How to Cite:
Kumar, T., Jha, A. J., Kumar, M., & Avneesh, S. (2022). Prospective Randomized comparison of Off-pump and On-pump Multivessel coronary artery bypasses surgery. *International Journal of Health Sciences*, *6*(S3), 11421–11432. https://doi.org/10.53730/ijhs.v6nS3.9488

Prospective Randomized comparison of Off-pump and On-pump Multivessel coronary artery bypasses surgery

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***Abstract*---**Aim: To ascertain the non-inferiority of off-pump CABG when compared to on-pump CABG in terms of angiographically assessed graft patency at 3 months. Material & Methods: This Prospective Randomized comparison of Off-pump and On-pump Multivessel coronary artery bypass surgery To Evaluate outcomes and graft patency (PROMOTE patency) trial was conducted in Indira Gandhi Institute of medical Sciences, Patna, Bihar, India over a period of one year. Results: A total of 300 patients were enrolled and were randomly assigned to either off-pump CABG (n = 150 patients) or on pump CABG (n = 150 patients). Of 300 patients, 280 patients at 1 month and 295 patients at 3 months survived and were analyzed for MACCE. The incidence of asymptomatic carotid artery stenosis was 0.66% (1 patient) in off-pump and 0.66% (1 patient) in on-pump group, p = 1.01 in our study. No difference was observed between the groups in terms of index of completeness of revascularization (number of grafts performed divided by number of grafts intended) 0.90 vs. 1.00 (p=0.7). Conclusion: There is no significant difference in overall graft patency rates at 3 months between off-pump and on-pump CABG groups when performed by experienced surgeons who have a

higher adoption of this strategy. Further, this study shows no difference in the graft patency among the 3 coronary artery territories and the different types of conduits between off-pump and on-pump CABG patients. At 3 months follow-up, off-pump CABG was associated with a fewer MACCE compared to on-pump CABG.

***Keywords*---**graft patency, after off- and on-pump, bypass surgery.

Introduction

Coronary artery bypass grafting has traditionally been performed with the use of cardiac arrest and extracorporeal cardiopulmonary bypass (conventional coronary artery bypass [CCABG]). However, some concern has been raised with regard to the safety of CCABG. Since the mid-1990s, therefore, a significant proportion of coronary artery bypass operations have been performed on the beating heart (off-pump coronary artery bypass, OPCAB). It has been suggested that the risk of perioperative stroke could be reduced by avoiding manipulation of the aorta, [1] although this was not confirmed by recent large-scale trials. [2-4] Smaller trials have documented a decreased inflammatory response, [5-7] less bleeding, [8-10] lower risk of atrial fibrillation, [8] smaller release of biochemical markers of myocardial injury, [10-12] and lower costs [13-15] related to OPCAB compared with CCABG.

Several relatively small single-center and multicenter randomized studies and large, risk-adjusted observational studies have reported that off-pump coronary artery bypass graft surgery (CABG) results in less morbidity than on-pump CABG. [16-23] In these studies and others, concerns have been raised about graft patency and long-term outcomes with the off-pump approach. [24-25]. This study was contemplated to assess whether the quality of revascularization in terms of graft patency in off-pump is noninferior to that of on-pump CABG by angiographic assessment when the procedure is performed by the surgeons with off-pump adoption rates in excess of 50% and have performed over 250 off-pump CABG procedures and negotiated the learning curve prior to participation in the trial.

Material and Methods

This Prospective Randomized comparison of Off-pump and On-pump Multivessel coronary artery bypass surgery To Evaluate outcomes and graft patency (PROMOTE patency) trial was conducted in Indira Gandhi Institute of medical Sciences, Patna, Bihar, India over a period of one year. The patients who met the inclusion and exclusion criteria were randomized in the ratio of 1:1 using block randomization, with a block size as 4, using software SAS version 9.2. A total of 300 patients were randomized and 300 patients (recruitment ranged from 26 to 56 patients per surgeon) were enrolled to either on-pump (n = 150) or off pump (n = 150) CABG.

