LITERATURE REVIEW

# Efficacy of High-dose Steroids for Visual Acuity Improvement in Methanol-induced Toxic Optic Neuropathy

**Theresia Yinski Pistari Gondosari, Syntia Nusanti**
Departement of Ophthalmology, Faculty of Medicine, Universitas Indonesia
*E-mail: yinski@hotmail.com*

**ABSTRACT**

**Introduction :** Methanol-induced toxic optic neuropathy (TON) is defined as a visual impairment due to optic nerve damage by methanol poisoning. Not only is this disease entity underdiagnosed at times, this sudden blindness is also often diagnosed at a stage where recovery of vision is no longer possible.
**Materials and Methods :** A literature search was conducted using PubMed, ClinicalKey, Google Scholar and ScienceDirect by combining the keywords 'methanol' or 'methyl alcohol', 'intoxication' or 'poisoning', 'toxic optic neuropathy', and 'visual acuity' with 'high-dose steroid'.
**Results :** The total amount of subjects in each article varied from 2 to 37, with mean age distribution of 26.34 to 55 years old, where most patients were male. The follow up duration varied from 1 week to 1 year. Four articles do not mention high-dose steroids treatment as therapy while the other four mention use of 1000 mg of intravenous methylprednisolone per day with divided doses of either 2x500 mg or 4x250 mg. Improvement percentages show 100% improvement in all studies that used high-dose steroids, while in the non-high-dose steroids studies the improvement percentages range from 33.33% to 90%.
**Summary :** High-dose steroids are showing efficacy in improving visual acuity and reducing the inflammation in methanol-induced TON. The period of how fast the therapy takes effect is inconclusive, as the mean follow-up time differs widely per study. However, because most of the reviewed studies here are retrospective case series, a larger, more comprehensive study is required to acknowledge more of the efficacy profile.

**Kata kunci :** methanol, toxic optic neuropathy, steroid, efficacy, visual acuity

Methanol-induced toxic optic neuropathy (TON) is defined as a visual impairment due to optic nerve damage by toxic methanol poisoning. Not only is this disease entity underdiagnosed at times, this sudden blindness is also often diagnosed at a stage where recovery of vision is no longer possible.[1]

Methanol intoxication, along with some side effects following alcohol consumption, has been known for centuries.[2] Cases are encountered in both epidemic and sporadic form. Methanol was one of the most notorious causes of toxic optic neuropathy in the twentieth century and many cases involved death. Nowadays, this intoxication has become rare in

developed countries, although it still occurs frequently in less developed areas.[3] In America, for example, it only accounts for 1% of total poisoning cases, while in Sanglah Hospital in Bali, Indonesia it accounts for 18% of total poisoning cases.[4] 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.

Methanol, also known as methyl alcohol or wood alcohol, is a colourless, flammable liquid that has a close resemblance and taste to conventional ethyl alcohol, and is mainly consumed by those in lower socioeconomic classes in developing countries, due to its low cost.[5] Almost all cases of acute methanol toxicity result from ingestion.[6] In the human body, methanol is metabolized by the enzyme alcohol dehydrogenase (ADH) in the liver via formaldehyde to formic acid; the latter being responsible for the adverse effects seen in methanol poisoning, such as blindness, cardiovascular instability and death. The toxicity evolves from a combination of metabolic acidosis ($H^+$ production) and an intrinsic toxicity from the formate anion itself.[1,5] Formic acid also inhibits the electron transport chain and mitochondrial function, resulting in disruption of ATP production and impairment of the ATP-dependent axonal transport system.[7]

Visual impairment can be the first sign of methanol intoxication, ranging from mild blurring of vision to severe bilateral visual loss or sudden complete blindness. The field defects are quite extensive and nearly always include the centrocecal area. As the disturbance progressively becomes more severe, however, central visual loss worsens with a decrease in visual acuity and colour vision and a central scotoma on perimetry. Hyperemia of the optic disc is the most common first ophthalmoscopic finding. Within the first 2 days a whitish, striated edema of the disc margins and nearby retina appears. This prominent disc edema can last up to 2 months and is followed by optic atrophy of mild to severe degree. In severe cases, the pupils become dilated and fixed.[8-9]

Treatment is directed at reversal of the inciting cause by stopping the substance abuse.[9] Besides that, traditionally ethanol and fomepizole are used as specific antidote therapy for methanol-induced TON by blocking the conversion of methanol to formic acid.[2] Correction of metabolic acidosis and hemodialysis may also be necessary.[5] As the toxicity of methanol is mostly inflammatory, in some acute cases high-dose intravenous steroids are given in order to reduce the inflammation of the retina and edema of the optic nerve by inhibiting the demyelination process, hence preventing permanent blindness. However, it has been shown that after 6 days the treatment is not effective in improving vision.[4,10] Therefore, the efficacy of high-dose steroids use remains controversial. In the Neuro-ophthalmology Division of Cipto Mangunkusumo Kirana hospital, methylprednisolone is commonly used with doses of 250 mg every 6 hours, for a period of 3 days or total 12 times of administration intravenously. However, there is still no official standard operating procedure regarding this matter.

