Original Article

SHORT TERM OUTCOME OF CORONARY REVASCULARIZATION (PCI) VERSUS MEDICAL MANAGEMENT IN PATIENTS WITH MODERATE CORONARY STENOSIS AND BORDERLINE FRACTIONAL FLOW RESERVE

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MT:Conducted the study and wrote the article. KS:Helped in review the article. SAA:Re-arranged data and corrected article. IA:Tables and figures. UA and MAD made corrections and did the proof reading.

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ABSTRACT

BACKGROUND: Assessment of Fractional flow reserve (FFR) becomes a valuable tool for measurement of functional severity of stenosis in coronary arteries. The "gray-zone" range of the fractional flow reserve with value of 0.75-0.80 is considered uncertain for determination of any patient treatment strategy at clinical level. Therefore, it is unclear that whether these lesions in gray zone FFR should be intervened or not.

OBJECTIVE: This study was conducted to compare the short term outcome of coronary revascularization (PCI) versus medical management in patients with moderate coronary stenosis and borderline fractional flow reserve.

MATERIAL AND METHODS: This Randomized controlled trial was conducted on 46 cases with moderate coronary lesions. Patients were randomly divided into two equal groups. Coronary angiography was done under local anesthesia .All FFR measurements were done as per standard protocol. One group received medical treatment and the other group underwent PCI. All cases were followed-up regularly for 6 months and were evaluated for the clinical outcomes of medical treatment or PCI. In case of any emergency, patients contacted telephonically. Data was obtained regarding clinical symptoms and on major adverse cardiac events were recorded. Data analyses was done with SPSS version 22.

RESULTS: Mean age of patients in PCI and medical management group were 55.52 ± 8.84 and 52.65 ± 11.49 years, respectively. Mean Fractional flow reserve in PCI and medical management group was 0.79 ± 0.01 and 0.77 ± 0.02 ($p<0.05$). Fractional flow reserve was high in PCI group than medical management group. In PCI gorup, 2(8.70%) cases had MACE and in medical management group, 3(12.04%) cases had MACE ($p>0.05$).

CONCLUSION: Insignificant difference was observed in MACE either patients undergo PCI or conservative management in patients with moderate coronary stenosis with border line FFR.

KEY WORDS: Coronary revascularization, Medical Management, Coronary lesions, fractional flow reserve, Major adverse cardiac events

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INTRODUCTION

Fractional flow reserve (FFR) is the ratio of distal to proximal blood flow across the stenotic coronary artery. Its normal rate is 1.0. [1] FFR shows the physiological significance of coronary artery stenosis where highest myocardial blood flow has been restricted due to existence of a stenosis. The basic consideration is given to the role of collaterals to myocardial perfusion in hyperemia. The FFR reproducibility measurements are excellent and are not influenced by physiological changing in BP and heart rate. [2]

According to a report up to 71% of percutaneous coronary interventions (PCIs) is done in the dearth of any kind of functional estimate. Coronary angiography is a method to identify hemodynamically important lesions, and majority people may experience needless revascularization procedures. [3, 4] Generally, more than 50% stenosis as assessed by coronary angiography is considered to be important stenosis. On the other hand, the study of necropsy and intravascular ultrasound shows that coronary lesions can be very serious which exhibit markedly vague or unconventional luminal shapes.[5, 6]

This compound morphology damages overall capacity of the coronary angiography to precisely portray coronary anatomy. Also, ability of coronary angiography can be limited by the trouble of coronary artery remodeling and by soundness of usual reference segment. Therefore, coronary angiography has substantial limitations to evaluate coronary artery stenosis.[7] One way to describe the pathophysiological importance of a transitional stenosis (having diameter of 50 to 70%) is determination of FFR.[8] FFR measurements link properly with non-invasive assessment of coronary artery. Stenosis with an FFR value of <0.75 are almost always able to bring myocardial ischemia. While stenosis with an FFR >0.80 may not be associated with the exercise-induced ischemia. FFR value between 0.75 to 0.80 is labeled as "grey zone" or borderline FFR. [9]

Hospitals in Pakistan have limited resources regarding PCI. There are few hospitals whose facilities for the coronary revascularization are overcrowded. Furthermore, mostly patients are non affording for suitable revascularization procedures. For our information, no study has been performed in Pakistan that provides guiding principle for cure of patients having grey-zone FFR measurements. So,this study was carried out to see whether PCI should be performed in patients having grey-zone capacity of FFR or not.

