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Original Article

Mannitol plus pilocarpine for primary acute angle-closure glaucoma: efficacy and safety analysis

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Abstract: Objective: To retrospectively analyze the efficacy and safety of mannitol (MAN) combined with pilocarpine (PC) in patients with primary acute angle-closure glaucoma (PAACG). Methods: A total of 103 PAACG patients were retrospectively enrolled and assigned to either the control group (PC alone) or the research group (MAN + PC). Treatment response, safety profiles, intraocular pressure (IOP), visual acuity (VA), hemodynamic parameters (end diastolic velocity [EDV], peak systolic velocity [PSV], and resistance index [RI]), anxiety/depression, and quality of life (Short-Form 36-Item Health Survey [SF-36]) were compared between the two groups. Furthermore, factors potentially associated with therapeutic efficacy and safety were analyzed. Results: The overall response rate was significantly higher in the research group than in the control group, whereas the incidence of adverse events were comparable between the two groups. After treatment, patients in the research group showed markedly lower IOP, PSV RI, and anxiety and depression scores, as well as significantly higher VA, EDV, and SF-36 scores, compared with the control group. However, none of these variables were independently associated with treatment efficacy or safety. Conclusion: MAN combined with PC is an effective and safe therapeutic strategy for PAACG patients. This combination therapy can improve patients' quality of life, reduce IOP, enhance VA, and improve central retinal artery hemodynamics.

Keywords: Mannitol, pilocarpine, primary acute angle-closure glaucoma, efficacy and safety, quality of life

Introduction

Primary acute angle-closure glaucoma (PAACG), an acute ophthalmic disease that poses a threat to human visual acuity (VA), is characterized by sudden onset, vision loss, and irreversibility [1]. The pathogenesis of PAACG is closely related to impaired aqueous outflow between the anterior (AC) and posterior chambers due to abrupt closure of the trabecular meshwork (TM) at the AC angle or excessive pupillary block. Such obstruction can lead to a sudden increase in intraocular pressure (IOP) and secondary optic neuropathy if not treated promptly [2, 3]. Patients often develop blurred vision, corneal edema, peri-limbal halos, moderate mydriasis, sudden headache, and other clinical features, which can negatively impact normal vision, daily activities, and quality of life (QoL) to varying degrees [4, 5]. Currently, the primary surgical modalities for PAACG include trabeculectomy, laser peripheral iridotomy, and phacoemulsification [6, 7], whereas pharmacological treatment mainly focuses on lowering IOP and mitigating inflammatory reactions [8, 9]. To date, there are few studies on combined treatment of mannitol (MAN) and pilocarpine (PC) for PAACG. Therefore, this study attempts to investigate this combined therapy to address existing gaps and provide potential novel insights into PAACG management.

PC, a non-selective muscarinic receptor agonist extracted from the leaves of tropical South American shrubs of *Lasiocaryum*, can induce pupillary constriction and modulate ciliary muscle contraction [10]. By promoting ciliary muscle contraction, PC promotes TM opening and accelerates aqueous humor outflow, thereby lowering IOP [11]. However, topical PC administration is limited by low ocular bioavailability and short precorneal residence time, which further limits its efficacy [12].

MAN is a naturally occurring six-carbon sugar alcohol with high osmotic and dehydrating prop-

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erties, which can lower IOP by increasing plasma osmolality [13, 14]. In addition, MAN may improve systemic metabolism, enhance vascular flow, and alleviate ocular edema by promoting water transport within tissues [15]. Both agents have demonstrated efficacy in controlling IOP in PAACG [16]. However, the clinical outcomes and potential synergistic effects of their combination remain unclear.

This study comprehensively evaluated the combined use of MAN and PC for PAACG, comparing its efficacy, safety, IOP, visual acuity (VA), and central retinal artery hemodynamics against PC monotherapy. Meanwhile, patient QoL was assessed, and potential determinants of treatment efficacy and safety were explored. This study addresses the current gap in multidimensional assessment and factor analysis of combined treatment for PAACG, shedding light on informing clinical decision-making.

