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Paracetamol Poisoning Outcome at Rozhhalat Emergency Hospital-Erbil City

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Original Article

ABSTRACT

Background: *Paracetamol poisoning (PP) is a common cause of hepatotoxicity and acute liver failure all over the world. Exploring the management outcomes of paracetamol poisoning is important for evaluation of management guidelines and facilities* ***Objective:*** *To evaluate the outcomes of paracetamol poisoning in Erbil city and exploring risk factors for adverse outcome of paracetamol poisoning among patients* ***Patients & Methods****: A clinical prospective follow up study conducted in Rozhhalat Emergency Hospital in Erbil city-Kurdistan through the period from 1st of August, 2019 to 31st of July, 2020 on sample of 65 patients with paracetamol poisoning. The patients were followed up for at least 48 hours after management for assessment of complications and outcome*

Results*: The complications of PP were absent in 90.7% of patients, while PP complications were liver failure (6.2%) and central nervous complications (3.1%). The final outcome of PP patients was either discharged with no complications (90.7%), or discharged with complications (9.3%). The significant risk factors in developing complications of paracetamol poisoning are alcohol consumption, therapeutic dose, increased number of ingested tablets and unstable patients.* ***Conclusions:*** *The main risk factors in developing complications of paracetamol poisoning are alcohol consumption, therapeutic dose, increased number of ingested tablets and unstable patients*

Keywords: *Paracetamol poisoning, Management, Complications, Outcome*

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1. INTRODUCTION

Paracetamol (acetaminophen) is a safe centrally acting analgesic and antipyretic drug with minimum anti-inflammatory characteristics [1]. The paracetamol poisoning is defined as either accidental or intentional overdose of paracetamol intake and self-harm is regarded the main cause for paracetamol poisoning for younger age population [2]. In adults, paracetamol dose not more than four gm/day is safe, while for children, not more than 60 mg/kg/day and toxicity were labeled in dose of 7.5-10 g/day or 140 mg/kg [3]. Although paracetamol is safe drug, but paracetamol overdose is the leading cause of hepatotoxicity which ranges in severity from asymptomatic, mild transaminitis to acute liver failure and sometimes death [4]. The paracetamol overdose is the predominant etiology of poisoning globally, and it is the most common cause of acute liver failure in United States and United Kingdom [5, 6]. The poisoning emergency centers in United states pointed for more than 100,000 paracetamol poisoning cases and 313 confirmed deaths due to paracetamol poisoning in one year, and in United Kingdom, about 80,000 paracetamol poisoning cases admitted to hospitals with paracetamol overdoses with confirmed death in about 150–250 cases [7].

Diagnosis of paracetamol toxicity is mainly done according to history, physical examination, serum levels of the drug, even if asymptomatic. The diagnosis needs also laboratory investigations like liver function tests and coagulation profile [8]. The best regimen in treating paracetamol intoxication must include N-acetyl cysteine [9]. Mechanism of action concentrated in preventing liver and renal toxicity by replenishing glutathione in recommended dose and earlier in acute phase [9]. The failure of treatment with intravenous N-acetyl cysteine documented following taking high amount of paracetamol or overdoses with slow gastrointestinal motility if combined with such as anticholinergics or opioid agents. All of these lead to earlier signs of hepatic failure even with treatment [10-12].

The main complications of paracetamol poisoning are Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, toxic epidermal necrolysis, blindness, nephrotoxicity and death. It is also the common cause of acute liver failure and represents the most frequent reason of liver transplantation [8]. Death incidence related to paracetamol poisoning is affected by early diagnosis and prompt treatment; mortality rates was less than 2% for cases with earlier management, while reached more than 10% with delayed management. The liver transplantation is recorded in about 1-3% of patients with severe liver failure in order to save lives [13, 14]. For

pediatric population; the children have a better prognosis than adults, commonly because of higher capacity to detoxify paracetamol. However, the prognosis of paracetamol poisoning patients depends on; creatinine level, arterial pH, prothrombin time and grades of encephalopathy [8].

In Iraq, the paracetamol poisoning is regarded as the third common cause of drug poisoning among children [15]. Modernization of lifestyles in our society last years with different socioeconomic and mental problems facing the community specifically younger age population leading to increase in suicidal attempts in Kurdistan, [16] in addition to scarcity of national literatures discussing the outcome of paracetamol poisoning among adults and children, all these urged us to conduct this study which aimed to evaluate the outcomes of paracetamol poisoning in Erbil city and exploring risk factors for adverse outcomes of paracetamol poisoning among patients.

