e-ISSN
2667-8675
Volume: 2 Issue: 1
March 2020

EJT
Eurasian Journal of Toxicology

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Editorial

Eurasian Journal of Toxicology yayın kurulu olarak dergimizin 2020 yılı 1. sayısını sizlere sunmaktan mutluluk duyuyoruz. Umarız bu sayıda öncekiler gibi, siz değerli okuyucularımız için ilginç ve katkı sağlayıcı olur. Bu sayıda geçtiğimiz aylarda ülkemizde de oldukça gündem olan "siyanür zehirlenmeleri" konusuna ilişkin bilgilerimizi güncelleme imkânı sağlayan bir derleme bulacaksınız. Ayrıca son yılların oldukça trend konusu olan PRP yöntemi ile ilgili bir diğer derlemeyi de sizlere ulaştırıyoruz. Bunlara ek olarak üç orijinal araştırma makalesi ve bir olgu sunumu Mart sayımızın içeriğini oluşturmakta.

Eserlerini bizimle paylaşan tüm yazarlarımıza ve değerlendirme sürecinde yer alan tüm hakemlerimize teşekkür ederiz. Dergimizi daha güncel ve daha iyi duruma getirmek noktasında siz değerli okuyucularımızın yapacakları katkılar ve eleştiriler bizleri oldukça memnun edecektir.

İnsanlık olarak kaygılı ve endişeli bir dönem geçirdiğimiz şu günlerde başta sağlık çalışanları olmak üzere tüm herkese esenlikler dileriz.

Saygılarımızla.

Eurasian Journal of Toxicology Editörler kurulu adına,

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Prof. Dr. Zeynep Çakır

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General Approach to Cyanide Poisoning: A Review Article

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Abstract

Cyanide is a rapidly acting, lethal poison that interfere with mitochondrial oxygen utilization. It has many natural, industrial and even household sources. Most common cause of cyanide poisoning is smoke inhalation. Intravenous and inhaled cyanide exposures produce more rapid onset of signs and symptoms than does oral or transdermal ingestions. The clinical presentation varies with the physicochemical form of cyanide, the dose, route of entry, co-toxicants delay since exposure. Central nervous system and cardiovascular system dysfunction are most prominent; also there are nonspecific sings such as nausea, vomiting, headache, dizziness, confusion, coma, seizures, dilated pupils, and abnormal vital signs. Cyanide toxicity expected to have two characteristic symptoms theoretically; those are cherry-red skin and odor of bitter almond from the victims' breath. Cyanide-poisoned patients have an elevated blood lactate concentration. A cutoff point of 8 mmol/L lactate level should be suggested as a diagnostic indicator of cyanide toxicity. Blood cyanide level is the confirmatory test for cyanide poisoning and but it is not routinely performed in most hospitals and may not correlate with toxicity; therefore it cannot guide treatment. The treatment of patients poisoned with cyanide includes supportive care and adjunctive antidotal therapy. Cyanide toxicity is rapidly lethal, so clinicians must stabilize the patient's airway, breathing and circulation first. Antidotal treatment of cyanide poisoning involves three strategies which are binding of cyanide, induction of methemoglobinemia, and use of sulfur donors. Hydroxocobalamin and dicobalt edetate are direct cyanide binding antidotes. In general hydroxocobalamin as first-line antidotal therapy is effective and safe in acute cyanide poisoning. Amily nitrite, sodium nitrite and 4dimethylaminophenol are the antidotes that induce methemoglobinemia. Nitrites are not suitable for fire victims, and those with poor cardiopulmonary reserve. Sodium thiosulfate is a sulfur donor antidote. Recommendation for antidotal treatment strategies in case of cyanide poisoning depends on the availability of antidotes and accuracy of the diagnosis.

Key words: Cyanide, poisoning, antidotes, hydrocobalamin, nitrites

Özet

Siyanür mitokondriyal oksijen kullanımını bozan, hızlı etki eden ölümcül bir zehirdir. Birçok doğal, endüstriyel ve hatta ev içi kaynağı vardır. Siyanür zehirlenmesinin en sık nedeni duman inhalasyonudur. Intravenöz ve inhale siyanür maruziyetleri oral veya transdermal maruziyetten daha hızlı semptom ve bulgu oluştururlar. Klinik presentasyon siyanürün fizikokimyasal formuna, dozuna, alınış şekline, maruziyetten itibaren olan ko-toksinlerin varlığına göre değişir. Santral sinir sistemi ve kardiyovasküler sistem disfonksiyonu ön plandadır; ayrıca bulantı, kusma, baş ağrısı, sersemlik, konfüzyon, koma, nöbet, dilate pupiller, ve anormal vital bulgular gibi nonspesifik bulgular olabilir. Siyanür toksisitesinde teorik olarak iki karakteristik semptom beklenir; bunlar kiraz kırmızısı deri ve kurbanın nefesinde acı badem kokusudur. Siyanür zehirlemesi olan hastaların kan laktat konsantrasyonları yükselir. Laktat için 8 mmol/L eşik değer siyanür zehirlenmesi için tanısal bir belirteç olarak önerilir. Kan siyanür düzeyi, siyanür zehirlenmesinde doğrulayıcı testtir ancak çoğu hastanede rutin olarak bakılmaz ve toksisite ile korele değildir; bu yüzden tedavide yol gösterici değildir. Siyanürle zehirlenen hastaların tedavisi destek tedaviyi ve yardımcı antidot tedavisini içerir. Siyanür zehirlenmesi hızla ölümcüldür, bu yüzden hekimler önce hastanın havayolunu, solunumunu ve dolaşımını stabilize etmelidirler. Siyanür zehirlenmesinde antidot tedavisi üç stratejiyi içerir bunlar siyanürün bağlanması, methemoglobinemi indüksiyonu ve sülfür donörlerinin kullanımıdır. Hidroksikobalamin ve dikobalt edta direkt siyanür bağlayan antidotlardır. Genel olarak hidroksikobalamin akut siyanür zehirlenmesinde ilk-sırada kullanılan etkili ve güvenilir antidottur. Amil nitrit, sodyum nitrit ve 4dimetilaminofenol methemoglobinemi yapan antidotlardır. Nitritler yangın madurları ve kardiyopulmoner rezervi düşükler için uygun değildir. Sodyum tiosülfat bir sülfür donörüdür. Siyanür zehirlenmesinde önerilen antidot tedavi stratejisi antidota ulaşabilirliğe ve tanının kesinliğine bağlıdır.

Anahtar kelimeler: Siyanür, zehir, antidot, hidroksikobalamin, nitrit

Introduction

Cyanide is a chemical compound that contains a cyano-group, consists of a carbon atom triple bonded to a nitrogen atom, in combination with other elements such as potassium or hydrogen[1]. It is a rapidly acting, lethal poison that interfere with mitochondrial oxygen utilization[2]. Cyanide used as a method of execution since ancient times; and with the media news about its repetitive use as a suicide agent last year in Turkey, attention to cyanide poisoning was increased. This paper aims to appraise the evidence base for the clinical management of cyanide toxicity.

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Received: 18.02.2020 • **Accepted:** 03.03.2020

Cite this article as: Isik Cikrikci G, Cevik Y. General approach to cyanide poisoning: a review article. Eurasian J Tox. 2020;2(1):1-6.

Etiology

Cyanide has many natural, industrial and even household sources. Most common cause of cyanide poisoning in Western countries is smoke inhalation[3]. Cyanide is formed during the incomplete combustion of nitrogen containing materials, such as wool, silk and melamine which are increasingly being used in homes[4]. Therefore, inhalation of toxic fumes in domestic fires can be the cause of cyanide toxicity among fire victims[4].

Occupational exposures account for a significant number of cyanide poisonings. Metal extraction in mining, electroplating in jewelry production, photography, plastics and rubber manufacturing and rodent pesticide and fumigants have all been implicated in cyanide poisonings[5]. Industrial consumption of cyanide can be either via inhalation or skin absorption. Ingestion of cyanide compounds either with suicidal intent or accidentally were also reported[6].

Iatrogenic toxicity due to administration of cyanide-group containing medications such as sodium nitroprusside (SNP), a medication used in the treatment of hypertensive emergencies, was also reported. Impaired renal functions, prolonged infusion duration and/or high doses of SNP infusion were defined risk factors for SNP induced cyanide toxicity[7].

There are also some food that contain cyanogenic glycosides, such as amygdalin, in their pits and seed[5]. Bitter almond, cherry laurel, apricot, plum, peach, pear, and apple are some examples. Although not a common cause of poisoning, those natural sources can produce cyanide toxicity when taken in large quantities[1].

Pathophysiology

Cyanide causes rapid toxicity upon exposure, in large part due to the inhibition of cytochrome-c oxidase-dependent cellular respiration[8]. It avidly binds to the ferric ion (Fe3+) of cytochrome oxidase a3 and inhibiting this final enzyme in the mitochondrial cytochrome complex. Cells cannot utilize oxygen because of their poisoned electron transport chain; and as a result cellular pseudohypoxia and acidosis occur[8]. Also a small amount of cyanide may bind to the ferrous (Fe2+) iron of hemoglobin, to form cyanohemoglobin, which is unable to transport oxygen, thereby further exacerbating tissue hypoxia[9].

Cyanide is rapidly absorbed through the respiratory tract and mucous membranes, and it can also be absorbed through the gastrointestinal tract and skin. Intravenous and inhaled cyanide exposures produce more rapid onset of signs and symptoms than does oral or transdermal ingestions because they provide fast diffusion and direct distribution to target organs via the bloodstream[10].

Cyanide metabolism and neutralization involve a number of mechanisms. The primary endogenous mechanism of cyanide detoxification is metabolism in the liver by rhodanese to thiocyanate, which is a nontoxic compound excreted in the urine. Second and a minor pathway for cyanide detoxification involves hydroxocobalamin, the precursor to vitamin B12, to form cyanocobalamin. It is also excreted in the urine. Third, small amounts of cyanide that are not detoxified can be excreted unmetabolized in breath, urine, and sweat[10].

Clinical presentation

The clinical presentation of cyanide poisoning varies with the physicochemical form of cyanide, the dose, route of entry, co-toxicants (carbon monoxide, etc.) and delay since exposure. Because of being more sensitive to hypoxia, central nervous system and cardiovascular system dysfunction are most prominent. Nonspecific sings of cyanide poisoning are nausea, vomiting, headache, dizziness, confusion, coma, seizures, dilated pupils, and abnormal vital signs[11]. It causes an initial tachypnea and hyperpnea with tachycardia and hypertension that progress to apnea and cardiovascular collapse with dysrhythmias soon[11]. Cyanide toxicity expected to have two characteristic symptoms theoretically; those are cherry-red skin and odor of bitter almond from the victims' breath[12]. However, odor is not a valid assumption because half of the population unable to detect this odor[12]. Also, presence of cherry-red skin upon initial presentation, which is a result of increased venous hemoglobin oxygen saturation, has not a predictable incidence[13].

Survivors of severe cyanide toxicity may develop neurologic sequel including Parkinsonism, dystonia and dyskinesia, reflective of the involvement of the structures within the basal ganglia[14]. Neuroimaging may demonstrate radiologic changes several weeks after the exposure. Effects of acute cyanide poisoning on brain structure and function is unpredictable[14]. Resolution of symptoms is variable, and treatment is supportive.

Diagnosis

Routine laboratory evaluation in the potentially poisoned patient should include fingerstick glucose concentration, acetaminophen and salicylate levels to rule common coingestions, electrocardiogram and pregnancy test in women of childbearing age. Specific testing in cases of potential cyanide poisoning should also include the basic chemistries and arterial blood gas to assess for high anion gap metabolic acidosis[15].

Cyanide-poisoned patients have an elevated blood lactate concentration. Multivariate analysis conferred hyperlactacidemia as the lone factor which significantly predicted cyanide poisoning at an odds of 73.0 (5.7-936.1)[16]. A cutoff point of 8 mmol/L lactate level should be suggested as a diagnostic indicator of cyanide toxicity[16]. In the setting of smoke inhalation, a plasma lactate > 10 mmol/L should be more sensitive[11].

A narrowing of the venous-arterial PO2 gradient, in other words venous hyperoxia, may be seen in the cyanide-poisoned patient. However, this is a nonspecific finding and can result from other inhibitors of oxidative phosphorylation, such as carbon monoxide, hydrogen sulfide, and azides[9]. Therefore carboxyhemoglobin and methemoglobin levels should be checked, particularly if there is any concern for concomitant exposure. Cyanide poisoning can also cause renal failure, hepatic failure, rhabdomyolysis and pulmonary edema; so relevant studies should be obtained as indicated.

Blood cyanide level is the confirmatory test for cyanide poisoning and but it is not routinely performed in most hospitals and may not correlate with toxicity; therefore it cannot guide treatment[11]. Thus, cyanide poisoning is an uncommon entity and making the diagnosis requires a high index of clinic suspicion based on history and presentation.

Management

The treatment of patients poisoned with cyanide includes supportive care and adjunctive antidotal therapy.

General treatment

Cyanide toxicity is rapidly lethal, so clinicians must stabilize the patient's airway, breathing and circulation first. Intravenous access must be established and cardiac monitoring must be started. Intubation is usually required and high-flow oxygen should be administered regardless of pulse oximetry reading because %100 oxygen may enhance the effectiveness of antidotal theraphy by competing with cyanide for the cytochrome oxidase binding sites[1]. Mouth to mouth resuscitation must be avoided in case of suspected cyanide toxicity. Supportive care, rapid IV boluses of isotonic fluid and vasopressors as needed for treatment of hypotension and benzodiazepines for treatment of seizures, should be performed. Hyperbaric oxygen has been advocated as a potential adjunct for cyanide toxicity; however, the evidence for its efficacy in this situation is limited and conflicting[3].

Decontamination

Decontamination is an important step for the management of patients with cyanide poisoning. Patients poisoned by cyanide through inhalation must be removed from source into fresh air and contaminated cloths must be taken off and appropriately discarded. In case of dermal exposures skin must be washed with soap and water or water alone, eyes must be irrigated with saline and contact lenses must be removed[1].

In cases of oral ingestion gastrointestinal decontamination should be performed rapidly. Activated charcoal of a single dose (1 g/kg, max 50 gr) may be administered if the victim is alert and ingestion occurred within 1 hour[9]. Emesis should not be induced and must be isolated[1]. Rescuers should wear protective suits such as face masks, eye shields and double gloving, during decontamination.

Antidotes

Cyanide is a rapidly lethal toxin and antidotal treatment must take place immediately in order to be effective. However, patients may benefit from receiving antidotes after some delay. In a case series antidote administered to 14 consecutive patients beginning a median 2.1 hours (15 min – 5 ½ hour) after cyanide ingestion or inhalation, and ten patient survived[17]. This confirms that excellent supportive care can gain additional time to treat with antidotes[11].

