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Original Article

EFFICACY OF HIGH-DOSE INTRAVENOUS STEROID TREATMENT IN METHANOL-INDUCED OPTIC NEUROPATHY: A SYSTEMATIC REVIEW

NIZMA PERMAISUARI[1*], NUR AISYAH RAHMAWATI[1], SYNTIA NUSANTI[2], HUSNI THAMRIN[3]

[1]Hadji Boejasin Pelaihari Hospital, South Kalimantan, Indonesia, [2]Neuro-ophthalmology Division, Department of Ophthalmology, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia, [3]Department of Ophthalmology, Hadji Boejasin Pelaihari Hospital, South Kalimantan, Indonesia

Email: permaisuari@hotmail.com

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ABSTRACT

Objective: Methanol-induced optic neuropathy is a visual impairment that results from damage to the optic nerve fibers caused by methanol. It is frequently bilateral with permanent visual deterioration. According to the American Academy of Clinical Toxicology (AACT), methanol-poisoned patients who present with ocular manifestations should be treated with fomepizole, ethanol, or hemodialysis, which do not remove the metabolites from the optic nerve. High-dose intravenous steroid treatment has been proposed in several studies to salvage vision because of its anti-inflammatory effect. This article examines the existing literature on the efficacy of high-dose intravenous steroid treatment in patients with methanol-induced optic neuropathy.

Methods: Literature searches were conducted using keywords and MeSH headings specifically chosen to identify published articles in CENTRAL, PubMed, ScienceDirect, ProQuest, EBSCO, and Google Scholar. Articles included were full-text, observational studies or randomized controlled trials published in English or Bahasa Indonesia.

Results: Four case series and one case report were found in the bibliographic databases. We identified 33 patients with bilateral optic neuropathy caused by methanol ingestion who were initially treated with 1 g intravenous methylprednisolone, administered as a single dose or as divided doses for 3–4 d, followed by oral prednisolone. There were visual improvements in 48 out of 56 patients (83%). No adverse events were reported.

Conclusion: Intravenous high-dose steroid treatment may benefit the visual status of patients with methanol-induced optic neuropathy. However, further studies are needed to determine the characteristics of patients who may benefit most from this regimen.

Keywords: High-Dose Steroid, Intoxication, Methanol, Optic Neuropathy

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INTRODUCTION

Toxic optic neuropathy is a visual impairment caused by damage to the optic nerve by several toxins, including drugs (ethambutol, isoniazid, antineoplastic drugs), metals (lead, mercury, and thallium), organic solvents, methanol, and carbon monoxide. Methanol is one of the most common etiologies reported [1]. According to a study by Yunard at Cipto Mangunkusumo General Hospital (Jakarta), the prevalence of methanol-induced toxic neuropathy in Indonesia is 31 cases in 2 y (2013–2014) [2]. At Sanglah General Hospital (Bali), the prevalence reported is 76 cases in 1 y (mid 2009–2010) [3].

Methanol is one of the simplest alcohol forms (CH_3OH), boils at 64.5 °C, and has a molecular weight of 32 g/mol. It is a clear, colorless, volatile, flammable liquid that has a faint, slightly alcoholic odor [4]. In several developing countries, methanol is consumed mainly as a homemade alcoholic beverage by people with low socioeconomic status. Methanol poisoning mostly occurs via oral ingestion of adulterated liquors, or by inhalation. Clinical characteristics of methanol poisoning are varied, but are usually limited to the central nervous system, eyes, and the gastrointestinal tract. The ophthalmologic symptoms are blurred vision, decreased visual acuity, photophobia, central scotoma, and blindness. Ocular examinations reveal mydriasis, hyperemia and edema of the optic disc, retinal edema, and optic atrophy [1, 4, 5].

