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ADMA, a Useful Biomarker in CO-Poisoned Children?

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Amaç:
Karbon monoksit zehirlenmesi (COP), tüm dünyadaki zehirlenme vakalarından kaynaklanan ölüm ve hastalıkların önde gelen nedenidir. Çocuklar COP'dan daha hızlı ve ciddi şekilde etkilendiklerinden, karboksihemoglobin (CO-Hb) ve / veya laktat seviyeleri normale dönse bile daha uzun bir tedavi süresi gerekebilir. Bu nedenle, tedavi süresini ve COP'un nihai sonuçlarını öngören yeni bir belirteçlere ihtiyaç vardır.
Gereç ve Yöntem:
Bu vaka kontrol çalışması, çocuk acil servisimize başvuran 18 yaşından küçük, 32 karbon monoksit zehirlenmesi olan hasta üzerinde gerçekleştirildi. Kontrol grubu yaş ve cinsiyet uyumlu 30 sağlıklı çocuk ile oluşturuldu. Hastalardan, arterial kan gazı, karboksihemoglobin, metemoglobin, laktat ve asimetrik dimetilarjinin (ADMA) analizi için kan örnekleri alındı.

Bulgular:
COP hastalarında, başvuru sırasındaki ve tedavi sonrası ADMA düzeyleri kontrol grubuyla karşılaştırıldığında anlamlı olarak yüksek olduğu görüldü ($P < 0.05$) (1.36 [0.89–6.94], 1.69 [0.76–7.81], 1.21 [0.73–3.18] nmol/L, sırasıyla). Başvurudaki ve 6 saat sonraki kontrolde CO-Hb ve ADMA düzeyleri arasında pozitif korelasyon saptanmadı (sırasıyla $P = 0.903$, $r = 0.218$, $P = 0.231$, $r = 0.022$). Başvuru sırasındaki laktat ve CO-Hb düzeyleri arasında pozitif korelasyon tespit edildi ($P = 0.018$, $r = 0.423$).

Sonuçlar:
Bu çalışma, COP olan hastalarda 6 saatlik % 100 oksijen tedavisinden sonra CO-Hb ve / veya laktat seviyelerinin normal aralığa dönmesine rağmen ADMA seviyelerinin hala yüksek olduğunu göstermiştir. Bu sonuçlara dayanarak, ADMA'nın COP olan hastaların takibinde faydalı bir biyobelirteç olabileceğini düşünüyoruz.
Anahtar Kelimeler: ADMA, biyobelirteç, karbon monoksit

ABSTRACT
Objective: Carbon monoxide poisoning (COP) is the leading cause of mortality and morbidity due to poisoning worldwide. Because children are affected more quick and severely from COP, they may require a longer treatment period, even if carboxyhemoglobin (CO-Hb) and/or lactate levels return to normal. Therefore, a new marker that predicts the duration of treatment and the final outcomes of COP is needed.
Methods: This case control study was conducted on 32 carbon monoxide–poisoned patients younger than 18 years who had been admitted to pediatric emergency department. The control group included age- and sex-matched 30 healthy children. Blood samples were obtained for analysis of arterial blood gases, CO-Hb percent, methemoglobine, lactate, and asymmetric dimethylarginine (ADMA).

Results:
Asymmetric dimethylarginine levels were significantly increased (P < 0.05) in patients with COP on admission and after the treatment when compared with controls (1.36 [0.89–6.94], 1.69 [0.76–7.81], 1.21 [0.73–3.18] nmol/L, respectively). There was no positive correlation between CO-Hb and ADMA levels on admission and at 6 hours (P = 0.903, r = 0.218, P = 0.231, r = 0.022, respectively). Positive correlation was found between lactate and CO-Hb levels on admission (P = 0.018, r = 0.423).

Conclusions:
This study showed that ADMA levels were still high after 6 hours of 100%oxygen therapy in children with COP, even CO-Hb and/or lactate levels return to normal range. On the basis of these results, we consider that ADMA may be a useful biomarker in patient with COP.

