Original Article

Role of Intravenous Lipid Emulsions in Improving Coma of Acute Antipsychotics Poisoning: A Randomized Controlled Trial in Poison Control Center of Ain Shams University Hospitals

Walaa Gomaa, Hend Salama Shalaby, Enas Abo Elwafa El-Taftazani, Nabil Nassif Rezk, Abdelhamid[1]

[1]*Department of Forensic Medicine and Clinical Toxicology, Faculty of Medicine-Ain Shams University, Cairo, Egypt*

Corresponding author: Hend Salama Shalaby
Mobile: 01005403711
Email:
Orchid ID:
Hend.salam149@gmail.com

ABSTRACT

Background: The prescription and use of antipsychotic medications have rapidly increased over the last two decades. Consequently, this is associated with an increase in antipsychotic overdoses. Acute poisoning by antipsychotics could result in various life-threatening toxic effects mainly on cardiovascular and central nervous systems. As acute antipsychotics overdose lacks specific antidote, the primary goal in treatment is aggressive supportive therapy. Recently, intravenous lipid emulsion (ILE) therapy has been used in the treatment of lipophilic drug toxicity including antipsychotics. **Aim of the study:** This study aimed to assess the adjuvant therapeutic role of lipid emulsion administration in improving the level of consciousness of acutely poisoned comatose patients by antipsychotic drugs presented to the Poison Control Center of Ain Shams University hospitals (PCC-ASUH). **Methods:** We conducted a randomized, controlled, parallel-group, single-blinded clinical trial during **six** months starting from October 2020 to March 2021. Forty patients with acute antipsychotics poisoning were randomly assigned into two equal groups. The standard therapy was administered to the control group while ILE was given to the second group in addition to the standard therapy. All patients underwent a medical history, clinical examination, and laboratory tests. The outcomes were assessed. **Results:** Intravenous lipid emulsion therapy was effective in improving level of consciousness via the assessment of Alert, Voice, Pain and Unresponsive (AVPU) score and Glasgow Coma Scale (GCS). The median GCS and the median AVPU scale assessed 12 hours after admission were significantly higher in the intervention group compared to the control group. Corrected QT interval (QTc) measured 12 hours after admission in addition to the length of hospital, and intensive care unit (ICU) stay were significantly shorter in the intervention group compared to the control group. **Conclusion:** It was concluded that ILE was an effective therapy in improving level of consciousness and correcting ECG abnormalities as prolonged QTc in acute antipsychotic poisoning, in addition to decreasing length of ICU and hospital stay. These promising responses encourage reasonable consideration of ILE as a new treatment modality.

Recommendations: Intravenous lipid emulsions are better to be provided for patients with acute antipsychotic poisoning with bad prognosis or at high risk of complications (e.g., intubation and shock) as a new modality of management for better prognosis.

Keywords: Antipsychotics; Central nervous system; Clinical Trial; Glasgow Coma Scale; Intravenous lipid emulsion; Poisoning

I. INTRODUCTION

The prescription and use of antipsychotic medications have rapidly increased over the last two decades in adult, adolescent, and pediatric populations. Consequently, it is associated with an increase in antipsychotic overdoses. They are commonly used as a method of suicide especially by people with psychotic or bipolar disorders (Hampton et al., 2014; Morrens et al., 2015).

Central nervous system (CNS) depression is the most frequent symptom of antipsychotic overdose that may cause deep coma that can lead to respiratory depression in patients with severe antipsychotics poisoning (Stassinos and Klein-Schwartz, 2017).

Additionally, antipsychotic toxicity has frequently been associated with cardiovascular symptoms. They include sinus tachycardia, hypotension, and electrocardiographic (ECG) abnormalities such as prolonged corrected QT (QTc) interval that may result in a potentially fatal arrhythmia (Borg et al., 2016; Zainuddin and Zaini, 2018).

Management of antipsychotics poisoning is mainly supportive without specific antidote. Therefore, it's important to assess new therapeutic approaches to lower morbidity and mortality rates (Thanacoody, 2020).

Intravenous lipid emulsion (ILE) has recently gained attention for its possible use as an antidote for drug toxicity. Research on animals has shown that ILE can be used to treat acute lipophilic drug overdose, including antipsychotics poisoning. Lack of data and poor-quality evidence, primarily case reports with few documented randomized controlled clinical studies, make it difficult to draw conclusions (Muller et al., 2015; Tampakis et al., 2020).

II. AIM OF THE WORK

This study is a randomized controlled clinical trial aimed to assess the adjuvant therapeutic role of lipid emulsion administration in improving the level of consciousness of acutely poisoned comatose patients by antipsychotic drugs presented to the Poison Control Center of Ain Shams University hospitals (PCC-ASUH) during the period starting from October 2020 to March 2021.

