

CLINICAL FINDINGS AND MANAGEMENT OF METHANOL INDUCED TOXIC OPTIC NEUROPATHY: LITERATURE REVIEW

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ABSTRACT

Methanol poisoning is a serious problem due to its high mortality and prevalence of health sequelae among survivors. Death from methanol poisoning has been reported in 8-36% and permanent vision loss has been observed in 20- 0% of acute trauma survivors. Formic acid that builds up in the optic nerve can disrupt the visual system and cause optic neuropathy. Vision loss is painless and usually occurs in both eyes within one to three days. This Systematic Review based on *Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA)* protocol. This protocol has administered in *The International Prospective Register of Systematic Reviews (PROSPERO)* database. The literature showed visual acuity and funduscopic examinations of methanol induced optic toxic neuropathy and high-dose steroid, erythropoietin and antioxidant as the therapy. Methanol poisoning is a serious problem due to its high mortality and prevalence of health sequelae among survivors. Pericapillary retinal edema and optic disc edema after blurred vision or "snowfield" vision, visual hallucinations, dense central fibroids, photophobia, peripheral constriction of the visual field, and decreased visual acuity even total blindness as a symptom can be found. Prevention of formic acid formation is the main steps of treatment.

Keywords: Methanol, Literature Review, Management

INTRODUCTION

Methanol induced toxic optic neuropathy is defined as a visual impairment due to optic nerve damage by toxic methanol poisoning. In the Czech Republic in 2012, there are 139 cases of poisoning and more than 50 deaths (Nurieva et al., 2018). In America, it accounts for 1% of total poisoning cases, while in Sanglah Hospital in Bali, Indonesia it accounts for 18% of total poisoning cases. In Cipto Mangunkusumo Kirana hospital

there were 52 reported cases of methanol-induced TON in 2013 and 20 new cases from January until October 2014 (Yinski & Nusanti, 2018). Methanol poisoning is a serious problem due to its high mortality and prevalence of health sequelae among survivors. Death from methanol poisoning has been reported in 8-36% and permanent vision loss has been observed in 20-0% of acute trauma survivors. Formic acid that builds up in the

optic nerve can disrupt the visual system and cause optic neuropathy. Vision loss is painless and usually occurs in both eyes within one to three days. Vision in some patients may improve or decrease in the following weeks. In the treatment of poisoning, timely prevention of methanol oxidation by alcohol dehydrogenase is very important. Therefore, the objective of this literature review was to know the clinical and therapeutic aspects of methanol-induced toxic optic neuropathy.

METHODS

Protocol and Registration

This Systematic Review based on *Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA)* protocol. This protocol has administered in *The International Prospective Register of Systematic Reviews (PROSPERO)* database.

Eligibility Criteria

Researcher collected cohort and controlled randomized clinical trial about methanol toxic optic neuropathy. Exclusion criteria included TON-inducing agents other than methanol and methanol intoxication that did not cause eye symptoms.

Searching Strategy and Data Collection

Data collected from SciHub and Scholar searches, with the keywords “methanol-toxic optic neuropathy”, “methanol induce optic neuropathy”, “methanol and optic neuropathy”, “toxic optic neuropathy”, “methanol intoxication”. Journal publication years which selected were 2017-2022. Researchs with exclusion criteria were not selected.

Quality Assesment and Data Synthesis

Research which fulfilled inclusion criteria assessed by critical appraisal with Newcastle Ottawa Quality Assessment Scale (NOS). Good quality research defined when NOS score 7 or more. Data analysis considered variable analysis, size of research and confidence interval.

RESULT

From the SciHub and Scholar searches, there are 479 journals with the keywords “methanol-toxic optic neuropathy”, “methanol induce optic neuropathy”, “methanol and optic neuropathy”, “toxic optic neuropathy”, “methanol intoxication”. Journal exclusion criteria were TON-inducing agents other than methanol, journal publication years other than 2017-2022, and methanol intoxication that did not cause eye symptoms. Thus obtained 18 journals that match the criteria. The literature showed visual acuity and funduscopic examinations of methanol induced optic toxic neuropathy and high-dose steroid, erythropoietin and antioxidant as the therapy.

DISCUSSION

Alcohol Intoxication

Intoxication means the effect of acute consumption of alcohol on different physiologic processes in the body, in acute intake or moderate levels of alcohol. Ocular findings may be related to reduction of Gammaaminobutyric acid (GABA) activity, which is a major inhibitory neurotransmitter in the brain. GABA has been found in different parts of the visual pathway, from retinal ganglion and bipolar cells to the

lateral geniculate nucleus, superior colliculus, and the visual cortex. Visual disturbance secondary to alcohol intoxication may manifest by impaired color perception, decreased contrast sensitivity, or abnormal eye movements. In a study on alcohol intoxication and its ocular findings by Visual Maze Test in volunteers of alcohol and placebo condition, there are significant differences were reported in the first fixation latency, total task time, and number and duration of fixations and saccades (Karimi et al., 2021).

