

# A comparison of two approaches to managing acute primary angle closure in Asian eyes

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**Purpose:** To review the management regimes of acute primary angle closure (APAC) in two hospitals in Singapore, and to identify the incidence of and risk factors for progression to glaucomatous optic neuropathy.

**Methods:** We conducted a retrospective review of 40 patients from National University Hospital (NUH) and 52 patients from Singapore National Eye Centre (SNEC) who were diagnosed with APAC. Patients were treated with similar protocols of intensive medical therapy until laser peripheral iridotomy could be performed. In the event of failed medical treatment, patients at NUH only underwent laser iridoplasty. The 1-year outcomes were reviewed.

**Results:** The demographic features of patients and presenting intraocular pressures (IOP) were similar in both centers. More patients from NUH presented within 3 days of symptom onset, compared to those from SNEC (90.0% versus 71.2%, respectively) ( $P = 0.037$ ). The mean  $\pm$  standard deviation time to break the attack was  $18.2 \pm 32.9$  hours at SNEC and  $9.80 \pm 10.6$  hours at NUH ( $P = 0.11$ ). The mean follow up duration was  $18.8 \pm 14.0$  months. Nineteen patients (36.5%) from SNEC and six patients (22.5%) from NUH developed raised IOP ( $P = 0.032$ ) within 1-year of the attack. Of these, glaucomatous optic neuropathy developed in thirteen patients (68.4%) from SNEC and all six patients (100%) from NUH. At final review, the mean IOP of the APAC eye was  $14.8 \pm 4.3$  mmHg from SNEC and  $13.4 \pm 3.0$  mmHg from NUH. There was no significant difference in final visual acuity or IOP between both groups.

**Conclusion:** Treatment strategies in both centers were effective in aborting an APAC attack. The development of raised IOP appears to be associated with a longer period of attack suggesting that greater urgency in aborting APAC attacks may entail better long term outcomes.

**Keywords:** acute primary angle closure, management, primary angle closure glaucoma

## Introduction

Acute primary angle closure (APAC) is a potentially blinding ocular emergency. Studies have shown that a single attack has been associated with permanent retinal nerve fiber layer loss, visual field defects, and optic disc pallor.<sup>1-3</sup> Despite Singapore having the highest reported incidence of APAC of any country studied to date, consensus on an ideal management protocol has yet to be devised for its ophthalmic centers.<sup>4</sup>

Previous studies conducted at different centers in Singapore revealed contradictory evidence for the risk of progression to primary angle closure glaucoma (PACG) following prior APAC after laser peripheral iridotomy (LPI). An initial study conducted at the National University Hospital (NUH) between 1990 and 1994 revealed that a majority (58.1%) of these Asian eyes required additional treatment with ocular hypotensive medication, and 32.7% of patients required filtration surgery after an APAC episode.<sup>5</sup> A decade later, Tan et al reported the long term outcomes of APAC patients at the same

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center and showed that only 21.4% of patients who presented between December 2003 and June 2006 developed chronically raised intraocular pressures post APAC.<sup>6</sup> This difference was attributed to a shorter duration of symptoms and earlier time to presentation for treatment in the latter population.

Conventionally, treatment of APAC involves the use of topical and systemic medication to reduce intraocular pressure (IOP), and definitive LPI is delayed until there is sufficient corneal clarity to be performed safely.<sup>7</sup> In patients not suitable for immediate definitive LPI, argon laser peripheral iridoplasty (ALPI) has been reported to be significantly more effective compared to medical therapy in reducing IOP during APAC, and this was independent of the duration of attack.<sup>8</sup>

There is conflicting evidence as to whether a delay in aborting an acute attack carries a significant risk of developing glaucomatous optic neuropathy (GON).<sup>9–11</sup> Cumulating evidence promotes a more rapid approach to IOP lowering in APAC, yet the role of alternative management protocols is inadequately answered.