2. PATIENTS and METHODS

The design of current study was clinical prospective follow up study conducted in Rozhhalat Emergency Hospital in Erbil city-Kurdistan through the period from 1st of August, 2019 to 31st of July, 2020. The study population was all patients with paracetamol poisoning presented or referred to Rozhhalat Emergency Hospital. Age ≥12 years, confirmed paracetamol poisoning according to International Statistical Classification of Diseases and Health Problems, Tenth Revision (ICD 10) were the inclusion criteria. The exclusion criteria were pediatric age (less than 12 years), not matching ICD codes but presented with a history of a single ingestion of < 2 g paracetamol, ingestion of < 4 g paracetamol for more than 24-hour duration, or no evidence of paracetamol ingestion. A sample of 65 patients with paracetamol poisoning was selected after eligibility to inclusion and exclusion criteria.

The data were collected by the researcher from the selected patients directly and fulfilling a prepared questionnaire. The questionnaire was designed by the researcher. The questionnaire included the followings: general characteristics (age, gender, weight, past medical history, previous deliberate self-harm, smoking and alcohol history), paracetamol characteristics (paracetamol type, recorded degree of toxicity, number of tablets ingested, duration of poisoning before presentation and antidote needed), symptoms of paracetamol poisoning, management (assessment, Glasgow Coma Scale, admission to, use of N-acetyl cystine, duration of hospital

admission and source of admission) and complication and outcomes of patients. Diagnosis of paracetamol poisoning for selected patients was made officially by Internal Medicine Specialist or Emergency Medicine Specialist on call depending on ICD-10 classification. The diagnosis is based on history, physical examination, symptoms and signs, in addition to further assessment by electrocardiography, random blood sugar, serum electrolyte, renal function tests, liver function test, complete blood picture and coagulation studies for assessment of patients and detect early complications of paracetamol poisoning. The patients were managed by medical staff in Emergency Department by oxygen, airway support, intravenous fluids, some of them with gastric lavage and some of them with N-acetyl cystine in regard to availability. The complications of N-acetyl cystine were detected among 4 patients treated by N-acetyl cystine with minor effect and managed accordingly. The patients were followed up for at least 48 hours after management for assessment of complication and outcome.

The collected data were analyzed using the Statistical Package for Social Sciences software version 22. Fischer's exact test was applied for analyzing the data as suitable. Level of significance (P. value) was regarded statistically significant if it was 0.05 or less.

3. RESULTS

This study included 65 patients with Paracetamol Poisoning (PP) with mean age of (20.8 years) and range of 12-40 years; 52.3% of patients were in age group 12-24 years and 47.7% of them were in age group of 25-40 years. Female PP patients were more than male PP patients with female to male ratio of 3.6:1. The mean weight of PP patients was (63.4 Kg); 38.5% of them had weight of 60-69 Kg. The past medical history of PP patients was negative in 75.4% of them, while positive past medical history (PMH) included hypertension (4.6%), diabetes mellitus (3.1%), depression (9.2%) and psychosis (7.7%). The previous deliberate self-harm was observed in (26.2%) of PP patients. Smoking status of PP patients revealed non-smoking (43.1%), current smoking (26.2%) and ex-smoking (30.7%). The alcohol consumption was found in occasion among 6.2% of PP patients. (**Table 1**). Pure paracetamol constituted 38.5% of PP cases, while combined paracetamol constituted 61.5% of them. The toxic degree of PP reported in 6.2% of PP patients, overdose for 63.1% of PP patients and therapeutic for 30.7% of them. The numbers of paracetamol tablets were distributed as followings; less than 5 tablets (3.1%), 5-

10 tablets (33.8%), 11-15 tablets (32.3%), 16-20 tablets (12.3%) and more than 20 tablets (18.5%). The duration of poisoning before presentation for PP patients was less than 1 hour for 32.3% of them, 1-2 hours for 27.7% of them, 3-4 hours for 15.4% of them and more than 4 hours for 24.6% of them. The antidote was needed for 81.3% of PP patients, (**Table 2**).

