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Study of sodium nitroprusside therapy for slow flow in coronary arteries after primary PCI

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Abstract
Intracoronary Sodium Nitroprusside is Effective in Treating Slow Flow During Primary PCI.
Objective: To study the effect of intracoronary sodium nitroprusside (SNP) for treatment of slow/no-flow phenomenon during primary coronary intervention in patients with acute coronary syndrome
Methods: The current study was done in 23patients with acute coronary syndrome, who developed slow flow in their coronary arteries immediately after Primary coronary angioplasty and stenting. Intracoronary sodium nitroprusside was given at 100 microgram per min boluses till good flow was achieved, Blood pressure was maintained by small iv boluses of 0.05 mg of Norepinephrine.
Results: Intracoronary SNP improved TIMI Grade 2 vs 3 ($p<0.001$), Ctfc 30 vs 26 ($p<0.001$), TMPG 1 vs 2 $p<0.001$) and MBG by QuBE 8 vs 12 ($p<0.002$).
Conclusions: Higher doses of Intracoronary SNP along with iv boluses of norepinephrine is very useful to improve slow flow in coronaries after primary Pci.

Keywords: sodium, therapy, coronaries, coronary

Introduction
Timely delivered primary percutaneous coronary intervention (P-PCI) has become the favoured reperfusion therapy for ST-elevation myocardial infarction (STEMI) [1]. However, this interventional technique has not abolished the unpredictable phenomenon of no-reflow. The coronary slow flow phenomenon (CSFP) is a post coronary angioplasty clinical entity, characterized by delayed distal vessel opacification in the absence of significant epicardial coronary stenosis. Its reported incidence of 1%-7% in patients undergoing coronary angioplasty. It has been linked to clinical manifestations of myocardial ischemia, life-threatening arrhythmias, sudden cardiac death, and recurrent acute coronary syndromes [2, 3, 4, 5].
The 2011 ACC PCI guidelines [6] give a class IIa recommendation for administration of an intracoronary vasodilator (specifically, adenosine, calcium channel blocker, or nitroprusside) to treat PCI-related no-reflow that occurs during primary or elective PCI.
Sodium Nitroprusside (SNP) is a nitric oxide donor that does not depend on intracellular metabolism to derive nitric oxide. The agent has shown some promising preliminary results when used to treat the no-reflow phenomenon but has not been examined in a prospective, controlled fashion. An initial small study of 20 patients showed significant benefit for treatment of the no-reflow phenomenon. The median injection dose was 200 micrograms given either through the guiding catheter or distally through the angioplasty balloon [15].
In this present study we have analyzed intracoronary effects of SNP for treatment of slow flow in patients in Primary Percutaneous Transluminal Coronary Angioplasty in Acute Coronary Syndrome Patients.

Aim and Objectives
To study the effect of intracoronary sodium nitroprusside for treatment of slow/no-flow phenomenon during primary coronary intervention in patients with acute coronary syndrome.

Material and Methods
Study Site
This study is carried out in the Department of Cardiology, KMC Hospital, Mangalore, India.

Inclusion criteria
Aged ≥18 years Informed CONSENT (verbal consent) prior to angiography Patients presenting as acute coronary syndrome (unstable angina, NSTEMI, STEMI), requiring Primary PCI Single vessel/ multi-vessel coronary artery disease TIMI flow 0/1/2 at angiography

Exclusion criteria
Contraindications to: P-PCI, iodinated contrast agents, or study medications: sodium nitroprusside (SNP), nor-Epinephrine SBP ≤90 mmHg Cardiogenic shock before PCI Culprit lesion not identified Patients with a coronary artery bypass graft Pregnancy

Study Design
Prospective Observational study

Study Duration
This study is carried out from June 2015 to June 2017 after ethical committee approval