Management of methanol-induced TON is a therapeutic challenge and the outcome is often unsatisfying. Several studies documented the usage of high-dose steroids as part of the therapy, but its effectiveness is questionable. Therefore, the purpose of this literature review is to know the efficacy of high-dose steroids use for visual acuity improvement in methanol-induced TON.

## METHOD

A literature search was conducted from Cochrane Library and MEDLINE database using PubMed, ClinicalKey, Google Scholar and ScienceDirect by combining the keywords ‘methanol’ or ‘methyl alcohol’, ‘intoxication’ or

'poisoning', 'toxic optic neuropathy', and 'visual acuity' with 'high-dose steroid'. Only articles published in English or Indonesian are included. Articles from reference lists were also checked for potentially relevant articles.

An initial screening was performed by reviewing abstracts to choose articles that related to the study purpose. They were then screened based on the inclusion and exclusion criteria. Inclusion criteria are all prospective and retrospective studies that submitted methanol-induced TON patients. Diagnosis of methanol-induced TON is based on positive history of methanol or methyl alcohol consumption, supported by positive laboratory results of methanol in plasma with decreasing visual function and/or optic nerve head abnormalities after consumption. The main outcome that should be reported from each study is visual acuity improvement. Restriction for publication date or follow up duration was not performed. Studies were excluded if they used animal models, if full text articles could not be accessed, or if articles were using languages other than Indonesian or English. All eligible studies were then rated based on their level of evidence, developed by the Oxford Center for Evidence-based Medicine 2011 Levels of Evidence.

The extracted information was processed through a data sheet. The processed data was then divided into basic characteristic and outcome tables. The basic characteristic data includes information of the author, year of publishing, level of evidence, number of subjects, gender, mean subjects' age, mean follow up time and elapse time to presentation. The outcome reviewed is mean visual acuity in decimals in the final follow up, based on whether the study using high-dose steroids or not. Improvement was noted on how the percentage of patients who experienced improvement among all of the subjects in each article. Subjects who were lost to follow up, and therefore were not able to present the visual acuity outcome, are not included in the analysis. The articles are presented in table form.

## RESULT

All reviewed articles were published from 2010 to 2013 and categorized in levels of evidence III to IV. One of the articles is a retrospective, descriptive study with evidence level III, and seven others were case series with evidence level IV. The total amount of subjects in each article varied from 2 to 37, with mean age distribution of 26.34 to 55 years old, where most patients were male. The duration of follow up varied from 1 week to 1 year. There are four articles that do not mention high-dose steroids treatment as therapy; one article mentions dexamethasone injection with a dosage of 2x4 mg per day, one mentions methylprednisolone 1x48 mg per day orally, and two articles do not mention any use of steroids. The other four articles mention use of 1000 mg of intravenous methylprednisolone per day, with variation of divided doses of either 2x500 mg or 4x250 mg

**Table 1.** Basic Characteristics of the Reviewed Articles

| No. | Author | Year | Level of Evidence | Subjects (patients) | Gender | Mean Age (years old) | Mean Follow-Up (months) | Elapse Time to Presentation |
|---|---|---|---|---|---|---|---|---|
| 1. | Sanaei-Zadeh et al11 | 2011 | IV | 37 | 96% male | 34.47 | 9 | N/A |
| 2. | Sharma et al12 | 2012 | IV | 4 | 87.5% male | 49.25 | 12 | 3.125 days |
| 3. | Triningrat et al4 | 2010 | III | 16 | 94% male | 28.8 | 0.25 | 29.2 hours |
| 4. | Samanta et al2 | 2012 | IV | 10 | 100% male | 55 | 1.5 | N/A |
| 5. | Pakravan et al13 | 2012 | IV | 2 | 100% male | 32.5 | 0.75 | 5 days |
| 6. | Surhio et al14 | 2013 | IV | 10 | 100% male | 39 | 3 | N/A |
| 7. | Abrishami et al10 | 2011 | IV | 6 | 100% male | 26.34 | 3 | N/A |
| 8. | Bellarinatasari et al15 | 2011 | IV | 3 | 100% male | 31.67 | 1 | 5.5 days |

The outcomes of the therapy for visual acuity improvement are summarized in table 2. In table 2, improvement percentages show 100% improvement in all studies that used high-dose steroids, while in the non-high-dose steroids studies the improvement percentages range from 33.33% to 90%, which implies some of the patients in these studies did not experience any improvement in their visual acuity. Three of the articles did not provide any details of the visual acuity for each patient in their studies so not all of the means of visual acuity in table 3 could be calculated.

**Table 2.** Visual Acuity Outcomes

| No. | Author | Treatment of High-dose steroids | Improvement Percentages | Visual Acuity First Visit | Visual Acuity Final Visit |
|---|---|---|---|---|---|
| 1. | Sanaei-Zadeh et al11 | No | 86.49% | N/A | N/A |
| 2. | Sharma et al12 | Yes | 100% | 0.0321 | 0.1098 |
| 3. | Triningrat et al4 | Yes | 100% | 0.0375 | 0.2727 |
| 4. | Samanta et al2 | No | 90% | N/A | N/A |
| 5. | Pakravan et al13 | Yes | 100% | 0 | 0.6758 |
| 6. | Surhio et al14 | No | 90% | N/A | N/A |
| 7. | Abrishami et al10 | Yes | 100% | 0.1276 | 0.48 |
| 8. | Bellarinatasari et al15 | No | 33.33% | 0.0089 | 0.0153 |

