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Aspirin desensitization in patients undergoing planned or urgent coronary stent implantation. A single-center experience

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ABSTRACT

Introduction: Dual antiplatelet therapy (aspirin and ADP-antagonists) is mandatory after stent implantation in order to avoid stent thrombosis, especially in the era of DES. In fact, a delayed re-endothelization process may enlarge the window of occurrence of stent thrombosis beyond 1-year after implantation. Allergy to acid acetylsalicylic is not a rare event and may influence the use and the choice of coronary stent with an important impact in terms of outcome especially in patients at high risk for in-stent restenosis. The aim of this study was to evaluate the safety and efficacy of a new intravenous rapid desensitization protocol in patients with acetylsalicylic acid sensitivity undergoing coronary stent implantation.
Methods: Among a total of 1385 patients undergoing coronary angioplasty at our catheterization laboratory from January 2007 to June 2011, a total of 43 patients (3.1%) had history of aspirin sensitivity characterized by respiratory or cutaneous manifestations (none had previous anaphylactic reactions). Twenty-three patients (53.5%) presented with acute coronary syndromes. All patients underwent a novel rapid desensitization procedure before or after cardiac catheterization (in case of ST-elevation myocardial infarctions, $n=5$). The desensitization procedure was based on intravenous administration of 9 sequential doses of aspirin (1, 2, 4, 8, 16, 32, 64, 128, 250 mg) over 4.5 h without the use of corticosteroids or antihistamines. Patients were followed for at least 30 days and up to 12 months to assess compliance with aspirin therapy and adverse events.
Results: The desensitization procedure was successful in 42 patients (97.6%). All patients underwent stent implantation (1.6 stents/patient). Drug-eluting stents were used in 36 patients (85.7%). At follow-up, all patients who successfully responded to the desensitization procedure did not develop any allergic reaction.
Conclusions: This study showed the safety and efficacy of a new rapid intravenous protocol desensitization for patients with history of aspirin sensitivity undergoing planned or urgent coronary stent implantation.
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1. Introduction

Coronary angioplasty currently represents the revascularization therapy of choice in the vast majority of patients with coronary artery disease, especially in the setting of acute coronary syndrome. The use of DES has further improved clinical outcome by reducing in-stent restenosis [1,2]. Dual antiplatelet therapy (aspirin and ADP-antagonists) is mandatory after stent implantation in order to avoid stent thrombosis, especially in the era of DES, where a delayed endothelization process may enlarge the window of occurrence of stent thrombosis beyond 1-year after implantation [3,4]. Allergy to acid acetylsalicylic is not a rare event and may influence the use and the choice of coronary stent with an important impact in terms of outcome especially in patients at high risk for in-stent restenosis. Acetylsalicylic acid desensitization therapy involves slowly increasing exposure to oral acetylsalicylic acid to reduce and/or eliminate pharmacologic and presumed immunologic reactions [5]. Several desensitization protocols have been described [6,7], with many of based on dosing intervals of up to 24 h. However, there is very limited experience with acetylsalicylic acid desensitization in patients undergoing coronary stenting, a setting where is needed prompt administration of aspirin. Therefore, the aim of this study was to evaluate the safety and efficacy of a new intravenous rapid desensitization procedure in patients with acetylsalicylic acid sensitivity undergoing coronary stent implantation

2. Methods

From January 2007 to June 2011, among a total of 1385 consecutive patients underwent PCI at our catheterization laboratory, 43 (3.0%) had histories of aspirin sensitivity. Aspirin sensitivity presented with respiratory ($n=18$; asthma and/or rhinitis) and cutaneous ($n=25$; urticaria and/or angioedema) manifestations. None of the cases involved previous anaphylactic reactions.

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After providing informed written consent, patients with aspirin sensitivity underwent a novel desensitization challenge procedure. Patients started the desensitization procedure in the general cardiology ward or in the cath lab. The protocol was based on intravenous administration of 9 sequential doses of aspirin, starting with dose of 1 mg (Table 1). Doses were increased every 30 min, with the overall procedure lasting 4.5 h (Table 1). In order to minimize fluid injections, two different dilutions were performed, with 500 mg diluted in 500 ml (First solution, with a concentration of 1 mg/ml)) and 2 g in 250 ml (Second Solution with a concentration of 16 mg/ml).