The first treatment is to assess and maintain airways, breathing, and circulation. According to the AACT, patients with methanol-induced toxic optic neuropathy should be treated with sodium bicarbonate (if the pH is below 7.3), fomepizole, or ethanol to delay metabolism of methanol to formic acid and to prevent its accumulation. Hemodialysis is indicated in metabolic acidosis, vision loss, and organ damage, to enhance the removal of methanol and its metabolites [4, 5].

In acute cases, methanol-induced toxicity is mostly caused by inflammation. High-dose intravenous steroid treatment followed by oral steroids have been proposed in several studies to salvage vision because of their anti-inflammatory effect. Steroids will reduce retinal inflammation and edema of the optic nerve, thus preventing permanent blindness [6]. However, the efficacy of high-dose steroid use remains controversial. In this article, we examine the existing literature to evaluate the efficacy of high-dose intravenous steroid treatment in patients with methanol-induced optic neuropathy.

MATERIALS AND METHODS

Literature search strategy

The literature search was performed using databases including CENTRAL, PubMed, Science Direct, ProQuest, and EBSCO. The search engine Google Scholar was also utilized. We included studies of any design. The literature review was conducted by using the following search terms: *"methanol" and "optic,"* in the title and abstract, combined with *"steroid," "prednisone," or "methylprednisolone"* in any field, and no time limits were set (the search contained articles published up until September 12, 2018). Bibliographic reference lists of articles found during the screening were searched manually to discover studies that were not identified in the search of the electronic literature databases.

Inclusion and exclusion criteria

Two authors (NP and NAR) independently screened titles and abstracts to select studies likely to provide relevant data. We retrieved and examined the full text of the selected studies independently for compliance with eligibility criteria. We included all human studies in patients diagnosed with toxic optic neuropathy induced by methanol ingestion who had received high-dose intravenous steroid treatment. Another inclusion criterion was that

the studies were written in English or Bahasa Indonesia. For this study, high-dose intravenous steroid treatment was defined as 1 g intravenous methylprednisolone daily, as a single dose or divided into multiple doses, given for any duration. The outcome variables of the therapeutic effect, which is the improvement in visual acuity after treatment, included hand movement, counting fingers, or improvement in reading line one of the Snellen chart, and were collected in follow-up visits. We excluded studies that described treatment regimens consisting of hemodialysis, ethanol, fomepizole, or sodium bicarbonate, or studies that did not report outcomes as mentioned above.

Data extraction

We extracted data from selected studies. Data included study design, patient characteristics (age, gender), intervention given (the dosage, frequency, and duration of treatment), outcome measures, and results.

RESULTS

Study selection

A total of five studies were identified for inclusion in the review. The search of the CENTRAL, PubMed, ScienceDirect, ProQuest, and EBSCO databases provided a total of 215 citations, while other additional searches using Google Scholar provided a total of 138 citations. After adjusting for duplicates, 271 studies remained. Of these, 251 studies were discarded after reviewing the abstracts, because these articles did not meet the eligibility criteria. Eight additional studies were discarded, because the full text was not available. The full text of the remaining 12 citations was examined in more detail. It appeared that seven studies did not meet the described inclusion criteria. Five studies met the inclusion criteria and were included in the systematic review. There were no additional studies in the references of the selected articles that met the inclusion criteria. We identified nonrandomized controlled trials or systematic reviews in our search. See flow diagram, fig. 1.

Study characteristics

The five studies finally selected for this review included three case series and one case report published in English, and also one case series published in Bahasa Indonesia. The duration of high-dose intravenous steroid treatment was 3–4 d in all studies. The included studies involved 33 participants. Two studies were conducted in Indonesia, and the other studies were conducted in India, Nepal, and the USA. Studies included in this systematic review were conducted by Yunard *et al.* (2016), Grecia *et al.* (2016), Sharma *et al.* (2012), Koehrer *et al.* (2011), and Shukla and Shikoh (2006) [2, 7-10].

