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ORIGINAL ARTICLE

Review of Various Chemical Biomarkers and Scoring Systems in Prediction of Outcome of Acute Carbon Monoxide Induced Neurotoxicity and Cardiotoxicity

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ABSTRACT

Background: Carbon monoxide (CO) poisoning is one of the most common fatal poisoning worldwide. CO poisoning is known to have several complications and high fatality rate. Cardiac dysfunction including arrhythmias and myocardial ischemia have often been reported in CO poisoning; scattered punctiform hemorrhages throughout the heart have been documented in autopsy samples. Whilst it is one of the most common lethal poisonings, neurological or psychiatric sequelae occurs in up to 67% of survivors. This suggests that CO is implicated in neuronal death, or loss of function of the cells in the central nervous system. Approximately half of those who survive severe CO poisoning develop delayed neurological sequelae (DNS) after a latency period of 2–40 days, with varied clinical manifestations, persistent neuropsychological effects, and no guarantee of complete recovery. However, they are potentially preventable if they are early recognized and adequately treated. The work aimed to give an overview on cardiac and neurological complications of CO poisoning and the role of chemical biomarkers such as neutrophil-lymphocyte ratio (NLR), neuron specific enolase (NSE), creatine kinase, troponin, creatine kinase MB and N- terminal pro brain natriuretic peptide (NT pro-BNP) and scoring systems such as modified early warning score (MEWS) and poison severity score (PSS) in early prediction of these complications.**Conclusions:** Prediction of complications in CO poisoned patients is believed to be a challenging task. Laboratory parameters and imaging studies have been used to predict late cardiac and neurological complications in CO poisoned patients. Many physiologic scoring systems are demonstrated as effective predictors of outcomes for patients in the emergency department**.** However, very few studies have applied scoring systems as predictors of CO poisoning outcome.

Keywords: Scoring Systems; Carbon Monoxide; Neurotoxicity; Cardiotoxicity.

INTRODUCTION

Carbon monoxide poisoning is a prevalent and deadly kind of airborne poisoning that occurs globally. It is a tasteless, odorless, and colorless gas that is released when carbonaceous particles are incompletely burned. Victims enter a state of unconsciousness before becoming aware of the fact that they are being poisoned [1].

Toxicity arises from the simultaneous occurrence of tissue hypoxia and direct cellular damage caused by carbon monoxide. The clinical manifestations in individuals with carbon monoxide poisoning varies from experiencing headache and dizziness to developing convulsions, coma, and ultimately death. The effects of CO poisoning on individuals can vary [2].

Laboratory measurements and imaging tests have been utilized to evaluate delayed cardiac and neurological problems with long-term consequences. [3].

Scoring systems are commonly used in medical practice to enhance clinical decision making. They help physicians in diagnosing diseases, evaluating patients' status, and forecasting the outcome. During emergency scenarios, scoring systems often prioritize simplicity and primarily rely on clinical data, with little to no inclusion of investigative procedures. Several scores have been created and verified for utilization in the emergency department [4].

Carbon monoxide induced neurotoxicity

Neuropathology following CO poisoning may be linked to neuronal death in the cortex, hippocampus, substantia nigra, and globus pallidus. Demyelination of the cerebral cortex is considered one of the most frequent anomalies linked to carbon monoxide poisoning characterized by presence of damage around blood vessels and combined with signs of a breakdown in the protective barrier between the blood and the brain [5].

Incidence

Carbon monoxide poisoning is a frequently occurring and deadly form of poisoning that often leads to the development of neurological or psychiatric complications in up to 67% of those who survive [6]. CO can result in the death or impairment of brain cells. Roughly 50% of individuals who survive acute CO poisoning experience delayed neurocognitive complications after a period of 2-40 days. As a result, it is crucial to provide appropriate and sufficient care following CO poisoning, with an emphasis on protecting the nervous system [7].

Pathogenesis

1) Anoxic and ischemic mechanism

Hypoxia or anoxia is considered one of the primary causes of neuronal cell death in many neurological illnesses it is triggered by different mechanisms that ultimately result in cell death or dysfunction. These mechanisms include reduced ATP synthesis, glutamate excitotoxicity, and oxidative stress that produce ischemic brain injury which is responsible for the development of delayed neurocognitive sequelae in the survivors after CO poisoning [8].

2) Oxidative stress mechanism

Oxidative stress occurs when there is an excessive synthesis of reactive oxygen species (ROS) and/or a decrease in the cell's antioxidant defense components.