MATERIALS AND METHODS:

This was a randomized controlled trial carried out in Punjab Institute of Cardiology,Lahore over a duration of six months in the year 2016. 46 patients with moderate coronary lesions (having diameter of 50 to 70%) presenting with chest pain and shortness of breath and meeting the inclusion criteria were included. The inclusion criteria was; patients with age between 25-70 years regardless of gender, with moderate coronary lesions (diameter stenosis 50-70%) and borderline FFR (i.e. 0.75 and 0.80). while patients with prior CABG or PCI, LVEF <30%, acute coronary syndrome in last 10 days, recent STEMI or Non-STEMI within last five days, renal dysfunction (eGFR<60 mL/min/1.73m2), left main stem lesions were excluded. Patients were divided in two groups; 23 patients were allocated to each group. For this sample size, we used 5% level of significance & 80% power of study. According to a previous study that reported MACE in 23% of patients managed with medicine (P1) and 5% in patients managed with coronary revascularization (P2)[32](Courtis 2008). Non-probability, consecutive sampling was done.

DATA COLLECTION: A written informed consent was obtained from all the patients before undergoing any procedure. Demographics of included patients was also recorded on Performa.

FFR MEASUREMENTS: All FFR measurements were done under standard protocol. Coronary angiography was done through femoral access, by using 6-French guiding catheter. Adenosine was given through venous access through ipsilateral femoral vein. After inserting the guiding catheter into coronary ostium, it was connected to the fluid-filled pressure transducer calibrated to zero at mid-chest level. Special attention was given to avoid inhibition of arterial pressure wave or differences in examined coronary guide pressure throughout the procedure to ensure maximal blood flow in ostium. A 0.014-inch pressure recording guide wire was visibly calibrated and advanced to the tip of guiding catheter and aortic pressure was noted (Pa). Intracoronary 0.5mg glyceryl trinitrate was also given. The wire was advanced distal to segment under examination and placed in distal part of vessel and distal coronary pressure was note (Pd). Hyperemia was induced by continuous infusion of adenosine at the rate of 140μg/kg/min. Vitals signs were continuously recorded. FFR was calculated as ratio

of mean "Pd" to mean "Pa" during maximal hyperemia. A manual pullback of FFR wire was done. Upon retraction of pressure sensor into guiding catheter, pressure curves were checked to reject any shift in transducer signals during measurements. If pressure shifting detected, measurement was rejected and procedure was repeated following similar protocol. Patients with 0.75 to 0.80 FFR were included. As the procedure does not need continuous fluoroscopy and the pressure monitoring is done when the fluoroscopy is off,thereby, no extra fluoroscopic exposure. Extra procedure time will usually be 5 to 7 minutes including 3 minutes for adenosine infusion response and remaining time for wire placement and reading.

FOLLOW UP: Patients were followed-up regularly for six months and were evaluated for the clinical outcomes of medical treatment and PCI. In case of any emergency, patients contacted telephonically, and a pre-structured performa was completed. Data was acquired regarding character and frequency of clinical symptoms and MACE (cardiac death, myocardial infarction or need of coronary revascularization procedure) were recorded.

STATISTICAL ANALYSIS: Analysis was done with SPSS version 22. The Student's- t test was used to compare mean values of FFR and the Chi square test was used to compare MACE between two groups. P-value ≤ 0.05 was considered significant.

RESULTS:

Mean age of patients in PCI group and medical management group were 55.52±8.84 and 52.65±11.49 years, respectively. In PCI group, 18 patients were male and 5 patients were females. While in medical management group there were 17 male and 6 were female. There were 16 patients in PCI group and 18 patients in medical management group who were hypertensive. There were 6 patients in PCI group who had hypercholesterolemia and in medical management group 4 patients had hypercholesterolemia. In PCI group 4 patients were diabetic and in medical management group 7 patients were diabetic. There were 18 patients who were smokers. i.e. (PCI=9, medical management=9) while the remaining patients in both groups were non-smokers. There was only 1 patient in PCI group who had family history for IHD and in medical management group 3 patients had family history for IHD. In PCI group 21(91.30%) patients were asymptomatic and 2(8.70%) patients had symptoms while in medical management group 20(86.96%) patients were asymptomatic and 3(12.04%) patients had symptoms. Table 1