Antidotal treatment of cyanide poisoning involves three strategies which are binding of cyanide, induction of methemoglobinemia, and use of sulfur donors.

- Direct cyanide binding: Hydroxocobalamin and dicobalt edetate are in this group.
  - o Hydroxocobalamin

Hydroxocobalamin has been employed as a cyanide antidote since the early 1970s[11]. It is a vitamin B12 precursor and with its cobalt component in its structure bind to intracellular cyanide with a greater affinity than cytochrome oxidase and forming cyanocobalamin; a stable molecule that excreted in the urine[18].

Hydroxocobalamin is available as Cyanokıt® (2.5 g/vial, 2 vials). Recommended initial dose is 5g intravenously over 15 minutes. Depending on the severity of poisoning it may be repeated for a total of 10g. Its pediatric dose is 70mg/kg[11].

Existed data suggest that hydroxocobalamin is lacking in clinically significant adverse effects; rare adverse effects included dyspnea, facial edema and urticaria[18]. It may cause a reddish discoloration of the skin, plasma, urine and mucous membranes[17]. Intravenous infusion of hydroxocobalamin has confounding effects on therapeutic measures such as total hemoglobin, carboxyhemoglobin, methemoglobin, and oxyhemoglobin, which makes the assessment of smoke inhalation victims difficult[18].

In general hydroxocobalamin as first-line antidotal therapy is effective and safe in acute cyanide poisoning[17].

  - o Dicobalt edetate

Dicobalt edetate is a cobalt compound, whose efficacy being based upon the fact that cyanide combines with cobalt to form a relatively non-toxic complexes[19]. It is found as Kelocyanor %1,5® (300mg/20ml) ampules at National Poison Counselling Center. Recommended adult dose is 300 mg over 1 minute, followed immediately by 50 ml of 50% dextrose[11].

Adverse effects reported have included hypertension, tachycardia, nausea, retrosternal pain, sweating, palpebral, facial and laryngeal edema, vomiting, urticaria and/or a feeling of impending doom; which appear particularly when administered in the absence of intoxication[19].

- Induction of methemoglobinemia: Amily nitrite, sodium nitrite and 4dimethylaminophenol are in this group.
  - o Nitrites

Nitrite-based cyanide antidotes oxidize hemoglobin to methemoglobin which provides an attractive alternative binding site for cyanide, in direct completion with the site on the cytochrome, and it formed a less toxic compound[2].

Amyl nitrite was the first cyanide antidote, since 1888. Its use is attractive for first aid because it's inhaled from a crushed capsule, so easy to use; however it only produces about 7% methomoglobin which is insufficient to bind a lethal dose of cyanide[1]. It should be administered one capsule at a time and held in front of the patient's mouth for 15 seconds, followed by rest for 15 seconds, until intravenous access is obtained and sodium nitrite infusion is started[11].

Sodium nitrite administered intravenously with adjustment to maintain methemoglobin levels ≤ 40%[2]. Its recommended adult dose is 300 mg within 3 -5 minutes, for pediatric patient dose is 6 mg/kg (max 300 mg)[1]. The dose is often repeated at 30 minutes if the clinical response is inadequate.

A significant adverse effect of the nitrites is hypotension, induced by the release of nitric oxide[11]. Another important consideration is the production of methemoglobin that shifts the oxygen-hemoglobin dissociation curve to the left further hindering oxygen delivery to tissues. So nitrites are not suitable for fire victims, and those with poor cardiopulmonary reserve[11]. Appropriate dose of sodium nitrite is adjusted according to the patient's hemoglobin levels[9]. Nitrites should also be avoided in pregnant patients because of the oxidative stress on fetal hemoglobin[1].

There were also new researches on better and safer antidotes against cyanide poisoning. It was demonstrated in an animal study that isosorbide dinitrate may have a potential to be an antidote against cyanide poisoning[20].

- o 4-Dimethylaminophenol

4-Dimethylaminophenol is a potent methomoglobin inducer which is used as a choice of antidote in German and Austria with a recommended intravenous dose of 3, 25 mg/kg.[11]. Adverse effects include reticulocytosis, nephrotoxicity, and hemolysis[21].

- Sulfur donors: Sodium thiosulfate is in this group.

Sodium thiosulfate applies a sulfur molecule to rhodanese and allows formation of thiocyanate and regeneration of the native enzyme[11]. Thicyanate excreted renally. Its recommended adult dose is 12.5 g by slow intravenous route and pediatric dose is 7 g/m^2 [11]. Adverse effects include local skin and muscle pain at infusion site, nausea, vomiting, headache and disorientation[2]. Its slow onset of action is a disadvantage for its use as the sole medication in antidotal theraphy[1].

Cyanide Antidote Kid which has been used for decades for acute cyanide poisoning, consists of 3 medications given together for their synergistic effect: amyl nitrite, sodium nitrite, and sodiumthiosulfate.

Table 1. Recommendation for antidotal treatment strategies in case of cyanide poisoning for adults

Situation	Recommended antidote regime
In case of probable cyanide intoxication	
• If hydroxocobalamin is available	Hydroxocobalamin (Cyanokit®) 5 g IV over 15 min AND Sodium thiosulfate 12.5 g IV over 30 min
• If hydroxocobalamin is not available o And if there is no contraindication to nitrites	Cyanide Antidote Kit® Amyl nitrite inhaled for 15 sec, followed by 15 sec rest until sodium nitrite infusion started AND Sodium nitrite 300 mg IV over 3-5 min AND Sodium thiosulfate 12.5 g IV over 30 min
• If hydroxocobalamin is not available o And if there is a contraindication to nitrites	Sodium thiosulfate 12.5 g IV over 30 min
• If hydroxocobalamin and Cyanide Antidot Kit are not available	4-Dimethylaminophenol 3.25 mg/kg over 1 min OR • And if the diagnosis is clear Dicobalt edetate (Kelocyanor %1,5®) 300 mg over 1 min
In case of questionable cyanide intoxication	
• If hydroxocobalamin is available	Hydroxocobalamin (Cyanokit®) 5 g IV over 15 min AND Sodium thiosulfate 12.5 g IV over 30 min
• If hydroxocobalamin is not available o And if Cyanide Antidot Kit is available	Sodium thiosulfate 12.5 g IV over 30 min

*Abbrevations: IV; intravenous, min; minute, g; gram

In line with the above information, recommendations regarding antidote selection in cyanide poisoning are summarized in Table 1[9].

Conclusion

Cyanide poisoning is a rapidly lethal, serious poisoning. Clinical features are dependent on the route, duration and amount of exposure. Serum lactate levels can be used for confirmation of the diagnosis and predict the severity of poisoning. Supportive care, decontamination and adjunctive antidotal therapy are the main element of management. Recommendation for antidotal treatment strategies in case of cyanide poisoning depends on the availability of antidotes and accuracy of the diagnosis.

References

1. Hamel J. A review of acute cyanide poisoning with a treatment update. Crit Care Nurse. 2011; 31(1):72-81; quiz 82.
2. Reade MC, Davies SR, Morley PT, Dennett J, Jacobs IC. Review article: management of cyanide poisoning. Emerg Med Australas. 2012; 24(3): 225-38.
3. MacLennan L, Moiemen N. Management of cyanide toxicity in patients with burns. Burns. 2015; 41(1): 18-24.
4. Kaita Y, Tarui T, Shoji T, Miyauchi H, Yamaguchi Y. Cyanide poisoning is a possible cause of cardiac arrest among fire victims, and empiric antidote treatment may improve outcomes. Am J Emerg Med. 2018; 36(5): 851-853.
5. Karadeniz H, Birincioğlu İ, Zazoğlu S, Ketenci HÇ. The importance of the toxicological analysis of death cases caused by cyanide poisoning: A case report. J For Med 2017; 31(2):96-100
6. Prochalska C, Megarbane B, El Balkhi S, Poupon J, Baud FJ, Garnier R. Poisoning with gold potassium cyanide and other metallic cyanides in a jeweler. Clin Toxicol (Phila). 2014; 52(8):907-8.
7. Thomas C, Svehla L, Moffett BS. Sodium-nitroprusside-induced cyanide toxicity in pediatric patients. Expert Opin Drug Saf. 2009; 8(5):599-602.
8. Sips PY, Shi X, Musso G, Nath AK, Zhao Y, Nielson J, et al. Identification of specific metabolic pathways as druggable targets regulating the sensitivity to cyanide poisoning. PLoS One. 2018; 13(6):e0193889. doi: 10.1371/journal.pone.0193889.
9. Shoma D, Mark S. Cyanide poisoning. (Revised 2019 Mar 25, Cited 2020 Feb 17.) Avaliable from: https://www.uptodate.com/contents/cyanide-poisoning.
10. Nelson L. Acute cyanide toxicity: mechanisms and manifestations. J Emerg Nurs. 2006; 32(4 Suppl):S8-11.
11. Borron SW, Baud FJ. Antidotes for acute cyanide poisoning. Curr Pharm Biotechnol. 2012; 13(10): 1940-8.
12. Suman SG, Gretarsdottir JM. Chemical and Clinical Aspects of Metal-Containing Antidotes for Poisoning by Cyanide. Met Ions Life Sci. 2019;14(19): 359-391.
13. Parker-Cote JL, Rizer J, Vakkalanka JP, Rege SV, Holstege CP. Challenges in the diagnosis of acute cyanide poisoning. Clin Toxicol (Phila). 2018;56(7): 609-617.
14. Mohan A, Lee T, Sachdev P. Surviving acute cyanide poisoning: a longitudinal neuropsychological investigation with interval MRI. BMJ Case Rep. 2014. doi: 10.1136/bcr-2013-203025.
15. Hsiao PJ, Chang CF, Chiu CC, Chan JS, Chiang WF, Wu CC, et al. High Anion Gap Metabolic Acidosis after a Suicide Attempt with Cyanide: The Rebirth of Cyanide Poisoning. Intern Med. 2015; 54(15): 1901-4.
16. Baud FJ, Haidar MK, Jouffroy R, Raphalen JH, Lamhaut L, Carli P. Determinants of Lactic Acidosis in Acute Cyanide Poisonings. Crit Care Med. 2018; 46(6): e523-e529. doi: 10.1097/CCM.0000000000003075.
17. Borron SW, Baud FJ, Mégarbane B, Bismuth C. Hydroxocobalamin for severe acute cyanide poisoning by ingestion or inhalation. Am J Emerg Med. 2007; 25(5): 551-8.
18. Thompson JP, Marrs TC. Hydroxocobalamin in cyanide poisoning. Clin Toxicol (Phila). 2012; 50(10): 875-85.
19. Marrs TC, Thompson JP. The efficacy and adverse effects of dicobalt edetate in cyanide poisoning. Clin Toxicol (Phila). 2016; 54(8): 609-14.
20. Lavon O, Avrahami A, Eisenkraft A. Effectiveness of isosorbide dinitrate in cyanide poisoning as a function of the administration timing. BMC Pharmacol Toxicol. 2017 Mar 14; 18(1):13.
21. Mégarbane B, Delahaye A, Goldgran-Tolédano D, Baud FJ. Antidotal treatment of cyanide poisoning. J Chin Med Assoc. 2003; 66(4):193-203

Review Article
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Platelet Rich Plasma

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Abstract

Platelet rich plasma (PRP) is a blood product obtained by centrifuge of blood which contains more thrombocytes than normal plasma. Although this measurement may be effected by given methods, thrombocyte count is approximately 3-5 times higher in PRP than ordinary plasma. PRP is not a drug but an autologous tissue graft and it is unlikely see allergic reactions and transmitted diseases after the procedure. PRPmay be classified according to the preparation technique and the resulting product content. Aim of the PRP therapy is to administer the rich contents of alpha and dens granules contained by platelets to the relevant medium. More comprehensive studies are needed about this specific therapy in order to clear all the question marks about the topic.

Key words: Platelet rich plasma, hemostasis, plasma components

Özet

PRP (Platelet Rich Plasma) kişinin kendi kanının yüksek hızlı merkez kaç kuvveti ile bileşenlerine ayrılması sonucu oluşan kan ürünüdür. Yönteme göre değişmekle birlikte ortalama trombosit sayısı 3-5 kat artar, yani PRP sınır değerinin üzerinde trombosit içeren plazmadır. PRP bir ilaç değil bir dokudur yani otolog bir greft olması nedeniyle alerjik reaksiyonlar oluşturması veya dışarıdan bir bulaşıcı hastalık taşıyabilmesi çok zordur.PRP hazırlanış tekniği ve sonunda oluşan ürün içeriğine göre sınıflandırılabilir. PRP kullanımındaki asıl amaç, trombositlerin içerdikleri alfa ve dens granürlerinin zengin içeriklerinin ortama tedavi amaçlı salınımının sağlanmasıdır. Sonuç olarak etkileri ve tedavi süreci ile ilgili soru işareti barındıran bu tedavi yöntemi ile ilgili daha fazla çalışma yapılmasına ihtiyaç vardır.

Anahtar kelimeler: Trombositten zengin plazma,hemostaz,plazmanın hücresel komponentleri

Platelet rich plasma (PRP) is a blood product obtained by centrifuge of blood which contains more thrombocytes than normal plasma. Although this measurement may be effected by given methods, thrombocyte count is approximately 3-5 times higher in PRP than ordinary plasma. Due to high concentration of platelets, PRP contains hyper-physiological amount of growth factors[1, 2]. Henceforth PRP accelerates healing in ligament and muscle injuries and this effect has been shown in animal trials[3]. Aim of the PRP therapy is to administer the rich contents of alpha and dens granules contained by platelets to the relevant medium.

Thrombocytes are small cells without nucleus and play a major role in hemostasis. Other future of thrombocytes is to release the certain cytokines, growth factors and bioactive factors in order to give a start and to organize the wound healing[4]. Thrombocyte count reaches to peak level in the early phases of wound healing. Platelets are in discoid shape when they are inactive. When they are activated by thrombin, platelets form pseudpods. Active platelets release coagulation and growth factors in which contained dense and alpha granules in to the medium. The sources of the protein profile of the platelets are megakaryocytes and plasma[5]. Contents of the alpha and dense granules are shown in the Table 1[6]. More than 200 different proteins contained by alpha granules are defined in a study which was conducted in 2007. More than 40 different proteins contained by dense granules are defined in another study. Those proteins were shown to be crucial proteins in regeneration and glycolysis processes. Coagulation, inflammation and wound remodeling have an effect the on quantity and quality of proteins synthesized in thrombocytes[7,8].

PRP was first described by Marx et. al. but its ancestor is effects of fibrin glue in wound healing investigated by Matras. In order to accelerate the activation of fibrin glue, high amount of thrombin and thrombocyte was added in 1975-1976. Natural process of wound healing had been tried to be imitated by this method. Following this attempt, this concept was named as tissue regeneration. PRP was first used maxillofacial surgery in the early 2000. FDA approved the PRP therapy for muscle and bone injuries in 2012[9]. Later on, therapeutic area of PRP was broadened.

