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ASPIRIN DESENSITIZATION IN PATIENTS WITH ASA HYPERSENSITIVITY IN ACUTE CORONARY SYNDROME

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Abstract
Background: Aspirin desensitization in patients with ASA hypersensitivity in acute coronary setting is very useful to prevent major cardiovascular event specially in stent thrombosis where PCI and stent placement was done. The aim of our study to assess the safety and efficacy of a rapid aspirin desensitization in patients with ASA hypersensitivity with ACS.
Method:It is a prospective, single centre, observational study and was conducted in Dayanand Medical College and Hospital cardiology department over a period of 4½ years (from 1st July 2013 to December 2017). Study population included all patients with ASA hypersensitivity with ACS with either sex irrespective to age after taking informed consent. Rapid aspirin desensitization done by as per protocol.
Results: Total 5480 patients with ACS admitted during the study period. In this period 17 patients were identified to have aspirin hypersensitivity with ACS. The mean age was 53.47 years (range 35-75 years) and in all 14 were male and 3 female. Primary disease in all these patients were STEMI in 11, NSTEMI in 5 and Unstable angina 1. In study population mucocutaneous reaction in the form of urticarial found in all participants The ASA desensitization was successful in 15 patients and unsuccessful in 1. Success rate was 94.12%.. All patients with successful desensitization were followed up for at least 6 months found that no one had reoccurrence of allergic reaction.
Conclusion: ASA desensitization is very simple, cheap, rapid, safe and very effective mean in patient with hypersensitivity to ASA in ACS.

Keywords: Aspirin Desensitization, ASA Hypersensitivity, Acute Coronary Syndrome.

INTRODUCTION

Over the last decade, cardiovascular disease (CVD) has become the leading cause of death worldwide. Between 1990 and 2013, deaths from CVD increased from 26% to 32% of all deaths globally, a reflection of the rapid epidemiologic transition, particularly in low- and middle-income countries.[1]According to the Global Burden of Disease study age-standardized estimates (2010), nearly a quarter (24.8%) of all deaths in India are attributable to CVD.[2]

Aspirin (ASA) is the cornerstone of antithrombotic therapy in patients with coronary artery disease (CAD), both in the acute and the chronic phase of treatment. Furthermore, combination therapy with aspirin and a P2Y12 receptor inhibitor is increasingly indicated for some patients with CAD. Combined aspirin and clopidogrel therapy reduced the 1-year incidence of cardiovascular events by approximately 20% compared with monotherapy alone. In patients with unstable angina, the recently reported Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial[3] and Clopidogrel for Reduction of Events During Observation (CREDO) trial[4] suggest that combination therapy with aspirin and clopidogrel reduce long-term coronary events. Subsequent to these trials, guidelines from the American College of Cardiology and American Heart Association added a class I indication for combination antiplatelet therapy for patients with acute coronary syndromes.[5]

Aspirin hypersensitivity, however, can affect up to 0.5–1.9% of the general population.[6,7,8] In patients with coronary artery disease the prevalence of

aspirin hypersensitivity has been reported between 1.5 and 2.6%.[6,9,10]
Although in patients with stable CAD requiring anti-platelet monotherapy, clopidogrel is recommended in practice guidelines for patients who are aspirin intolerant., however no such guidelines exist for patients needing dual-anti platelet therapy. ASA desensitization represents an alternative approach in such patients and further desensitization may be a cost-effective therapeutic intervention in patients with aspirin intolerance compared with more expensive and less efficacious therapeutic alternatives such as combination of clopidogrel with prasugrel/ticagrelor or clopidogrel with cilasazol. [11,12]

Aspirin desensitization has been successfully conducted in patients with aspirin-induced urticaria, angioedema, and asthma[13] and can be effectively undertaken in the majority of patients except those with systemic reactions [14]. Desensitization protocols generally involve gradual increases in patient exposure to ASA with the goal of mitigating or abolishing immune-mediated reaction.

However, many desensitization protocols require several days to be completed, making them unpractical. In addition, although several successful aspirin desensitization protocols have been published, but there does not appear to be an internationally agreed standard approach [13,15,16]

Thus, despite the availability of desensitization protocols, such procedures are rarely undertaken in India. In a recent international survey of cardiologists, only 42% of respondents reported that they carried out ASA desensitization protocols, however Indian data is limited on its use.[17]

In our study we attempted to devise a procedure that would allow patients with CAD to begin ASA therapy safely within a few hours and define the safety and efficacy of the procedure.

