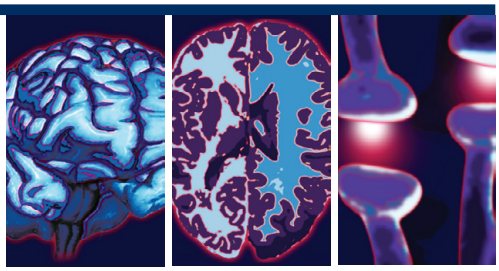
Research Article



The Importance of Magnetic Resonance Imaging Findings and Serum Carboxy hemoglobin Levels in the Prediction of Late Neuropsychosis in Carbon Monoxide Poisoning

Figen Turkdogan†

ABSTRACT

The effects of carbon monoxide poisoning(CO) on the central nervous system in the late period after discharge are still controversial. The aim was to evaluate late stage neuropsychosis (NP) findings of carbon monoxide with serum carboxyhemoglobin (COHb) levels and magnetic resonance imaging (MRI) findings. Of the 363 patients who applied to emergency service due to CO between January 2017 and December 2014 were included in this retrospective study. The patients who had a COHb level higher than 5% and those who underwent MRI in the acute-subacute period were followed for 60 months and their development states were recorded. Mean age of the patients was 49.2 ± 8.2 years, 123 (33.9%) were female, and approximate follow-up time was 60 months. Neuropsychosis symptoms were found in 33 (17.3%) of the 363 patients followed. Carboxyoglobin level and exposure time to CO were found to be higher in cases with neuropsychosis and MRI groups III and IV (p=0.001). NP and mortality were most frequent in MRI group IV (p=0.001). In addition, serum COHb level was found to be low in MRI groups I and II, while it was found to be high in groups III and IV (p=0.004). In the correlation of MRI groups with the variables, moderate and strong positive correlation was found with NP (r=0.684), serum COHb level (r=0.889), mortality (r=0.274), CO exposure time (r=0.425) (p=0.001). Mortality rate was found to be higher in MRI group IV, in patients with a COHb level higher than 56.8% and in male patients. In late periodneuropsychosis prediction of carbon monoxide poisoning, serum carboxyhemoglobin levels and MRI findings may be helpful values in the risk prediction.

Keywords: Carbon monoxide poisoning; Emergency department; Late-period neuro-psychosis; Magnetic resonance imaging

Introduction

Carbon monoxide (CO) is still one of the most common poisonings in daily life and emergencies, which can result in death and sequelae. It is a colorless, odorless and non-irritant gas that occurs as a result of incomplete combustion of fuels [1,2].

Carbon monoxide easily replaces oxygen in hemoglobin. The resulting carboxyhemoglobin (COHb) reduces the oxygen-carrying capacity of blood, resulting in tissue hypoxia. Carbon monoxide binds to hemoglobin with 240 times higher affinity than oxygen, impairing the release of oxygen to tissues and oxygen transport [3,4]. Immediately after carbon monoxide poisoning and/or after a certain latent period, various neurological conditions may occur in 2-40% of the patients[5]. These sequelae are thought to occur from lipid peroxidation and inflammatory cascade in central nervous system [6,7]. Although the mechanism is still unknown, the cause is thought to be diffuse demyelination of the cerebral white matter [8]. Suggested mechanisms

University of Turkey, Turkey
†Author for correspondences: Figen Turkdogan, Associate professor, University of Turkey, Email: turkdogandr@gmail.com

are cellular hypoxia, neurotoxicity, neutrophil activation, accumulation of peroxynitrates in the endothelium, apoptosis or programmed cell death [9-14].

It is very important to show and define the sensitive points of the brain in detail with advanced radiological imaging methods in terms of planning the treatment. New technological developments provide great convenience in diagnosis and defining pathologies. For this purpose, Magnetic Resonance Imaging (MRI) was used in the evaluation of brain tissue and diseases in the study. Thus, the data obtained with MRI method enables the determination of treatment approaches. Serum COHb level and Magnetic Resonance Imaging (MRI) in acute and subacute phases of carbon monoxide poisoning were compared in the study. The findings obtained were evaluated between one month and 60 months after the patients were discharged. The aim was to show the effects on the brain in late period after discharge in CO poisoning.

Materials and Methods

■ Study design and population

In this cross-sectional cohort study, 2793 patients were found who were older than 18 years of age and who were admitted to emergency service due to CO poisoning between January 2007 and December 2014. Of these patients, 363 cases who had a COHb level higher than 5% and those who underwent MRI in the acute-subacute period were included in the study.