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Received: 13.01.2020 • **Accepted:** 20.03.2020
Cite this article as: Turgut MC, Akgol Gur ST, Erbay MF. Platelet rich plasma. Eurasian J Tox. 2020;2(1):7-10.

PRP imitates natural mechanism of wound healing and growth factors, chemokines, and proteins released by alpha and dense granules in which contained platelets leads to tissue regeneration. Because of PRP contains hyper-physiological amount of growth factors, PRP improves healing in chronic wounds and accelerates the healing in acute injuries[10,11].

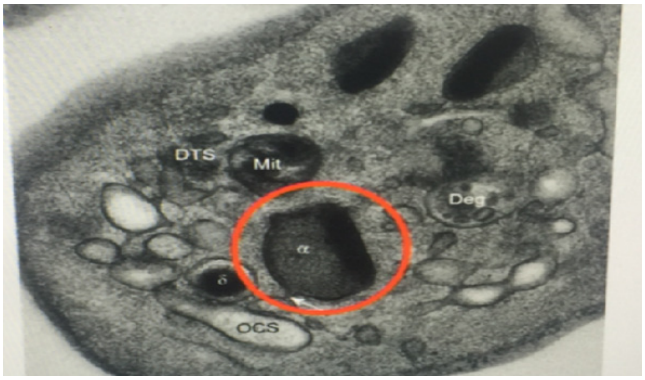

Image 1. Alpha granules under the microscope

Preparing PRP and PRP variations

Cellular components of the plasma are distributed as 93% erythrocytes, 6% platelets and 1% leukocytes. PRP contains 3-5 times higher amount of thrombocyte than complete blood. PRP is obtained by centrifuge of anticoagulated autologous complete blood. Citrate is added to complete blood before the centrifuge in order to bind the ionized calcium. So that coagulation is prevented. After the centrifuge, complete blood dissociates into 3 layers (Table 2). Upper layer contains plasma, middle layer contains thrombocytes and leukocytes which known as "buffy coat" and lower layer contains erythrocytes. It is reported that buffy coat and plasma layers may be centrifuged following the first process and PRP and platelet poor plasma may be dissociated further.

PRP may be classified as pure-platelet rich plasma (P-PRP), leukocyte and platelet rich plasma, (L-PRP), pure platelet rich fibrin (P-PRF), leucocyte and platelet rich fibrin (L-PRF) in relation to preparation method and end product. PRP must be prepared in sterile laboratory environment (Image 2). Moreover, there are many commercial PRP kits in order to obtain it.

Recently there are 4 different platelet rich plasma products[12]. Those are classified in accordance with platelet and leukocyte contents of the end product.

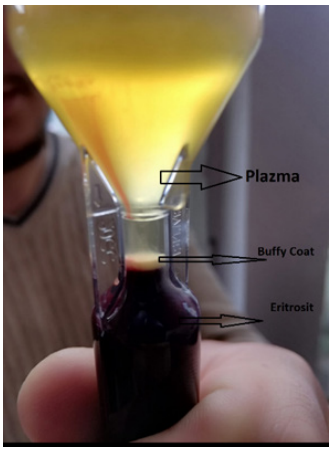

Image 2. 3 dissociated layers of complete blood after centrifuge.

P-PRP

P-PRP is dissociated from leukocytes by plasmapheresis alike methods. It is harder, longer and more expensive to obtain P-PRP than other products. There are approximately no leukocytes in it, if there is any. It may be injected in liquid form. It may be loaded to active membrane or gel.

L-PRP

Standard centrifuge methods are performed to obtain L-PRP. Obtained plasma contains thrombocytes and leukocytes. It may be used in a liquid form or activated gel form as P-PRP. Most known and most produced PRP kind is L-PRP. Aim of the kits is to make more practical to obtain L-PRP.

1. Pure Platelet Rich Plasma (P-PRP)	→	Fibrine clot (+)
2. Leucocyte – Platelet Rich Plasma(L-PRP)	→	Fibrin clot (+)
3. Pure Platelet Rich Fibrin (P-PRF)	→	Fibrin clot (-)
4. Leucocyte – Platelet Rich Fibrin (L-PRF)	→	Fibrin clot (-)

Table 1. Contents of the granules of thrombocytes

Alpha Granules	Dense Granules
-Integral membrane proteins	-Cations
-Coagulation proteins	-Phosphates
-Adhesion proteins	-Bioactive amines
-Chemokines	-Nucleotidies
-Growth Factor	
-Pro-angiogenic and Anti-angiogenic factors	
-Microbiological proteins	

Indications of PRP
• Soft Tissue Injuries
• Bone Healing
• Cosmetic and Aesthetic Purposes
• Algology
• Chondral - Osteochondral Lesions
• Lateral epicondylitis
• Osteoarthritis
• Tendinopathies
• Acute or chronic ligament injuries
• Acute or chronic muscle injuries
• Rotator cuff rehabilitation
• ACL reconstruction
• Meniscus injuries

P-PRF

P-PRF results from two phases of centrifuge. Leukocytes are dissociated in the first phase. After aforementioned phase, added CaCl activates thrombocytes and result in platelet-fibrin clot. Because P-PRF is solid it does not fit for injection. Spesific future of this method is utilizing the seperation gel.

L-PRF

It was first described by Choukroun et. al. This method is cheap and simple. Anticoagulant substance does not added to centrifuge tube. There is no need to use activator. It can be used as an autologous biomaterial. Leukocytes and thrombocytes interacts with each other. L-PRF is also known as "the ideal blood product" because it is the most natural product among others. It does not fit for injection but may be used as a solid biomaterial.

Recently indications of PRP therapy get wider. Higher amounts of blood result in higher amount of PRP, theoretically. Small lesions like epicondylitits necessitates 3 ml of PRP however big lesions like rotatory cuff tears necessitates 5-6 ml of PRP. Local ice packs, elevation and activity modification is suggested in case patients might have local inflamatory reaction during 24-48 hours following the injection. Asetaminofens and opioids may be used for analgesic pusposes but non steroid anti inflamatory drugs (NSAIDs) are not suggested for 2-4 weeks. NSAIDs inhibts the prostoglandin pathway and may block the benefits stimulated by growth factors.

Contraindications

PRP is not a drug but an autologous tissue graft and it is unlikely see allergic reactions and transmitted diseases after the procedure. However serious allergic reactions may be encountered when cattle thrombin is used for activating thrombin, during the preparation of PRP. Local inflammation, pain and edema may occur after PRP therapy. Although it is claimed that PRP stimulates the growth factors and theoretically this condition may provoke the development neoplasms; there is no solid evidence to support this hypothesis[4]. Contraindications of PRP includes malignancy and metastasis, active infection, thrombocytopenia, anemia, pregnancy and lactation and allergy to cattle thrombin[13].

Discussion

Even though there are so many reports about the PRP in the current literature and 25% of the papers published in the last 5 years, authors do not concur the effects and protocols of the PRP. Unfortunately, there is no guideline about how to use PRP in muscle and bone diseases. However, it is reported that PRP does not cause any side effects according to AAOS guideline.

There are 3 basic debates about PRP therapy. First of them whether thrombocytes should be activated when it is injected to the relevant medium. If platelets to be activated, whether CaCl or cattle thrombin must be selected as a platelet activator. Researches showed that activated thrombocytes releases 12 different cytokines into the medium via alpha granules[14]. Especially PDGF and TGF are released in higher concentrations among other cytokines. Both PDGF and TGF binds to present clot and they are released rhythmically for a long period and attracts mesenchymal stem cells and leads to mitogenic activity[15].

Second debate topic is the comparison of the effectivity of L-PRP and L-PRF. L-PRF, firstly developed by Chokuron et. al. in 2001, is thought to be safer and more practical because thrombin and CaCl are not needed in the preparation period of L-PRF and there is a one certain protocol to administer it[14,16]. Disadvantageous sides of the L-PRF are limited obtainable amount of the L-PRF and specificity of donor[17].

Third debate topic is the leukocyte content of PRP. Nowadays since leukocytes may increase the local inflammation, leukocyte poor substances are believed to be superior to leukocyte rich ones[18].

It is believed that PRP is beneficial since it increases cell proliferation and matrix synthesis however the reasons of the different effects of it on the individual basis is still unknown. Also the is no concurrence about the optimum PRP formula, duration and doses of administration and rehabilitation after PRP proper protocol. More comprehensive studies are needed about this specific therapy in order to clear all the question marks about the topic.

References

1. Nguyen RT, Borg-Stein J, McInnis K. Applications of platelet-rich plasma in musculoskeletal and sports medicine: an evidence-based approach. PM&R. 2011;3(3):226-50.
2. Paoloni J, De Vos RJ, Hamilton B, Murrell GA, Orchard J. Platelet-rich plasma treatment for ligament and tendon injuries. Clinical Journal of Sport Medicine. 2011;21(1):37-45.
3. Rees JD, Maffulli N, Cook J. Management of tendinopathy. The American journal of sports medicine. 2009;37(9):1855-67.
4. Foster TE, Puskas BL, Mandelbaum BR, Gerhardt MB, Rodeo SA. Platelet-rich plasma: from basic science to clinical applications. The American journal of sports medicine. 2009;37(11):2259-72.
5. Park JE, Barbul A. Understanding the role of immune regulation in wound healing. The American Journal of Surgery. 2004;187(5):S11-S6.
6. Siegel A, Lüscher E. Non-identity of the α-granules of human blood platelets with typical lysosomes. Nature. 1967;215(5102):745.
7. Maynard D, Heijnen H, Horne M, White J, Gahl W. Proteomic analysis of platelet α-granules using mass spectrometry. Journal of Thrombosis and Haemostasis. 2007;5(9):1945-55.
8. Rendu F, Brohard-Bohn B. The platelet release reaction: granules' constituents, secretion and functions. Platelets. 2001;12(5):261-73.
9. Sonnleitner D, Huemer P, Sullivan DY. A simplified technique for producing platelet-rich plasma and platelet concentrate for intraoral bone grafting techniques: a technical note. International Journal of Oral & Maxillofacial Implants. 2000;15(6).
10. Khan KM, Cook JL, Bonar F, Harcourt P, Åstrom M. Histopathology of common tendinopathies. Sports Medicine. 1999;27(6):393-408.
11. de Mos M, van der Windt AE, Jahr H, van Schie HT, Weinans H, Verhaar JA, et al. Can platelet-rich plasma enhance tendon repair? A cell culture study. The American journal of sports medicine. 2008;36(6):1171-8.
12. Yıldız C, Özgürtaş T. Trombositten zengin plazma. TOTBİD Dergisi, 2017, 16(3): 247-58
13. Sampson S, Gerhardt M, Mandelbaum B. Platelet rich plasma injection grafts for musculoskeletal injuries: a review. Current reviews in musculoskeletal medicine. 2008;1(3-4):165-74.
14. Breen A, O'Brien T, Pandit A. Fibrin as a delivery system for therapeutic drugs and biomolecules. Tissue Engineering Part B: Reviews. 2009;15(2):201-14.
15. Catelas I, Dwyer JF, Helgerson S. Controlled release of bioactive transforming growth factor beta-1 from fibrin gels in vitro. Tissue Engineering Part C: Methods. 2008;14(2):119-28.
16. Choukroun J, Adda F, Schoeffler C, Vervelle A. Une opportunité en paro-implantologie: le PRF. Implantodontie. 2001;42(55):e62.
17. Prakash S, Thakur A. Platelet concentrates: past, present and future. Journal of maxillofacial and oral surgery. 2011;10(1):45-9.
18. Jain A, Bedi RK, Mittal K. Platelet-rich plasma therapy: a novel application in regenerative medicine. Asian journal of transfusion science. 2015;9(2):113.

Original Article

Eurasian Journal of Toxicology

Evaluation of Patients Admitted To Emergency Department Due To Drug-Related Suicide Attempt

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Abstract

Objective: Suicide is the self-injurious behavior that is intended to kill oneself and it is called as suicide attempt if not resulted with death. Although the ranking varies by countries, the drug-related suicide attempt is always in the top three methods. The aim of this study was to investigate the data of the patients admitted to emergency department (ED) due to drug-related suicide attempt.

Material and Methods: This is a retrospective, cross sectional, observational, single centered study that was conducted in a research hospital. Patients over 18 years of age admitted to ED with a drug-related suicide attempt between 01.01.2019 and 31.12.2019 were included. Age, gender, nationality, admission complaints, presence of psychiatric illness and medication usage history, drugs used for suicidal intervention, follow-up duration at ED, patient outcome, psychiatric consultation status at ED were checked.

Results: A total of 330 patients were included. Three fourth (74.8%) of the patients were female and median age was 31 (IQR 23 – 38). Ten (3%) patient were refugees. Only 51 (15.5%) of patients had a known history of psychiatric illness. Most commonly used drugs for suicidal intervention were paracetamol, NSAIDs (Non Steroid Anti-inflammatory Drugs), antibiotics and antidepressants. Suicide attempt with antipsychotic and antidepressant drugs were significantly higher at patients with positive psychiatric illness history. Median follow-up duration at ED was 375 min (IQR 221 - 642) and most of the patients (81.7%) were discharged. Number of patients consulted with psychiatrist was only 63 (19.1%).

Conclusion: Our study demonstrated that being female, young, being a migrant, having a psychiatric illness and being in the warmer months of the year were related with the increased suicide attempts. Parasetamol, NSAID and antibiotics were most commonly used drugs and suicide attempt with antidepressants and antipsychotic drugs were significantly higher in the presence of psychiatric illness history. Most of the time the clinical course of drug-related suicide attempt cases were benign and they were discharged after follow-up at ED. Frequency of consultation with a psychiatrist was very low. Suicide is a public health problem and it is estimated that an ED admission related to self-injury is the highest risk factor for a future completed suicide. Therefore, all patients admitted to ED due to suicide attempt must be consulted with the psychiatrist for further evaluation in terms of risk of future suicidal behavior and implementation of targeted treatment approaches.

Key words: Suicide, drug-related, toxicity

Özet

Amaç: Suisit kişinin kendini öldürmek amaçlı kendine zarar vermesi davranışıdır ve eğer ölümle sonuçlanmazsa buna suisit girişimi denir. Sıralama ülkeden ülkeye değişse de ilaçla intihar her zaman en sık kullanılan ilk üç yöntem arasındadır. Bu çalışmanın amacı acil servise (AS) ilaçla intihar girişimi nedeniyle başvurmuş hastaların verilerini incelemektir.