MATERIALS AND METHODS

It is a prospective, single centre, observational study. The aim of our study to assess the safety and efficacy of a rapid aspirin desensitization in patients with aspirin hypersensitivity presenting with ACS. This study was conducted at Cardiac center of Dayanand Medical College and Hospital over a period of 4.5 years (from July 2013 to December 2017). The study protocol was approved by the ethics committee at our centre and all patients gave their informed written consent to participate in this study.

All patients presenting with ACS over this time period were assessed and patients with ASA hypersensitivity were included in the study group. Any patients with stable coronary artery disease, decompensated heart failure and those who were unwilling to provide written informed consent to participate in the study were excluded from the study.

Patient's demographic and clinical data, adverse reactions associated with aspirin hypersensitivity, details of antiplatelet treatment regimen were collected. In addition patients data regarding biochemical investigations, cardiac imaging and type of management was gathered and assessed. Follow up of all patients was done after aspirin desensitization for at least 12 months to assess compliance with therapy, rate and causes of readmission and recurrence of ASA hypersensitivity which was done either on follow-up OPD visits or telephonically. Major adverse cardiac events were defined as the composite of cardiac death, myocardial infarction, probable/definite stent thrombosis (ST), unstable angina, or stroke

Desensitization protocol (Figure 1)
A good intravenous access was obtained in all patients before desensitization. All patients received pre-treatment with I.V. antihistamines and corticosteroids 5 minutes prior to starting of desensitization procedure. Three tablets of Aspirin 350 mg each were dissolved in 1050 ml distilled water resulting in a dose 1mg/ml of solution. Subsequently sequential doses of aspirin (5, 15, 30, 60, 120, 240, and 500 mg) were given after every 15 minute intervals and procedure was concluded within 90 minutes. Patients vital signs including pulse rate, blood pressure, oxygen saturation and allergic reaction in form of muco-cutaneous, naso-ocular, and pulmonary reactions were closed observed every 30 minutes during the procedure and every one hourly after completion of procedure for 6 hours. ASA administration was immediately discontinued if patient showed any evidence of hypersensitivity reaction.

In view of recurrence of hypersensitivity post desensitization procedure, all patients were instructed to continue with aspirin 75-150 mg daily.

Data Analysis
Continuous data are expressed as mean±SD, and categorical data are expressed as frequencies (percent). All statistical analyses were performed using the SPSS software

RESULTS

Table 1 - Baseline Characteristics

Total patients		17 (100)
Mean Age (years)		51.71 ± 10.03 years
Gender	• Male (%) • Female (%)	14 (82.4) 3 (17.6)
Co-morbidites	• Chronic Smokers (%) • Past history of hypertension (%) • Past history of diabetes (%) • Past history of hypothyroidism (%) • Past history of drug allergy (%)	1 (5.9) 7 (41.2) 4 (23.5) 1 (5.9) 2 (11.8)
Clinical presentation of ACS (%)	• STEMI • NSTEMI	12(70.6) 5 (29.4)
ASA related hypersensitivity reaction (%)	• Urticaria • Asthma • Anaphylaxis	17 (100) 0 0
Biochemical investigations	• Mean hemoglobin • Mean erythrocyte sedimentation rate • Mean random blood sugar • Mean serum. creatinine • Mean serum cholesterol	14.65 ± 1.7 11.65±8.6 133.59±49.1 0.88±0.20 173.5± 45.6
Echocardiograhy – LV function (LVEF %)	• Normal (LVEF 50- 70 %) • LV Dysfunction (LVEF < 50 %)	6 (35.3) 11(64.7)
Coronary Angiography	• Single vessel disease • Double vessel disease • Triple vessel disease	13 (76.5) 3 (17.6) 1 (5.9)

values in brackets indicate percentage of total patients

Table 2 - Type of management

Treatment of ACS	• PTCA & Stenting • CABG • Medical Management	15 (88.2) 0 2 (11.8)
Number of Stent placed	• 1 • 2 • 3	13 (86.7) 2 (13.3) 0
Type of Stent	• Bare metal stent • Drug eluting stent a) First generation b) Second generation	1 (6.6) 1 (6.6) 13 (86.7)
Drug at time of Discharge	• Clopedogrel • Prosugrel • Ticagrelor • Beta Blockers • CCBs • AEC inhibitors / AT Antagonists • Statins • Nitrates	8(47.1) 1 (5.9) 8 (47.1) 12 (70.6) 0 6(35.3) 17(100) 13(76.5)

