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Investigation of deaths related to methyl alcohol intoxication in İzmir: A 5-year retrospective study

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Abstract

Methyl alcohol consumption results in serious poisoning symptoms and even causes death, so it is not used in legal alcoholic beverages. We aimed to examine deaths due to methyl alcohol intoxication in our region through forensic autopsies performed in İzmir-Türkiye to compare these data with international studies. A total of 13,701 autopsies performed between 2016-2021 were scanned retrospectively. 214 cases in which the exact cause of death was methanol intoxication were included in the study. All the cases were analyzed in terms of age, gender, date of death, place of death, length of hospitalization, methanol levels detected in blood and the vitreous humor, ethanol presence in blood, and pathological findings. The ratio of autopsies of the exact cause of death of methanol poisoning to total autopsies is 1.56%. Of these cases, 94.9% were male and 5.1% were female. The age range was 25–80 years, with a mean age of 53.4. According to the age distributions, the highest rate was 39.3% in the sixth decade. The highest number of cases was 129 (60.3%) in 2020. In the analysis of blood methanol levels, the concentration was found to be in the range of 0-642 mg/dl and the mean was 178 mg/dl. During the COVID-19 pandemic, there has been a significant increase in methanol poisoning cases associated with the economic and social problems experienced in Türkiye. Our study showed that methanol poisoning deaths are especially common in men aged 50-60 years so this group is at higher risk of methanol poisoning.

Keywords: Methanol intoxication, autopsy, alcohol poisoning

Introduction

Methanol, or methyl alcohol, is a type of alcohol that was formerly obtained by distilling wood and is now used as an industrial solvent [1]. In addition to its use in industry, it is also found in some household cleaning agents, paints, adhesives, and solvents [2,3]. Pure methyl alcohol is a colorless, clear, flammable liquid substance at room temperature. When it is ingested, metabolites that are more toxic than itself, so it is not used in legal alcoholic beverages [4,5].

Methyl alcohol intoxication is most common after oral ingestion. The reasons for oral intake are unknowingly consuming illegal liquor containing methanol, ready and low-cost access to methanol-containing substances such as cologne and spirits, or for suicidal purposes. However, poisoning can also occur after inhaling methyl alcohol vapor or dermal exposure in industry [1,3,5]. Rarely, serious cases of transdermal toxicity have been attributed to the application of methanol-containing liquids to the skin to alleviate arthrosis pain [6,7].

Methanol has a relatively low toxicity, but the metabolites it is transformed into after consumption are responsible for methanol poisoning. It is rapidly absorbed from the gastrointestinal tract and distributed to all body fluids before being oxidized in the liver [1,2,4]. From there, methanol is first converted to formaldehyde by the alcohol dehydrogenase enzyme, and the formaldehyde is then converted to formic acid in a very short time (1–2 minutes) by the aldehyde dehydrogenase enzyme [2,3]. The elimination of formic acid is slow and its accumulation quite high, which allows it to trigger tissue hypoxia by inhibiting the cytochrome oxidase enzyme complex in the terminal phase of the chain of respiratory reactions in mitochondria [1,5]. High accumulated

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formic acid also decreases serum bicarbonate levels and cause anion gap metabolic acidosis, thereby increasing mortality and morbidity [1,3,5]. The oral ingestion of methanol usually results in symptoms after 12–24 hours, as it takes time to convert to toxic metabolites. This latent period may cause delays in diagnosis and treatment [2,4].

The early symptoms of patients with methanol poisoning may include dizziness, headache, vision problems, and gastrointestinal complaints such as nausea, vomiting, and abdominal pain [1,2]. Oxidative stress created by formic acid is responsible for especially retinal toxicity as end-organ damage. Despite treatment, some patients may have permanent neurological and visual sequelae [2,3,8]. In the late period of methanol poisoning, severe metabolic acidosis, confusion, coma, and respiratory and circulatory failure may develop and could even result in death. Research has determined that the severity of symptoms correlates with the severity of metabolic acidosis that develops in the patient rather than the amount of methanol ingested [2,3,9]. Further, if a patient consumes ethanol with methanol, clinical signs and symptoms of poisoning will appear later, since ethanol competes with methanol for the alcohol dehydrogenase enzyme [1,5].