Sampling Method
Consecutive Sampling

Methodology

Baseline demographic (Age, Sex), clinical and angiographic characteristics have be recorded in all the patients. In all cases, Primary-PCI has been performed in line with accepted practice with trans-radial or femoral arterial access using 6-7
Fr sheaths. Patients were pre-treated with dual antiplatelet therapy with aspirin (300 mg loading dose and 75 mg/day maintenance) and clopidogrel 300 mg loading dose, with a maintenance dose of 75 mg OD given for up to 12 months. All angiograms were filmed at 15 frames/s.
. All patients are commenced on a beta-blocker, angiotensin converting enzyme (ACE) inhibitor and high-dose statin in addition to dual antiplatelet therapy, unless contraindicated, according to international guidelines.
The eligible patients after completion of angioplasty were selected by the operator (consultant's discretion) for sodium nitroprusside (100 mcg/ bolus followed by 20 ml of saline bolus every minute upto 4mg) [19]. with IV Noradrenaline boluses for BP maintenance). The number of boluses of the study medication used was left to the discretion of the operator. Medication boluses will be administered until TIMI grade 3 flow was achieved or until systolic blood pressure decreased to < 90 mmHg. The operator was also free to use nor-epinephrine as inotropic support for managing systemic hypotension.
Glycoprotein IIb/IIIa receptor inhibitors were given to all patients. Heart rate and invasive arterial blood pressure monitoring were maintained and monitored throughout the entire procedure.

Study end points

Primary end points of the study

-Improvement in coronary blood flow in the infarct related artery after angioplasty, as determined by the corrected TIMI frame count (cTFC) Thrombolysis in myocardial infarction frame counts was assessed by an experienced operator according to standardized methods as described previously. The qualifying cine run will be the first one obtained after satisfactory relief of the epicardial culprit stenosis.
-ST Segment resolution in patients with ST elevation MI
ST-segment resolution was measured immediately after angioplasty using 12-lead ECG tracing. Complete ST resolution will be defined as >70% reduction in ST segment elevation of the lead with the highest elevation on admission.

Secondary end points

The incidence of patients with MACE in each treatment group till discharge.

Statistical Analysis

Data is expressed as Mean ± SD if normally distributed or median and interquartile ranges. The difference between the angiographic variables and the drugs is also expressed using stem and leaf plots. Wilcoxon signed rank test is applied to find out the difference in CSFP in patients before and after treatment with SNP. Chi-square test is done for categorical variables. A p value <0.05 is be considered statistically significant. Statistical analysis is performed using SPSS version 16.

Results and Observations

- **Clinical and Stent characteristics**

Table 1: Clinical characteristics of the study population

Parameter	SNP (n=23)
Age	58 ± 9.82
Sex	
Male	16
Female	7
DM	9
Arrythmia	4
CHB	2
AF	1

Table 2: Angiographic characteristics of the study population

Parameter	SNP (n=23)
Vessels Diseased	
1	14
2	7
3	2
Culprit Artery	
LAD	12
LCX	3
RCA	8
Drug Dose	995 ± 338 (mcg)
Nor Epinephrine	14
Stent Length	29 ± 12.37
Stent Diameter	3 ± 0.39

- **Angiographic parameters assessing improvement in coronary flow**
- **TIMI Flow Grades**

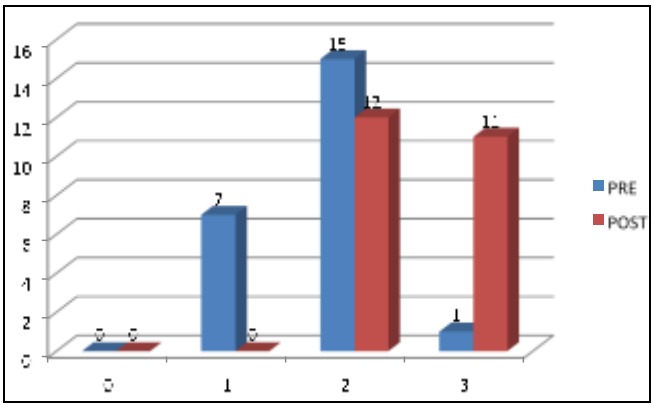

Fig 1: Bar diagram showing number of patients who received SNP for slow flow on Y axis and TIMI frame grades before and after receiving the drug on X axis

Figure 1 shows bar diagram analysis of patients who received SNP for slow flow. 0, 7, 15, 1 patients had TIMI 0, 1, 2, 3 flow grades respectively. After receiving SNP all the patients showed increase in the flow grades to TIMI 2 (12 patients) and TIMI 3 (11 patients) respectively. In the pre SNP group the median was TIMI 2 at baseline before receiving the drug which improved to maximum of TIMI 3 however the median was around TIMI 2.. On further analyzing this difference statistically we found that the difference was statistically significant. SNP induced significant improvements in TIMI flow grade (p 0.001)

