

Association of Sulfur Mustard-induced Ocular Problems with Serum and Blood Biochemical Parameters Changes

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KEYWORDS

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ABSTRACT

Background & objective: Many biochemical features of sulfur mustard (SM) intoxication remained unknown. So far, the direct association between biochemical parameter changes and ocular problems in patients exposed to SM is not evaluated. The current study aimed at evaluating the associations between the ocular findings in patients with SM intoxication and the changes of serum and blood biochemical parameters.

Methods: In the current study, 372 patients exposed to SM and 128 matched controls were compared concerning the association between their ocular problems and biochemical parameters. Ocular problems include photophobia, ocular surface discomfort (OSD), etc. Biochemical parameters include uric acid, creatinine (Cr), hematocrit (HCT), total, direct and indirect bilirubin, high-density lipoproteins (HDL), alanine aminotransferase (ALT), calcium (Ca), fasting blood sugar (FBS), mean corpuscular hemoglobin concentration (MCHC), etc.

Results: The SM-exposed group with photophobia, OSD, tearing, blurred vision, abnormal tear status, and slit-lamp findings had significantly higher mean serum and blood levels of uric acid, Cr, HCT, and total and indirect bilirubin than the controls. The SM-exposed group with photophobia, tearing, ocular pain, blurred vision, bulbar conjunctival and limbal abnormalities had significantly higher mean serum and blood levels of HDL, ALT, Ca, FBS, MCHC, and HDL, indirect and total bilirubin, compared to the control group.

Conclusion: The association of photophobia with uric acid, OSD and tearing with Cr, photophobia with HDL, ocular pain with Ca, and blurred vision with FBS may be explained for their known ocular effects in the SM-exposed subjects. SM-induced biochemical changes may intensify the ocular problems induced by the direct effects of SM.

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Introduction

Current chemical weapons are the nerve agents (sarin, tabun, VX, cyclosarin, and soman), the vesicant or blister agents (eg, sulfur mustard), choking agents (phosgene and chlorine), incapacitating agents (fentanyl and adamsite), riot control agents (mace and pepper spray), blood agents (cyanide), and toxic industrial chemical agents (formaldehyde, hydrofluoric acid, and ammonia) (1). Sulfur mustard (SM) is the

most famous vesicant agent used since World War I and still in huge amounts is stored elsewhere in the world. Due to high diffusion in nearly all tissue, there is no organ to remain intact during severe intoxication with SM (2). Lungs, eyes, and skin are amongst the most important organs involved during exposure. SM causes respiratory system damages (chronic obstructive lung disease and lung fibrosis), eye lesions (recurrent corneal ulceration, chronic conjunctivitis,

and dry eye), skin lesions (blisters, abnormal pigmentation, and cancer), bone marrow depression, and cancers (3). Apparent clinical features of SM intoxication- especially in eyes- lungs and skin are recognized in animal and human from many years ago(4-6). Cytotoxic effects of SM lead to disruption of normal cellular functions and diffused metabolic abnormalities such as enzymatic deficiencies, mitotic and cell division abnormalities, bone marrow depression, and hematopoietic disturbances. In fact, SM disrupts cellular activities through binding to amino acids, amines, and proteins (7). Apart from SM, there were few papers in the literature on the association of serum and blood biochemical changes and ocular problems. Recently, many papers shed light on some hidden biochemical and immunological aspects of SM intoxication. Some of these papers are especially focused on direct association between the involvement of major organs and immune system (8-13). Also, there are some studies indicating changes of serum and blood biochemical parameters induced by SM, such as blood uric acid and serum creatinine (14,15), serum transaminases and alkaline phosphatases (16), lipid profile (17), and blood sugar (18). But, none of them evaluated the direct association between biochemical parameter changes with ocular problems in the patients exposed to SM. Still, many biochemical features of SM intoxication are unknown.

Regardless of the rationales that seem ambiguous in many occasions, the current study aimed at evaluating the associations between ocular findings in patients with SM intoxication and their serum and blood biochemical parameter changes.

Materials and methods

Study design and participant

The current study was a part of Sardasht-Iran Cohort Study (SICS) (19). The participants were 372 documented patients exposed to SM as cases and 128 non-exposed controls matched with the cases. All participants underwent a thorough ocular history taking, and examination and evaluation of serum and blood biochemical parameters. Presence of any ocular symptoms such as photophobia, ocular surface dis-

comfort (burning, itching, and redness), foreign body sensation, tearing, blurred vision, pain, and dry eye sensation were recorded. The conditions of lids, tear meniscus, bulbar conjunctiva, limbal tissue, cornea, and anterior segment were evaluated using a slit-lamp biomicroscopy (Nidek, Gamagori, Japan).

