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Ophthalmologic Nursing of Valproic Acid Combined with Dexamethasone for Patients with Glaucoma

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Abstract

Objective: This study aimed to evaluate the therapeutic effect of valproic acid (VPA) with or without dexamethasone (DEX) on patients with glaucoma.

Materials and Methods: A total of 346 patients with glaucoma (with an intraocular pressure <16 mmHg) were recruited in the first branch of Mudanjiang Medical University Affiliated Hongqi Hospital. Patients with glaucoma at least one eye received placebo (n=84), VPA (n=88, 500 mg per day), DEX (n=85, 0.7 mg per day) or VPA-DEX (n=89) for 3 months continued on glaucoma therapy. Blood VPA concentrations, best-corrected visual acuity (BCVA), retinopathy study (RS), Retinal vein occlusion (RVO), mean of visual fields, log of the minimum angle of resolution (LogMAR) visual acuity, and multifocal electroretinogram (ERG) and central retinal thickness (CRT) were used compared the therapeutic efficacy of VPA-DEX.

Results: Outcomes showed that VPA-DEX, VPA and DEX showed better BCVA, RVO and improvement than placebo during 3 months treatment. Median LogMar visual acuity, the multifocal ERG (Latency and amplitudes) and mean deviation on visual fields were significantly improved by VPA-DEX compared to VPA, DEX and placebo group. The most common treatment-emergent adverse events were increased and hypertension intraocular pressure (IOP).

Conclusion: Ophthalmologic nursing of VPA-DEX results in improvements of visual acuity in patients with glaucoma. Treatment of VPA-DEX is safe and efficacy in improving BCVA and RVO, which provides benefits in patients with RVO.

Keywords: Glaucoma; Valproic acid; Dexamethasone; BCVA; RVO

Introduction

Glaucoma is a chronic eye disease and worldwide leading cause of irreversible vision loss [1]. Glaucoma is one of leading causes of blindness and visual impairment, which is age-related and thus affects quality of life [2]. Impaired microcirculation at the level of the optic nerve head is regarded as one of the main mechanisms of pathogenesis of glaucoma and may be accelerated as a result of glaucoma surgery [3]. In addition, patients with glaucoma have been shown to have progression of visual function despite intraocular pressure (IOP) control [4]. Furthermore, although many glaucoma medications are developed, more efficient treatments need to explore to improve the symptoms of glaucoma.

Valproic acid (VPA) has been shown to improve collagen and contrast threshold sensitivities in clinical patients [5]. VPA has been widely used to human diseases, such as mood disorders, epilepsy, migraines, neuropathic pain and glaucoma [6]. Previously, VPA exerts therapeutic efficacy

by regulating glutamate neurotransmissions, gamma-aminobutyric acid, pro-survival protein kinases and histone deacetylase [7]. In addition, oral VPA improves visual acuity in patients with advanced glaucoma in a prospective randomized study [8]. Furthermore, VPA has been shown to reduce muscle collagen content and renal fibrosis and cutaneous radiation syndrome [9]. However, the efficacy of single treatment of VPA is limited and needs further investigate in patients with glaucoma.

Dexamethasone (DEX) therapy has been used to reduce inflammation, improve structural complications and long-term visual loss in patients with uveitis [10]. DEX has a favorable safety profile by controlling IOP for patients with glaucoma [11]. DEX implant will rise the short-term IOP, but it is safe and acceptable in patients with glaucoma or ocular hypertension [12]. In addition, a previous study has been identified the tolerance of intravitreal DEX in patients glaucoma, and the results show that DEX is well tolerance [13]. Furthermore, DEX medical intervention can be performed in patients with glaucoma by reduction of IPO and improvement of visual acuity in patients with glaucoma [14]. However, clinical efficacy and safety profile of DEX should further analyze in patients with glaucoma.

The purpose of this study was to examine the clinical efficacy and safety profile of ophthalmologic nursing of VPA combined with DEX for patients with glaucoma. This study also prospectively examined whether combined treatment of VPA and DEX could improve the BCVA, LogMAR visual acuity, mean deviation on visual fields, and multifocal ERG and CRT on optical coherence tomography in patients with glaucoma.