## DISCUSSION

Methanol, known as methyl alcohol, has a chemical formula of $CH_3OH$ with a molecular weight of 32.04 g/mol, and a boiling point of 64.5°C. It is a clear, light, volatile, flammable, colourless and slightly alcoholic odour liquid, produced by the reaction of hydrogen with carbon monoxide or carbon dioxide, making it highly toxic.[4,16] Methanol is known as wood alcohol because it was distilled from wood in the 1920s and 1930s. Today, almost all methanol is made synthetically by the catalytic reduction of carbon monoxide or carbon dioxide in the presence of hydrogen.[6] It is a common, organic solvent constituent which is used widely, and is commercially available in the chemical industry and marine solvents, and is available to the public in a variety of products such as antifreeze, adhesives, enamels, stains, dyes, solvent varnishes, thinners, paint removers, photocopying fluids, shellacs, fumes and windshield cleaning fluids. Because it is cheap and easily available, it is frequently used in adulterated alcoholic beverages, and can therefore be accidentally ingested when it is added to ethyl alcohol.[8,10,12-14] These facts may explain why in this literature review, in 5 out of 8 articles, the subjects were 100% male, while in the other 3 articles most of the subjects were also male with mean age range from 26 to 55 years old, as they are still at a productive working age and men usually work outside of the households, creating more exposure to industrial products at work.

Even though toxicity can also occur from prolonged inhalation (for example, fumes inhaled in a room with inadequate ventilation), or (rarely) through skin absorption, almost all cases of acute methanol toxicity result from ingestion. It is a common problem in many parts of the developing world, especially among members of lower socioeconomic classes. It may occur from intentional overdose; accidental poison ingestion; methanol contamination of grain spirits; consumption of fluids containing methanol, by alcoholics who are deprived of their alcoholic beverage of choice; substituted for, or added to, ethyl alcohol, to resemble its taste and smell; suicidal ingestion of products containing methanol, and unintended consumption of such products for example by children. Methanol is in fact cheaper than ethanol and may be used to fortify illicit spirits.[1,6,10] In this review, all of the toxicity came from ingestion as they were present in drinks. Possible reason could be that men tend to consume more alcohol beverages than women. However, there were no details regarding the reasons for intoxication.

In the body, methanol is metabolized in a sequential fashion, principally in the liver. It is oxidized by the ADH enzyme to formaldehyde, which does not accumulate to a significant degree, but is rapidly converted within a half-life of 1-2 minutes by the formaldehyde dehydrogenase enzyme into formic acid, which is metabolized more slowly and accumulates. It also explains why it does not appear as an accumulation of formaldehyde in the blood. Its half-life can take as long as 20 hours in humans. At physiological pH, formic acid dissociates to a formate and a hydrogen ion. The formate then enters the metabolic cycle as it is then converted into 10-formyl tetrahydrofolate (combined with tetrahydrofolate) by the ATP-dependent activity of 10-formyl tetrahydrofolate synthetase. This is followed by the oxidation of 10-formyl tetrahydrofolate to carbon dioxide and water, which is catalyzed by 10-formyl tetrahydrofolate dehydrogenase (including recycling of tetrahydrofolate) in a slow detoxification pathway mechanism. Hence, the oxidation of formate is dependent on hepatic tetrahydrofolate concentrations, which is controlled by two main factors: firstly, the presence of adequate dietary folic acid (tetrahydrofolate is derived from folic acid) and secondly, the efficiency with which tetrahydrofolate is regenerated during formate oxidation.[6,10,14]

Methanol itself actually has a relatively low toxicity, but it is highly toxic for humans if ingested due to the transformation of methanol into its toxic metabolites. Toxicity develops from a combined effect of the metabolic acidosis and the toxicity of the formate itself.[1,6] Systemic acidosis is directly produced through the accumulation of formic acid by delivering protons, as it dissociates to formate and hydrogen ions. Lactate is produced as formic acid interferes with intracellular aerobic respiration and promotes anaerobic metabolism. As lactate concentrations rise and tissue hypoxia increases, the pH falls further and leads to worsening acidosis that promotes the generation of further undissociated formic acid, enabling the greater diffusion movement of formic acid across cellular membranes into cells, leading to further central nervous system depression and hypotension, which in turn leads to more lactic acid production, causing a downward spiral of worsening acidosis.[6,16] In cases of methanol poisoning, due to its slow clearance, formate accumulates as the generation of formic acid exceeds the capacity to eliminate it. There is a direct correlation between its concentration and increased morbidity and mortality.[10,14] However, compared with formate, undissociated formic acid still is three times more potent as an inhibitor of mitochondrial cytochrome oxidase; the final step in mitochondrial electron transport.[6]

Susceptibility among people to the acute effects of methanol is highly variable.