Ethical considerations

The study was approved by the Ethical Committee of Board of Research Ethics of Janbazan Medical and Engineering Research Center (JMERC), the Board of Research of the Ministry of Health and Medical Education and Shahed University, Tehran, Iran. Written informed consent was obtained from all participants ultimately selected for the study inclusion.

Blood sampling

After completion of the clinical examination, 10-mL blood samples were taken from the brachial vein of fasting subjects in the case and control groups. Blood samples were collected into the sterile tubes containing anticoagulant agent [ethylenediaminetetraacetic acid (EDTA)] for the evaluation of hematological parameters and non-anticoagulant tubes for biochemical tests. Blood samples in non-anticoagulant tubes were centrifuged at 3000 rpm for 5 minutes and serum samples were harvested and kept at -70°C until testing.

Biochemical parameters evaluation

Serum and blood biochemical parameters including urea, creatinine (Cr), uric acid, cholesterol, triglyceride (TG), low-density lipoprotein (LDL), intermediate-density lipoproteins (IDL), high-density lipoproteins (HDL), calcium (Ca), phosphorous (P), total and direct bilirubin, alanine aminotransferase (ALT) or serum glutamic pyruvic transaminase (SGPT), enzyme aspartate aminotransferase (AST) or serum glutamic oxaloacetic transaminase (SGOT), and alkaline phosphatase (ALP) were determined using commercially available kits from Pars Azmoon (Tehran, Iran). Serum samples were analyzed with a BT 3000 Plus biochemical analyzer (Biotechnica, Italy). The BT 3000 analyzer is a commercial colorimetric assay kit using the spectrophotometric method.

Determination of the hematological parameters

The complete blood count (CBC) was performed with a hematology cell counter (Sysmex KX-21, Japan). Routine hematological parameters were determined including red blood cell count (RBC), platelet count (PLT), hemoglobin content (Hb), hematocrit (HCT), red cell distribution width (RDW), mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and mean platelet volume (MPV).

Statistical analysis

Statistical analysis was performed by the Mann-

Whitney and Spearman rank correlation tests using SPSS version 16. The median values of the first and third quartiles (Q1, Q3) were selected. The differences were considered significant at P value ≤ 0.05 .

Results

Orderly, participants exposed to SM with photophobia, ocular surface discomfort (OSD) (burning, itching, and redness), tearing, blurred vision, abnormal tear status, and any findings on slit-lamp examination had significantly higher mean serum and blood levels of uric acid, Cr, HCT, total bilirubin, and indirect bilirubin than the controls (P=0.035, <0.0001, 0.003, 0.003, 0.034, 0.031, respectively) (tables 1- 3).

Table 1. Association of Ocular Symptoms and Blood/Serum Biochemical Parameters

	Control						Exposed						P-value ^b
	N	Mean	SD	Median	Q1	Q3	N	Mean	SD	Median	Q1	Q3	
Uric Acid													
Photophobia													
No	102	5.745	1.153	5.8	5	6.4	238	5.887	1.159	5.8	5.1	6.6	0.301
Yes	26	5.431	0.863	5.55	5	6	135	5.934	1.140	5.85	5.1	6.5	0.035
P-value ^a	0.197						0.705						
Creatinine													
Ocular discomfort													
No	103	1.038	0.263	1	0.9	1.1	264	1.078	0.174	1.1	1	1.2	0.091
Yes	25	0.972	0.131	1	0.9	1	109	1.098	0.159	1.1	1	1.2	0.001>
P-value ^a	0.226						0.302						
Tearing													
No	95	1.035	0.273	1	0.9	1.1	246	1.078	0.166	1.1	1	1.2	0.078
Yes	33	0.997	0.123	1	0.9	1.1	127	1.096	0.177	1.1	1	1.2	0.003
P-value ^a	0.442						0.333						
Calcium													
Eye pain													
No	114	10.05	0.77	9.9	9.5	10.5	343	9.79	0.53	9.8	9.5	10.1	0.001>
Yes	14	9.91	0.6	9.85	9.5	10.5	30	10.07	0.76	10.1	9.5	10.5	0.493
P-value ^a	0.513						0.008						
FBS, mg%													
Blurring of vision													
No	80	94.95	22.65	88.00	84.00	98.00	214	93.11	17.93	90.00	84.0	97.0	0.468
Yes	48	92.30	17.14	90.00	84.00	95.00	159	100.15	29.90	93.00	86.0	103	0.084
P-value ^a	0.486						0.005						