Three groups were formed according to the findings and COHb levels of the patients; those with COHb level lower than 20% were classified as mild, those with COHb level between 20 and 30% as moderate and those with COHb level higher than 30% as 'severe'.

Four groups were formed according to the MRI findings of the cases; those who had normal MRI findings were in Group I; those who had lesions in a single area and smaller than $1cm^2$ were in Group II; those who had lesions in a one or two areas and up to $2cm^2$ were in Group III; and those who had more than two and/or bilateral lesions larger than $2cm^2$ were in Group IV.

Diagnosis, admission dates and contact information of the patients and their demographic, clinical and laboratory data were taken retrospectively from the hospital record system. The patients whose records were not accessed were reached through telephone or email. The patients were followed for approximately 60 months after they were discharged and their neuropsychiatric changes were found.

All patients with diseases about the brain (for exp. Cerebrovascular disease, epilepsy, Parkinson's, brain tumour), psychiatric diseases, chronic liver diseases, chronic renal failure, congestive heart failure, chronic heart and valve diseases, infectious and chronic inflammatory diseases, severe anemia and hematological diseases were excluded from the study.

Carbon monoxide late-period neuropsychosis diagnosis was made by Neurology, Psychiatry and Emergency specialists based on American and European Neurology Committee.

The study was conducted in accordance with Helsinki Declaration of Human Rights after institutional local ethics committee approval was taken.

Laboratory Design

Hemogram, biochemistry and artery blood gas of the patients were taken on admission to the emergency service. They were worked for about 45-60 minutes. Hemogram was measured by using Beckman Coulter Automated CBC Analyser (Beckman Coulter, Inc., Fullerton, CA, USA). Biochemistry blood was analysed with Cobas 6000 (C6000-Core, Cobas c-501 series, Hitachi, Roche, USA).

COHb levels of the patients were obtained from arterial blood gas analyses by using Acobas®b221 Blood Gas system (Roche, Basel, Switzerland). The diagnosis of CO poisoning was made based on the patient's clinical level and serum COHb level being >5%. CO exposure time was defined as the approximate CO inhalation time.

Radiological Imaging

Magnetic resonance imaging: Axial T1A SE (TR: 484, TE: 11), axial and sagittal T2A turbo SE (TR:2660, TE: 99) and axial "fluid-attenuated inversion recovery" (FLAIR) (TR: 9000, TE: 87, TI: 2499) images of all patients were obtained with 1.5 T MRG device (Siemens, MagnetomAera 1.5T, Germany). MRI findings were reported by Radiologists.

Statistical analysis: The data obtained from this study were analysed with SPSS 15.0 (SPSS, Inc, Chicago, IL) software package. Kolmogorov-Smirnov test was used to examine whether the

variables were normally distributed. While analysing the differences between the groups, independent samples t test was used for the variables which were normally distributed and Mann Whitney U and Kruskal Wallis-H tests were used for the variables which were not normally distributed. In case of significant difference in Kruskal Wallis-H test, the groups with difference were found by using Post-Hoc Multiple Comparison Test. Chi-square analysis was used while examining the correlations between the groups with normal variables. Pearson Correlation Analysis was used on the normally distributed data. Level of significance was taken as 0,05 while interpreting the results.

Results

In this retrospective cohort study, mean age of the patients was 49.2±8.2 (241 male, 123 female, distribution 32-66 years, 33.9% female), mean follow-up time was 60 months.

Neuropsychosis symptoms were found in 33 (17.3%) of the 363 patients followed for approximately 60 months after discharge. Of these 33 patients, 17(4.7%) were male, while 16 (4.4%) were female. In the neuropsychosis group, carboxyoglobin level (49.4%, p=0.001), in addition CO exposure time, White Blood Cell (WBC), Red Cell Distribution Width (RDW), Mean Platelet Volume (MPV), mean corpuscular hemoglobin concentration (MCHC), **Mean Corpuscular Volume** (MCV), mean corpuscular hemoglobin (MCH) were statistically significant when compared with the group which did not develop neuropsychosis (p=0.001). However, mean age, gender, blood sugar and liver enzymes were found to be statistically insignificant.

In analyses in terms of magnetic resonance imaging groups, age, blood sugar and liver enzymes were not statistically significant. However, COHb, CO exposure time, WBC, RDW, MPV, MCHC, MCV and MCH were statistically significant in terms of MRI findings groups (p=0.001).