Data and methods

Patient information

This retrospective study included 103 PAACG patients admitted to Pudong Gongli Hospital, Shanghai University of Medicine & Health Sciences between April 2022 and April 2025. According to treatment regimen, patients were divided into either the control group (n=50; PC monotherapy) or the research group (n=53; MAN + PC). This study was approved by the Ethics Committee of Pudong Gongli Hospital, Shanghai University of Medicine & Health Sciences.

Inclusion criteria: Patients meeting the clinical diagnostic criteria for PAACG and confirmed to be in the acute attack phase; First episode of PAACG; IOP>32 mmHg. Exclusion criteria: Secondary glaucoma; Known allergies to the used drugs; Disorders of vital organs including liver, heart, kidney; Severe hypertension, nervous system diseases, or mental illness; Poor patient compliance or inability to cooperate with the treatment.

Methods

The control group received PC eye drops (1% concentration), 2-3 drops per application, once every 2-4 hours. On the basis of the control group, the research group received additional intravenous MAN (20% concentration) 250 mL administered over 40-60 minutes (infusion rate: 250-375 ml/h) once daily. Both groups were treated for 3 months.

Endpoints

(1) Efficacy. Criteria for assessing treatment response: complete disappearance of acute symptoms was defined as a marked response; partial disappearance of acute symptoms was defined as a response; persistence of acute symptoms after treatment was defined as a non-response. The overall response rate (ORR) = (marked response + response cases)/total cases *100%.

(2) Safety. Adverse reactions including conjunctival congestion, eye pain, eye itching, eye dryness were recorded, and the incidence of adverse events was calculated. Ophthalmic adverse events were graded according to established criteria [17]. Mild: minimal symptoms not requiring drug discontinuance or intervention; Moderate: obvious symptoms affecting daily life, requiring local medication; Severe: intolerable symptoms requiring drug discontinuance or causing serious complications.

(3) IOP. IOP was measured pre- and post-treatment using a Goldmann applanation tonometer.

(4) VA. Best corrected visual acuity (BCVA) was assessed before and after treatment using a standard logarithmic VA chart. After optimal refractive correction was achieved through subjective refraction with trial lenses, BCVA was recorded as a decimal number.

(5) Hemodynamic parameters (HDPs). Pre- and post-treatment end diastolic velocity (EDV), peak systolic velocity (PSV), and resistance index (RI) of the central retinal artery were measured using a color Doppler ultrasound system (7-12 MHz). Patients were instructed to lie supine with eyes closed lightly. The central retinal artery, located adjacent to the optic nerve, was identified to measure PSV and EDV. RI was calculated using the formula: RI = (PSV - EDV)/PSV. Each hemodynamic index was measured three times consecutively, with the mean taken as the final measurement value. All measurements and image analyses were performed by

Table 1. Comparison of baseline characteristics between the two treatment groups

Indicators	Control group (n=50)	Research group (n=53)	χ^2/t/Z	*P*
Age (years)	58.32±7.12	57.25±9.99	0.623	0.535
Sex (male/female)	24/26	22/31	0.439	0.508
Disease course (d)	2.00 (2.00, 3.00)	3.00 (2.00, 3.00)	-1.624	0.104
Intraocular pressure (mmHg)	35.63±5.18	36.32±5.88	0.630	0.530
Marital status (married/unmarried)	39/11	35/18	1.820	0.177
Residence (rural/urban)	18/32	14/39	1.104	0.294

Table 2. Comparison of treatment response between the two treatment groups

Indicators	Control group (n=50)	Research group (n=53)	*P*
Marked response	22 (44.00)	32 (60.38)	
Response	15 (30.00)	17 (32.08)	
Non-response	13 (26.00)	4 (7.55)	
Overall response	37 (74.00)	49 (92.45)	0.016

the same sonographer blinded to patient allocation and treatment outcomes.