III. PATIENTS AND METHODS

Study design, setting, and ethical considerations:

The current study is a controlled randomized parallel-group, single-blinded clinical trial, conducted on acutely poisoned patients with antipsychotic drugs who were admitted to the ICU of the PCC-ASUH during six months starting from the beginning of October 2020 to the end of March 2021. All ethical considerations were considered including administrative approval to carry out the study obtained from the PCC-ASUH. The study protocol was approved by the Institutional Review Board of the Faculty of Medicine at Ain-Shams University (Assurance No. FWA 000017585, IRB No. MS 671/2020). The current study was registered on clinicaltrials.gov (NCT04807634). An informed consent was obtained from the patients' legal guardians (as the patients under the study were comatose and unable to participate in the consent process). Participation was voluntary and the patients or

their legal guardians had the right to withdraw from the study at any time. The patient's name was omitted and substituted by a code number. Confidentiality was considered for every piece of information came to the researchers' knowledge during their work. The collected data were used only for the purpose of the study.

Sample Size:

Forty patients were enrolled in the current study and randomly assigned into two groups, intervention group (n=20 patients) and control group (n=20 patients). Depending on the primary outcome, an improvement in consciousness level as determined by the Glasgow Coma Scale (GCS), sample size was computed using the G power 3.1.9.4 software. The following assumptions are made: an effect size of 0.95, estimated in accordance with Taftachi et al. (2012), an alpha error of 5%, a power of 80%, and an allocation ratio = 1.

Patients' selection criteria:

Inclusion Criteria:

We included 40 adult patients of both sex with history of acute exposure to any type of antipsychotic drugs and admitted in the ICU of PCC-ASUH during the study period. Acute antipsychotic drug toxicity was identified by identifying the substance in the container brought by the patient's family, taking a medical history from the patients' legal guardians, and looking for the most typical suggestive clinical symptoms, such as coma, hypotension, and a prolonged QTc interval ***(Thanacoody, 2020)***.

Exclusion Criteria:

1. Patients who were presented with conditions that may interfere with the clinical and hemodynamic parameters and laboratory variables (e.g., Patients less than 18 years and more than 65 years as well as pregnant and lactating females).
2. Patients who reported co-ingestion of other substances along with antipsychotic drugs.
3. Patients who presented with a delay time greater than 12 hours after antipsychotic ingestion or received any treatment before admission to the PCC-ASUH (Elgazzar et al., 2022).
4. Patients with renal insufficiency or hepatic damage as severe fat metabolism disorder may be developed due to ILE administration (El Bahri, 2016).
5. Patients with head trauma or having any metabolic disease (e.g., renal and hepatic diseases) that may cause disturbance of consciousness and interfere with antipsychotics poisoning manifestations (Taftachi et al., 2012).
6. Patients having a history of underlying cardiac illness and/or ECG abnormalities, including prolonged QTc intervals unrelated to antipsychotic medication toxicity (Basiouny et al., 2022).
7. Patients with a known history of hyperlipidemia and those showing hypersensitivity to ILE ingredients as fish, egg, soybean, or peanut protein as ILE should be avoided in these patients (Raman et al., 2017).

Methods:

By using a random number generator website, the forty patients were randomly divided into two equal groups (control and intervention groups, 20 patients each, allocation ratio: 1:1). Doig and Simpson (2005) recommended using sequentially numbered, sealed opaque envelopes to conceal the distribution order.

Patients assigned to the control group received the standard care for acute antipsychotic toxicity in the ICU in accordance with the PCC-ASUH protocol based on the international guidelines, which included initial patient stabilization, maintaining patent airways, oxygen administration, ventilatory support when necessary, treating hypotension with intravenous fluids and vasopressors, and continuous cardiac monitoring until all symptoms and ECG abnormalities were resolved.

Patients assigned to the intervention group received ILE (SMOFlipid 20%; a combination of soybean oil, medium-chain triglycerides, olive, and fish oil) in addition to the conventional treatment that was given to patients in the control group. Intravenous lipid emulsion (ILE) was administrated as an initial bolus dose of 1.5 mL/kg over 1 to 2 minutes followed by a continuous rate infusion of 0.25 ml/kg/min for the next 30 to 60 minutes. After the infusion was completed, the patient was continuously reassessed for the possible requirement of an additional bolus dose if necessary (Purg et al., 2016). Patients were closely monitored during the hospital stay to detect any adverse effects.

For all patients, demographic, toxicological data, and time elapsed between the toxic exposure and hospital admission were collected. Additionally, a full clinical examination including monitoring of vital signs and assessment of the level of consciousness was done.

Assessment of the level of consciousness of all patients under the study was carried out on admission and every 12 hours by using Glasgow coma scale (GCS) and Alert, Voice, Pain, Unresponsive (AVPU) scale till the patient's discharge or death. The Glasgow Coma Scale is used to objectively describe the extent of impaired consciousness. It provides a score in the range 3-15 (Teasdale and Jennett, 1974). AVPU is a straightforward scale that is useful to rapidly grade a patient's gross level of consciousness, responsiveness, or mental status (Hoffmann et al., 2016).