In all studies, the primary outcome assessed was visual improvement from baseline. The timing of collecting the outcome measures varied among the studies, from 3 mo to 1 y. Secondary outcomes included changes in the optic disc and adverse events of the treatment. Two studies, including the studies by Koehrer *et al.* (2011) and Shukla and Shikoh (2006), evaluated changes of the optic disc. Two studies by Sharma *et al.* (2012), Shukla and Shikoh (2006) reported adverse events of the treatments table 1.

Outcome measures

When we combined the results of all case series, the treatment was effective in about 83% of cases (table 2). Changes to the optic disc are shown in table 1. No adverse effects were reported.

Table 1: Summary of included studies evaluating the efficacy of high-dose intravenous steroid treatment of methanol-induced optic neuropathy

Author, year of publication	Study design	*n*	Study population		Intervention	Outcome measures	Result
			Age (y)	Sex			
Yunard *et al.*, 2016	Case series	*n* = 13 (of 31 patients)	N/A	Male	Intravenous high-dose MP	Visual acuity improvement	Visual acuity improvement (eyes): Improvement: 14 No change: 3 Worsening: 1 LFU: 4 patients
Grecia *et al.*, 2016	Case report	*n* = 1	46	Male	500 mg IV MP twice a day for 4 d; followed by 75 mg oral prednisolone for the first 4 mo and 50 mg for the next 4 mo	Visual acuity	Baseline: Visual acuity was light perception in right eye and 20/800 in left eye. Final: Visual acuity was finger count at 5 cm in right eye and 20/400 in left eye.
Sharma *et al.*, 2012	Case series	*n* = 1 (of 8 patients)	60	Female	500 mg MP in 200 ml RL IV administration over 2 h twice a day for 3 d; followed by oral prednisolone 1 mg/kg/day for 11 d	Visual acuity and side effects of the treatment	-Visual acuity Baseline: NLP bilateral 1 y: HM bilateral -Side effects: None were observed.
Koehrer *et al.*, 2011	Case series	*n* = 1 (of 2 patients)	37	Male	1 g IV MP once daily for 3 d; followed by oral prednisolone	Visual acuity and fundus examination	-Visual acuity unchanged. -Fundus examination Baseline: Bilateral papilledema. The optic nerve head showed slight temporal pallor with a swollen contour. 3 mo: Bilateral optic atrophy with glaucoma-like cupping
Shukla and Shikoh, 2006	Case series	n = 17 (of 17 patients)	22–42	NA	1 g IV MP in 500 ml RL over 2 h for 3 d; followed by 40 mg oral prednisolone for 14 d, then tapered 4–6 w	Visual outcome, fundus examination, and complication	-Visual outcome in 3 mo (patients): Improvement: 15 No change: 1 Late deterioration: 1 -Funduscopy (at day 7): decrease in peripapillary and disc edema in most of the treated eyes. -There is no complication

CDR, Cup-to-disc ratio; HM, Hand movement; LFU, Lost to follow-up; MP, Methylprednisolone; NLP, No light perception; RL, Ringer's lactate solution; RNFL, Retinal nerve fiber layer