Gereç ve yöntem: Bu çalışma bir araştırma hastanesinde yapılmış retrospektif, kesitsel, gözlemsel, tek merkezli bir çalışmadır. 01.01.2019 ve 31.12.2019 tarihlerinde 18 yaş üstü ilaçla intihar girişimi nedeniyle acil servise başvuran hastalar dahil edilmiştir. Yaş, cinsiyet, başvuru şikayeti, psikiyatrik hastalık ve ilaç kullanım öyküsü, suisit amaçlı kullanılan ilaçlar, AS'de takip süresi, hasta sonlanımı, AS'de psikiyatri konsültasyonu istenip istenmediği incelenmiştir.

Bulgular: Toplam 330 hasta dahil edilmiştir. Hastaların dörtte üçü (74.8%) kadındır ve medyan yaş 31 (IQR 23 – 38)'dir. On (3%) hasta göçmendir. Hastaların sadece 51 (15.5%)'inde bilinen psikiyatrik hastalık öyküsü vardır. İntihar girişimi amaçlı en sık kullanılan ilaçlar parasetamol, NSAIDler (Non Steroid Anti-inflamatuar İlaçlar), antibiyotikler ve antidepresanlardır. Antidepresan ve antipsikotikler ile intihar girişimi psikiyatrik hastalık öyküsü pozitif olanlarda belirgin olarak yüksektir. AS'de medyan takip süresi 375 dkdır IQR 221 - 642) ve hastaların çoğu (81.7%) taburcu olmuştur. Psikiyatri ile konsülte edilen hasta sayısı sadece 63 (19.1%)'dür.

Sonuç: Çalışmamız kadın, genç, göçmen, psikiyatrik hastalık sahibi olmanın ve yılın sıcak aylarında olmanın artmış intihar girişimi ile ilgili olduğunu göstermiştir. Prasetamol, NSAID ve antibiyotikler en sık kullanılan ilaçlardır ve antidepresan ve antipsikotikler ile intihar girişimi psikiyatrik hastalık varlığında anlamlı olarak yüksektir. Çoğu zaman ilaçla intihar girişimi vakalarının klinik seyri benindir ve AS'deki takip sonrası taburcu edilmişlerdir. Psikiyatrist ile konsültasyon sıklığı çok düşüktür. Suisit bir halk sağlığı sorunudur ve AS'e kendine zarar verme nedenli başvuruların gelecekte tamamlanmış bir intihar için en yüksek risk faktörü olduğu tahmin edilmektedir. Bu yüzden AS'e intihar girişimi ile başvuran tüm hastaların gelecekteki intihar davranışı açısından risklerin değerlendirilmesi ve hedefe yönelik tedavi yaklaşımlarının uygulanması için psikiyatrist ile konsülte edilmeleri gerekir.

Anahtar kelimeler: Suisit, ilaç-ilişkili, toksisite, psikiyatri konsültasyonu

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Received: 09.03.2020 • **Accepted:** 13.03.2020

Cite this article as: Isik Cikrikci G, Safak T, Sencanlar Cetiner H, Cevik Y. Evaluation of patients admitted to emergency department due to drug-related suicide attempt. Eurasian J Tox. 2020;2(1):11-14.

Introduction

Suicide is the self-injurious behavior that is intended to kill oneself and it is called as suicide attempt if not resulted with death. World Health Organization (WHO) reported, one person die due to suicide every 40 seconds and suicide is the second leading cause of death among 15-29 year olds globally[1]. According to Turkey Statistical Institute (TUIK)'s data, the suicide rate in Turkey has increased compared to the beginning of the 2000s and has 3161 people committed suicide in 2018[2]. There are indications that for each adult who died by suicide there may have been more than 20 others attempting suicide[1]. So, considering those huge numbers, suicide is an undeniably important public health problem.

Methods used in suicide differ according to their lethality which is determined by the time span between the initiation of a suicidal act and expected death, and availability of medical aid [3]. Although the ranking varies by countries, the drug-related suicide attempt is always in the top three rows[4]. Recognition of frequently used medicines for suicidal interventions will help the physician to notice and better manage the clinical scenarios that may occur due to toxicity.

The aim of this study was to investigate the data of the patients admitted to emergency department (ED) due to drug-related suicide attempt in 2019 to identify the commonly used drug groups for suicidal interventions. Thus, it is aimed to increase awareness of physicians about toxicological findings that may develop at those patients.

Material and Methods

This is a retrospective, cross sectional, observational, single centered study that was conducted in a research hospital with the approval of the local Medicine Expertise Training Board. Patients over 18 years of age admitted to ED with a drug-related suicide attempt between 01.01.2019 and 31.12.2019 were included. Suicide attempts with any other method such as hanging, firearm etc. and accidental drug misuse were excluded.

Age, gender, nationality, admission complaints, presence of psychiatric illness and medication usage history, drugs used for suicidal intervention, follow-up duration at ED, patient outcome (discharge, admission to service, admission to intensive care unit (ICU)), psychiatric consultation status at ED were checked by using the data at patient files and hospital registration system.

Statistical Analyzes

The statistical analysis was performed using the Statistical Package for the Social Sciences version 22.0 (SPSS Inc., Chicago, IL, USA). After assessing normal distribution using the Kolmogorov-Smirnov test, all variables were described in terms of mean ± standard deviation or median and interquartile range (IQR) (25–%75) and the qualitative data were expressed as case number (n) and percentages (%). Categorical variables were analyzed using the Pearson chi-squared test. A p-value of <0.05 was considered to be statistically significant.

Results

Characteristics of 330 patients whose data were available and meeting the inclusion criteria were examined. Three fourth (74.8%) of the patients were female and median age was 31 (IQR 23 – 38). Ten (3%) patient were refugees. Only 51 (15.5%) of patients had a known history of psychiatric illness. Most of the suicide attempts were done in the summer (Table 1).

Table 1. Characteristics of drug-related suicide attempted patients

Variable	Number (freguency)
Gender	
Female	247 (74.8%)
Male	83 (25.2%)
Age	31 (IQR 23 – 38)
Nationalıty	
Turkish	320 (97%)
Others	10 (3%)
Presence of psychiatric illness history	
Not known	279 (84.5%)
Yes	51 (15.5)
Seasonal frequency of suicide attempts	
Winter	85 (25.8%)
Autumn	69 (21%)
Summer	110 (33.3%)
Spring	65 (19.8%)

Most commonly used drugs for suicidal intervention were paracetamol, NSAIDs (Non Steroid Anti-inflammatory Drugs), antibiotics and antidepressants. Suicide attempt with anti-diabetic and cardiovascular system drugs (such as beta blockers, antihypertensive drugs) were rare (Table 2). It was observed that most patients had multiple drug intake and frequently used drugs such as paracetamol and NSAIDs commonly involved in these combinations. SSRIs (Selective Serotonin Reuptake Inhibitors) were most commonly used antidepressant drugs for suicidal interventions. Also suicide attempt with antipsychotic and antidepressant drugs were significantly higher at patients with positive psychiatric illness history (p <.001 for all circumstances) (Table 3).

Median follow-up duration at ED was 375 min (IQR 221 - 642) and most of the patients (81.7%) were discharged.

Table 2. Drugs used for suicidal intervention

Drug group	n	%
Paracetamol	**64**	**19.4**
Paracetamol + NSAID	25	
Paracetamol + antibiotics	15	
Paracetamol + any other drugs	14	
NSAID	**89**	**27**
NSAID + antibiotics	27	
NSAID + any other drugs	51	
Antibiotics	**67**	**20.3**
Antibiotics + paracetamol + NSAID	7	
GIS drugs	**33**	**10**
Cardıovascular system drugs	**17**	**5.2**
Anti-diabetic drugs	**3**	**.9**
Vitamin and iron supplements	**25**	**7.6**
Antipsychotic drugs	**39**	**11.8**
Antidepressant drugs	**74**	**22.4**
Antidepressant + antipsychotic drugs	12	
Others	**142**	**43**

*Abbreviation: NSAID: non-steroid anti-inflammatory drug, n: number

Table 3. Relation between suicide intervention with antipsychotic and antidepressant drugs and presence of psychiatric illness history (as number and frequency)

Presence of psychiatric illness history	Suicide attempt with Antipsychotic	P value	Suicide attempt with Antidepressants	P value
Unknown	22 (7.9%)	**<.001**	47 (16.8%)	**<.001**
Yes	17 (33.3%)		26 (51%)	

Table 4. Variables related to ED process of the drug-related suicide attempt cases

Variable	Median (ınterquartile range 25 -75) or number (frequency)
Follow-up duration at ED	375 min (IQR 221 - 642)
Psychiatric consultation status	
Yes	63 (19.1%)
No	267 (80.9)
Outcome	
Discharged	266 (81.7%)
Service admission	17 (4.7%)
Intensive care unit admission	46 (13.7%)
Applied active charcoal	160 (48.5%)
Applied gastric lavage	18 (5.5%)
Period between the drug intake and ED application	96.5 min (IQR 60 – 180)

Seventeen (4.7%) patient admitted to service and 46 (13.7%) patient admitted to intensive care unit. Nearly half of the patients applied active charcoal but only 18 (5.5%) applied gastric lavage. We also analyzed the period between the drug intake and ED admission. Median time of this duration was 96.5 min (IQR 60 – 180). Number of patients consulted with psychiatrist was only 63 (19.1%) (Table 4).

Discussion

Life time prevalence of suicide attempts is 3% and admission of patients due to drug-related suicide attempt to the EDs is a common entity[5]. Studies demonstrated that in most countries, the risk of nonfatal suicidal behavior is higher among young people, women, and socially disadvantaged people[3]. At different studies about the drug-related suicide attempt from different parts of the Turkey, similarly with our results, more than 70% of the patients were female [6, 7]. Pereira et al mentioned about a new developmental phase called emerging adulthood in their study, at which young people gain important social and professional identities in matters such as marriage, financial independence from their parents and the formation of a family. It was emphasized that if the young adults could not cope with the problems they faced during this period they might consider suicide as a solution to these problems[8]. This may explain, as in our study, why suicide attempts are more common among young adults.

In our study ten patient were refugees. The incidence of psychiatric problems is quite high among refuges and there have been studies that reported high incidences of suicide and self-harm in this group which might be due to many reason such as experiencing severe trauma (like torture), as a consequence of the refugee process itself, or the stress of settling into a new culture [9]. Risk factors related to suicidal behaviors are very complex and seasonality and daylight exposure might have a potential role on this behavior. Agugliа et al. demonstrated that high-lethality suicide attempts peaked in the months with a higher sunlight exposure (June and July)[10]. Similarly, frequency of suicide attempts was higher in summer in our study.

Coherent with the literature because of being cheap and easily accessible, drugs most commonly used for suicide attempt were paracetamol, NSAIDs and antibiotics in our study[6]. Tandoğan et al. demonstrated that the amount of paracetamol that patient declared to intake and paracetamol blood levels were not correlated[11]. Therefore, it might be recommended to check blood paracetamol levels at every patient admitted to ED due to drug-intake. Our study demonstrated that 15.5% of our patients had a known psychiatric disease history and suicide attempt with antipsychotic and antidepressant drugs were significantly higher in those group. It can be estimated that these people attempted suicide with their own prescript drugs. It is known that past psychiatric history is a risk factor for suicide[12]. On the other hand the risk of suicidality posed by antidepressants remains in question. There is no clear evidence that treatment of depressed patients with antidepressant drugs increases the average risk of suicidality; however there may be an age-specific effect, such that antidepressants may raise the risk of suicide attempts or preparatory acts in patients aged 18 to 24 years during the first several weeks of treatment[13].

When these patients were evaluated by the toxicological point of view, it can be estimated that in most cases, poisoning progressed with mild clinical symptoms. Our data demonstrated most of the patients were discharged after an average of six hours follow-up. In our study less than half of the patients applied active charcoal and this number was less than that were in similar studies[7]. Number of gastric lavage applied patients were only 18. This might be due to duration of time between the drug intake and ED application which was longer than one hour. We also evaluated the psychiatric consultation status of patients and only one fifth of them were consulted with the psychiatrist. There are many factors increasing the risk of future suicidal behaviors such as previous suicide attempt, suicidal ideation, lethality of past attempts, hostility, subjective depressive symptoms, fewer reasons for living, comorbid borderline personality disorder, cigarette smoking, presence of family history of suicidal acts, past drug use and early parental separation[14]. Therefore, psychiatric consultation at ED is very important because better understanding of those may allow the identification of at-risk subjects and the implementation of targeted treatment approaches[15].

Conclusion

Our study demonstrated that being female, young, being a migrant, having a psychiatric illness and being in the warmer months of the year were related with the increased suicide attempts. Parasetamol, NSAID and antibiotics were most commonly used drugs and suicide attempt with antidepressants and antipsychotic drugs were significantly higher in the presence of psychiatric illness history. Most of the time the clinical course of drug-related suicide attempt cases were benign and they were discharged after follow-up at ED.

Frequency of consultation with a psychiatrist was very low. Suicide is a public health problem and it is estimated that an ED admission related to self-injury is the highest risk factor for a future completed suicide [15]. Therefore all patients admitted to ED due to suicide attempt must be consulted with the psychiatrist for further evaluation in terms of risk of future suicidal behavior and implementation of targeted treatment approaches.