(6) Psychological status. Patient anxiety and depression were assessed using the Self-Rating Anxiety/Depression Scale (SAS/SDS) before and after treatment. Both scales contain 20 items with a maximum score of 80 points. Higher scores indicate more severe depression and anxiety.

(7) Quality of Life (QoL). QoL was evaluated using the Short-Form 36-Item Health Survey (SF-36), covering mental health, social functioning, physical health, and environment, with a maximum of 100 points per item. Higher scores indicate better QoL. The Chinese-version SF-36 has been verified for its reliability and validity in the Chinese population, with a Cronbach's alpha range of 0.72-0.88 across domains, demonstrating good internal consistency [18].

Statistical analysis

All statistical analyses were conducted using SPSS version 22.0. Continuous variables were expressed as mean ± standard deviation (SD). Between-group comparisons were performed using the independent samples t-test, while within-group comparisons were assessed using the paired t-test. Categorical variables were expressed as counts and percentages (n, %), and comparisons between groups were made using the χ^2 test or Fisher's exact test (applied when the expected frequency was less than 5). Potential determinants of therapeutic efficacy and safety were identified using univariate and multivariate logistic regression analyses (Enter method), with collinearity diagnostics performed prior to model construction. A two-tailed *P*-value of <0.05 was considered statistically significant.

Results

Baseline characteristics

Comparisons of baseline characteristics, including age, sex, disease course, IOP, marital status, and place of residence, revealed no significant inter-group differences (*P*>0.05, **Table 1**), indicating good baseline comparability.

Treatment response

The overall response rate (ORR) was 92.45% in the research group, significantly higher than 74.00% in the control group (*P*<0.05, **Table 2**).

Safety profile

The overall incidence of adverse events, including conjunctival congestion, ocular pain, eye itching, and eye dryness, was 5.66% in the research group, which was compared to 12.00% in the con group (*P*>0.05; **Table 3**). All adverse events were mild and transient and resolved spontaneously after drug discontinuation or symptomatic treatment.

IOP and VA

No significant differences were identified in pre-treatment IOP or VA between the two

Table 3. Comparison of safety profile between the two treatment groups

Indicators	Control group (n=50)	Research group (n=53)	*P*
Conjunctival congestion	2 (4.00)	0 (0.00)	
Ocular pain	1 (2.00)	1 (1.89)	
Eye itching	2 (4.00)	1 (1.89)	
Eye dryness	1 (2.00)	1 (1.89)	
Total	6 (12.00)	3 (5.66)	0.310

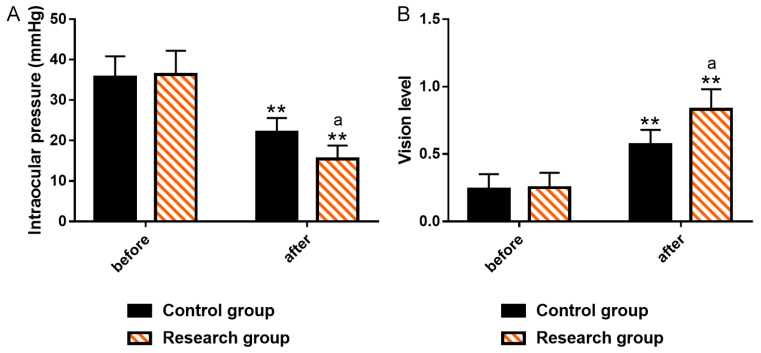

Figure 1. (A) Comparison of intraocular pressure and (B) visual acuity between the two treatment groups. Note: **P<0.01, vs. before treatment; P<0.05 vs. Control.

groups (P>0.05). Following treatment, IOP decreased significantly while VA improved significantly in both groups (both P<0.01). Notably, the magnitudes in IOP and VA changes were more pronounced in the research group compared with the control group (P<0.05; **Figure 1**).

HDPs

No significant differences were identified between the two groups in baseline hemodynamic parameters, including EDV, PSV, and RI (P>0.05). After treatment, EDV increased significantly in both groups, with a significantly higher post-treatment EDV observed in the research group (P<0.05). In contrast, PSV and RI decreased significantly after treatment, with significantly lower levels observed in the research group (both P<0.05; **Figure 2**).