AVPU scale is based on the following criteria: (Rajabi Kheirabadi et al., 2015)

- **Alert (A):** The patient is aware of the examiner and can respond to the environment around him independently. The patient can also follow commands, open his eyes spontaneously, and track objects.
- **Verbally Responsive (V):** The patient's eyes do not open spontaneously but open only in response to a verbal stimulus directed toward him. The patient can react to that verbal stimulus directly and in a meaningful way.
- **Physically (Painfully) Responsive (P):** The patient's eyes do not open spontaneously. The patient will only respond to the application of painful stimuli by an examiner. He may move, moan, or cry out directly in response to the painful stimuli.
- **Unresponsive (U):** The patient neither responds spontaneously nor responds to verbal or painful stimuli.

On admission, a 12-lead ECG was done and repeated after 12 hours of admission, then every 24 h till the patient's discharge or death. The Bazett formula, $QTc = \sqrt{QT/RR}$, was used to determine the corrected QT interval (QTc). If the QTc is longer than 0.45 sec in men and 0.47 sec in women, a prolonged QTc is known ***(Corponi et al., 2019).***

Full laboratory investigations were done at admission and routinely including [random blood sugar, serum electrolytes (Na, K), liver enzymes (ALT, AST), kidney function tests (serum urea and creatinine) and arterial blood gas analysis (ABG)].

All patients were prospectively monitored for level of consciousness, vital signs, ECG, QTc interval, and the presence of any complications until discharge from the hospital.

Outcome measures:

- Time for improvement in conscious level assessed by GCS and AVPU scale despite presence of other clinical manifestations of antipsychotics toxicity.
- Time for improvement of ECG changes and QTc interval.
- The need for intubation and mechanical ventilation, in addition to the time elapsed between intubation and extubation.
- Duration of ICU stay and total length of hospital stay.
- Mortality rate.

Statistical analysis

Data were tabulated and statistically analyzed using Statistical Package for Social Science (SPSS) version 25 software (SPSS Inc., Chicago, IL). Data normality was checked using Shapiro test and was found to be normally distributed. Mean and standard deviation (±SD) were presented for parametric numerical data. Number and percentage were obtained for non-quantitative variables. Chi-Square (X^2) test was used to assess the statistical significance of the difference between qualitative variables. Fisher exact test was used when one expected cell or more were less than 5. Independent Student t-test was used to assess the statistical significance of the difference between two independent study group means. *P* value ≤ 0.05 was considered significant.

IV. RESULTS

Patients under the study were homogenous according to demographic, basal (clinical, vital), and intoxication data that abolish any factor that may affect the outcome measures so, the patients under study of both groups were ready for comparison **(Table 1 and 2).** Both groups were homogeneous regarding age and sex. All acutely intoxicated patients with antipsychotics under the study presented with history of clozapine (clozapex® 100mg) toxicity. Regarding the route of exposure, all patients reported oral ingestion and the manner of poisoning in the studied patients was suicidal.

As regards the conventional treatment effect in the control group (A), AVPU score and GCS were improved after 12 hours. Also, AVPU score and GCS of patients who received ILE as adjuvant therapy in the intervention group (B) showed a significant difference **(Table 3 and 5).**

According to AVPU score and GCS in both groups, **table (4)** showed that there was no significant difference between the control and the intervention groups regarding their AVPU score recorded on admission. Conversely, a significant difference was observed between both groups regarding AVPU score mean values recorded after 12 hours following admission (*p* value = 0.01) where the intervention group developed better AVPU score compared with the control group.

About 30% of the patients who received ILE reached score "A" after 12 hours compared to 0% in the control group.

There was no significant difference between the control and the intervention groups regarding GCS on admission; however, there was a highly significant difference between both groups regarding mean GCS after 12 hours (*p* value <0.001). The intervention group showed a better GCS (13.3±1.45) than the control group (7.25±2.07) after 12 hours of admission.

In the control group (A), the ECG findings after 12 hours reported no significant improvement. On the other hand, ILE effect on ECG findings in the intervention group (B) after 12 hours showed a highly significant improvement **Table (7).**

Also, ILE could improve ECG changes as a significant difference was observed between the two groups regarding the ECG findings after 12 hours where 70% of patients treated with ILE showed normal ECG compared to 20% in the control group and 80% of the control patients continued to have sinus tachycardia after 12 hours of admission compared to 30% in the intervention group **Table (8)**.

The mean time to reach GCS 15 and score "A" was significantly longer in the control group compared with the intervention group. In addition, the length of ICU stay and the total length of hospital stay were significantly shorter in patients who received ILE therapy compared with the control patients. Four patients (two patients in each group) needed endotracheal intubation. ILE could decrease the time for extubation with a significant difference observed between the two groups (*p* value = 0.03) as the intubated patients who received ILE therapy required 12 hours to be extubated compared to 84 ±16.97 hours in the control group **Table (9).**

Table (1): Student's t-test, Chi square test, and Fisher Exact test statistical analysis of age, sex, residence, intoxication data, and medical history among acutely intoxicated patients with antipsychotics under the study.

