Leucocytes' Parameters for Prediction of the Complications of Acute Corrosive Toxicity

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KEYWORDS
Caustic,
Leucocytes,
Neutrophils,
Neutrophil-to-lymphocyte ratio,
Complications,
Predictors.

ABSTRACT

Acute corrosive toxicity is a serious problem in clinical toxicology as it may be associated with severe complications. Prediction of complications related to corrosive toxicity is very important for better management and outcome. Inflammation is considered a predisposing factor for the development of corrosive toxicity complications. Leucocytes are a component of the inflammatory process. The aim of this study is to evaluate leucocytes' parameters as predictors for complications of acute corrosive toxicity. Forty four patients with acute corrosive toxicity were subjected to history taking (personal and toxicological), general and local oral examination. A venous blood sample was obtained from each participant. Total and differential leucocyte counts together with neutrophil-to-lymphocyte ratio were obtained. Total leucocyte count, neutrophil count and neutrophil-to-lymphocyte ratio were good predictors for complications at cut off > 15100/mm^3, > 9308/mm^3 and > 2.42 respectively. It is concluded that total leucocyte count, neutrophil count and neutrophil-to-lymphocyte ratio could serve as good predictor markers for corrosive toxicity complications.

Introduction

Caustic agents are substances that can cause chemical destruction as soon as they come in contact with body tissues including skin, eyes, digestive tract and respiratory tract (Radenkova-Saeva et al., 2016).

The problem of acute corrosive toxicity is of a special concern worldwide. Corrosive ingestion is reported to be the second common cause of poisoning in children and the third cause in adults. About 5000 – 15000 cases of corrosive ingestion are reported annually in the United States (Park, 2014; Rollin et al., 2015). Moreover, 20% of adolescent and adult poisoned cases admitted to Rashid Hospital, Dubai during 2012 were due to caustic agents (Hameed et al., 2014). In Egypt, it was found that caustic agents were responsible for 58% of toxicity among children in middle delta poison control centers (Sobeeh, 2017).

Manifestations of corrosive poisoning depend on the exposed surface (Barek and Haque, 2013). Cutaneous corrosive exposure results in severe pain, blistering and ulcer formation. Sore throat, cough, chest crepitation and respiratory distress are manifestations of inhalational exposure. Ingestion results in severe pain, oropharyngeal burns, vomiting, dysphagia and drooling of saliva. In severe cases, oesophageal or gastric perforation with associated mediastinitis or peritonitis may occur. Shock and death may also occur (Dargan, 2016).

Corrosive poisoning may be associated with some serious complications such as respiratory complications, anaemia, renal failure, disseminated intravascular co-agulopathy and gastrointestinal complications

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including stenosis or stricture (Chibishev et al., 2014; Lee et al., 2014).

Inflammation plays an important role in the development of corrosive toxicity complications (Chibishev et al., 2012). Total and differential leucocyte counts had been used to assess the individual inflammatory status. Neutrophil-to-lymphocyte ratio (N/L ratio) was reported by some authors as a prognostic parameter in some medical and toxicological conditions such as heart failure, cancers, infectious conditions, postoperative complications, pesticides and carbon monoxide poisoning (Dundar et al., 2014; Durmus et al., 2015; Karabacak et al., 2015; Kim et al., 2015).

Early prediction of patients who are at high risk to develop complications is important to achieve better management and long term outcome. Therefore, this study aimed to evaluate leucocytes' parameters in prediction of corrosive toxicity complications.

Patients and Methods

This prospective study started from September, 2016 to August, 2017 on patients admitted to Tanta Poison Control Center with acute corrosive toxicity. The protocol of the study was approved by the research ethics committee of Faculty of Medicine, Tanta University. A written informed consent was obtained from each patient or his/her guardian. Confidentiality was secured by the use of a code number for each patient and the data were analyzed anonymously.

Patients

The study was conducted on all patients presented with corrosive toxicity. Patients with chronic diseases (such as: cardiovascular diseases, diabetes mellitus, renal or hepatic diseases, tumors, inflammatory or infectious conditions, abnormal thyroid function and metabolic syndromes), mixed intoxication or associated trauma were excluded. Asymptomatic patients were also excluded.

