , lead dislodgement , sensing dysfunction and exit block.

Complications	Definition
Infection / Erosion	Local inflammation and abscess formation in generator pocket or erosion of part of the system with secondary infection or fever with positive blood cultures without a focus of infection elsewhere
Failure to capture	Failure to capture with threshold of at least 5mV with any pulse duration
Failure to sense	Failure to sense atrial or ventricular electrogram with any pacemaker programming
Lead fracture	Was considered when a definite fracture could be seen radio graphically or during the procedure of replacement of the lead
Lead dislodgement	Was considered if lead failure was due to change in position of the lead tip
Insulation failure	Improper capture or sensing with low impedance
Exit block at lead-myocardial junction	Failure to capture , usually due to micro dislodgement , with no evident dislocation or fracture with capture resumed by lead repositioning
Failure to capture due to unknown cause	
Haemothorax / Pnemothorax	Haemothorax or Pneumothorax resulting from the procedure of implantation
Wound haematoma	Wound haemoatoma which may or may not require intervention
Inappropriate muscle stimulation	Pectoral muscle or diaphragmatic stimulation by generator pulse

The out patient records were scrutinized for any evidence of sensing failure, especially atrial leads, nature of presentation before pulse generator change, record of stimulation threshold and impedance wherever available and adequacy of follow up . All re procedures were analyzed systematically.

Results

From 1982 to June 2007, a total of 80 patients till the age of eighteen underwent permanent pacemaker implantation from the institute. Records of nine patients were not available for scrutiny. Two of these patients were marked to have died. All missing records were for implantations prior to 1990. A total of 71 patient's records were available for analysis.

The patients

Thirty six percentage of patients were under 9 years of age. Only nine percent (n = 6) comprised children upto age 3. Females comprised 46 percentage of cases. The number of cases of pediatric pacemaker implantation steadily increased. The proportion of patients with structural heart disease also increased.