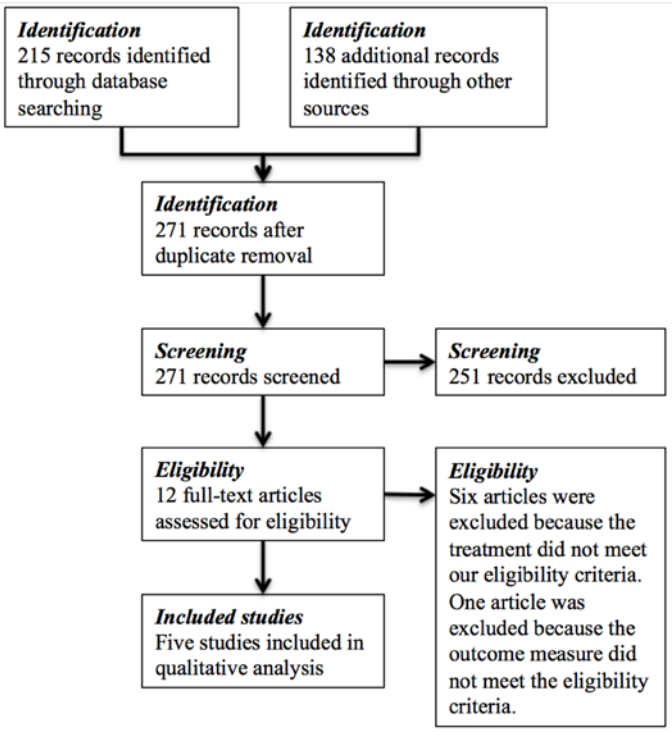

Fig. 1: PRISMA flowchart of literature search

Table 2: Rates of visual improvement in patients following high-dose intravenous steroid treatment

Author, Year of publication	Visual improvement % (*n*/*N* eyes)
Yunard *et al.*, 2016	77 (14/18)
Grecia *et al.*, 2016	100 (2/2)
Sharma *et al.*, 2012	100 (2/2)
Koehrer *et al.*, 2011	0 (0/2)
Shukla and Shikoh, 2006	88 (30/34)

n, Number of eyes with visual improvement; *N*, Total eyes

DISCUSSION

Methanol is metabolized in the liver to formaldehyde by alcohol dehydrogenase, then to formic acid by formaldehyde dehydrogenase, and then, ultimately, to its end products, water and carbon dioxide. Formaldehyde is rapidly metabolized, but formic acid is slowly metabolized and, as a result, it accumulates and exceeds the body's capacity to eliminate it. Formic acid is a metabolite that causes ocular toxicity. It specifically targets the optic disc and retrolaminar section, which are vulnerable to histotoxic hypoxia. Binding of formic acid and cytochrome oxidase might disrupt the function of the mitochondria in the optic nerve, thus causing depletion of adenosine triphosphate in the optic nerve. Hypoxia causes myelin sheath damage, nerve conduction deficit, and axoplasmic flow stasis. The optic nerve fiber and, consequently, the optic disc start to swell, resulting in loss of vision [8, 11-13]. Visual impairment commonly occurs 12–24 h after exposure [5, 6]. Permanent blindness may occur with ingestion of 10 ml methanol; the smallest reported amount to cause blindness is 4 ml [2, 5].

On the Asian subcontinent, methanol poisoning remains frequent, especially in poor socioeconomic groups where methanol is occasionally diluted in local spirits or used as a homemade alcoholic beverage. The characteristic demographics from all studies, except the study conducted by Shukla and Shikoh (2006), showed that 94% of the patients were male. This finding is similar to results of studies by Triningrat *et al.* (2010) and Samanta *et al.* (2012) [3, 14]. According to the World Health Organization, more males than females consume alcohol in all regions [15]. Despite similar amounts of alcohol consumption, more dopamine release was found in the ventral striatum compared to other striatal subregions, which is correlated with pleasure, reinforcement, and addiction formation. This may contribute to a subject's positive effects of alcohol intoxication [16]. Age ranges from 22 to 60 y were reported in the study population of methanol poisoning studies conducted by Desai *et al.* (2013) and Paasma *et al.* (2009) [17, 18]. Additionally, Paasma *et al.* (2009) also observed that the population that drank most frequently comprises middle-aged males who are emotionally instable, highly curious, and sensation seeking, with low resistance to social pressure [18].

In four articles, the baseline visual acuity of the patients was mostly categorized as blind (<3/60). The prognosis of the visual outcome is mostly correlated with the severity of the metabolic acidosis and the serum methanol concentrations [1]. Therefore, according to the AACT, patients with metabolic acidosis should be treated with sodium bicarbonate and hemodialysis, and all patients should be given fomepizole or ethanol to delay metabolism of methanol to formic acid and to prevent its accumulation [4]. In all studies examined here, metabolic acidosis has been ruled out, but no methanol serum concentrations were reported. In the studies, visual improvements were seen in 83% of the eyes of all patients in the final follow-up.