Key Words: *ADMA, biomarker, carbon monoxide*

INTRODUCTION

Carbon monoxide poisoning (COP) is the leading cause of mortality and morbidity due to poisoning worldwide (1). After inhalation of CO via the lungs, it easily diffuses from lungs into the bloodstream and then forms carboxyhemoglobin (CO-Hb) with hemoglobin (Hb), which is a tight but slowly reversible Complex. When CO-Hb levels rise, the cerebral blood vessels become dilated, and coronary blood flow and capillary density increased. Continued exposure results with central respiratory depression due to cerebral hypoxia. Especially, ventricular arrhythmias develop with cardiac involvement. (2-5)

Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of endothelial nitric oxide synthase. (5,6) ADMA causes a decrease in NO levels leading to endothelial dysfunction (7). In this respect, increased levels of ADMA may indicate endothelial dysfunction in patients exposed to CO gas. The aim of this study was to determine the changes of ADMA levels, as an oxidative stres marker, in patients with COP on admission and after treatment. To the best of our knowledge, our study is the first to analyze ADMA levels in children with COP.

METHODS

This case control study was conducted on CO-poisoned patients younger than 18 years who had been admitted to pediatric emergency department of Necmettin Erbakan University Meram Medical Faculty, between October 2016 and May 2017.

The diagnosis of COP was based on history, clinical examination, and CO-Hb percent (CO-Hb%) greater than 3% at the time of admission. All patients received high-flow 100% oxygen therapy with nonrebreathing mask with an oxygen reservoir bag for at least 6 hours. The control group included age- and sex-matched 30 healthy children.

Blood samples were obtained for analysis of arterial blood gases, CO-Hb%, MetHb%, lactate, and ADMA on admission and after 6 hours of treatment. CK, CK-MB, LDH, troponin I, AST and ALT, urea, creatinine, and complete blood count were measured only at admission.

Statistical Analysis

The collected data were computerized and statistically analyzed using Statistical Package for the Social Sciences (SPSS for Windows, version 15.0). Quantitative data were summarized as mean ± SD. If not normally distributed, parameters were presented as median (range). The Kolmogorov-Smirnov test was applied to check distribution of parameters. Data that did not normally distributed (ADMA levels) were log-transformed for analysis. Independent t test or Mann-Whitney U test was used to compare groups, and the associations between parameters were assessed using the Pearson or Spearman correlation test. Paired samples t test or Wilcoxon-signed rank test was used to compare pretreatment and posttreatment values of the study group. Results were considered significant if $P \leq 0.05$.

RESULTS

Thirty-eight patients had admitted to pediatric emergency department during this period with CO poisoning. The groups were similar with respect to age ($P > 0.05$). Loss of consciousness was not present in any patient and cardiovascular and respiratory system examinations of all patients were normal.

Asymmetric dimethylarginine levels were significantly increased in patients with COP on admission and after the treatment when compared with controls ($P < 0.05$). Asymmetric dimethylarginine levels did not significantly differ in patients with COP after the treatment when compared with baseline ($P > 0.05$). Serum ADMA values were not correlated with other parameters before and after treatment. After log transformation, serum ADMA values were not correlated with other parameters before and after treatment. There was no positive correlation between CO-Hb and ADMA levels on admission and at 6 hours ($P = 0.903$, $r = 0.218$, $P = 0.231$, $r = 0.022$, respectively). Positive correlation was found between lactate and CO-Hb levels on admission ($P = 0.018$, $r = 0.423$). Therewas no statistically difference between symptomatic and asymptomatic patients in terms of both ADMA and CO-Hb levels ($P > 0.05$). Serum CK, CK-MB, LDH, lactate, CO-Hb%, and metHb% values were significantly decreased in patients with COP after the treatment when compared with the baseline.

DISCUSSION

Although the pathophysiology of COP is complex and incompletely understood, oxidative stress plays an important role. Recent studies focused on tissue damage due to CO-induced oxidative stres (8,9). Here we showed that levels of ADMA, which is an oxidative stress biomarker, were elevated in patients with COP.

This study mainly focused on ADMA levels of children with acute COP. Carbon monoxide exposure–induced oxidative stres leads to an increase in ADMA levels. A subsequent decrease in NO levels results with endothelial dysfunction. In our study, we found that ADMA levels were significantly increased in patients with COP before and after treatment when compared with controls. Although high levels of WBC, ANC, CO-Hb, lactate, CK, and CK-MB levels returned to normal after treatment, ADMA levels continued to be high. This suggests that possible oxidative stress is continuing after 100% oxygen therapy, even if CO-Hb and/or lactate levels return to normal. In conclusion, on the basis of these results, we consider that ADMA may be a useful biomarker in patients with COP, especially where CO-Hb and lactate level may be normal in delayed cases. However, this study has been conducted on a small sample size, so it is felt that further larger clinical trials should be conducted to clarify the role of ADMA in CO-induced endothelial dysfunction in children.

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