In terms of magnetic resonance imaging groups, gender, mortality, COHb groups and neuropsychosis development were found to be statistically significant (p=0.001) In terms of analysis of neuropsychosis groups with variables, gender was found to be insignificant (p=0.082), while COHb groups, mortality and MRI groups were found to be statistically significant (p=0.001).In terms of analysis of carboxyhemoglobin groups with variables, gender (p=.008), mortality (p=0.004), neuropsychosis and MRI groups were found to be statistically significant (p=0.001)

In the correlation of magnetic resonance imaging groups with the variables, moderate and strong positive correlation was found with NP (r=0.684), serum COHb level (r=0.889), mortality (r=0.274), CO exposure time (r=0.425), RDW (r=0.355), MPV (r=0.543) and MCHC (r=0.399) (p=0.001). However, no correlation was found with age, gender and blood sugar (p<0.05)

Discussion

Carbon monoxide continues to be the most common cause of poisoning in emergency services in the whole world. In studies, late findings of CO poisoning have been defined in limited number of studies. Even cases with high carboxyhemoglobin level are discharged when their clinical conditions improve. The number of studies on late cranial pathologies of these cases which become asymptomatic in time is almost none or they have one or few cases. For this reason, for the first time in literature, we showed that MRI findings, high COHb levels and exposure time can predict neuropsychosis cases in patients admitted to the emergency service due to CO regardless of advanced age.

Changes related with carbon monoxide poisoning occur in organs such as the brain and the heart where oxygen demand is high. It has been found that after CO poisoning10-30% of the cases develop personality changes, parkinsonism, incontinence, dementia and delayed neuropsychiatric syndrome characterized with psychosis, while young people also had peripheral neuropathy in addition to these [15] .

Central nervous system histopathological findings consist of necrosis and demyelination areas. They are also known to create direct toxic effects by binding to proteins such as neuroglobin, cytochrome oxidase, cytochrome P-450, dopamine beta hydroxylase, tryptophan oxygenase in brain regions rich for iron such as globuspallidusand substantia nigra. In some cases, damage to the hippocampus and thalamus, cortical atrophy, loss in Purkinje and internal granular layer cells of the cerebellum can be seen. In addition to greymatter lesions, CO poisoning cause demyelination and destruction in cerebral white matter. Although white matter

lesions are seen in regions such as frontal and parietal cortex, centrum semiovale and brain stem, parieto-occipital region is reported to be the most affected region [16-22].

In our study, the highest involvement of MRI findings was found in the white matter and parieto-occipital region. In addition, it was found that early period COHb level and mortality and late period neuropsychosis were both higher and more permanent in areas with high involvement. In patients with Group I and II MRI findings, COHb levels were found as 17.7% and 30.7%, respectively and NP was found in only 1 (0.3%) in Group II. However, in Group III and IV patients who had more prevalent and more severe MRI findings, COHb level was found as 44.6% and 56.8%, respectively, NP was found in 12(3.3%) in Group III and 20(5.5%) in Group IV.

White matter involvement is characteristic in CO poisoning and involvement degree is associated with clinical prognosis in acute and subacute period (23-25). White matter involvement may occur in three forms. The first is the multiple small necrotic areas in the interhemispheric commissures and centrum semiovale, the second is diffuse necrosis areas that tend to merge in the deep white matter and the third is demyelination in which the axons are relatively preserved in the deep white matter. The third form is the most frequent in delayed encephalopathy. White matter lesions were reported to develop due to reversible demyelination of white matter lesions as a result of MRI follow-ups of four cases with delayed encephalopathy [23-25]. Vion-Dury et al. [26] suggested that demyelination is an active process that still continues long after poisoning based on a case with persistent signal increase and mental retardation in T2A sections in white matter one year after intoxication. Inagaki et al. [27] explained the diffuse white matter hyper intensity that continued unchanged in T2A images with irreversible axonal damage in a case that they followed for 18 months with serial MRI. They thought that on-going psychiatric symptoms might be associated with white matter damage. Similar white matter involvement was found almost in all of the cases with neurological sequelae in the chronic period published by Uchino et al. [28].