Ingestion of as little as 4 ml of methanol has been reported to cause complete and permanent visual loss by destruction of the optic nerve. The minimum lethal dose is considered to be between 300 mg/kg and 1 g/kg.[15] However, the toxic effect is said to be ameliorated and the onset of signs and symptoms may be delayed beyond 24 hours as methanol's half-life is prolonged up to 96 hours if it is co-ingested together with ethyl alcohol.[4,13,17] In this literature review, there are only 3 journals which provide data about average volume of the consumption. Samanta et al and Pakravan et al mentioned a dose of about 100 ml and 300 ml. Those clearly exceeded the minimum dosage that induces visual loss. Bellarinatasari et al only put the amount of methanol consumption ranging from 1 glass to more than 3 glasses, without mentioning any exact mililiter or the volume size of the glass.

In case of ingestion, methanol is absorbed rapidly from the gastric mucose. The mean absorption of methanol following oral administration has a half-life of 5-8 minutes, and achieve a peak concentration within 30-90 minutes after ingestion, depending on the presence or absence of food. Food in the dygestive system, especially lipid and protein, will slow down the absorption of methanol.[1,4,6,10] However, there were no details in the journals reviewed regarding food intake shortly before or after the methanol consumption.

Toxic exposure to methanol typically results in an initial transient central nervous system depression, followed by an asymptomatic latent period lasting between 12 to 24 hours, or up to 90 hours if ethanol is co-ingested. This latent period is generally shorter with increasing doses and will be longer in those individuals who have co-ingested ethanol. It is then followed by the development of formic acidemia, uncompensated metabolic acidosis, visual toxicity, coma, and, in extreme cases, death. Visual disturbances generally develop between 18 and 48 hours after methanol ingestion and can range from mild photophobia and misty or blurred vision to markedly reduced visual acuity or complete blindness.[6,17] These latent periods may explain that, even though not all of the articles provide data about how long the duration or elapse time period to presentation is, most of the patients seek out hospital treatment after more than 24 hours. Even though there is an initial transient central nervous system depression, which patients are aware of, it is followed by the latent period, during which they are unaware of the toxic changes happening to their bodies. After methanol consumption the symptoms only develop after 24 hours, due to the accumulation of the toxic formic acid. This may explain why patients might seek medical attention a lot later after consumption, for example after the visual disturbances start to occur.

Humans are uniquely sensitive to methanol-induced neurotoxicity because of the limited capacity to oxidize - and thus detoxify - formate. Formate has been hypothesized to produce retinal and optic nerve toxicity by disrupting retinal mitochondrial energy production, inhibiting its function and increasing oxidative stress. *In vitro* studies have shown that formate acts as a mitochondrial toxin, inhibiting the activity of the essential mitochondrial enzyme, cytochrome oxidase complex, at the terminal end of the respiratory chain in the mitochondria by binding to the sixth coordination position of ferric heme ion. Cytochrome oxidase complex is the vital component of the mitochondrial electron transport chain, as it is involved in adenosine triphosphate (ATP) synthesis, thus inhibiting its activity means preventing oxidative metabolism and producing tissue histotoxic hypoxia.[16] However, ocular changes are reported to correlate with the degree of acidosis as the inhibition of cytochrome oxidase by formic acid increases with decreasing pH.[12] This suggests that the active inhibitor is mostly the undissociated acid, because the concentration of the latter increases with

pH decrease, and because the inner membrane of the mitochondria is only permeable to undissociated acid. Therefore, as the pH level drops, cytochrome oxidase inhibition is potentiated and the onset of cellular injury is hastened.[6] None of the journals reviewed in this study provide data about formate concentration in the patients.

Ocular toxicity is caused by undissociated formic acid, which specifically targets the optic disc and retrolaminar section of the optic nerve directly, causing optic disc edema, breakdown of the myelin sheaths and optic nerve lesions. The undissociated formic acid binds to cytochrome oxidase causing histotoxic hypoxia, thereby inhibiting retinal and optic nerve mitochondrial function and depleting retinal and optic nerve ATP. The depletion of ATP reduces the activity of the membrane Na–K–ATPase pump, which halts conduction of the action potential, damages the myelin sheaths and causes loss of vision. It also leads to stasis of axoplasmic flow that results in intra-axonal swelling and optic disc edema. This axoplasmic flow slowing appears to also occur from swelling of the cytoplasm of the astrocytes and oligodendroglia in the retrolaminar space, as well as from compressive obstruction of orthograde axoplasmic flow. As myelin sheaths are damaged they start to swell, causing a compression-type injury to the nerve fibers. This prevents further axoplasmic flow of proteins, mitochondria and neurotubules from the cell body to the fiber of the axoplasm. As cells become deficient in these essentials they become more susceptible to formic acid-induced injury, which causes neuronal conduction deficits and loss of vision.[10,13]

The selective damage to the retrolaminar optic nerve and retina can be caused by an increased exposure to formic acid, due to a copious blood flow through the choriocapillaries, and from the cerebral spinal fluid, thereby allowing formic acid to diffuse to the adjacent optic disc and the retrolaminar section of the optic nerve. These cells are also selectively vulnerable to histotoxic hypoxia, as optic nerve fibers and their myelin sheaths have fewer mitochondrias and low reserves of cytochrome oxidase, due to their low metabolic requirements. Retinal damage is also believed to be due to the inhibition of retinal hexokinase by formaldehyde, an intermediate metabolite of methanol.[18]

