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Original Article

Patient characterization and predictors of aspirin desensitization response

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Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

Background: Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) may limit the use of aspirin in patients with cardiovascular diseases. Aspirin desensitization, which is a resource-intensive process, can offer such patients access to aspirin through the induction of temporary tolerance to aspirin. However, there is limited information on aspirin desensitization response in patients undergoing aspirin desensitization for cardiac indications in Asia.
Objective: To characterize patients who have undergone aspirin desensitization, evaluate their responses to the procedure, and identify risk factor(s) associated with failure of aspirin desensitization.
Methods: We conducted a retrospective review of medical records of patients who underwent aspirin desensitization in Singapore General Hospital between 1 June 2014 and 31 October 2017. Chi-square or Fisher exact test were used to analyze categorical data while independent samples *t* test or Wilcoxon rank-sum test were used for continuous data where appropriate. Multivariate logistic regression was used to identify predictors of aspirin desensitization failure.
Results: All 214 patients in our study had cardiovascular indications for aspirin, with angioedema being the most common type of index reaction experienced with NSAIDs (n = 104, 48.6%). One hundred sixty-five patients (77.1%) achieved successful aspirin desensitization. In the selected sample analysis of patients with true NSAID hypersensitivity (n = 163), an index reaction of angioedema to NSAIDs was found to be significantly associated with a higher risk of failing aspirin desensitization (odds ratio, 7.21; 95% confidence interval, 1.94–26.71).
Conclusion: Majority of the patients who underwent aspirin desensitization in our institution were able to achieve tolerance to aspirin. An index reaction of angioedema to NSAIDs was identified as a risk factor for aspirin desensitization failure. This information can aid in the risk stratification of patients undergoing aspirin desensitization and ensure efficient resource allocation for this procedure.

Keywords: Aspirin; Non-steroidal anti-inflammatory drugs; Hypersensitivity; Cardiovascular diseases; risk factors; Desensitization

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Author Contributions

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INTRODUCTION

Aspirin therapy is a well-established therapy for secondary prevention of cardiovascular events in individuals with established atherosclerotic cardiovascular disease, providing reduction in the risk of subsequent myocardial infarction, stroke, and vascular death [1]. Aspirin is also a cornerstone component of dual antiplatelet therapy (DAPT) with a $P2Y_{12}$ receptor blocker (ticagrelor/prasugrel/clopidogrel) [2, 3]. Patients who require DAPT include those who have undergone percutaneous coronary intervention with stent placement [2] as DAPT has been demonstrated to reduce the risk of stent thrombosis [4]. However, aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), particularly those that inhibit cyclooxygenase-1 (COX-1), are often implicated with the occurrence of hypersensitivity reactions. The prevalence of aspirin hypersensitivity has been reported to range from 0.5% to 1.9% of the general population [5]. These reactions can range from respiratory symptoms (e.g., bronchial obstruction, rhinorrhea, dyspnea) and cutaneous manifestations (e.g., urticaria, angioedema) to anaphylaxis [6].

Unfortunately, hypersensitivity to NSAIDs may restrict the use of aspirin in cardiac patients. Although clopidogrel may be used as an alternative to aspirin in those with coronary artery disease (CAD) and aspirin intolerance, DAPT of aspirin and a $P2Y_{12}$ blocker remains the mainstay therapy recommended in guidelines for those who have undergone stent placement [2, 7]. Given the pivotal role of aspirin in patients with CAD, the option of aspirin desensitization will enable patients with aspirin hypersensitivity access to this potentially life-saving medication.

Desensitization refers to the procedure to induce temporary tolerance to drug antigens [8]. Aspirin desensitization typically begins with a very small amount of aspirin, with the dose being gradually increased at regular intervals over several hours until the target dose is attained [9]. Patients are then required to take regular doses of aspirin to maintain the desensitized state [9, 10]. In Singapore General Hospital (SGH), aspirin desensitization consists of 11 steps, with aspirin doses administered in intervals of 20 to 30 minutes (**Supplementary material 1**). This strategy of desensitizing patients to aspirin has been shown to be effective in those with CAD [11-13]. Specifically, aspirin desensitization has been reported to allow >90% of patients with cardiovascular indication for aspirin to achieve tolerance to this medication [11].