Methods

All patients were subjected to personal history taking including name, age, sex and residence. Toxicological history (nature of the agent; acid or alkali, mode of poisoning and time between intoxication and hospital admission) was also obtained. Vital signs were measured and manifestations related to corrosive toxicity were recorded. General examination and local examination of the mouth were performed for each patient.

A venous blood sample (three ml) was withdrawn - under aseptic conditions- from each participant for complete blood picture analysis. Total and differential leucocyte counts were obtained according to Hall and Malia (1991) using kits obtained from Biodiagnostic Co. Ltd., Egypt. Neutrophil-to-lymphocyte ratio was obtained by dividing the number of neutrophils by the number of lymphocytes (Gürağaç and Demirer, 2016). Patients were observed for development of systemic complications, accordingly cases were divided into complicated and non-complicated groups.

Statistical analysis

Data were analyzed by SPSS program v.20. Quantitative data were expressed as median and interquartile range (expressed as 25^{th}-75^{th} percentiles) as they were not normally distributed as revealed by Shapiro-Wilk test for normality. For comparison between the studied groups, Mann-Whitney U test was performed. For qualitative data, they were expressed as numbers and percentages in brackets and Pearson's Chi square test was used to examine association between two variables. Receiver operation characteristics (ROC) curve analysis was carried out to test the discrimination power of the studied leucocytes' parameters to predict

complications. Areas under ROC curve (AUC), sensitivity, specificity, were calculated. Significance was adopted at p value < 0.05 for interpretation of results of tests (Dawson-Saunders and Trapp, 2001).

Results

This study included 44 patients with acute corrosive toxicity admitted to Poison Control Center, Emergency Hospital, Tanta University. Eleven patients (25%) showed complications; six patients had respiratory complications only, three cases had surgical complications and two patients had combined respiratory and surgical complications. The remaining 33 patients (75%) did not show complications. The age of the participants ranged from 1 to 56 years (median: 5 years). Males represented 52.3% of the studied patients compared to 47.7% females. The majority of patients were from rural areas (65.9%). Regarding age, no significant difference was found between patients with or without complications. Additionally, sex distribution and residence showed no statistically significant association with the development of complications (Table 1).

Most of the study participants (79.5%) alleged accidental corrosive poisoning. Acidic substances were more commonly ingested than their alkaline counterparts (63.6% versus 36.4% respectively). The duration between caustic toxicity and hospital arrival ranged from 0.5 to 10 hours. Both mode of toxicity and duration between poisoning and hospital arrival showed no statistically significant association with the development of complications. Alternatively, there was statistical significant association between the nature of the ingested substance and the development of complications where alkaline agents were involved in 81.8% of complicated cases versus 21.2% of non-complicated ones (p = 0.001) (Table 1).

Table (1): Statistical analysis of socio-demographic data and toxicity characteristics of the studied groups (44 patients).

Sociodemographic data								Tests of significance	
		Complicated group (n=11)		Non-complicated group (n=33)		Total (n=44)		Test statistic	p value
Age (years)	Range	2.00-45.00		1.00-56.00		1.00-56.00		Z_{mw} = 1.104	0.283
	Median	5.00		5.00		5.00			
	IQR	4.00-22.00		2.00-18.00		2.00-20.00			
	Mean rank	26.18		21.27					
		n	%	n	%	n	%		
Sex	Female	8	72.7%	13	39.4%	21	47.7%	X^2= 3.674	0.055
	Male	3	27.3%	20	60.6%	23	52.3%		
Residence	Rural	6	54.5%	23	69.7%	29	65.9%	X^2=. 303	0.582
	Urban	5	45.5%	10	30.3%	15	34.1%		
Mode	Accidental	7	63.6%	28	84.8%	35	79.5%	X^2= 1.164	0.281
	Suicidal	4	36.4%	5	15.2%	9	20.5%		
Nature	Acidic	2	18.2%	26	78.8%	28	63.6%	X^2= 10.607	0.001*
	Alkaline	9	81.8%	7	21.2%	16	36.4%		
Delay (hours)	Range	0.50-3.00		0.50-10.00		0.50-10.00		Z_{mw} = 1.065	0.287
	Median	1.00		2.00		2.00			
	IQR	1.00-2.00		1.00-3.00		1.00-3.00			
	Mean rank	19.05		23.65					

*Significant; n: number; X^2: chi-square test; IQR: interquartile range; Z_{mw}: Mann-Whitney U test.