Corrected TIMI Frame Counts

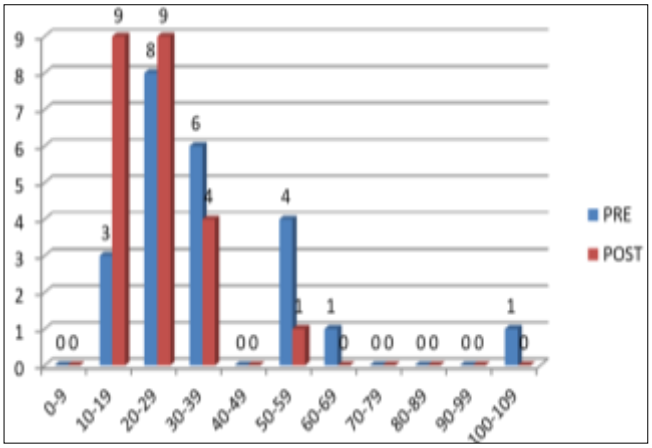

Fig 2: Bar diagram showing number of patients who received SNP for slow flow on Y axis and corrected TIMI frame count before and after receiving the drug on X axis

Figure 3 shows bar diagram analysis of patients who received SNP for slow flow. About 12 patients had cTFC > 30 before giving SNP which improved in 7 patients, however 5 patients still had cTFC > 30 with only 1 patient having cTFC > 40 inspite of SNP use. In SNP group majority of patients showed greater reduction in the cTFC after receiving the drugs. The following stem and leaf plot shows the improvement of patients with corrected TIMI flow count (cTFC) before and after giving SNP.

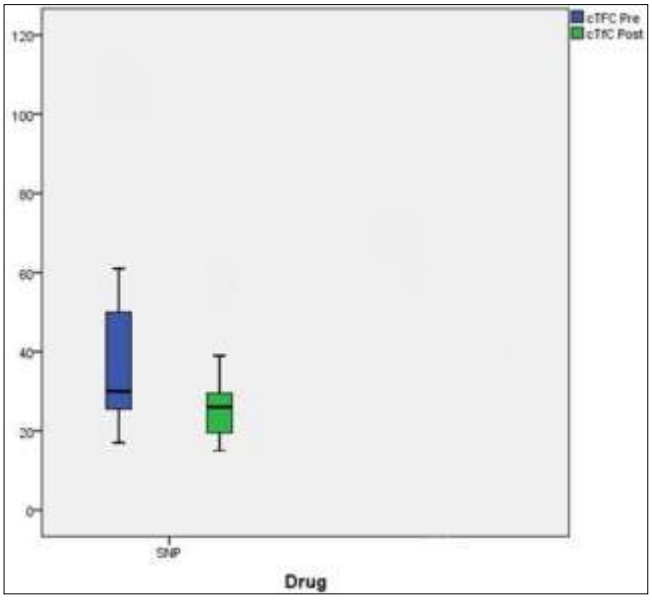

Fig 3: Stem and Leaf plot Showing improvement in the ptscTFC before and after giving drug

Figure 4 shows that the pre SNP group had a median of about 30 with an IQR of (25-50). After receiving SNP there was reduction in the median to 26 with significant reduction in the (IQR) Inter Quartile Range to (19-30). SNP induced significant improvements in cTFC ($p < 0.001$) (Fig. 4)

- Myocardial Blush Grade

The following stem and leaf plot shows the improvement of patients with myocardial blush grade (MBG) before and after giving SNP.

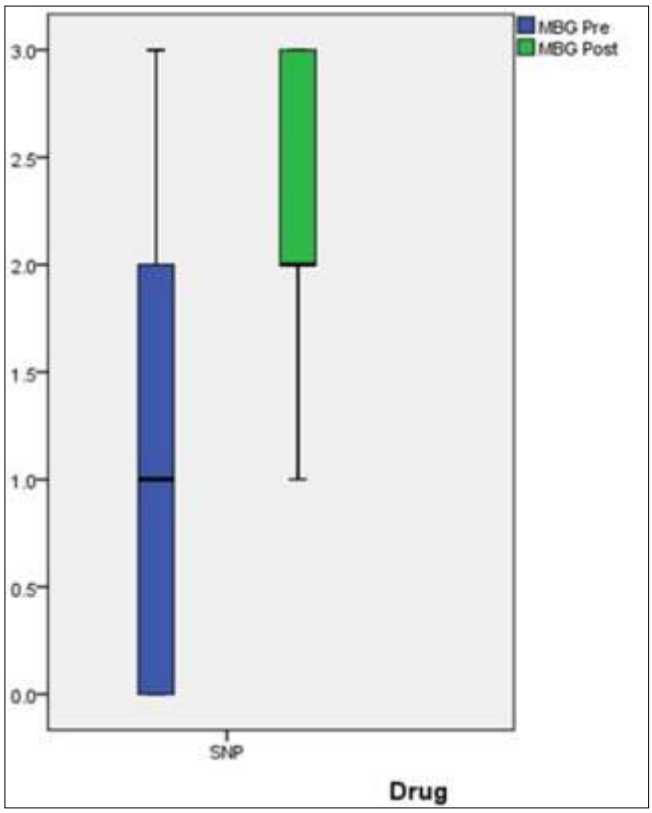

Fig 4: Stem and Leaf plot Showing improvement in the pts MBG before and after giving drug