Despite the effectiveness of aspirin desensitization, the procedure is associated with risks of reactions. Potential reactions include urticaria, angioedema, bronchospasm, and dyspnea [14-16]. Such aspirin-induced reactions can last up to several hours [17] and may require treatment with medications such as antihistamines and corticosteroids [14]. Due to the risk of reaction, aspirin desensitization should be carried out in a setting with access to resuscitation facilities [18] and well-trained personnel familiar with the management of acute hypersensitivity reactions and anaphylaxis [19].

Risk factors associated with reactions during aspirin desensitization have been explored in several studies [15, 20-22]. Initial reaction of angioedema to aspirin and having a reaction to aspirin within the past year before desensitization were identified as factors associated with increased risk of reaction during aspirin desensitization [15]. However, these studies mainly focused on patients with aspirin-exacerbated respiratory disease (AERD) which is anecdotally not as commonly seen in our patient population. The desensitization protocol

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for patients who require aspirin for AERD typically begins and ends at a dose of 40 mg and 325 mg of aspirin respectively [23, 24]. These doses are much higher than those used in aspirin desensitization for cardiovascular indication, which can start at 1mg and end at 100 mg [14]. As hypersensitivity reactions to aspirin may be dose dependent [18, 25], the risk factors identified in studies that focused on AERD patients may not apply to cardiac patients. Furthermore, geographical and regional differences in NSAID hypersensitivity patterns have been observed in previous studies [5]. In 2013, McMullan and Wedner [15] published a study examining the outcomes of aspirin desensitization in chiefly Caucasian cardiac patients. However, different desensitization protocols were used within the same study on a relatively small Caucasian-centric patient population, making information gleaned less generalizable. Consequently, there is a dearth of information on risk factors for desensitization failure for patients undergoing aspirin desensitization for cardiac indications in Asia.

Further to that, data on characteristics of patients who underwent aspirin desensitization, desensitization effectiveness, and predictors of aspirin desensitization response are limited. With these information, risk-stratification can be performed for future patients prior to aspirin desensitization. This may help to improve the safety and effectiveness of aspirin desensitization via identification of high-risk patients and anticipation of reaction(s). Risk stratification may also help to improve the allocation of hospital resources through appropriate prioritization of patients for facilities with greater monitoring capacity. As such, this study aims to characterize patients who have undergone aspirin desensitization, analyze the success and failure rates, and to identify risk factors that may predict failure of aspirin desensitization.

MATERIALS AND METHODS

Study design and patient population

A retrospective review of medical records of patients referred to the SGH inpatient drug desensitization team for aspirin desensitization between 1 June 2014 and 31 October 2017 was conducted. Electronic notes from the Sunrise Clinical Manager system and hospital inpatient discharge summaries were reviewed for data collection. Patients <21 years old at the time of desensitization and those referred for aspirin desensitization but in which the procedure was ultimately not carried out were excluded. The study protocol was approved by the SingHealth Centralized Institutional Review Board (IRB approval number: 2019/2819).

Data collection

The research application, REDcap, was utilized for data collection. Demographic details and hypersensitivity-related characteristics were collected for patient characterization. Examples of data collected under these categories were age at the time of desensitization, type of NSAIDs with documented hypersensitivity, the corresponding reactions, and presence of any hypersensitivity reaction to aspirin within the past one year prior to desensitization.

Data regarding the patient's response to aspirin desensitization were also collected for the analysis of procedure outcomes. For every reaction event documented during the desensitization, details on the dose as well as the type of reaction that occurred were recorded. For patients who commenced aspirin therapy following completion of aspirin desensitization, data on any discontinuation of aspirin postdesensitization were collected. Alternative antiplatelet usage was also recorded for patients who could not tolerate aspirin.

Definition

We defined the index hypersensitivity reaction to NSAIDs as the earliest reaction to NSAIDs documented in the electronic medical records prior to aspirin desensitization. Occurrence of reaction during aspirin desensitization was defined as the presence of reaction after ingesting the aspirin dose at any step, from step 1 to 11 of the protocol. Completion of aspirin desensitization was defined as the receipt of all 11 doses of aspirin in the protocol.