In a histopathology study, Sharpe et al found that, although there was myelin degeneration behind the lamina cribrosa and cerebral hemispheric white matter, axons were preserved.[19] Histopathological changes were found most pronounced in the outer retina with evidence of inner segment swelling, photoreceptor mitochondrial disruption and the appearance of fragmented photoreceptor nuclei in the outer nuclear layer. The nature of both the observed functional and structural alterations are consistent with formate-induced inhibition of mitochondrial energy production, resulting in photoreceptor dysfunction and pathology.[20] Besides photoreceptors, electrophysiologic testing also showed that methanol affects the Muller cells and the retrolaminar portion of the optic nerve. Post-morbid studies have demonstrated bilateral central necrosis of the optic nerves from behind the lamina cribrosa to the orbital apex.[16]

There is a differential sensitivity of photoreceptors to the cytotoxic actions of formic acid, with a partial recovery of rod-dominated responses, and no recovery of UV-cone-mediated responses. However, there is still very little information available on the potential for recovery of retinal function after toxic exposure to methanol-derived formate.[17]

Methanol intoxication can reduce vision to any level, including total, irrevocable blindness. Visual loss is typically profound; it may range from mild blurring of the vision, that progresses to alteration of visual fields and sometimes to finger counting, to no light perception at all (complete blindness).[8,16] This is relevant to

this literature review, as most of the patients in the reviewed articles experienced blurry vision on their first visit to the hospital, with a mean visual acuity ranging from 0 to 0.1. Visual loss is believed to be caused by optic nerve necrosis, or demyelination from interruption of mitochondrial function in the retrolaminar optic nerve.

Among those 6 articles that provided data about fundus appearance in their first visit, most showed hyperemia of the optic discs. Most patients with methanol intoxication also have clinical evidence of ophthalmologic abnormalities. Early signs of methanol intoxication are hyperemia of the optic discs with blurred margins in the acute stage and reduced pupillary responses to light. Peripapillary retinal edema and optic disc edema can develop within the first 2 days. The edema can be shown as marked thickening of peripapillary retinal nerve fiber layer in optical coherence tomography (OCT).[13] 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.[10] Disc edema is reported to last up to 3 months and is followed by optic nerve atrophy, which corresponds with the study from Abrishami et al.[5,21] In contrast, Pakravan et al stated that the hyperemic optic discs turned pale in some patients, which is not consequent with the time of follow up, which was less than 1 month. A similar case was mentioned in the study from Bellarinatasari et al, which stated that the optic discs were even already pale in one of the patients' first visit. However, there was no data of elapse time to presentation of that patient.

Field defects are quite extensive. Concentric contraction of the visual field often occurs with central scotomas. Scotomas, which can be central or centrocecal, predominate in cases of partial visual loss. However, it is usually difficult to perform perimetry due to poor vision, as the initial visual acuity is usually quite bad or below one meter finger counting.[2] That is the reason why in this literature review, data about field defects were not available.

Definitive diagnosis of methanol poisoning requires a confirmed increase in the serum methanol level.[1] As methanol metabolism proceeds, the serum bicarbonate falls concomitantly with a rise in the anion gap and a fall in the serum osmolality.[12] Therefore, other biochemical findings include a large osmolal and anion gap, a high serum formate level and a reduced serum bicarbonate level.[21] Arterial acidity seems to correlate best with formate levels. pH values smaller than 7.2 indicate severe intoxication.[1] There are only two studies here provided data about pH, which were Sanaei-Zadeh et al with 7.16 and Triningrat et al with 7.18. Both indicated severe intoxication.

Generally, initial symptoms presented by the patient are nausea and vomiting. These may seem insignificant, so the physician can falsely conclude that the patient has not been seriously intoxicated. Between 18–48 hours after ingestion of methanol, the patient may begin to experience respiratory distress, headache and visual loss. Abdominal cramps, generalized weakness, confusion, and drowsiness are also commonly present at this stage. In later stages drowsiness may progress to obtundation, coma, often progressing to death due to respiratory failure. A raised osmolal and anion-gap metabolic acidosis are two of the hallmarks of methanol intoxication, and they occur simultaneously with the accumulation of formic acid. 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.[5,16,21]

The most characteristic central nervous system findings demonstrated on magnetic resonance imaging (MRI) in methanol toxicity, are bilateral putaminal abnormalities. The MRI may show edema

and necrotic damage of the putamen, part of basal ganglia of the brain (seen as putaminal hyperintense lesions on T2-weighted images or hypodensity in the putamen in non-enhanced computed tomography / CT images) and hemorrhages in the subcortical white matter. Sanaei-Zadeh et al similarly mentioned that there were bilateral hypodensity of the putamen and globus pallidus in all patients.[11] The same was shown in study by Sharma et al; a CT scan showed a hypodense area and necrosis of the basal ganglion, particularly the putamen.[12] The putamen is known to have high rates of oxygen and glucose consumption, and for these reasons it is thought to be more vulnerable to the adverse effects of formic acid.[22] Although initial MRI may not demonstrate optic abnormalities despite the presence of blindness on clinical examination, case reports indicate that a repeated scan, one month after methanol poisoning, can demonstrate atrophy of the optic chiasm and pre-chiasmatic optic nerves. The persistence of occipital lesions in the cerebral cortex on MRI may suggest that visual impairment is permanent.[6]