As a result of CO poisoning, globuspallidus necrosis, white matter lesions with demyelination or necrosis, spongy lesions of cerebral cortex and necrotic lesions of the hippocampus were shown with MRI in acute and subacute period. The most frequent finding was bilateral, symmetric signal density increase in the white matter. This involvement was found in the group with prevalent MRI findings. 17 of the cases were found to have diffuse and symmetric involvement in the white matter. 5 of the cases were found to have diffuse asymmetric involvement. The lowest involvement was found in hippocampus with three cases, it was in the form of patchy signal increase and NP was not found in these cases. It is obvious that clinical symptoms and signs of poisoning are more associated with white matter involvement in acute and subacute period. However, the fact that many of the asymptomatic cases have white matter involvement brings to mind that this association may be valid not only in acute and subacute period, but also in the chronic period. In addition, we believe that permanent demyelination in white matter in some of the cases without NP shows that demyelination is generally irreversible in CO poisoning and NP either lasts long or has a permanent association in cases without reversible demyelination.

White matter involvement in acute and subacute period after carbon monoxide poisoning is usually bilateral and symmetrical. Involvement does not prefer any area in most. However, there are also asymmetric involvements [23,25,29]. Another study showed asymmetric signal increase in 12 of the 13 cases in chronic period and parieto-occipital region was the region with most frequent involvement [28]. Lesions were shown in many cases in the corpus callosum in subacute period [23]. In a study with 62 cases, corpus callosum atrophy was shown with quantitative measurements in 80% cases as a result of 6-month-long follow-up. These studies showed with volumetric grading that involvement was diffuse and mild in many cases [30].

White matter involvement in chronic period was found to be similar with other studies; however, it differed in that it was symmetrical. The fact that the lesions in acute and subacute period were asymmetric, unlike the late period, suggests that some areas of the brain are potentially more sensitive to hypoxia. This situation may have emerged with the effect of chronic ischemic changes due to aging of the cases. We did not detect asymmetric involvement in cases with low mean age. Involvement in the hippocampus in the form of signal increase was observed in three cases. However, the fact that we did not examine the hippocampus might have caused us

to overlook mild lesions. Lesions were found in minimal and moderate groups of MRI findings in corpus callosum. Mild NP that resolved over time was observed in two cases. Clinic and prognosis were found to have good course in these regions.

Since necrosis is the main pathology in CO poisoning, it is a natural and expected finding that areas damaged in early period undergo atrophy in late period. However, this issue is not clear yet. Some studies showing cerebellar involvement in early period have been published [25,31,32]. In our study, mild cerebellar cortex involvement, signal increase in cerebral cortex and atrophic appearance were found in most of the cases. We think that these cases developed due to CO poisoning and that they may be frequent lesions in the chronic period. In their study, Chang et al.[23] found cerebellar atrophy in MRI follow-ups and they attributed the cause of atrophy to CO poisoning. Cerebellum was found to be normal in all of the cases inUchino et al.'s study [28]. However, the atrophy findings in the cerebellum might have been attributed to aging and considered normal and compatible with their ages. The relationship between carboxyhemoglobin level and severity of poisoning continues to be controversial. In addition to studies indicating correlation between blood COHb level and severity of poisoning [33-35], there are also studies showing that this relationship is present only in mild poisonings [36,37].

There was a correlation between COHb level and symptoms, findings and NP in our study. While COHb was 29.4% in neuropsychosis negative group, it was 49.4% in positive group. In addition, more MRI findings were seen in acute and subacute phase in the group with high COHb level. Thus, we think that this accompanying NP progresses more permanently.

Some studies have reported that establishing a relationship between high COHb levels of CO poisoning and clinical findings and prognosis does not yield healthy results. The time of exposure is more important. In CO poisoning, chronic exposure may progress more severe than the picture that occurs with acute CO poisoning, even if COHb is low [38-41]. However, the severity of CO poisoning has been reported to depend on the degree of COHb saturation in blood. Poisoning symptoms start at 20% COHb and these symptoms get severe when COHb is 40%. Death usually occurs when COHb level rises to 60% or above [42,43].

In our study, CO exposure was 2,54 hours in non-NP group, while it was 5.85 hours in NP group. In addition, it was found that as CO exposure time increased, this time extended to 2,49 hours in the group with minimal MRI findings and to 6,1 hours in the group with high MRI findings. It was found that MRI findings, NP incidence, mortality frequency in acute period and frequency of permanent NP cases in late period were found to increase as this time increased. In addition, high COHb level, long CO exposure and group IV MRI findings were NP determinants irrespective of age. COHb levels and CO exposure time were found to be significantly higher in patients with Group III and IV MRI findings when compared with Group I and II MRI findings. While early period mortality was found as 1.4% in the group with high MRI findings, mortality was found as 0.6% in the group with minimal findings. We believe that the fact that COHb level was high in similar studies, but low as 52.1% in our study was caused by more frequent mortality due to long CO exposure time. In addition, the fact that MRI findings had strong positive correlations with serum COHb levels, CO exposure time, mortality and neuropsychosis can be a predictive value of the severity of poisoning.