This trial complies with the principles of The Declaration of Helsinki and was approved by the institutional ethics committees by the participating institutions

and all patients gave an informed written consent to participate in the study. The inclusion criteria were male or female aged ≥ 21 years and ≤ 70 years, and multivessel CAD, with triple vessel disease or left main coronary artery (LMCA) stenosis, requiring isolated CABG and with left ventricular ejection fraction (LVEF) of ≥ 40%. Exclusion criteria were CABG with concomitant procedures, contra-indications to either off-pump or on-pump CABG, chronic atrial fibrillation, and serum creatinine > 1.3% mg/dL. Graft patency was assessed at 3 months by either 128 slice multidetector computed tomographic angiography (MDCT) or conventional catheter coronary angiography (CAG).

Methodology

Graft patency was evaluated on the basis of type of conduit and coronary artery territory, as well as the number of anastomoses patent per patient. The graft evaluation was made similar to Fitzgibbon grading of grafts: A (excellent) vs. B (stenosed) and O (occluded). In this study, graft patency was graded as A (excellent patency) vs. B (partially stenosed) and O (occluded) grafts. All the graft angiograms (MDCTand CAG) were analyzed at the trial coordinating center by a single team comprising of a cardiologist and a radiologist with knowledge of the number and distribution of grafts performed but blinded for the type of revascularization technique used(on-pump or off-pump). The occurrence of MACCE was recorded as secondary outcomes at first and third month postoperatively.

Preoperative optimization of medical therapy

Withdrawal of anti-platelet drugs was done 4 days prior to surgery and low molecular weight heparin was started.

Surgical techniques

Premedication, anesthetic protocols, surgical access to the heart via a standard median sternotomy, conduit harvesting techniques, and distal and proximal anastomotic techniques were similar between the groups. Heparin dose was adjusted to achieve target activated clotting time of > 480 s and > 350 s for on-pump and off-pump groups respectively. Heparin was reversed using protamine at a dose of 1.3 mg/100 IU heparin in both the groups. The surgical techniques of revascularization were followed as described earlier. On-pump technique: Myocardial protection was achieved by cold (4 °C) ante grade blood and potassium cardioplegia. The distal coronary anastomoses were performed with either 7–0 or 8–0 polypropylene continuous suturing techniques and the proximal anastomoses were performed using 6–0 polypropylene sutures as described earlier.

Off-pump technique: The method of exposure and stabilization of heart to perform distal coronary anastomoses consisted of the technique previously described. Target artery stabilization was achieved with vacuum stabilizers - Octopus 4 or Evolution (Medtronic Inc., Minneapolis, MN, USA) or ACROBAT-i Stabilizer System (Maquet GmbH & Co, Rastatt, Germany), and clearview intra coronary shunts were used [Medtronic Inc. Minneapolis, MN, USA] in all coronary arteries measuring more than 1.25 mm in diameter while constructing the distal

anastomoses. Visualization of the anastomotic area was enhanced by using humidified carbon dioxide blower/mister (Medtronic Inc. Grand Rapids, Mich) to disperse the blood from the site of distal anastomosis. Postoperatively, all patients received dual antiplatelet therapy (aspirin 75 mg, clopidogrel 75 mg) once daily. Patients in whom endarterectomy was performed on any of the coronary arteries received acenocoumarol with target international normalized ratio (INR) of around 2.0 for 3 months.

Statistical methods

Statistical analysis was performed by the trial coordinating center using software SAS version 9.2. Continuous variables have been expressed as median, mean ± standard deviation. The categorical variables have been expressed as raw numbers and percentages. The differences were analyzed with chi-square, Fisher exact test (if cell frequency was less than 5), and two sample t test. The statistical significance for all the tests was accepted at a probability level < 0.05.