Psychological status

Baseline SAS/SDS scores were comparable between the two groups (P>0.05). Following treatment, both SAS and SDS scores decreased significantly in each group (P<0.05), with significantly lower post-treatment scores observed in the research group (P<0.05; **Figure 3**).

QoL

As shown in **Figure 4**, post-treatment SF-36 scores in all assessed domains, including mental health, social functioning, physical health, and environmental health, were significantly higher in the research group than the control group (all P<0.05).

Determinants of therapeutic efficacy and safety in PAACG patients

According to treatment outcomes, patients were allocated into an ineffective-or-unsafe group (n=21) and an effective-and-safe group (n=82). Univariate analysis identified age, disease duration, pre-treatment IOP, pre-treatment VA, pre-treatment RI, and therapeutic method as factors significantly associated with treatment efficacy and safety (P<0.05). However, all these variables failed to reach statistical significance in the subsequent multivariate analysis (P>0.05). Collinearity diagnostics showed that the variance inflation factor (VIF) values for all included variables was below 2, suggesting no significant multicollinearity (**Tables 4**, **5**).

Discussion

Primary acute angle-closure glaucoma (PAACG) affects approximately 20 million people globally and occurs predominantly in women and individuals aged 60-69 years [19, 20]. Although treatment strategies, including elimination of pupillary block, widening of anterior chamber angle, and reduction of peripheral anterior synechiae, are effective in controlling disease, some patients still require adjunctive drug intervention or additional surgical intervention to achieve satisfactory disease control [21]. This study seeks to identify safe and effective medical therapies for PAACG patients, thereby improving clinical outcomes.

In the present study, the ORR was significantly higher in the research group compared with the control group (92.45% vs. 74.00%), indicating

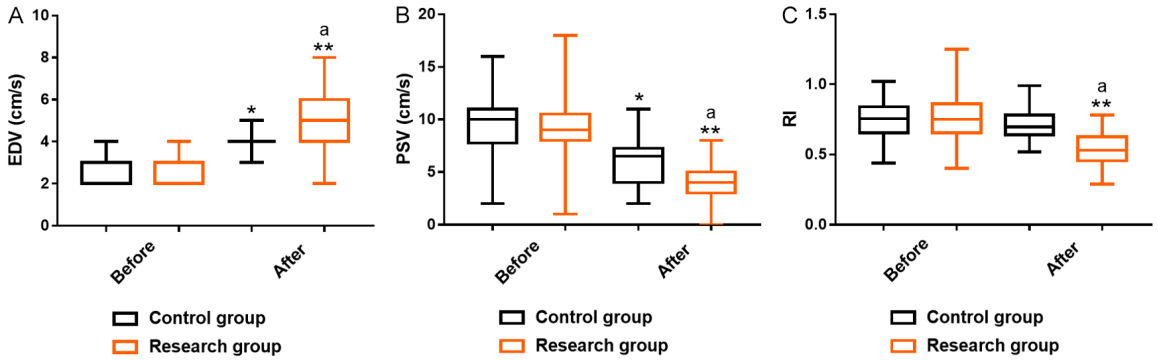

Figure 2. Comparison of HDPs between the two treatment groups. A. EDV. B. PSV. C. RI. Note: **P*<0.05 and ***P*<0.01, vs. before treatment; *P*<0.05 vs. control group. HDPs, Hemodynamic parameters; EDV, end diastolic velocity; PSV, peak systolic velocity; RI, resistance index.