Figure (1) shows that most of the studied cases had normal pulse rate, blood pressure and respiratory rate (61.4%, 79.5% and 59.1% respectively). Increased body temperature was recorded in 54.5% of the studied patients.

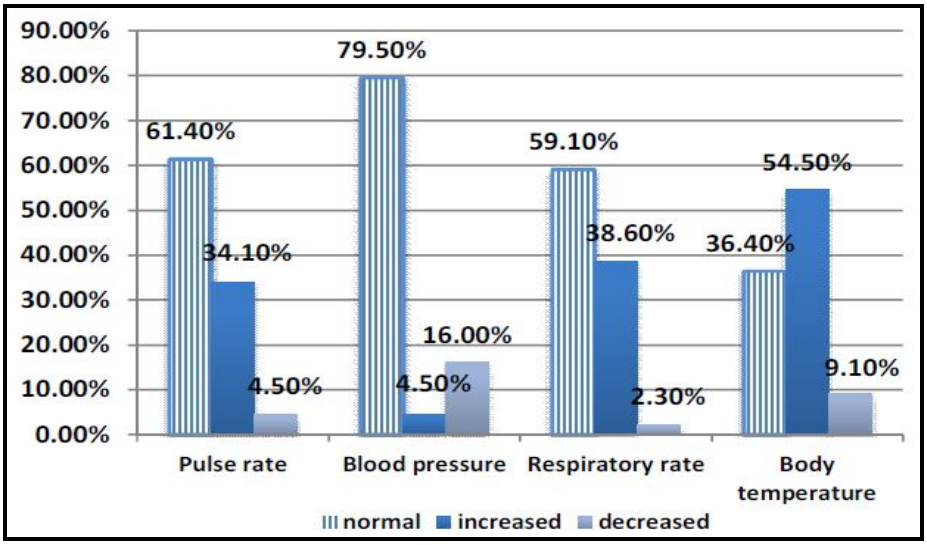

Fig. (1): Vital signs characteristics in the studied patient (44 patients).

Oral erythema and edema were the most frequent signs (84.1% and 70.5% respectively) followed by vomiting (68.2%) then dysphagia (40.9%). Chest crepitation, epigastric tenderness and hematemesis were reported in 36.4%, 20.5% and 18.2% of the studied patients respectively. Cough and hoarseness of voice were found in 13.6% and 11.4% respectively. Stridor was reported in 2.3% of cases (Figure 2).

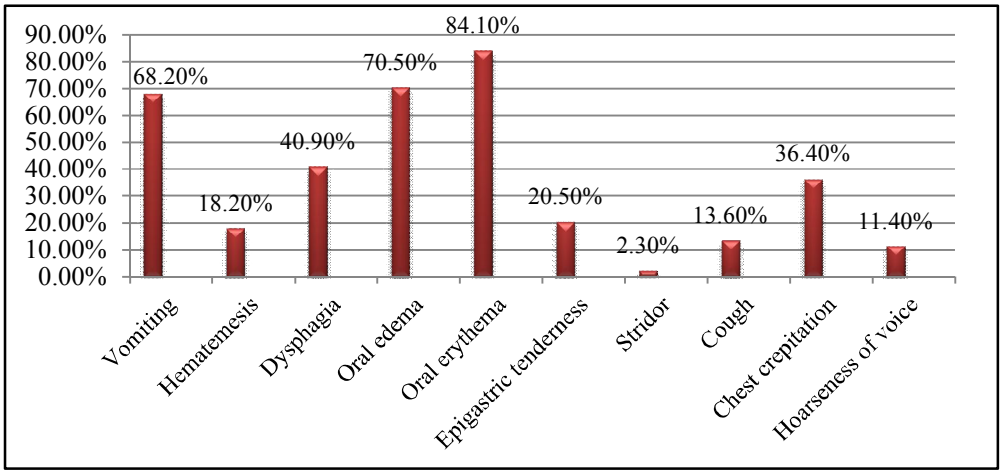

Fig. (2): Incidence of clinical manifestations related to corrosive toxicity in the studied patients (44 patients).