Within Singapore, the NUH advocates conventional medical treatment and ALPI is performed if the attack is not broken within an hour. Conversely, at another center, the Singapore National Eye Centre (SNEC), topical and intravenous drugs are used as the primary therapy, and ALPI is extremely rarely implemented. The duration of the attack and outcomes at 1-year in patients at both centers are expected to be different.

In this study, we aimed to compare the two approaches in Singapore regarding the incidence of progression to GON, and to identify risk factors predicting progression to GON.

## Methods

This was a retrospective cohort study of consecutive patients who were diagnosed with APAC at two hospitals in Singapore: SNEC and NUH. At NUH, 40 consecutive patients who presented with APAC between December 2003 and June 2006 were included, as previously described.<sup>6</sup> At SNEC, the charts of 52 consecutive patients who presented between June 2010 and November 2011 were reviewed. Patients were identified from a logbook of acute cases in the emergency department as well as from the database of another ongoing APAC trial at the center. The study protocol had the approval of the institutional review board of the respective clinical ethics committees, and was conducted in accordance to the tenets of the Declaration of Helsinki.

The criteria used to define APAC are as follows: (1) At least two of these symptoms: ocular or periocular pain,

nausea and/or vomiting, an antecedent history of intermittent blurring of vision with haloes around lights; (2) The presenting IOP of  $>21$  mmHg, as measured by Goldmann applanation tonometry, with the presence of at least three of the following signs: conjunctival injection, corneal epithelial edema, a mid-dilated unreactive pupil and a shallow anterior chamber with iridotrabecular contact.

Following APAC resolution, the development of PACG was defined as eyes with IOP  $>21$  mmHg measured by Goldmann applanation tonometry without the use of ocular hypotensive medication associated with glaucomatous optic neuropathy (defined as loss of neuroretinal rim with a vertical cup:disc ratio of  $\geq 0.6$ , and/or notching attributable to glaucoma) and reproducible visual field loss compatible with glaucoma on static white-on-white threshold perimetry (program 2402 SITA, Humphrey Instruments, Dublin, CA, USA); that is, glaucoma hemifield test results outside normal limits and/or an abnormal pattern standard deviation with  $P < 0.05$  occurring in the normal population.<sup>6</sup> Reliability criteria for perimetry used were fixation losses  $<20\%$ , false positive and false negative of  $<33\%$  each, and the presence of the visual field defect in at least two reliable visual field tests.<sup>6</sup>

Patients who were diagnosed with secondary angle closure, such as from peripheral anterior synechiae in neovascular glaucoma, and those with evidence of primary angle closure glaucoma in the APAC eye at presentation, were excluded. The presenting features at the time of diagnosis, such as initial visual acuity (VA) and initial IOP, acute treatment and subsequent management, as well as outcomes at 1-year were analyzed.

Initial treatment for APAC at NUH, as previously described, was similar to management at SNEC.<sup>6</sup> A protocol of intravenous acetazolamide (500 mg, unless the patient had sulfonamide allergy or other contraindications) and eye drops, including topical pilocarpine (4%), timolol (0.5%), brimonidine (0.1%), and prednisolone acetate (1%) or betamethasone (0.1%), were instituted. Patients were reviewed 1 to 2 hours later and immediate LPI with sequential Argon and Nd:YAG laser was performed if the cornea was clear.<sup>6</sup>

Resolution of APAC was defined as IOP  $<21$  mmHg with resolution of acute symptoms. If the IOP remained elevated ( $>21$  mmHg) with persistent corneal haze despite 2 hours of treatment, the management strategies at the two centers diverged. At NUH, ALPI was performed with settings of 500 mW power, 100  $\mu$ m spot diameter, and 200 ms duration, followed by a definitive LPI once corneal clarity improved. At SNEC,

a trial of systemic medications, such as intravenous mannitol, or further acetazolamide was implemented. The patient charts were reviewed 1-year after APAC, and the development of raised IOP after aborting the attack was recorded and compared between centers. The cup-to-disc ratio and IOP were reviewed together with serial visual field tests to determine the incidence of progression to GON within 1-year of the attack.

