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ORIGINAL ARTICLE

Comparison between Clopidogrel and Ticagrelor in Cases of Antiplatelet Therapy for Treating Acute Coronary Syndromes: a Retrospective Longitudinal Comparative Study

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ABSTRACT

Aim: This purpose of this study was to compare the effects of clopidogrel and ticagrelor in cases of antiplatelet therapy for treating acute coronary syndromes

Study design: retrospective longitudinal comparative study

Place and duration: This Study was conducted at Sandeman Provincial Hospital Quetta, Pakistan over a period of two years, from February 2019 to July 2021

Methodology: A study population of 1002 patients was taken, each diagnosed with acute coronary syndrome. The inclusion criteria for these patients included that they had been previously treated with antiplatelet therapy and had been subject to invasive therapy and management. The multiplate analyzer was used to measure the platelet count for each patient. Patient history was taken and the response of each patient to the medication was recorded throughout the interval of one year. The outcome after one year on the medication was also noted and analyzed.

Results: Ticagrelor was given to patients who were young and possessed a lesser chance of having diabetes. These patients also presented with an elevated ST segment or had previously suffered from a myocardial infarction, the p value was recorded to be greater than 0.05. It was noted that patients who were treated with ticagrelor had a lower risk score of bleeding. Patients who were treated with ticagrelor also showed a lower risk score for the global registry of acute coronary events (grace) where the results showed that patients treated with ticagrelor had a score of 121 ± 27 versus 127± 31.5 and the p value was equated as 0.002.

There were greatly reduced results for the high platelet reactivity in patients treated with ticagrelor. When patients treated with clopidogrel were compared with patients treated with ticagrelor the high platelet reactivity results showed that it was 37.5% versus 16.7% respectively with the p-value of less than 0.0001.

Conclusion: The results from the study concluded that in case of patients who were categorized as lower risk, ticagrelor was prescribed more frequently, but it was not prescribed as frequently in the case of higher risk patients. Ticagrelor was also discontinued in case of side effects such as bleeding, trouble breathing or bradyarrythmia. However, these side effects were not common. Discontinuation rates were higher after most cases of coronary artery bypass graft surgery. These higher discontinuation rates were noted in patients who were treated without the use of revascularization. There is a need for more research to be done on this and educating surgeons on the benefits and pitfalls of the medication and its effects is also needed.

Keywords: Ticagrelor, clopidogrel, acute coronary syndromes. comparison

INTRODUCTION

For patients who have presented with acute coronary syndrome, antiplatelet therapy is a common and favored therapy practice (1). It consists of prescribing the patient with a painkiller such as aspirin and a medication to combat the P2Y12 receptor (2). One of the most used medications which act as a P2Y12 receptor antagonist is clopidogrel which is commonly prescribed for myocardial infarction (3). However, it comes with several limitations. The most significant disadvantage this medication has is the difference in the variability of patient active metabolite levels and the effect of the drug itself (4). To counter this effect ticagrelor has been prescribed since it does not metabolism to act. Ticagrelor to a significantly new chemical class and is also characterized as a P2Y12 receptor antagonist (5). It is preferred by surgeons and physicians for its direct acting nature and its efficiency in the clinical outcomes (6). The Plato trial (platelet inhibition and patient outcomes) is proof of this efficiency since it used the medication ticagrelor in therapy to note the outcomes of patients who had an acute coronary syndrome (7). The trial compared the results with patients who were prescribed with clopidogrel in order to effectively measure the efficiency of the drug (8). The trial reported that ticagrelor had a much higher efficiency rate than clopidogrel. This trial utilizes a study population of patients who had invasive management and also patients who had noninvasive management planned (9). This trial was the stepping stone for a recommending ticagrelor as a preferred first choice therapy for patients with acute coronary syndrome globally. Despite the advancement

associated in antiplatelet therapy due to ticagrelor, significant side effects have also been recorded such as a significant increase in major bleeding caused after a noncoronary artery bypass grafting surgery (10). Since ticagrelor is a more powerful antiplatelet agent, the significant increase in bleeding is expected when compared to clopidogrel. Other risks associated with ticagrelor are dyspnea and ventricular pauses (11). The inclusion criteria for this study was vigorous and this includes any patient who is not compliant or is considered a high risk patient for suffering any drug related side effects (12). This study evaluates the different prescription patterns and the rates associated with adverse drug related effects. The drug related effects include side effects such as bleeding, trouble breathing or bradyarrythmia (13). The current study was conducted to compare the effects of clopidogrel and ticagrelor in cases of antiplatelet therapy for treating acute coronary syndromes