Table (2) shows significantly higher total leucocyte count (TLC), neutrophil count (NC) and N/L ratio in the patients developed complications compared to those without complications (medians were 16400/mm^3, 10640/mm^3 and 3.04 versus 11000/mm^3, 5940/mm^3 and 1.29 respectively). On the other hand, lymphocyte count, monocyte count, eosinophil count and basophil count showed no significant differences between both groups.

Table (2): Leucocytes' parameters in the studied groups (44 patients).

		Complications			Tests of significance	
		Complicated group (n=11)	Non-complicated group (n=33)	Total (n=44)	Test statistic	p value
Total leucocyte count	**Range**	9600-18900	4200-17900	4200-18900	Z_{mw}=2.874	0.004*
	Median	16400	11000	12350		
	IQR	12200-17900	9400-14200	9600-15350		
	Mean rank	32.14	19.29			
Neutrophil count	**Range**	4992-14364	2310-9308	2310-14364	Z_{mw}=3.917	<0.001*
	Median	10640	5940	6727		
	IQR	9516-12596	4173-7654	4390-9077		
	Mean rank	35.64	18.12			
Lymphocyte count	**Range**	2196-5084	1386-9078	1386-9078	Z_{mw}=0.176	0.860
	Median	3938	4066	4007		
	IQR	3496-4620	3125-4664	3176.50-4635		
	Mean rank	21.91	22.70			
Monocyte count	**Range**	328-1504	0.00-3020	0.00-3020	Z_{mw}=0.352	0.725
	Median	620.00	594.00	602.00		
	IQR	352.00-756.00	372.0-868.0	362.00-812.00		
	Mean rank	23.68	22.11			
Eosinophil count	**Range**	0.00-376.00	0.00-642.00	0.00-642.00	Z_{mw}=1.106	0.269
	Median	304.00	130.00	179.00		
	IQR	165.00-328.00	.00-284.00	21.00-314.00		
	Mean rank	26.18	21.27			
Basophil count	**Range**	0.00-358.00	0.00-302.00	0.00-358.00	Z_{mw}=0.776	0.438
	Median	0.00	0.00	0.00		
	IQR	0.00-165.00	0.00-96.00	0.00-139.00		
	Mean rank	24.82	21.73			
N/L ratio	**Range**	1.33-4.33	0.84-2.42	.84-4.33	Z_{mw}=3.864	<0.001*
	Median	3.04	1.29	1.46		
	IQR	2.06-3.90	1.11-1.70	1.15-2.36		
	Mean rank	35.45	18.18			

*Significant; n: number; X^2: chi-square test; IQR: interquartile range; Z_{mw}: Mann-Whitney U test

Table (3): The best cut-off values, sensitivity, specificity, and AUC of total leucocyte count, neutrophil count and neutrophil-to-lymphocyte ratio in predicting complications (44 patients).

	Cut-off value	Sensitivity %	Specificity %	ROC-AUC	95% CI	p value
Total leucocyte count	> 15.100	72.73	87.88	0.792	0.643 to 0.899	0.004*
Neutrophil count	> 9308	81.82	100.00	0.898	0.769 to 0.969	<0.001*
Neutrophil-to-lymphocyte ratio	> 2.42	63.64	100.00	0.893	0.762 to 0.966	<0.001*

According to the analysis of ROC curve for predicting occurrence of complications, TLC, NC and N/L ratio were significantly valid ($p < 0.05$); with good performance in discriminating cases with complications (AUCs were 0.792, 0.898 and 0.893 for TLC, NC and N/L ratio respectively). TLC at a cut off > 15100/mm^3 had 72.73% sensitivity and 87.88% specificity. Neutrophil count had 81.82% sensitivity and 100% specificity at a cut off > 9308/mm^3. At a cut off > 2.42, N/L ratio had 63.64 % sensitivity and 100% specificity (Table 3 & Figure 3).