Extant studies have reported that putaminal hemorrhage, necrosis, cortical and subcortical lesions, intracerebral hemorrhage, and intraventricular hemorrhage can be detected via MRI in methanol poisoning cases [7,8]. One study also indicated that hypodense lesions due to ischemic event can be seen in bilateral occipital lobe and putamen on CT scans [10]. In examinations of postmortem specimens, cerebral edema, intracerebral hemorrhage, optic neuritis, hemorrhage and necrosis in the putamen, congestion and edema in the lung, intraalveolar hemorrhage, myocardial hypertrophy, fatty changes in the liver, and tubular necrosis in the kidneys also emerged [11-13].

The present study aims to evaluate deaths after methyl alcohol ingestion in our region of Türkiye, through forensic autopsies performed by the Izmir Council of Forensic Medicine and to compare these data with international studies.

Material and Methods

This study was carried out with the approval of the İzmir Katip Çelebi University Non-Interventional Research Ethics Committee with the protocol number 256, dated 15/04/2021, and the permission of the Ministry of Justice, Council of Forensic Medicine. To start, a total of 13,701 autopsies performed by the Ministry of Justice, Council of Forensic Medicine Izmir Group Presidency between January 1, 2016 and June 15, 2021 were scanned retrospectively. The cases were found in the autopsy archives of the Council of Forensic Medicine Izmir Group Presidency Morgue Specialization and National Judicial Information System. Epicrisis documents (hospitalized cases), autopsy findings, forensic investigation documents, and postmortem toxicology and pathology reports were examined, yielding 214 cases with methanol intoxication as the definitive cause of death for the study. All included cases were evaluated in terms of age, gender, date of death, place of death (hospital, residence, non-residence), length of hospitalization, methanol levels detected in blood and the vitreous humor, ethanol presence in blood, and pathological findings. The first blood samples taken at the hospital of 38 cases where blood could not be drawn at autopsy were considered.

Methyl alcohol in biological samples was analyzed with Headspace-Gas Chromatography (HS-GC) and Headspace-Gas Chromatography/Mass Spectrometry (HS-GC/MS) devices at Council of Forensic Medicine Izmir Group Presidency Chemistry Department. For the analysis of illegal, legal and medicinal substances found with methyl alcohol, the samples were prepared with the solid phase extraction (SPE) method as the pre-phase step and then analyzed with the Liquid Chromatography-Sequential Mass Spectrometry (LC-MS/MS) device. The limits of detection and limits of quantification were calculated as LOD=4mg/dl, LOQ=5mg/dl. However, since ethanol formation naturally occurs in postmortem blood after death, it was decided that it is not appropriate to report values below 10mg/dl as positive. For this reason, although the LOQ was 5mg/dl, the reporting limit was determined as 10mg/dl. The blood samples taken at the hospital and during the autopsy were both analyzed with the same methods on the same devices. The obtained data were transferred to forms prepared for this study and entered into SPSS 22.0 (Statistical Package for Social Science) for statistical data analysis.

Results

Between January 1, 2016 and June 15, 2021, 13,701 autopsies were performed by the Council of Forensic Medicine Izmir Group Presidency, from which we determined that the exact cause of death in 214 (1.56%) cases was methanol poisoning. Of these, 203 (94.9%) were male with a median age of 54 (range 25–80) years, and 11 (5.1%) were female with a median age of 47 (range 35–63) years. The mean age of total cases was 53 (range 25-80) years with a median age of 54 years. Upon analyzing the age distributions, the highest rate was 84 (39.3%) cases in the sixth decade, followed by the fifth (22.9%) and seventh decades (22.4%). Additionally, 2 cases were in the third decade and 1 was in the ninth decade (Figure 1).

The highest number of cases was 129 (60.3%) in 2020, with a peak of 52 cases in October of that year (Figures 2 and 3). When the cases were analyzed by month, 27.1% of all cases died in October. According to death days, 17.8% died on Saturday; there was no significant difference between other days of the week. When the death places of the cases were examined, 134 (62.6%) cases died in the hospital, 59 (27.6%) died in their residence, and 21 (9.8%) died outside of their residence (Table 1). Additionally,

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80 (37.4%) cases were not hospitalized, 42 (19.6%) died on their first day in the hospital, and 45 (21%) died after 1–3 days of hospitalization (Table 2).