METHODOLOGY

This retrospective longitudinal comparative study was conducted at Sandeman Provincial Hospital Quetta, Pakistan over a period of two years, from February 2019 to July 2021. A study population of 1002 patients was taken, each diagnosed with acute coronary syndrome. The inclusion criteria for these patients included that they had been previously treated with dual antiplatelet therapy and had been subject to invasive therapy and management. The multiplate analyzer was used to measure the platelet count for each patient (14). The exclusion criteria existed for patients who had a 100 × 109 /l and less platelet count. The exclusion criteria also included patients who had a platelet function disorder or had been administered a fibrinolytic agent 24 hours to a week prior to the enrollment, respectively (15). The attending physician was responsible for the treatment plan of each patient and for the patient management as well. Each patient gave their written consent to be involved within the study and the international guidelines for ticagrelor as the first choice of drugs for patients suffering from acute coronary syndrome were followed (16). Permission was taken from the ethical review committee of the institute.

The patients were asked for their medical history, where a database was created consisting of the different medications the patients were on, the medications they had been pre-treated with, their demographic information and the procedural variables were procured from the hospital database. Patients follow up data was collected to achieve end outcomes, by collecting the data through the admissions database and following up on the patient's health and status after a period of 30 days and one year. To analyze the side effects of the medication particularly, dyspnea, a questionnaire was filled. The questionnaire was administered after a progress of one year. Case notes were analyzed and updated periodically, and the attending physician required to sign off on all data listed.

Chronic therapy requires patients who had been pretreated with medications such as aspirin, prescribed 75mg daily; ticagrelor prescribed 180 mg daily; and clopidogrel prescribed 70 mg daily; all of which are commonly used as antiplatelet medications (17). The patients were given aspirin prescribed more than 300 mg, ticagrelor prescribed more 200 mg and clopidogrel prescribed more than 300 mg given more than 3h, 3h and 6h respectively before the enrollment of the patients in the trial.

Blood for platelet function screening was gathered utilizing a 21-gauge needle from an outer blood vessel before angiography or, alternatively, in the cardiac catheterization research laboratory from the arterial sheath right away after insertion as well as prior to heparin management (18). All samples were collected in tubes anticoagulated with heparin (25 μg/ mL) as well as evaluated 30 15 min post-collection. Platelet aggregation was determined in whole blood by several electrode impedance aggregometry with the Multiplate analyzer as formerly explained. High on-treatment platelet reactivity (HPR) was specified as > 46 AU.

Categorical variables were revealed as frequencies and percentages. Continuous variables were revealed as mean standard deviation or mean and also interquartile variety for non-parametric variables. Analytical analyses were done with Chi-squared tests for categorical data and also independent t-tests or the Mann-- Whitney U test for constant information (19). As the assignment of antiplatelet therapy went to the discernment of the treating physicians, there was substantial discontinuation, as well as switching of the main method to evaluation was an 'on-treatment' evaluation. For all analytical analyses, a P-value < 0.05 was taken into consideration significant. All statistical evaluations were carried out utilizing SPSS version 22.

RESULTS

Ticagrelor was referred to patients for treatment if they were young and possessed a lesser chance of having diabetes. These patients also presented with an elevated ST segment or had previously suffered from a myocardial infarction, the p value was recorded to be greater than 0.05. It was noted that patients who were treated with ticagrelor had a lower risk score of bleeding. This was analyzed by their lower CRUSADE score which is used to predict the chances of a major bleed occurring in patients who have been hospitalized for a myocardial infraction with non-ST-elevation. The CRUSADE model stands for the rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the acc/aha guidelines. The results were noted as 21 ± 9.5 versus 22.5 ± 10.2 where is the value of p was presented as less than 0.0001. Patients who were treated with ticagrelor also showed a lower risk score for the global registry of acute coronary events (grace) where the results showed that patients treated with ticagrelor had a score of 121 ± 27 versus 127± 31.5 and the p value was equated as 0.002. There were significant reduced results for the high platelet reactivity in patients treated with ticagrelor. When patients treated with clopidogrel were compared with patients treated with ticagrelor the high platelet reactivity results showed that it was 37.5% versus 16.7% respectively with the p-value of less than 0.0001. However, the results were similar for both groups of patients when the major and minor bleeding rates were analyzed in the non-coronary artery bypass grafting-related thrombolysis. There was also similarity present in the results for the rate of discontinuation for both medications. The rates of

discontinuation were noted a year after the patients were discharged where the results were 29.7% versus 28% with the p-value of 0.63. The rates of drug discontinuation while being treated for the two medications were also similar where the p value was 0.17 and the results were when 20.3% for ticagrelor and 16.7% for clopidogrel. There was a higher rate of discontinuation in the case of ticagrelor due to dyspnea and other adverse events as compared to clopidogrel. The dyspnea rates were 3.4% for ticagrelor as compared to the 0% for clopidogrel where the p-value is less than 0.0001. The drug-related adverse event rates were 9.4% for ticagrelor as compared to the 2.2% for clopidogrel where the p-value equal to 0.0001.