Per protocol, none of the patients were pretreated with antihistamines or corticosteroids. Blood pressure, pulse, and saturation were measured every 30 min, and cutaneous, naso-ocular, and pulmonary reactions were monitored closely until 4 h after coronary intervention. Aspirin administration was immediately discontinued if cutaneous, respiratory, or systemic signs of sensitivity occurred.

Coronary angioplasty was performed with standard techniques. Use of stents, type of stents and stent implantation techniques, as much as the use of directional or rotational atherectomy, IVUS, glycoprotein IIb-IIIa inhibitors, was left at the discretion of the operators. All patients received high-dose bolus of clopidogrel (600 mg) at the time of hospitalization or before angioplasty. Prasugrel was used in ACS patients starting from April 2010. Dual antiplatelet therapy was prescribed for 12 months in ACS patients and those treated with DES. All patients were followed for at least 30 days and up to 1 year to monitor the incidence of major adverse events and compliance with aspirin therapy.

3. Statistics

Statistical analysis was performed with the SPSS 17.0 statistical package. Categorical variables are presented as percentage, whereas continuous variables are presented as mean ± standard deviation. Kaplan–Meier curves were used to estimate event-free survival at follow-up.

4. Results

Baseline demographic characteristics of the study population are shown in Table 2. There was a large prevalence of male gender and hypertension. More than 50% of patients had acute coronary syndrome as indication to angiography and/or angioplasty. The desensitization procedure was performed before cardiac catheterization in 24 patients (55.8%), whereas in remaining patients the protocol was started in the cath lab, during the procedure, or after the procedure (among patients with STEMI). The desensitization procedure was immediately successful in 42 patients (97.6%). Non-serious adverse reactions occurred in the 1 patients who had histories of chronic idiopathic urticaria in whom the procedure failed. She experienced urticaria 12 h after the last dose, that was successfully treated with corticosteroids.

PCI was performed in 39 patients (90.6%) and was successful in all cases, without any complication. Procedural characteristics are shown in Table 3. A total of 1.6 stents/patient were used; the mean stent length was 26.8 ± 15.4 mm. Multivessel PCI was performed in 3 patients (6.9%). All patients underwent stent implantation. DES were used in 25 patients (64.1%) ($n = 4$ sirolimus, $n = 7$ paclitaxel, $n = 7$ Tacrolimus, $n = 12$ everolimus, $n = 12$ Biolimus). All patients undergoing primary PCI ($n = 5$) for ST-elevation myocardial infarctions were treated with bare-metal stents (Table 3). In patients treated with DES and in those with acute coronary syndromes, combined therapy with aspirin and clopidogrel was continued for 12 months. Prasugrel was administrated after PCI in 3 patients.

All patients were followed for at least 30 days and up to 12 months. In all 42 patients who successfully responded to the desensitization protocol during hospitalization, long-term treatment with aspirin 100 mg was maintained and well tolerated. During follow-up, 1 patient was hospitalized at 7 months due in-stent restenosis (event-free survival of 97.2%) and received an additional DES. Major adverse cardiac events did not occur in the remaining patients.

5. Discussion

This is the largest report investigating a new aspirin desensitization protocol in patients with CAD undergoing coronary stenting (both BMS and DES), including patients with STEMI and therefore at high-risk for thrombotic complications. This protocol, compared with others previously described [8,9], is more rapid and does not require the administration of antihistamines or corticosteroids. We found that it is safe and effective, with approximately 97% patients responding to the desensitization procedure, all of whom maintained treatment with aspirin without developing allergic reactions.

Dual antiplatelet therapy based on acid acetylsalicylic and thienopyridines, is mandatory after stent implantation in order to avoid

Table 1
Aspirin desensitization protocol.

Time (min)	Aspirin dose (mg)	Cumulative aspirin dose (mg)
0	1	1
30	2	3
60	4	7
90	8	15
120	16	31
150	32	63
180	64	127
210	125	252
240	250	502

Table 2
Baseline characteristics.