Figure 6 shows that pre SNP group had an median of 1 with an IQR of 0-2. After receiving SNP the median increased to 2 with IQR of 2-3. (Fig. 6)

TIMI myocardial perfusion grade (TMPG)

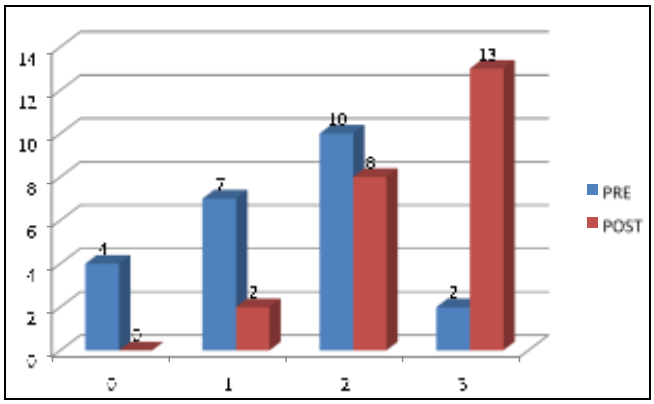

Fig 5: Bar diagram showing TMPG before and after receiving the drug on X axis and number of patients who received SNP for slow flow on Y axis.

Figure 8 shows bar diagram analysis of patients who received SNP for slow flow. 4, 7, 10, 2 patients had TMPG of 0, 1, 2, 3 flow grades respectively. After receiving SNP the all the patients showed increase in the flow grades to TMPG 2 (8 patients) and TMPG 3 (13 patients) respectively.

Pre SNP group had an median of 1 with an IQR of 0-2. After receiving SNP the median increased to 2 with IQR of 2-3. SNP induced significant improvements in TMPG ($p < 0.001$)

- Myocardial Blush by QuBE Software

The following stem and leaf plot shows the improvement of patients by analysis of myocardial blush by QuBE before and after giving SNP.

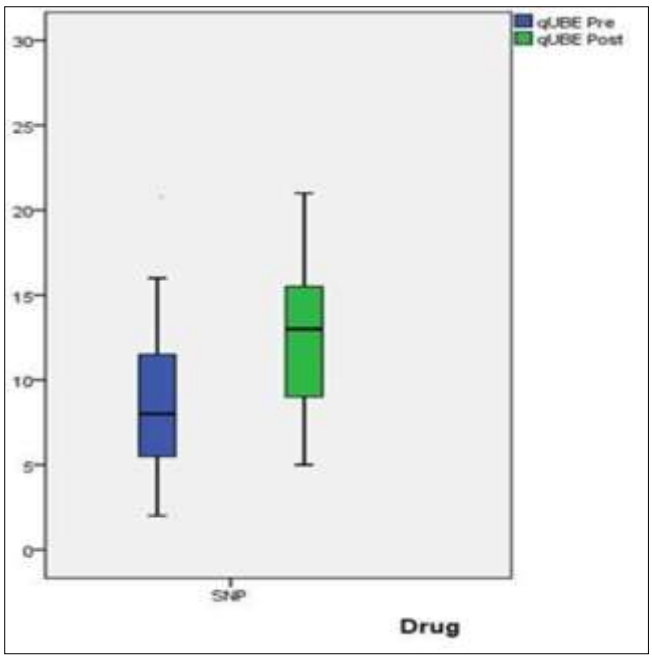

Fig 6: Stem and Leaf plot Showing improvement in QuBE before and after Giving drug

Figure 11 shows that pre SNP group had an median of 8 with an IQR of 5-
12. After receiving SNP the median increased to 13 with IQR of 9-16. SNP induced significant improvements in QuBE value (p <0.002) (Fig. 11)

- ST Segment resolution

The following stem and leaf plot shows the improvement in patients ECG in the ST segment before and after giving SNP.