Table 2. Association of Ocular Symptoms and Some Blood/Serum Biochemical Parameters

		Control					Case					P-value ^b	
	N	Mean	SD	Median	Q1	Q3	N	Mean	SD	Median	Q1	Q3	
HDL													
Photophobia													
No	102	26.78	9.66	25	20	35	238	28.35	10.53	27	21	36	0.198
Yes	26	30.96	11.62	31	22	38	135	31.11	11.9	30	22	39	0.953
P-value ^a	0.061					0.021							
Bulbar conjunctiva													
Normal	126	27.74	10.3	26	20	36	337	28.85	10.43	28	21	36	0.307
Abnormal	2	24.5	0.71	24.5	24	25	36	33.89	15.43	31	23	47	---
P-value ^a	---					0.009							
HCT													
Blurring of vision													
No	80	44.6	3.4	44.7	42.3	46.3	214	44.9	3.1	44.9	43.1	47	0.473
Yes	48	43.3	4	43.7	41.6	46.3	159	45.2	3.7	45.3	43.2	47.5	0.003
P-value ^a	0.052					0.396							
MCHC													
Bulbar conjunctiva													
Normal	126	35.6	1.4	35.7	34.8	36.4	337	35.2	1.3	35.2	34.5	36	0.004
Abnormal	2	35.7	0.2	35.7	35.5	35.8	36	35.8	1.5	35.8	34.9	36.3	----
P-value ^a	---					0.010							

Table 3. Association of Ocular Symptoms and Some Blood/ Serum Biochemical Parameters

		Control					Case					P-value ^b	
	N	Mean	SD	Median	Q1	Q3	N	Mean	SD	Median	Q1	Q3	
Total Bilirubin													
Tear status													
Normal	117	0.9	0.4	0.8	0.7	1.1	321	0.9	0.4	0.8	0.7	1	1.000
Abnormal	11	0.8	0.1	0.8	0.7	0.8	52	1	0.3	0.9	0.8	1.2	0.034
P-value ^a	0.412					0.085							
Limbal tissue													
Normal	128	0.7	0.34	0.6	0.5	0.8	362	0.7	0.29	0.6	0.5	0.8	1.000
Abnormal	0	---	---	---	---	---	11	0.91	0.36	0.85	0.6	1.2	---
P-value ^a	---					0.019							
Indirect Bilirubin													
Any findings in slit-lamp													
No	113	0.72	0.35	0.6	0.5	0.8	292	0.7	0.3	0.6	0.5	0.8	0.567
Yes	15	0.54	0.17	0.55	0.4	0.6	81	0.71	0.29	0.7	0.5	0.8	0.031
P-value ^a	0.053					0.789							
Limbal tissue													
Normal	128	0.7	0.34	0.6	0.5	0.8	362	0.7	0.29	0.6	0.5	0.8	1.000
Abnormal	0	---	---	---	---	---	11	0.91	0.36	0.85	0.6	1.2	---

P-value ^a	---						0.019						
ALT													
Tearing													
No	95	21	8	20	16	25	246	20	6	19	16	22	0.212
Yes	33	22	6	20	18	27	127	23	11	20	16	26	0.616
P-value ^a	0.513						0.001>						

Patients exposed to SM developing photophobia had significantly higher mean serum levels of uric acid than the matched controls ($P=0.035$). Patients exposed to SM with ocular discomfort had significantly higher mean serum levels of creatinine than the matched controls ($P < 0.001$). Patients exposed to SM developing tearing had significantly higher mean serum levels of creatinine than the matched controls ($P=0.003$). Despite significantly lower mean serum levels of calcium in the subjects exposed to SM without ocular pain than the matched controls, the subjects exposed to SM with ocular pain had significantly higher mean serum levels of calcium than the matched subjects exposed to SM without ocular pain ($P=0.008$). Patients exposed to SM developing blurred vision had significantly higher mean serum levels of FBS than the matched subjects exposed to SM without blurred vision ($P=0.005$).

P-value^a: Comparison between each group (the Mann-Whitney test)

P-value^b: Comparison between the control and SM-exposed subjects of each group (the Mann-Whitney test)

FBS, Fasting blood sugar

Patients exposed to SM developing blurring of vision had significantly higher mean serum levels of HCT than the matched controls ($P=0.003$). Patients exposed to SM with photophobia had significantly higher mean serum levels of HDL than the matched subjects who exposed to SM without photophobia ($P=0.021$). Patients exposed to SM developing bulbar conjunctival abnormality had significantly higher mean blood levels of MCHC than the matched subjects exposed to SM without bulbar conjunctival abnormality ($P=0.010$). Patients exposed to SM developing bulbar conjunctival abnormality had significantly higher mean serum levels of HDL than the matched

subjects exposed to SM without bulbar conjunctival abnormality ($P=0.009$).