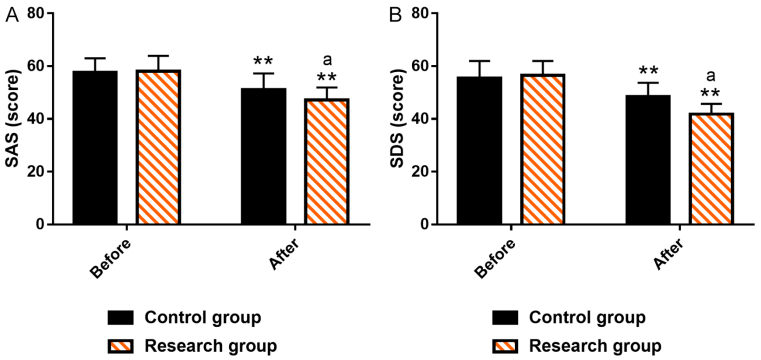

Figure 3. Comparison of psychological status of patients between the two treatment groups. A. SAS. B. SDS. Note: **P*<0.05 and ***P*<0.01 *vs.* before treatment; *P*<0.05 *vs.* Control. SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale.

that combination therapy provides superior clinical efficacy than PC monotherapy in PAACG patients. Yen CY et al. [22] reported that PC administration following laser peripheral iridotomy effectively reduced disease recurrence without causing significant discomfort or major complications, supporting the clinical utility and safety of PC in angle-closure glaucoma management.

Although the total incidence of adverse events was lower in the research group (5.66% vs. 12.00%), it didn't reach statistical significance. Furthermore, all adverse events observed in this study were mild and transient. Previous studies have shown that prolonged administration, high doses, or rapid intravenous infusion of MAN may increase the risk of side effects [23, 24]. The favorable safety profile observed in the present study may be related to the low dose used and the reasonable control of the intravenous injection rate. Similarly, Liang Z et al. [25] reported that preoperative intravenous MAN injection in patients with primary angle-closure glaucoma reduced intraoperative complications and improved postoperative outcomes, further supporting the clinical safety and therapeutic value of MAN.

Elevated IOP is a hallmark of PAACG and is primarily influenced by factors such as aqueous humor production, aqueous humor outflow resistance, and episcleral venous pressure. Sustained elevation of IOP may lead to irreversible optic nerve damage and permanent vision impairment [26-28]. Therefore, rapid IOP reduction and visual function preservation are critical in PAACG treatment. In this study, both treatment groups exhibited significant reductions in IOP and improvements in VA after treatment, with more pronounced improvements observed in the research group. These findings suggest that the combination of MAN and PC provides enhanced control of IOP and superior recovery of visual function. PC, while effectively opening the anterior chamber angle for PAACG, can work collaboratively with MAN to further enhance anti-PAACG efficacy. Echoing our results, a prospective study shows that MAN used in vitrectomy and non-vitrectomy patients also has a significant effect on reducing IOP [30]. However, Chen L et al. [29] reported different findings that PC reduced IOP in healthy individ-

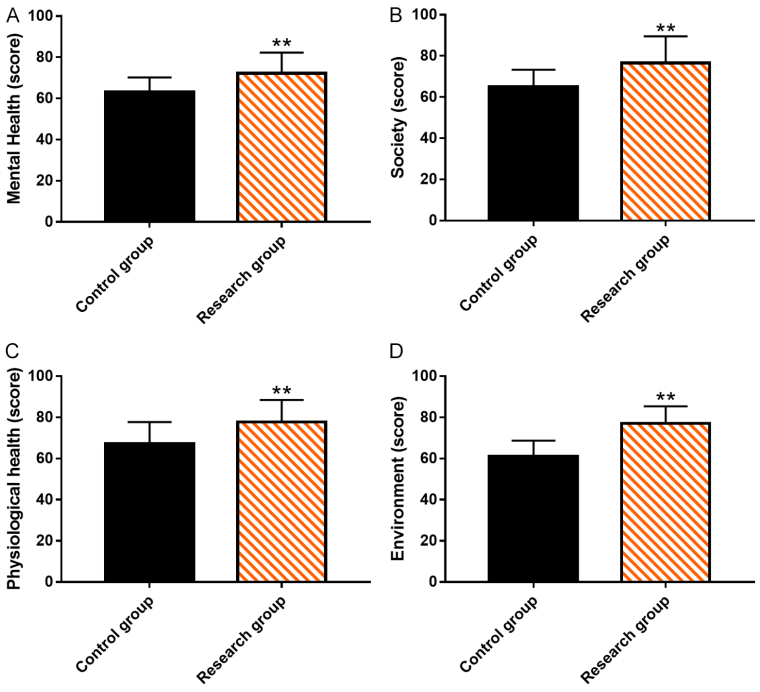

Figure 4. Comparison of quality-of-life scores between the two treatment groups. A. Mental health. B. Social functioning. C. Physiological health. D. Environment health. Note: **P<0.01 vs. Control.