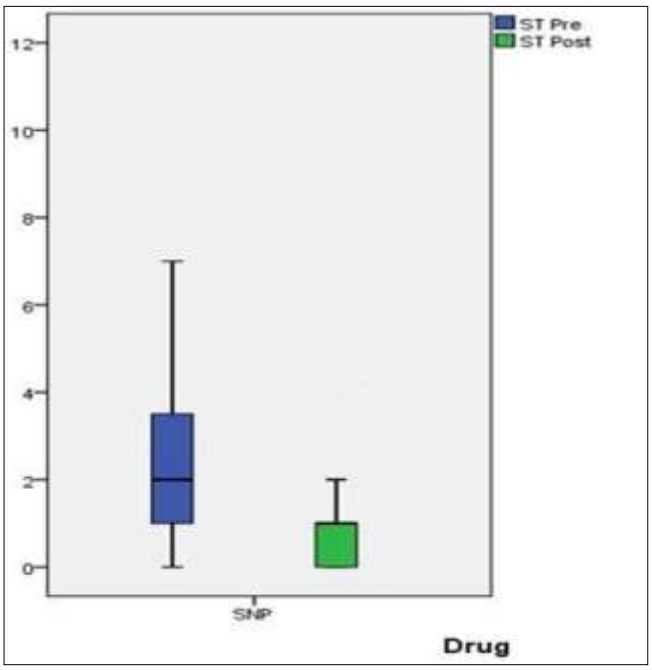

Fig 7: Stem and Leaf plot Showing improvement ST elevation before and after giving drug

Figure 12 shows that pre SNP group had an median of 2 with an IQR of 1-4. After receiving SNP the median decreased to 1 with IQR of 0-1. SNP induced significant improvements in ST resolution (p <0.001) (Fig. 12)

- In-hospital complications

All the patients were followed up for MACE till discharge.

Table 3: MACE till Discharge

	At Discharge
MACE	SNP
	n= 23
Cardiogenic Shock	5
Myocardial Infraction	0
Reinfarction	0
Recurrent MI	0
Contrast Induced Nephropathy	1
Cerebrovascular Event	0
Severe Heart Failure	0
Major Bleeding	0
Death	1

Table 4 summarizes in-hospital complications. No patient suffered myocardial infraction, reinfarction, recurrent MI, cerebrovascular event or severe heart failure. However, one patient expired. The cause of death in the patient was due to combination of both cardiogenic shock with acute renal failure.

One patient developed contrast induced nephropathy. A total 5 patients developed cardiogenic shock.

Discussion

Intracoronary administration of SNP in patients with AMI who had undergone primary PCI complicated by slow flow improved coronary flow in the present study.

Slow flow is caused by a malfunction in vasomotion of small vessels: that of the endothelium at the microcirculation level, spasms in resistant vessels, coagulation of platelets, activation of inflammatory cells, and shower embolization [20-22].

It is suggested that coronary blood flow disorders caused by these factors may be improved by the administration of nitrogen oxide (NO).NO is secreted from the endothelium and has multiple functions, such as vasodilation, anti-coagulation of platelets as well as anti-inflammatory functions [23], so it is an important vasodilatory factor in small resistant vessels, playing a useful role in the control of coronary blood flow. SNP is a direct donor of NO, so it requires no intracellular metabolism to derive NO, reaches micro-vessels directly, and improves the resistance of small-vessels.

Also, SNP has a strong and fast-acting vasodilatory effect, but its half-life is very short (1–3 min), even if the patient‘s blood pressure is lowered using SNP. It was reported that SNP was effective for treating slow flow in experiments on animals [24].

In this study, we confirmed the efficacy of SNP for Slow flow after its administration to coronary arteries. A few reports have suggested the efficacy of SNP for SF in humans. Hillegass *et al.* [15] reported the efficacy of SNP in 19 cases of SF and their method of administration was via a guiding catheter, and the administration dose varied (maximum dose: 1000 mcg). Wang *et al.* [25] and Pascer*iet*

al [26] reported the efficacy of SNP for SF that occurred in AMI patients that had undergone PCI using the same method.

Recently, a meta-analysis by Zhao S et.al [19] and Qiang Su *et al*. [27], showed that intracoronary SNP can significantly reduce the incidence of angiographic slow flow during PPCI, as well as the incidence of MACE.