Material and Methods

Study Design

This randomized, placebo-controlled 3-month clinical trials was used to analyze the treatment effects of DEX (0.7 mg/day) and/or VPA (500 mg/day) in patients with glaucoma. Patients (n = 364) with glaucoma were enrolled at Department of 2nd ophthalmology in The First Branch of Mudanjiang Medical University Affiliated Hongqi Hospital between May 2017 and July 2019. The exclusion criteria included as follow:

1. History of glaucoma;
2. Ischemic RVO;
3. Intraocular surgery or laser therapy;
4. Bacterial, fungal, viral or parasitic infection.

Inclusion criteria included as follow:

1. age >18 years;
2. intraocular pressure <16 mmHg;
3. BCVA score more than 34 letters.

The protocols in this study were approved by an Ethics Committee of The first branch of Mudanjiang Medical University Affiliated Hongqi Hospital. All patients provided written informed consent (NCT01660802).

Study Treatment

A total of 346 patients with glaucoma received placebo (n=84), VPA (n=88), DEX (n=85) or VPA-DEX (n=89) for 3 months continued therapy. Patients received study treatment and assigned to 0.7 mg of intravitreal injection of DEX by using a single-use applicator system. Type of VPA (500) therapy for glaucoma patients was oral.

Outcomes Measures

The mean change in LogMAR visual acuity from baseline during 3 months was evaluated measured using the ETDRS. The mean CRT changes for all patients were evaluated using optical coherence tomography. Key safety evaluations for each patient included biomicroscopy/ophthalmology, IOP and treatment-emergent adverse events (TEAEs). TEAEs included onset or an increase in severity or any serious adverse event after receive treatment with VPA and/or DEX. All patients were visited by investigators every 15 days from baseline.

Statistical Analysis

Data are shown as mean± standard deviation (SD) or number (%). The SPSS software (version 17.0, Chicago IL, USA) was used for statistical analysis. The baseline characteristics between the groups were compared using independent t-test, Chi-square, or Mann-Whitney U test. The median visual acuity was analyzed used the Wilcoxon Signed-rank test. A p value less than 0.05 was considered statistically significant.

Results

Characteristic of Patients With Glaucoma

Glaucomatous patients were randomized to treatment with placebo (n=84), VPA (n=88), DEX (n=85) or VPA-DEX (n=89) for 3-month therapy. Characteristics of patients with glaucoma are shown in (Table 1). The percentage of male patients (n=198) was more than female patients [198 (57.2%) vs. 148 (42.8%)] among 346 glaucomatous patients. The percentage of male and female patients was approximate equal.

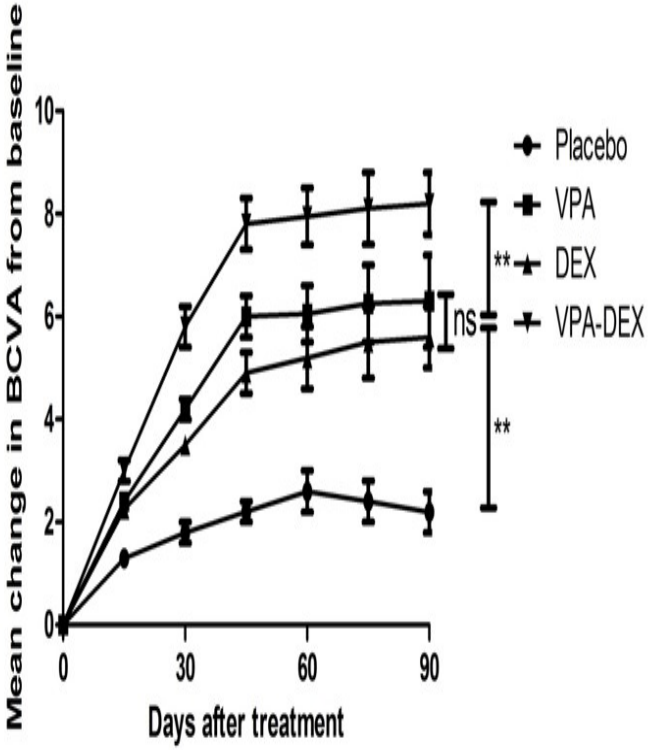

*Figure 1: Mean change in BCVA from baseline. **p < 0.01. Data are shown as mean± standard deviation (SD). DEX, dexamethasone; VPA, valproic acid; BCVA, best-corrected visual acuity.*

