J Nepal Health Res Counc 2021 Apr-Jun;19(51): 295-9

DOI: https://doi.org/10.33314/jnhrc.v19i2.3477

Safety and Efficacy of Single vs Dual Antiplatelets Therapy After Atrial Septal Defect Device Closure

Chandra Mani Adhikari,[1] Dipanker Prajapati,[1] Amrit Bogati,[1] Kiran Prasad Acharya,[1] Anjana Acharya,[1] Roshani Shahi,[1] Swikirty Shrestha,[1] Vijay Ghimire,[1] Kavindra Thapa,[1] Kunjang Sherpa[1]

ABSTRACT

Background: Atrial septal defect device closure has become a standard procedure. Antiplatelet therapy is used to prevent thrombus formation in the device. There is no clear recommendation about the antiplatelets drugs. This study aims to evaluate the safety and efficacy of Aspirin vs (Aspirin +Clopidogrel) after device closure.

Methods: A cross-sectional study was conducted among all consecutive adult patients (≥18 years) who underwent atrial septal defect device closure from May 2019 to April 2020 and meet the inclusion criteria were included. After successful ASD device closure patients were treated with ASA or combination of ASA and Clopidogrel for six months on physician discretion. Patients were followed up for six months to observe for Transient ischemic attack, Stroke, thrombus in the device, myocardial infarction, major bleeding, minor bleeding and increases in headache episodes compared to baseline.

Results: This study consisted of 130 patients: 65 in the Aspirin Group, and 65 patients in Aspirin and Clopidogrel group. There was no Transient ischemic attack, Stroke, Myocardial infarction, thrombus, major bleeding in both groups. There was no significant difference between two groups in ecchymosis; Aspirin group 4(6.1%) vs. aspirin and Clopidogrel group 3(4.6%) [Difference, 1.54% {95, % CI, -1.45%to 4.53%}]; P=0.648. There was no significant difference in increase in headache episodes compared to baseline for six months after the device closure in Aspirin Group 3(4.6%) VS Aspirin and Clopidogrel group 2 (3.0%) group [difference, 1.54% {95% CI, -1.45%to 4.53%}]; P=0.648.

Conclusions: Our study suggests that single antiplatelet therapy with Aspirin is as safe and effective as aspirin and clopidogrel after device closure.

Keywords: Atrial septal defect; ASD device closure; clopidogrel

INTRODUCTION

Atrial septal defect (ASD) device closure has become a standard procedure. Post-procedural complications include thrombus formation on the septal occluder in about 0-10% of cases.[1] Different regiments of aspirin (ASA) and clopidogrel therapy are applied based on empirical data, local experience and case reports from the literature to prevent this complication.

Most centers use either ASA alone or a combination of ASA and clopidogrel (75 mg) for 6 months. The only study that supports the use of dual antiplatelet therapy is the CANOA study.[2] It suggests that dual antiplatelet therapy for three months following ASD device closure reduces number and severity of migraine headaches.[2] However dual antiplatelets therapy may significantly increase the risk of bleeding as seen with the use Clopidogrel is associated with increased major bleeding in post PCI patients.[3]

This study aims to evaluate the safety and efficacy of ASA vs. ASA +Clopidogrel after ASD device closure.

METHODS

This was a prospective cross-sectional study conducted at Shahid Gangalal National Heart Centre, Kathmandu, Nepal. All the consecutive adult patients (≥18 years) who underwent ASD device closure in department of cardiology at Shahid Gangalal National Heart Centre from May 2019 to April 2020 and meet the inclusion criteria were included in this study. The study was approved by the Institutional review board (IRB) of National heart Centre.

The Inclusion criteria were 1. All Patient's ≥ 18-year-old, who underwent transcatheter ASD closure with

Correspondence: Dr Chandra Mani Adhikari,Department of Cardiology, Shahid Gangalal National Heart Centre Kathmandu, Nepal. Email: cmadhikari@sgnhc.org.np, Phone: +9779851212111.

the Amplatzer Septal Occluder device (AGA medical Corp., MN, USA). 2. Absence of bleeding disorders 3. Hemoglobin level more than 11 mg /dL before the procedure. 4. Normal Platelet Count (150000-450000). The Exclusion Criteria were 1. Allergy or intolerance to any of the antithrombotic drugs (aspirin, clopidogrel) used in the study. 2. Need for anticoagulation therapy (Atrial Fibrillation). 3. Use of ASD closure devices other than the Amplatzer Septal Occluder device. 4. Refusal to sign the informed consent. 5. Pregnancy or breast-feeding or planning to become pregnant during the study. 6. Previous stroke. 7. History of coronary artery disease (CAD).