The common symptoms of PP reported among patients were vomiting in 33 (50.8%), followed by; abdominal pain 32 (49.2%), nausea 31 (47.7%), confusion 8 (12.3%), agitation 5 (7.7%), and coma in only one patient (0.8%) , all other symptoms reported in 8 patients (12.3%). (**Figure 1**). Most of PP patients were stable on admission, while 15.4% of them were unstable. The Glasgow coma scale (GCS) of PP patients was less than 8 in one patient, 8-12 GCS scale in 13.8% of PP patients and 13-15 scale in 84.6% of them. About two thirds of PP patients were admitted to ER, 9.2% of them were admitted to intensive care unit (ICU), one patient was admitted to RCU and 23.1% of them were admitted to ward. The N-acetyl cystine was given to 70.8% of PP patients. Duration of hospital admission for PP patients was classified into; 6 hours (41.6%), 24 hours (21.5%), 48 hours (15.4%) and more than 48 hours (21.5%). The sources of admission to hospital for PP patients were either relative (93.8%) or referral (6.2%), (**Table 3**). Complications of PP were absent in 90.7% of patients, while PP complications were liver failure (6.2%) and central nervous complications (3.1%). The final outcome of PP patients was either discharged without complications (90.7%), or discharged with complications (9.3%). (**Table 4**).

No significant differences were observed between PP patients with no complications and PP patients with complications regarding age (p=0.4), gender (p=0.1), weight (p=0.2), PMH (p=0.7), previous deliberate self-harm (p=0.5) and smoking (p=0.8). There was a significant association between alcohol history of PP patients and poor outcome (p=0.004), 33.3% of PP patients with complications had alcohol history in comparison to 3.4% of PP patients with no complications. (**Table 5**).

No significant differences were observed between PP patients with no complications and PP patients with complications regarding paracetamol type (p=0.1), duration of poisoning before presentation (p=0.4) and antidote needed (p=0.2). Therapeutic dose of PP was significantly related with poor outcome of PP patients (p=0.01). A highly significant association was observed between increased number of Paracetamol tablets and poor outcome of PP patients (p<0.001),(**Table 6**).

There was a highly significant association between unstable PP patients on admission and

poor outcome of PP patients (p<0.001). No significant differences were observed between PP patients with no complications and PP patients with complications regarding GCS (p=0.5), admission to (p=0.7), N-acetyl cystine (p=0.09) and duration of hospital admission (p=0.2). There was a highly significant association between referred PP patients and poor outcome (p<0.001), (**Table 7**).

Table 1. General characteristics of PP patients.

Variable		No.	%
Age	12-24 years	34	52.3
	25-40 years	31	47.7
Gender	Male	14	21.5
	Female	51	78.5
Weight	<50 Kg	5	7.7
	51-59 Kg	18	27.7
	60-69 Kg	25	38.5
	70-79 Kg	10	15.4
	≥80 Kg	7	10.7
PMH	Negative	49	75.4
	HT	3	4.6
	DM	2	3.1
	Depression	6	9.2
	Psychosis	5	7.7
Previous deliberate self-harm	Yes	17	26.2
	No	48	73.8
Smoking	Non-smoker	28	43.1
	Current smoker	17	26.2
	Ex-smoker	20	30.7
Alcohol	No	61	93.8
	On occasion	4	6.2
Total		**65**	**100.0**

Table 2. Paracetamol characteristics of PP patients.

Variable		No.	%
Paracetamol type	Pure Paracetamol	25	38.5
	Combined	40	61.5
Recorded degree of toxicity	Toxic	4	6.2
	Overdose	41	63.1
	Therapeutic	20	30.7
Number of tablets	<5	2	3.1
	5-10	22	33.8
	11-15	21	32.3
	16-20	8	12.3
	>20	12	18.5
Duration of poisoning before presentation (hour)	<1	21	32.3
	1-2	18	27.7
	3-4	10	15.4
	>4	16	24.6
Antidote needed	Yes	52	81.3
	No	12	18.8
Total		**65**	**100.0**