Desensitization outcomes were classified as 'success' or 'failure.' In general, 'success' was defined as completion of aspirin desensitization without occurrence of significant hypersensitivity reaction. This included patients who commenced on long-term aspirin therapy, as well as those who did not start aspirin therapy due to reasons other than hypersensitivity reactions. Patients who experienced minor reactions during the procedure but managed to complete the entire course of desensitization and commence on long-term aspirin therapy were also classified as 'success' cases.

Conversely, the 'failure' group included patients who experienced hypersensitivity reaction during the procedure that precluded the commencement of aspirin therapy. Patients who started on aspirin but discontinued subsequently due to hypersensitivity reaction were also classified as 'failure' cases.

Statistical analysis

Categorical data were reported as number (percentages). Normally distributed continuous data were reported as mean ± standard deviation while nonnormally distributed continuous data were reported as median (range or interquartile range). For comparison of characteristics between success and failure group, Chi-square test or Fisher exact test was used for categorical data while continuous data were analyzed using independent sample *t* test or Wilcoxon rank-sum test. Characteristics found to differ with a *p* value of <0.1 were considered for inclusion into multivariate analysis (logistic regression model). Odds ratio (OR) were reported with its 95% confidence interval (CI) to quantify the associations between the characteristics and failure of aspirin desensitization. A *p* value of <0.05 was considered statistically significant in the multivariate analysis.

Two sets of analyses were conducted, one involving the full study population and another selected sample excluding patients who have unknown reactions to NSAIDs or reactions not suggestive of NSAID hypersensitivity. This is because these excluded patients may not have true NSAID hypersensitivity and thus, may be more likely to complete aspirin desensitization successfully. As the inclusion of such patients may potentially influence the risk factors identified for failure of aspirin desensitization, a selected sample analysis excluding these patients was performed.

All statistical analyses were performed using IBM SPSS Statistics ver. 25.0 (IBM Co., Armonk, NY, USA).

RESULTS

Between 1 June 2014 and 31 October 2017, a total of 214 patients met the criteria for inclusion in this study.

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Patient characteristics

Tables 1 and **2** shows the characteristics of the 214 patients included in this study. Majority of the study population were males (n = 150, 70.1%) and most of them were Chinese (n = 153, 71.5%). The mean age at time of desensitization was 59.3 years while the average body mass index (BMI) was 26.5 kg/m^2. More than half of the study population had documented hypersensitivity to aspirin (n = 141, 65.9%) and angioedema was the most commonly reported reaction to NSAIDs (n = 104, 48.6%). The top 3 comorbidities of the study population were diabetes mellitus (n = 68, 31.8%), musculoskeletal and bone conditions (n = 36, 16.8%), and chronic kidney disease (n = 29, 13.6%). Aspirin therapy was indicated in all patients for treatment of cardiovascular diseases and majority of them (n = 208, 97.2%) had no prior history of aspirin desensitization.

Outcomes of aspirin desensitization

A total of 208 patients (97.2%) completed aspirin desensitization while 6 patients discontinued the procedure due to development of hypersensitivity reaction. The success rate was 77.1% (n = 165). This included 10 patients who experienced minor reactions during the procedure but managed to complete desensitization and eventually commence on aspirin therapy.

As presented in **Table 3**, 57 patients (26.6%) experienced reaction during desensitization, with angioedema being the most common type of reaction experienced (n = 44, 77.2%). Majority of these reactions occurred at step 10 (n = 6, 10.5%) or 11 (n = 50, 87.7%).