uals but did not significantly affect patients with primary open-angle glaucoma (POAG). This discrepancy may be attributable to differences in disease pathophysiology. Unlike PAACG, POAG is primarily characterized by chronic dysfunction of aqueous outflow pathways rather than acute angle closure and pupillary block.

Central retinal artery hemodynamics were evaluated for both groups in this study. The post-treatment EDV was markedly increased while the PSV and RI were significantly reduced in the research group compared with the baseline and the control group, suggesting that the combined treatment was superior in improving hemodynamics in PAACG patients. As reported by Montazeri K et al. [14], MAN may contribute to hemodynamic stabilization while effectively reducing IOP, which is consistent with our observations.

Psychological assessment further proved that the combined MAN and PC treatment was associated with more pronounced reduction in anxiety and depression scores than PC monotherapy. Quality-of-life analysis revealed significantly better post-treatment outcomes in the combined treatment group, as evidenced by significantly higher SF-36 scores across all assessed domains, including mental health, social functioning, physiological health, and environment health. These findings suggest that the advantages of MAN + PC therapy extend beyond physiological improvement and may positively influence broader patient-centered outcomes.

Finally, none of the indices included in this study were identified as significant independent correlates of therapeutic efficacy and safety in PAACG patients. However, the marginal significance observed for therapeutic method (P= 0.052), disease duration, and pre-treatment VA≥0.24 may serve as promising protective factors for clinical outcomes, whereas a prolonged disease duration exceeding 2 days may be, to some extent, associated with an increased risk of adverse outcomes. These observations warrant further validation in studies with larger sample sizes. Furthermore, the limited sample size of this study (n=103), with only 21 cases in the ineffective-or-unsafe group, likely resulted in insufficient statistical power to detect independent effects. To account for these limitations, statistical thresholds were adjusted for clinical interpretation: variables with univariate P<0.05 and multivariate P<0.10 were considered trend factors. Consequently, therapeutic method, disease duration, and pre-treatment VA were interpreted as potential trend factors, despite not reaching conventional significance in multivariate analysis. Overall, the loss of significance for predictors identified in univariate analysis primarily reflects the inherent clinical complexity, including collinearity among key factors (e.g., age, disease course, VA, and IOP), rather than a contradiction in the data. Hence, the above findings underscore the need for cautious interpretation and larger, adequately powered studies to clarify independent determinants of treatment efficacy and safety in PAACG.

Several limitations of this study should be acknowledged. First, no cost-benefit analysis

Table 4. Univariate analysis of factors associated with composite treatment outcomes in patients with primary acute angle-closure glaucoma