In the acute phase of toxic optic neuropathy induced by methanol intoxication, most patients have a normal-appearing optic disc, but hyperemia and swelling might occur and result in a papilledema-like appearance, similar to the findings in the study by Koehrer *et al.* (2011) [6, 10]. Different studies reported varying outcomes after high-dose steroid treatment. A study conducted by Shukla and Shikoh (2006) reported that most patients in the study showed a

decrease of optic disc swelling, which is relevant to the study by Zhao *et al.* (2015) [10, 19]. However, a study by Koehrer *et al.* (2011) showed different results. The baseline fundus examination showed a slight temporal pallor of the optic nerve, which is a sign of optic atrophy [9]. There is no treatment to reverse atrophy of the optic nerve, only treatment to limit further optic nerve damage (if possible). Regular consumption of alcohol by the patient may have contributed to the poor outcome in this study.

High-dose intravenous pulse steroid treatment, using an anti-inflammatory, neuroprotective, and immunosuppressant agent has clinical benefits, is effective for other types of optic neuropathies, including optic neuritis and traumatic optic neuropathy. Methanol toxicity in acute cases is mostly caused by inflammation [13, 19-21]. Bhalsing *et al.* (2017) reported that high-dose steroid treatment might reduce edema of the optic nerve sheaths, resulting in good recovery of vision and preventing permanent blindness. Meanwhile, other treatments could not remove the metabolites from the optic nerve [6].

Several studies reported that it is important to start treatment as soon as possible. Intravenous methylprednisolone given 6 d after methanol ingestion is not effective in improving vision [3, 11]. Only three studies reported the interval between methanol consumption and the start of the treatment, which ranged from 3 to 45 d. Delayed treatment and signs of optic atrophy at the initial clinical presentation may result in bad outcomes.

Steroid treatment inhibits the immune system and the inflammatory response, thus increasing the risk of infection or reactivation of latent infection. However, no adverse event was found in two studies, which reported similar results as the article by Surhio *et al.* (2013) [22]. After confirming the diagnosis of methanol-induced optic neuropathy, chest X-ray, stool exam, tuberculin skin test, and internist consult for initiation of corticosteroid therapy might be done to prevent the potential risk of high-dose corticosteroid therapy. Steroid dosages were tapered off in all studies to prevent withdrawal effects after high-dose steroid administration [22].

LIMITATIONS

Based on current evidence, a clear recommendation on the use of high-dose corticosteroids for treatment of methanol-induced optic neuropathy cannot be made. Studies are few in number and are of poor methodological quality. In the articles included in this review, we found that 83% of eyes had improvements in the visual acuity. However, it must be noted that these five studies are prospective case series or case reports. We found no RCT or systematic reviews. Unfortunately, many case reports and case series lack an informative abstract and title; thus, we may have possibly missed some studies. However, we also performed manual searches to further identify publications relevant to our study. Case series and case reports also have a publication bias that tends to publish only positive results.

CONCLUSION

Most patients in this study presented with blindness. High-dose intravenous methylprednisolone can be used to improve visual outcome in methanol-induced optic neuropathy. There were no adverse events reported in the examined studies; however, contraindications need to be carefully considered for safety reasons.