Table 1. Baseline demographics and characteristics of patients (n = 214)

Characteristic	Value
Age at time of desensitization (yr)	59.3 ± 12.4
≥50 years old	167 (78.0)
Body mass index* (kg/m^2)	26.5 ± 4.8
18.5–22.9	37 (17.3)
23.0–27.4	90 (42.1)
≥27.5	76 (35.5)
Male sex	150 (70.1)
Race	
Chinese	153 (71.5)
Malay	28 (13.1)
Indian	22 (10.3)
Others†	11 (5.1)
Smoking status	
Never	139 (65.0)
Current	42 (19.6)
Ex	33 (15.4)
Comorbidities	
Diabetes mellitus	68 (31.8)
Musculoskeletal and bone conditions	36 (16.8)
Chronic kidney disease	29 (13.6)
Atopic disease‡	25 (11.7)
Others	67 (31.3)
Regular medications used	
Beta-blocker	108 (50.5)
ACE-inhibitor	41 (19.2)
Antihistamine	7 (3.3)
Immunosuppressant	6 (2.8)
Leukotriene receptor antagonist	2 (0.9)

Values are presented as mean ± standard deviation or number (%).
*One patient did not have documented height and weight; body mass index classification (Asians): normal, 18.0–22.9 kg/m^2; overweight, 23.0–27.4 kg/m^2; obese, ≥27.5 kg/m^2. †Includes Eurasian, Sikh, Filipino, Burmese and Bangladeshi. ‡Includes asthma and allergic rhinitis.

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Table 2. Baseline hypersensitivity characteristics (n = 214)

Characteristic	Value
Inciting NSAID with documented history of hypersensitivity	
Aspirin	141 (65.9)
Acetic acids	47 (22.0)
Propionic acids	28 (13.1)
Fenamic acids	25 (11.7)
Coxibs	7 (3.3)
Pyrazolones	3 (1.4)
Oxicams	1 (0.5)
Unknown NSAID	9 (4.2)
Type of index reaction to NSAID	
Angioedema	104 (48.6)
Rash	65 (30.4)
Urticaria	11 (5.1)
Respiratory symptoms	7 (3.3)
Itch	7 (3.3)
Anaphylaxis	1 (0.5)
Skin swelling	1 (0.5)
Near syncope	1 (0.5)
Others*	5 (2.3)
Unknown reaction	47 (22.0)
No. of non-NSAID drugs with documented hypersensitivity	0 (0–4)
Hypersensitivity to ≥ 1 non-NSAID drugs	89 (41.8)
Type of non-NSAID drugs with documented hypersensitivity	
Antibiotics and related compounds†	47 (52.8)
Pain management agents	37 (41.6)
Cardiovascular drugs	9 (10.1)
Antihistamines	7 (7.9)
Stimulants	6 (6.7)
Asthma management agents	3 (3.4)
Others	18 (20.2)
Type of reaction to the non-NSAID drugs	
Rash	27 (30.3)
Angioedema	20 (22.5)
Anaphylaxis	4 (4.5)
Respiratory symptoms	1 (1.1)
Pruritus	1 (1.1)
Skin swelling	1 (1.1)
Others	2 (2.2)
Unknown reaction	51 (57.3)
No. of previous aspirin desensitization	0 (0–2)
Reaction to aspirin in the past 1 year prior to desensitization	27 (12.6)

Values are presented as number (%) or median (range).
NSAID, nonsteroidal anti-inflammatory drug.
*Includes fever, giddiness, stomach-ache, teary eyes, palpitations. †Includes clavulanic acid.

Postdesensitization, a total of 151 patients (70.6%) initiated aspirin therapy, of which 30 (19.9%) had aspirin discontinued subsequently. Out of these 30 patients, 2 (6.7%) were discontinued due to hypersensitivity reactions and were considered to have failed aspirin desensitization. Among those who did not start aspirin therapy or had to discontinue aspirin subsequently (n = 93), clopidogrel (n = 42, 44.7%), or ticagrelor (n = 26, 27.7%) were used as alternative treatment if antiplatelet therapy was indicated.

Risk factors associated with failure of aspirin desensitization

Supplementary material 2 details the comparison of characteristics between 'success' and 'failure' group. For the analysis involving the full study population (n = 214), having propionic acid as the inciting NSAID ($p = 0.094$), an index NSAID reaction of rash ($p = 0.035$) or

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Table 3. Outcomes of aspirin desensitization (n = 214)