Parameters \ Groups		Group A (N=20)		Group B (N=20)		t	P value
		Mean	SD	Mean	SD		
Age (years)		28.75	9.87	24.30	6.63	1.67	0.10
		N	%	N	%	X^2	P value
Sex	Male	7	35%	10	50%	0.92	0.34
	Female	13	65%	10	50%		
Residence	Urban	8	40%	13	65%	2.51	0.11
	Rural	12	60%	7	35%		
Amount (tabs)		10.53	5.92	10.58	4.32	0.03	0.98
Delay time (hours)		4.35	4.26	2.42	2.22	1.79	0.09
Pre-consultation management	Negative	13	65%	15	75%	1.63**	0.61
	Proper	2	10%	3	15%		
	Improper	5	25%	2	10%		
History of medical diseases	Negative	18	90%	20	100%	2.11**	0.49
	HTN	2	10%	0	0%		
History of psychiatric diseases	Negative	13	65%	15	75%	0.48*	0.49
	Positive	7	35%	5	25%		

t: Student's t-test statistical analysis, *: Chi square test was used, **: Fisher Exact test was used, SD: Standard deviation, p>0.05: non-significant difference, Group A: Control group, Group B: Intervention group.

Table (2): Student's t-test statistical analysis of the baseline vital data and laboratory data of acutely intoxicated patients with antipsychotics under the study.

Parameters \ Groups	Group A (N=20)	Group B (N=20)	t	P value
	Mean ± SD	Mean ± SD		
Heart rate (beats/min)	117.50±17.56	117.40±10.99	0.02	0.98
Systolic blood pressure (mmHg)	121.50±21.10	115.00±10.51	1.23	0.23
Diastolic blood pressure (mmHg)	75.00±12.35	71.50±6.71	1.11	0.28
Respiratory rate (breaths/min)	28.40±5.49	26.50±4.03	1.25	0.22
Temperature (°C)	37.23±0.38	37.11±0.26	1.12	0.27
Glucose (mg/dL)	129.05±33.05	121.75±27.90	0.76	0.46
Sodium (mmol/L)	140.40±4.10	138.75±2.83	1.48	0.15
Potassium (mmol/L)	3.36±0.53	3.34±0.67	0.05	0.96
pH	7.36±0.04	7.37±0.08	0.46	0.65
PCO2 (mmHg)	41.52±7.52	41.15±8.27	0.15	0.88
HCO3 (mmol/L)	22.94±2.96	22.58±4.36	0.31	0.76
Lactate (mmol/L)	3.52±1.96	2.25±1.07	2.54	**0.02***
Creatinine (mg/dL)	0.72±0.24	0.72±0.18	0.00	1.00
Urea (mg/dL)	11.34±4.78	13.50±5.09	1.38	0.18
AST (U/L)	19.10±8.02	17.90±2.77	0.63	0.53
ALT (U/L)	17.70±3.26	18.10±5.15	0.29	0.77

t: Student's t-test statistical analysis, SD: Standard deviation, pH: potential of hydrogen, PCO_2: partial pressure of carbon dioxide, HCO_3: bicarbonate, AST: aspartate aminotransferase; ALT: alanine transaminase, p>0.05: non-significant difference, *is significant when p<0.05, Group A: Control group, Group B: Intervention group.

Table (3): Marginal homogeneity test statistical analysis of AVPU Score of the control group (A) and the intervention group (B) on admission and after 12 hours.

Group A		**N**	**%**	**P value**
AVPU on admission	A	0	0	**0.003**
	V	0	0	
	P	14	70	
	U	6	30	
AVPU after 12 hours	A	0	0	
	V	5	25	
	P	13	65	
	U	2	10	
Group B		**N**	**%**	**P value**
AVPU on admission	A	0	0	**<0.001**
	V	0	0	
	P	12	60	
	U	8	40	
AVPU after 12 hours	A	6	30	
	V	8	40	
	P	6	30	
	U	0	0	

AVPU: Alert, Voice, Pain, Unresponsive Score, P<0.05: significant difference, P<0.001: highly significant difference, Group A: Control group, Group B: Intervention group.

Table (4): Chi square test statistical analysis comparing AVPU Score on admission and after 12 hours between the control group (A) and intervention group (B).

Groups / **Parameters**		**Group A (N=20)**		**Group B (N=20)**		**X^2**	**P value**
		N	**%**	**N**	**%**		
AVPU on admission	A	0	0	0	0	0.44	0.51
	V	0	0	0	0		
	P	14	70	12	60		
	U	6	30	8	40		
AVPU after 12 hours	A	0	0	6	30	10.90	**0.01***
	V	5	25	8	40		
	P	13	65	6	30		
	U	2	10	0	0		

AVPU: Alert, Voice, Pain, Unresponsive Score, X^2: Chi square test, P>0.05: non- significant difference, P<0.05: significant difference, *is significant when p<0.05, Group A: Control group, Group B: Intervention group.

Table (5): Paired samples t-test statistical analysis of GCS of the control group (A) and the intervention group (B) on admission and after 12 hours.

Group A	**Mean**	**SD**	**T**	**P value**
GCS on admission	5.30	1.72	8.31	**<0.001**
GCS after 12 hours	7.25	2.07		
Group B	**Mean**	**SD**	**T**	**P value**
GCS on admission	4.95	2.06	24.39	**<0.001**
GCS after 12 hours	13.30	1.45		

t: Paired samples t-test, GCS: Glasgow coma scale, P<0.001: highly significant difference, Group A: Control group, Group B: intervention group.

