*Original Article*

# Efficacy of Cytidine-5′-diphosp-bocholine Combined with Compound Anisodine in the Treatment of Early Optic Nerve Contusion

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**Abstract**

**Purpose**: To investigate the efficacy of anisodine combined with cytidine-5'-diphosp-bocholine (citicoline) in the treatment of early optic nerve contusion.

**Methods**: A total of 33 subjects eligible for inclusion were selected from 105 patients clinically diagnosed with optic nerve contusion. These patients were subsequently divided into the control group ($n$=16) and the intervention group ($n$=17). In the control group, the participants received therapy consisting of glucocorticoids, mannitol, vasodilators and vitamin B. The patients in the intervention group additionally received anisodine in combination with citicoline. The visual acuity was graded on a scale from 0 to 8.

**Results**: Prior to treatment, the 25th, 50th and 75th percentiles of visual acuity grade were 3, 4 and 6.75 for the controls, and 3, 4 and 6.5 for the patients in the intervention group ($P$=0.97). After treatment, the 25th, 50th and 75th percentiles of visual acuity grade were 4, 6 and 7.75 in the control group, and 7, 7 and 8 in the intervention group ($P$=0.046). A significant difference was observed in both control ($P$=0.005) and intervention groups ($P$=0.001) when comparing presenting visual acuity before and after treatment.

**Conclusion**: The combination of anisodine and citicoline with standard steroid and mannitol therapy appears to be effective in the treatment of early optic nerve contusion. (***Eye Science 2012; 27:37–40***)

**Keywords**: optic nerve contusion; medical treatment; compound anisodine; cytidine-5'-diphosp-bocholine (citicoline)

Optic nerve contusion is a common eye disease. In clinic settings, some repairing and protective therapies have been performed to improve tropical blood circulation and nourish optic nerve, which relieves optic nerve damages to some extent, prevent optic atrophy, and alleviate irreversible loss of vision[1]. Previous clinical investigations indicated that both compound anisodine and cytidine-5'-diphosp-bocholine (citicoline) possess a protective effect upon optic nerve contusion and glaucomatous optic nerve injuries[2–4]. To further explore an effective treatment protecting optic nerve after optic nerve contusion, the present authors modified the traditional therapy by supplementing compound anisodine and citicoline to treat the patients with early optic nerve contusion and to observe its clinical efficacy.

## Subjects and methods

### General information

The clinical information of 105 subjects who were diagnosed with optic nerve contusion in People's Hospital of Lianjiang between June, 2008 and June, 2011 was compiled. Inclusion criteria: patients who had eyeball contusion within 72 h and had remained sober. Exclusion criteria: patients who had traumatic lens dislocation vitreous or anterior chamber hemor rhage severely affecting visual acuity; traumatic macular hole; retinal detachment; hematoma; or fracture inducing optic nerve compression and optic nerve avulsion detected by an orbit CT scan. Causes of contusion: 38 cases were injured by traffic accidents, 32 by boxing matches, 21 by basketball, football, or tennis matches, eight by slingshot or steel ball bullets shot, four by collisions, and two by explosions. If both eyes of the patients met inclusion and exclusion criteria, the eye with more severe contusion and poorer visual acuity was selected for subsequent observations. This study followed the tenets of the Declaration of Helsinki.

### Grouping and treatment procedure

The enrolled individuals were divided into the

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control and the experimental groups. In the control group, the patients received comprehensive therapy of glucocorticoid (hexadecadrol via intravenous drip at a dose of 30 mg/d for 5 days, then the dose was reduced by 5 mg every 3 days), dehydration (20% mannitol was given at a dose of 250ml/d via intravenous drip), vasodilator (composite salvia miltior rhiza injection was administered at a dose of 16 ml/d via intravenous drip), and vitamin B medicine (vi tamin B1, 0.1 g; vitamin B12 was given at a daily dose of 500 mg via intramuscular injection). In the experimental group, the patients received the control treatment supplemented by compound anisodine (2 ml anisodine was injected into superficial temporal artery via subcutaneous injection once daily for 14 consecutive days), and combined with citicoline injection (0.5 g was administered via intramuscular injection once daily for 10 consecutive days).