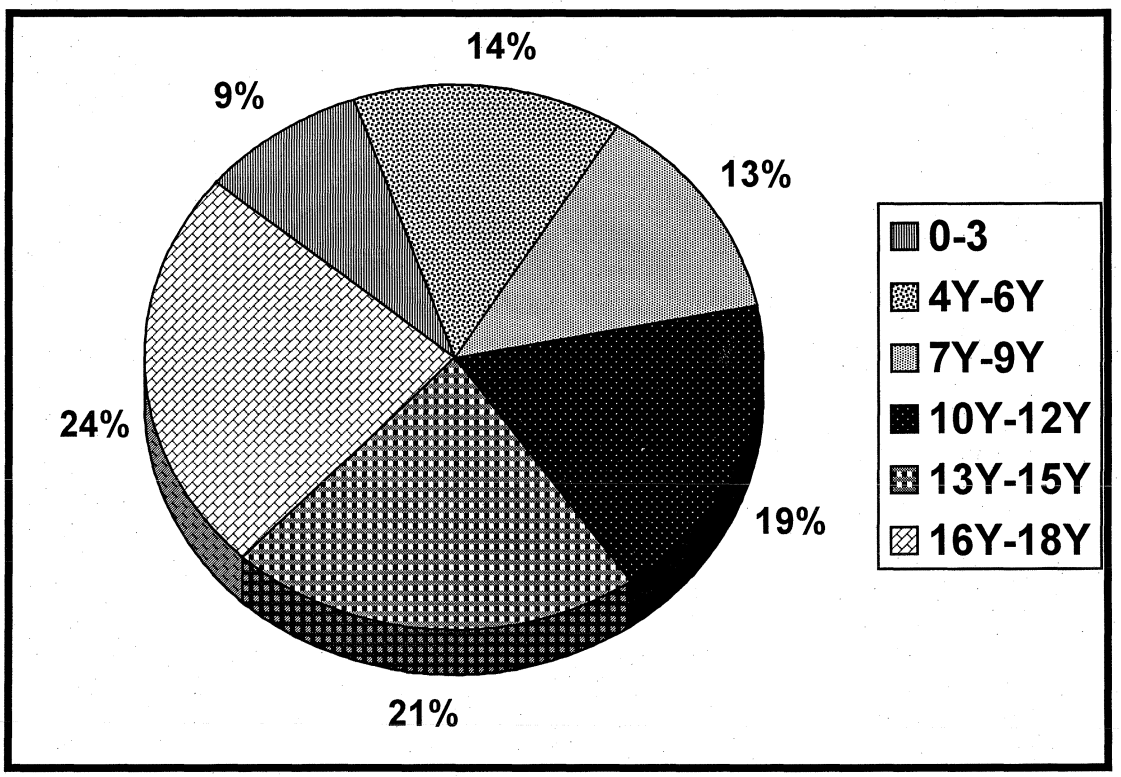

Figure 1. Age groups who underwent permanent pacemaker implantation

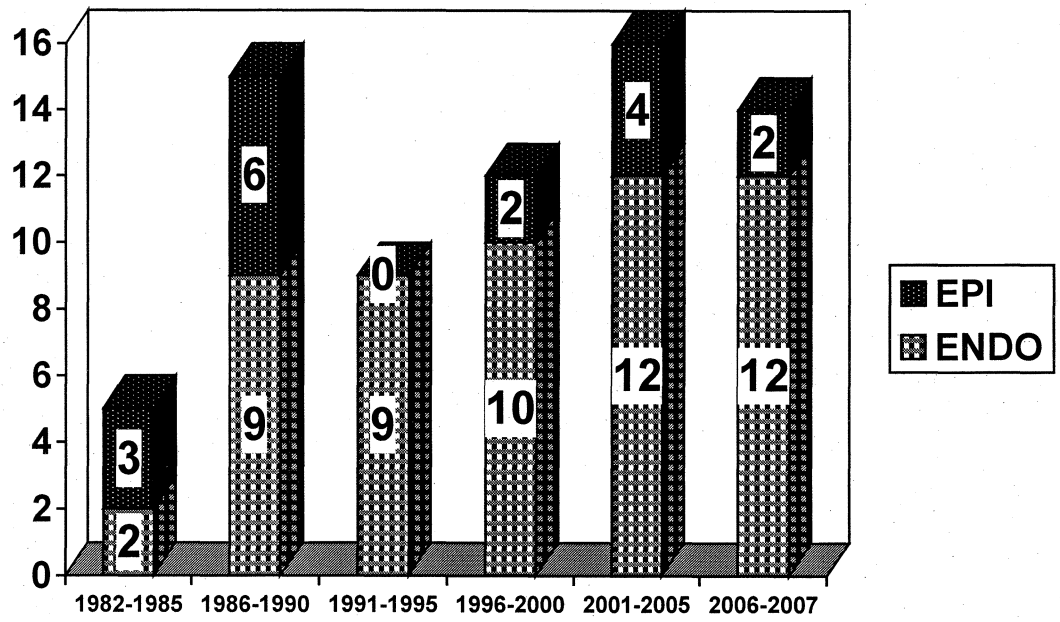

Figure 2. The distribution of cases over the years , the epicardial and endocardial cases shown separately.

The distribution of structural heart disease is given in Table 1. Thirty two of the seventy one patients had structural heart disease. Some of the structural heart disease did not have direct bearing on the arrhythmia eg one patient with mitral valve prolapse and mild MR who had congenital complete heart block.

STRUCTURAL HEART DISEASE	NUMBER
VSD	*11*
TOF	*5*
ASD	*4*
DTGA	*2*
DORV	*1*
TAPVC	*1*
LTGA	*3*
SINGLE VENTRICLE	*1*
OTHERS	*4*

	Date of Implantation		*Total*
	1982-1990	*1991-2007*	
No SHD	*13*	*26*	*39*
VSD	*3*	*8*	*11*
TOF	*0*	*5*	*5*
LTGA	*0*	*3*	*3*
Others	*4*	*9*	*13*
Total	*20*	*51*	*71*

Tables 1 and 2 : Structural heart disease seen in this series and date of Implantation

Till age of six the predominant diagnosis was congenital complete heart block (n-9)or post operative AV block (n -8) . Above age six, there were 19 case of CCHB, 16 cases of sinus node dysfunction, 9 cases of post operative AV block and 10 cases of high grade AV block including one post operative case.

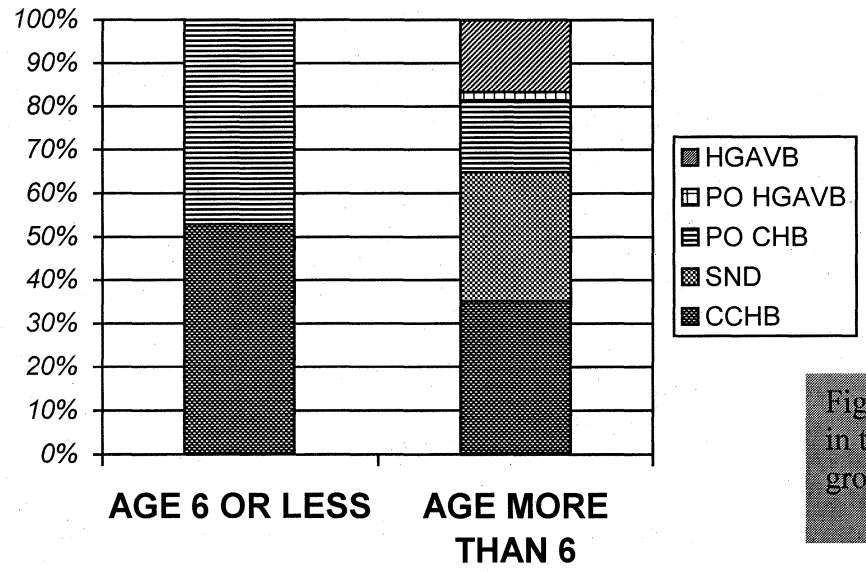

Figure 3 ; Diagnosis in the different age groups

The patients who had high grade AV block as their diagnosis included two patients who had permanent pacemaker implantation two and seven years after surgery (for LTGA,VSD and LTGA,VSD and PS) ; the other patients who did not have any surgery included 3 patients with no structural heart disease , one patient with LTGA ,two patients with small VSDs and one patient who had myocarditis. The patients with sinus node dysfunction included ten without any structural heart disease, three cases of post operative ASD closure, one case of DTGA with implantation 12 years after a Sennings procedure and one case with a restrictive cardiomyopathy.