The main objective of the study was to study the efficacy and safety of dual vs single antiplatelet therapy post ASD device closure. We collected the information about patient's name, age, gender, maximum ASD size in transesophageal echocardiography (TEE), device size; hemoglobin, platelets count and patients were also inquired about the increase in headache after device closure.

It is widely accepted fact till date that the antiplatelets therapy after ASD device closure is necessary to prevent the thrombus formation. However, the optimal antiplatelet therapy strategy is not clear till date due to lack of randomized studies. Thus, the choice is largely based on treating physician's discretion, empirical data and local experience. Hence in our organization, some of the operators prefer single antiplatelets while others prefer dual therapy. In our study patients were categorized into 2 groups as per the antiplatelets therapy during discharge.

After successful ASD device closure patients were treated with ASA 75mg once daily or combination of ASA 75mg and Clopidogrel 75mg for six months on physician discretion. Group A consist of patients treated with ASA and group B consist of patients treated with ASA and clopidogrel. For the primary outcome of the study patients were followed up to observe for the occurrence for Transient ischemic attack, Stroke, thrombus in the device and myocardial infraction. For the safety outcome, the occurrence of major bleeding defined by intracerebral hemorrhage, gastrointestinal tract hemorrhage, hemarthrosis, hemopericardium hematuria, vaginal bleeding other than menses, hemoptysis, epistaxis, any hemorrhage which required medical therapy including blood transfusion. Minor Bleeding defined as bleeding that did not require blood transfusion or medical intervention, and other adverse event include increases in headache episodes compared to baseline for six months after the successful device closure were evaluated.

In a study done by Krumsdorf et al. [4] the overall incidence of thrombus formation after successful ASD/PFO device implantation was 2%. Based upon the above study taking 99% confidence interval and margin of error of 4% the minimum sample size required was 82. In our study we have taken 131 patients (66 in Aspirin group and 65 in Aspirin+ Clopidogrel group).

RESULTS

Patients were enrolled from May 2019 to April 2020, and the last patient follow-up was completed in October 2020. The flow of patient participation through the study is shown in Figure 1. A total of 140 patients diagnosed with an ASD for whom transcatheter ASD closure was planned were screened. Of these, 10 patients were excluded from the study because in three cases device closure was unsuccessful, in three case ASD device closure with non-amplatzer devices was used, two patients had Atrial Fibrillation and one case was excluded due to history of coronary artery disease (CAD), One case died due to noncardiac cause after three months on follow up and could not complete 6 months of follow up and was excluded. The final study population consisted of 130 patients: 65 in the Group A, and 65 patients in Group B.

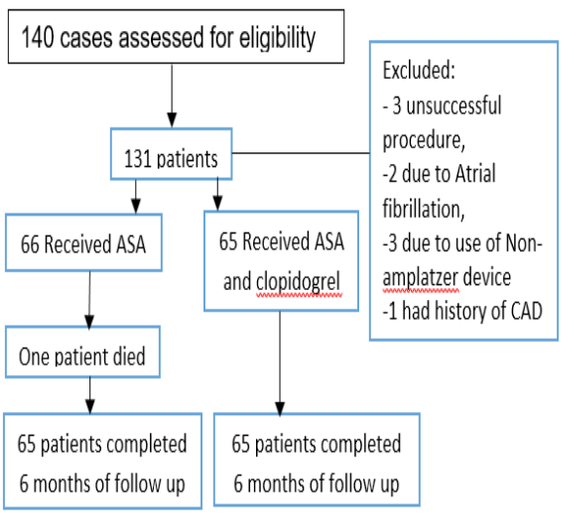

Figure 1. Flowchart of the Study Population

The baseline and procedural characteristics of the study population, according to treatment received, are shown in Table 1. Among the 130 cases who completed 6 months of follow up age ranged from 18 to 70 years with the mean±SD)35.7± 12.9 years, 88 (67.6%) patients were women. ASD size measured by TEE ranged from 8 mm to

33 mm with mean size±SD of 19.8±5.3) mm. The device size ranged from 10 mm to 40 mm with the mean ±SD of 26.6±6.1) mm. There were no significant difference between-group differences regarding baseline and procedural characteristics

Table 1. Baseline and Procedural Characteristics of the Study Population.