Table 5: Meta -analysis by Zhao *et al* (19)

Study	Year	Study Design	Age (NG/CG)	Sample Size (NG/CG)	Administration	Interventions		Outcomes
						NG	CG	
Zhao et al.[8]	2013	RCT	63 ± 9/64 ± 10	80/82	Intracoronary	Thrombus aspiration + Tirofban 10 μg/kg + NTP100 μg	Thrombus aspiration + Tirofban 10 μg/kg	Final TFG, CTFC, TMPG; complete STR; MACE
Niccoli et al.[9]	2013	RCT	63 ± 10/64 ± 13	80/80	Intracoronary	Thrombus aspiration + NTP 60 μg as fast bolus + NTP 100 μg as slow bolus	Thrombus aspiration + identical volume of saline solution	Final TFG, CTFC, MBG; complete STR; MACE
Nayel et al.[10]	2013	RCT	—	20/20	Intracoronary	100–300 μg NTP	No treatment	Final TFG, MBG
Sakamoto et al.[11]	2010	RCT	—	56/53	Intracoronary	50–150 μg NTP	No treatment	CTFC
Pan et al.[12]	2009	RCT	52 ± 11/54 ± 13	46/46	Intracoronary	100 μg NTP	100 μg Nitroglycerin	Final TFG, CTFC; MACE
Shinozaki et al.[13]	2007	Retrospective cohort	69 ± 11/69 ± 11	60/60	Intracoronary	120 μg NTP	No treatment	Final TFG, CTFC, MBG; MACE
Amit et al.[14]	2006	RCT	62 ± 11/62 ± 12	48/50	Intracoronary	60 μg NTP	Identical volume of saline	Final TFG, CTFC, MBG; complete STR; MACE

NG, NTP group; CG, control group; TFG, TIMI flow grade; CTFC, corrected TIMI frame count; TMPG, TIMI myocardial perfusion grade; MBG, myocardial blush grade; STR, ST segment resolution; MACE, major adverse cardiac events.

Table 6: Systemic Review by Su et.al [27]

Study	Age Exptl/Ctrl	Participants Exptl/Ctrl	Administration	Interventions trail/control		Outcomes
Pan et al. [6]	52 ± 11/ 54 ± 13	46/46	Intracoronary	100 μg Nitroprusside (diluted to 20 μg/ml)	100 μg Nitroglycerin	CTFC; final TIMI flow grade of <3; rehospitalization due to cardiovascular events; MACE
Hendler et al. [7]	60/63	10/10	Intracoronary	Nitroprusside (100–500 μg)	Nitroglycerin, (200–400 μg)	CTFC; final TIMI flow grade of <3; left ventricular ejection fraction
Amit et al. [8]	62 ± 11/ 62 ± 12	48/50	Intracoronary	60 μg of nitroprusside diluted in saline solution as a 5-mL bolus	Identical volume of saline solution	CTFC; final TIMI flow grade of <3; ST segment elevation resolution; rehospitalization due to cardiovascular events; MACE
Sakamoto et al. [9]	–	56/53	Intracoronary	Nitroprusside (50–150 μg)	No treatment	CTFC; final infarct size

Their results also agree with our findings that SNP improved TIMI Grade, cTFC, TMPG and MBG. However none of the studies used digital method for assessing improvement in myocardial blush. Our study also showed improvement in myocardial blush score by using digital method of QuBE software [28]. On an average the dosage of drugs in the studies varied from 100-200 mcg, but we suggest using higher dosages of SNP (995 ± 338 mcg was the average dosage of SNP used in our study) for better angiographic and clinical outcomes.

We analyzed post SNP patients with respect to improvement in TIMI grades and cTFC Counts (Figure 3 and Figure 5)

Micro vascular obstruction following PCI is a multi-factorial phenomenon with diverse etiologies in different clinical settings and is associated with adverse outcome. Prevention of MVO following elective coronary intervention is beneficial in reducing cardiac injury and improving clinical outcome. Until recently, it was unclear whether the unfavourable outcome associated with MVO following primary infarct PCI reflected a causal effect or whether the micro circulatory injury was an epi phenomenon mirroring greater myocardial damage. The TAPAS study has proven that prevention of MVO during primary PCI may reduce cardiac injury and improve clinical outcome. Several preventive measures effectively decrease the degree of MVO and improve clinical outcome in the setting of both acute infarct and elective PCI.

There are several limitations to the present study.

First, the number of cases was low so further studies on a larger number of patients are warranted.

Second, the treatment was not randomized, and finally the patients studied were heterogeneous for several factors like age.