Follow up

The follow up ranged from minimum of one month to 24 years , mean follow up of 7.9 years. A total of 14 cases were lost to follow up during the entire period. Majority of these patients are being followed up in other institutes. Five of the 14 with limited follow up had their pacemaker implantation before 1991.

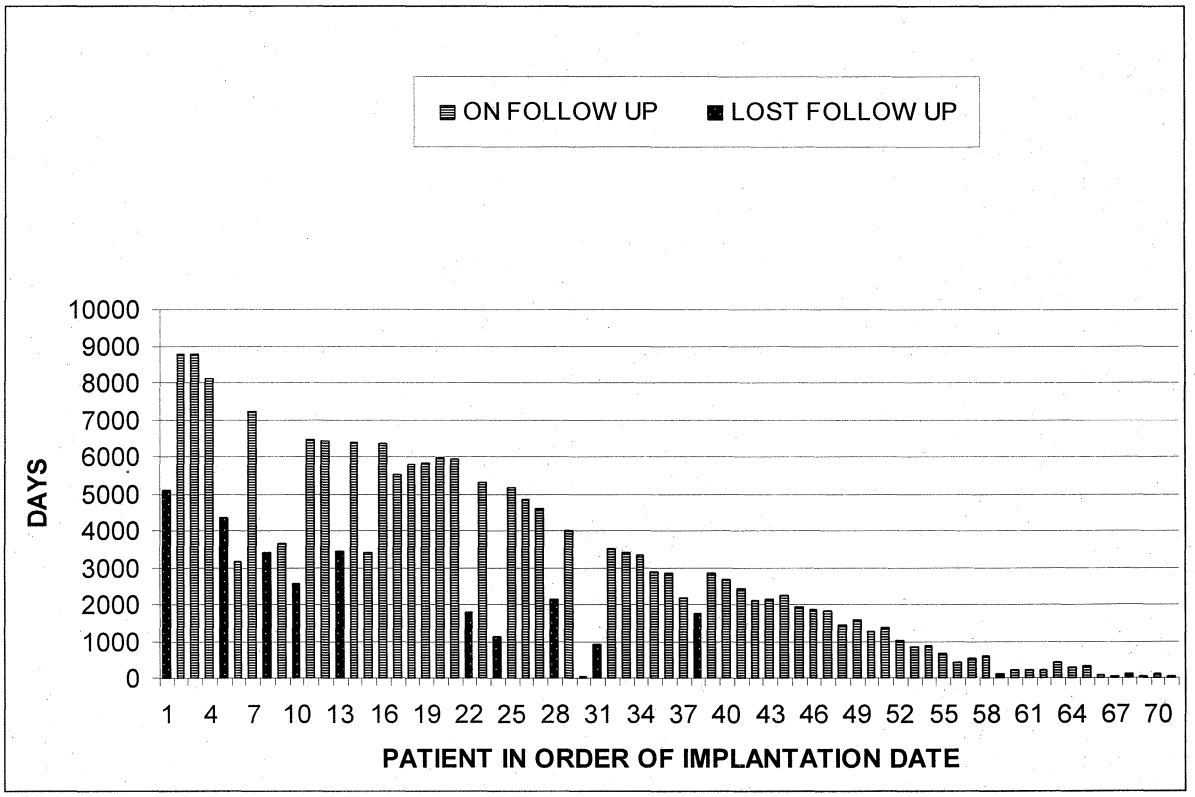

Figure 4: Follow up of the cases , those lost to follow up is marked darker.

Patient Survival

Of all the patients analyzed there was only one mortality . This was a 4 year old male patient who underwent pacemaker implantation with an endocardial lead in the right ventricle 20 days after a VSD closure surgery complicated by post operative complete AV Block in 1996. The patient had a sudden death at home 40 days after the pacemaker implantation.

The pacing characteristics

Of all patients, seven had VDDD pacemaker , one patient had an AAI pacemaker and one had DDD pacemaker as their initial implantation. The rest 62 patients had VVI mode. All epicardial (n- 17) were VVI mode. Mode other than VVI was used mainly in children more than 7 years with or without structural heart disease.

BASELINE CHARECTERESTICS		*PM MODE*			
		VVI	AAI	DDD	VDD
		n	**n**	**n**	**n**
DATE OF IMPLANT	*< 1991*	20	0	0	0
	1991- TODATE	42	1	1	7
SHD	*ABSENT*	34	1	0	4
	PRESENT	28	0	1	3
DIAGNOSIS	*CCHB*	26	0	0	4
	SND	14	1	1	0
	PO CHB	12	0	0	3
	PO HGAVB	1	0	0	0
	HGAVB	9	0	0	0
AGE	*0-6*	16	0	0	1
	7-18	46	1	1	6

Table 3 : pacemaker mode and baseline characteristics

The most important variables analyzed with respect to their effect on short and long term follow up were age , date of implantation and whether an endocardial or epicardial system was used as initial pacemaker therapy. Whether permanent pacemaker implantation was done post operatively or not also influenced outcome. Permanent pacemaker implantation was considered post operative if it was done

within 30 days of surgery or within the same surgical admission. There were 16 such cases. There were nine other post surgical cases ,but in whom permanent pacemaker implantation was done more than one month after surgery, this included one patient who had 2:1 AV block noticed 2 years after surgery but underwent permanent pacemaker implantation only 11 years after the initial surgery for VSD and PS.