**Evaluation indexes of treatment efficacy**

Visual acuity was evaluated as no light percep tion, light perception, hand movement, index, 0.02~0.1, 0.1~0.3, 0.3~0.5, 0.5~0.7, and >0.7, and recorded on a scale from 0 to 8. The patients' visual acuity was statistically compared before and 14 d after treatment.

**Statistical analysis**

SPSS 11.5 software package was used for statistical analysis. In both groups, the patients' visual acuity was graded before and after treatments, and the graded visual acuities were analyzed by non-parametric rank sum test. $P<0.05$ was considered as statistically significant.

## Results

According to the inclusion and exclusion criteria in this study, 33 out of 105 cases were enrolled and randomly divided into the control group ($n$=16) and the experimental group ($n$=17); 7 female, 26 male; aged between 15 and 42 years old (29.9±8.7 on average). The average ages in the control and experimental groups were 29.5±9.3 and 30.3±8.4 years, respectively, with no significant difference ($t$=0.157, $P$=0.695). The treatment time ranged from 0.5 to 41 h (7.7±10.8 h on average); 8.0±10.9 h for the patients in the control group and 7.4±11.0 h for those in the experimental group. No statistical significance was noted between the two groups ($t$=–0.138, $P$=0.891). Regarding the graded visual acuity, the 25%, 50% and 75% quantiles in the control group were 3, 4, and 6.75, respectively, before treatment, and 3, 4, and 6.5, respectively in the experimental group before treatment. No significant difference was observed between the two groups ($Z$=–0.037, $P$=0.971).

After treatment, the 25%, 50%, and 75% quantiles of the graded visual acuity in the control group and experimental group were 4, 6 and 7.75, and 7, 7 and 8, respectively. A significant difference was noted between the two groups in terms of the grading of visual acuity ($Z$=–2.831, $P$=0.005). A statistical significance was found when comparing the graded visual acuity before and after treatment in the experimental group ($Z$=–3.318, $P$=0.001). A significant difference was observed when comparing the visual acuity between two groups after treatment ($Z$=–1.995, $P$=0.046).

**Table 1** Comparison on the clinical information of patients between two groups

| | $n$ | Age (yr) | Treatment time (h) | Graded visual acuity before treatment (25%, 50%, and 75% quantiles) | Graded visual acuity after treatment (25%, 50%, and 75% quantiles) |
|---|---|---|---|---|---|
| Control group | 16 | 29.5±9.3 | 8.0±10.9 | 3,4,6.75 | 4,6,7.75 |
| Experimental group | 17 | 30.3±8.4 | 7.4±11.0 | 3,4,6.5 | 7,7,8 |
| $P$ | | 0.695 | 0.891 | 0.971 | 0.046 |

## Discussion

Optic nerve contusion commonly occurs in clinical settings, which frequently induces irreversible visual injury or loss. Current treatments yield low clinical efficacy and undesirable prognosis[1], probably due to the following reasons:

First, the patients should receive emergent treatment within several hours after injury to achieve good clinical efficacy, especially for those with the symptoms of optic canal compression. If the treatment was delayed, ischemia and edema might exac-

erbate optic nerve compression, worsen ischemia and anoxia of optic nerve, and subsequently aggravate edema and injury of optic nerve. Meantime, a majority of patients with optic nerve contusion have been constantly accompanied by craniocerebra trauma, systemic severe injuries, and other ocular damages.

Compared with those evident traumas, the optic nerve injuries were usually neglected in such emergencies. Consequently, the status of the affected eyes was unlikely to be evaluated in a timely manner, and treatment time was postponed, leading to severe irreversible visual function damages.