Nevertheless, the generation of ROS serves no. t just as a pathogenic mechanism but also as a stimulus for a physiological redox signal [9]. Endogenous (CO) plays a vital role in the functioning of the central nervous and cardiovascular systems. However, significant fluctuations in the synthesis and levels of ROS and CO can disrupt the pathways of these substances in neurons. This disruption can lead to the development of neurological or neuropsychiatric disorders [10].

3) ***Nitric oxide***

Nitric oxide (NO) induces the presynaptic release of monoamine neurotransmitters by activation of N- methyl d- aspartate (NMDA) receptors. It also can initiate neuronal damage by the generation of NO-derived oxidants. NO-mediated oxidative stress could potentially serve as a shared molecular connection between several mechanisms of CO poisoning[11].

4) ***Intracellular enzymes activation***

Reduction in ATP production activates the intracellular proteases and lipases induce mitochondrial membrane depolarization, resulting in cell death and the release of substances of neurotransmitters, particularly glutamate neurotransmitter which increases cellular dysfunction and apoptosis by activation of N-methyl-d-aspartate receptors [12].

5) ***Neurotransmitters mechanism***

Some neurotransmitters as norepinephrine and dopamine are elevated after CO exposure with the generation of reactive O_2 species. These neurotransmitters may be responsible for oxidative stress and the increase of radical production after CO poisoning. It also may be due to external toxicity, metabolic acidosis, ion channel disturbances inflammatory process, and apoptosis [13].

Biomarkers of neurotoxicity

1) Chemical biomarkers

Many studies have measured the level of serum lactate, serum S 100 B protein and serum anion gap and studied their relation to the development of neurocognitive sequelae. These studies found that CO poisoning may increase the formation of myelin basic protein and delayed neurological sequalae (DNS) occurs as a result of excessive myelin and neuron loss [14].There was an increase in the level of some biomarkers such as N- terminal pro brain natriuretic peptide(NT pro-BNP), troponin, creatine kinase, and creatine kinase MB which is indicative of the development of delayed neurological sequelae and all these biomarkers are related to cardiac injury and these correlates with finding that people with myocardial dysfunction are at great risk for development of DNS and QT prolongation of ECG of patient with CO poisoning is considered an early predictor of DNS [15].

Furthermore, the neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), and platelet lymphocyte ratio (PLR) are regarded as straightforward inflammatory biomarkers of neurotoxicity. These biomarkers can be easily obtained by analyzing the complete blood cell (CBC) counts from the peripheral blood. These markers have practical value in predicting outcomes in different clinical situations characterized by inflammatory reactions [16]. Studies have shown that some chemical Biomarkers such as Neuron Specific Enolase

(NSE) have the potential to accurately predict the occurrence of neurocognitive sequelae [14].

Neuron specific enolase (NSE)

It is a type of enzyme involved in the breakdown of glucose called glycolysis. Specifically, it is a subtype of enolase that catalyzes the hydrolysis of 2-phospho-D-glycerate. This enzyme exists in the form of multiple dimeric isoenzymes. The human brain has three isoenzymes: αα, αγ, and γγ. The αγ and γγ-enolase isoenzymes are alternatively referred to as NSE. [17]. The presence of these isoenzymes was initially observed in neurons and neuroendocrine cells. Serum NSE has been employed as a precise indicator for the process of neuron regeneration and re-innervation. Exposure to brain-damaging substances such as solvents, chromium, 1-bromopropane, and 2,5-hexanedione resulted in increased levels of serum NSE. It was also increased in patients with stroke and cardiac arrest [18]. It is also considered one of the major brain proteins that constitutes between 0.4 % and 2.2 % of the total soluble brain protein according to its dstribution. Within certain neurons, NSE comprises around 3-4% of the overall soluble protein content. Consequently, it serves as a widely employed biomarker for identifying neuronal and neuroendocrine cells due to its exceptional specificity for these types of tissues. Typically, it is not actively secreted, but it is discharged upon damage to the axon. Hence, the measurement of serum NSE level can serve as an indicator of neuronal cell injury in patients suffering from various illnesses, such as traumatic and hypoxic brain damage, status epilepticus, and cardiac arrest [19].

Although NSE is commonly used as a biomarker, only a limited number of research have examined the relationship between serum NSE levels and impaired awareness in patients with carbon monoxide poisoning, in order to assess CNS injury [20]. A study on CO poisoned patients showed that the initial serum NSE measured in the Emergency Department served as an early predictor of DNS development [19].

