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Original Article

Safety of Prasugrel in Indian patients – Multicentric registry of 1000 cases

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ABSTRACT

Background: Clopidogrel has been the only available antiplatelet drug used along with aspirin in patients of ACS. In recent years 2 new antiplatelet drugs (Prasugrel and Ticagrelor) have become available. Prasugrel in the dose of 10 mg OD has been found to be more efficacious but with increased risk of major bleeding. For this reason it has not gained widespread usage in ACS patients undergoing PCI. There are no systematic data on the use of Prasugrel in Indian population.

Method: This is a prospective, multicentric, hospital registry of 1000 patients with ACS undergoing PCI who were administered Prasugrel. The primary safety endpoint of this study was major and minor bleeding while the efficacy endpoint is the composite of CV death, nonfatal MI, nonfatal stroke up to 30 days after PCI. Patients with high bleeding risk were excluded.

Results: Most patients (91%) received loading dose of Prasugrel along with the maintenance dose getting according to the defined protocol. Patients were followed up to 30 days post

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procedure. Primary efficacy end point was reached in 3 patients only with two of them dying due to possible stent thrombosis and the third requiring revascularization of the target vessel for stent thrombosis. One major and 19 minor bleeding complications were recorded, with access site bleeding in 0.7% & non-access site bleeding in 1.2% of the subjects.

Conclusion: Prasugrel was found to be effective & not associated with a high incidence of bleeding in the high risk ACS patients when those at a high bleeding risk were excluded.

1. Background

Dual antiplatelet therapy with aspirin and clopidogrel has been established to be efficacious in the treatment of acute coronary syndrome with PCI. However many patients continue to have recurrent atherothrombotic events on this therapy despite these positive effects. More over delayed onset of action and modest antiplatelet effect with significant interpatient variability has led to the development of newer antiplatelet drugs.

Prasugrel, a prodrug, needs to be converted to its active metabolite before binding to the platelet P2Y12 receptor to have its antiplatelet effect. Its efficacy has been well established in both phase 2 and phase 3 trials testing Prasugrel as compared to standard dose clopidogrel in patients undergoing PCI for ACS. Results revealed positive trends towards reduced ischaemic events i.e. significantly less nonfatal MI & significantly lower rate of stent thrombosis in the follow up period. These benefits were limited by more complications including higher rate of both life-threatening & fatal bleeding as compared to clopidogrel. These side effects were however found to be more in specified high risk subgroups like elderly age group (>75 yrs), previous stroke/TIA and those weighing less than 60 kg, with no net benefit.[1] Hence the drug has not gained widespread usage especially in our country because of the fear of bleeding. TRITON TIMI 38 had no subjects included from South Asian countries as also lack of systematic Indian data on the subject led us to plan this multicentric registry in order to find out the incidence of bleeding complications with use of Prasugrel in conjunction with aspirin, as well as to establish its efficacy in our kind of population.

2. Methods

This is a prospective investigator initiated multicentric hospital registry.

2.1. Study population

1000 patients, presenting with ACS and scheduled to undergo PCI & given Prasugrel along with aspirin as antiplatelet agents were included in the study. ACS included both unstable angina & NSTEMI diagnosed as per standard definitions as well as STEMI i.e. primary PCI as also those undergoing delayed PCI following initial medical management.

2.2. Exclusions

Patients with CVA/TIA (diagnosed significant intracranial pathology), those >75 yrs of age and those weighing <60 kg were excluded from the study as well as the ones with increased risk of bleeding, anaemia or thrombocytopenia.

2.3. Study protocol

Those included in the study received loading dose of Prasugrel (60 mg) following delineation of the coronary status and maintained by 10 mg once daily. Patients preloaded with clopidogrel and subsequently switched over to Prasugrel maintenance dose were also included in the registry. The protocol for such patients was that if preloading was done with clopidogrel 600 mg within previous one week then it was followed up with only maintenance dose of Prasugrel 10 mg once daily. Patients on maintenance dose of clopidogrel for over a week were reloaded with Prasugrel with subsequent maintenance dose of Prasugrel (SWAP study).[2] Choice of the number of vessels treated and use of adjunctive medication during PCI was left to the treating physician. After enrolment patients were maintained on standard medication and were followed up physically at screening, at baseline & loading dose, at 24 h and at 30 days post procedure with a telephonic review at 15 days in between.

2.4. End points

Primary safety end point was TIMI major bleeding not related to CABG, non CABG related life-threatening & TIMI major and minor bleeding.[3]

Efficacy was studied by a composite of cardiovascular death, nonfatal MI and nonfatal stroke up to 30 days post procedure.