Aspirin desensitization response	Value
Patients who experienced reaction during desensitization (n = 57, 26.6%)	
Type of reactions experienced	
Angioedema	44 (77.2)
Rash	10 (17.5)
Respiratory symptoms	5 (8.8)
Itch	4 (7.0)
Rhinorrhea	1 (1.8)
Neck tightness	1 (1.8)
Others*	4 (7.0)
Step at which reaction occurred	
9	1 (1.8)
10	6 (10.5)
11	50 (87.7)
Cumulative aspirin dose at which reaction occurred (mg)	244.2 ± 38.2
Patients who did not start aspirin therapy (n = 63, 29.4%)	
Reasons for not commencing aspirin therapy	
Reaction during or after procedure	47 (74.6)
Not indicated	18 (28.6)
Choice of SAPT with alternative agents for minor CAD	3 (4.8)
Prioritization of other issues	2 (3.2)
Patients who started aspirin therapy (n = 151, 70.6%)	
Aspirin therapy discontinued subsequently	30 (19.9)
Reason for discontinuation of aspirin therapy	
No longer indicated	11 (36.7)
Bleeding	5 (16.7)
Adverse drug reactions	5 (16.7)
Stopping for procedure	3 (10.0)
Hypersensitivity reaction	2 (6.7)
Others	4 (13.3)

Values are presented as number (%) or mean ± standard deviation.
SAPT, single antiplatelet therapy; CAD, coronary artery disease.
*Includes fever, numbness over jaw, nasal voice, and conjunctivitis.

angioedema ($p < 0.001$), and having atopic disease as comorbidity ($p = 0.012$) were found to differ between the 2 groups with a p value of <0.1 (**Supplementary material 1**) and were included in the logistic regression model. Documented hypersensitivity to aspirin and reaction to aspirin in the past 1 year prior to desensitization were also included due to their clinical relevance [15]. **Table 4** presents the results of the multivariate analysis. Having an index reaction of angioedema to NSAIDs (OR, 5.88; 95% CI, 2.60–13.30) and atopic disease as comorbidity (OR,

Table 4. Multivariate analysis of association between patient characteristics and failure of aspirin desensitization

Variable	All patients (n = 214)		Selected sample† (n = 163)	
	Adjusted OR	95% CI	Adjusted OR	95% CI
Inciting NSAID with documented hypersensitivity				
Aspirin	1.15	0.53–2.48	1.15	0.47–2.83
Propionic acid	2.27	0.84–6.10	-	-
Acetic acid	-	-	2.03	0.80–5.15
Type of NSAID reaction				
Rash	0.80	0.32–1.95	0.92	0.32–2.66
Angioedema	5.88	2.60–13.30*	7.21	1.94–26.71*
Comorbidities				
Atopic disease	3.13	1.16–8.42*	2.27	0.71–7.29
Diabetes mellitus	-	-	0.50	0.19–1.34
Reaction to aspirin in the past 1 year prior to aspirin desensitization	0.40	0.12–1.30	0.47	0.14–1.58

OR, odds ratio; CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug.
*$p < 0.05$, statistically significant differences. †Excluded patients who have unknown reactions to NSAIDs (n = 47) or reactions not suggestive of hypersensitivity to NSAIDs (n = 4).

3.13; 95% CI, 1.16–8.42) remained significantly associated with a higher risk of failing aspirin desensitization after adjusting for potential confounders.

The second analysis excluded patients with unknown reactions to NSAIDs (n = 47) or reactions not suggestive of hypersensitivity to NSAIDs such as giddiness and fever (n = 4). A total of 163 patients were included in this selected sample. The success rate was 74.2% (n = 121). Forty patients (85.1%) with unknown reactions to NSAIDs and all patients (100%) with reactions not suggestive of hypersensitivity to NSAIDs achieved successful desensitization. Variables considered for inclusion into this selected sample multivariate analysis were NSAIDs with acetic acid functional group as the inciting drug ($p = 0.048$), unknown NSAID as the inciting drug ($p = 0.004$), an index NSAID reaction of rash ($p = 0.006$) and angioedema ($p < 0.001$), as well as, comorbidities of atopic disease ($p = 0.083$) and diabetes ($p = 0.073$) (**Supplementary material 2**). Unknown inciting NSAID was excluded from the multivariate analysis due to small number of cases. The logistic regression model (**Table 4**) showed that only index NSAID reaction of angioedema remained significantly associated (OR, 7.21; 95% CI, 1.94–26.71) with a higher risk of failing aspirin desensitization.