Table (6): Student's t-test statistical analysis comparing GCS on admission and after 12 hours between the control group (A) and intervention group (B).

Groups / Parameters	Group A (N=20) Mean ± SD	Group B (N=20) Mean ± SD	t	P value
GCS on admission	5.30±1.72	4.95±2.06	0.58	0.56
GCS after 12 hours	7.25±2.07	13.30±1.45	10.68	**<0.001**

t=Student t test, GCS: Glasgow coma scale, SD: Standard deviation, P>0.05: non-significant difference, P<0.001: highly significant difference, Group A: Control group, Group B: Intervention group.

Table (7): Marginal homogeneity test statistical analysis of the electrocardiographic findings in the control group (A) and the intervention group (B) on admission and after 12 hours.

Group A		**N**	**%**	**P value**
Electrocardiographic findings on admission	Sinus tachycardia	16	80	0.06
	Sinus tachycardia + Prolonged QTc	4	20	
Electrocardiographic findings after 12 hours	Normal	4	20	
	Sinus tachycardia	13	65	
	Sinus tachycardia + Prolonged QTc	3	15	
Group B		**N**	**%**	**P value**
Electrocardiographic findings on admission	Normal	0	0	**<0.001**
	Sinus tachycardia	15	75	
	Sinus tachycardia + Prolonged QTc	5	25	
Electrocardiographic findings after 12 hours	Normal	14	70	
	Sinus tachycardia	4	20	
	Sinus tachycardia + Prolonged QTc	2	10	

p>0.05: non-significant difference, P<0.001: highly significant difference, Group A: Control group, Group B: intervention group, QTc: Corrected QT interval.

Table (8): Fisher exact test statistical analysis comparing the electrocardiographic findings on admission and after 12 hours between the control group (A) and intervention group (B).

Groups / Parameters		Group A (N=20)		Group B (N=20)		X^2	P value
		N	%	N	%		
Electrocardiographic findings on admission	Normal	0	0	0	0	0.14	1.00
	Sinus tachycardia	16	80	15	75		
	Sinus tachycardia + Prolonged QTc	4	20	5	25		
Electrocardiographic findings after 12 hours	Normal	4	20	14	70	10.54	**0.003**
	Sinus tachycardia	13	65	4	20		
	Sinus tachycardia + Prolonged QTc	3	15	2	10		

X^2: Fisher Exact test, P>0.05: non- significant difference, P<0.001: highly significant difference, Group A: Control group, Group B: Intervention group, QTc: Corrected QT interval.

Table (9): Student's t-test statistical analysis of mean time to reach GCS "15" and score "A" for AVPU Score, the length of ICU stay, the total length of hospital stay, and time to extubation among acutely intoxicated patients with antipsychotics under the study.

Groups / Parameters	Group A (N=20) Mean ± SD	Group B (N=20) Mean ± SD	T	P value
Time to reach GCS "15" and score "A" (hours)	52.40±21.43	18.00±6.16	6.90	**<0.001**
Length of ICU stay (days)	2.23±0.90	0.77±0.26	7.02	**<0.001**
Total length of hospital stay (days)	2.83±1.00	1.09±0.35	7.34	**<0.001**
Time to extubation (hours)	84 ±16.97	12±0.0	6	**0.03**

t=Student t test, AVPU: Alert, Voice, Pain, Unresponsive Score, GCS: Glasgow Coma Scale, SD: Standard deviation, P<0.05: significant difference, P<0.001: highly significant difference, Group A: Control group, Group B: Intervention group.

V. DISCUSSION

The rising prevalence of acute antipsychotic overdose and associated high morbidity are real challenges for health care professionals. Antipsychotic overdose has no known particular antidote; therefore, the treatment is mainly symptomatic (Thanacoody, 2020).

Over the last few years, many experimental and anecdotal evidence showed that ILEs can reverse some hemodynamic, electrocardiographic, and neurological parameters and potentially decrease morbidity and mortality in poisoned patients. Recently, ILEs in the form of Intralipid® 20% have been used in clinical practice for reducing the bioavailability and toxicity of lipophilic poisonous agents in the circulation (Putic and Jović-Stošić, 2015).

The use of ILE therapy to treat lipophilic drug toxicity is causing considerable concern. Consequently, randomized controlled clinical studies are required to evaluate the effectiveness, safety, indications, and optimum regimen for ILE therapy (Gosselin et al., 2016).

Considering lacking clinical trials that evaluate the role of ILE therapy, our study was designed to assess the adjuvant therapeutic role of lipid administration on the outcomes of acute antipsychotic drugs poisoning.

Our study demonstrated that, all acutely intoxicated patients with antipsychotics under the study presented with a history of clozapine (clozapex® 100mg) toxicity. Also, Ibrahim et al. (2022) concluded that most patients with acute clozapine toxicity admitted to PCC-ASUH had ingested clozapine 100 mg tablets.

Clozapine is the most commonly prescribed antipsychotic drug because of the lower incidence of extrapyramidal symptoms such as tardive dyskinesia, and its efficacy in treating negative symptoms of schizophrenia (Wagner et al., 2021).