values in brackets indicate percentage of total patients

Table 3 - Patient Outcomes

Procedure success • Successful Desensitization • Unsuccessful Desensitization • Success rate	 16 1 94.12%
Allergic reaction in unsuccessful Desensitization • Urticaria • Anaphylaxis • Death	 1 0 0
Mean follow up	1year ± 2 months
On follow up • Readmissions (%) ▪ In desensitized patients ▪ In failed desensitized patients • Major cardiac event ▪ In desensitized patients ▪ In failed desensitized patients	 4 3 (unrelated to allergic reaction) 1 2 1
Recurrence of allergic reaction in desensitized patients	0

values in brackets indicate percentage of total patients

Table 4 Comparison of various study protocols and outcomes

Study	Protocol Followed		Pretreatment with Antihistamines and Steroids	No.of patients	ACS patients	Success rate
	Total Duration	Max dose				
• Wongs et al. in 2000	2h 40m	325 mg	Yes	11	8	81.8%
• Silberman S. et al. in 2005	3.5 h	100 mg	No	16	12	93.5 %
• Hernandez BV et al. in 2016	1.5-2 h	100 mg	No	12	10	83.3%
• ADAPTED Registry in 2017	5.5 h	100 mg	No	315	233	95.4 %
• Our study	1h 30 m	500 mg	Yes	17	17	94.1%

