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RESEARCH ARTICLE

USEFULNESS OF FRACTIONAL FLOW RESERVE GUIDED PERCUTANEOUS CORONARY INTERVENTION IN DECISION MAKING AND COST EFFECTIVENESS: A REAL WORLD SCENARIO FROM DEVELOPING COUNTRY

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ABSTRACT

Objective: This study was devised in view of the real life application of FFR in catheterisation laboratory from a developing world country and to evaluate the cost effectiveness of the same. **Background:** FFR has been proved to be superior to angiographic ally driven PCI in various studies also it has been proven to be economically beneficial. However there is difference between trials and real life situation. Considering this we conducted this study and evaluated clinical outcome and cost effectiveness associated with use of FFR. **Methods:** We conducted a retrospective study which included all patients who underwent FFR in our hospital. Coronary angiograms of these patients were retrospectively analysed by two interventional cardiologists and decision regarding the lesion were made. The proposed decisions and their associated costs were compared with the actual procedure and costs incurred with the use of FFR. Also patients were evaluated for any adverse outcome after the procedure to the time of analysis. **Results:** 38 patients underwent FFR in our hospital. 12 patients had SVD, 13 patients had DVD, 3 patients had TVD and 2 patients had LMCA disease. Mean FFR value in our study was 0.84 ± 0.09 and 36.8% of all lesions had $FFR \leq 0.80$ and 16.2% had $FFR 0.75-0.80$. LAD was the most common vessel interrogated (27 patients). Total 42 lesions were analysed in 38 patients. Concordance between cardiologist opinion and FFR results were seen in 47.6% lesions. On basis of angiography alone intervention cardiologists decided 22 lesions to be stented but after estimation of FFR, 16 lesions were stented. Overall in 22 lesions decision was changed of which 14 lesions were deferred and 8 lesions were those which underwent PCI. On evaluation total cost of procedures as per decision of intervention cardiologist was found to be Rs 2603254 and actual total cost was Rs 2887954 with a difference of Rs 284700, which was not significant statistically. If further it was considered that FFR wire was used as guide wire for the patients who later underwent PCI after FFR, and cost of guide wire was reduced from the actual cost then Rs 207900 was the difference. Out of 38 patients we were able to contact 32 patients only. Mean duration of follow up was 12.7 ± 7.14 mths. Amongst the 32 patients only 2 patients complained of class II angina. One patient later underwent CABG and was asymptomatic on follow up. **Conclusion:** Despite few number of patients this study reinforces that clinical trials don't represent real life scenario and cost effective analysis may not be achieved in each set of situations. However, despite the increased cost we support the use of FFR for guiding revascularisation in intermediate severity lesions as it helps to classify these lesions correctly into significant or non significant. More so deferring of insignificant lesions and attending to significant lesions both are important to improve outcome.

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INTRODUCTION

The evaluation of patients suspected of ischemic heart disease should start with non invasive test followed by a conventional angiogram. But often patients may be subjected to coronary angiogram prior to non invasive testing (Topol, 1993).

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In absence of such prior evaluation in any patient it is difficult to analyse the significance of an intermediate coronary lesion in the catheterization laboratory. More so just evaluation of angiographic severity of such lesion doesn't help to differentiate physiologically significant lesion from a physiologically insignificant lesion because of inherent limitations of coronary luminograms (Topol, 1995). It is impractical to consider these patients for a non-invasive test

after detection of intermediate coronary lesion in coronary angiography. In this situation evaluation of FFR has been proved to be useful in assessing functional significance of lesion in catheterisation laboratory across all spectrums of presentation and in single or multivessel disease (Chamuleau, 2002; De Bruyne, 2000; De Bruyne, 2001; Leesar, 2003; Jan Willem Bech, 2001). An FFR value of 0.80 or less identifies ischemia-causing coronary stenoses with an accuracy of >90% (De Bruyne, 2001; Pijl, 1996; Pijls, 1995). Assessment of any lesion whether it is physiologically significant is very important because presence of myocardial ischemia is an important risk factor for an adverse clinical outcome (Beller, 2000; Shaw, 2004; Shaw, 2008) and revascularization of stenotic coronary lesions that induce ischemia can improve a patient's functional status and outcome (Shaw, 2008; Davies, 1997; Erne, 2007). On the contrary PCI of physiologically insignificant lesions is not evidence based and also unnecessarily expensive and might even be harmful because the risk of periprocedural myocardial infarction or subacute stent thrombosis is not negligible, even with drug-eluting stents (Windecker, 2005; Kastrati, 2005). However despite of advantages, iFFR is still not common in developing countries considering the cost involved. However FAME trial showed a cost effective analysis of FFR but this was due to randomisation of all patients in angiographic group to undergo PCI with DES which tipped cost analysis heavily in favour of FFR guided PCI. In real life scenario this is not the case and interventional cardiologist look to FFR in cases of lesions of undetermined significance (Stephen, 2011). Considering this we devised a retrospective study involving patients who underwent FFR in our institute.