Methanol poisoning is known to cause visual disturbances, central nervous system abnormalities such as confusion, coma or even death (Liberski et al., 2022). Ocular toxicity is the most prominent feature of the toxic effects of methanol leading to ganglion cell atrophy, severe optic neuropathy, and ultimately, permanent and irreversible visual atrophy and loss of vision. Vision loss associated with methanol poisoning usually begins within 12-8 hours as bilateral optic nerve damage is relatively severe and painless; can be temporary or incremental (Pakdel, 2019).

Studies of chronic exposure to methanol, especially dermal and inhalation, have been rarer and have appeared in only a limited number of case reports. Chronic methanol poisoning can result in neurological sequelae such as potentially irreversible vision loss. Vision loss is caused by the affinity of the toxic metabolite of methanol, formic acid, to the optical pathway. Therefore, methanol poisoning is an important differential diagnosis in unexplained vision loss. On cranial MRI, the most characteristic imaging feature of methanol poisoning is bilateral

symmetrical basal ganglia (Mojica et al., 2020).

Methanol-Induced Optic Neuropathy

Pathophysiology

Methanol can cause eye damage through two independent pathways, retinal damage and optic neuropathy. The first pathway deals with damage to Muller cells and photoreceptors. Intrinsic damage to retinal photoreceptors has been reported following methanol ingestion, where rod cells appear to be more sensitive to this insult than cones. Key findings on examination include nystagmus, dilated pupils, disc swelling, and optic disc congestion. Demyelination of the posterior optic nerve is a histopathological feature of the disease (Karimi et al., 2021). Formic acid is thought to damage oxidative pathways through inhibition of mitochondrial cytochrome C oxidase, primarily affecting sensitive areas of the circulation, including areas of the circulatory system, central nervous system and optic nerve, causes axial swelling of the optic nerve, damaged axial flow with mitochondrial edema and fragmentation of nerve fibers. Finally, increased production of reactive oxygen mediators leads to neuronal lysis (Liberski et al., 2022; Sweetlove et al., 2002; Taşlı et al., 2018; Yinski & Nusanti, 2018). Acute demyelination of the optic nerve due to the toxic effects of formic acid can lead to axon degeneration due to lack of nutritional support myelin and disruption of normal axon-myelin interactions (Nurieva et al., 2019).

Clinical Examination

In general, the first symptoms of patients are nausea and vomiting. Between 18 and 8

hours after ingestion of methanol, patients may begin to experience respiratory distress, headache, and loss of vision, abdominal cramps, general weakness, confusion and somnolence. In later stages, somnolence can progress to dizziness, coma, often progressing to death from respiratory failure. Interruption of normal cellular respiration by formic acid then leads to the production of lactic acidosis. The severity of the acidosis is a rough guide to the severity of the intoxication and ocular changes were reported to correlate with the degree of acidosis (Yinski & Nusanti, 2018).

The physical examination should focus on vital signs (especially respiratory rate) and the neurologic, visual, and cardiopulmonary status. Visual acuity and funduscopy examinations should be performed. The objective signs of ocular toxicity of methanol include dilated pupils, which are partially reactive or nonreactive to light, and optic disk hyperemia with blurring of the disk margins, and later pallor. Pseudopapillitis, blurring of disk margin may look like papillary edema, but there is no diopter difference between the fundus and the disk is commonly found (Bickley et al., 2009; Sickinga, 2017; Woo & Hirsch, 2016).

Pericapillary retinal edema is commonly observed after acute methanol intoxication. Pericapillary retinal edema and optic disc edema may develop within the first 2 days. Edema may be shown as marked thickening of the periretinal nerve fiber layer on optical coherence tomography (OCT). Other experimental rat models of exposure to methanol have documented early alterations of the electroretinogram followed by mitochondrial edema and disruption

in the photoreceptor inner segment, retinal pigment epithelium, and optic nerve on subsequent electron microscopy (Klein et al., 2017; Pressman et al., 2020). Typically the hyperemia of the optic disc may subside, but the surrounding retinal edema may persist for several weeks. However, in the chronic phase, OCT may show the retinal thickness was diffusely decreased. The possible mechanism explaining the reduced vascular density may be the loss of capillaries secondary to the loss of nerve fibers and ganglion cells. Loss of RNFL and the ganglion cell layer (GCL) happens as a result of two separate mechanisms. Formic acid is a toxic metabolite produced after oral administration of methanol that directly enters ganglion cells and causes severe structural and functional damage. Damage to ganglion cells then leads to loss of nerve fibers. In addition, edema following RNFL injury can cause compartment syndrome (Hassanpour et al., 2022). EEG recording can demonstrate a decrease in b-waves. The field errors are quite extensive. Concentric contraction of the visual field often occurs with central fibroids. Fibroids, which can be central or central, predominate in cases of partial visual loss (Lim et al., 2019; Yinski & Nusanti, 2018). [8, 18]

Sign and Symptom

The ophthalmic retina is one of the most oxygen-consuming tissues, and the axons of the retinal ganglion cells, which form the optic nerve, are selectively vulnerable to tissue hypoxia caused by formic acids because they are highly energy dependent. Symptoms of methanol optic neuropathy manifest after 6 to 8 hours, depending on the amount of methanol ingested, the

ability to drink with ethanol, and body mass (Nurieva et al., 2019). It is manifested by blurred vision or "snowfield" vision, visual hallucinations, dense central fibroids, photophobia, peripheral constriction of the visual field, and decreased visual acuity even total blindness. Blurred vision with normal consciousness is a strong suspicious sign of an methanol poisonous (MP). The pupils of MP patients are mydriatic, with a delayed or nonresponse to light (Karimi et al., 2021; Nekoukar et al., 2021; Perera et al., 2020). In many cases, restoration of visual functions with the resolution of pathologic changes to the fundus and improvement of VA occurs 1-2 months after methanol exposure. However, longterm visual impairment may be present in 25-40% of patients (Nurieva et al., 2019).