## Statistical analysis

All analyses were performed using SPSS version 20 (IBM Corporation, Armonk, NY, USA) and R version 2.14.0 (R Foundation for Statistical Computing, Vienna, Austria). Mean with standard deviation (SD) were calculated for continuous variables and frequency with percentage (%) were tabulated for categorical variables.

Differences in distribution of continuous variables between SNEC and NUH were assessed using Mann–Whitney *U*-tests. Associations between categorical variables and hospitals (SNEC and NUH) were assessed using Fisher's exact tests. Online calculators developed by Daniel Soper and Richard Lowry were used for the  $3 \times 2$  and  $4 \times 2$  Fisher's exact tests, respectively.<sup>12,13</sup>

For all tests, *P*-values < 0.05 were considered statistically significant.

## Results

A total of 92 patients who presented to the two centers with APAC were studied. The demographic features of the patients are summarized in Table 1. Values are expressed as means  $\pm$  SD. Across both centers, the majority of patients were Chinese (89.1%) and female (70.7%), and the mean age was  $61.5 \pm 9.7$  years. The mean IOP at presentation was  $58.2 \pm 11.6$  mmHg and the majority of patients (80.9%) presented within 3 days

of having symptoms. The mean follow up duration was  $18.8 \pm 14$  months.

More patients who attended NUH presented within 3 days of the onset of symptoms, compared to those at SNEC, and this difference was significant ( $P = 0.037$ ). There were no significant differences in the presenting VA ( $P = 0.59$ ), IOP ( $P = 0.97$ ), time to perform LPI ( $P = 0.30$ ), or the duration to break the attack ( $P = 0.11$ ). These data are summarized in Table 2.

The differences in treatment between both centers were evaluated (Table 3). In both groups, the majority of patients were given intravenous diamox (98.1% and 95.0% at SNEC and NUH, respectively). More patients were given oral diamox in SNEC than NUH ( $P = 0.001$ ). Intravenous mannitol was given to 32.7% of patients in SNEC, whereas it was used in only one patient in NUH. In contrast, ALPI was performed on 30.0% of patients at NUH, compared to none at SNEC. The mean time to break the attack was  $18.2 \pm 32.9$  hours at SNEC and  $9.80 \pm 10.6$  hours at NUH, and this difference was not significant ( $P = 0.11$ ). There were no adverse reactions to medical treatment or immediate complications from laser treatment observed in this study.

Of the patients from NUH, 12 had ALPI, compared to 28 patients who did not (Table 4). The initial visual acuity was poorer in the ALPI group ( $P = 0.018$ ), although the initial IOP was not significantly different ( $P = 0.47$ ). The time to LPI was slower in the medically managed group (21.50 hours) than the ALPI group (11.75 hours) but this was not statistically significant ( $P = 0.516$ ). The mean time to break the attack was 8.64 hours in the group that did not have ALPI, and 12.50 hours in the group that had ALPI ( $P = 0.086$ ).

Once the attack was successfully aborted, the IOP in 19 patients from SNEC and 6 patients from NUH increased

**Table 1** Demographic characteristics of all subjects who presented with APAC

Demographics	All (n = 92)	SNEC (n = 52)	NUH (n = 40)	P-value
Age (years)*	61.5 (9.70)	62.58 (8.50)	60.10 (11.01)	0.157
Gender				
Female <sup>§</sup>	65 (70.7)	36 (69.2)	29c (72.5)	0.819
Race <sup>§</sup>				
Chinese	82 (89.1)	45 (86.5)	37 (92.5)	0.845
Malay	9 (9.8)	6 (11.5)	3 (7.5)	
Others	1 (1.1)	1 (1.9)	0 (0.0)	

**Notes:** Data presented are mean (standard deviation) or frequency (percentage), where appropriate; \*Mann–Whitney *U*-test; <sup>§</sup>Fisher's exact test.