Treatment of methanol poisoning must be promptly instituted. Supportive therapy is aimed at initiating airway management, correcting electrolyte disturbances and providing adequate hydration. Gastric lavage is only useful if the patient is presented within 2 hours of ingestion.[1] Patients that are presented relatively early, who have ingested methanol but have not yet developed visual symptoms, have the potential for prevention of loss of vision. Even patients who have already lost their vision may experience some degree of recovery if treatment is promptly instituted.[5]

The three principal goals of medical treatment consist of correction of metabolic acidosis, inhibition of the methanol metabolism and elimination enhancement of the unmetabolized compound and existing toxic metabolites.[12] For the patient presented with ophthalmological abnormalities or significant acidosis, the acidosis should be corrected with alkalinisation by buffering intravenous sodium bicarbonate. The further generation of toxic metabolite should be blocked by the administration of fomepizole or ethanol, and formic acid metabolism and elimination can be enhanced by the administration of intravenous folinic acid. Hemodialysis may also be required to further correct severe metabolic abnormalities and to enhance methanol and formate elimination.[1,8,16] It is indicated for renal failure or peak blood methanol concentration levels of over 50 mg/dl to help eliminating the toxin, because it is associated with severe toxicity until the methanol concentration is <20 mg/dl and the acidosis is largely corrected.[5,21]

For the methanol poisoned patient without clinical evidence of toxicity, the first priority is to inhibit or delay methanol metabolism with antidotes until toxicity is eliminated from the system either naturally or by use of dialysis. This can be achieved by the use of either oral or intravenous administration of ethanol and 4-methylpyrazole (fomepizole). Traditionally ethanol is used as a first line antidote therapy, as it competitively interferes with the metabolism of methanol by occupying the receptor sites of ADH, thus preventing the slower metabolism of methanol into its by-products. Ethanol, like methanol, is metabolized by ADH, and the enzyme has 10-20 times higher affinity for ethanol compared with methanol. Thus, ethanol administration is most useful prior to the conversion of methanol to toxic metabolites and has little role in patients with low methanol concentrations with a marked acidosis. Ethanol is indicated for significant methanol ingestion or a methanol concentration of ≥20 mg/dl. Ethanol therapy should continue until the serum methanol concentration is <20 mg/dl and the patient is asymptomatic with a normal arterial pH. There is no clinical data to confirm the superiority of fomepizole over ethanol in the treatment of adults, or of pediatric methanol poisoning. However,

fomepizole is the preferred antidote for methanol poisoning, as it has 500-1000 times greater affinity for ADH than ethanol and can completely inhibit ADH at a much lower serum concentration. Besides that, not only because it is easier to administer and has longer duration of action, but there are also significant disadvantages associated with ethanol; such as complex dosing, difficulties with maintaining therapeutic concentrations, the need for more comprehensive clinical and laboratory monitoring, and more adverse effects such as central nervous system depression. However, fomepizole use is limited because of its high acquisition cost and lack of availability.[1,5,6,9,12]

Supplemental therapy such as folate and folinic acid may also be given, because folate is believed to enhance formic acid metabolism and is therefore postulated to reduce toxicity. Folate serves as a metabolic substrate or catalyst and supports the use of folinic acid as an adjunct in the management of methanol-poisoned patients. Folinic acid, which is also known as citrovorum factor, leucovorin calcium or 5-formyl tetrahydrofolate, is the reduced derivative form of folic acid. *In vivo* it is rapidly converted to tetrahydrofolic acid derivatives that are the primary bioactive and storage forms of folate in the body. The presence of folinic acid is thought to enhance formate oxidation by preventing the development of enzyme catalyst deficient metabolic pathways, with doses of 1 mg/kg/body weight, up to a total dose of 50 mg, administered every 4–6 hours until methanol and formate have been eliminated. Although folinic acid is preferred to folic acid as it does not require metabolic reduction, folic acid is a suitable alternative if folinic acid is unavailable.[6] Thiamine or vitamin B1 supplementation may also give benefits in patients with a history of prolonged alcohol consumption or chronic ethanol abuse, because patients who frequently ingest methanol are often ethanol abusers as well.[22] The common element in toxic optic neuropathy appears to be the disruption of the mechanisms participating in the correction of the oxidative stress. Alcohol is responsible for the disruption of anti-oxidant mechanisms. Even though the mechanism is not clear, the concentration or availability of some anti-oxidants plays a protective role against the development of optic neuropathy, despite exposure to toxin. Because of that, B-group vitamins are useful for decreasing the risk of neuropathy.[15]

The rationale for using steroids in methanol-induced TON is based on the clinical experience with the drug being effective in other forms of optic neuropathies, such as traumatic optic neuropathy and optic neuritis, as the steroid in high dose with its elimination half-life between 1.8-5.2 hours, is believed to be able to reach the optic nerve.[9,15,26] As the toxicity of methanol is mostly inflammatory, in some acute cases high-dose intravenous pulse steroids are given and the therapy has been observed to have some potential clinical benefit of anti-inflammatory, neuroprotective (free radical - scavenging) and immunosuppressant effect, therefore alleviating signs of retinal inflammation inhibits the demyelination process, reducing the edema of the optic nerve sheaths caused by the histotoxic anoxia, thus giving good recovery in vision and preventing permanent blindness.[13,16,18,23]