In Egypt, recent studies from Tanta University Poison Control Center and the National Poisoning Center in Cairo have explored acute clozapine poisoning as a frequent category among central nervous system pharmaceutical drug poisonings (Mubarak et al., 2019).

In the present study, all patients were presented with depressed level of consciousness. In agreement with this finding, it has been reported that impaired consciousness is a common manifestation of acute antipsychotic poisoning that ranges from sedation to frank coma (Hammad et al., 2016).

Similarly, a high frequency of CNS depression has been documented in a retrospective analysis of patients with acute clozapine poisoning (Gawlikowski et al., 2011).

It's crucial and life-saving to provide poisoned patients with prompt, accurate triage and monitoring. The simplest and quickest approach for determining neurologic status is the AVPU scale, which has four categories of consciousness (Rajabi Kheirabadi et al., 2015).

The present study showed that there was a significant difference of AVPU score on admission and after 12 hours in the control group (A) that received the conventional treatment. In addition, a significant improvement of AVPU score on admission and after 12 hours was observed in the intervention group (B) that received ILE therapy. So, both conventional management and ILE were effective in improving AVPU score in patients with antipsychotics poisoning. However, when comparing the control group (A) treated by conventional treatment only with intervention group (B) treated by conventional treatment plus ILE therapy, there was no significant difference between the control and the intervention groups regarding their AVPU scores recorded on admission. Conversely, a significant difference was observed between both groups regarding AVPU score mean values recorded after 12 hours following admission where the intervention group developed better AVPU score compared with the control group. About 30% of the patients who received ILE reached score "A" after 12 hours compared to 0% in the control group.

Our study showed a significant difference of the GCS on admission and after 12 hours in the control group (A) and in the intervention group (B). Both the conventional and the intervention treatment could improve GCS in cases with antipsychotics poisoning.

As regard the comparison between the control and the intervention groups, our study reported no significant difference between the control and the intervention groups regarding GCS on admission; however, there was a highly significant difference between both groups regarding mean GCS after 12 hours (p value <0.001).

These results came in agreement with Basiouny et al. (2022) who conducted a controlled randomized single-blinded clinical trial on 40 patients presented with acute antipsychotics toxicity in Tanta University Poison Control Center. The control group received the standard supportive treatment only, whereas the intervention group received the standard supportive treatment plus ILE 20% infusion with a dose of 1.5 mL/kg over 1 to 2 min as initial bolus dose followed by a maintenance dose (6 mL/kg) IV infusion over 1 hour. A highly significant difference was found between both groups ($p < 0.001$) in favor of the intervention group.

Similarly, Elgazzar et al. (2021) evaluated the role of ILE in clozapine intoxication by a randomized controlled trial conducted on 40 patients with acute clozapine poisoning. The mean GCS values at 6 hours and 12 hours after admission were significantly higher in the intervention group that received ILE compared to the control group that received the standard treatment only.

Also, in a randomized controlled trial by Taftachi et al. (2012) to evaluate the efficacy of ILE as an antidote in the reversal of

coma after lipophilic drug overdose, all patients in the case group received 10 cc/kg intralipid 10% infusion and the patients in the control group just received the supportive care. A significant improvement of GCS was reported 6 hours after admission in the case group compared to the control group.

Forty-eight uses of ILE were reported from 61 participating centers, including 30 patients presented with disturbed level of consciousness. In this case series, improvements were seen for GCS in patients with central nervous system toxicity as there was a significant elevation in GCS from immediately prior to ILE administration to 30 min after use (Cave et al., 2014).

On the contrary to our results, Downes et al. (2014) reported no benefit from ILE administration in a dose of a 500 mL infusion of a 20% solution over a 20 min period in several CNS depressants overdose (e.g., quetiapine, olanzapine, benzodiazepines, and tricyclic antidepressants). Intubation was not avoided in the majority of patients and there was no significant improvement in those patients not requiring intubation.

The "lipid sink" theory is the most widely accepted mechanism for how ILE protects against being intoxicated by lipophilic medications. It has been hypothesized that lipophilic substances, such as antipsychotic medications, are transferred from their site of action to a new inert compartment created by the ILE itself in the vessels (Moshiri et al., 2014). Additionally, ILE provides high-energy essential fatty acids and polyunsaturated fatty acids that are essential for the brain's metabolism and the production of bioactive chemicals. Recently, Nie et al. (2020) reported that ILE may perform its CNS protective effects through reducing the blood brain barrier permeability.

Prolonged QTc interval is a fatal complication reported in various antipsychotic drugs toxicity as it may cause fatal arrhythmias including torsade de pointes and ventricular fibrillation (Chohan et al., 2015). El-Gharbawy and Ghonem (2018) also reported that there is a significant correlation between the prolonged QTc interval, the increased mortality rate, and the need for ICU admission and mechanical ventilation.

Antipsychotic drugs including clozapine block voltage-gated potassium channels causing longer ventricular repolarization and consequently a prolonged QTc interval. Additionally, the commonly observed tachycardia is caused by the antagonistic effects of clozapine on alpha-adrenergic and muscarinic receptors (Ansermot et al., 2019).