Patients who were prescribed ticagrelor showed considerably reduced platelet sensitivity when boosted with adenosine diphosphate than patients administered clopidogrel where the value of P was less than 0.0001 (20). The percentage of individuals with HPR was also significantly decreased in the ticagrelor group (15.9% vs 36 .4%, respectively, where the value of P was less than 0.0001. Medicine efficiency MACE at 1 year was numerically decreased in those treated with ticagrelor (6.9 % vs 12%, P = 0.07), however, this did not reach analytical significance. An intention-to-treat analysis produced comparable results, with MACE at 1 year being numerically lower yet not statistically different in those treated with ticagrelor (9.2% vs 11.8%, P = 0.11).

The on-treatment analysis demonstrated that TIMI significant blood loss was irregular, taking place in none of the ticagrelor dealt with the group as well as in 1.2% of the clopidogrel treated team (P = 0.09). TIMI minor blood loss at 1 year was a lot more usual and occurred at similar prices in the ticagrelor-treated people contrasted to the clopidogrel-treated people (11.5% vs 12.9%, P = 0.74). An intention-to-treat evaluation produced extremely comparable outcomes, with TIMI major or minor blood loss occurring in 14% of those treated with ticagrelor as well as 13.6% of those treated with clopidogrel (P = 0.78).

Table 1: Percentage of population with HPR

	Ticagrelor	Clopidogrel
Percentage of population with HPR	18%	39%

Table 2: On treatment Analysis

	30-day Result			One -year Result		
	Ticagrelor, n=273	Clopidogrel, n=779	P-value	Ticagrelor, n=254	Clopidogrel, n=769	P-value
Death	0	10	0.11	3	20	0.09
Spontaneous MI	0	7	0.16	6	31	0.23
Peri-procedural MI	12	38	0.79	10	33	0.81
Stroke	3	4	0.49	4	16	0.24
Stent thrombosis	0	2	0.57	4	8	0.83
All MACE	14	46	0.57	20	87	0.07
Bleeding outcomes						
TIMI major bleeding	0	5	4	0	9	0.08
TIMI minor bleeding	23	48	47	33	87	0.74

Table 3: Demographics, clinical characteristics and management strategies

	All MI, n = 1002	Ticagrelor, n = 263	Clopidogrel, n=739	P-value
Age (years)	64.5 ± 8.2	62.5 ± 8.9	65 ± 7.5	0.0002
Gender (Male)	753	189	564	0.167
Weight (Kg)	68.5 ± 5.6	68.5 ± 5.7	68.5 ± 5.6	0.923
Diabetes	205	100	105	0.008
Hypertension	692	194	498	0.261
Dyslipidemia	635	135	500	0.126
Smoker	265	64	201	0.344
Family history of premature CAD	367	156	211	0.867
Previous MI	245	40	205	0.001
Stroke	64	11	53	0.053
Heart Failure	18	2	16	0.073
Renal Dysfunction	54	11	43	0.192
Atrial Fibrillation	67	12	55	0.044
STEMI	195	37	158	0.019
NSTEMI	805	309	496	
CRUSADE	21 ± 9.5	21 ± 9.5	22.5 ± 10.2	< 0.0001
GRACE	124 ± 29.2	121 ± 27	127± 31.5	0.002
PCI	271	68	203	0.008
CABG	613	189	424	
Medical	152	48	104	

DISCUSSION

This study done on patients with myocardial infarction who were divided into two groups and each group was treated with two separate medications in order to analyze their outcome and their discontinuation rate. These two medicines were ticagrelor and clopidogrel. This exploration concentrates on additionally shown that, amazingly, those treated with ticagrelor were at diminished ischemic risk, being more youthful with less risk of being endangered or

exposed to side effects and a lower mean GRACE rating (21). Suspension of both ticagrelor and clopidogrel before 1 year was normal and occurred at a comparable rate, with the steadiest reasons being termination preceding CABG just as remedy for a lot more limited period. Our study showed that there was a decision inclination while assigning antiplatelet treatment. Amazingly, those treated with ticagrelor had a lower general ischemic risk, being more youthful with a decreased event of diabetes, earlier coronary localized necrosis just as a lower-class score (22). This looking for unmistakable to our companion. These results suggest that, as clinical experts, we may be extra focused on avoiding hurt than ischemic benefit (23). A significant impact of this study is that assuming we allot utilization of ticagrelor to comprise of those at higher ischemic risk, then, at that point, we might determine a bigger remedial advantage in logical practice.