Pairwise comparison of AUCs of TLC, NC and N/L ratio revealed significant differences between TLC and NC ($p = 0.034$). While, there were non-significant differences between AUCs of TLC versus N/L ratio and NC versus N/L ratio ($p = 0.150$ and 0.903 respectively).

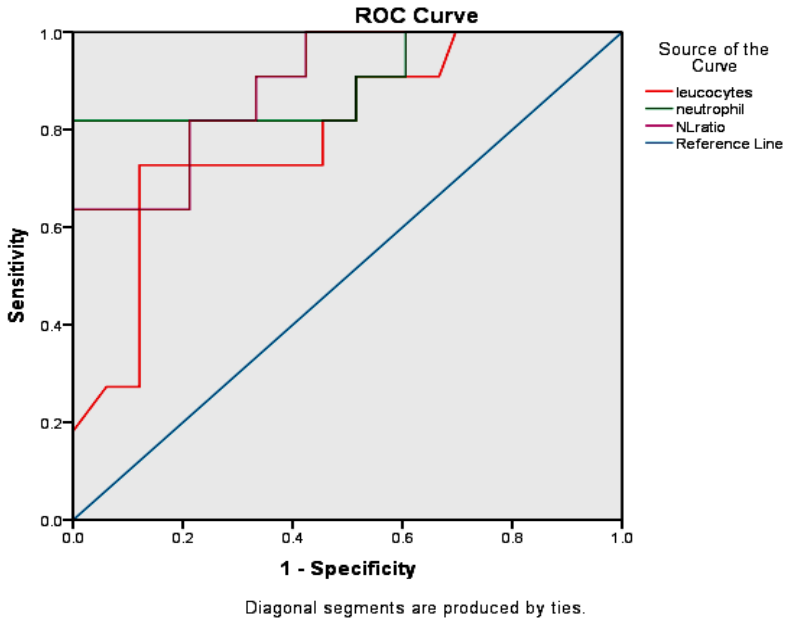

Fig. (3): The Receiver Operating Characteristic curve for total leucocyte count, neutrophil count and neutrophil-to-lymphocyte ratio.

Discussion

White blood cells count is considered an easy, cheap, available and routine test that can be carried out in different medical institutions. However, little data are available about the utility of leucocytes' parameters in prediction of complications of corrosive toxicity (Kim et al., 2015).

Both socio-demographic data and toxicological characteristics together with clinical manifestations of patients included in the current study were more or less in line with comparable previous Egyptian and international studies (Seif et al., 2016; Caganova et al., 2017).

Out of 44 patients included in this study, 11 patients (25%) developed complications. According to Chibishev et al. (2014), 23.61% of the cases developed complications. In the same time Caganova et al. (2017) registered 15.5% of respiratory complicated cases among corrosive intoxicated patients.

The current study investigated leucocytes' parameters as markers for complications prediction in acute corrosive toxicity. It was found that there was a significant increase in TLC, NC and N/L ratio in patients who developed complications.

Kim et al. (2015) in a retrospective study on 41 patients revealed that TLC, NC and N/L ratio were higher in complicated versus non-complicated group. Uyar and Kok (2017) found that N/L ratio was significantly higher in patients with esophagus and gastric injury versus non-injured patients. Furthermore, total leucocyte count could predict the mortality and severity of mucosal injury in corrosive toxicity (Rigo et al., 2002; Havanond and Havanond, 2007).

Inflammatory response plays an important role in the development of the gastrointestinal complications following corrosive ingestion. Formation of small vessels thrombosis, bacterial invasion and granulation tissue development are the primary steps for subsequent tissue fibrosis and oesophageal and/or gastric stricture (Chibishev et al., 2012). In addition, the acute phase of corrosive injury is associated with inflammatory reaction as manifested by intraepithelial & sub epithelial leucocytosis and basal cell hyperplasia (Aghaji and Chukwu, 1993).