Results

A total of 300 patients were enrolled and were randomly assigned to either off-pump CABG (n = 150 patients) or on pump CABG (n = 150 patients). Of 300 patients, 280 patients at 1 month and 295 patients at 3 months survived and were analyzed for MACCE. Baseline variables, intraoperative (Table 1) and postoperative variables (Table 2) were comparable between the groups. The incidence of asymptomatic carotid artery stenosis was 0.66% (1 patient) in off-pump and 0.66% (1 patient) in on-pump group, p = 1.01 in our study (Table 1). All patients in the trial had EF ≥40%. Euro score II was calculated for all patients and the median score is less than 1 (off-pump group 0.97 and on-pump group 0.96) which indicates a low-risk population in both groups. The results were analyzed as intention to treat analysis. A total of 1005 grafts were used in 300 patients. The median number of grafts per patient in off-pump was 3.00 (Q1:3.00 and Q3:4.00) vs. on-pump 4.00 (Q1:3.00 toQ3:4.00), and mean number of grafts/patient was off-pump 3.45 ± 0.75 vs. on-pump 3.64 ± 0.70) (p = 0.01) (Table 1).

A total of 88 patients received two or more arterial grafts (right internal thoracic artery (RITA)/radial artery). Right ITA in 31 patients and as in situ graft in 11 patients and as a free graft in 23 patients. There was no significant difference in the number of sequential anastomoses between the two groups (p=0.77). The distribution of grafts among various territories is mentioned in (Table 3). No difference was observed between the groups in terms of index of completeness of revascularization (number of grafts performed divided by number of grafts intended) 0.90 vs. 1.00 (p=0.7). A total of four deaths occurred in the study. One mortality occurred in off-pump group (postoperative period) and 3 in on-pump group (1 postoperative period and 2 at 3 months). Three deaths were due to noncardiovascular cause and one due to pneumonia. There is no significant difference in mortality at 3 months between off-pump and on-pump groups (1.93%) odds ratio: (0.60, CI 0.330 0.03–3.49, p = 0.80). There was no significant difference between the groups in the outcome of nonfatal MI [none in off-pump and 1.96% (3 patients) in on-pump group (p = 0.32), CVS [0.00% in off pump and

1.96% (3 patients) in on-pump group (p = 0.32). Cumulative combined MACCE in off-pump group (0.59%) was significantly lower than on-pump group (5.62%) with an odds ratio of 0.108 (CI 0.01–0.86, p = 0.01). At 3 months follow-up, off-pump CABG was associated with a fewer MACCE compared to on-pump CABG (Table 4).

The modality of graft evaluation was not uniform due to non-availability of MDCT facility at some centers where the graft evaluation was done by catheter CAG. The baseline characteristics were comparable between patients who underwent graft evaluation and who declined graft evaluation. However, the patients who underwent graft evaluation are younger than the patients who declined graft evaluation (56.81 ± 7.10 vs. 59.62 ± 6.90, p = 0.05) (Table 5). The comparison between A grade grafts vs. B and O grade grafts showed that there was no significant difference in the patency rates of various bypass conduits [LITA: off-pump 118/129 (90.4%) vs. on-pump 118/127 (89.7%), (p = 0.62); RITA: off-pump 17/29 (88.6%) vs. on-pump 44/57 (77.1%), (p = 0.82); radial artery (RA) graft: off-pump 36/53 (67.9%) vs. on-pump 69/80 (86.2%), (p = 0.64); saphenous vein graft (SVG): off pump 130/143 (90.9%) vs. on-pump 363/409 (86.06%), (p = 0.90)] between the groups. Among the 3 coronary artery territories, patency rates of grafts were also similar [left anterior descending artery (LAD) territory: off-pump 117/149 (78.5%) vs. on-pump 296/340 (90.06%), (p = 0.61); left circumflex artery (LCx) territory: off-pump 122/137 (89.0%) vs. on-pump 289/309 (88.37%), (p = 0.70), and right coronary artery (RCA) territory: off-pump 48/54 (88.8%) vs. on-pump 95/122 (81.94%), (p = 0.71)] (Table 6)