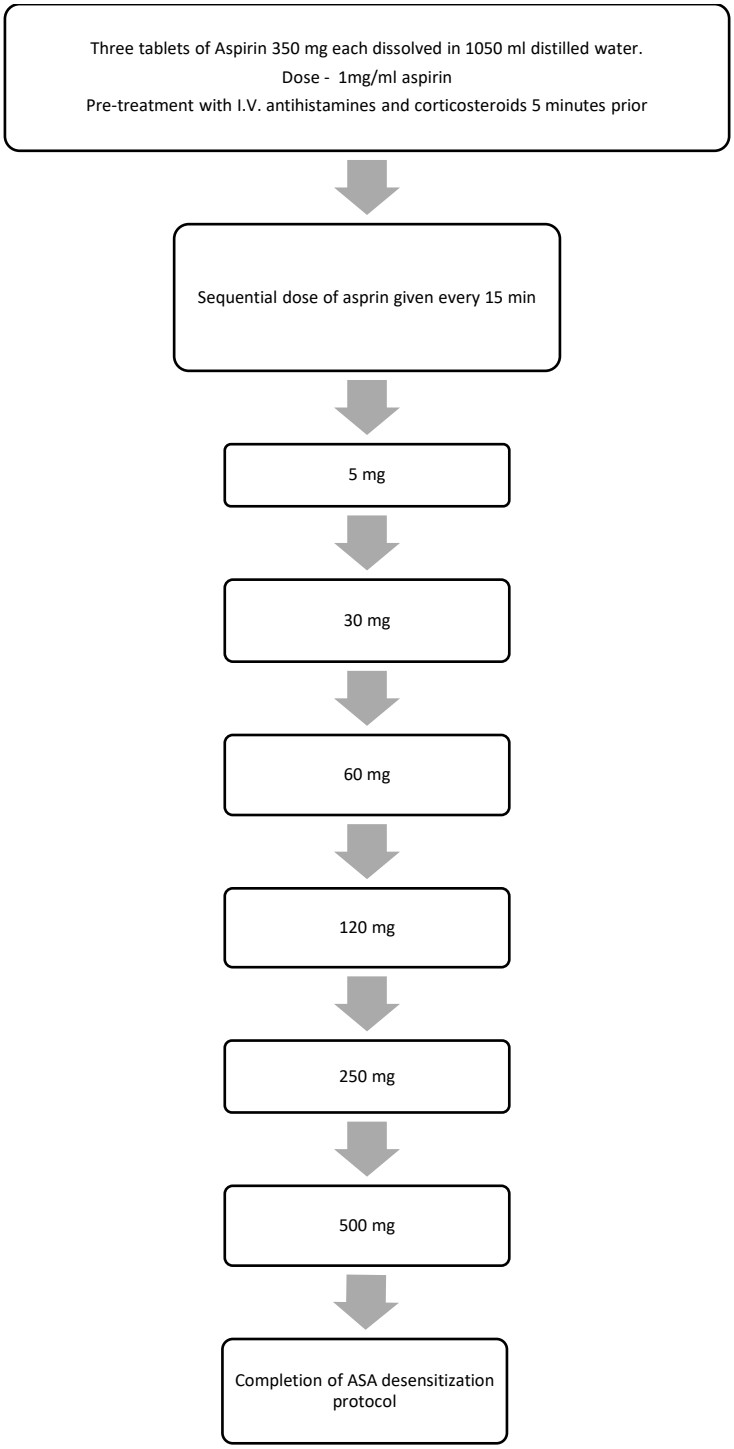

Figure 1 Desensitization protocol

This study was conducted over a period of 4.5 years from July 2013 to
December 2017 at Dayanand Medical College and Hospital, Dept. of Cardiology. A total of 5480 patients with acute coronary syndrome were admitted during the study period. Out of these 18 patients (0.32%) were identified to have aspirin hypersensitivity. One of these patients had concomitant clopidogrel hypersensitivity and was excluded from study. Thus a total of 17 acute coronary syndrome patients were included in the study with associated aspirin hypersensitivity of which 14 were male and 3 were female.

The mean age of study population was 51.71 years. Past history of hypertension, diabetes, hypothyroidism, drug allergy were found in 7, 4, 1 and 2 (41.2, 23.5, 5.9 and 11.8%) patients respectively. Clinically patients with ACS presented with STEMI in 12 patients and

UA/NSTEMI in 5 patients. Urticaria was present in all patients who had ASA related hypersensitivity and no one had aspirin induced respiratory disease or Anaphylaxis.

On echocardiographic evaluation, normal LV function (i.e. LVEF 50- 70 %) was present in 6 patients(35.3 %) and LV Dysfunction (LVEF <50 %) in 11 patients (64.7%). On Coronary Angiography, single vessel disease was present in 13 (76.5 %), Double vessel disease in 3 (17.6%) and triple vessel disease in 1 (5.9%) patient.

After coronary angiography, PTCA and Stenting was done in 15 patients (88.2%), medical Management in 2 (11.8) patient and no one undergone CABG. In patients who underwent primary PTCA, single stents were implanted in 13 patients (86.7%) and double in 2 patients(13.3%). Bare metal stent was placed in 1 (6.6%), first generation drug eluting stent in 1 (6.6%)and second generation drug eluting stent in 13 (86.7%) patients.

Aspirin desensitization procedure was successful in 16 patients and unsuccessful in 1. Overall success rate was 94.12%. Patient with unsuccessful desensitization developed a skin rash, in lieu of which desensitization procedure was terminated and intravenous antihistaminic and steroids were given for symptom resolution. All patients with successful desensitization were discharged on dual anti platelet therapy with oral aspirin 75-150 mg daily in combination with a p2y12 inhibitor (Clopedogrel in 8 patients, Prasugrel in 1 and Ticagrelor in 8 patients) and patient with unsuccessful desensitization was placed on ticagrelor and cilostazol combination.

On 6 months follow up, 3 out of 16 (18.8 %) successfully desensitized patients were admitted, of which 2 had major cardiac event and 1 had unstable angina. 1 patient who had failed desensitization procedure was also subsequently admitted with ACS and on coronary angiography was found to have stent thrombosis.

All patients with successful desensitization were followed up for at least 1 year and were assessed for compliance to treatment and reoccurrence of allergic reaction. No patient reported adverse allergic reaction over the follow-up period.

DISCUSSION

To the best of our knowledge, the present study is the only study conducted in India to explore the use of an ASA rapid desensitization protocol in a cohort of patients presenting with symptoms of acute coronary syndrome.

The key findings from this small series study with limited follow-up suggest that (1) a simple and rapid bedside ASA desensitization protocol was effective in patients with aspirin hypersensitivity in whom aspirin is imperative (CAD or ACS patients, in particular if percutaneous coronary intervention and stenting are contemplated) allowing long-term treatment with a standard dose of aspirin. In 94.1% of the patients, successful tolerance was induced and long term aspirin pursued uneventfully; (2) the ASA desensitization protocol was safe with no serious adverse reaction at short term and long term (≤1 year); and (3) the risk of follow-up major cardiac event, seemed to be independent of recurrent ASA hypersensitivity.