**Abbreviations:** NUH, National University Hospital; SNEC, Singapore National Eye Centre.

**Table 2** Comparison of characteristics of the attack eye by hospital

Characteristics	SNEC (n = 52)	NUH (n = 40)	P-value
Duration of symptoms <sup>§</sup>			
$\leq 3$ days	37 (71.2%)	36 (90.0%)	0.037
$> 3$ days	15 (28.8%)	4 (10.0%)	
Initial VA of attack eye	1.05 (0.76)	0.98 (0.56)	0.590
Initial IOP	55.7 (12.1)	54.7 (12.2)	0.974
Time to LPI (hours)*	13.2 (19.8)	18.6 (27.4)	0.302
Duration to break attack (hours)*	18.2 (32.9)	9.8 (10.6)	0.109

**Notes:** Data presented as mean (standard deviation) or frequency (percentage), where appropriate; \*Mann–Whitney *U*-test; <sup>§</sup>Fisher's exact test.

**Abbreviations:** IOP, intraocular pressure; LPI, laser peripheral iridotomy; NUH, National University Hospital; SNEC, Singapore National Eye Centre; VA, visual acuity.

**Table 3** Management of patients during acute attack

Management	SNEC (n = 52)	NUH (n = 40)	P-value*
Use of IV diamox			
No	1 (1.9%)	2 (5.0%)	0.578
Yes	51 (98.1%)	38 (95.0%)	
Use of oral diamox			
No	21 (40.4%)	31 (77.5%)	0.001
Yes	31 (59.6%)	9 (22.5%)	
Use of mannitol			
No	35 (67.3%)	39 (97.5%)	<0.001
Yes	17 (32.7%)	1 (2.6%)	
Iridoplasty done			
No	52 (100.0%)	28 (70.0%)	<0.001
Yes	0 (0.0%)	12 (30.0%)	

**Notes:** Data presented are frequency (percentage); \*Fisher's exact test.

**Abbreviations:** IV, intravenous; NUH, National University Hospital; SNEC, Singapore National Eye Centre.

( $P = 0.032$ ) within 1-year (Table 5). Of these, GON developed in 13 patients from SNEC and all six patients from NUH. All patients who developed raised IOP, including patients with raised IOP after APAC and patients who developed PACG with suboptimal IOP, were first treated with topical ocular hypotensive medication.

The indication for cataract surgery in both groups was a visually significant cataract. Seventeen patients from SNEC and 13 patients from NUH had cataract surgery and there was no significant difference in the time until surgery was performed ( $P = 0.700$ ). In the group of patients who developed GON, one patient from SNEC and seven from NUH underwent combined phacoemulsification and trabeculectomy with mitomycin-C. From NUH, one patient had trabeculectomy with mitomycin-C alone, and another had combined cataract surgery with the insertion of a glaucoma drainage device.

At final review, the mean IOP of the APAC eye was  $14.8 \pm 4.3$  mmHg from SNEC and  $13.4 \pm 3.0$  mmHg from NUH. There was no significant difference in VA ( $P = 0.491$ ) or IOP ( $P = 0.224$ ) between both groups.

## Discussion

This is the first study to compare the visual outcomes following APAC with different management approaches within an Asian population with similar demographic features. In contrast to Caucasians, studies suggest poorer outcomes in Asians after APAC, with more Asians developing chronic angle closure glaucoma and eventually requiring surgical intervention.<sup>14</sup> Studies have suggested that APAC attacks damage the drainage angle and cause irreversible ischemic changes to the optic nerve head, and