Age

The age at implantation was an important predictor of events on follow up. Patients were divided into two groups – age 0-6 yrs and 7- 18 yrs. The proportion of patients with structural heart disease was not different between age groups. But the younger aged patients predominantly had ventricular septal defect and Tetrology of Fallot while the elder children had other heart diseases mainly ASD and mitral valve disease and non CHD like restrictive cardiomyopathy (1 patient). The diagnosis prior to pacemaker implantation was different for the two age groups (see figure 3) and the proportion of post operative patients were higher in the below 6 years category (47% Vs 20% , p 0.035).

The proportion undergoing epicardial pacemaker implantation was different in the two groups (53% vs 15%, p 0.003). Age did not influence the site of venous access in the case of endocardial pacemaker implantation.

Early complications after permanent pacemaker implantation was seen more commonly in the younger age group (35% Vs 13 %, p= 0.048). On long term follow up the younger group also had more number of lead changes; 6 lead changes Vs 7 lead changes in the elder children (p = .049). The number of re procedures including lead relocation, lead replacement and generator replacement was not different between the age categories.

AGE *BASELINE*		DATE IMP		PM MODE				SHD		SYSTEM	
		< 1991	1991-TODATE	VVI	AAI	DDD	VDD	ABSENT	PRESENT	ENDO	EPI
AGE	0-6	4	13	16	0	0	1	8	9	8	9
	7-18	16	38	46	1	1	6	31	23	46	8

Table 4: Age and baseline characteristics

Pacemaker implantation in the first decade

Twenty patients less than 19 years underwent pacemaker implantation before 1991, including nine epicardial pacemaker implantation .But out of these 20 cases only 8 patients was aged less than 10 yrs and only 4 was aged 6 years or less. This included only 2 immediate post operative cases. Structural heart disease was seen in 7 out of 20 cases while it was present in 24 out of 51 cases done after 1990. Significant difference was seen in the distribution of indications for pacing; there were only two post operative complete heart block patients in this category that had pacemaker implantation prior to 1991. The other patients who had structural heart disease had small VSD (n= 2), LTGA (n=1), post myocarditis with high grade AV block and ASD and mild mitral valve disease. The incidence of early complications was not influenced by date of implantation. The number of repeat procedures were high in these patients – 28 re procedures in 20 patients, mainly pulse generator changes. This was statistically significant .The average follow up in this group is 15.2 years. Five out of the 20 patients are not currently under follow up. There is no reported mortality in this group.

In comparison, the baseline characteristics of patients who underwent pacemaker implantation after 1990 is different. It included 23 patients with structural heart disease out of 51 cases, which was not significantly different compared to the implantations prior to 1991. However the proportion of post operative cases were high (35% Vs 10%, p= .01), indicating that the structural heart disease is major and that included many patients with post op complete heart block. This is evident from the diagnosis of these patients. (See figure 10) .There was only 19 re procedures for the total of 51 patients in this age group. The average follow up in this group is only 4.74 years.

Epicardial and transvenous pacemaker systems.

A total of nine out of the seventeen epicardial pacemaker implantation was done before 1991 .Epicardial pacemaker implantation was done in only 7 patients with structural heart disease, while the rest of the 25 patients with structural heart disease underwent endocardial pacemaker implantation. Early complications after pacemaker implantation were not different between the two modes of implantation. As mentioned previously, age and time of implantation determined epicardial pacemaker implantation rather than presence of structural heart disease or diagnosis

		SYSTEM		P
		ENDOCARDIAL	*EPICARDIAL*	
AGE	*0-6*	8	9	0.003
	7-18	46	8	
DATE OF IMPLANT	*< 1991*	11	9	0.013
	1991-TODATE	43	8	
SHD	*ABSENT*	31	8	0.2
	PRESENT	23	9	
DIAGNOSIS	*CCHB*	22	8	0.19
	SND	12	4	
	PO CHB	10	5	
	PO HGAVB	1	0	
	HGAVB	9	0	
POST OP	*NO*	43	12	0.31
	YES	11	5	