References

1. World Health Organization. Programmes: Mental health. Available from: https://www.who.int/mental_health/prevention/suicide/suicideprevent/en/ Accessed 03 March 2020.
2. Türkiye İstatistik Kurumu: Temel İstatistikler, Nüfus ve Demografi, Hayati İstatistikler, İntihar sayısı ve kaba intihar hızı Avaliable from: http://tuik.gov.tr/UstMenu.do?metod=temelist Accesed 03 March 2020.
3. Zalar B, Kores Plesničar B, Zalar I, Mertik M. Suicide and Suicide Attempt Descriptors by Multimethod Approach. Psychiatr Danub. 2018;30(3):317-322.
4. Geyik FD, Töre Altun G, Çitak N, Akarsu Ayazoğlu T, Gül YG, Toptaş M. Evaluation of Patients Hospitalized in Intensive Care Unit Due to Drug-Related Suicide Attempt and Access to Drugs: A Single Center Prospective Study. Medical Bulletin of Haseki. 2014; 52(2): 111-115
5. Nock MK, Borges G, Bromet EJ, Alonso J, Angermeyer M, Beautrais A et al. Cross-national prevalence and risk factors for suicidal ideation, plans and attempts. Br J Psychiatry. 2008;192(2):98-105.
6. Akça HŞ, Özdemir S, Kokulu K, Algın A, Eroğlu SE. Psychiatric Evaluation of Suicidal Drug Intake in the Emergency Department. Eurasian J Tox. 2019;1(3):91-96
7. Utlu SG. Demographic Analysis of Suicide Victims Presenting to The Emergency Department with Drug-induced Intoxication. Eurasian J Tox. 2019; 1 (1): 25-28
8. Pereira AS, Willhelm AR, Koller SH, Almeida RMM. Risk and protective factors for suicide attempt in emerging adulthood. Cien Saude Colet. 2018; 23(11): 3767-3777.
9. Yüzbaşıoğlu Y, Çıkrıkçı Işık G. Retrospective analysis of forensic cases in refugees admitted to emergency department. Am J Emerg Med. 2019;37(9):1691-1693.
10. Aguglia A, Serafini G, Solano P, Giacomini G, Conigliaro C, Salvi V et al. The role of seasonality and photoperiod on the lethality of suicide attempts: A case-control study. J Affect Disord. 2019;246:895-901.
11. Tandoğan M, Emektar E, Dağar S, YüzbaşıoğluY, Karaatlı RH, Çevik Y. Acil Servise Parasetamol İntoksikasyonu Nedeniyle Başvuran Hastaların Değerlendirilmesi. Eurasian J Tox. 2019; 1 (1): 11-14
12. Sawa M, Koishikawa H, Osaki Y. Risk Factors of a Suicide Reattempt by Seasonality and the Method of a Previous Suicide Attempt: A Cohort Study in a Japanese Primary Care Hospital. Suicide Life Threat Behav. 2017;47(6):688-695
13. Leon AC. The revised warning for antidepressants and suicidality: unveiling the black box of statistical analyses. Am J Psychiatry. 2007;164(12):1786-9.
14. Pawlak JM, Miechowicz I, Dmitrzak-Węglarz M, Szczepankiewicz A, Zaremba D, Kapelski P et al. Are suicide risk factors gender specific? Psychiatr Pol. 2018;52(1):21-32
15. Zeppegno P, Gramaglia C, Castello LM, Bert F, Gualano MR, Ressico F et al. Suicide attempts and emergency room psychiatric consultation. BMC Psychiatry. 2015;15:13.

Original Article

Eurasian Journal of Toxicology

Could NCM-3S Be Used In The Intubation Decision of Patients Showing Toxicity Findings After Synthetic Cannabinoid Abuse?

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Abstract

Objective: We aimed to evaluate the need for endotracheal intubation of patients with NCM scoring system by using findings of examinations, vital parameters, and results of blood gas tests of the patients coming to the emergency room (ER) with acute toxicity caused by synthetic cannabinoid.

Material and Methods: Information regarding the 140 patients (out of all 319905 patients coming to the ER in 1 year) between the ages of 15-65, showing findings of acute toxicity caused by synthetic cannabinoid, such as complaints at first admission, sex, demographic characteristics, vital signs, examination findings, results of performed imaging and lab tests, administered treatments, information on the service in which the patients stay or are referred are all retrospectively reviewed. The ones who need intubation are evaluated under risky patient group (RPG) while the ones that have been discharged from the ER are evaluated as non-risk group (NRPG).

Results: When the intubation need of the patients is reviewed, it has been seen that there is statistically significant difference in the respiratory rate measured in the ER, systolic blood pressure, O2 saturation, Glasgow coma score, PCO2 values and pulse rate of patients in the risk group. NCM-3S scoring has been created to evaluate the intubation need of patients showing acute toxicity of synthetic cannabinoid.

Conclusion: It has been concluded that NCM-3S score, which we created using pulse rate, systolic blood pressure, respiratory rate, fingertip oxygen saturation, mental state and PCO2 values of patients showing signs of acute toxicity of synthetic cannabinoid in the ER, can be used in projecting the intubation need of patients.

Key words: Synthetic cannabinoid, emergency service, symptom and findings

Özet

Amaç: Acil servise sentetik kannabinoid akut toksisitesi ile başvuranlarda; muayene bulguları, vital parametreleri ve kan gazı test sonuçlarına göre geliştirdiğimiz NCM skorlama sistemi ile hastaların endotrakeal entübasyon ihtiyacını değerlendirmeyi amaçladık.

Metod: Acil servise 1 yıl boyunca başvuran 319905 hastadan sentetik kannabinoid akut toksisite bulguları gösteren 15- 65 yaş aralığındaki 140 hastanın başvuru şikayetleri, cinsiyeti, demografik özellikleri, vital bulguları, muayene bulguları, yapılmış olan görüntüleme ve laboratuar testleri, uygulanan tedavi, yattığı veya sevk edildiği bölüm bilgileri retrospektif olarak incelendi. Entübasyon ihtiyacı olan hastalar riskli hasta grubu olarak, acil servisden taburcu olan hastalar riskli olmayan grup olarak değerlendirildi.

Bulgular: Hastaların entübasyon ihtiyacını değerlendirmek için Riskli hasta grubunda acil serviste ölçülen solunum sayısı, sistolik kan basıncı, saturasyon O^2, Glaskow koma skoru, PCO^2 değeri ve nabız dakika sayısında istatistiksel olarak anlamlı fark tespit edildi. Sentetik kannabinoid akut toksisitesi gösteren hastaların entübasyon ihtiyacını değerlendirmek için NCM-3S skorlaması oluşturuldu.

Sonuç: Acil serviste Sentetik kannabinoid akut toksisite bulguları gösteren hastalarda ölçülen nabız dakika sayısının, sistolik kan basıncının, solunum sayısının, parmak ucu sat O^2 değerinin, mental durumunun, PCO^2 değeri ile oluşturduğumuz NCM-3S skorunun hastaların entübasyon ihtiyacını öngörmede kullanılabileceği sonucuna varılmıştır.

Anahtar kelimeler: Sentetik kannabinoid, acil servis, semptom ve bulgular

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Received: 06.01.2020 • **Accepted:** 19.03.2020

Cite this article as: Sutasir MN. Could ncm-3s be used in the intubation decision of patients showing toxicity findings after synthetic cannabinoid abuse? Eurasian J Tox. 2020;2(1):15-22.

Introduction

Psychoactive substances (Psychotropic) are chemicals that essentially affect the central nervous system and cause temporary changes in perception, mental state, level of consciousness and behavior by changing the functions of the brain. Over the last years, there has been a massive increase in new psychoactive substances which are also called legal highs, designer drugs, herbal highs, and research chemicals[1]. Even though synthetic cannabinoids (SC) are generally consumed in the form of cigarettes (with pipes, cigarettes or hookahs), rectal or oral (in vapor) have also been reported[2]. These chemicals show their effect by activating the cannabinoid receptors in the body. Cannabinoid receptors have two known sub-groups which are Cannabinoid 1 (CB1) receptor and Cannabinoid 2 (CB2) receptor. The CB1 receptor is more localized in the brain while the CB2 receptor can be found within the immune system. Synthetic cannabinoids typically have a full agonist effect on CB1 receptors hence causing maximum effect even with low doses[3].

Even though resembling cannabis, since SCs do not have any record in any mass spectrometer system and do not have reference standards, they cannot be identified[4,5]. The patients generally apply to hospital with neurological, psychiatric, cardiac, and respiratory disorder findings[6]. Among the cases, serious conditions such as acute coronary syndrome (ACS), seizure, stroke, rhabdomyolysis, acute renal failure, and respiratory depression have also been notified. A significant number of cases were monitored in the ICU, some of them even reported to have died during their stay[7,8,9,10]. For an emergency physician, it is not easy to manage a case that is thought to be SC toxicity. The reason for this is the obligation to make a timely and correct decision about a patient with somnolence and vomiting and who cannot be communicated or have any other relatives except for hospital staff and of whom it is utterly difficult to obtain any medical history or information. In this study, we aimed to evaluate the need for endotracheal intubation (ETI) of patients applying to ER after SC abuse, through NCM-3S scoring system (respiratory rate, systolic blood pressure, O_2 saturation ($satO_2$), Glasgow Coma Score (GCS), PCO2 value and pulse rate) we developed using first examination findings, vital signs and results of blood gas test.

Materials and Methods

The study is initiated with the approval (number 1058) of the 3rd step Training and Research ethics committee, dated 01/09/2015. The study, which was planned retrospectively, included 140 cases between the ages 15-65 with statements of synthetic cannabinoid abuse in their story, out of 319905 patients applying to the ER between the dates July the 1st, 2014 and June the 30th, 2015. The study is performed as per the principals of the "World Medical Association Declaration of Helsinki".

The hospital automation records, judicial reports, and ambulance records of patients coming to the ER either by walking or by ambulance and who have statements (either by themselves or by their relatives) of synthetic cannabinoid abuse, have retrospectively been reviewed (for 1 year). Patients' complaints at first admission, sex, demographic characteristics, vital signs, examination findings, results of performed imaging and lab tests, administered treatments, information on the service in which the patients stay or are referred are all retrospectively reviewed through patient files or automation system of the hospital, and the information of patients who qualify to be included in the study is registered in the form we created.

Vital signs of the patients (arterial blood pressure, pulse, fever, oxygen saturation), Glasgow Coma Score points, effects after substance exposure (palpitation, sweating, nausea, vomiting, xerostomia, fatigue, edginess, chest pain, dyspnea, headache, uneasiness, itchiness, eye redness, drowsiness, blurred vision, eye burning, skin redness, dizziness, somnolence, spasm, hand numbness) are reviewed. Physical examination findings which can be related to substance use such as wakefulness, somnolence, stupor, coma, agitation, hallucination, anxiety, confusion, euphory, convulsion, increased muscular tonus, flushing, tachypnea, cyanoses, arrhythmia, conjunctival hyperemia, nystagmus, mydriasis, myosis, hyperpyrexia, salivation, lacrimation, urinary incontinence, erection, diarrhea, emesis, hyperreflexia and, hypoventilation, and hyperventilation.

In lab tests, pH, pO_2, pCO_2, HCO_3, BE levels are checked from the blood gas samples drawn in the ER. Results such as the applied intubation, referral to ICU and exitus are retrospectively reviewed via patient files and hospital automation system and registered in patient forms. The patients who need intubation and are referred to the ICU are evaluated as risky patient group (RPG), and the patients who are discharged from the ER are evaluated as non-risky patient group (NRPG). In light of the study, we created NCM-3S scoring to evaluate patients' need for intubation. The scoring system, which is created as per respiratory rate, systolic blood pressure, O_2 saturation ($satO_2$), Glasgow Coma Score (GCS), PCO2 value and pulse rate is shown in Table 1.

For statistical analysis, SPSS for Windows software is used. In descriptive statistics of the data, values such as mean, standard deviation, median lowest, highest, frequency, and proportion are used. Variable distribution is measured with the Kolmogorov-Smmirnov test. In the analysis of quantitative data, the Mann-Whitney test and unpaired t-test are used. In the analysis of qualitative data, the chi-square test is used, and when chi-square conditions are not ensured, the Fischer test is used. The effect level is reviewed through univariate and multivariate logistic regression analysis. In the survival analysis, SPSS 22.0 software is used. The statistical alpha significance level is accepted as $p<0,05$.

Table 1. NCM-3S scoring system

NCM- 3S	0	1	2	3
Respiratory Rate	12-16	<12 / >16		
Systolic blood pressure	90-140	60-90 >160	<60	
O_2 Saturation	95 and above	90-94	85-90	<85
Glasgow coma score (Mental)	14-15	9-13	7-8	<6
P CO_2	<45	45-60	61-80	80>
Pulse rate	60-100	30-59 100-120	<30 >120	

Results

The mean age of participating 140 patients was 27,2 ± 8,1 and 129 of the patients (92,1%) were male. 77 of the patients (55%) were brought to the ER by an ambulance, 49 of them (35%) by walking and 14 of them (10%) are brought by being carried by their relatives.

Patients on SC only form 67,1% of the participants while patients on both alcohol and SC form 11,4% and patients on other pleasure-inducing substances along with SC form 21,4%. When the method of SC abuse is reviewed, the most frequent abuse method was with hand-rolled cigarettes by 76 patients (54,3%). When the symptoms of the first admission of patients in ER are reviewed, the most frequent symptom is somnolence with 42 patients (30%), vomiting with 38 patients (27,1%) and palpitation with 37 patients (26,4%) (Table 2). Admission vital signs, fingertip saturation, and GCS values and admission blood gas parameters of patients at the time of the first admission to ER are stated in Table 3. When RPG and NRPG patients are evaluated, among all patient groups, 24 patients (17.14%) underwent ETI and there was statistical significance between blood pressure, respiratory rate, pCO2, SpO2, GCS, pH, pO2 and NCM-3S scores of these patients (Table 4,5). In the ROC analysis performed for the decision of applying ETI for the patients admitted to the ER following SC abuse, NCM-3S score, age, diastolic BP, pulse, mean arterial pressure, systolic BP, pCO2, SpO2, GCS, pH, pO2 values of 24 patients underwent ETI (17.14%) are reviewed and the highest AUC values were NCM score (AUC: 0.932) and pCO2 (AUC: 0.909), respectively (Figure 1).