Baseline characteristics	Value
Age	66 ± 11
Male gender (%)	81.3
Diabetes (%)	27.9
Hypertension (%)	65.1
Hypercholesterolemia	44.2
Smoking	39.5
Previous MI	18.6
Previous PCI	6.9
Previous CABG	4.6
Previous Stroke	6.9
Indication for angiography and/or PCI	
Stable angina or instrumental evidence of ischemia	46.5
UA/NSTEMI	34.8
Recent STEMI	7
STEMI	11.6
Therapy at admission	
β blockers	27.9
Thienopyridine	41.8
Statins	46.5
Diuretics	6.9
Nitrates	30 2
Angiotensin-converting enzyme inhibitors	55.8
Angiotensin II receptor blockers	13.9
Calcium antagonists	20.9

Table 3
Angiographic and procedural characteristics.

Variable	Value
CAD	93
Multivessel disease	32.5
PCI	90.6
Multivessel PCI	6.9
Treated vessel	
LM	0
LAD	60.9
CX	17.4
RCA	21.7
DES	64.1
GP IIb-IIIa inhibitors	78.6
Thrombectomy	20.9
IABP	0
Procedural success	100
Prasugrel administration	9.3

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stent thrombosis, especially after DES implantation [3,4]. However, aspirin sensitivity often discourages from stent implantation, especially drug-eluting stents, therefore denying a percutaneous treatment to those patients with complex anatomy and at high-risk for in-stent restenosis.

Three types of aspirin sensitivity have been described so far: respiratory sensitivity (asthma and/or rhinitis), cutaneous sensitivity (urticaria and/or angioedema), and systemic sensitivity (anaphylactic reaction) [5]. The prevalence of aspirin-exacerbated respiratory tract disease is approximately 10%, and for aspirin-induced urticaria, the prevalence varies from 0.07% to 0.2% in the general population [5,11]. In our study, the desensitization protocol was unsuccessful in only 1 patient who had chronic urticaria. Similar findings have been observed in previous reports, which showed that the desensitization protocol is more likely to be unsuccessful in patients who have continuing urticaria independent of aspirin [12]. Therefore, extreme attention should be paid to such a patient who should undergo strict clinical evaluation for early detection of any adverse reaction. Many aspirin desensitization protocols reported are time consuming and needs several days to be completed. [6,8,9]. In addition, dedicated protocols have been developed for patients with specific types of aspirin hypersensitivity. Szczeklik and Stevenson [13] described a strategy for desensitizing patients with respiratory manifestations. This protocol, also referred to as the "Scripps Clinic protocol," involves small incremental oral doses of aspirin administered over the course of 2 to 3 days, until 400 to 650 mg is tolerated. Although a long interval between doses can guarantee the safety of the procedure, as symptoms can be detected at each given dose, the entire procedure requires several days to be completed. Such protocols, however, are not practical in patients with acute coronary syndromes or in those who undergo stent implantation and therefore require the immediate administration of aspirin. The simplified protocol of Silberman et al. [14] required only 2.5 h. In a recent report, Rossini et al. [15], reported on the safety of a new oral protocol. Because of the greater risk of the included population, they lowered the starting dose from 5 to 1 mg, which added 3 h to the protocol.

In order to start the protocol in the cath lab soon at the beginning of the procedure, especially in the setting of primary angioplasty, and therefore to overcome the limitation of oral administration, we propose a new intravenous protocol starting from 1 mg and doubling the dose in order to achieve in 4.5 h the recommended dose of 500 mg [16].

6. Limitations

This is a prospective non-randomized trial. In addition, a larger sample size would have further improved our results. Finally, we included patients with a history of aspirin allergy, that therefore was mostly self-reported or based on previous patient's dossier, but not routinely confirmed by dedicated diagnostic tests.

7. Conclusions

This study showed the safety and efficacy of a new rapid intravenous protocol desensitization for patients with history of aspirin sensitivity undergoing planned or urgent coronary stent implantation.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [17].

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