In this investigation, 105 patients with optic nerve contusion were admitted to our ophthalmic department between 2008 and 2011. A majority of cases ($n$= 72, 68% ) were accompanied by craniocerebra trauma, systemic severe injuries, or other ocular diseases.

Second, optic nerve is a part of the central nervous system. Most optic nerve injuries are irreversible. At present, the clinical and basic researches are unable to fully explain the underlying pathogenesis. Thus, no efficacious and specific treatment has been reported in clinical practice to date[1]. The main clinical treatments of optic nerve contusion are classified into surgical and non-surgical approaches. The surgery aims to releasing the optic nerve from compression; the non-surgical therapy adopts a substantial dose of glucocorticoid supplemented by the administration of dehydrating agents, vasodilator agents, and medication for neurotrophic drug in an attempt to alleviate optic nerve edema, improve tropical blood circulation, enhance neurotrophy, and prevent deteriorating optic nerve damages[1].

This study was designed to observe the clinical efficacy of non-surgical treatment upon the patients affected by optic nerve contusion without explicit indications for surgery. Thus, individuals with evident optic nerve compression and serious ocular injuries were excluded from our study; patients with optic nerve damages alone were selected and received traditional therapy in combination with compound anisodine and citicoline. Compound anosidine is commonly utilized as a neuroprotective agent, which mainly consists of hydrobromide anisodine, procaine hydrochloride and vitamins. The underlying pharmacological mechanisms of the neuroprotection exerted by compound anisodine are as follows: first, it has anticholinergic effects, such as mitigating smooth muscle spasm. Second, it acts on optic vegetative nervous system and plays a role in regulating choroidal vessels, enhancing choroidal blood circulation, reducing the incidence of vasospasm, and elevating the motor function of eye vessels. Third, it stably functions to protect vascular endothelial cells, alliviate optic nerve edema, and lighten circulation barriers. Previous studies revealed that conpound anisodine can improve visual function after glaucoma surgery and gain advantages over alternative vasodilators regarding the treatment of optic nerve contusion[2,4]. The pharmacological mechanisms of the neuroprotection exerted by citicoline are as follows: first, citicoline participates in the biosysthesis of internal lecithin, increases oxygen consumption of the brain, and enhances tropical blood flow. Second, the metabolin-inosine, as the precursor of adenine, directly penetrates cell membrane and enters into cells, gets involved in internal energy metabolism and protein synthesis, and enhances the activity of pyruvic oxidase, especially CoA, enabling the optic nerve cells at low-energy level and hypoxia condition to continue metabolism[5]. Third, it regulates the concentrations of various neurotransmitters and stimulates the uplink systemic function of brainstem reticular structure[3,6]. During the early stage of optic injuries induced by external force, the nervous system stays in shock and the cellular metabolism is inhibited. Neuronal apoptosis might occur due to dysbolism, while some nerve cells restore function by self-repairing. However, citicoline is able to exert an effect on certain nerve cells and play an active role in repairing damaged cells. In addition, it can act on cerebral and visual cortex and enhance visual function by increasing the content of dopamine in the central nervous system. An experimental study[5] indicated that citicoline properly repaired the injured nerve cells. A clinical trial also suggested the efficacy of citicoline on optical contusions. The present study aims to improve optic nerve microcirculation and increase the activity of mitochodria located in optic nerve cells by using the combination of two drugs. In addition, it is designed to promote the recovery or regeneration of injured optic nerve fibers that were still ac-

tive to a certain extent, and ameliorate and recover visual function[7].

This clinical trial revealed that conventional therapy in combination with compound anisodine and citicoline is relatively safe since no apparent complications have been noted in 17 cases of the experimental group, which yields better clinical efficacy compared with conventional treatment. The relatively significant efficacy is possibly correlated with the fact that the patients enrolled in this investigation had mild ocular injuries (excluding the cases with complicated and severe trauma). The results in this study indicated that conventional treatment combined with compound anisodine and citicoline has a certain efficacy and multiple advantages including mild adverse reactions and high safety. It thus deserves widespread application in clinical settings.

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