Table 2. Effects following SC abuse and distribution of ER finding

Symptoms following abuse	n	%
Somnolence	42	30,0%
Vomiting	38	27,1%
Palpitation	37	26,4%
Fainting	30	21,4%
Nausea	27	19,3%
Chest pain	25	17,9%
Dyspnea	20	14,3%
Drowsiness	20	14,3%
Spasm	19	13,6%
Fatigue	15	7,1%
Uneasiness	12	10,7%
Seizure	13	9,3%
Other (Eye redness, sweating, tremor, edginess, skin redness, dizziness, hot flash, blurred vision, eye burning, xerostomia, itchiness, hand numbness)	66	47,1%
Findings of Examination		
Somnolence (Lethargy)	36	25,7%
Wakefulness	31	22,1%
Confusion	28	20,0%
Arrhythmia	26	18,6%
Mydriasis	25	17,9%
Agitation	24	17,1%
Hypoventilation	23	16,4%
Tachypnea	21	15,0%
Stupor	17	12,1%
Euphoria	12	8,6%
Emesis	10	7,1%
Other neurological findings (increased muscular tonus, coma, convulsion, hyperreflexia, myosis, nystagmus, anxiety, fixed dilated pupils)	43	31,4%
Other (conjunctival hyperemia, cyanoses, salivation, erection, flushing, lacrimation, diarrhea, hyperpyrexia, urinary incontinence, hyperventilation)	31	22,1%

Discussion

It has been seen that the majority of the patients admitted to the ER due to SC abuse were male and a part of the young patient population. When the patients are evaluated as per their SC abuse along with alcohol and other pleasure-inducing substances; it was seen that the majority went to the ER due to sole SC abuse however substances such as cannabis, extasy, alcohol, heroin, cocaine, cigarettes, energy drinks,

Table 3. Patients' admission parameters and first blood gas measures

Admission Parameters	Median	Min-Max
Systolic Pressure	110,0	60 - 160
Diastolic Pressure	63,5	40 - 100
Mean Pressure	80,0	47 - 120
Pulse	92,0	30 - 140
Respiratory Rate	14,0	0,0 - 25,0
Fever	36,5	35 - 37
SPO_2	94,0	57 - 100
GCS	15,0	3,0 - 15,0
Ph	7,3	6,5 - 7,5
PO_2	80,0	52 - 102
PCO2	50,0	37 - 148
BE	-1,0	-9,2 - 11,0
HCO_3	23,0	15,8 - 31,0

Table 4. Comparison between patients who underwent endotracheal intubation and who did not undergo endotracheal intubation as per values

	ETI N/A		ETI Applied		
	Median	Mean ± SD	Median	Mean ± SD	p
Blood gas pH,	7.3	7.3±0.1	7.2	7.1±0.2	0.000
pO_2,	80.0	79.7±10.7	81.5	82.3±4.6	0.697
pCO_2,	48.0	50.7±11.3	75.0	82.9±33.0	0.000
Systolic pressure	110.0	114.0±15.6	92.5	94.8±17.9	0.000
Diastolic pressure	70	67.1±11.5	50.0	53.7±9.1	0.000
Mean pressure	83,3	82.7±12.1	66.7	67.4±11.5	0.000
Pulse	91.5	92.9±13.8	101.0	92.7±30.4	0.337
Respiratory rate	15.0	15.6±4.1	10.0	9.4±2.9	0.000
Sat O_2	95.0	94.6±4.7	86.0	84.8±8.3	0.000
GCS	15.0	13.6±2.5	5.0	6.3±3.2	0.000

ETI; endotracheal intubation

Table 5. RGP and NRGP evaluation as per age, diastolic BP, pulse, mean arterial pressure, systolic BP, pCO2, SpO2, GCS, pH, pO2

			Asymptotic 95% Confidence Interval	
Test Result Variable(s)	Area	Asymptotic Sig.[b]	Lower Bound	Upper Bound
Age	,594	,147	,467	,721
Diastolic BP	,244	,000	,142	,346
MBP	,222	,000	,116	,328
Pulse	,551	,434	,403	,699
Respiratory Rate	,047	,000	,015	,079
Systolic BP	,238	,000	,124	,352
pCO_2	,909	,000	,830	,988
SpO_2	,087	,000	,010	,165
GCS	,101	,000	,018	,184
pH	,078	,000	,011	,146
pO_2	,158	,000	,048	,268
Total Score	,932	,000	,863	1,000

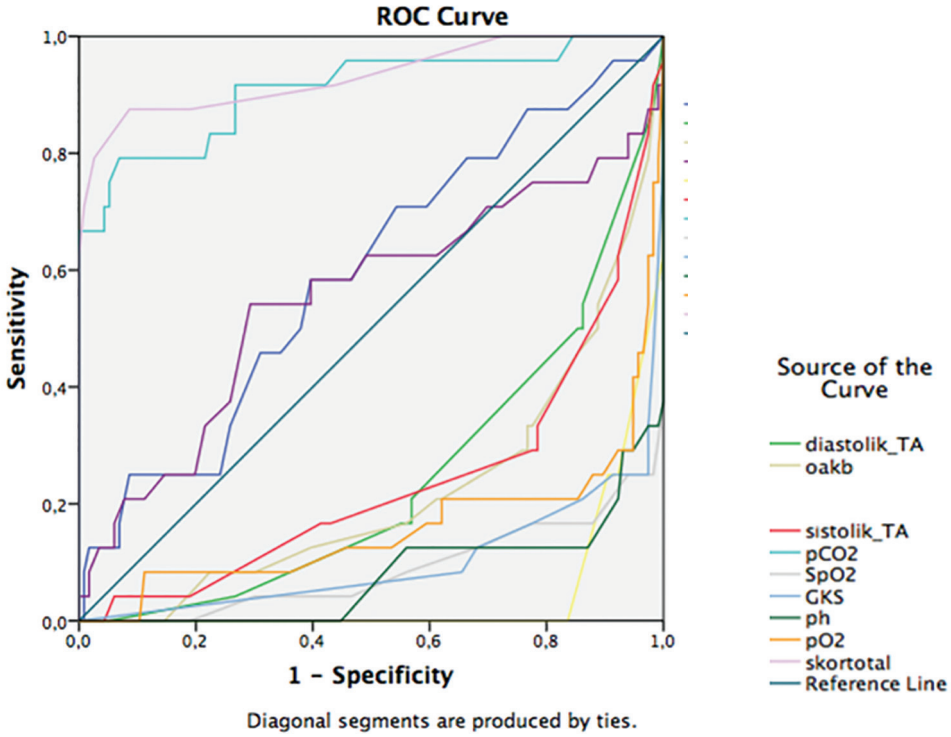

Figure 1. Roc analysis performed to define the need for ETI as per age, diastolic BP, pulse, mean arterial pressure, systolic BP, pCO2, SpO2, GCS, pH, pO2 and NCM-3S score values

and methylenedioxymethamphetamine are frequently used together[6,11,12]. The fact that in this study, the percentage of alcohol consumers with SC is 11,4% and other pleasure-inducing substance users' is 21,4% show that just as the literature suggests, other psychotropic substances can be used along with SC. Usage of other substances along with SC is a topic that requires consideration especially during emergency interventions of intoxication cases and when planning a course of treatment against substance abuse. As stated in the literature, the acute physical effects of SCs vary from sweating, nausea, vomiting, hypertension/hypotension, chest pain, dyspnea, tachycardia/bradycardia, respiratory depression, mental fog, confusion, psychomotor agitation, somnolence and sedation[11,12,13]. Yoshito Kamijo et al carried out a multicenter retrospective study in Japan and saw 24,9% vomiting, 23,6% uneasiness, 15,6% nausea, 14,5% palpitation, 9,3% confusion[14]. And in our study, we have seen 30% somnolence, 27,1% vomiting, 26,4% palpitation. When the examination findings following SC abuse are reviewed, we have seen sweating, nausea, vomiting, tachycardia, arrhythmia, hypotension, hypertension, anxiety, clonus, hypertonicity, fasciculations, ataxia, mydriasis, nystagmus, tremor, somnolence, hallucination, decreased motor coordination, confusion, stupor, and state of coma[4,6,11,13,15]. All these findings suggest that what is stated in literature coincide with the examination results in our study and that when patients come to the ER with SC abuse, psychological, neurological, cardiac, metabolic, gastrointestinal, muscular, ocular findings can be seen.

Many other studies performed on patients with SC abuse show us that following evaluation in which the first examination and treatment were performed in ERs, the patients who underwent intubation were followed in ICUs[7,9,15]. There are scoring systems used in evaluating the severity and discharge of patients of risk groups in ERs and ICUs[16]. It is possible to define the risk status of patients with simple bedside flow diagrams which include respiratory, cardiac and mental status evaluations[17]. Acute Physiology and Chronic Health Evaluation (APACHE), is the first model of scoring systems developed to have an idea about the prognosis of patients. However, as this system was too complicated for routine usage, the APACHE II system was created[18]. The calculation is made with the worst values of the results of biochemical analyses which are done with the blood tests performed in the first 24 hours following the admission of patients. For this reason, APACHE II is not a suitable system to be performed swiftly in the ERs[19]. Another scoring system is called Mainz Emergency Evaluation Score (MEES) and is a descriptive scoring system, also including GCS[20]. In this system, in addition to GCS, 7 other parameters such as arterial systolic blood pressure, pulse, respiratory rate, oxygen saturation value, EKG changes, and pain measurement are included in the evaluation[16]. Modified Early Warning Score (mEWS) is another validated bedside flow diagram used in emergency service admissions. In this system, five basic physiological parameters are evaluated. These are systolic arterial blood pressure, pulse, respiratory rate, body temperature measurement, and AVPU scale and they are

used to evaluate consciousness (21,22). Many early warning systems are developed by taking pulse, blood pressure, respiratory rate, fever and level of consciousness as basis. In our study, the values stated in the literature have been considered as well. Pulse, blood pressure, respiratory rate and mental state at the first admission to the ER are evaluated and saturation and blood gas PCO_2 (of which results come out in short notice) values which are taken in the ER are added to the evaluation. However, there could not be found any study related to the planning of the need for ETI, based on the combined evaluation of the physiological and clinical state of the patients at the time of admission along with the first blood gas test results, as can be seen in our study. As can be seen in the literature, in the evaluations of blood gas of intubated patients after SC abuse, respiratory acidosis, hypoxia and pCO^2 values of patients are above normal (7,9,15). In our study, it has been seen that compared to the NRPG, RPG had lower pH and higher pCO_2 values. The topic of respiratory depression after SC abuse is a debated issue. In experimental studies, a decrease in respiratory rate, hypoxia, hypercapnia, acidosis effects have been proven (23,24). Nevertheless, there is not adequate information regarding its direct effect leading to respiratory depression on patients. It is suggested that SCs could cause an increase in resistance in bronchia and a decrease in respiratory rate. And in some cases, it is known to need mechanical ventilation due to respiratory failure (23,25). It is likely to see the effects on the respiratory system being created through the central nervous system and cardiovascular system. Other studies of literature have also shown acute respiratory acidosis and acute metabolic acidosis in patients (25,26,27). It is seen both in our study and in the literature review that in SC toxicity cases, hypoventilation results in respiratory acidosis and this leads to respiratory depression and ETI is applied to these patients. It is also seen that in RPG, systolic blood pressure, GCS value, pulse rate, respiratory rate, saturation and pCO2 value measured in the ER, as a part of the NCM-3S scoring system we developed, are significant in determining the need for ETI in SC toxicity cases.

Factors such as illegal supply of SCs, difficulty in running lab analysis due to their unpredictable and constantly changing structure, inadequate anamnesis from patients after SC abuse, change in consciousness and confusion, neurological changes that can lead to stupor and coma and finally the fact that the study was prepared in a single center thus having a limited number of patients are the constraints of our study.

Conclusion

A patient coming to the ER with SC abuse is one of the difficult cases to manage for ER physicians. The reasons behind this difficulty can be said to be patients coming to the ER with an ambulance, thus the ability to obtain very limited anamnesis, most frequently not having any relative with them except for medical personnel, difficulty in respiration and changes in consciousness level. SCs are known to have hypoxia, hypercapnia and acidosis effects. Many patients require mechanical ventilation due to respiratory failure. All these situations led us to the conclusion that NCM-3S score we created by using pulse rate, systolic blood pressure, respiratory rate, fingertip O^2 saturation, mental state and PCO^2 value measured in ER at first admission, can be used in projecting the need for intubation of patients in SC toxicity cases.

References

1. A S Başak. New Generation psycho-active subtances symposium book. Istanbul Forensic Medicine Institute. 2013 p. 5-6.
2. Vandrey R, Dunn KE, Fry JA, Girling ER. A survey study to characterize use of Spice products (synthetic cannabinoids). Drug Alcohol Depend. 2012; 120:238-41.
3. Bretteville-Jensen AL, Tuv SS, Bilgrei OR, Fijeld B. Synthetic Cannabinoids and Cathinones: Prevalence and Markets. Forensic Sci Rev. 2013;25:8-26.
4. Cohen J, Morrison S, Greenberg J, Saidinejad M. Clinical Presentation of Intoxication Due to Synthetic Cannabinoids. Pediatrics. 2012;129;1064-7.
5. Gregori A, Damiano F, Bonavia, M, Mileo V, Varani F, et al. Identification of two cannabimimetic compounds WIN48098 and AM679 in illegal products. Sci Justice. 2013;53:286-92.
6. Forrester MB, Kleinschmidt K, Schwarz E, Young A. Synthetic cannabinoid exposures reported to Texas poison centers. J Addict Dis. 2011;30:351.
7. Aksel G, Bozan O, Kayacı M, Güneysel O, Sezgin SB. Rising Threat; Bonzai. Turk J Emerg Med. 2015;15:75-8.
8. Izci F, Izci V, Izci S , Setenay M , Koc I, et al. Lipid infusion therapy in sinus tachycardia induced with synthetic cannabinoid intoxication: two cases report. Bulletin of Clinical Psychopharmacology. 2015;25:209.
9. Salçın E, Gümüşel M, Eroğlu SE, Kabaroğlu KA, Akoğlu H. Bonzai-İlişkili Solunumsal/Kardiyovasküler Komplikasyonların Analizi: Üniversite Hastanesi Deneyimi. Journal of Kartal Training & Research Hospital/Kartal Egitim ve Arastirma Hastanesi Tip Dergisi. 2016;27:16-20.
10. Solak SK, Vural A, Demirgan S, Ceylan P, Karaca Ö, et al. Yoğun Bakım Ünitesindeki Bonzai Zehirlenme Olgularının Retrospektif Analizi. İKSST Derg. 2018;10:7-11
11. Schneir AB, Cullen J, Ly BT. "Spice" girls: Synthetic cannabinoid intoxication. J Emerg Med. 2011;40:296-9.
12. Bozkurt M, Umut G, Evren C, Karabulut V. Clinical characteristics and laboratory test results of patients admitted to outpatient clinic for synthetic cannabinoid usage. The Journal of Psychiatry and Neurological Sciences. 2014;27:328-34.

13. Hoyte CO, Jacob J, Monte AA, Al-Jumaan M, Bronstein AC, et al. A characterization ofsynthetic cannabinoid exposures reported to the National Poison Data System in 2010. Ann Emerg Med. 2012;60:435-8.

14. Kamijo Y, Takai M, Fujita Y, Hirose Y, Iwasaki Y, et al. A Multicenter Retrospective Survey of Poisoning after Consumption of Products Containing Synthetic Chemicals in Japan. Intern Med. 2014;53:2439-45.

15. Küçük E, Küçük İ, Kirazaldı YY, Acil serviste sentetik kannabinoidler. Genel Tıp Derg. 2015;25:18-22.

16. Gremec S, Gasparovic V. Comparison of APACHE II, MEES and Glasgow Coma Scale in patients with nontraumatic coma for prediction of mortality. Critical Care. 2001;5:19-23.

17. Lee A, Bishop G, Hillman KM, Daffurn K. The Medical Emergency Team. Anaesthesia and İntensive Care 1995;23:183-6.

18. Unertl K, Kottler BM. Prognostic scores in intensive care. Anaesthesist. 1997;46: 471–80.

19. Olsson T. Risk Prediction at the Emergency Department. Acta Universitatis Upsaliensis. 2004.

20. Hennes HJ, Reinnhardt T, Dick W. The Mainz Evaluation Scoring for assessment of emergency patient. Emerg Med. 1992;18:130-136.

21. Subbe CP, Davies RG, Williams E, Rutherford P, Gemmell L. Effect of introducing the Modified Early Warning Score on clinical outcomes, cardio-pulmonary arrests and intensive care utilisation in acute medical admissions. Anaesthesia. 2003;58:775-803.

22. Subbe CP, Kruger M, Rutherford P, Gemmell L. Validation of a Modified early Warning score in medical admission. Q J Med. 2001;94:521-526.