TABLE-1: Baseline characteristics of patients

	Treatment Groups	
	Medical Therapy	PCI
n	**23**	**23**
Age (years)	55.52±8.84	52.65±11.49
Male	18 (%)	17 (%)
Female	5 (%)	6 (%)
Hypertension	16 (%)	18 (%)
Hypercholesterolemia	6 (%)	4 (%)
Diabetes	19 (%)	16 (%)
Smoking	9 (%)	9 (%)
Family history of IHD	1 (%)	3 (%)
Asymptomatic	21(91.30%)	20(86.96%)
Symptoms	2(8.70%)	3(13.04%)
FFR	0.79±0.01	0.77±0.02

TABLE-2: Vessel involved in stenosis

		Treatment Groups		Total
		Medical Therapy	PCI	
LAD	**Proximal**	14	10	24
	Mid	8	2	10
	Distal	0	0	0
Total		**22**	**12**	**34**
LCX	**Proximal**	0	0	0
	Mid	0	2	2
	Distal	0	0	0
Total		**0**	**2**	**2**
RCA	**Proximal**	0	6	6
	Mid	0	2	2
	Distal	1	1	2
Total		**1**	**9**	**10**

TABLE-3: Major Adverse Cardiac Events in both groups

	Treatment Group		Total	P-value
	Medical therapy	PCI		
MACE	2(8.70%)	3(13.04%)	5(10.87%)	0.636
Cardiac Death	0(0%)	0(0%)	0(0%)	
MI	1(50%)	1(33.33%)	2(40%)	
TVR	0(0%)	1(33.33%)	1(20%)	
Emergent CABG	1(50%)	1(33.33%)	2(40%)	

LAD was involved in in most of the cases. In medical therapy group, proximal LAD was invovled in 14 cases, mid-LAD in 8 cases. In PCI group, proximal LAD was invovled in 10 cases while no patient had disease in mid-LAD .RCA was invovled in 1 case in distal region and was given medical treatment while in PCI group, 6 had proximal RCA, 2 had mid-RCA while 1 had distal RCA involved. Table 2

In PCI group, 2(8.70%) patients had MACE and in medical management group, 3(12.04%) patients had MACE. Insignificant assocation was observed between both groups regarding MACE. Table 3

DISCUSSION:

In recent years FFR measurement to assess functional severity of stenosis of coronary artery has proved to be a necessary instrument for clinical

assessment in cardiac catheterization laboratory. [2, 10, 11] Patients with stable coronary artery disease (for example left main stem disease, tandem lesions, single or multi-vessel disease, diffuse disease, bifurcation lesions, in-stent restenosis, bypass grafts and even in previous myocardial infarction), FFR measurement is applicable. [11-18]

FFR is differentiated by higher spatial and segmental resolution compared to as that of any other noninvasive stress tests. A FFR less than 0.75 is very precise for ischemia as validated in many studies. However, a value of FFR more than 0.80 strongly favors medical treatment with 90% sensitivity.[19-22] When patients were managed medically, the combined event rate for death or acute MI was less than 1% per year. It was found in several trials like DEFER study which reported that there is a trend to an increased event rate in cases who underwent PCI regardless of FFR≥0.75. But, each patient can still have inducible ischemia with FFR >0.75.[23-25]

Legalery et al., selected a high FFR 0.80 and observed the equal 1-year MACE rate in conservative and PCI patients. FFR measurement ranged between 0.75-0.80. So, this level was documented as ''gray-zone'' as reported by task force of the European Society of Cardiology and by scientific statement of American Heart Association for PCI regarding physiological assessment of coronary artery disease in cardiac catheterization laboratory. Since the verdict to conduct FFR assessment is normally made in case when the existing clinical & angiographic findings leave the cardiologist ambiguous whether to do PCI or not for coronary lesion, several cardiologists choose PCI when the FFR ranged between 0.75-0.80, so that ischemic lesions cannot be left untreated.[13, 26]

Previous literature showed the safety of using FFR before proceeding for PCI in cases of moderate coronary lesions with FFR ≥0.75. But, the reported mean FFR was >0.85, proposing that major number of cases had FFR >0.80 and limited number of cases had FFR ranged in 0.75- 0.80.[11, 27-29] Several studies reported similar mean FFR cut-off value 0.80 rather than 0.75 for conservative management. Nevertheless, literature also proposed that conservative management in moderate coronary lesions with ''grey zone'' FFR value might raise the chances of cardiac events.[26, 30] In this study patients whose FFR was in between 0.75-0.80 and who were on medical management among them MACE were observed in only 2(8.70%) patients and patients who underwent PCI among them MACE were seen in 3(13.04%) patients. Reported percentage for MACE in this study is less than that of reported by Legalery et al.