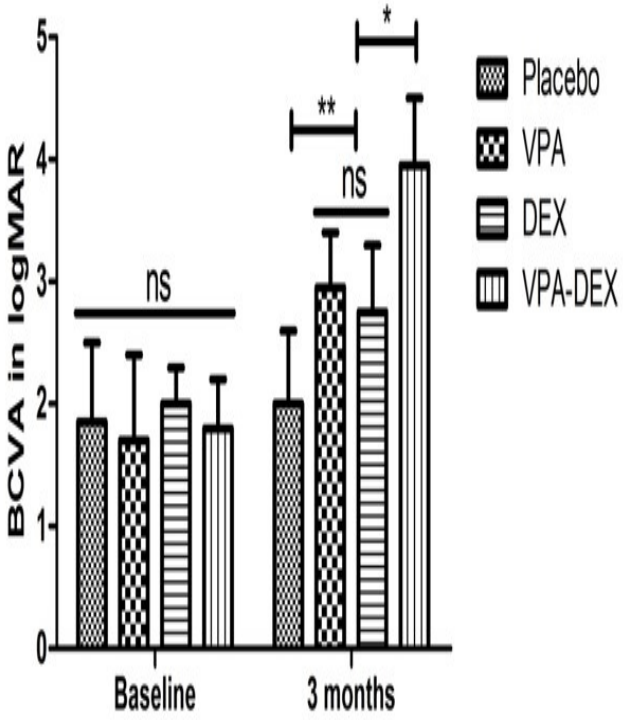

*Figure 2: Log of the minimum angle of resolution best-corrected (BVCA) visual acuity over time in VPA, DEX, VPA-DEX and placebo. **p<0.01. Data are shown as mean± standard deviation (SD). DEX, dexamethasone; VPA, valproic acid; BCVA, best-corrected visual acuity.*

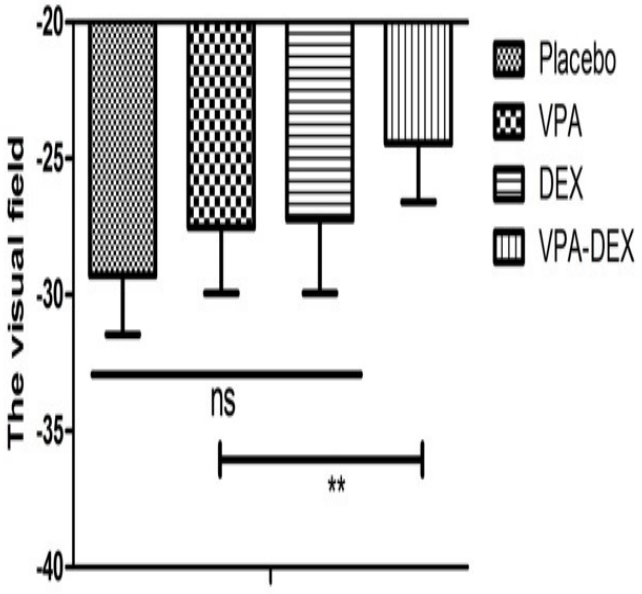

*Figure 3: The visual field mean deviation on month 3 after receiving treatment of VPA and/or DEX. **p<0.01. Data are shown as mean± standard deviation (SD). DEX, dexamethasone; VPA, valproic acid.*