Stent thrombosis was defined as definite/probable stent thrombosis according to ARC criteria.

The study had approval of the local Ethics committees and written informed consent was taken from all the participants.

3. Results

A total of 1000 patients undergoing PCI for Acute coronary syndrome & treated with prasugrel were included in the study. The mean age of the patients was 55.99 yrs. Average

weight of the patients was 72.88 kg. Of the whole lot 89.2% were males. Hypertension was the commonest associated risk factor, about 50% and 38.9% were diabetics. Tobacco use was seen in 25.7% of the study population. The indications for PCI included 49.5% unstable angina, 19.4% NSTEMI and 31.1% STEMI (Table 1). Most of the patients were given Prasugrel subsequent to the delineation of their coronary anatomy following an angiogram.

Majority of the patients (90.9%) received loading dose (60 mg) either pre-procedure or during procedure and were followed up with 10 mg once daily whereas the rest 9.1% (who had been preloaded with clopidogrel) were given only the maintenance dose i.e. 10 mg once daily. Almost all the patients got a DES placed during the procedure with a few undergoing PCI with DEB for specified indications.

A total of 26 adverse events were noticed during the study period. Primary efficacy end point was reached in 3 patients with two of them died due to possible stent thrombosis and the third required revascularization of the target vessel for stent thrombosis. A different vessel intervention (although not a study end point) was required in 2 patients as also two other patients required hospitalization, however for non cardiac issues (Table 2). Safety end points were noticed in 20 of the subjects with one patient while undergoing delayed angioplasty following an STEMI, developed hemorrhagic pericardial effusion following 2 days post PCI and required surgical drainage for relief from the resulting tamponade. The other 19 patients experienced minor bleeds in the form of access site i.e. groin haematomas (0.7%), and non access site (1.2%) i.e. epistaxis, gum bleeding and bleeding from haemorrhoids (Table 3).

4. Discussion

Antiplatelet therapy is the corner stone in the success of PCI. Various drugs have been in vogue for the purpose with rising interest in the development of newer agents with improved efficacy & reduced side effects profile. Prasugrel & Ticagrelor are two such agents which have been extensively studied & and found to be more efficacious in most of the situations barring a few conditions (with high bleeding risk). TRITON TIMI 38[1] was one such trial involving over 13000 moderate - high risk Acute Coronary Syndrome patients, where its significantly higher efficacy in terms of composite of death, non fatal MI/urgent TVR and stent thrombosis was established beyond doubt. The effect was noticed to be more pronounced in STEMI patients.

Mean age of patients included in our study was 55.99 yrs. It is significantly younger than those included in the major trial testing Prasugrel i.e. 61 yrs. in TRITON TIMI 38. Whereas number of diabetics included were 38.9% in our study vs. 23% in TRITON TIMI 38. STEMIs constituted 31.1% of our study population as compared to 26% in TRITON TIMI 38. All these findings re-emphasize that our population is more prone to have diabetes and coronary artery disease at a relatively younger age, as well as STEMI may be a more common presentation in our part of the world.

With regards to efficacy of the study drug, we observed 0.3% primary composite end point at 30 days post procedure whereas primary efficacy end point was seen in 6.5% of patients receiving Prasugrel at 30 days & 9.9% of patients at 15 months with 7.4% having MI, 2.5% requiring urgent TVR & 1.1% having stent thrombosis in TRITON TIMI 38 (Table 4). This difference could possibly be due to relatively younger & probably more stable population included in our study as well as especially with exclusion of the high risk elderly population as indicated by TRITON TIMI 38 should have affected the outcome to such a degree.

As with any other antiplatelet drug, bleeding was the commonest side effect noticed with Prasugrel. We found major bleeding in only one patient (0.1%) and minor bleeding in another 1.9% of the patients at 30 days post procedure. TRITON TIMI 38 revealed that at 30 days bleeding complications occurred similarly in both Prasugrel (1.03%) and Clopidogrel (0.87%) arms (Table 5). However by the end of the study (at 15 months) the bleeding rates significantly increased to the tune of 2.4% with Prasugrel as compared to 1.8% patients with clopidogrel including both life-threatening bleeding (non fatal/fatal bleeding). Similar rates of bleeding have earlier been reported with clopidogrel in CURE[4] (clopidogrel vs. placebo) major bleed was seen in 3.7% vs. 2.7% placebo. CLARITY TIMI 28[5] showed in STEMI patients that Clopidogrel & Placebo groups had similar number of bleeding complications. COMMIT[6] (STEMI) study again revealed no significant differences in bleeding episodes. CREDO[7] – an observational study similarly showed low incidence of bleeding. These differences in the efficacy & safety parameters as compared to previous large scale studies could possibly be due to exclusion of

Table 1 – Baseline characteristics of the patients (n = 1000).