MATERIALS AND METHODS

Study patients: This study was a retrospective study which included patients from July 2010 to March 2013 at Sri Jayadeva Institution of Cardiovascular sciences and research Hospital, Bangalore, India. All patients who underwent fractional flow reserve estimation during this period were evaluated.

Study design: Coronary angiograms of all the patients who had undergone FFR evaluation were retrospectively analysed by two interventional cardiologists who were blinded to the results of FFR. After discussion and mutual consensus, decision regarding the lesions was taken amongst the reviewing cardiologist. They classified lesions into two groups: one which they decided to treat medically and the other in which they decided to do PCI. The decisions and the cost analysis were then compared with the outcome of FFR and actual intervention done with the patient. Finally all patients were contacted personally/on telephone and asked regarding any event, hospitalisation, revascularisation and death.

Pressure Measurements and calculation of FFR: At the time of catheterization, 6/7 French coronary diagnostic/guiding catheters were used. A 0.014 inch sensor-tipped PCI guide wire (Pressure wire, Radi Medical, Uppsala, Sweden) was introduced. The wire was set at zero, calibrated, advanced through the catheter, introduced into the coronary artery, and positioned distal to the stenosis (Beller, 2000; Pijls, 1993; De Bruyne, 1994; De Bruyne, 1995; Emanuelsson, 1991; Lamm, 1993; Serruys, 1993). Adenosine was administered to induced maximum hyperemia, either intravenously (140µg/kg/min. When steady-state hyperemia was achieved, FFR was calculated as the ratio of the mean distal intracoronary pressure

measured by the wire to the mean aortic pressure measured by the guiding catheter (Pijls, 1993; De Bruyne, 1994). If the FFR was ≥ 0.80 , revascularization was deferred. If the FFR was < 0.80 , myocardial revascularization was done.

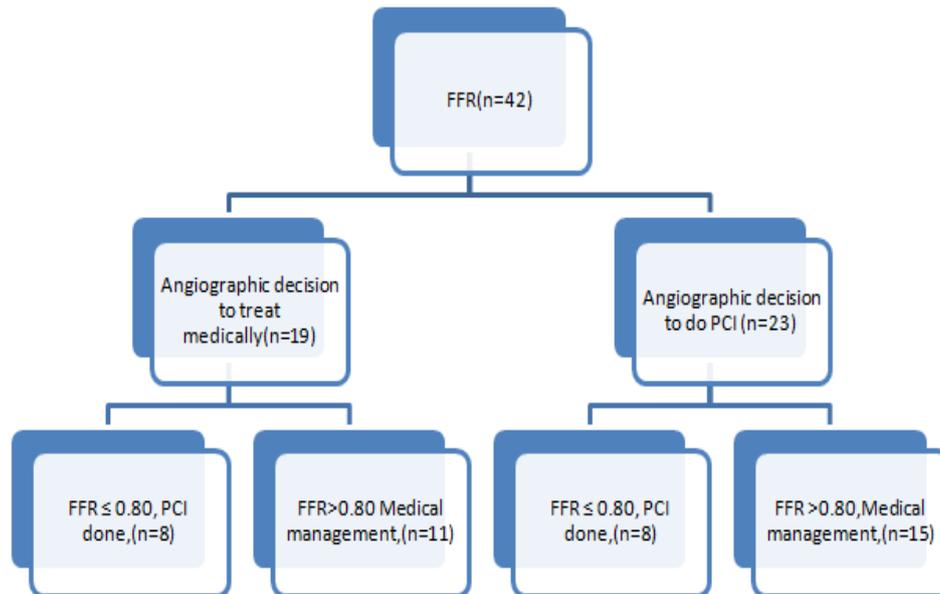
Statistical analysis: Continuous variables were expressed as mean \pm SD, and categorical variables as counts and percentage. Unpaired Student's t test was used for continuous variables to calculate p value.