P-value^a: Comparison between each group (the Mann-Whitney test)

P-value^b: Comparison between the control and SM-exposed subjects of each group (the Mann-Whitney test)

- HCT, Hematocrit
- HDL, High-density lipoproteins
- MCHC, Mean corpuscular hemoglobin concentration
- HDL, High-density lipoprotein

Participants exposed to SM with abnormal tear status had significantly higher mean serum levels of total bilirubin than the matched controls ($P=0.034$). Patients exposed to SM with any findings in slit-lamp had significantly higher mean serum levels of indirect bilirubin than the matched controls ($P=0.031$). Patients exposed to SM developing tearing had significantly higher mean serum levels of ALT than the matched subjects exposed to SM without tearing ($P < 0.001$). Patients exposed to SM developing limbal tissue abnormality had significantly higher mean serum levels of indirect bilirubin than the matched subjects exposed to SM without limbal tissue abnormality ($P=0.019$).

Patients exposed to SM with limbal tissue abnormality had significantly higher mean serum levels of total bilirubin than the matched subjects exposed to SM without limbal tissue abnormality ($P=0.015$).

P-value^a: Comparison between each group (the Mann-Whitney test)

P-value^b: Comparison between the control and SM-exposed subjects of each group (the Mann-Whitney test)

ALT, Alanine aminotransferase

Also, Patients exposed to SM with photophobia, tearing, ocular pain, blurred vision, bulbar conjunctival abnormalities, and limbal tissue abnormalities had significantly higher mean serum levels of HDL, ALT, Ca, FBS, MCHC, and HDL, indirect and total bilirubin compared with the subjects exposed to SM without such abnormalities ($P=0.021$, <0.0001 , 0.008 , 0.005 , 0.010 , and 0.009 , 0.019 , and 0.015 , respectively) (tables 1-3). The biochemical parameter changes including blood uric acid, Cr, HCT, total bilirubin, and indirect bilirubin were significantly different between the SM-exposed subjects with ocular problems and the matched controls. On the other hand, the tables 1-3 indicate that the biochemical parameter changes including HDL, ALT, Ca, FBS, MCHC, HDL, and indirect and total bilirubin were significantly different between the cases exposed to SM developing with some ocular problems and the SM-exposed ones without the same ocular problems.

Discussion

The findings of the current study showed that patients exposed to SM with photophobia, OSD, tearing, blurred vision, abnormal tear status, and any slit-lamp findings had significantly higher mean serum and blood levels of uric acid, Cr, HCT, total bilirubin, and indirect bilirubin than the matched controls. On the other hand, subjects exposed to SM with photophobia, tearing, ocular pain, blurred vision, bulbar conjunctival abnormality, and limbal tissue abnormalities had significantly higher mean serum and blood levels of HDL, ALT, Ca, FBS, MCHC, and indirect and total bilirubin than the matched subjects exposed to SM without such findings.

Patients exposed to SM developing bulbar conjunctival abnormality had significantly higher mean serum levels of HDL than the matched subjects exposed to SM without bulbar conjunctival abnormality.

HDL level in the patients exposed to SM with photophobia was significantly higher than the SM-exposed subjects without photophobia. Increased serum level of HDL in the subjects exposed to SM developing photophobia may be due to its protective role, but this increase was not enough to protect against this prob-

lem. Thus, some other mechanisms may be involved. In the current study, the mean serum HDL level in both groups were lower than the normal range of HDL, which can be due to genetic, nutritional, and geographic reasons and their lifestyle.