DISCUSSION

Hypersensitivity to NSAIDs may limit the use of aspirin in patients with cardiovascular diseases due to cross-reactivity [26]. For patients with NSAID hypersensitivity who require aspirin therapy for cardiac conditions (e.g., postmyocardial revascularization), aspirin desensitization is recommended by guidelines as an option [3] to enable patients to receive this important medication via the induction of temporary tolerance to aspirin [15]. This study sought to elucidate characteristics of patients who have undergone aspirin desensitization. As the incidence of cardiovascular diseases is known to increase with older age [27], it is unsurprising that majority of the study population were ≥50 years old (78.0%). Higher BMI has also been shown to be associated with heightened risk for cardiovascular morbidity [28], which may explain why most of the study population (77.6%) was overweight or obese. The most common type of index reaction experienced by the patients with NSAIDs was angioedema (n = 104, 48.6%) and a total of 110 patients (51.4%) had angioedema and/or urticaria with NSAIDs. This is in line with multiple studies that have reported angioedema and urticaria as the most common reaction induced by NSAIDs [29-31]. These reactions are considered true NSAID hypersensitivity reactions as they are typically caused by COX-1 inhibition [32], which results in increased production of leukotrienes that is responsible for vasodilation and plasma leakage to the skin [33, 34].

This study also sought to analyze the outcomes of aspirin desensitization. The success rate of aspirin desensitization was 77.1%. This is lower as compared to previous studies [14, 31], which have reported success rates of up to 98.6% for aspirin desensitization in patients with CAD [31]. The difference in success rates could be attributed to variations in success and failure definitions between studies. In our study, many patients who experienced reactions after receiving the last aspirin dose were deemed to have 'failed' aspirin desensitization even though they have completed the desensitization protocol and tolerated at least 157.7 mg of aspirin. However, based on the study by Cortellini et al. [31], patients who 'failed' aspirin desensitization were those who had to discontinue the procedure due to hypersensitivity reaction and did not achieve a cumulative 100-mg aspirin tolerance. Due to the differences in definition, some of the patients who were considered to have 'failed' desensitization in our

study may not have been classified as failures in another study, thereby leading to differences in the reported success rates.

In our study, reactions developed in 57 patients (26.6%) during aspirin desensitization. For all of these patients, the reactions occurred at steps 9, 10, or 11 of the protocol which relates to a cumulative aspirin dose of 77.7 mg to 257.7 mg. These patients reacted at higher cumulative doses of aspirin which is in line with the fact that hypersensitivity reaction to aspirin may be dose dependent [18, 25]. There were 10 patients who experienced reaction at step 10 or 11 of aspirin desensitization but still managed to commence on aspirin therapy. This suggests the possibility of initiating aspirin even in patients who develop reaction during desensitization. However, both the cumulative dose at which the reaction occurred, and the type of reaction should be evaluated carefully when deciding if aspirin therapy should be started for the patient.

A second analysis was performed to determine the effects of excluding patients who have unknown reactions to NSAIDs or reactions not suggestive of hypersensitivity to NSAIDs (n = 51). This was based on the concept that these patients may not have true hypersensitivity to NSAIDs and thus, were possibly more likely to achieve successful aspirin desensitization. The success rate decreased from 77.1% to 74.2% when this group of patients was excluded, suggesting that the success rate among patients who had true NSAIDs hypersensitivity lies between 74.2% to 77.1%. All the patients who had reactions not suggestive of hypersensitivity to NSAIDs (n = 4) underwent aspirin desensitization successfully. These patients likely did not have true NSAID hypersensitivity and thus, were all able to undergo aspirin desensitization without reactions. For such patients, aspirin desensitization may not have been necessary. Detailed history taking is imperative so that patients are not subjected to aspirin desensitization unnecessarily. Among patients with unknown reactions to NSAIDs (n = 47), 85.1% achieved successful aspirin desensitization. This success rate is higher than the success rate of 74.2% to 77.1% among patients deemed to have true NSAID hypersensitivity. The higher success rate among patients with unknown reactions to NSAIDs reflects the likelihood that a significant proportion of these patients did not have true NSAID hypersensitivity and consequently, were more likely to complete aspirin desensitization successfully.