No definitive recommendations can be made for treatment of noreflow once it has occurred because proposed interventions have not been studied in randomized trials. However, based on reports from multiple nonrandomized studies and the paucity of alternative proven therapeutic options, administration of vasodilators should be considered.

In our personal practice, SNP given as boluses of 100mcg and 0.8mg noradrenaline diluted in 10 ml NS was given IV concurrently to maintain SBP > 90 during the procedure so as to prevent fall in SBP during treatment to slow flow with intracoronary SNP. In our study around 14 patients received SNP along with noradrenaline by this method. We have

observed that after administration of systemic noradrenaline the heart rate goes up improving the systolic blood pressure, cardiac output and in turn reducing the incidence of peri-procedural hypotension and subsequent decreased coronary perfusion leading to slow flow. Using norepinephrine in small doses helps to maintain stable BP and this facilitates administration of higher doses of SNP compared to other studies with SNP.Addition of NE to SNP significantly improves cTFC. This exciting finding needs further evaluation with larger sample size trials. Nor Epinephrine may improve cTFC my improving coronary macro and micro level obstruction.

Unfortunately, there is limited data comparing the efficacy of different strategies. There is no random to guide for selection of therapies for reversal of existing slow flow. The goal of the various pharmacological and mechanical therapeutic strategies that are targeted at prevention and reversal of MVO and slow flow is to minimize cardiac injury. Specific interventions targeted at reperfusion injury that activate intracellular cardio-protective signalling pathways have been shown to improve tissue perfusion and decrease myocardial injury following PCI. These approaches hold great promise for achievement of further myocardial preservation. Ultimately, strategies designed to reduce MVO and to activate intracellular cardio protective mechanisms converge at the tissue level. Reduction of

MVO is cardio protective and cardio protection is associated with improved tissue perfusion. Future research should be directed at refining these techniques and implementing them for reversal of slow flow once it has occurred.

Conclusions

IC SNP can be used for treatment of slow flow phenomenon in patients with AMI undergoing primary PCI Intracoronary SNP improved TIMI Grade, cTFC, TMPG ,MBG and MBG by QuBE We suggest using higher dosages of SNP (995 ± 338 mcg was the average dosage of SNP used in our study) for better angiographic and clinical outcomes.

SNP improved ST segment resolution in the study population

IC SNP preceded by Systemic noradrenaline in treatment of slow flow helps prevent the hypotension associated with SNP use.

Refrences

1. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: A quantitative review of 23 randomised trials. Lancet, 2003.
2. Cutri N, Zeitz C, Kucia AM, Beltrame JF. STT wave changes during acute coronary syndrome presentation in patients with the coronary slow flow phenomenon. International Journal of Cardiology, 2011.
3. Horjeti B, Goda A. Acute ischemia manifestation in a patient with coronary slow flow phenomenon. In: Journal of Electrocardiology, 2012.
4. Wozakowska-Kapłon B, Niedziela J, Krzyzak P, Stec S. Clinical manifestations of slow coronary flow from acute coronary syndrome to serious arrhythmias. Cardiology Journal, 2009.
5. Saya S, Hennebry TA, Lozano P, Lazzara R, Schechter E. Coronary slow flow phenomenon and risk for sudden cardiac death due to ventricular arrhythmias. Clinical Cardiology, 2008;
6. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, *et al*. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: Executive Summary: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Journal of the American College of Cardiology, 2011.
7. de Bruyne B, Hersbach F, Pijls NHJ, Bartunek J, Bech JW, Heyndrickx GR, *et al*. Abnormal epicardial coronary resistance in patients with diffuse atherosclerosis but “normal” coronary angiography. Circulation, 2001.
8. Maseri A, Crea F, Kaski JC, Crake T. Mechanisms of angina pectoris in syndrome X. Journal of the American College of Cardiology, 1991.
9. Tambe AA, Demany MA, Zimmerman HA, Mascarenhas E. Angina pectoris and slow flow velocity of dye in coronary arteries-A new angiographic finding. American Heart Journal, 1972.
10. Mosseri M, Yarom R, Gotsman MS, Hasin Y. Histologic evidence for small-vessel coronary artery disease in patients with angina pectoris and patent large coronary arteries. Circulation, 1986.
11. Pekdemir H, Polat G, Cin VG, Çamsari A, Cicek D, Akkus MN, *et al*. Elevated plasma endothelin-1 levels in coronary sinus during rapid right atrial pacing in patients with slow coronary flow. International Journal of Cardiology. 2004;
12. Chatzizisis YS, Coskun AU, Jonas M, Edelman ER, Feldman CL, Stone PH, *et al*. Role of Endothelial Shear Stress in the Natural History of Coronary Atherosclerosis and Vascular Remodeling. Molecular, Cellular, and Vascular Behavior. Journal of the American College of Cardiology, 2007.
13. Kantarci M, Gündogdu F, Doganay S, Duran C, Kalkan ME, Sagsoz ME, *et al*. Arterial bending angle and wall morphology correlate with slow coronary flow: Determination with multidetector CT coronary angiography. European Journal of Radiology, 2011.
14. Karakaya O, Koçer A, Esen AM, Kargin R, Barutcu I. Impaired cerebral circulation in patients with slow coronary flow. Tohoku Journal of Experimental Medicine, 2011.
15. Hillegass WB, Dean NA, Liao L, Rhinehart RG, Myers PR. Treatment of no-reflow and impaired flow with the nitric oxide donor nitroprusside following percutaneous coronary interventions: Initial human clinical experience. Journal of the American College of Cardiology, 2001.
16. Barcin C, Denktas AE, Lennon RJ, Hammes L von, Higano ST, Holmes DR, *et al*. Comparison of Combination Therapy of Adenosine and Nitroprusside with Adenosine Alone in the Treatment of Angiographic No-Reflow Phenomenon. Catheterization and Cardiovascular Interventions, 2004.
17. Amit G, Cafri C, Yaroslavtsev S, Fuchs S, Paltiel O, Abu-Ful A, *et al*. Intracoronary nitroprusside for the prevention of the no-reflow phenomenon after primary percutaneous coronary intervention in acute myocardial infarction. A randomized, double-blind, placebo-controlled clinical trial. American Heart Journal, 2006.
18. Kobatake R, Sato T, Fujiwara Y, Sunami H, Yoshioka R, Ikeda T, *et al*. Comparison of the effects of