Mean Age (yrs)	55.99
ACS	
NSTEMI *n* (%)	194 (19.4)
Unstable angina *n* (%)	495 (49.5)
STEMI *n* (%)	311 (31.1)
Risk factors	
Hypertension *n* (%)	502 (50.2)
Diabetes Mellitus *n* (%)	389 (38.9)
Tobacco use *n* (%)	257 (25.7)
Previous history	
MI *n* (%)	100 (10)
CABG *n* (%)	23 (2.3)
Anti thrombin used	
Heparin *n* (%)	545 (54.5)
Heparin + GPI *n* (%)	245 (24.5)
Bivalirudin *n* (%)	210 (21)

Table 2 – Adverse events (n).

Death (possible stent thrombosis)	2
Target vessel revascularization	1
Different vessel intervention	2
Rehospitalisation	
Cardiac cause	0
Non cardiac cause	2

Table 3 – Bleeding rates (n = 1000).

Access site *n* (%)	7 (0.7)
Non access site *n* (%)	12 (1.2)

Table 4 – Efficacy (primary composite end point) (%).

Our registry (30 days)	TRITON TIMI 38[1] (15 months)		PCI-CURE[8] (8 months)		PLATO[9] (12 months)	
Prasugrel	Prasugrel	Clopidogrel	Placebo	Clopidogrel	Ticagrelor	Clopidogrel
0.3	9.9	12.1	6.4	4.5	9.8	11.1

Table 5 – Comparison of major bleeding rates in important trials (%).

Time	Our registry	TRITON TIMI 38[1]		PCI-CURE[8]		PLATO[9]	
	Prasugrel	Prasugrel	Clopidogrel	Placebo	Clopidogrel	Ticagrelor	Clopidogrel
30 days	0.1	1.03	0.87	1.4	1.6	NA	NA
End of study	NA	2.4	1.8	2.5	2.7	7.9	7.7

certain high risk groups including elderly patients (>75 yrs), weight < 60 kg & previous h/o bleed (intra cerebral). Barring these situations Prasugrel was found to be as efficacious as reported earlier & was also found to be relatively safe & may not be as risky as with inclusion of all unselective cases.

5. Conclusions

In the background of acute coronary syndrome, patients scheduled to undergo PCI, when given Prasugrel, was associated with significantly reduced incidence of primary events as shown in earlier trials. Non inclusion of the patients at high risk of bleeding as seen in our study leads to very low bleeding events and favourable outcomes in most. Prasugrel may thus be a more efficacious & less complicating drug in high risk ACS patients.

6. Limitations

It was an exploratory study where bleeding rates were observed to be comparatively quite low and thus making it difficult for any kind of subset analysis. Moreover follow up was undertaken up to 30 days post procedure which could have possibly excluded the bleeding episodes which might occur on prolonged maintenance dosages.

Conflicts of interest

All authors have none to declare.

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REFERENCES

1. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes: TRITON TIMI 38 study. *N Engl J Med*. 2007;357:2001–2015.
2. Angiolillo DJ, Saucedo JF, DeRaad R, et al. Increased platelet inhibition after switching from maintenance clopidogrel to prasugrel in patients with acute coronary syndromes: the SWAP (Switching Anti Platelet) study. *J Am Coll Cardiol*. 2010;56:1017–1023.
3. TIMI definitions for commonly used terms in Clinical Trials. http://www.timi.org/wp-content/uploads/2010/10/TIMI-Definitions.pdf.
4. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation: CURE trial. *N Engl J Med*. 2001;345:494–502.
5. Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST segment elevation: CLARITY-TIMI 28. *N Engl J Med*. 2005;352:1179–1189.
6. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomized placebo-controlled trial: COMMIT trail. *Lancet*. 2005;366:1607–1621.
7. Steinhubl SR, Berger PB, Mann 3rd JT, et al. Clopidogrel for the reduction of events during observation. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial: CREDO study. *JAMA*. 2002;288:2411–2420.
8. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pre-treatment with clopidogrel and aspirin followed by long term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet*. 2001;358:527–533.
9. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes: the PLATO study. *N Engl J Med*. 2009;361:1045–1057.