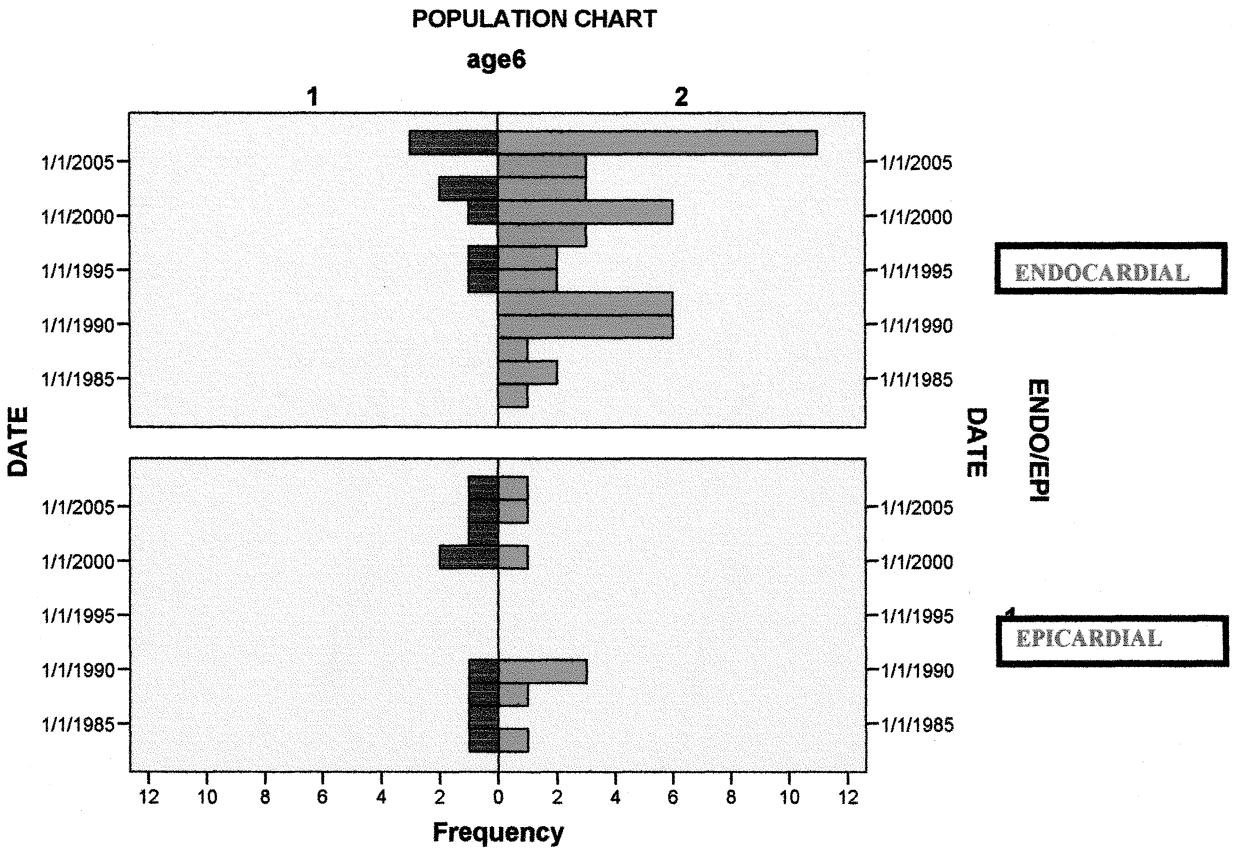

Figure 5: The distribution of case over the years for endocardial and epicardial implantation, for age groups below 6 years (Blue bars) and above 6 years (green bars)

As is seen from the population chart the epicardial pacemaker implantation has not increased in frequency, unlike the transvenous implantation.

Early complications

Early complications within one month included lead dislodgement (n- 4) , capture failure of unknown cause (n- 4), definite or suspected lead fracture (n -2) , one case of muscle stimulation and 3 cases of minor wound infections. Only post operative implantation and age at implantation tended to influence the early complications.

		EARLY COMPLICATIONS(up to 1 month)		
		ABSENT	PRESENT	p
AGE	*0-6*	11	6	0.07
	7-18	46	8	
DATE OF IMPLANT	*< 1991*	17	3	0.39
	1991- TODATE	40	11	
ENDO/EPI	*ENDO*	44	10	0.42
	EPI	13	4	
SHD	*ABSENT*	33	6	0.31
	PRESENT	24	8	
POST OP	*NO*	47	8	0.052
	YES	10	6	

Table 6: Early complications after procedure

Re procedure

Over the many years of follow up many patients had re procedures, mainly related to battery replacements. But the more important aspect of pacemaker procedure is reprocedures and freedom reprocedures in the early part of follow up as these may reflect lead related problems or chronically increased thresholds as well as procedure related complications. For such a data, all re procedures that happened within 4 years of permanent pacemaker implantation was analyzed. Patients who did not have a reprocedures but were followed up less than 4 years were excluded from this analysis. In this analysis only post operative implantation of permanent pacemaker influenced the incidence of re operations.

However when the whole population under follow up was evaluated for the number of reprocedures , patients who had procedure before 1991 had 27 reprocedures including 9 lead replacements while those after 1991 had 19 reprocedures with 9 lead replacements . The mean follow for the first group is 15.5 patient years while for the second group is only 4.7 years. The number of lead changes is statistically significant ($p = 0.02$) but with higher mean follow up period for the pre 1991 group.

The patients with epicardial pacemakers had 21 reprocedures including 11 lead changes(mean follow up 10.26 yrs) while endocardial paced patients had 26 re procedures including 7 lead changes (mean follow up 6.9 yrs). The number of lead changes is statistically significant ($p = 0.03$) but with higher mean follow up period. Other parameters did not correlate with number of lead changes.

One patient was converted from endocardial system to epicardial system since the RV was hypoplastic after surgery for VSD. Two patients , both without structural heart disease was converted from epicardial to endocardial , one five years after implantation when re operated for lead fracture and the other for suspected fracture of the lead 2 months after permanent pacemaker implantation.

Reprocedures in four years		No Reprocedure	Reprocedure	P
AGE	*0-6*	8	4	0.23
	7-18	29	6	
DIAGNOSIS	*CCHB*	17	5	0.16
	SND	10	1	
	PO CHB	4	4	
	PO HGAVB	1	0	
	HGAVB	5	0	
DATE OF IMPLANT	*Before 1991*	15	4	0.9
	From 1991	22	6	
ENDO/EPI	*Endocardial*	27	6	0.42
	Epicardial	10	4	
POST OP	*NO*	32	6	0.059
	Post Operative	5	4	

Table 7; Re procedure rate and influencing factors.