Study limitation: The present study had some limitations. It was a single centred and retrospective study. For this reason, it was difficult to access the follow-up data of the patients. Considering that the basal MRI findings of the patients before CO poisoning were not known, it was not possible to predict the differences that developed due to COHb's effect.

Conclusion

Inco poisoning, neuropsychological disorders that may develop in post-discharge late period may easily be overlooked. Especially taking into consideration serum COHb levels and MRI findings may be guiding in preventing neuropsychosis that may develop in the future and making early diagnoses. If these results can be supported with multi centred and prospective studies, they can be very useful in all patients with CO poisoning due to health economics policies.

References

1. Omaye ST. Metabolic modulation of carbon monoxide toxicity. *Toxicology* 180(1),139-50 (2002).
2. Raub JA, Mathiue-Nolf M, Hampson NB, Thom SR. Carbon monoxide poisoninga public health perspective. *Toxicology* 145(1), 1-14 (2000).
3. Ernst A, Zibrak JD. Carbon monoxide poisoning. *N. Engl. J. Med* 339(1), 1603-1606 (1998).
4. Turner M, Hamilton-Farrell MR, Clark RJ. Carbon monoxide poisoning: an update. *J. Accid. Emerg Med* 16(1), 92-96 (1999).
5. Kao LW, Nanaga KA. Carbonmonoxide poisoning. *Emerg. Med. Clin. North. Am* 22(4), 985-1018 (2004).
6. Pianidosi CA. Carbonmonoxide, oxygen transport and oxygen metabolism. *J. of. Hyperbaric. Med* 2(1), 27-44 (1987).
7. Hardy KR, Thom SR. Pathophysiology and treatment of carbonmonoxide poisoning. *J. Toxicol. Clin. Toxicol* 32(1), 613-629 (1994).
8. Kim JH, Chang KH, Song IC, *et al.* Delayed encephalopathy of acute carbon monoxideintoxication:diffusivity of cerebral white matter lesions. *Am. J. Neuroradiol* 24(1), 1592-1597 (2003).
9. Okeda R, Funata N, Takano T. The pathogenesis ofcarbon monoxide encephalopathy in the acute phase-physiological and morphological correlation. *Acta. Neuropathol* 54(1), 1-10 (1981).
10. Thom SR, Bhopale VM, Fisher D. Delayed neuropathology after carbonmonoxide poisoning is immune-mediated. *Proc. Natl. Acad. Sci USA* 101(1), 13660-13665 (2004).
11. Zhang J, Piantadosi CA. Mitochondrial oxidative stress after carbonmonoxide hypoxiain therat brain.*J. Clin. Invest* 90(1), 1193-9a (1992).
12. ThomSR. Carbonmonoxide-mediated brain lipid peroxidation in therat. *J. Appl. Physiol* 68(1), 997-1003 (1990).
13. Thom SR, XuYA, Ischiropoulo sH. Vascular endothelial cells generate per-oxynitrite in response to carbonmonoxide exposure. *Chem. Res. Toxicol* 10(1), 1023-1031 (1997).
14. Piantidosi CA, Schmechel DE, Zhang J. Is neuronal degeneration mediated by apoptosis after carbon monoxide poisoning? Undersea and Hyperbaric Medicine 22(1), 15-16 (1995).
15. Prockop LD, Chichkova RI. Carbon monoxide intoxication: an updated review. *J. Neurol.Sci* 262(1-2), 122-30 (2007).
16. Schochet SS, Nelson J. Exogenous toxic-metabolic diseases including vitamin deficiency, in: Textbook of Neuropathology. Davis RL, Robertson DM, Williams & Wilkins 511-546 (1997).
17. Auer RN, Sutherland GR. Hypoxia and related conditions in Greenfields Neuropathology. Graham DI, Lantos PL, 7th ed Arnold pbl, London 1:233-264 (2002).
18. Ernst A, Zibrak JD. Carbon monoxide poisoning. *N. Engl. J. Med* 1603-1608 (1998).
19. Raub JA, Benignus VA. Carbon monoxide and the nervous system. *Neurosci. Biobehav. Rev* 26(1), 925-940 (2002).