	Group A (n=65)	Group B (n=65)	p-value
Age, Mean (SD) years	34.54±14.17	37±11.65	0.28
Sex Male n (%) Female n (%)	 16 (24.6) 49 (75.4)	 26 (40) 39 (60)	0.061
Risk Factors Hypertension (N/%) Diabetes(N/%)	 4 (6.2) 1 (1.5)	 7 (10.8) 1 (1.5)	0.457
ASD size on TEE Mean± SD mm	19.7±5.4	19.8±5.4	0.9
Device Size Mean± SD mm	26.4±6.4	26.7±5.9	0.8
Dilated RA and RV (N/%)	65(100)	65(100)	1.0
TRPG Mean± SD mmHg	35.0±9.5	36.0±10.6	0.5
TR Mild (N/%)	47 (47.3)	42(64.6)	
TR moderate (N/%)	17(26.2)	20(30.8)	0.467
TR severe (N/%)	1 (1.5)	3 (4.6)	
Hb Mean± SD mm	13.3±1.4	13.8±1.4	.05
Platelets Mean± SD mm	291953±75880	274830±79240	.2

During the 6 months of follow up there were no Transient ischemic attack, Stroke, Myocardial infarction, thrombus in the device in both groups.

During the 6 months of follow up there was no major bleeding in both groups. There was no significant difference between two groups in ecchymosis, Group A: 4(6.1%) vs. Group B:3 (4.6%) [Difference, 1.54% {95, % CI, -1.45%to 4.53%}]; P=0.648. There was no significant difference in increase in headache episodes compared to baseline for six months after the device closure in Group A 3(4.6%) VS Group B 2 (3.0%) group [difference, 1.54% {95% CI, -1.45%to 4.53%}]; P=0.648 as shown in Table 3.

Table 3. Safety outcome and other adverse events in the study population.

	Antiplatelet therapy				
	Group A	Group B	Difference	95% CI	p-value
Ecchymosis	4 (6.15)	3 (4.62)	1.54%	1.45%-4.53%	0.648
Headache	3 (4.62)	2 (3.08)	1.54%	1.45%-4.53%	0.648

DISCUSSION

Transcatheter ASD closure has been well established as the treatment of choice for most patients with hemodynamically significant ASD. This treatment offers a very high success rate, extremely low rate of complications (including cerebrovascular events), rapid recovery after the treatment and the minimally invasive approach when compared with surgery.[5] Combination of high success rate, low rate of complications, and more rapid recovery rate is of particular importance considering that most adult patients receiving this treatment are of the working age.[2]

To prevent the post-procedural thrombus formation on the device antithrombotic therapy is prescribed. But Antithrombotic therapy following transcatheter ASD closure remains empirical with aspirin for 6 months being commonly prescribed.[2] Indication of dual antiplatelets is based on the preliminary observational retrospective studies. They suggested an association of lower incidence and severity of migraine headaches following ASD closure when ticlopidine or clopidogrel is added to ASA.[6-9] Indian guidelines for indications and timing of intervention for common congenital heart diseases suggests that single antiplatelets therapy with ASA in patients with device of ≤30 mm for total duration of 6 months. In patients with Device >30 mm ASA and clopidogrel were given for 3 months followed by aspirin alone for 3 more months.[10] The 2020 ESC Guidelines for the management of adult congenital heart disease suggests that though thromboembolic events appear to be very rare after ASD device closure, antiplatelet therapy is required for at least 6 months (ASA 75 mg once daily minimum).[11]

Our study showed that single antiplatelet therapy with ASA is as effective as dual antiplatelet therapy with ASA and clopidogrel. It also has showed that it is safe with no significant difference in adverse outcome of increased

episode of headache, ecchymosis and major bleeding.

In the study done by Polzin et al, suggest that additional antiplatelet medication with clopidogrel is questionable when new generation SJM or Occlutech devices are used. Though, high on-treatment platelet reactivity (HTPR) to clopidogrel is very frequent (71% of their patients), there was no thrombus formation, stroke and myocardial infarction. On the other hand, there were three major bleedings including two life-threatening bleeding were observed (one intracranial hemorrhage) in treated with clopidogrel.[12]

In the recently published study, New-onset migraine attacks after ASD closure improved or resolved spontaneously within 6 to 12 months in most patients. No significant rebound effect was observed after clopidogrel cessation at 3 months. This study demonstrates a low rate of migraine events beyond 3 months following transcatheter ASD closure and support the early discontinuation of clopidogrel therapy if administered.[13]

Though an observational study, our study clearly suggest that single antiplatelet therapy is as effective and safe as compared to ASA and clopidogrel after ASD device closure in our patients. The major limitation of this study was a single center observational study conducted for only one year. As the randomization of patients into 2 groups was not done and only the patients were divided into 2 groups based upon the antiplatelet prescription modality, this is another major limitation of the study. Large scaled, multicentered randomized controlled trials conducted for long duration has to be done to overcome such limitations.

CONCLUSIONS

Our study suggests that single antiplatelet therapy with ASA is as safe and effective as ASA and clopidogrel after ASD device closure in Nepalese patients but a large scale, multicenter trial is necessary to make a clear recommendation on its use.