Visual loss is highly variable, can be partial or complete, and can develop from hours to several days after methanol ingestion. The degree of pupillary light reflex impairment may reflect the severity of the systemic toxicity. Other acute ophthalmologic observations included hyperemia or pallid optic disc edema that is often fairly mild and retinal edema extending along the arcades. Patients also sometimes have cystoid macular edema, pseudocherry red spot, retinal haemorrhages, and engorgement of retinal veins. Optic atrophy with or without deep excavation of the disc frequently develops weeks after severe intoxication (Pressman et al., 2020).

Therapy

Prevention of formic acid formation by inhibition of the hepatic alcohol dehydrogenase enzyme and restoration of normal

pH to reduce formic acid infiltration by sodium bicarbonate or dialysis are the main steps of treatment (Karimi et al., 2021). Ethanol, a competitive inhibitor of hepatic alcohol dehydrogenase, is one of the main treatment options for methanol poisoning. Fomepizole is another competitive aldehyde dehydrogenase inhibitor that also prevents formic acid formation in methanol poisoning. Fomepizole/-methylpyrazole (Antizol) works in a similar way to ethanol. It is a more potent competitive inhibitor of alcohol dehydrogenase (ADH) and moreover, it does not cause hypoglycemia or sedation. Fomepizole is relatively easier to administer than ethanol and does not require monitoring of serum drug concentrations. It is tempting to assume that in developing countries, where fomepizole may not be readily available, ethanol becomes the agent of choice (Pressman et al., 2020). Fomepizole is more expensive, but safer than ethanol because it has a longer duration of action and does not require hourly dose adjustments. In addition, administration of fomepizole did not depress the central nervous system. Administration of fomepizole was initiated with a loading dose of 15 mg/kg b /dL, arteries. Blood pH returned to normal, and the patient was symptom-free (Karimi et al., 2021; Souza et al., 2018).

Several other treatment options, such as high-dose prednisolone, erythropoietin, and alpha lipoic acid as an antioxidant, have also been reported to have promising effects in optic neuropathy. methanol toxicity, but prospective studies are needed to determine the exact role of these treatment options (Taşlı et al., 2018). Among the drugs used for acute methanol-induced optic

neuropathy, high-dose intravenous methylprednisolone may be beneficial in restoring the patient's vision. High-dose intravenous steroids have been reported to benefit the visual status of patients with methanol-induced TON, as long as the interval between methanol consumption and treatment is short. Early management helps to reverse optic nerve damage and restore visual status. It is very important to start treatment as soon as possible, as intravenous methylprednisolone 6 days after oral methanol has been shown to be ineffective and not to improve vision. For this reason, the effectiveness of high-dose steroid use remains controversial. In the neurology department of Cipto Mangunkusumo Kirana Hospital, methylprednisolone is usually given at a dose of 250 mg, every 6 hours for a period of 3 days, i.e. 1 g per day in divided doses (Yinski & Nusanti, 2018). Intravenous erythropoietin (EPO) added to high-dose intravenous steroids has been found to be an effective combination therapy. The EPOMAON (Erythropoietin in Methanol-Associated Optic Neuropathy) trial was designed as a randomized, controlled trial to evaluate the efficacy of three consecutive days of intravenous EPO 20,000 IU in improving Visual results three months after treatment (Karimi et al., 2021).

Antioxidant therapy shows significant potential as a possible future therapy for methanol-induced toxic optic neuropathy. An experimental study in rats showed that the histology of retinal tissue was improved following administration of TEMPOL (hydroxy2,2,6,6-tetramethylpiperidinyl1oxyl), a superoxide dismutase (SOD) mimetic. This study showed that

the histology of retinal tissue improved after administration of TEMPOL. This suggests that the antioxidant TEMPOL can reduce the concentration of free radicals while acting as a neuroprotectant in methanol intoxication, resulting in better cell structure (Setiohadji et al., 2018).

SUMMARY

Methanol poisoning is a serious problem due to its high mortality and prevalence of health sequelae among survivors. Pericapillary retinal edema and optic disc edema after blurred vision or "snowfield" vision, visual hallucinations, dense central fibroids, photophobia, peripheral constriction of the visual field, and decreased visual acuity even total blindness as a symptom can be found. Prevention of formic acid formation is the main steps of treatment. High-dose prednisolone, erythropoietin, and alpha lipoic acid as an antioxidant, have been reported as a therapy.

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