Predictable with past investigations, we found ticagrelor to have substantially more powerful platelet hindrance and an essentially diminished consistency of HPR (24). Along these lines, one might expect that ticagrelor treatment would absolutely be connected with better blood misfortune. Regardless, in this review, at 1 year, there was no non-CAB-related TIMI significant blood misfortune in those treated with ticagrelor, and costs of non-CABG-related TIMI minor draining were comparable with ticagrelor and clopidogrel treatment (25). It is possible that this may be connected with the distinctions in standard ascribes between both treatment gatherings. The ticagrelor group had a genuinely decreased mission hazard score, yet the numerical contrast was nearly nothing, with the two techniques being inside the generally safe cluster. An assessment from the SWEDEHEART PC library, the greatest certifiable review contrasting ticagrelor and clopidogrel, found that ticagrelor was connected with a little expansion in re-confirmation, with discharging with ticagrelor versus clopidogrel happening in 5.5% versus 5.2% (corrected risk proportion 1.20 (1.04- - 1.40)) (26). In our study, dyspnea was often revealed in the year conforming to myocardial localized necrosis, occurring at equivalent costs in customers treated with ticagrelor and furthermore clopidogrel (37% versus 34.8%, P = 0.82). Dyspnea is a very much recorded, portion subordinate troublesome effect of ticagrelor just as a likely reason for the early stopping of the drug (27). Nevertheless, dyspnea following coronary dead tissue may occur for an assortment of different reasons, including heart failure, successive ischemia, respiratory framework diseases, weakness, unfriendly responses to beta-blockers and previous respiratory framework problems (28).

The paces of suspension of ticagrelor because of dyspnea have really contrasted essentially in past examination, shifting from 0.9% in the PLATO test to 14.3% in review partner research (29). There was a higher pace of suspension on account of ticagrelor because of dyspnea and other antagonistic occasions when contrasted with clopidogrel. The dyspnea rates were 3.4% for ticagrelor when contrasted with the 0% for clopidogrel where the p-esteem is under 0.0001. The medication related unfavorable occasion rates were 9.4% for ticagrelor when contrasted with the 2.2% for clopidogrel where the p-esteem is equivalent to 0.0001.

The component for the variation in the announced costs of dyspnea-related cessation is probably going to be multifactorial. All things considered, almost certainly, individual and furthermore clinical expert instruction plays a critical capacity. Cessation of both ticagrelor and furthermore clopidogrel soon after enrolment was normal just as happened at tantamount rates. Perhaps the most widely recognized elements for cessation in medical care office was CABG, while in the year holding fast to release, the most normal justification behind stopping was remedy for under a year. Remedy term of under a year was significantly more normal in those took care of without revascularization contrasted and those dealt with PCI (29). A constraint of our review is the observational plan, which implied that the therapy occupations went to the circumspection of managing clinical experts. Choice predisposition caused extensive pattern contrasts between those treated with ticagrelor and furthermore clopidogrel, which without anyone else is a fundamental finding of this exploration study. The examination was not fueled to find differentiations in ischemic outcomes; notwithstanding, our discoveries follow the higher abatement of repeating ischemic occasions in those treated with ticagrelor in the PLATO study. We didn't observe a differentiation in TIMI huge or little blood draining between the treatment sessions. One potential portrayal for this is that gauge distinctions between the groups implied that the ticagrelor bunch had a diminished draining danger.

CONCLUSION

The results from the study concluded that in case of patients who were categorized as lower risk, ticagrelor was prescribed more frequently, but it was not prescribed as frequently in the case of higher risk patients. Ticagrelor was also discontinued in case of side effects such as bleeding, breathing problems or bradyarrythmia. However, these side effects were not common. Discontinuation rates were higher after most cases of coronary artery bypass graft surgery. These higher discontinuation rates were noted in patients who were treated without the use of revascularization. There is a need for more research to be done on this and educating surgeons on the benefits and pitfalls of the medication and its effects is also needed.

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