23. Jinwala FN, Gupta M. Synthetic cannabis and respiratory depression. J Child AdolescPsychopharmacol. 2012;22:459-62.

24. Schmid K, Niederhoffer N, Szabo B. Analysis of the respiratory effectsof cannabinoids in rats. Naunyn Schmiedebergs Arch Pharmacol. 2003;368:301-8.

25. Altınışık U, Altınışık HB, Şimşek T, Doğu T, Şimşek E, et al. Yoğun Bakım Ünitesinde Takip Edilen Sentetik Kannabinoid (Bonzai) Zehirlenmesi Olgularının KlinikÖzellikleri. J Turk Soc Intens Care. 2015;13:117-21.

26. Besli GE, Ikiz MA, Yildirim S, Saltik S. Synthetic cannabinoid abuse in adolescents: a case series. The Journal of Emergency Medicine. 2015;49:644–50.

27. Seely KA, Prather PL, James LP, Moran JH. Marijuana-based drugs: innovative therapeutics or designer drugs of abuse? Mol Interv. 2011;11:36-51.

Original Article

Eurasian Journal of Toxicology

The Importance of Hyperbaric Oxygen Therapy In The Management of Carbon Monoxide Poisoning Is Neglected

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Abstract

Objectives: Carbon-monoxide (CO) is a common cause of toxicity with high morbidity and mortality. Hyperbaric oxygen (HBO) therapy or normobaric oxygen (NBO) therapy should be used for acute CO-poisoned patients, though the effects of HBO versus NBO therapy on long-term neurocognitive outcomes remain unclear. The aim of this study is to investigate the rates of HBO therapy in patients admitted to our clinic with CO poisoning.

Material and Methods: This is a retrospective, cross sectional, observational, single centered study that was conducted in a research hospital. Patient files with a diagnosis of CO poisoning based on the ICD10 codes between January 2018 to December 2019 were investigated. Demographic data, median time of stay in emergency department (ED), indication of HBO treatment and if the patient administered HBO were investigated. Carboxyhemoglobin level (COHb) greater than 25% considered as the indication of HBO. The statistical analysis was performed using the Statistical Package for the Social Sciences version 22.0. Mann–Whitney's U test and Student t test were used for the comparison of numerical variables in independent groups. Categorical variables were analyzed using the Pearson chi-squared test. A p-value of <0.05 was considered to be statistically significant.

Results: A total of 152 files were investigated, 80 cases with CO level higher than 5% at admission were included. Number of patients with HBO indication, which considered as COHb level greater than 25%, was 30 and only 8 (26.6%) of them received HBO therapy. Average length of stay at ED was significantly higher at HBO indication positive group (p < .001). There was no difference in terms of COHb level at admission and average length of stay at ED according to HBO treatment status in patients with HBO indication; but COHb level before discharge was significantly lower at the HBO therapy administered group (p .019).

Conclusion: Our study demonstrated that most of the CO poisoned patients with HBO indication were not administered this therapy. Although the current literature provides conflicting data on the effectiveness of HBO therapy at CO poisoning, we considered that HBO should be administered in case of severe CO poisoning to reduce mortality and delayed neurological sequel. However, since CO poisoning is a common condition, there is a need for multicenter, prospective, advanced studies in which patients are followed up for a long time in terms of mortality and morbidity in order to reach consensus and create a management guide.

Key words: Carbon monoxide poisoning; hyperbaric oxygen; neurological sequela; mortality

Özet

Amaç: Karbon-monoksit (CO) yüksek mortalite ve morbiditeye sahip sık karşılaşılan bir toksisitedir. Akut CO zehirlenmesi olan hastalarda hiperbarik oksijen (HBO) tedavisi ve normobarik oksijen (NBO) tedavileri kullanılır, ancak uzun dönem nörokognitif sonlanımda HBO'nun NBO'ya göre etkisi halen belirsizdir. Bu çalışmanın amacı bizim kliniğimize CO zehirlenmesi ile başvuran hastaların HBO tedavisi alma oranlarını incelemektir.

Gereç ve yöntem: Bu bir araştırma hastanesinde yapılan retrospektif, kesitsel, gözlemsel, tek merkezli bir çalışmadır. Ocak 2018 ile Aralık 2019 arasında ICD10 kodlarına göre CO zehirlenmesi tanısı konan hastaların dosyaları incelenmiştir. Demografik veri, acil serviste (AS) ortalama kalış süresi, HBO tedavi endikasyonları ve hastanın HBO alıp almadığı incelenmiştir. Karboksihemoglobin seviyesinin (COHb) %25'ten büyük olması HBO için endikasyon kabul edilmiştir. İstatistiksel analiz SPSS versiyon 22.0 ile yapılmıştır. Bağımsız gruplar arasında numerik değişkenlerin karşılaştırılmasında Mann–Whitney's U testi ve Student t testi kullanılmıştır. Kategorik değişkenler Pearson ki-kare testi ile analiz edilmiştir. P değeri <0.05 istatistiksel açıdan anlamlı kabul edilmiştir.

Bulgular: Toplam 152 dosya incelenmiş CO seviyesi %5'ten büyük olan 80 vaka dahil edilmiştir. HBO endikasyonu olan ki bu COHb seviyesi %25'ten büyük olanlar olarak belirlenmiştir, 30 olup sadece 8 (26,6%) tanesi HBO tedavisi almıştır. Ortama AS'de kalış süresi HBO endikasyonu olan grupta belirgin olarak daha yükseltir (p < .001). HBO endikasyonu olan hastalarda HBO tedavisi alma durumuna göre başvurudaki COHb seviyeleri ve ortalama AS'de kalış süresi açısından fark yoktur; ancak taburculuk öncesi COHb seviyesi HBO tedavisi alan grupta belirgin olarak daha düşüktür (p .019).

Sonuç: Çalışmamız HBO endikasyonu olan CO zehirlenmesi olan hastaların çoğunun bu tedaviyi almadığını göstermiştir. Her ne kadar CO zehirlenmesinde HBO'nun etkinliğiyle ilgili mevcut literatür tutarsız veri sunsa da, biz ciddi CO zehirlenmesi olan hastalarda mortaliteyi ve gecikmiş nörolojik sekeli azaltmak için HBO verilmesi gerektiğini düşünüyoruz. Ancak, CO zehirlenmesi yaygın bir durum olduğundan, bu konuda bir konsensusa ulaşmak ve bir yönetim kılavuzu oluşturmak için hastaların mortalite ve morbidite açısından daha uzun süreli takip edildiği çok-merkezli, prospektif ileri çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Karbon-monoksit zehirlenmesi; Hiperbarik oksijen, nörolojik sekel, mortalite

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Received: 05.03.2020 • **Accepted:** 12.03.2020

Cite this article as: Isik Cikrikci G, Safak T, Sencanlar Cetiner H, Cevik Y. The importance of hyperbaric oxygen therapy in the management of carbon monoxide poisoning is neglected. Eurasian J Tox. 2020;2(1):23-28.

Introduction

Carbon-monoxide (CO) is a colorless, odorless and tasteless toxic gas which is produced as a result of the incomplete burning of organic matter; that causes tissue hypoxia particularly in the heart and brain[1]. It is a common cause of toxicity with high morbidity and mortality worldwide that it accounts for 30% of the poisoning cases that end with death in Turkey[2]. Delayed neuropsychological squeal with symptoms such as movement disorders, cognitive impairment or affective disorders is an important morbidity of those patient group[3].

Normobaric oxygen (NBO) and hyperbaric oxygen (HBO) therapies are two basic treatment modalities for CO toxicity. Advantages of treatment with HBO include increased dissolved-oxygen content in blood and accelerated elimination of CO; also its potential benefit is prevention of lipid peroxidation in the brain and preservation of ATP levels[4]. There are many studies in the literature that indicate comparing with CO poisoning patients treated with NBO, HBO treated patients have a lower incidence of neuropsychological squeal[5, 6]. On the other hand HBO has some disadvantages such as risks associated with the transport of the patient to a treatment center, hyperoxic seizures, barotrauma and increased treatment costs[4]. Also there are some conflicting published results about effectiveness of HBO. Juurlink et al. demonstrated that existing randomized trials do not establish whether the administration of HBO to patients with carbon monoxide poisoning reduces the incidence of adverse neurologic outcomes[7].

In the clinical decision process, it is difficult to establish the benefit-risk ratio of HBO because of the reasons mentioned above. The aim of this study is to investigate the rates of hyperbaric oxygen therapy in patients admitted to our clinic with carbon monoxide poisoning.

Material and Methods

This is a retrospective, cross sectional, observational, single centered study that was conducted in a research hospital with the approval of the local Medicine Expertise Training Board. Those patient files with a diagnosis of carbon monoxide poisoning based on the ICD10 (International Statistical Classification of Diseases and Related Health Problems) codes in the hospital data registration system between January 2018 to December 2019 were investigated. Cases whose carboxyhemoglobin (COHb) levels at the time of admission were reached and since smoking habits of the patients were unknown, those with a level of COHb above 10 percent were included in the study. Those cases with a carboxyhemoglobin level less than 10 percent and missing data were excluded.

Demographic data, median time of stay in emergency department (ED), indication of HBO treatment and if the patient administered HBO were investigated. It was not possible to reach the admission complaints of the patients due to the missing data at patient files and records. Therefore carboxyhemoglobin level greater than 25% considered as the indication of HBO.

Statistical Analyzes

The statistical analysis was performed using the Statistical Package for the Social Sciences version 22.0 (SPSS Inc., Chicago, IL, USA). After assessing normal distribution using the Kolmogorov-Smirnov test, all variables were described in terms of mean ± standard deviation or median and interquartile range (IQR) (25–%75). The descriptive analyses were presented using frequencies for the ordinal variables. Mann–Whitney's U test and Student t test were used for the comparison of numerical variables in independent groups. Categorical variables were analyzed using the Pearson chi-squared test. A p-value of <0.05 was considered to be statistically significant.

Results

A total of 152 files were investigated, 80 cases with CO level higher than 5% at admission were included. Forty-eight of them were female and 32 were male, median age of cases was 40.50 (IQR25.25 – 52). Median CO level of whole study group at admission was 20.85 (IQR 13.4 – 29.85) and average length of stay at ED was 363 min (IQR 287 – 544 min). Number of patients with HBO indication, which considered as COHb level greater than 25%, was 30 and only 8 (26.6%) of them received HBO therapy (Table 1).

There was no difference between the patients with or without HBO indication in terms of age, gender and COHb levels before discharge. However, average length of stay at ED was significantly higher at HBO indication positive group ($p < .001$) (Table 2).

We also analyzed the variables according to HBO treatment status in patients with HBO indication. There was no difference in terms of COHb level at admission and average length of stay at ED. However COHb level before discharge was significantly lower at the HBO therapy administered group (p .019) (Table 3).

Discussion

Our study demonstrated that only 26% of patients with COHb levels greater than 25 percent administered HBO

Table 1. Descriptive variables of the study group

Descriptive variables	
Gender*	
Female	48 (60%)
Male	32 (40%)
Age**	40.50 (25.25 – 52)
CO level at admission**	20.85 (13.4 – 29.85)
Average length of stay at ED**	363 min (287 – 544)
Indication for HBO*	
No	50 (62.5%)
Yes	30 (37.5%)
Number of patients received HBO therapy	8 (26.6%)

Abbreviations: CO: carbonmonoxide; ED: emergency department; HBO: hyperbaric oxygen
*number (frequency%)
**median (Inter quartile range 25 – 75)

Table 2. Analyses of the variables according to HBO indication

Descriptive variable	HBO indication negative	HBO indication positive	p value
Gender*			.119
Female	27	21	
Male	23	9	
Age **	38.5 ± 29.6	45.4 ± 36.4	.06
CO level at admission***	14.35 (12.55 – 19.87)	31.2 (27.62 – 34.95)	**< .001**
CO level before discharge***	3.8 (1.7 – 5.3)	3.8 (0.1 – 7.1)	.619
Average length of stay at ED***	342 min (250 – 405)	533 min (341 – 781)	**<.001**

Abbreviations: CO: carbonmonoxide; ED: emergency department; HBO: hyperbaric oxygen
*number (frequency%)
**mean ± 2 Standart deviation
***median (Inter quartile range 25 – 75)

Table 3. Analyses of the variables according to HBO treatment status in patients with HBO indication

Descriptive variable	HBO treatment negative	HBO treatment positive	p value
Gender*			.96
Female	18	3	
Male	5	4	
Age**	45.13 ± 37.46	46.29 ± 35.36	.886
CO level at admission**	32.39 ±6.58	31.77 ± 5.76	.799
CO level before discharge***	4.1 (2.9 – 8.3)	0.1 (0.02 – 1.9)	**.019**
Average length of stay at ED***	523min (326 – 768)	533 min (396 – 1124)	.54

Abbreviations: CO: carbonmonoxide; ED: emergency department; HBO: hyperbaric oxygen
*number (frequency%)
**mean ± 2 Standart deviation
***median (Inter quartile range 25 – 75)

therapy. Hyperbaric oxygen chambers are available at only 20 cities in Turkey and our hospital is at one of them. So, for patients living in other cities it seems more impossible to achieve HBO treatment. Also COHb level is just one of the indications for HBO therapy at CO poisoning so accurate number of patients with HBO indication may be higher. Therefore, even if there is an indication for HBO, it can be estimated that the rate of CO poisoned patients administered HBO is lower than 26% nationwide.

Moderate to severe CO poisoning can cause profound effects on vital organs. Cardiac dysfunctions including arrhythmia, left ventricular systolic dysfunction, and myocardial infarction may be associated with increased mortality [8]. Also survivors of CO poisoning suffer from long-term neurocognitive squeal related to brain injury which is an important cause of morbidity. Those symptoms include impaired memory, cognitive dysfunction, depression, anxiety, and/or vestibular and motor deficits[9]. Although HBO use is recommended for such serious poisonings by the experts in the hyperbaric medicine field, American College of Emergency Physicians acknowledges HBO as a therapeutic option for CO poisoning, but its use is not mandatory[9]. So there were conflicting opinions on this issue.

Most of the studies in the literature recommend administration of HBO in CO patients with neurological deficits, cardiac ischemia, loss of consciousness, metabolic acidosis, and COHb values >25%[10]. Rose et al. demonstrated that hyperbaric oxygen is associated with reduced acute and reduced 1-year mortality[11]. In another study Weaver et al. demonstrated that three hyperbaric-oxygen treatments within a 24-hour period appeared to reduce the risk of cognitive squeal 6 weeks and 12 months after acute CO poisoning[4]. On the other hand at a more recent study Wang et al indicated that HBO therapy significantly reduces the risk of memory impairment compared to NBO, but two sessions of HBO might not be better for memory impairment than one session of HBO[12].