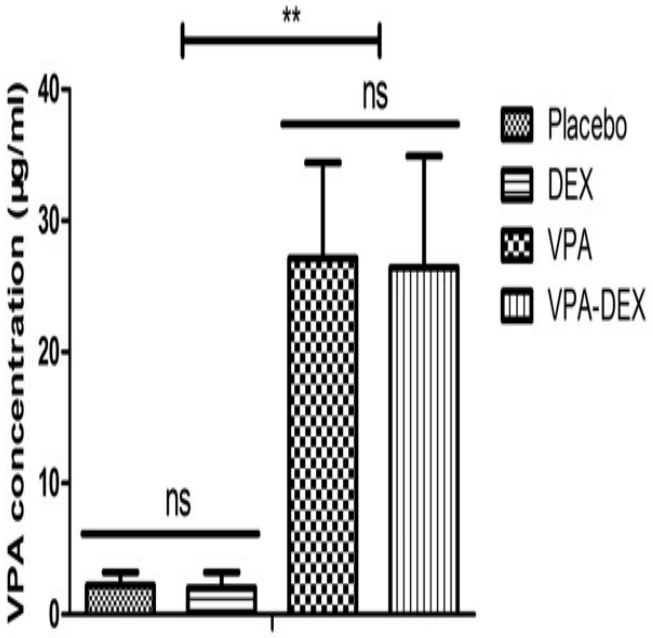

*Figure 4: Concentration level of blood VPA measured on month 3 after therapy. **p<0.01. VPA, valproic acid.*

Table 1: Characteristics of patients with glaucoma.

	Placebo	VPA	DEX	VPA-DEX
Number	84 (24.3%)	88 (25.4%)	85 (24.6%)	89 (25.7%)
Male	46 (13.3%)	51 (14.7%)	47 (13.6%)	54 (15.6%)
Female	38 (11.0%)	37 (10.7%)	38 (11.0%)	35 (10.1%)
Age (years)	51.2 ± 10.4	52.5 ± 11.6	50.6 ± 9.5	52.6 ± 11.2
Visual acuity	0.4 ± 0.2	0.4 ± 0.1	0.5± 0.2	0.4 ± 0.2
IPO (mm Hg)	14.6± 2.4	14.8± 3.0	14.2± 2.8	14.9± 2.6
Visual fields	-28.8 ± 3.6	-28.4 ± 4.6	-28.5 ± 3.4	-28.2 ± 4.0
BCVA (letters)	51.6 ± 11.2	53.0 ± 12.5	52.4 ± 10.8	52.2 ± 11.5
CRT (μm)	682 ± 102	688 ± 112	690 ± 124	693 ± 108

Table 2: Treatment-emergent adverse events during the 3-month treatment.

	Placebo	VPA	DEX	VPA-DEX
IOP increased	20 (23.8%)	24 (23.8%)	22 (23.8%)	26 (23.8%)
Conjunctival hemorrhage	10 (11.9%)	11 (12.5%)	13 (15.3%)	14 (15.7%)
Conjunctival hyperemia	11 (13.1%)	13 (14.8%)	15 (17.6%)	16 (18.0%)
Visual acuity reduced	3 (3.6%)	5 (5.7%)	4 (4.7%)	6 (6.7%)
Conjunctival edema	2 (2.4%)	3 (3.4%)	4 (4.7%)	4 (4.5%)
Ocular hypertension	4 (4.8%)	5 (5.7%)	3 (3.5%)	4 (4.5%)
Eye pain	6 (7.1%)	7 (8.0%)	6 (7.1%)	8 (9.0%)
Headache	4 (4.8%)	2 (2.3%)	1 (1.2%)	4 (4.5%)
Vitreous hemorrhage	5 (6.0%)	3 (3.4%)	4 (4.7%)	6 (6.7%)

Efficacy Outcomes

The therapeutic efficacy of VPA-DEX was investigated in this study. As shown in (Figure 1), VPA-DEX significantly improved the mean change in BCVA from baseline compared to VPA, DEX and placebo ($p<0.01$). The median logMAR BCVA was higher in VPA-DEX group than those patients received VPA, DEX and placebo treatment (0.45 vs. 0.30, 0.20 and 0.18, respectively) (Figure 2). The visual field mean deviation on month 3 were −29.86 ± 2.56, −27.45 ± 2.35, −27.24 ± 2.70, −24.44 ± 2.15 at 3 months in VPA-DEX, VPA, DEX and placebo group, respectively, which was statistically significant changes noted in VPA-DEX, VPA, DEX compared to placebo group (Figure 3). No significant improvements were observed in the multifocal ERG (Latency and amplitudes) and CRT on optical coherence tomography in VPA-DEX, VPA and DEX group.