In the examination of the toxicology reports, we found that methanol, ethanol, medical drugs, narcotic/sedative/stimulant substances, and a carboxyhemoglobin (1 case) were present in the blood. After classifying these findings, methanol alone was found in the blood of 24.8% of the cases; medical drugs alongside methanol were detected in 45.3% of them; and in 17.3%, methanol, ethanol, and medical drugs were found together (Table 3). Considering the presence of methanol and ethanol in the blood, 77.1% of the cases had methanol in their autopsy blood, 6.1% did not have methanol, and 16.8% had methanol in their first blood samples taken at the hospital. We also found that 77.1% of cases did not have ethanol in their blood, while 22.9% of them did (Table 4). In our assessment of blood methanol levels, the concentration was in the range of 0–642 mg/dl, 0–100 mg/dl in 78 (36.4%) cases, 100–200 mg/dl in 62 (29%), and 200–300 mg/dl in 35 (16.4%). Methanol was also present at very high levels (600–700 mg/dl) in 3 cases (Table 5). The mean blood methanol concentration was found 178 mg/dl and the median value was 133 mg/dl. Vitreous humor was taken in 178 (83%) cases, of which methanol was found in the vitreous humor in 133 (62.1%) cases and undetermined in 45 (21%) (Table 6). The methanol levels detected in the vitreous humor were in the range of 0-655 mg/dl, similar to those in the blood. The mean methanol concentration in the vitreous humor was found 144 mg/dl and the median value was 91 mg/dl.

We then evaluated the methanol concentrations in the blood and vitreous humor together of 178 cases whose vitreous humor was obtained. We detected that 64 of the 68 cases that had blood methanol levels of 0–100 mg/dl also had vitreous humor methanol levels in that range. Additionally, the blood methanol levels of 51 cases were 100–200 mg/dl, and 30 of them had vitreous humor methanol levels of 100–200 mg/dl as well. Another 26 cases had blood methanol levels of 200–300 mg/dl, 14 of which had vitreous humor methanol levels also at 200–300 mg/dl. These findings show that the blood and vitreous humor methanol concentrations were very similar (Table 7).

In the analysis of the postmortem samples' pathological findings, the most common findings were intraalveolar edema (52.8%) and intraalveolar bleeding (39.7%) in the lungs. In addition, acute pneumonia was detected in 25.2% of the cases, fat embolism in 5.6%, and bronchiolitis in 4.2%. The pathological findings in the brain were intraparenchymal hemorrhage (11.6%) and subarachnoid hemorrhage (10.7%), while the leading pathologies in the heart were severe atheromatous plaque (17.2%), acute myocardial infarction (7.4%), and myocardial hypertrophy (3.7%). In the liver, we found cirrhosis in 5.6% of cases, severe steatosis in 1.4%, and fibrosis in 0.4% (Figure 4).

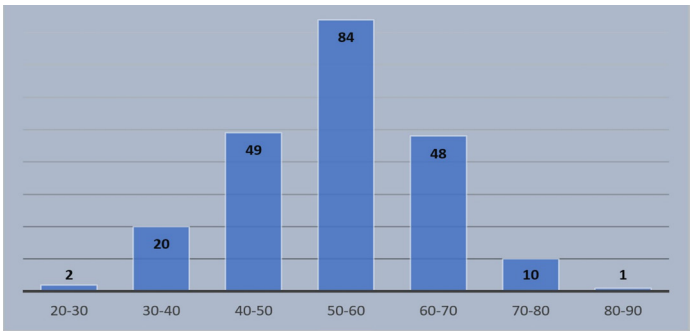

Figure 1. Distribution of deaths by ages

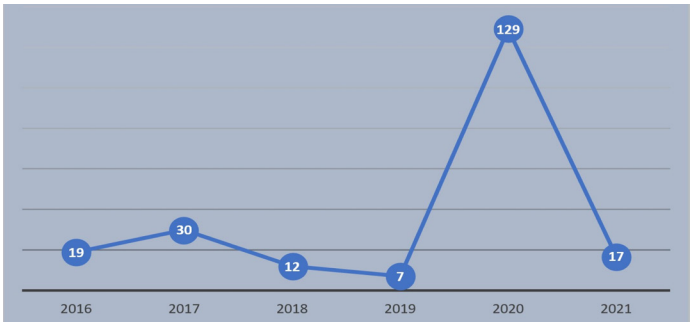

Figure 2. Distribution of deaths by years

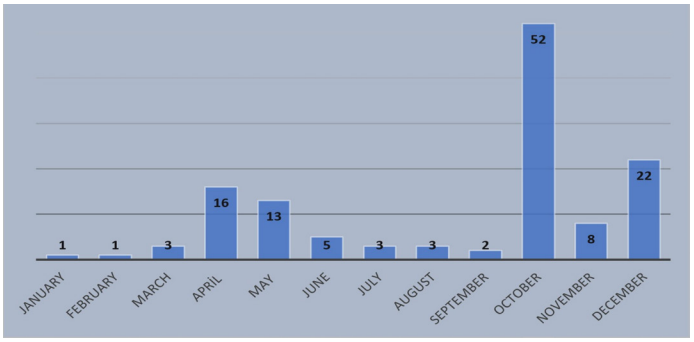

Figure 3. Distribution of deaths by months in 2020

Table 1. Death places of cases

Place of death	Frequency	Percentage
Hospital	134	62.60%
Residence	59	27.60%
Non-residence	21	9.80%
Total	214	100.00%