There were also publications on the opposite view. The 2017 ACEP Clinical Policy on CO Poisoning provides Level B recommendations that HBO therapy or high-flow NBO therapy should be used for acute CO-poisoned patients, though the effects of HBO versus NBO therapy on long-term neurocognitive outcomes remain unclear[13]. Even that Huang et al. demonstrated that risk for neurological squeal was higher in patients with CO poisoning who received HBO than in those who did not[14]. Possible contributing factors to this result may be those; firstly patients who had risk for neurologic squeal were more likely to receive HBO and secondly because HBO reduces mortality, the high-risk survivors tended to develop neurologic squeal afterwards[14].

Another variable that affects the effectiveness of HBO treatment is time. In study of Liao et al. multivariable logistic regressions revealed that longer duration from CO exposure to HBO, loss of consciousness, and the presence of multiple victims were independent predictors of delayed neuropsychiatric squeal development in patients with CO poisoning who received HBO[15]. So, studies recommend administration of HBO therapy as early as possible, especially within 4-6 hours after poisoning[16].

Conclusion

Our study demonstrated that most of the CO poisoned patients with HBO indication were not administered this therapy. Although the current literature provides conflicting data on the effectiveness of HBO therapy at CO poisoning, we considered that HBO should be administered in case of severe CO poisoning to reduce mortality and delayed neurological sequel. However, since CO poisoning is a common condition, there is a need for multicenter, prospective, advanced studies in which patients are followed up for a long time in terms of mortality and morbidity in order to reach consensus and create a management guide.

Limitations

Since the study was retrospective, it had many limitations. Firstly, complaint of the patients at admission to ED were not recorded to hospital registry system. Therefore HBO indications other than carboxyhemoglobin level could not be determined. Secondly, we knew the discharge time of the patients who administered HBO, but the time they reached to HBO chamber were unknown; and that makes impossible to calculate the duration from CO exposure to HBO therapy. Also, those patients were not followed up. So it was not possible to evaluate whether there was a difference in term of morbidity in patient who administered and not administered HBO.

References

1. Temrel TA, Bilge S. Myocardial Repolarization Parameters and Neutrophil-to-Lymphocyte Ratio are Associated with Cardiotoxicity in Carbon Monoxide Poisoning. Cardiovasc Toxicol. 2019. doi: 10.1007/s12012-019-09560-7
2. Irem G, Çevik Y, Keskin AT, Emektar E, Demirci OL, Şafak T, et al. Copeptin levels in carbon monoxide poisoning. Turk J Med Sci. 2017; 47(2):653-657.
3. Lettow I, Hoffmann A, Burmeister HP, Toepper R. Delayed neuropsychological sequelae after carbon monoxide poisoning]. Fortschr Neurol Psychiatr. 2018; 86(6): 342-347.
4. Weaver LK, Hopkins RO, Chan KJ, Churchill S, Elliott CG, Clemmer TP, et al. Hyperbaric oxygen for acute carbon monoxide poisoning. N Engl J Med. 2002; 347(14):1057-67.

5. Kuo SC, Hsu CK, Tsai CT, Chieh MJ. Hyperbaric Oxygen Therapy and Acute Carbon Monoxide Poisoning. Hu Li Za Zhi. 2018; 65(4): 11-17.

6. Lin CH, Su WH, Chen YC, Feng PH, Shen WC, Ong JR, et al. Treatment with normobaric or hyperbaric oxygen and its effect on neuropsychometric dysfunction after carbon monoxide poisoning: A systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore). 2018; 97(39):e12456. doi: 10.1097/MD.0000000000012456.

7. Juurlink DN, Buckley NA, Stanbrook MB, Isbister GK, Bennett M, McGuigan MA. Hyperbaric oxygen for carbon monoxide poisoning. Cochrane Database Syst Rev. 2005; (1):CD002041.

8. Çorbacıoğlu ŞK, Çıkrıkçı G, Çevik Y. ST-Segment Elevation Myocardial Infarction Due to Carbon Monoxide Poisoning. JAEMCR 2015; 6: 46-8

9. Rose JJ, Wang L, Xu Q, McTiernan CF, Shiva S, Tejero J et al. Carbon Monoxide Poisoning: Pathogenesis, Management, and Future Directions of Therapy. Am J Respir Crit Care Med. 2017; 195(5):596-606.

10. Eichhorn L, Thudium M, Jüttner B. The Diagnosis and Treatment of Carbon Monoxide Poisoning. Dtsch Arztebl Int. 2018; 115(51-52): 863-870.

11. Rose JJ, Nouraie M, Gauthier MC, Pizon AF, Saul MI, Donahoe MP et al. Clinical Outcomes and Mortality Impact of Hyperbaric Oxygen Therapy in Patients With Carbon Monoxide Poisoning. Crit Care Med. 2018; 46(7):e649-e655. doi: 10.1097/CCM.0000000000003135.

12. Wang W, Cheng J, Zhang J, Wang K. Effect of Hyperbaric Oxygen on Neurologic Sequelae and All-Cause Mortality in Patients with Carbon Monoxide Poisoning: A Meta-Analysis of Randomized Controlled Trials. Med Sci Monit. 2019; 25:7684-7693.

13. Ng PC, Long B, Koyfman A. Clinical chameleons: an emergency medicine focused review of carbon monoxide poisoning. Intern Emerg Med. 2018; 13(2):223-229.

14. Huang CC, Ho CH, Chen YC, Hsu CC, Wang YF, Lin HJ et al. Impact of Hyperbaric Oxygen Therapy on Subsequent Neurological Sequelae Following Carbon Monoxide Poisoning. J Clin Med. 2018; 7(10). pii: E349. doi: 10.3390/jcm7100349.

15. Liao SC, Mao YC, Yang KJ, Wang KC, Wu LY, Yang CC. Targeting optimal time for hyperbaric oxygen therapy following carbon monoxide poisoning for prevention of delayed neuropsychiatric sequelae: A retrospective study. J Neurol Sci. 2019; 396: 187-192.

16. Altintop I, Akcin ME, Tatli M, Ilbasmis MS. Factors that influence the decision for hyperbaric oxygen therapy (HBOT) in cases of carbon monoxide poisoning: a retrospective study. Ann Burns Fire Disasters. 2018; 31(3):168-173.

Case Report
Eurasian Journal of Toxicology

Ethylene Oxide Intoxication: A Case Series

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Abstract

Ethylene oxide is a colorless, inflammable, explosive and toxic gas with a slight odor which is slightly heavier than air. It used for sterilization of the materials in healthcare sector and for sterilization purposes in pharmaceutical sector etc. Eight patients including 7 females and 1 male referred to our emergency clinic after ethylene oxide gas leak in sterilization unit of a company. Age average of the patients was 28 (min: 19, max:53) years. Inspection of the patients in the emergency service was nonspecific. Blood analyses of the patients were also nonspecific. The patients were discharged from emergency service by their own request while they were treated in the emergency service. Three patients then referred because of nausea and vomiting 3 days after. Blood analyses performed again were also nonspecific. Physiological saline was administrated for hydration and 4 mg of ondanstarone was administrated; the patients were discharged upon recovery of the complaints. The aim of the present study was to present monitoring and treatment of possible intoxication by ethylene oxide which is commonly used in sterilization units.

Key words: Ethylene oxide, Intoxication, Sterilization

Özet

Etilen oksit renksiz, yanıcı, patlayıcı ve hafif bir kokuya sahip, havadan biraz daha ağır olan zehirli bir gazdır. Sağlık sektöründe malzemelerin sterilizasyonu ve ilaç sektöründe sterilizasyon amaçları için kullanılır. 7 kadın ve 1 erkek olmak üzere sekiz hasta, bir şirketin sterilizasyon ünitesinde etilen oksit gazı sızıntısından sonra acil kliniğimize başvurdu. Hastaların yaş ortalaması 28 (en az 19, en çok 53) idi. Acil servisteki hastaların muayenesinde özellik saptanmadı. Hastaların laboratuvar bulgularında özellik yoktu. Hastalar acil serviste tedavi ederken acil servisten kendi istekleri ile taburcu edildi. Üç gün sonra ise hastaların üçü bulantı ve kusma şikayeti ile tekrar acil servise başvurdu. Tekrarlanan kan analizlerinde herhangi bir patolojik bulgu saptanmadı. Hidrasyon amaçlı serum fizyolojik uygulaması yapıldı ve 4 mg ondanstaron uygulandı. Hastalar şikayetlerin düzelmesi üzerine taburcu edildi. Bu çalışmanın amacı, sterilizasyon ünitelerinde yaygın olarak kullanılan etilen oksit ile olası zehirlenmelerin izlenmesini ve tedavisini sunmaktır.

Anahtar kelimeler: Etilen oksit, Zehirlenme, Sterilizasyon

Introduction

Ethylene oxide is a colorless, inflammable, explosive and toxic gas with a slight odor which is slightly heavier than air. Ethylene oxide has been discovered in 1859; bacteriocyte characteristics was discovered in World War 2. Ethylene oxide has been used for sterilization since 1960[1]. It is also used for sterilization of the materials in healthcare sector and for sterilization purposes in pharmaceutical sector etc. The gas penetrates through inhalation or skin. It is metabolized by two different pathways. The metabolites are excreted in the urine within 24 hours following the exposure. Small portion of the gas is discharged as carbodioxide or small metabolites from gastrointestinal system. Acute or chronic effects due to ethylene oxide toxicity were reported in animal and human experiments. The aim of this study was to present monitoring and treatment of possible intoxication by ethylene oxide which is commonly used in sterilization units.

Cases

Eight patients including 7 females and 1 male referred to our emergency clinic after ethylene oxide gas leak in sterilization unit of a company by emergency ambulance at 3:00 p.m. so Ethylene oxide poisoning has been set with anamnesis of patients and no diagnosis test has been performed.Age average of the patients was 28 (min: 19, max:53). Glascow Coma Score (GCS) was 15, pupils were isochoric and vital signs were within normal limits during inspection of 8 patients in the emergency service. Common compliant of the patients were nausea. There was not any pathology detected in the ECG and physical examination of the patients was normal. Blood count, biochemistry and urine analysis of the patients were normal. Hydration was performed by intravenous infusion of 1000 ml isotonic and 10 mg metochlopramide within 100 ml of isotonic fluid for nausea. Intoxication Hotline, 114 was contacted for ethylene oxide intoxication

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Received: 21.05.2019 • **Accepted:** 22.07.2019
Cite this article as: Dikmetas C, Dogan S, Kalafat UM, Tapkan RB, Dorter M, Bildik B, Cander B. Ethylene oxide intoxication: a case series. Eurasian J Tox. 2020;2(1):29-30.

and a follow-up for 48 hours was planned; however, the patients expressed that they felt well and were discharged by their own request. Three female patients referred emergency service again upon recurrence of nausea 3 days after. Physical examination was repeated again and it was nonspecific. Blood count, biochemistry and urine analysis of the patients which were repeated were normal. Hydration was performed by intravenous infusion of 1000 ml isotonic and 4 mg ondansetron was administrated within 100 ml isotonic solution. There was not any specific finding during follow-up and complaints of the patients regressed; the patients were discharged after arrangement of their medical treatments.

Discussion

Ethylene oxide is a gas used for sterilization of heat-sensitive materials[2]. Security precautions must be taken in the units where ethylene oxide is used for sterilization; the areas where tubes, cartridges and sterilizators are kept must be controlled by sensors[5]. The exposure level allowed for ethylene oxide is 1 ppm per eight hours[3, 4]. Acute or chronic effects due to ethylene oxide toxicity were reported in animal and human experiments[3, 4]. Early symptoms of acute over-exposure to ethylene oxide include nausea, vomiting, headache, irritation on eyes and respiratory tracts. The individual may feel a strange taste in the mouth[1]. All 8 patients had nausea complaint. Nevertheless, three patients referred to emergency service upon persistence of nausea complaint. Pulmonary edema, somnolence, weakness and incoordination may appear as late finding. The aforementioned findings were not detected in 8 patients. The outcomes of the researches suggest that changes in the blood cells and spontaneous miscarriages may be associated with exposure to ethylene oxide. Pregnancy was not detected in the tests performed on female patients. Skin contact of liquid and gas forms of ethylene oxide may cause burn and allergic reactions. Edema and erythema appeared on the skin transforms to bulla and desquamation. Recovery is completed within three weeks. However, brown pigmentation may persist. Ethylene oxide solutions of 40% to 50% are very dangerous. It causes diffuse bullas even after short contact. Pure liquid ethylene oxide causes freezing. On the contrary, eyes are relatively insensitive to ethylene oxide. However, some corneal irritation may appear[1]. Sterilization by ethylene oxide is still important; and labor safety precautions should be kept at highest priority due to its toxicity; an emergency precaution action plan should exist in workplaces in case of any leak. However, patient's occupation should be investigated during history taking and the emergency medicine physician should considered leak of ethylene oxide when a patient refers from a workplace using ethylene oxide.

Conclusion

Ethylene oxide is a colorless toxic gas. This gas is commonly used for sterilization; and labor safety precautions for ethylene oxide gas should be taken seriously for ethylene oxide gas and the patients should be closely followed for severe adverse events in case of a leak; workplace of a patient with complaints of nausea etc. should be investigated and gas exposure such as ethylene oxide should be considered by emergency physician.

References

1. Zenciroğlu D. Etilen Oksid ile Sterilizasyon; Nasıl çalışır? Kullanılan Cihazların Özellikleri nelerdir? Nasıl Denetlenir? Olumlu ve Olumsuz Yönleri Nelerdir? Formaldehid ile sterilizasyon yöntemi ile kıyaslama. Önlemler ve Gaza Maruz Kalan Personele Uygulanacak İşlemler. In Günaydın M, editors. 4. Sterilizasyon ve Dezenfeksiyon Kongresi;2005 April 20-24; Samsun, Turkey, 2005;121-124
2. Eren Y, Güven H, Çomoğlu SS. Olası Etilen Oksit Nöropatisi. Turkiye Klinikleri J Neur 2017; 12(1): 6-10.
3. Bleecker ML. Toxic peripheral neuropathy. In: Rom WN, Markowitz SB, eds. Environmental And Occupational Medicine. 4th ed. Philadelphia:Lippincott Williams & Wilkins, 2007. p.645-646.
4. Liteplo RG, Meek ME, Lewis M. Ethyleneoxid.Concise international chemical assessment document; 54. World Health Organization Geneva; 2003. p.17-18.
5. Genç M, Sterilizasyonda Beklenmeyen Durumlar.In Esen Ş, Perçin D, Mehmet Ali Özinel M.A, Günaydın M, Zenciroğlu D, editors. 7. Ulusal Sterilizasyon Dezenfeksiyon Kongresi;2011 March 16-20; Antalya, Turkey 2011. p167-182.