Safety Outcomes and Adverse Effects

Treatment-emergent adverse events (TEAEs) were recorded during 3 months period. The outcomes in (Figure 4) demonstrated that the mean serum levels of VPA at 3 months were 26.2 ± 8.4, 25.8 ± 8.8, 26 ± 8.9, 26 ± 8.9 μg/ml in VPA-DEX, VPA and DEX group, respectively. During the period of treatment, the most common TEAEs were conjunctival hemorrhage, conjunctival hyperemia and increased IOP (Table 2). No other TEAEs were observed and no patients received cataract surgery during the study.

Discussion

Clinical studies have shown beneficial effect of DEX in patients with glaucoma [15]. A previous study identified that 3-month VPA therapy increased visual acuity in patients with advanced glaucoma [8]. In the present study,

we analyzed the therapeutic efficacy of VPA-DEX in patients with glaucoma in 3-month period. Here, we found that a 3 months VPA-DEX therapy markedly improved the visual acuity and visual field in patients with glaucoma. Notably, VPA-DEX significantly improved the mean change in BCVA, the median logMAR BCVA and the visual field mean deviation from baseline at 3 months compared to VPA, DEX and placebo group. Importantly, the benefits of VPA-DEX treatment provide the potential application for patients with glaucoma.

Data have found that VPA could improve visual function in patients with advanced stage glaucoma [8]. Adjuvant VPA treatment improved saccadic eye movements in schizophrenia [16]. Outcomes in this study demonstrated that VPA treatment significantly improved the mean change in BCVA, the median logMAR BCVA and the visual field mean deviation compared to placebo. However, no significant improvements were observed in the multifocal ERG, the mean deviation, and CRT on optical coherence tomography among VPA, DEX and placebo groups. Probably, the beneficial effects of VPA could be more pronounced in patients with glaucoma.

DEX treatment could use to anti-glaucoma medications and manage patients with glaucoma [14]. Short-term safety of DEX implant for treatment of macular edema due to retinal vein occlusion, in eyes with glaucoma or treated ocular hypertension has been clarified in clinic [12]. Intravitreal injection of DEX 0.7 mg might be as a potent method for the prevention of secondary glaucoma, which is clinical safety in a long-term treatment [17]. Outcomes in this study found that DEX treatment significantly improved the symptoms of glaucoma compared to placebo. No significant differences were observed between DEX and VPA groups in improvements of the visual field mean deviation and the mean change in BCVA.

Clinically, DEX treatment seems to be equally effective as acetazolamide-DEX in the treatment of glaucoma [11]. In this study, we found that DEX-VPA treatment presented better outcomes than either DEX or VPA in patients with glaucoma. Pharmacokinetics analysis of DEX-VPA showed that DEX-VPA was safe and acceptable in clinical glaucoma patients. The most common TEAEs were conjunctival hemorrhage, hyperemia and increased IOP. None of the patients received DEX and/or VPA showed unacceptable adverse effects and received cataract surgery in our study. Interestingly, DEX-VPA provided best outcomes in improving the mean change in BCVA, the median logMAR BCVA and the visual field mean deviation than DEX, VPA and placebo.

Conclusion

Data in this study indicate that ophthalmologic nursing DEX-VPA therapy can be beneficial for improving glaucomatous symptoms and visual function in patients with glaucoma, which may be an idea therapeutic schedule. However, more clinical investigations should perform to help in further confirmation of the findings of our study.

Conflicts Of Interest

There are no conflicts of interest.