As seen from the above table only post operative status significantly influenced the early complications and incidence of reprocedures. The plot below shows the survival free of complications or re procedures within first 4 years of implantation for all patients with four years of follow up.

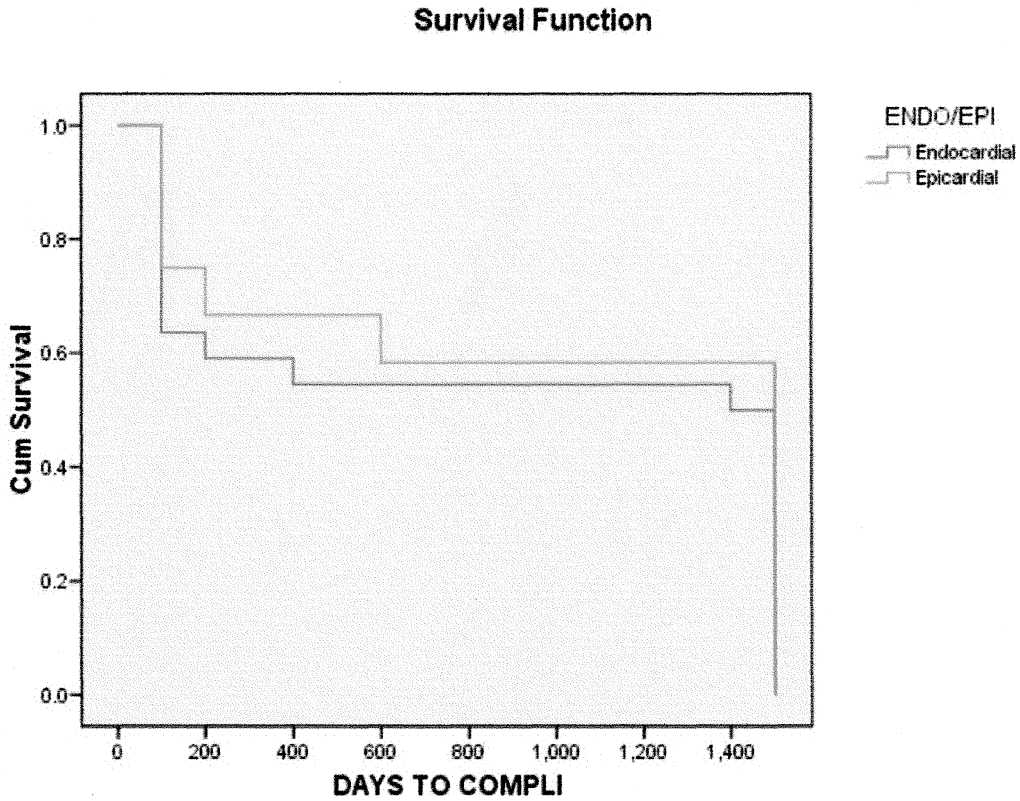

Figure 6 : Days to event free survival: There is no difference for endocardial Vs epicardial pacemaker

Days to complications were not influenced by whether endocardial or epicardial pacemaker was implanted. However as can be seen, it was influenced by whether the implantation was post operative or not, however p values did not reach significance.

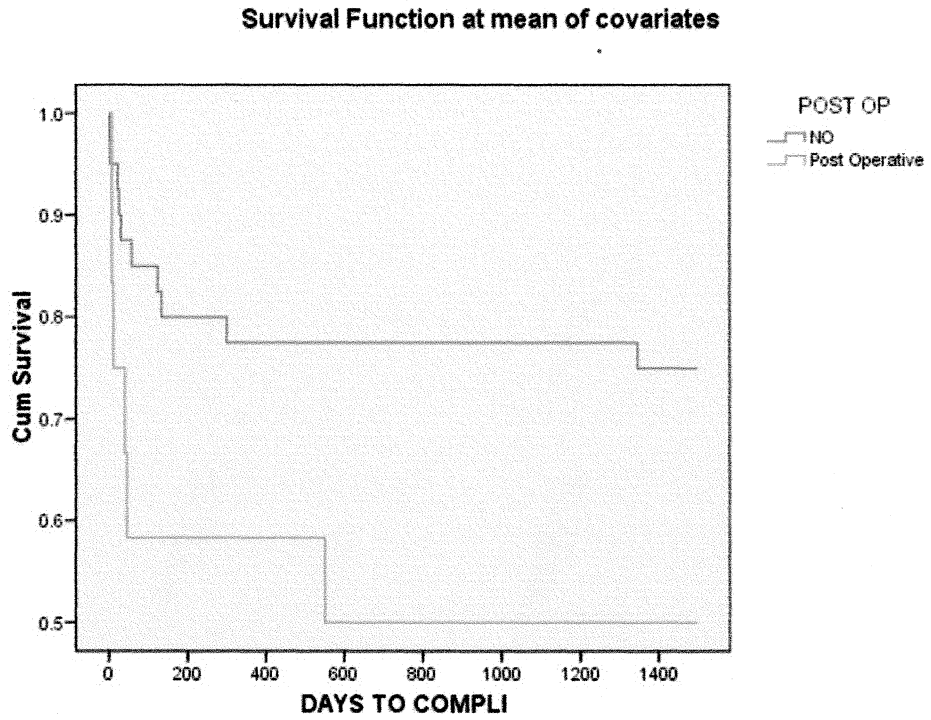

Figure 7: Event free survival after permanent pacemaker implantation; post operative cases had lesser survival (p- 0.059)

Fifty percent of patients who had permanent pacemaker implantation after surgery had a complication or reprocedures within 4 years while only 25 % of those permanent pacemaker implantation without a surgery had a similar event, after exclusion of those with follow up less than four years.