**Table 4** Comparison of the management of subjects from NUH by iridoplasty status

Characteristics	Iridoplasty done		P-value
	No (n = 28)	Yes (n = 12)	
Initial VA of attack eye	0.81 (0.41)	1.37 (0.66)	0.018
Initial IOP	53.6 (11.2)	57.2 (14.6)	0.469
Duration of symptoms			
≤3 days	26 (92.9%)	10 (83.3%)	0.570
>3 days	2 (7.1%)	2 (16.7%)	
Use of IV diamox			
No	2 (7.1%)	0 (0.0%)	1.000
Yes	26 (92.9%)	12 (100%)	
Use of oral diamox			
No	21 (75.0%)	10 (83.3%)	0.697
Yes	7 (25.0%)	2 (16.7%)	
Use of mannitol			
No	27 (96.4%)	12 (100.0%)	1.000
Yes	1 (3.6%)	0 (0.0%)	
Time to LPI (hours)	21.5 (32.0)	11.8 (8.4)	0.516
Duration to break attack (hours)	8.6 (11.2)	12.5 (9.1)	0.086
Time to IOP rise			
No rise	21 (75.0%)	10 (83.3%)	1.000
≤12 months	4 (14.3%)	1 (8.3%)	
>12 months	3 (10.7%)	1 (8.3%)	
Development of raised IOP			
No	23 (71.4%)	11 (83.3%)	0.648
Yes	5 (28.6%)	1 (16.7%)	
Development of GON			
No	23 (71.4%)	11 (83.3%)	0.648
Yes	5 (28.6%)	1 (16.7%)	

**Notes:** Data presented as mean (standard deviation) or frequency (percentage), where appropriate; Mann-Whitney *U*-test or Fisher's exact test is used, where appropriate.

**Abbreviations:** GON, glaucomatous optic neuropathy; IOP, intraocular pressure; IV, intravenous; LPI, laser peripheral iridotomy; NUH, National University Hospital; SNEC, Singapore National Eye Centre; VA, visual acuity.

**Table 5** One year outcome after acute primary angle closure

Outcome	SNEC (n = 52)	NUH (n = 40)	P-value*
Development of raised IOP <sup>§</sup>			
No	33 (63.5%)	34 (77.5%)	0.032
Yes	19 (36.5%)	6 (22.5%)	
Cataract surgery			
No	35 (67.3%)	27 (67.5%)	1.000
Yes	17 (32.7%)	13 (32.5%)	
Time to cataract surgery			0.700
≤3 months	10 (58.8%)	5 (45.5%)	
>3 months	7 (41.2%)	6 (54.5%)	
Development of GON			
No	39 (75.0%)	34 (75.0%)	0.303
Yes	13 (25.0%)	6 (25.0%)	
Time to glaucoma surgery			
No surgery	51 (98.1%)	32 (80.0%)	0.011
≤12 months	1 (1.9%)	5 (12.5%)	
>12 months	0 (0.0%)	3 (7.5%)	

**Notes:** Data presented as frequency (percentage); \*P-value based on Fisher's exact test; <sup>§</sup>defined as IOP >21 mmHg.

**Abbreviations:** GON, glaucomatous optic neuropathy; IOP, intraocular pressure; NUH, National University Hospital; SNEC, Singapore National Eye Centre.



prompt therapy to abort the attack could limit the insult to these ocular structures.<sup>1-3,9</sup> Whether or not more rapid lowering of IOP with a paracentesis is superior to our more gradual reductions in the high risk Asian population has yet to be proven. It is generally considered only in recalcitrant cases, considering the technical difficulties and potential complications.

The duration from the onset to termination of APAC exposes the optic nerve to high intraocular pressures and is expected to influence outcomes in eyes with APAC. Furthermore, a study has shown that more than 50% of patients fail to respond to medical treatment during the acute attack, and patients with delayed presentation have a relative risk of 2.78 times for developing chronic glaucoma.<sup>10</sup> This suggests that a more aggressive approach with rapid IOP lowering should be advocated.