FFR value in gray-zone is related with ambiguity regarding the decision of treatment. It is vague whether any dissimilarity in clinical result exists when PCI of FFR- assessed lesions is in medium range.[31] Numerous trials have verified the protection to defer revascularization (PCI) in cases of reasonable coronary stenosis detected on FFR results i.e ≥0.75.[11, 27, 31] Alternatively, many studies illustrate that in the patients having moderate coronary lesions and borderline FFR capacity, delay in PCI will be related with an upper rate of MACE and higher frequency of angina.[24, 32] MACE consists of cardiac death, myocardial infarction and coronary revascularization. Therefore it is undecided and controversial till now that we should carry out PCI of the patients having grey-zone value of FFR, or recommend them medical remedy. [31]

Lockie T, et al., demonstrated that FFR value is related to 98% success and 1.5% complication.[33] Siebert et al., pointed out pooled sensitivity and specificity for FFR were 81.7% (95% CI: 77.0-85.7%) and 78.7% (95% CI: 74.3-82.7%), respectively.[34]

Chamuleau et al., detected that FFR cut-off 0.79, as predictable for cardiac events during follow-up.[35] Courtis et al., conducted a study to evaluate patients with moderate coronary lesions and FFR ranges 0.75-0.80 (average 0.77), showed a 23% cardiac event rate at 1-year follow-up in patients who had conservative management, significantly >5% MACE rate than patients with the same conditions who had PCI.[32]

Results of this study regarding MACE in patients who were on medical management and patients who underwent PCI were 8.70% vs. 13.04%. These results are in contradiction to results reported by Courtis. This may be due to the difference in the follow up time period. As in this study follow up time period was 6 months and in Courtis study he followed the patients for 1 year. In previous studies in which patients with mean FFR measurements >0.85 as well as having moderate coronary lesions were included have reported a 5–11% cardiac event rate at 1 years related with delay of revascularization.[11, 21, 27, 28]

In this study only 2(8.70%) patients who were on medical management experienced MACE. This is in line with the reported range for cardiac events at a follow up time period of 1 year. However the FFR range in this study was 0.75-0.80. Detection of the

functionally significant stenosis even in existence of an earlier infarction in myocardial territory can be evaluated with FFR 0.75 as previously many studies have reported that a cut-off FFR 0.75 was also appropriate for this purpose. Meuwissen et al., in his study observed the difference in micro vascular resistance influence hemodynamic parameters which were utilized in assessment of coronary stenosis, in which micro vascular resistance significantly increases and ultimately leading to higher FFR values inspite of a fixed stenosis anatomically. A micro vascular damage which may lead to the reduced maximal hyperemic flow reaction is established with the fact that an injured myocardial bed is related with following underestimation of functional severity of coronary stenosis.[25, 36-40]

Lavi et al., studied the outcome of drug-eluting stents on cardiovascular events on patients whose borderline FFR values i.e. FFR $\geq$0.75 and $<$0.90. Comparison was made between conservative treatment group and 2 interventionally treated groups, which were treated with DES or either bare-metal stents. No difference was observed in outcome between the deferred group and DES-treated group. However, these results showed that there was a significant difference in favor of the BMS group when compared with deferred group (MACE after 2 year=16% and 28%, respectively; P = 0.03).

Lindstaedt in his study included 48 patients from delayed PCI and 49 patients with early PCI. Between these groups there was no dissimilarity in risk profile. Mean follow-up time period of 24$\pm$16 months, in delayed PCI group event-free survival was significantly better. Insignificant difference has been observed regarding the occurrence of angina. MACE was 20.8% among patients who were deferred and patients who had PCI, MACE among them was observed in 46.2% patients. Still these values are much higher as compared to the results of this study.[31] On the basis of results of this study and results reported in previous studies, borderline FFR measurement in cases randomized to conservative management without putting them at a higher risk of ''hard'' events, like death related to cardiac events and infarction. Therefore, it's reasonable to advise medical management and continued surveillance as a first line therapy.

The limitations of study were small sample size and short follow up duration, so patinets must be followed up for longer duration of study with large sample volume.

CONCLUSION:

Results of this study showed that no significant difference was observed in MACE in patients with conservative management and PCI. i.e. [MACE: 8.70% (Medical Management) vs. 12.04% (PCI) with moderate coronary lesions with border line FFR.

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