Lead Survival

Lead survival estimates were calculated for 1 year and 5 years ; The number of patients who required lead change within this time for the number of patients who were on follow up for at least one year or 5 years were calculated. The lead survival at 1 year was 90.5% and at 5 years was 84.6 %. Lead survival at 5 years are 91% for endocardial leads and 66% for epicardial leads (p = 0.036).

Lead survival was also significantly better for children aged more than 10 years (p=0.02). No other factors correlated with lead survival. Lead survival at 1 year was also significantly better for endocardial leads (p = 0.032)

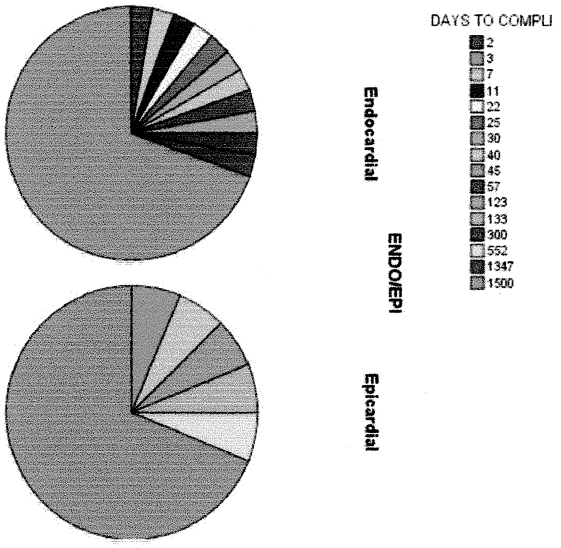

Figure 8 : Complication and early reprocedures , for epicardial and endocardial leads , the days to reproedure is given in legend. The proportion of patients having reprocedures is same.

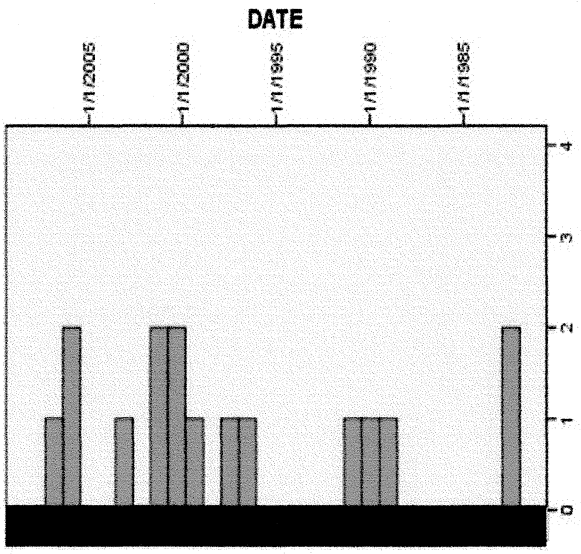

Figure 9 : Time distribution of post operative cases of permanent pacemaker implantation

Discussion

Pediatric patients requiring pacemaker is a niche population. The natural history after permanent pacemaker implantation in them is not clear cut. The procedure has however seen many technological advancements[9]. Medium or long term studies after permanent pacemaker implantation is limited in number and such studies are only available from developed countries.

This study, a long term follow up of patients undergoing permanent pacemaker implantation under the age of eighteen is a unique study; over 25 years of follow is available and over 80% of the study population is still under follow up.

Till 1991 most of the patients were cases of congenital complete AV block. The proportion after 1991 is more like what is described in western literature with majority of patients being post surgical. This corresponds with the procedural volume of pediatric surgery department of the institute. Many SND patients had previous surgery for conditions like DTGA and ASD.

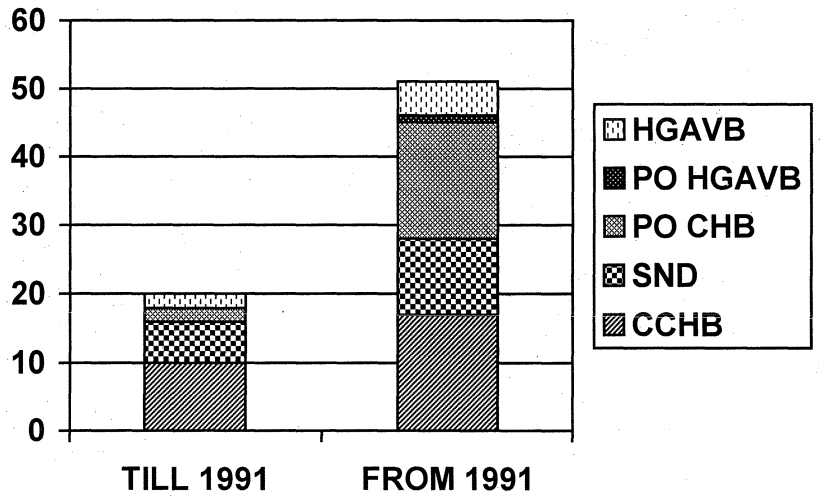

Figure 10: Distribution of pre procedure diagnosis according to date of implantation