Of 103 patients in on-pump CABG group who underwent graft evaluation, 111 (93%) patients had grade A grafts and of 113 patients in off-pump CABG group, and 118 (91%) patients had grade A grafts. Of 340 grafts in on-pump CABG group, 287 (84%) grafts were grade A grafts and of 771 grafts in off-pump CABG group 680 (84%) grafts were grade A grafts (Table 7). The results show that off-pump CABG is non-inferior to on pump CABG with a significant p value (p = 0.0001), thus rejecting the null hypothesis (off-pump CABG is inferior to on pump CABG).

Table 1
Baseline and intra-operative variables compared between off-pump and on-pump CABG

Variables	Off-pump CABG (n = 150)		On-pump CABG (n = 150)		P value
	Number	%	Number	%	
Age (mean ± SD)	55.24 ± 7.88		58.8 ± 7.2		0.46
Females	25	16.67	20	13.33	0.89
Males	125	83.33	130	86.67	
Diabetes	83	55.33	107	71.33	0.78
Hypertension	103	68.67	109	72.67	0.45
Smoking	20	13.33	18	12	0.88
Dyslipidemia	98	65.33	87	58	0.90
Carotid artery stenosis > 60%*	1	0.667	1	0.667	1.01
Transient ischemic attacks	2	1.333	0	0	–
COPD*	5	3.333	2	1.333	0.58

Myocardial infarction	58	38.67	52	34.67	0.23
Left main disease	26	17.33	21	14	0.86
Prior PTCA	8	5.333	8	5.333	0.62
Blood usage	80	53.33	80	53.33	0.20
Number of grafts (mean ± SD)	3.60 ± 0.88		3.64 ± 0.70		0.01
Median	3.00 (Q1:3.00 and Q3:4.00)		4.00 (Q1:3.00 to Q3:4.00)		

Table 2
In-hospital outcomes compared between off-pump and on-pump CABG

Variables	Off-pump CABG (n = 150)		On-pump CABG (n = 150)		P value
	Number	%	Number	%	
Re-exploration*	5	3.33	6	4	> 0.90
Intra and post-operative IABP*	2	1.33	8	5.33	0.57
Post-operative CVA	0	0	0	0	–
AKI requiring RRT	0	0	0	0	–
Pulmonary complications	0	0	2	1.33	–
GI complications	0	0	1	0.66	–
Post-operative atrial fibrillation	17	11.33	7	4.66	0.20
DSWI*	1	0.66	2	1.33	> 0.80
Post-operative MI	0	0	0	0	–
Re-revascularization	0	0	0	0	–
ICU stay (mean ± SD)	2.28 ± 2.01		2.38 ± 1.77		0.30
Ward stay (mean ± SD)	5.82 ± 1.80		5.39 ± 1.20		0.68
Death*	1	0.66	1	0.66	> 0.97

Table 3
Distribution of grafts to various coronary artery territories

Graft distribution (1005 grafts) in the entire cohort of patients (300)				Graft distribution (750 grafts) in the patients (200) underwent graft evaluation			
Conduits	Territories*	Off-pump CABG	On-pump CABG	Conduits	Territories*	Off-pump CABG	On-pump CABG
LITA (347)	LAD (301)	105	157	LITA (256)	LAD (233)	102	101
	LCx (17)	13	4		LCx (14)	10	4
	RCA (5)	2	3		RCA (4)	1	3
RITA (73)	LAD (17)	13	4	RITA (50)	LAD (11)	6	5
	LCx (48)	22	26		LCx (21)	11	10
	RCA (18)	11	6		RCA (11)	6	5
RA (115)	LAD (8)	6	2	RA (91)	LAD (5)	4	1
	LCx (49)	23	26		LCx (49)	20	29
	RCA (44)	21	23		RCA (26)	14	12
SVG (602)	LAD (95)	43	52	SVG (452)	LAD (79)	31	38
	LCx (251)	93	138		LCx (204)	88	79
	RCA (222)	91	121		RCA (176)	79	91