RESULTS

38 patients underwent FFR in the specified period in our institute. Amongst these patients 15 patients had history of myocardial infarction, 9 patients presented with effort angina and 8 patients presented with unstable angina. Amongst remaining 6 patients, 4 patients had TMT positive during routine evaluation while 1 patient presented due to peripheral vascular disease and incidentally detected to have co-existing coronary artery disease, and 1 patient presented with fatigability symptoms which were thought to be angina equivalent. Out of all patients 5 had initially undergone PCI and 1 had undergone CABG. Out of all 18(47.3%) patients had diabetes, 19(50%) had hypertension and 17(44.7%) were smokers. Serum lipid levels were available in 13 patients only of which 12 patients had low HDL and only 3 had raised LDL. In the patient population 19 patients had had no angina, 17 had class II angina and 2 patients had class III angina. Demographic profile of patients is shown in table 1. Of the whole group of patients only 9 patients underwent non invasive evaluation of which 6 patients underwent TMT, 3 patients underwent MPI and one patient underwent CT coronary angiogram prior to procedure. Echo reports were available in 31 patients. 17 patients had LVEF > 60%, 11 patients had LVEF = 45-60% and 3 patients had LVEF = 30-45%.

Angiographic and FFR comparison: Considering >70% stenosis as significant, 12 patients had SVD, 13 patients had DVD, 3 patients had TVD and 2 patients had LMCA disease, both of them had DVD along with it. Mean FFR value in our study was 0.84 ± 0.09 and 36.8% of all lesions had $FFR \leq 0.80$ and 16.2% had $FFR 0.75-0.80$. LAD was the most common vessel interrogated (27 patients) that to proximal LAD (17 patients), LCX was the target vessel in 5 patients and OM in 2 patients, while RCA was interrogated in 6 patients. Total 42 lesions were analysed in 38 patients. Concordance between cardiologist opinion and FFR results were seen in 47.6% lesions. On basis of angiography alone interventional cardiologist decided 22 lesions to be stented but after estimation of FFR, 16 lesions were stented. Overall in 22 lesions decision was changed of which 14 lesions were lesion which were deferred and 8 lesions were those which underwent PCI. Sensitivity, specificity, positive predictive value and negative predictive value of interventional cardiologists were 50%(8/16), 42.3%(11/26), 42.1%(8/19) and 57.8%(11/19) respectively. Amongst the patient who underwent PCI, 15 patients received DES while 3 received BMS

Cost difference between the approaches: Economic evaluation was also done. Cost was estimated as per the initial decision of cardiologists and it was compared with the actual cost incurred. Estimate was done with reference to rates at the time of analysis. Choice of stent was decided by the interventional cardiologists considering the coronary angiogram and clinical scenario.



On evaluation total cost of procedures as per decision of intervention cardiologist was found to be Rs 2603254 and actual total cost was Rs 2887954 with a difference of Rs 284700, which was not significant statistically.

Medications at time of discharge: 36 patients were discharged on dual antiplatelet while 2 patients were on single antiplatelet. Out of 38, 33 patients were receiving beta-blockers, 28 patients were receiving ACE inhibitor while 7 were receiving ARBs. All patients were receiving statins. 10 patients were discharged on nitrates while 2 patients were on additional one anti-anginal and 5 patients were on additional two anti-anginals. 3 patients were receiving CCBs.

Follow up outcomes: Out of 38 patients we were able to contact 32 patients only. Mean duration of follow up was 12.7 ± 7.14 mths with a minimum follow up of 3 months and maximum of 26 months. Amongst the 32 patients only 2 patients complained of class II angina. One patient had persistent class III angina after the procedure and was admitted for unstable angina later. He later underwent CABG and was asymptomatic on follow up. That patient had TVD on baseline evaluation and FFR was done in LAD which was insignificant while in other two vessels visually disease was insignificant. Among the symptomatic patient with class II angina, one had undergone PCI to LAD after FFR was found to be significant while in other patient lesions was found to have insignificant and she had insignificant disease in two other vessels at initial evaluation.

DISCUSSION

In this retrospective analysis of 38 patients we found that concordance of severity assessed by angiography and FFR is about 48% which means that >50% intermediate lesions would be classified wrong using only angiography. Sensitivity, specificity and predictive values were also low. These were different and lower than other studies, one reason can be few number of patients in our study, which means missing 1 lesion will change parameters by 2.3% while in other study missing would change values by 1.2% (Joshua, 2002).

Also these values depend on the experience of cardiologist with experience of >10 yrs concordance is as high as 63%. In our study mean value of FFR was 0.84 ± 0.09 indicating that majority were physiologically insignificant lesions. We took a cut off of 0.80 in our study. In our routine strategy, the choice of a threshold 0.80 aimed to give priority to the exclusion of ischaemia, at the risk of reduced specificity. We used FFR in LMCA disease also in which studies have shown good ability of FFR to predict outcome (Bech, 2001; Jasti, 2004). Regarding cost analysis, FFR was slightly costlier affair in our study but the difference was not statistically significant. Besides cost other outcome are definitely improved by using FFR for intermediate lesions as proven (Pijls, 1996). The cost benefit of FFR as shown in prospective trial (Nico, 2010) may be due to enrolling strategy of trial itself.