2) Radiological biomarkers

Computed topography (CT) brain and magnetic resonance imaging (MRI) can show neurological abnormalities in the form of focal and generalized neuroanatomical abnormalities which can early predict the development of delayed neurological sequelae also some CT findings showed hypoxic encephalopathy, and this correlated with the development of DNS [21].

3) Proton magnetic resonance spectroscopy

Moreover, the pathophysiology of CO poisoning can be evaluated using proton magnetic resonance spectroscopy which can monitor the neurochemical disturbances. It was demonstrated that a high lactate level was an early predictor of poor outcome and application of proton magnetic resonance spectroscopy within one week of CO poisoning can be an early predictor of DNS [22].

Carbon monoxide induced cardiotoxicity

Cardiotoxicity refers to the development of cardiac malfunction due to electrical disturbances or muscular injury, resulting in a

weakened heart that is unable to adequately pump blood. Cardiotoxicity can result from chemotherapy drugs called anthracyclines, issues arising from anorexia nervosa, the harmful effects of consuming heavy metals, or the prolonged misuse or excessive consumption of potent stimulants like cocaine [23].

Research has shown that myocardial damage is a separate factor that predicts a negative short-term prognosis in patients with severe CO poisoning, as well as long-term mortality in individuals with moderate-to-severe carbon monoxide intoxication. Hence, it is imperative for emergency physicians to consistently detect indicators of myocardial injury by the use of ECG, cardiac markers, and other laboratory or imaging procedures such as echocardiography or coronography [24].

Pathogenesis:

Many mechanisms may be responsible for the development of cardiac Ischemia and dysfunction occur by carbon monoxide poisoning. Animal studies have shown that when exposed to CO poisoning, the body first responds by increasing the amount of blood pumped by the heart and extracting more oxygen. However, these compensatory mechanisms eventually get overloaded, resulting in a collapse of the cardiovascular system [6].

1) Anoxia

A decrease in oxygen supply, an increase in O_2 requirement with elevated myocardial contractility resulting from carbon monoxide intoxication has the potential to initiate myocardial infarction in individuals with preexisting cardiac conditions. Elevated amounts of carbon monoxide (CO) can heighten the likelihood of thrombosis by binding to heme that is attached to fibrinogen, leading to the clumping together of platelets[25,26].

2) **Oxidative phosphorylation inhibition**

The suppression of oxidative phosphorylation and the significant enhancement of carbon monoxide's binding affinity to myoglobin, which is 60 times more than the affinity of oxygen to myoglobin, leads to cardiac dysfunction and myocardial infarction in myocytes, even without any pre-existing coronary illness. In addition, it raises the likelihood of arrhythmia development due to the suppression of oxidative phosphorylation and decreased ATP synthesis, which disrupts calcium balance. This disruption causes an increase in calcium sensitivity of myofilaments, elevated levels of diastolic intracellular calcium, and a condition of heightened adrenergic activity [27].

3) Nitric oxide (NO)

CO increases NO synthase expression, which mediates NO-induced myocardial damage during ischemia–reperfusion [28].

Biomarkers of cardiotoxicity

1) Chemical biomarkers

Brain natriuretic peptide (BNP) and N-terminal pro BNP (NT-pro BNP) serve as crucial diagnostic and prognostic indicators for confirmed heart failure and cardiac dysfunction. [29]. The natriuretic peptide family primarily consists of atrial natriuretic peptide (ANP), which is predominantly produced and released by atrial myocytes, along with B-type natriuretic peptide (BNP)

and C-type natriuretic peptide (CNP). BNP was initially extracted from pig brain tissue and given the term brain natriuretic peptide. However, further research has revealed that its production and release primarily occur in ventricular myocytes [30]. Research has shown that there is a direct relationship between the level of BNP and the extent of cardiac damage in patients with carbon monoxide poisoning [31].

Cardiac troponin, specifically troponin I (TnI) and troponin T (TnT), is located inside cardiac muscle cells and is released into the bloodstream when the outer membrane of these cells is damaged. In the past, only traditional troponin tests were accessible for identifying cardiac troponin levels in the blood at concentrations of 100 ng/L or higher. Technological progress has resulted in the creation of more advanced assays called high-sensitive troponin assays, capable of detecting troponin at far lower quantities. Troponin is a highly accurate and precise indicator of damage to the heart muscle, and it is commonly used in medical settings to diagnose and predict outcomes in cases of acute myocardial infarction [32]. Nevertheless, troponin levels can also rise in various other diseases, including hypertensive crisis, renal failure, rhabdomyolysis, sepsis, chronic vascular insufficiency, and drug-induced heart damage [33].) A study on CO poisoned patients revealed that troponin T level was higher in patients with severe CO toxicity than in patients with mild CO intoxication [34].