Table 2. Hospitalization time of cases

Length of hospitalization	Frequency	Percentage
None	80	37.40%
Deaths on first day in hospital	42	19.60%
1-3 days	45	21.00%
3-5 days	16	7.50%
5-7 days	5	2.30%
>7 days	26	12.10%
Total	214	100%

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Table 3. Substances detected in the autopsy blood or the first blood (taken at the hospital) of the cases

Substances in the blood	Frequency	Percentage
Methanol	53	24.80%
Methanol+ethanol	10	4.70%
Methanol+ethanol+medical drug	37	17.30%
Medical drug	11	5.10%
Ethanol+medical drug	2	0.90%
Methanol+medical drug	97	45.30%
Methanol+narcotic/sedative/stimulant substances	3	1.40%
Methanol+carboxyhemoglobin	1	0.50%
Total	214	100%

Table 4. Ethanol presence in blood

Ethanol	Frequency	Percentage
Positive	49	22.90%
Negative	165	77.10%
Total	214	100%

Table 5. Methanol levels detected in blood

Methanol concentration	Frequency	Percentage
0-100 mg/dL*	78	36.40%
100-200 mg/dL	62	29.00%
200-300 mg/dL	35	16.40%
300-400 mg/dL	15	7.00%
400-500 mg/dL	16	7.50%
500-600 mg/dL	5	2.30%
600-700 mg/dL	3	1.40%
Total	214	100%

*Cases in which methanol concentrations were not detected (13 cases) are included in range 0-100 mg/dl

Table 6. Methanol presence in vitreous humor

Methanol	Frequency	Percentage
No sample	36	16.80%
Negative	45	21.00%
Positive	133	62.10%
Total	214	100%

Table 7. Evaluation the methanol concentrations in the blood and intraocular fluid together of 178 cases whose intraocular fluid was obtained are shown, 36 cases whose intraocular fluid was not taken were not included in table

		Methanol levels detected in vitreous humor							
		0-100 mg/dL	**100-200 mg/dL**	**200-300 mg/dL**	**300-400 mg/dL**	**400-500 mg/dL**	**500-600 mg/dL**	**600-700 mg/dL**	**Total**
Methanol levels in blood	**0-100 mg/dL**	64	4	0	0	0	0	0	68
	100-200 mg/dL	19	30	2	0	0	0	0	51
	200-300 mg/dL	9	1	14	2	0	0	0	26
	300-400 mg/dL	2	0	1	9	1	0	0	13
	400-500 mg/dL	2	0	0	1	5	5	0	13
	500-600 mg/dL	0	0	0	0	1	3	1	5
	600-700 mg/dL	0	0	0	0	0	0	2	2
	Total	96	35	17	12	7	8	3	178