Corticosteroids are originally used for substitution therapy in adrenal insufficiency, but are now commonly used for its anti-inflammatory and immunosuppressive actions.[24] The immunosuppressive and anti-inflammatory actions of glucocorticoids are inextricably linked, perhaps because they both involve inhibition of leukocyte functions. Not only does it lead to a decreased number of circulation eosinophils, basophils, up to 70% of lymphocytes and 90% of monocytes, but it also profoundly alters the immune responses of lymphocytes by inhibiting leukocytes migration to the inflammed sites about 4-6 hours after its

administration, up until 24 hours of administration.[25]

Corticosteroids can prevent or suppress inflammation in response to multiple inciting stress events, including radiant, mechanical, chemical, infectious, and immunological stimuli. Multiple mechanisms are involved in the suppression of inflammation by corticosteroids, by inhibiting the production by multiple cells of factors that are critical in generating the inflammatory response. The corticosteroids inhibit the early inflammation phenomenon such as edema, fibrin deposit, capillary dilation, leukocytes migration to the inflammed sites and phagocytosis activity. As a result, there is decreased release of vasoactive and chemoattractive factors, diminished secretion of lipolytic and proteolytic enzymes, decreased extravasation of leukocytes to areas of injury and ultimately decreased fibrosis. The net effect of these actions on various cell types is to markedly diminish the inflammatory response.[25]

On the cellular level, corticosteroids work by affecting the protein synthesis. The molecules enter the cell through the plasm membrane through a passive diffusion mechanism in the target tissue, then interact with specific protein receptor in the cytoplasm, creating a receptor-steroid complex. This complex undergoes a conformation change and moves to the nucleus to bind with chromatin and stimulate the RNA transcription and specific protein synthesis. In the lymphoid and fibroblast, steroids stimulate protein synthesis which inhibit or toxic to the cells, hence creating the catabolic effect.[24]

Because of its multiple effects to inhibit the immune system and the inflammatory response, steroids use is also associated with an increased susceptibility to infection and a risk for reactivation of latent infection, such as tuberculosis. Besides this, it may also promote ulceration in peptic ulcer. Therefore, steroids should be given after meals, and antacids may be given in between meals, to provide benefits to preventing ulcerations. Corticosteroids also tend to decrease bone density by multiple mechanisms, including inhibition of gonadal steroid hormones, diminished gastrointestinal absorption of calcium and inhibition of bone formation due to suppresive effects on osteoblasts and secondary increases in parathyroid hormone, thereby increasing bone resorption (due to inhibition of intestinal calcium uptake) and in the end, resulting in osteoporosis.[25]

However, a large dosis over a short course of therapy up to 1 week is unlikely to be harmful. The contraindication for corticosteroids administration are systemic infections such as fungal sepsis, uncontrolled hypertension and hypersensitivity to steroid preparation.[26] It should be remembered that a high-dose administration should always be followed by tapering off dosage because withdrawal of corticosteroid therapy may lead to a flare-up or acute adrenal insufficiency, which is fatal.[24,25]

Intravenous high-dose steroids are reported to benefit the visual status of methanol-induced TON patients, provided that the interval of the time period in between methanol consumption and treatment is short.[12] Its early management aids in reversing optic nerve damage and revival of visual status.[14] Initiating treatment as soon as possible is very important, because it is shown that intravenous methylprednisolone given 6 days after ingestion of methanol has no efficacy and is not effective in improving vision.[4,10,27] Because of this, the efficacy of high-dose steroids use remains controversial. In the Neuro-ophthalmology Division of Cipto Mangunkusumo Kirana hospital, methylprednisolone is commonly used with doses of 250 mg every 6 hours, for a period of 3 days, or 1 g per day divided into 4 doses. However, the efficacy of this treatment seems to be low and until now there is no official standard operating procedure regarding this matter yet.

In this literature review, the elapsed time between ingestion of methanol, hospital admittance, and start of treatment (for some with high-dose steroids) were less than 6 days. Therefore, steroid therapy still gave some beneficial effects. The other therapies, such as sodium bicarbonate, ethanol or hemodialysis, are basically given to correct the general condition, such as the metabolic acidosis, and to inhibit further metabolism of methanol into its metabolites. Even though hemodialysis may help to enhance the clearance of the toxic metabolites from blood, it does not extract metabolites out of the optic nerve. Therefore, high-dose steroids still have place in methanol-induced TON management in order to treat the inflammatory process in the optic nerve. The addition of high-dose steroids is believed to help improving the visual acuity in methanol-induced TON. The mean visual acuity at the patient first presentation before therapy ranges from 0.0089 to 0.1276, while after therapy the visual acuity ranges from 0.0153 to 0.6758. From the studies where high-dose steroids were not given, improvement is shown to be from 33.33 to 90%, while in those which use high-dose steroids along with the other therapies, improvement is shown to be 100%, which means all patients experienced improvement in their visual acuity. However, the follow up periods range quite widely in this review, so it is quite difficult to get a reliable conclusion of how quick the therapy takes effect on vision improvement.