Furthermore, pneumonic infection and aspiration pneumonia that may complicate acute corrosive toxicity are considered as a part of inflammatory pulmonary disorders (Chang et al., 2011). Moreover, oxidative stress which plays a significant role in the development of such complications is accompanied by an inflammatory response that is manifested biochemically by leukocytosis, neutrophilia and lymphocytopenia (Kim et al., 2015). These data could explain the significant elevation in TLC and NC in patients who developed complications in the present study.

High neutrophil count reflects inflammation. Low lymphocyte count reflects poor general health and physiologic stress. Neutrophil-to-lymphocyte ratio combines these two independent markers of inflammation. In several studies, it has been shown that N/L ratio is an indicator of systemic inflammation (Karabacak et al., 2015). Neutrophil-to-lymphocyte ratio has a beneficial role in prediction of inflammatory process even when leucocyte count is within the normal range (Gürağaç and Demirer, 2016). Accordingly, there was a significant increase in N/L ratio in the complicated group versus non-complicated group.

In the current study TLC, NC and N/L ratio were good predictors for acute corrosive toxicity complications (AUCs: 0.792, 0.898 and 0.893 respectively) at cut off (> 15100/mm^3, > 9308/mm^3 and > 2.42 respectively). Moreover, there was significant differences in the AUCs

between TLC and NC (p = 0.034). While there was no significant differences between AUCs of TLC versus N/L ratio and NC versus N/L ratio (p = 0.150 and 0.903 respectively).

These findings partially coincided with data reported by Kim et al. (2015) who revealed that both TLC and NC were good predictors while N/L ratio was a fair predictor for corrosive toxicity complications (AUCs: 0.819, 0.832, and 0.750 respectively) with no significant difference in the AUCs between the three parameters. Additionally, they found that the optimal cut-off values of TLC, NC and the N/L ratio were 12060/µL, 9607/µL and 2.72 respectively. Slight difference may be attributed to the difference in the percentage or severity of complications.

The small sample and uni-centered nature of the study are considered the main limitations of the current study. Further multi-centered studies with larger sample size are recommended for better evaluation and adjustment of leucocytes' parameters as predictors of corrosive toxicity complications.

Conclusion

It is concluded that each of TLC, NC and N/L ratio are good markers for predicting acute corrosive toxicity complications. Patients with TLC > 15100/mm3, NC > 9308/mm3 or N/L ratio > 2.42 are at a higher risk for complications.

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قياسات كرات الدم البيضاء للتنبؤ بمضاعفات التسمم الحاد بالمواد الكاوية

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***قسم الباثولوجيا الاكلينيكية كلية الطب – جامعة طنطا**

يعتبر التسمم الحاد بالمواد الكاوية مشكلة خطيرة في علم السموم السريري لما قد يصاحبه من مضاعفات شديدة. ولذا فان التنبؤ بهذه المضاعفات هام جدا من أجل علاج أفضل ونتيجة أفضل للمريض. ويعتبر الالتهاب عاملا مهيئا لحدوث مضاعفات التسمم بالمواد الكاوية. وحيث ان كرات الدم البيضاء هي مكون أساسى لعملية الالتهاب فان هذه الدراسة تهدف الى تقييم قياسات كرات الدم البيضاء فى التنبؤ بمضاعفات التسمم بالمواد الكاوية. وقد تم اجراء هذه الدراسة فى مركز طنطا لعلاج التسمم على ٤٤ مريضا مصابا بالتسمم الحاد بالمواد الكاوية حيث تم أخذ التاريخ الشخصي والسمي للمريض وإجراء الفحص العام والموضعى للفم وتم الحصول على عينة الدم الوريدي من كل مشارك وتسجيل التعداد الكلي والتفاضلى لكرات الدم البيضاء ونسبة خلايا العدلات إلى اللمفاويات. وأظهرت النتائج ان العدد الكلى لكريات الدم البيضاء، وخلايا العدلات ونسبة خلايا العدلات إلى اللمفاويات كانت قياسات جيدة فى التنبؤ بالمضاعفات عند أكثر من ١٥١٠٠ / مم ٣، ٩٣٠٨ / مم ٣ و ٢,٤٢ على التوالي.