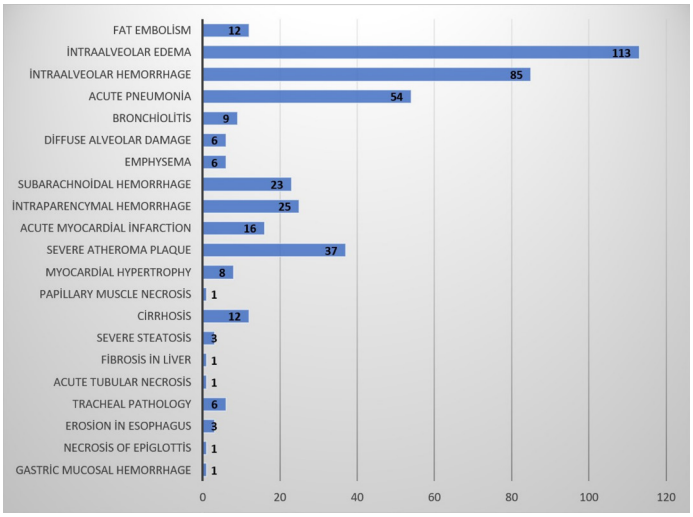

Figure 4. Pathological findings in postmortem samples

Discussion

In our study, we retrospectively analyzed 214 cases in which an autopsy was performed between January 1, 2016 and June 15, 2021 and the exact cause of death was methanol intoxication. In total, 94.9% (n=203) of the cases were male and 5.1% (n=11) were female. Previous studies have shown that methyl alcohol poisoning is mostly seen in males [8,9,14,15]. Most notable of these, Karadeniz et al. retrospectively scanned autopsy data from 20 years and reported that all 13 cases whose cause of death was methyl alcohol poisoning were male [12]. In our study, we also saw more male cases, which is compatible with the literature. Additionally, the mean age of the cases was 53.4. Considering the age distribution, the highest rate at 84 (39.3%) cases was in the sixth decade, followed by the fifth (22.9%) and seventh decades (22.4%). In similar studies, methanol intoxication cases were mostly seen in the middle to older age groups. Kurtas et

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al. reported that 383 cases were mostly in the 40–50 year age range, followed by the 30–40 age range [13]. Patil et al. similarly revealed the mean age of 24 methanol poisoning cases to be 40.3, and in Hadipourzadeh et al., the mean age of 154 cases was 31.9 [16,17]. Accordingly, the cases in our study had a higher mean age than in the literature.

In methanol poisoning cases, ethanol, medical drugs, and other substances can be detected in the blood besides methanol. Celik et al. examined 74 cases of alcohol intoxication in which methyl alcohol alone in the blood appeared in 36.5% (n=27) of cases, medical drugs in addition to methyl alcohol in 5.4% (n=4), and ethyl alcohol alongside methyl alcohol in 1.4% (n=1) [15]. Karadeniz et al. also reported that 8 of 13 methanol poisoning cases had ethyl alcohol in the blood in amounts ranging from 55 to 244 mg/dl [12]. In our study, just methanol was found in the blood in 24.8% (n=53) of the cases, while in 45.3% (n=97) of the cases, there was a medical drug in addition to methanol, and in 17.3% (n=37) ethanol and medical drugs were found in addition to methanol. The detection of both ethanol and methanol in autopsy blood may result from the fact that methanol is usually mixed with ethanol in illegal alcoholic beverages or if hospitalized patients are given treatment that utilizes ethanol.

Methanol poisoning is associated with high mortality and morbidity [13,18]. It can be fatal if 60–240 ml of methyl alcohol pure form is consumed, though individual differences are seen in methanol poisoning depending on metabolism, the amount of folate in the person's diet, and the simultaneous consumption of methanol and ethanol [3,4]. An exact lethal dose is not known, but the minimum has been reported to be 1 g/kg (body weight) if ethanol is not concurrently ingested [2-4]. Celik et al. told that methanol was found in the range of 74–602 mg/dl in the postmortem autopsy blood of 35 cases of methanol poisoning, with the mean blood level 322.8 mg/dl [15]. Meanwhile, Kurtas et al. reported that the blood methanol levels detected in the autopsy blood of 383 cases were 0–826 mg/dl, with 334 of the cases above 100 mg/dl [13]. In Kassasbeh's study, methanol amount to 56–400 mg/dl in the autopsy blood of 16 cases with a mean concentration of 220.7 mg/dl; in 12 of those cases, the methanol levels were above 100 mg/dl [14]. Karaarslan et al. determined that the blood methanol level was between 31 and 560 mg/dl in 12 cases of methanol intoxication at an average concentration of 206.8 mg/dl [19]. In our study, the blood methanol levels in 65 cases (30.3%) were less than 100 mg/dl, in 62 (29%) cases 100–200 mg/dl, in 35 (16.4%) cases 200–300 mg/dl, and in 13 (6.1%) they were negative. That methanol was detected at toxic doses above 100 mg/dl in the blood in the majority of our cases and the mean concentration was 178 mg/dl is compatible with the literature.

Methanol may be negative in autopsy blood depending on the time of hospital admission after methanol ingestion or the duration of treatment in the hospital [11]. In our study, 6 of the 13 cases in which methanol was not detected in the blood were treated in the hospital for more than 7 days, and 2 cases received treatment for 5–7 days. This indicates that methanol may be measured at lower doses or be negative in autopsy blood as the hospital stay is prolonged. Especially in cases where methanol is not detected in the blood, postmortem pathological findings, forensic investigation, and epicrisis documents are crucial to determine exact cause of death in suspected methanol poisoning cases.