ACKNOWLEDGEMENT

To all the doctors, Nurses and Catheterization laboratory staff of Shahid Gangalal National Heart center who are involved in Atrial Septal Defects device closure.

Author Affiliations

[1]Department of Cardiology, Shahid Gangalal National Heart Centre, Kathmandu, Nepal

Competing interests: None declared

REFERENCES

1. Franke A, Kuhl HP. The role of antiplatelet agents in the management of patients receiving intracardiac closure devices. Current pharmaceutical design. 2006 Apr 1;12(10):1287-91.[DOI]
2. Rodés-Cabau J, Horlick E, Ibrahim R, Cheema AN, Labinaz M, Nadeem N, et al. Effect of clopidogrel and aspirin vs aspirin alone on migraine headaches after transcatheter atrial septal defect closure: the CANOA randomized clinical trial. Jama. 2015 Nov 24;314(20):2147-54.[DOI] [PMID 26551304]
3. Tsai TT, Ho PM, Xu S, Power JD, Carroll NM, Shetterly SM, et al. Increased risk of bleeding in patients on clopidogrel therapy after drug-eluting stents implantation: insights from the HMO Research Network-Stent Registry (HMORN-stent). Circ Cardiovasc Interv. 2010;3(3):230-5.[DOI][PMID 20442361]
4. Kurmsdorf U, Ostermayer S, Billinger K. Incidence and clinical course of thrombus formation on atrial septal defect and patent foramen ovale closure devices on 1000 consecutive patients. J Am Coll Cardiol. 2004; 43:302-9. [DOI][PMID 14736453]
5. Du ZD, Hijazi ZM, Kleinman CS, Silverman NH, Larntz K; Amplatzer Investigators. Comparison between transcatheter and surgical closure of secundum atrial septal defect in children and adults: results of a multicenter nonrandomized trial. J AmCollCardiol. 2002;39(11):1836-1844.[DOI]
6. SharifiM, Dehghani M, Mehdipour M, Al-Bustami O, Emrani F, Burks J. Intense migraines secondary to percutaneous closure of atrial septal defects. J IntervCardiol. 2005;18(3):181-183.[DOI] [PMID 15966922]
7. Wilmshurst PT, Nightingale S,Walsh KP, MorrisonWL. Clopidogrel reducesmigraine with aura after transcatheter closure of persistent foramen ovale and atrial septal defects. Heart.2005;91(9):1173-1175. [DOI] [PMID 16103551] PMC 1769061
8. Rodés-Cabau J, Mineau S, Marrero A, Houde C, Mackey A, Côté JM, et al. Incidence, timing, and predictive factors of new-onset migraine headache attack after transcatheter closure of atrial septal defect or patent foramen ovale. The American journal of cardiology. 2008 Mar 1;101(5):688-92.[DOI]PMID 18308022
9. Kato Y, Kobayashi T, Ishido H, Hayashi T, Furuya D, Tanahashi N. Migraine attacks after transcatheter closure of atrial septal defect. Cephalalgia.2013;33(15):1229-1237. [DOI][PMID 23720500]

10. Saxena A, Relan J, Agarwal R, Awasthy N, Azad S, Chakrabarty M, et al. Indian guidelines for indications and timing of intervention for common congenital heart diseases: Revised and updated consensus statement of the Working group on management of congenital heart diseases. Ann Pediatr Card 2019; 12:254-86.[DOI] [PMID31516283] [PMC 6716301]

11. The Task Force for the management of adult congenital heart disease of the European Society of Cardiology (ESC). 2020 ESC Guidelines for the management of adult congenital heart disease. European Heart Journal 2020; 00:1-83.

12. Amin Polzin, Lisa Dannenberg, Valérie- Sophia Popp, Malte Kelm, Tobias Zeus. Antiplatelet effects of clopidogrel and aspirinafter interventional patent foramen ovale/ atrium septum defect closure. Platelets; 2015:[DOI] [PMID 26556101]

13. Jérôme Wintzer-Wehekind,Eric Horlick,Reda Ibrahim, Asim N. Cheema, Marino Labinaz, Najaf Nadeem, Mark Osten, MD; Mélanie Côté, MSc; Josep Ramon Marsal, Donald Rivest, Alier Marrero, Christine Houde, Josep Rodés-Cabau. Effect of Clopidogrel and Aspirin vs Aspirin Alone on Migraine Headaches After Transcatheter Atrial Septal Defect Closure One-Year Results of the CANOA Randomized Clinical Trial. JAMA Cardiol.2020.[DOI] [PMID 32965476]