In all trials comparing angiography guided group with FFR guided group, only those patients are included in angiographic guided PCI arm which undergo stenting for intermediate severity lesions while in real life scenario coronary angiography alone also excludes many intermediate lesions. Non inclusion of such patients tips the cost balance in favour of FFR guided strategy. The cost analysis will be in favour of FFR, if more and more lesions are considered significant on angiography and they turn out to be non significant on FFR, in a given set of intermediate lesions. This may be the reason for variation of difference in cost in our study and study by Stephen *et al.* (2011).

They have shown that the hemodynamic significance of intermediate lesions was underestimated by cardiologists, resulting in a net under treatment when guided by the angiogram alone which would lead to less number of stents in angiography guided revascularisation group (Stephen *et al.*, 2011). However angiography only strategy would have missed lesion which were significant and should have been attended, but cost analysis in such scenario come in favour of angiographic driven group. We had a follow up of 32 patients from duration 3-26 months, which revealed low adverse events on follow up. This was in accordance of other studies (Jan Willem Bech, 2001; Nattawut Wongpraparut, 2005) However our study had few patients so adverse events were also low.

Table 1. Baseline characteristics of study patients

| | | Patients(n=38) |
|----------------------------|--------|----------------|
| Age | | 59.37±10.8 |
| Male | | 33(86.8%) |
| Risk factors | | |
| Diabetes | | 18(47.3%) |
| Hypertension | | 19(50%) |
| Smoking | | 17(44.7%) |
| Past history | | |
| PCI | | 5(13%) |
| CABG | | 1(2.6%) |
| Angina | | |
| I | | 0 |
| II | | 17(44.7%) |
| III | | 2(5.2%) |
| IV | | 0 |
| Non-invasive evaluation | | 9(23.6%) |
| Stable angina | | 9(23.6%) |
| Unstable angina | | 8(21%) |
| Post myocardial infarction | | 15(39.4%) |
| Other indications | | 6(15.7%) |
| LVEF ^a | | |
| >60% | | 17(44.7%) |
| 45-60% | | 11(28.9%) |
| 30-45% | | 3(7.8%) |
| Medications at discharge | | |
| Antiplatelet | Single | 2(5.2%) |
| | Double | 36(94.7%) |
| Beta blocker | | 33(86.8%) |
| ACE Inhibitors | | 28(73.6%) |
| ARB | | 7(18.4%) |
| Statins | | 38(100%) |
| Nitrates | | 10(26.3%) |
| Additional antianginal | One | 2(5.2%) |
| | Two | 5(13.1%) |
| CCB | | 3(7.8%) |

^aEcho reports were available in 31 patients only.

Table 2.

| Vessels involved ^a | |
|-------------------------------|-----------|
| Single | 12(31.5%) |
| Double | 13(34.2%) |
| Triple | 3(7.8%) |
| LMCA | 2(5.2%) |
| No of lesions analysed | 42 |
| Lesion site | |
| LMCA | 2(4.7%) |
| LAD | 27(64.2%) |
| LCX | 5(11.9%) |
| RCA | 6(14.2%) |
| OM | 2(4.7%) |
| FFR>0.80 | 27(64.2%) |
| FFR≤0.80 | 15(39.4%) |
| DES used | 15 |
| BMS used | 3 |
| Treatment strategy | |
| Same as angiography | 20 |
| Changed to medical | 14 |
| Changed to PCI | 8 |

^a>70% lesion was considered as significant stenosis.

Besides one more important thing was majority of patients were discharged on recommended medical therapy with 100% of patients on statins. This was better than other trial (Jan Willem Bech, 2001). However it has to be noted that along with intervention medical therapy is also as very important (Bernard De Bruyne, 2012).

Limitation: There are few limitations of this study. First it is a retrospective study and number of patients is less only. No data about the factors which can limit the efficacy of FFR like co-existing LVH, RA pressure were available.

There was lack of data about the risk factors and follow up. It would have been better if data on medications at follow up was also available to analyse the efficacy of procedure with reference to angina.

Conclusion

Despite few number of patients this study reinforces that clinical trials don't represent real life scenario and cost effective analysis may not be achieved in each set of situations. However, despite the increased cost we support the use of FFR for guiding revascularisation in intermediate severity lesions as it helps to classify these lesions correctly into significant or non significant. More so deferring of insignificant lesions and attending to significant lesions both are important to improve outcome.

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