Total conduits	Total territories*	443	562	Total conduits	Total territories	372	378
1005	1005			750	750		

Table 4
Cumulative MACCE between off-pump and on-pump CABG at 3 months

Variables	Technique of CABG (no of patients)	Yes n (%)	No n (%)	Rate	Risk ratio (95% CI)	Odds Odds ratio (95% CI)	p value
Mortality	Off-pump CABG (140)	1 (0.59)	139 (99.87)	0.0060	0.36 (0.03–3.40)	0.069 0.330 (0.03–3.49)	0.80
	On-pump CABG (175)	4 (1.96)	171 (98.65)	0.0176		0.0017	
Non-fatal MI	Off-pump CABG (140)	0 (0.00)	140 (100.00)	0	0	00	0.32
	On-pump CABG (175)	3 (1.93)	172 (98.14)	0.020		0.020	
CVA	Off-pump CABG (140)	0 (0.00)	140 (100.00)	0	0	00	0.28
	On-pump CABG (175)	2 (1.90)	173 (98.36)	0.020		0.021	
Total MACCE	Off-pump CABG (140)	1 (0.59)	139 (99.87)	0.007	0.10 (0.01–0.80)	0.064 0.108 (0.01–0.86)	0.01
	On-pump CABG (175)	12 (5.62)	163 (0.76)	0.050		0.051	

Table 5
Comparison of baselines variables between the patients in whom angio is performed and not performed

Variables		Angio not done (77)	n (%)	Angio done (225)	n (%)	p value
Age (mean ± SD)		56.81 ± 7.10		59.62 ± 6.90		0.05
Sex	Female	10	13.33	28	12.44	0.20
	Male	65	86.67	197	87.56	
Smoking	No	62	82.67	191	84.89	0.82
	Yes	13	17.33	34	15.11	
Hypertension	No	31	41.33	79	35.11	0.59
	Yes	44	58.67	146	64.89	
Diabetes mellitus	No	26	34.67	80	35.56	0.71
	Yes	49	65.33	145	64.44	
Dyslipidemia	No	39	52	12	5.333	0.24
	Yes	38	50.67	213	94.67	
COPD	No	73	97.33	221	98.22	> 0.05*
	Yes	2	2.667	4	1.778	
Carotid artery stenosis > 60%	No	74	98.67	224	99.56	0.02*
	Yes	1	1.333	1	0.444	
Transient	No	75	100	223	99.11	> 0.05*

ischemic attack	Yes	0	0	2	0.889	
Cerebro vascular accident	No	73	97.33	221	98.22	0.05*
	Yes	2	2.667	4	1.778	
Myocardial infarction	No	56	74.67	137	60.89	0.40
	Yes	19	25.33	88	39.11	
Prior PTCA	No	71	94.67	210	93.33	0.05*
	Yes	4	5.333	15	6.667	
Left main disease	No	61	81.33	195	86.67	0.88
	Yes	14	18.67	39	17.33	
Surgery	Off-pump	26	34.67	129	57.33	0.61
	On-pump	49	65.33	96	42.67	

Table 6
Rates of grade A grafts (excellent patency similar to Fitzgibbon's grading) in various conduits and territories