Patients exposed to SM with abnormal tear status had significantly higher mean serum levels of total bilirubin than the matched controls. This difference could not be attributed to exposure to SM, because there was no difference between the SM-exposed subjects and the controls with normal tear status. It may be due to other unknown SM-induced mechanisms. Patients exposed to SM with abnormal tear status and limbal tissue abnormality, respectively, had significantly higher mean serum levels of total bilirubin and indirect bilirubin than their matched SM-exposed subjects without these abnormalities. Bilirubin is an endogenous antioxidant (20) and can suppress inflammation in the vasculature (21). Yasuda et al., showed that the increase in serum bilirubin levels may have a protective role against diabetic retinopathy in persons with either diabetes or impaired glucose metabolism, independent of known risk factors for diabetic retinopathy (22). Therefore, in the current study, the elevated level of bilirubin in the SM-exposed subjects with limbal tissue abnormalities may have a protective effect, but the level was not enough to protect against the abnormality; hence, other mechanisms may be involved. Topically applied SM in guinea pig liver was hepatotoxic and caused severe steatosis and a significant rise in SGOT/AST and glutamic pyruvate transaminase SGPT/ALT levels that reached the maximum 3 days after application. Partial recovery was achieved on the day 6 (23). Dermal application of SM in mice caused an increase in serum transaminases and ALP (16). Amongst liver function tests, total serum bilirubin (but not direct bilirubin, SGOT, SGPT, and ALP) was significantly higher in hospitalized vs. non-hospitalized SM-exposed patients (24). In the current study, the SM-exposed patients with tearing had significantly higher levels of serum ALT than the SM-exposed ones without such complication. This was consistent with the findings of the current study in patients exposed to SM with tearing,

compared with the SM-exposed group without such problem.

Although, associations between ocular findings and serum and blood biochemical alterations in SM-exposed humans are not yet reported in the literature that makes comparative studies difficult; there are some studies on serum and blood biochemical alterations in humans and animals exposed to SM, regardless of their ocular problems.

Cutaneous and pulmonary exposures to high concentration of SM in mice significantly increased circulatory blood uric acid and serum creatinine (14,15). Also, there are few studies on the association of some serum and blood biochemical alterations (eg, Ca and uric acid) and OSD under pathologic conditions other than SM exposure. Long-term elevation in serum uric acid caused deposition of uric acid crystals on ocular surface and induced ocular surface discomfort such as photophobia (25,26). It was consistent with the current study findings on comparing the SM-exposed and control subjects with photophobia, which can be attributed to the local effects of SM or systemic effects of uric acid on ocular surface.

Balali mood et al., reported significantly higher levels of HCT after SM exposure in 40 male patients within the age range of 16 to 20 years; this level and the levels of Hb were significantly correlated with the severity of respiratory complications (27). In another study, total counts for RBC and MCV (but not MCH and MCHC) were significantly higher in cases with more severe intoxication (28,29). Seven days after percutaneous administration of 2 x LD50 of SM, a significant weight-loss and increase in RBC and Hb were observed in mice (30). In the SM-exposed human, the mean number of RBCs and Hb levels were not significantly different, compared with those of the controls, but increased during the 5-year follow-up. This might be related to chronic pulmonary disorders (31). Also in the present study, the SM-exposed subjects with blurred vision had significantly higher levels of HCT than the matched controls. On the other hand, the SM-exposed subjects with bulbar conjunctival abnormalities had significantly higher levels of

MCHC than the matched subjects exposed to SM without such abnormality.

A single dermal application of 1.0 x LD50 of SM in mice caused a significant hyperglycemia 24 hours after the application. Liver glycogen content decreased; while brain, muscles, and kidney glycogen contents did not change (18). In parallel, the SM-exposed subjects with blurred vision had significantly higher mean blood levels of FBS than the matched subjects exposed to SM without such problem. In the experimental dogs, significant lipid profile changes were observed in the alpha-fraction, which gradually shifted to the beta-fraction of lipoproteins, appeared up to 24 hours after exposure to SM (17). It was consistent with the current study findings in the SM-exposed subjects with photophobia and bulbar conjunctival abnormalities, compared with the ones exposed to SM without such abnormalities.

The majority of studies indicated the effects of SM on local or intracellular Ca deposition or changes not on the serum Ca levels (32-35). Association of band keratopathy with the elevation of serum Ca and creatinine was suggested in some studies other than SM exposure (33). In chronic renal failure, increase in serum Ca-Pi products may induce red irritated eyes (36). In such patients, a band-shaped keratopathy and photophobia developed, in addition to the limbal and conjunctival calcification, mostly secondary to an induced tertiary hyperparathyroidism (37). In the current study, despite significantly lower mean serum levels of Ca in the SM-exposed subjects without ocular pain than their matched controls; those SM-exposed subjects with ocular pain had significantly higher mean serum levels of Ca than the SM-exposed subjects without such abnormality.

In conclusion, SM-induced biochemical parameter alterations, especially in serum and blood uric acid, Cr, HDL, Ca, and FBS, may additionally intensify the direct effects of SM on ocular tissues and increase ocular problems such as photophobia, OSD, tearing, ocular pain, and blurred vision. However, the rationales for associations between other ocular problems and biochemical changes may seem inexplicable in

the SM-exposed patients; more investigations are needed.

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Conflict of interests

The authors declared no conflict of interest.

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