In our study, all patients were presented with sinus tachycardia on admission and 22.5% of patients showed prolonged QTc interval. As regard the conventional treatment, no significant difference of ECG findings on admission and after 12 hours in the control group (A). However, a highly significant difference of ECG findings in the intervention group (B) that received ILE therapy on admission and after 12 hours. Also, when comparing the two groups, a highly significant difference was observed between the control group and the intervention group regarding the ECG findings after 12 hours where 70% of patients treated with ILE showed normal ECG compared to 20% in the control group that still had sinus tachycardia plus prolonged QTc interval. Also 80% of the control patients continued to have only sinus tachycardia after

12 hours of admission compared to 30% in the intervention group. The administration of ILE in this study was effective in the rapid control of the prolonged QTc interval and was accompanied by a decreased incidence of prolonged QTc interval at 12 hours after admission in comparison with the control patients.

Elgazzar et al. (2021) and Basiouny et al. (2022) results also supported our study findings concerning the effect of ILEs on prolonged QTc interval in clozapine and antipsychotics poisoned patients, respectively. The administration of ILEs was associated with a decreased frequency of prolonged QTc interval at 12 hours after admission in the intervention group compared to the control group.

Hieger and Peters (2020) demonstrated the effect of ILE therapy in quetiapine overdose. The patient was presented with decreased blood pressure (78/35 mm Hg), tachycardia (HR was 141 b/m), and significant QT prolongation (QTc= 0.558 sec). After administration of ILE therapy, the QTc was normalized to 0.44 sec and the patient became vitally stable.

Furthermore, Bartos and Knudsen (2013) reported a case with quetiapine overdose, developed severe hypotension and ECG changes as sinus tachycardia, prolonged QRS and QTc intervals. The cardiovascular collapse was refractory to volume resuscitation and vasopressor treatment. Subsequently, ILE 20% was given as 170ml bolus intravenously followed by an infusion of 500 mL over 1h and within the first hour of its administration, circulation became stable. Recently, Thanacoody (2020) reported that ILE is recommended in patients with cardiovascular collapse and also with those with severe antipsychotics overdose refractory to vasopressors.

On the other hand, Downes et al. (2014) reported that the administration of ILE had no effect on QTc prolongation secondary to the co-ingestion of carbamazepine and amisulpride.

It is known that free fatty acids have some effects on ion channels leading to their cardioprotective effects. In cardiomyocytes, long-chain fatty acids contribute to positive inotropic effect by increasing calcium influx via the calcium channels (Karakılıç et al., 2017; Paneta and Waring, 2019).

As a result of ILE provision of fatty acids, induction of the reversal of mitochondrial dysfunction, inotropic effects, suppression of the release of nitric oxide, and reversal of sodium channel blockage in the cardiac cells, QTc interval prolonging can be controlled (Ok et al., 2018).

Only four patients in the present study required endotracheal intubation (two patients in each group) and all patients under the study were completely improved with no recorded mortality in both groups. Intubation was mainly performed to enhance the airway management as disturbed conscious level could impair oxygenation, ventilation, and airway status. Also, El-Gharbawy and Ghonem (2018) reported that acute antipsychotic intoxicated patients needed intubation for controlling chest complications rather than cardiovascular side effects.

Regarding the extubation, a significant difference was observed between the control and the intervention groups (p value= 0.03). The intubated patients who received ILE

therapy required 12 hours to be extubated compared to 84 hours in the control group.

The mean time to reach GCS 15 and score "A" was significantly longer in the control group compared with the intervention group (52.4±21.43 vs 18±6.16 hours). In addition, the length of ICU stay, and the total length of hospital stay were significantly shorter in patients who received ILE therapy compared with the control patients.

This coincides with Arslan et al. (2013) and Elgazzar et al. (2021) who observed a rapid improvement in the patients' conditions and a shorter hospital stay after ILE therapy in antipsychotics poisoning. This could be explained by the observed function of the ILE in quickly regaining of consciousness and normalizing the prolonged QTc interval. This is supported by Mubarak et al. (2019) who reported a significant correlation between GCS and the duration of hospital stay as low GCS can be a predictor of prolonged hospital stay.

Basiouny et al. (2022) also reported significantly shorter length of hospital stay in the intervention group compared to the control group; however, as regard intubation, only one patient in the intervention group needed intubation compared to three patients in the control group and no significant difference was found between both groups.

In a study of ILE as an antidote in the reversal of coma after lipophilic drug overdose including antipsychotic drugs, there was no significant statistical difference between the intervention group that received ILE and the control group regarding elapsed time between intubation and extubation. However, a significant difference was found between both groups in terms of GCS (Taftachi et al., 2012).

In the current study, all patients survived with neither recorded deaths nor adverse effects reported from ILE administration. This coincides with Elgazzar et al. (2021) and Basiouny et al. (2022) who also reported survival of all patients and the safety of ILE administration as adjuvant therapy for clozapine and antipsychotic drugs poisoning, respectively.