nitroprusside versus nicorandil on the slow/no-reflow phenomenon during coronary interventions for acute myocardial infarction. Heart and Vessels, 2011.
19. Zhao S, Qi G, Tian W, Chen L, Sun Y. Effect of intracoronary nitroprusside in preventing no reflow phenomenon during primary percutaneous coronary intervention: A meta-analysis. Journal of Interventional Cardiology, 2014.
20. Lloyd-Jones DM, Bloch KD. The vascular biology of nitric oxide and its role in atherogenesis. Annual Review of Medicine, 1996.
21. Gavin JB, Maxwell L, Edgar SG. Microvascular involvement in cardiac pathology. In: Journal of Molecular and Cellular Cardiology, 1998.
22. Yun KH, Jeong MH, Oh SK, Rhee SJ, Park EM, Lee EM, *et al*. Response of high-sensitivity C-reactive protein to percutaneous coronary intervention in patients with acute coronary syndrome. Heart and Vessels, 2009.
23. Myers PR, Banitt PF, Guerra R, Harrison DG. Characteristics of canine coronary resistance arteries: Importance of endothelium. American Journal of Physiology - Heart and Circulatory Physiology, 1989.
24. Wang WZ, Anderson G, Fleming JT, Peter FW, Franken RJPM, Acland RD, *et al*. Lack of nitric oxide contributes to vasospasm during ischemia/reperfusion injury. Plastic and Reconstructive Surgery, 1997.
25. Wang HJ, Lo PH, Lin JJ, Lee H, Hung JS. Treatment of slow/no-reflow phenomenon with intracoronary nitroprusside injection in primary coronary intervention for acute myocardial infraction. Catheterization and Cardiovascular Interventions, 2004.
26. Pasceri V, Pristipino C, Pelliccia F, Granatelli A, Speciale G, Roncella A, *et al*. Effects of the nitric oxide donor nitroprusside on no-reflow phenomenon during coronary interventions for acute myocardial infarction. American Journal of Cardiology, 2005.
27. Su Q, Li L, Naing KA, Sun Y. Safety and Effectiveness of Nitroprusside in Preventing No-Reflow During Percutaneous Coronary Intervention: A Systematic Review. Cell Biochemistry and Biophysics, 2014.
28. Vogelzang M, Vlaar PJ, Svilaas T, Amo D, Nijsten MWN, Zijlstra F. Computer-assisted myocardial blush quantification after percutaneous coronary angioplasty for acute myocardial infarction: A substudy from the TAPAS trial. European Heart Journal. 2009;