Indicators	Ineffective-or-unsafe group (n=21)	Effective-and-safe group (n=82)	χ^2	*P*
Age (years)			5.063	0.024
<57 (n=47)	5 (23.81)	42 (51.22)		
≥57 (n=56)	16 (76.19)	40 (48.78)		
Sex			0.460	0.497
Male (n=46)	8 (38.10)	38 (46.34)		
Female (n=57)	13 (61.90)	44 (53.66)		
Disease duration (d)			7.322	0.007
≤2 (n=61)	7 (33.33)	54 (65.85)		
>2 (n=42)	14 (66.67)	28 (34.15)		
Marital status			1.288	0.256
Married (n=74)	13 (61.90)	61 (74.39)		
Unmarried (n=29)	8 (38.10)	21 (25.61)		
Residence			1.712	0.191
Rural area (n=32)	9 (42.86)	23 (28.05)		
City (n=71)	12 (57.14)	59 (71.95)		
Pre-treatment intraocular pressure (mmHg)			4.628	0.031
<36.5 (n=51)	6 (28.57)	45 (54.88)		
≥36.5 (n=52)	15 (71.43)	37 (45.12)		
Pre-treatment visual acuity			5.531	0.019
<0.24 (n=50)	15 (71.43)	35 (42.68)		
≥0.24 (n=53)	6 (28.57)	47 (57.32)		
Pre-treatment EDV (cm/s)			0.691	0.406
<3.00 (n=27)	7 (33.33)	20 (24.39)		
≥3.00 (n=76)	14 (66.67)	62 (75.61)		
Pre-treatment PSV (cm/s)			0.336	0.562
<9.00 (n=40)	7 (33.33)	33 (40.24)		
≥9.00 (n=63)	14 (66.67)	49 (59.76)		
Pre-treatment RI			4.628	0.031
<0.75 (n=51)	6 (28.57)	45 (54.88)		
≥0.75 (n=52)	15 (71.43)	37 (45.12)		
Therapeutic method			5.531	0.019
Pilocarpine (n=50)	15 (71.43)	35 (42.68)		
Mannitol + pilocarpine (n=53)	6 (28.57)	47 (57.32)		

Note: EDV, end diastolic velocity; PSV, peak systolic velocity; RI, resistance index.

was performed. Future studies should compare the cost benefit of the combined therapy with conventional treatments, such as laser peripheral iridectomy and trabeculectomy, to evaluate its economic feasibility and clinical applicability. Second, long-term follow-up data were unavailable. Prospective studies with extended follow-up periods (>3 years) are warranted for evaluating long-term efficacy, safety, and prognosis associated with this treatment strategy. Third, the stratified applicability of this combination therapy across patients with different disease severities remains unclear. Fourth, this was a retrospective study based on consecutively enrolled patients, and no formal sample size calculation was performed before patient inclusion. Future prospective studies with rigorous sample size estimation are therefore required to validate the present findings. Fifth, detailed information regarding the onset, duration, and causality assessment of adverse events was unavailable, limiting the compre-

Table 5. Multivariate logistic regression analysis of factors associated with composite treatment outcomes in patients with primary acute angle-closure glaucoma

Indicators	B	SE	WALD	P	OR	95% CI
Age (years)	0.975	0.629	2.402	0.121	2.650	0.773-9.088
Disease duration (d)	1.118	0.596	3.520	0.061	3.059	0.951-9.834
Pre-treatment intraocular pressure (mmHg)	0.783	0.616	1.615	0.204	2.189	0.654-7.327
Pre-treatment visual acuity	-1.098	0.607	3.277	0.070	0.333	0.102-1.095
Pre-treatment RI	0.944	0.608	2.413	0.120	2.570	0.781-8.454
Therapeutic method	-1.175	0.606	3.766	0.052	0.309	0.094-1.012

Note: RI, resistance index; SE, Standard Error; OR, Odds Ratio; CI, Confidence Interval.

hensiveness of the safety evaluation. Finally, the retrospective non-randomized design may have introduced selection bias. In addition, the relatively small sample size (103 cases, only 21 positive events) may have limited the statistical power of the multivariate analyses. Therefore, multi-center, large-scale prospective studies are warranted to further verify the findings in this study.

Conclusion

MAN combined with PC demonstrated favorable treatment outcome and safety in PAACG patients. Compared with PC monotherapy, the combination therapy effectively reduced IOP, improved VA, enhanced central retinal artery hemodynamics, alleviated anxiety and depression, and improved quality of life. These findings suggest that MAN combined with PC may represent a promising therapeutic option for PAACG management. Additionally, therapeutic method, disease duration, and pre-treatment VA showed potential associations with therapeutic outcomes, although they failed to reach statistical significance in multivariate analyses. Future studies with larger sample sizes and prospective designs are needed to confirm these observations.

Disclosure of conflict of interest

None.

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