VI. CONCLUSION

The current study highlights the great importance of administration of intravenous lipid emulsion as adjuvant therapy in acute antipsychotic poisoning. ILE was considered a safe therapy if given within the recommended dose. ILE has a crucial role in improving level of consciousness and correcting ECG abnormalities as prolonged QTc, in addition, it could decrease the total length of ICU and hospital stay.

VII. RECOMMENDATIONS

Intravenous lipid emulsions are better to be provided for patients with acute antipsychotic poisoning with bad prognosis or at high risk of complications (e.g., intubation and shock) as a new modality of management for better prognosis.

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دور المُستحلبات الدهنية الوريدية في تحسن الغيبوبة الناتجة عن التسمم الحاد بمضادات الذهان: تجربة مُضبطة عشوائية في مركز علاج التسمم بمستشفيات جامعة عين شمس

هند سلامة شلبي [1]، إيناس أبو الوفا التفتازاني [1] ، نبيل نصيف رزق [1] ، ولاء جمعة عبد الحميد [1]

[1]قسم الطب الشرعي والسموم الإكلينيكية ، كلية الطب جامعة عين شمس ، القاهرة ، جمهورية مصر العربية

المقدمة: لقد زاد وصف الأدوية المضادة للذهان واستخدامها خلال العقدين الماضيين وبالتالي ارتبط هذا بتزايد في الجرعات الزائدة من مضادات الذهان. يمكن أن يؤدي التسمم الحاد بمضادات الذهان إلى تأثيرات سامة مختلفة تهدد الحياة، خاصةً على القلب والأوعية الدموية والجهاز العصبي المركزي. نظرًا لأنه لا يوجد ترياق محدد للتسمم الحاد من مضادات الذهان ، فإن الهدف الأساسي في العلاج هو العلاج الداعم القوي. على الرغم من الاهتمام المتزايد باستخدام العلاج بالمستحلبات الدهنية الوريدية في علاج التسمم بالأدوية المُحبة للدهون بما في ذلك مضادات الذهان، إلا أن هناك ندرة في البيانات، مع وجود أدلة منخفضة الجودة تعتمد بشكل رئيسي على تقارير الحالة مع عدد قليل من التجارب السريرية العشوائية المُضبطة. ***الهدف من الدراسة:*** تعتبر هذه الدراسة تجربة سريرية عشوائية مُضبطة تهدف إلى تقييم الدور العلاجي المساعد للدهون في تحسين مستوى الوعي لدى المرضى الذين يعانون من الغيبوبة الناتجة عن التسمم الحاد بالأدوية المضادة للذهان والذين تم حجزهم بمركز علاج التسمم بمستشفيات جامعة عين شمس.
طريقة البحث: لقد قُمنا بإجراء تجربة سريرية عشوائية مُضبطة ومتوازية وحيدة التعمية خلال ستة أشهر بدءًا من أكتوبر 2020 إلى مارس 2021. وتم تقسيم أربعين مريضًا يعانون من التسمم الحاد بمضادات الذهان عشوائيًا إلى مجموعتين متساويتين. تم إعطاء العلاج التقليدي للمجموعة الضابطة بينما تم إعطاء المُستحلبات الدهنية الوريدية للمجموعة الثانية بالإضافة إلى العلاج التقليدي. خضع جميع المرضى للتاريخ الطبي والفحص الإكلينيكي والفحوصات المعملية وقد تم تقييم النتائج. ***نتائج البحث:*** كان العلاج بالمُستحلبات الدهنية الوريدية فعالاً في تحسين مستوى الوعي من خلال التقييم باستخدام مقياس "التنبيه والصوت والألم وعدم الاستجابة" ومقياس "غلاسكو للغيبوبة". كان متوسط مقياس "التنبيه والصوت والألم وعدم الاستجابة" ومقياس "غلاسكو للغيبوبة" الذي تم تقييمهما بعد مرور 12 ساعة من حجز المرضى أعلى بكثير في مجموعة التدخل مقارنة بالمجموعة الضابطة. وقد كانت فترة الكيو تي المُصححة التي تم قياسها بعد مرور 12 ساعة من حجز المرضى بالإضافة إلى فترة الإقامة في المستشفى وبوحدة العناية المركزة أقصر بكثير في مجموعة التدخل مقارنة بالمجموعة الضابطة. ***الخلاصة:*** تعتبر المُستحلبات الدهنية الوريدية علاجاً فعالاً في تحسين مستوى الوعي وتصحيح الإضطرابات برسم القلب مثل طول فترة الكيو تي المُصححة في التسمم الحاد بمضادات الذهان، بالإضافة إلى تقليل فترة الإقامة في وحدة العناية المركزة والمستشفى. تشجع هذه الاستجابات الواعدة على النظر بشكل اعتباري في استخدام المُستحلبات الدهنية الوريدية كطريقة علاج جديدة.
التوصيات: من الأفضل تقديم المُستحلبات الدهنية الوريدية للمرضى الذين يعانون من التسمم الحاد بمضادات الذهان إذا كان من المتوقع نتائج سيئة أو المعرضين لخطر كبير للمضاعفات (مثل الحاجة إلى تركيب أنبوبة حنجرية والصدمة) وذلك كطريقة جديدة للعلاج من أجل نتائج أفضل.