20. Uemura K, Harada K, Sadamitsu D, *et al.* Apoptotic and necrotic brain lesions in a fatal case of carbon monoxide poisoning. Forensic Sci Int 116(1), 213-219 (2001).
21. Sohn YH, Jeong Y, Kim HS, *et al.* The brain lesion responsible for parkinsonism after carbon monoxide poisoning. *Arch. Neurol* 57(8),1214-8 (2000).
22. Porter SS, Hopkins RO, Weaver LK, *et al.* Corpus callosum atrophy and neuropsyhological outcome following carbon monoxide poisoning. *Arch. Clin. Neuropsychol* 17(1), 195-204 (2002).
23. Chang KH, Han MH, Kim HS, *et al.* Delaye dencephalopathy after acute carbonmonoxide intoxication: MR imaging features and distribution of cerebral white matter lesions. *Radiology* 184(1), 117-122 (1992).
24. Horowitz AL, Kaplan R, Sarpel G. Carbonmonoxidetoxicity: MR imaging in thebrain. *Radiology*; 162(1), 787-788 (1987).
25. O'donnel P, Buxton PJ, Pitkin A, *et al.* The magnetic resonance imaging appearances of the brain in acute carbon monoxide poisoning. *Clin. Radiol* 55(1), 273-280 (2000).
26. Vion–Dury J, Jiddane M, Van Bunnen Y, *et al.* Sequelae of CO poisoning: MRI study of twocases. J Neuroradiol 1987; 14:60-5.
27. Inagaki T, Ishino H, Seno H, *et al.* A long termfollow-up study of serial magnetic resonance images in patients with delayed encephalopathy afteracute carbonmonoxide poisoning. *Psychiatr. Clin. Neurosci* 51(1), 421-3 (1997).
28. Uchino A, Hasuo K, Shida K, *et al.* MRI of the brain in chronic carbon monoxide poisoning. *Neuroradiology* 36(1), 399-401 (1994).
29. Taylor R, Holgate RC. Carbon monoxide poisoning: asymmetri candunilateral changes on CT. *Am. J. Neuroradiol* 9(1), 975-997 (1988).
30. Porter SS. Corpus callosum atrophy and neuro psychological outcome following carbon monoxide poisoning. *Arch. Clin. Neuro.psychol* 17(1), 195-204 (2002).
31. Karabacakoğlu A, Karaköse S, Deniz E, *et al.* Cranial MRI findings in acute carbonmonoxide intoxication. Diagnostic and Interventional Radiology 7(1), 488-493 (2001).
32. Mascalchi M, Petruzzi P, Zampa V. MRI of cerebellar whitematter damage due to carbonmonoxidepoisoning: casereport. Neuroradiology 38(1), 73-74 (1996).
33. Cevik AA, Unluoglu I, Yanturali S, *et al.* Inter relation between the Poisoning Severity Score, carboxy haemoglobin levels and in-hospitalclinicalcourse of carbonmonoxide poisoning. *Int. J. Clin. Pract* 60(1),1558-1564 (2006).
34. Varon J, Marik PE, Fromm RE Jr, *et al.* Carbon monoxide poisoning: a review for clinicians. *J Emerg.Med* 17(1), 87-93 (1999).
35. Ilano AL, Raffin TA. Management of carbon monoxide poisoning. Chest 97(1), 165-169 (1990).
36. Kao LW, Nañagas KA. Carbon monoxide poisoning. *Emerg. Med. Clin. North. Am* 22(1), 985-1018 (2004).
37. Harper A, Croft-Baker J. Carbon monoxide poisoning: un-detected by both patients and their doctors. *Age. Ageing* 33(1), 105-109 (2004).
38. Kandis H, Katırcı Y, Çakır Z, *et al.* Retrospective Analysis of Cases Presenting to the Emergency Department with Carbon Monoxide Intoxication. *Academic. J. of. Emerg. Med* 5(1), 21-25 (2007).
39. Katırcı Y. The frequency of neuropsychiatric disorders and related factors in patients poisoned with carbonmonoxide. Master thesis; Erzurum, 2005.
40. Rodaplı Ü. Carbonmonoxidepoisoning. *J. of. Emerg. Med* 130-134 (2000).
41. Gorman DF, Runciman WB. Carbon monoxide poisoning. *Anaesth. Intensive. Care* 19(1), 506–511 1991.
42. Vural N. Toxicology, Ankara University Press, Ankara UniversityPharmacy. Fake. Publications, Ankara 1984; 56.
43. Ellenhorn M, Barceloux D. Diagnosis and Treatment of Human Poisoning. *Med. Toxico* 10(1),181-189 (1986).