More number of children less than 6 years old underwent the procedure after the year 2000. More number of patients also had pacing mode other than VVI also in this period. The complication and re procedure rate was not significantly affected by time of implantation because of the more complicated cases taken up after 2000. The advent of active fixation leads also did not influence the complication rate mainly because of the above mentioned reason. In this study post operative cases were the ones more likely to have less event free survival. The proportion of post operative cases increased after the year 2000. This may be the reason why technical advancements did not decrease the incidence of early complications.

The lead survival at 1 year was 90.5% and at 5 years was 84.6 %. This is comparable to long term studies already published.

Sachweh[10] et al published their 20 year experience with cardiac pacing in a university hospital in Germany. They used mainly epicardial pacing (69%) for most of their post operative patients(78% of epicardial procedures). They also used epicardial atrial and dual chamber pacing. Their patients were also high risk subsets; the mortality rate was 11% after mean follow up of 3.8 years. The transvenous group had higher age (7+-3.6 vs 4.5+-4.2 yrs for epicardial) and had only 46% post operative cases. Predictably the lead related re operation was significantly higher for epicardial pacemaker, mainly due to increasing stimulus thresholds. The post operative state is likely to produce epicardial fibrosis with resultant increase in threshold and the younger age of children paced epicardially is likely to increase battery drain because of higher heart rate. In our study however only 5 out off 16 post operative cases underwent epicardial pacemaker implantation.

Silvetti et al [11]published their findings in 292 pediatric patients from Italy in 2006. The first pacing system was implanted with endocardial leads in 65 patients and with epicardial leads in 127 patients. Seventy seven percent of their patients

had structural heart disease. In their results lead survival was worst for epicardial conventional leads. The early complications were however not different for endocardial and epicardial leads, although more number of patients had a system up gradation with change to endocardial pacing . They do not mention the need for early re intervention after permanent pacemaker implantation. The lead failure at 5 yrs was 15.4%, which is comparable to our study. However, they had many more DDD and atrial based pacing modalities used in both epicardial and endocardial location.

In another study of 32 children with CCHB , re intervention time was 42% in a median period of 5.7 years. Of the 26 patients with pacemaker , four had lead displacement, 4 had lead fractures and 3 had pacemaker related infections . Two other patients had lead dysfunction which was managed by re programming.[12]

Records of 155 patients (mean age 9.2±4.7 years) who underwent endocardial implantation of pacemaker between 1993 and 2003 were reviewed retrospectively by Celikar et al from Turkey[13] . Indications for pacing included atrioventricular block in 76% and sinus node dysfunction in 22% patients. Pacing modes were VVIR in 72%, VDD in 13%, AAIR in 8%, and DDD in 7% of patients at the initial implantation time. Of all electrodes, 95% had steroid elution and 53% had an active fixation mechanism. Mean follow-up period was 37±28 (1-120) months. Forty-five (29%) patients had 21 minor and 45 major complications. Forty-four of 76 revisions were due to lead problems and battery extraction. Most of the lead problems were dislodgment and stretching (n=14). The use of active fixation leads did not reduce lead related complications .However seven of the eight early lead dislodgements occurred in passive fixation group.

Cohen et al published their 17 year experience of epicardial pacing in children in 2001[14] .A total of 123 patients underwent 207 epicardial lead (60

atrial/147 ventricular, 40% steroid) implantations (median age at implant was 4.1 years [range 1 day to 21 years]). Congenital heart disease was present in 103 (84%) of the patients. Epicardial leads were followed for 29 months (range 1 to 207 months). The 1-, 2-, and 5-year lead survival was 96%, 90%, and 74%, respectively. Neither congenital heart disease, lead implantation with a concomitant cardiac operation, age or weight at implantation, nor the chamber paced was predictive of lead failure. The 5-year freedom from survival for steroid-eluting leads was 83%, whereas for nonsteroid-eluting leads, the survival was 73%The surgical approach significantly correlated with lead failure. None of the 29 subxiphoid-implanted leads failed during the present study

In our study , the 5 year lead survival for epicardial pacemaker was 66% . Non steroid eluting leads were used for most of them. The predominant surgical approach was by lateral thoracotomy. Here post operative permanent pacemaker implantation tended to influence the outcome.

Conclusion

The long term experience of pacing in children less than 18 years showed acceptable short term results and good long term results with reasonable lead survival comparable to studies from developed countries. Our results indicate that endocardial pacing is feasible in children. Although lead-related complications were relatively frequent, they could be managed without significant morbidity and mortality. Of the factors influencing survival free of events, permanent pacemaker implantation after surgery appears to be most important. There was no significant difference between endocardial and epicardial pacing in short or medium term outcome. Lead survival is however better with endocardial lead placement. Continued experience may result in further improvements in endocardial pacing in children.

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