However, the single patient with failed desensitization also emphasizes the need for close supervision during and after the challenge because of the potential for delayed and severe hypersensitivity reactions.

Hypersensitivity reactions to aspirin have either a pharmacological or immunological basis, although patients may present with mixed reactions There are three basic clinical types of hypersensitivity reaction to aspirin: respiratory, cutaneous and systemic [14,15,18]. Aspirin desensitization has been successfully conducted in patients with aspirin-induced urticaria, angioedema, and asthma and can be effectively undertaken in the majority of patients except those with systemic reactions [14].

Desensitization for drug allergy has been defined the elimination of pharmacological and immunological reactions by slowly increasing exposure to the drug [14]. Although there does not appear to be an internationally agreed standard approach on aspirin desensitization, in general, patients are treated with increasing incremental doses of aspirin over set time intervals. After a positive response to aspirin and subsequent recovery, the dose at which the response occurred is repeated until no reaction occurs and the dose is increased until a maximum dose is reached. The desensitized state only exists as long as regular aspirin continues to be administered; an interruption of 1–5 days returns the patient to a desensitized state [19,20].

As described above, allergic reactions to ASA form a clinical spectrum, and not all patients with a reported ASA allergy have ASA-induced anaphylactic reaction. Avoiding ASA in the patient subsets with aspirin induced airway disease and aspirin induced cutaneous reactions would be a significant disadvantage from a long-term pharmacotherapy standpoint for the majority of these patients.

Despite the availability of multiple ASA desensitization protocols, these are not commonly used in real-world practice. Physician hesitation is evident from the fact, that a recent international survey of cardiologist reported use of aspirin desensitization by only 42% of respondents.[17]Indeed, the fact that these may be time-consuming, labour intensive and require clinical expertise are potential causes for physicians to not embrace these protocols particularly in settings such as the treatment of patients with ACS.

The Scripps Clinic protocol [16] involves small incremental oral doses of aspirin administered over the course of 2 to 3 days, until a dose of 400 to 650 mg is tolerated. Although a long interval between doses can safeguard against undesired reactions, as symptoms can be detected at each given dose, a desensitization procedure requiring several days to be completed is not practical in patients with ACS or those who undergo stent implantation who require immediate administration of ASA

The simplified protocol of Silberman et al [13] required only 2.5 hours. The protocol was validated on 16 patients, not all of which included patients of ACS with a success rate of 93.5%. In our study rapid ASA desensitization was highly effective in patient with ACS with success rate around 94.1%. The success rate in our study reproduced results from a diverse range of studies following different rapid desensitization protocols.(Table 4)

These protocols are particularly useful in patients with ACS, as it can be completed within a few hours, thus allowing for rapid desensitization. Our protocol included graduated administration of oral aspirin in incremental doses with a maximum dose of 500 mg provided within 1.5 hours. As compared to other rapid desensitization protocols, in our protocol desensitization could be achieved much faster than other studies with a higher aspirin dose provided.

Similar to our approach Wong et al,[21] performed rapid desensitization on 11 patients with history of ASA associated hypersensitivity, with a higher maximum dose of 325 mg within 3hrs. In his study, similar to ours, 91% of the patients were pre-treated with intravenous antihistamines or corticosteroids. The effect of pre-treatment could explain the utilization of higher dose of aspirin in the study protocols and faster protocol times.

In addition to being rapid and highly efficacious, the procedure was also very safe and economical, with no serious adverse reaction noted during desensitization. Furthermore, these protocols allow for immediate tolerance to be achieved in more than 90% of patients, who can then safely undergo interventional procedures, including stent placement, with dual anti-platelet therapy.

Conclusion

Aspirin is a cornerstone of treatment for patients with cardiovascular disease. ASA desensitization is very simple, cheap, rapid, safe and very effective mean in patient with hypersensitivity to ASA presenting with ACS. Low-dose ASA can be safely continued long term without the occurrence of late adverse hypersensitivity events.

Limitations

Further population-based studies are needed to better document prevalence of ASA allergy and clinical subtypes in cardiovascular patients. Further studies are also needed in Indian subcontinent, to ascertain prevalence, risk factors, response to therapy in Indian population. Standardization of an ASA challenge/desensitization protocol is required to facilitate optimal management of the cardiovascular patient with ASA allergy

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