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AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

All authors have none to declare

REFERENCES

1. Grzybowski A, Zulsdorff M, Wilhelm H, Tonagel F. Toxic optic neuropathies: an updated review. Acta Ophthalmol 2015;93:402-10.
2. Yunard A, Nusanti S, Sidik M. Methanol toxic optic neuropathy (characteristic and evaluation of therapy). Ophthalmol India 2016;42:38-44.
3. Triningrat AAM, Rahayu NMK, Manuaba IBP. Visual acuity of methanol intoxicated patients before and after hemodialysis, methylprednisolone and prednisone therapy. J Oftalmol Indonesia 2010;7:129-32.
4. Barceloux DG, Bond GR, Krenzelok EP, Cooper H, Vale JA. American academy of clinical toxicology practice guidelines on the treatment of methanol poisoning. Clin Toxicol 2002;40:415-46.
5. Nand L, Chander S, Kashyap R, Gupta D, Jhobta A. Methyl alcohol poisoning: a manifestation of typical toxicity and outcome. J Assoc Physicians India 2014;62:756-9.
6. Bhalsing S, Jhunjhunwala R. Clinical study of methanol alcohol blindness. Int J Health Sci Res 2017;3:166-9.
7. Grecia OR, Alejandro MAA, Anna HAW, Paolah MGM, Andrade LAM. Bilateral optic neuropathy secondary to fragrance ingestion. MOJ Clin Med Case Rep 2016;4:00116.
8. Sharma R, Marasini S, Sharma AK, Shrestha JK, Nepal BP. Methanol poisoning: ocular and neurological manifestations. Optometry Vision Sci 2012;89:178-82.
9. Koehrer P, Garcher CC, Bron AM. Methanol poisoning: two case studies of blindness in Indonesia. Int Ophthalmol 2011;31:517-24.
10. Shukla M, Shikoh I. Intravenous methylprednisolone could salvage vision in methyl alcohol poisoning. Indian J Ophthalmol 2006;54:68-9.
11. Abrishami M, Khalifeh M, Shoayb M, Abrishami M. Therapeutic effects of high-dose intravenous prednisolone in methanol-induced toxic optic neuropathy. J Ocul Pharmacol Ther 2011;27:261-3.
12. Sanaei Zadeh H, Zamani N, Shadnia S. Outcomes of visual disturbances after methanol poisoning. Clin Toxicol 2011;49:102-7.
13. Pakravan M, Sanjari N. Erythropoietin treatment for methanol optic neuropathy. J Neurol Ophthalmol 2012;32:325-8.
14. Samanta SK, Fariduddin K, Mahapatra N, Bhunia J, Mondal P. Hooch blindness: a community study report on a few indoor patients of toxic optic neuropathy following consumption of adulterated alcohol in West Bengal. Nepal J Ophthalmol 2012;4:162-4.
15. Wilsnack RW, Wilsnack SC, Obot IS. Why study gender, alcohol, and culture? In: Obot IS, Room R. editors. Alcohol, gender and drinking problems: perspectives from low and middle income countries. Geneva: World Health Organization; 2005. p. 3.
16. Urban NBL, Kegeles LS, Slifstein M, Xu X, Martinez D, Sakr E, *et al.* Differences in striatal dopamine release in young adults after oral alcohol challenge: a positron emission tomography imaging study with raclopride. Biol Psychiatry 2010;68:689-96.
17. Desai T, Sudhalkar A, Vyas U, Khamar B. Methanol poisoning: predictors of visual outcomes. JAMA Ophthalmol 2013;131:358-64.
18. Paasma R, Hovda KE, Jacobsen D. Methanol poisoning and long term sequelae–a six years follow-up after a large methanol outbreak. BMC Clin Pharmacol 2009;9:5.
19. Zhao XJ, Lu L, Li M, Yang H. Ophthalmic findings in two cases of methanol optic neuropathy with relapsed vision disturbance. Int J Ophthalmol 2015;8:427-9.
20. Kerrison JB. Optic neuropathies caused by toxins and adverse drug reactions. Ophthalmol Clin N Am 2004;17:481-8.
21. Shah S, Pandey V, Thakore N, Mehta I. Study of 63 cases of methyl alcohol poisoning (hooch tragedy in Ahmedabad). J Assoc Physician I 2012;60:34-6.
22. Surhio SA, Memon S, Memon M, Nizamani NB, Talpur KI. Alcohol related toxic optic neuropathy case series. Pak J Ophthalmol 2013;29:173-6.