In our study, the duration of symptoms was classified into greater or less than 3 days, as a previous study showed that a mean presentation within 3 days of symptoms was associated with good visual outcome.<sup>6</sup> We found that patients who presented to SNEC had a longer duration of symptoms prior to presentation ( $P = 0.037$ ), and this was associated with the development of raised IOP that was statistically significant ( $P = 0.032$ ). However, we found that there was no significant difference in final VA or the development of GON between the two groups. Our results complement the findings of a recent study involving 42 eyes of 41 Singapore patients, which identified that delayed presentation is a risk factor for future PACG.<sup>6</sup> Although our study duration may be too short to demonstrate a difference in GON development, it is likely that raised IOP may preclude eventual progression to GON. In contrast, another study conducted in Singapore of 90 patients found that delayed presentation was not associated with the late development of chronic IOP rise or the prevalence of PACG.<sup>9</sup> However, this study did not exclude patients with preexisting glaucoma, which may confound the results. A follow up study on our group of patients would be informative.

ALPI has been shown to dramatically reduce IOP and permit corneal clearing for LPI to be performed.<sup>8,15</sup> In cases of APAC that are unresponsive to medical treatment, and LPI is prevented by corneal haze, ALPI has been shown to be effective in all cases for rapid and significant IOP reduction.<sup>16</sup> However, this approach has not shown to significantly affect outcomes, and exposes patients to procedural risks, such as corneal decompensation and iris and lens damage. The patients with recalcitrant attacks were selected for ALPI after failed medical therapy, and hence had a longer

mean duration to break the attack compared to patients who were treated medically. Increased inflammation from a combination of ALPI and LPI compared to LPI only may also be contributory. However, the time to LPI was faster in the ALPI group, which may be important during the out-of-hours setting when manpower is scarce. Of note, none of the patients in our study developed any complications after ALPI.

A comparison between the use of ALPI and systemic medications (acetazolamide  $\pm$  mannitol) found that ALPI rapidly lowered IOP compared to systemic medication in the first 2 hours of treatment, following which there was no difference in mean final IOP or a need for glaucoma medications.<sup>17</sup> Medical therapy alone was shown to successfully abort an APAC attack within 12 hours in 76.2% of patients and within 24 hours in 89.2% of patients.<sup>18</sup>

In our study, patients treated medically had a longer interval to LPI compared to the ALPI group. A possible explanation for this may be that patients who were treated medically during the out-of-hours setting had successful IOP lowering that allowed for LPI to be delayed until the next morning. However, in patients with failed medical therapy and persistently raised IOP, ALPI would provide an important window of corneal clarity when the LPI may be performed. In this case, LPI would have to be completed with relative urgency.

Although our patient numbers may be too small to detect statistically significant differences in the time taken to break an attack of APAC between the two centers ( $P = 0.11$ ), it may be considered clinically relevant as it entails prompt symptomatic relief for patients. This must be balanced against the availability of an experienced ophthalmologist who can competently perform ALPI at whatever time the APAC patient presents. Both approaches seem acceptable options and may be chosen by personal preference.

There are several limitations to our study design. This is a retrospective study with a small sample size and a short 1-year follow up duration. Despite a protocol for the initial management of APAC, patients are managed at the discretion of the onsite ophthalmologist, and thresholds for another treatment strategy may differ accordingly. Disc evaluation in the acute setting, as well as PACG diagnosis, is difficult in the context of a hazy cornea. We evaluated the optic disc once the attack was broken and the cornea was clearer. Therefore, the patients are promptly referred to the glaucoma services for further evaluation and subsequent management in the respective hospitals. The diagnoses of PACG and conversion to GON were made by glaucoma-trained

consultant ophthalmologists. Furthermore, the follow up care and documentation by different ophthalmologists was not standardized. While a similar time to cataract surgery existed in each group, it is difficult to extract the effect of this on the final outcomes as our study was inadequately powered to detect this.

In conclusion, treatment strategies in both centers were effective in aborting an APAC attack regardless of the duration of symptoms prior to treatment. However, the development of raised IOP, but not GON, was associated with a longer period of attack. Our findings validate the sense of urgency when dealing with patients with APAC as the length of attack may entail poorer outcomes. Prospective studies with longer follow up periods are needed to determine if patients with raised IOP are at risk of eventually developing GON.

## Disclosure

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