Our study also aimed to identify any risk factors that might predict failure of aspirin desensitization in the study population. Presence of atopic disease and index reaction of angioedema to NSAIDs were found to be associated with a higher risk of failing aspirin desensitization in the first analysis where all 214 patients were included. However, only index reaction of angioedema to NSAIDs was identified as a risk factor for failure of aspirin desensitization in the second analysis involving the selected sample. The first analysis included patients who have unknown reactions to NSAIDs as well as patients with reactions not suggestive of hypersensitivity to NSAIDs. This may account for differing risk factors in the second analysis. As the selected sample included only patients with documented hypersensitivity reactions to NSAIDs, the risk factor identified with this selected sample is likely more accurate and reliable for predicting failure of aspirin desensitization in patients with NSAID hypersensitivity.

Our observation that angioedema to NSAIDs is associated with desensitization failure is also supported by literature. A previous smaller study involving 81 patients with self-reported histories of NSAID hypersensitivity found that those who experienced angioedema after ingesting aspirin were more likely to experience a reaction during aspirin desensitization

[15]. We postulate that this may be contributed by their greater capacity to produce cysteinyl-leukotrienes, which subsequently induces reactions when aspirin is administered. Leukotriene C4 synthase (LTC4S) is the enzyme involved in production of cysteinyl-leukotrienes, which triggers hypersensitivity reactions [35]. The C allele of *LTC4S* gene promoter has been found to occur more frequently in patients who experience cutaneous reactions to NSAIDs [36]. This variant allele has been thought to be responsible for the increased expression of LTC4S which thereby boosts the cells' capacity to produce cysteinyl-leukotrienes [37]. As such, these patients may be at higher risk of developing reactions during aspirin desensitization.

In our study, we identified risk factors for desensitization failure from patients with documented true NSAID hypersensitivity in order to improve the applicability of these risk factors in our target population of patients with true NSAID hypersensitivity. Identification of risk factors for drug desensitization is paramount in the development of a risk-stratified algorithm for aspirin desensitization. With risk-stratification, patients with an index reaction of angioedema to NSAIDs can be prioritized for facilities with greater monitoring capacity such as high-dependency units. These patients may also benefit from specialized allergist input to better manage any hypersensitivity reactions that occur via methods such as protocol modification and individualization.

Our study is not without limitations. The lack of access to cross-institution databases limited the ability to trace patients who sought care in a different institution after desensitization, which could potentially affect the data collected on post-desensitization status. In addition, the patient population of this study was limited to patients who underwent aspirin desensitization in SGH. This may limit the generalization of the findings to patients undergoing aspirin desensitization in other institutions as the characteristics of these patients as well as the desensitization protocols may differ from that of our institution. As such, future research could involve the collaboration of various institutions, allowing investigators to access other institutions' databases as well as to explore risk factors that may be more generalizable to patients undergoing aspirin desensitization.

Developing an aspirin desensitization algorithm and studying the safety and efficacy of risk-stratification could also be potential topics for future studies to confirm the importance of risk-stratifying patients prior to aspirin desensitization.

In conclusion, this study sought to shed light on the characteristics and outcomes of patients who underwent aspirin desensitization, as well as to identify risk factors associated with failure of the procedure. All the patients included in the study had a cardiovascular indication for aspirin and cutaneous reactions were the most common type of index reaction to NSAIDs. A large proportion of patients underwent aspirin desensitization successfully and were able to commence on long-term aspirin therapy. Index reaction of angioedema to NSAIDs was identified as the risk factor for failure of aspirin desensitization in patients with NSAID hypersensitivity. This allows risk-stratification of future patients which could potentially aid in improving safety and efficacy of the procedure.

SUPPLEMENTARY MATERIALS

Supplementary materials 1 and 2 can be found via 10.5415/apallergy.2021.11.e20.

Supplementary material 1

Institution aspirin desensitization protocol

Click here to view

Supplementary material 2

Univariate analysis – comparison of characteristics between 'success' and 'failure' group

Click here to view

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