2) Electrocardiography (ECG)

A study has demonstrated that the most frequent electrocardiography (ECG) alteration in patients with carbon monoxide (CO) poisoning is the lengthening of the QT interval. This change is attributed to the increased late component of the inward sodium current in ventricular myocytes caused by CO. The mechanism behind this effect involves the elevation of nitric oxide (NO) levels, which leads to the S-nitrosylation of the voltage-gated sodium channel in the heart muscle. It also proved that the increased late sodium current mediated by CO was proarrhythmic. Furthermore, T wave and ST segment changes, ST-segment elevation myocardial infarction (STEMI), tachycardia or bradycardia, A-V block, atrial fibrillation, premature ventricular contraction and ventricular fibrillation were detected in patients with CO poisoning [35].

Scoring systems

Many physiologic scoring systems are demonstrated as effective predictors of outcomes for patients at the emergency department. Medical scores, criteria, and classification systems are methods used to evaluate and categorize medical conditions essential for the decision-making and management of patients in emergency departments are valuable because they allow clinicians to accurately forecast the result, evaluate risk levels, assess conditions, and provide accurate diagnosis of diseases[36].There was correlation between MEWS components and the need for ICU admission, also there was significant elevation in MEWS parameters in both mechanically ventilated and non-survivors when compared to non-mechanically ventilated patients and survivors [37]. PSS was a good predictor of poor outcomes, it

may be suitable for prognostic evaluation of CO poisoning on admission and can help in follow-up patients during hospitalization [38]. Ensuring safety standards for patient release, determining the appropriate length of stay in the emergency room, and establishing the duration of hospital admission are crucial aspects of emergency medicine. These scoring systems primarily target critically sick patients to assess abnormalities in several physiological indicators, enabling the detection of severity and prediction of outcomes. The ideal scoring system would have the following characteristics (based on variables that can be easily and routinely recorded, well calibrated, with a high level of discrimination, can be applied for all people and in different countries and can predict the quality of life after discharge. They play an essential role in the management of patients in the emergency department.[4].

Early warning scores (EWS) are utilized to promptly identify, intervene, and escalate the care of patients displaying indications of clinical deterioration. These scores are vital in enhancing patient outcomes and safety. Early warning scores can be derived from either a single physiological parameter or a combination of multiple factors. These scores are calculated by assigning weights to each variable and then combining them to reflect the severity of acute sickness. Healthcare professionals, typically nursing staff, can utilize these scores to construct an algorithm that suggests suitable clinical interventions depending on the calculated score. This facilitates a shared platform for communication among healthcare providers to attain enhanced results [39].

Modified early warning scoring (MEWS) is an effective predictor of the outcome for prehospital patients, but its role as a predictor of outcomes for patients at the emergency department needs more studies [40].

Based on the state and quality of the original case records, this outcome was deemed satisfactory [41]. The poisons were categorized into five levels of poisoning severity (0 = none, 1 = minor, 2 = moderate, 3 = severe, and 4 = deadly) according to the PSS. This is a comprehensive assessment of the case, taking into account the most severe clinical characteristics. Typically, it necessitates monitoring all cases, although it can also be utilized at admission or at other points throughout poisoning [39].

CONCLUSION

Prediction of complications in CO poisoned patients is believed to be a challenging task. Laboratory parameters and imaging studies have been used to predict late cardiac and neurological complications in CO poisoned patients. Many physiologic scoring systems are demonstrated as effective predictors of outcomes for patients in the emergency department**.** However, very few studies have applied scoring systems as predictors of CO poisoning outcome.

RECOMMENDATION

- Health educational programs should be directed to increase the public awareness about sources of CO and the preventive measures to avoid the accidental CO poisoning

- Public service messages broadcast in mainstream media should emphasize the dangers associated with CO poisoning and advise about proper heating procedures for home and workplace and increasing the availability of CO detectors
- Health education about the early manifestations of CO poisoning to avoid the misdiagnosis
- Increasing the availability of hyperbaric oxygen therapy centers to prevent the development of delayed neurological sequalae.

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