References

1. Peralta E, Muir KW and Rosdahl JA (2018) Systematic Review of Knowledge Assessments for Glaucoma Patients. Seminars in ophthalmology 33: 377-388.
2. Nag A, Lu H, Arno M (2017) Evaluation of the Myocilin Mutation Gln368Stop Demonstrates Reduced Penetrance for Glaucoma in European Populations. Ophthalmology 124: 547-553.
3. Kaushik S, Joshi G and Pandav SS (2018) Pathogenesis and surgical resolution of acute hydrops in primary congenital glaucoma. Clinical & experimental ophthalmology 46: 569-570.
4. Guo R, Shen W, Su C, Jiang S and Wang J (2017) Relationship between the Pathogenesis of Glaucoma and miRNA. Ophthalmic research 57: 194-199.
5. Buchheit T, Hsia HJ, Cooter M (2019) The Impact of Surgical Amputation and Valproic Acid on Pain and Functional Trajectory: Results from the Veterans Integrated Pain Evaluation Research (VIPER) Randomized, Double-Blinded Placebo-Controlled Trial. Pain Med 20(10): 2004-2017.
6. Seet LF, Toh LZ, Finger SN, Chu SWL and Wong TT (2019) Valproic acid exerts specific cellular and molecular anti-inflammatory effects in post-operative conjunctiva. J Mol Med (Berl) 97: 63-75.
7. Kimura A, Guo X, Noro T (2015) Valproic acid prevents retinal degeneration in a murine model of normal tension glaucoma. Neuroscience letters 588: 108-113.
8. Mahalingam K, Chaurasia AK, Gowtham L (2018) Therapeutic potential of valproic acid in advanced glaucoma: A pilot study. Indian journal of ophthalmology 66: 1104-1108.
9. Seet LF, Toh LZ, Finger SN, Chu SW, Stefanovic B, et al. (2016) Valproic acid suppresses collagen by selective regulation of Smads in conjunctival fibrosis. J Mol Med (Berl) 94: 321-334.
10. Ahn SJ, Joung J, Lee SH and Lee BR (2018) Intravitreal dexamethasone implant therapy for the treatment of cystoid macular Oedema due to hydroxychloroquine retinopathy: a case report and literature review. BMC ophthalmology 18: 310.
11. Lorenz K, Wasielica-Poslednik J, Bell K (2017) Efficacy and safety of preoperative IOP reduction using a preservative-free fixed combination of dorzolamide/timolol eye drops versus oral acetazolamide and dexamethasone eye drops and assessment of the clinical outcome of trabeculectomy in glaucoma. PloS one 12: e0171636.
12. Theodoropoulou S, Ellabban AA, Johnston RL, Cilliers H, Mohamed Q, et al. (2017) Short-term safety of dexamethasone implant for treatment of macular edema due to retinal vein occlusion, in eyes with glaucoma or treated ocular hypertension. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie 255: 725-732.
13. Vie AL, Kodjikian L, Malcles A (2017) Tolerance of Intravitreal Dexamethasone Implants in Patients with Ocular Hypertension or Open-Angle Glaucoma. Retina 37: 173-178.
14. Srinivasan R, Sharma U, George R, Raman R, Sharma T (2019) Intraocular Pressure Changes after Dexamethasone Implant in Patients with Glaucoma and Steroid Responders. Retina 39: 157-162.
15. Yang CH, Qureshi AA, Churchill WH, Saavedra AP (2014) Long-term plasmapheresis in conjunction with thalidomide and dexamethasone for the treatment of cutaneous ulcers and neovascular glaucoma in recalcitrant type I cryoglobulinemia. JAMA dermatology 150: 426-428.

16. Larrison AL, Babin SL, Xing Y, Patel SS, Wassef AA, et al. ((2011) Effects of adjunct valproic acid on clinical symptoms and saccadic eye movements in schizophrenia. Human psychopharmacology 26: 517-525.
17. Meyer LM and Schonfeld CL (2013) Secondary glaucoma after intravitreal dexamethasone 0.7 mg implant in patients with retinal vein occlusion: a one-year follow-up. Journal of ocular pharmacology and therapeutics : the official journal of the Association for Ocular Pharmacology and Therapeutics 29: 560-565.

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