Conduit	Grade A grafts/total grafts (percentage)	Off-pump CABG Grade A grafts/total grafts (percentage)	On-pump CABG Grade A grafts/total grafts (percentage)	p value
LITA	202/225 (89.7%)	104/115 (90.4%)	105/119 (88.2%)	0.62
RITA	44/57 (77.1%)	17/29 (88.6%)	15/26 (57.6%)	0.82
RA	69/80 (86.2%)	36/53 (67.9%)	38/51 (74.5%)	0.64
SVG	363/409 (86.06%)	130/143 (90.9%)	163/204 (79.9%)	0.90
All conduits	680/771 (84.2%)	287/340 (84.4%)	321/400 (80.2%)	0.67
Territories	Grade A grafts/total grafts (percentage)	Off-pump CABG Grade A grafts/total grafts (percentage)	On-pump CABG Grade A grafts/total grafts (percentage)	p value
LAD	296/340 (90.06%)	117/149 (78.5%)	142/167 (85.2%)	0.61
LCX	289/309 (88.37%)	122/137 (89.0%)	103/133 (77.4%)	0.70
RCA	95/122 (81.94%)	48/54 (88.8%)	76/100 (76%)	0.42
All territories	680/771 (84.2%)	287/340 (84.4%)	321/400 (80.2%)	0.71

Table 7
Non-inferiority test results for all grafts and subjects

Variable	Off-pump group	On-pump group	95% CI for difference	NI margin (% of on-pump group)	P value	Non-inferiority attained (yes/no)			
	Total	Patent n (%)	Total	Patent n (%)	Low	Upper				
Grafts	340	287 (84)	771	680 (84)	− 0.051	0.040	10	− 0.0892	0.0001	Yes
							5	− 0.0381	0.0301	Yes
Subjects	103	111 (93)	113	118 (91)	− 0.055	0.070	10	− 0.0902	< 0.0005	Yes
							5	− 0.0411	< 0.0291	Yes

Discussion

Puskas et al, [19] who reported arterial patency rates to the LAD of 97.2% off pump and 98.7% on pump. However, in the ROOBY study, there were significantly fewer widely patent (FitzGibbon A) LIMA pedicle grafts with off-pump than on-pump CABG (89.0% versus 93.2%; *P*<0.01). This is an important finding because other studies have reported patency based on open versus occluded grafts but have not reported the quality of LIMA grafts by distinguishing between FitzGibbon A and B patency classification.[19, 21, 25]. In our study, impaired graft patency was most evident when not only considering the proportion of totally occluded grafts but also the number of stenotic grafts by using the FitzGibbon score,[27] as also seen in the ROOBY trial.[26]Although graft occlusion may, theoretically, be caused by hypercoagulability, stenosis is more likely to be caused by technical anastomotic issues and operator experience has been suggested to be an important variable for graft patency after OPCAB. Undoubtedly, performing an anastomosis on a beating heart is more technically challenging than on the cardioplegic heart and may require a longer learning curve.

The possible reason for lower graft patency in off pump technique in ROOBY trial [28] was thought to be the inexperience of the surgeons involved in the study as evidenced by a higher conversion rates from off-pump to on-pump technique (12.7%). In our study, the conversion rate was 1.27%. There has been no significant difference in the index of completeness of revascularization between the groups in our study though higher rates of incomplete revascularization were reported by several authors [29, 30]. This can also be attributed to the experience of the surgeons who participated in the study. The graft patency rates at 3 months with various bypass conduits among the different coronary territories were similar between off and on-pump groups, which coincide with the results of Puskas and colleagues [19] and Magee et al.[31] who reported similar patency rates at 1 year.

The evaluation of graft patency was not uniform and was done by either MDCT or catheter CAG. In 80 % of patients, graft evaluation was done by MDCT, which despite its accuracy for detection of bypass graft occlusions does not provide information on graft flow but was used in recent large studies comparing late off pump and on-pump graft patency trials.[32-33] Less than 10% of screened patients were enrolled in the study due to difficulty in obtaining the consent for early angiographic evaluation. Only 75% of patients (849 grafts) were subjected to angiographic graft evaluation. Only low-risk patients were enrolled in this study.

Conclusion

There is no significant difference in overall graft patency rates at 3 months between off-pump and on-pump CABG groups when performed by experienced surgeons who have a higher adoption of this strategy. Further, this study shows no difference in the graft patency among the 3 coronary artery territories and the different types of conduits between off-pump and on-pump CABG patients. At 3 months follow-up, off-pump CABG was associated with a fewer MACCE compared to on-pump CABG.

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