## SUMMARY

High-dose steroids are beneficial and showing efficacy in improving visual acuity and reducing the inflammation in methanol-induced TON. The period of how fast the therapy takes effect is inconclusive, as the mean follow up time differs quite widely per study. The use of high-dose steroids should be carefully considered in cases of patients suffering from infection, as they are known to suppress the body immune system, therefore increasing the risks of infection. It should, however, be kept in mind that most of the reviewed studies here are retrospective case series. A larger, more comprehensive study is required in order to acknowledge more of the efficacy profile of high-dose steroids as treatment in methanol-induced TON to help improving visual acuity.

## References


1. Sharma P, Sharma R. Toxic optic neuropathy. Indian J Ophthalmol. 2011; 59 (2): 137-41.
2. 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 (7): 162-4.
3. Koehrer P, Creuzot-Garcher C, Bron AM. Methanol poisoning: two case studies of blindness in indonesia. Int Ophthalmol. 2011; 31: 517-24.
4. Triningrat AAMP, Rahayu NMK, Manuaba IBP. Visual acuity of methanol intoxicated patients before and after hemodialysis, methyprednisolone and prednisone therapy. JOI. 2010; 7 (4): 129-32.
5. Fiebai B. A review of neuro-ophthalmologic emergencies. Nigerian Health J. 2010; 10 (1-2): 1-5.
6. 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 (4): 415-46.
7. 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: 1-5.
8. Riordan-Eva P, Hoyt WF. Neuro-ophthalmology. In: Vaughan D, Asbury T, Riordan-Eva P (eds). General ophthalmology. New York: McGraw-Hill Companies; 2003. p. 2. Available at: http://www.oculist.net/others/ebook/generalophthal/server-java/arknoid/amed/vaughan/co_chapters/ch014/ch014_p02.html (last cited: November 9th, 2014).
9. Kline LB, Bhatti MT, Chung SM, Eggenberger E, Foroozan R, Golnik KC, et al. Neuro-ophthalmology. San Francisco: American Academy of Ophthalmology; 2011. p. 154-7.
10. Abrishami M, Khalifeh M, Shoayb M, Abrishami M. Therapeutic effects of high-dose intravenous prednisolone in methanol-induced toxic optic neuropathy. J Ocul Pharmacol Th. 2011; 27 (3): 261-3.
11. Sanaei-Zadeh H, Zamani N, Shadnia S. Outcomes of visual disturbances after methanol poisoning. Clin Toxicol. 2011; 49: 102-7.
12. Sharma R, Marasini S, Sharma AK, Shrestha JK, Nepal BP. Methanol poisoning: ocular and neurological manifestations. Am Acad Opt. 2012; 89 (2): 178-82.
13. Pakravan M, Sanjari N. Erythropoietin treatment for methanol optic neuropathy. J Neuro Ophthalmol. 2012; 32: 325-8.

14. Surhio SA, Memon S, Memon M, Nizamani NB, Talpur KI. Alcohol related toxic optic neuropathy case series. Pak J Ophthalmol. 2013; 29 (3): 173-6.
15. Bellarinatasari N, Hartono. Toxic optic neuropathy due to metanol in dr. sardjito hospital (lapen intoxication). Sains Med. 2011; 3 (2): 177-84.
16. Kerrison JB. Optic neuropathies caused by toxins and adverse drug reactions. Ophthalmol Clin N Am. 2004; 17: 481-8.
17. Seme MT, Summerfelt P, Neitz J, Eells JT, Henry MM. Differential recovery of retinal function after mitochondrial inhibition by methanol intoxication. Invest Ophth Vis Sci. 2001; 42 (3): 834-41.
18. 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.
19. Sharpe JA, Hostovsky M, Bilbao JM, Rewcastle NB. Methanol optic neuropathy: a histopathological study. Neurology. 1982; 32: 1093–100.
20. Seme MT, Summerfelt P, Henry MM, Neitz J, Eells JT. Formate-induced inhibition of photoreceptor function in methanol intoxication. J Pharmacol Exp Ther. 1999; 289 (1): 361-70.
21. Phillips PH. Toxic and deficiency optic neuropathies. In: Miller NR, Newman NJ (eds). Walsh and hoyt's clinical neuro-ophthalmology. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 447-59.
22. Azeemuddin M, Naqi R. MRI findings in methanol intoxication: a report of three cases. J Pak Med Assoc. 2012; 2: 1-4.
23. Rotenstreich Y, Assia EI. Late treatment of methanol blindness. Br J Ophthalmol. 1997; 81 (5): 416-7.
24. Schimmer BP, Parker KL. Adrenocorticotropic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of the synthesis and actions of adrenocortical hormones. In: Hardman JG, Limbird LE (eds). Goodman & gilmans the pharmacological basic of therapeutics. 10th ed. New York: McGraw-Hill; 2001. p. 1649-77.
25. Suherman SK. Adrenokortikotropin, adrenokortikosteroid, analog-sintetik dan antagonisnya. In: Ganiswarna SG (ed). Farmakologi dan terapi. Jakarta: Gaya Baru; 1995. p. 482-500.
26. Sinha A, Bagga A. Pulse steroid therapy. Indian J Pediatr. 2008; 75: 1057-66.
27. Fujihara M, Kikuchi M, Kurimot Y. Methanol-induced retinal toxicity patient examined by optical coherence tomography. Jpn J Ophthalmol. 2006; 50: 239-41.