Due to the formation of toxic metabolites after ingesting methanol, clinical manifestations of methanol poisoning usually appear after 12–24 hours, which may delay hospital admission [13]. It has been established that early admission is very important for survival in methanol poisoning cases, especially the first 2–3 days after methanol consumption [9,20]. One study indicated that 13 of 20 patients who died after hospital admission died in the first 24 hours after ingesting methanol, while in another, 5 of 17 patients died in the first 48 hours [16,21]. Simani et al. also revealed that 82 of 516 cases died at the time of admission to the hospital [22]. Consistent with the literature, in our study, 87 (64.9%) of the 134 patients who arrived at the hospital died within the first 3 days of their stay, demonstrating how important early diagnosis and treatment are in methanol poisoning. Additionally, we determined that 80 (37.4%) cases that we analyzed died before reaching the hospital. This relatively high rate of out-of-hospital mortality can be explained by the latent period when symptoms have not yet started [12,14]. Similarly, Kurtas et al. reported that 248 (64.7%) of 383 methanol intoxication cases died at home, while for Kassasbeh the rate was 15 (93.7%) of 16 cases [13,14]. However, from our own study, the reason why the remaining 134 (62.6%) of the 214 cases died in the hospital is that deaths most occurred during the 2020 methanol poisoning pandemic in Izmir, and the patients likely went to the hospital earlier because of the awareness of intoxication symptoms.

Previous studies have reported postmortem methanol poisoning findings such as cerebral congestion and edema, hypoxic necrotic findings in the white matter, intraalveolar edema and bleeding, fatty changes in the liver, myocardial hypertrophy, glomerulotubular changes in the kidneys, and infarction and necrosis in the putamen [11,12,21,23]. In our study, we found similar pathological findings predominantly in the lungs, brain, and heart. The accumulation of metabolites in the optic nerve, which are more toxic than methanol itself, are responsible for visual disorders and optic nerve atrophy [8,11]. Since optic nerve sampling was not sufficient in our study, we could not detect any such pathological findings.

Methanol poisoning can be observed sporadically or epidemically. The most common cause of methanol poisoning epidemics is increased demand for local, homemade, or illegal liquor production, as it is cheaper [17,24]. During the COVID-19 pandemic, for instance, there have been many economic, social, and health problems around the world and in Türkiye, resulting in an observed significant increase in methyl alcohol poisoning cases [25]. Especially with our country's high unemployment rate, decreased purchasing power, and limited alcohol purchasing

hours stemming from the pandemic, low-cost, homemade alcoholic beverages have become a source of income for some sectors, leading to the increased production of illegal drinks and their demand. Indeed, our study revealed that the highest number of methanol poisoning cases was in 2020 at 129 (60.3%) cases, peaking in October (52 cases). Alcoholics especially may also turn to other more easily accessible alcoholic substances, such as cologne and disinfectant, when they cannot access conventional alcohol. In particular, the increased consumption of homemade alcohol due to pandemic restrictions and the rising prices of legal alcoholic beverages after tax increases have led low-income citizens to manufacture and buy cheap drinks, so the methyl alcohol user profile has spread to a wider base in Türkiye. In addition, with the contribution of information pollution in the media, the consumption of various alcoholic liquids, such as disinfectant, for protection against the coronavirus may have raised the incidence of methanol intoxication [22].

Limitations

Our study only includes methyl alcohol intoxication cases who were autopsied and not patients who survived. Additionally, we could not evaluate optic nerve findings because there was not enough optic nerve pathological sampling.

Conclusion

Methanol intoxication is a serious health problem around the world and in our country with severe consequences. It may cause neurological sequelae and permanent vision loss, and in some cases may even result in death. According to our study, methanol poisoning deaths are especially common in men aged 50-60 years, indicating that this group is at higher risk of methanol poisoning. Especially in specific regions, methanol poisoning epidemics may occur as a result of the excessive consumption of illegal liquor, so taking necessary precautions as soon as methyl alcohol poisoning is detected may reduce related deaths. We believe that to significantly reduce the amount of deaths due to methyl alcohol intoxication, however, it is necessary to decrease the production of methyl alcohol, increase societal knowledge of the issue, and make necessary legal arrangements.

Conflict of Interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure

The authors declare that they have received no financial support for the study.

Ethical Approval

This study was carried out with the approval of the İzmir Katip Çelebi University Non-Interventional Research Ethics Committee with the protocol number 256, dated 15/04/2021, and the permission of the Ministry of Justice, Council of Forensic Medicine.

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