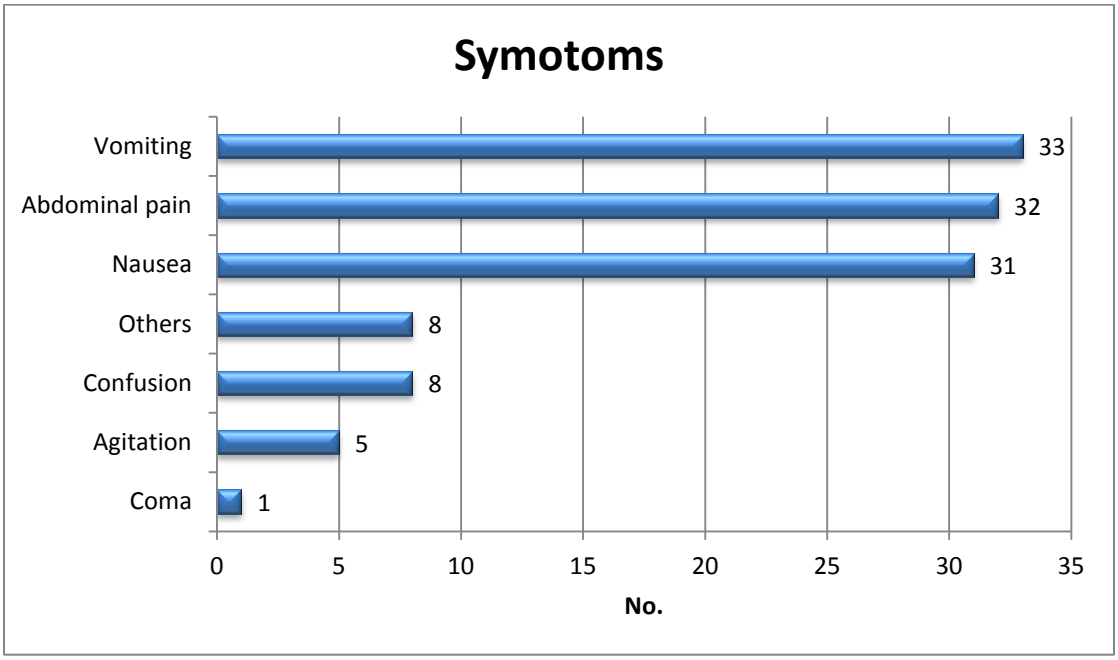

Figure 1. Symptoms of PP.

Table 3. Management of PP patients.

Variable		No.	%
Assessment	Vitally stable	55	84.6
	Unstable	10	15.4
GCS	<8	1	1.5
	8 - 12	9	13.8
	13-15	55	84.6
Admission to	ER	43	66.2
	ICU	6	9.2
	RCU	1	1.5
	Ward	15	23.1
N-acetyl cystine	Given	46	70.8
	Not given	19	29.2
Duration of hospital admission	6 hours	27	41.6
	24 hours	14	21.5
	48 hours	10	15.4
	>48 hours	14	21.5
Source of admission	Relative	61	93.8
	Referral	4	6.2
Total		**65**	**100.0**

GCS: Glasgow Coma Scale, ER: Emergency Reward, ICU: Intensive Care Unit, RCU: Respiratory Care Unit.

Table 4. Complications and outcome of PP.

Variable		No.	%
Complications	No complications	59	90.7
	Liver failure	4	6.2
	CNS complications	2	3.1
Outcome	Discharged without complications	59	90.7
	Discharged with complications	6	9.3
Total		**65**	**100.0**

Table 5. Distribution of patients' general characteristics according to outcome.

Variable		Outcome				*P. value*
		No complication		Complications		
		No.	%	No.	%	
Age	12-24 years	30	50.8	4	66.7	0.4 NS
	25-40 years	29	49.2	2	33.3	
Gender	Male	14	23.7	0	0.0	0.1 NS
	Female	45	76.3	6	100	
Weight	<50 Kg	5	8.5	0	0.0	0.2 NS
	51-59 Kg	14	23.7	4	66.7	
	60-69 Kg	23	39	2	33.3	
	70-79 Kg	10	16.9	0	0.0	
	≥80 Kg	7	11.9	0	0.0	
PMH	Negative	43	72.9	6	100	0.7 NS
	HT	3	5.1	0	0.0	
	DM	2	3.4	0	0.0	
	Depression	6	10.2	0	0.0	
	Psychosis	5	8.5	0	0.0	

Previous deliberate self-harm	Yes	16	27.1	1	16.7	0.5 NS
	No	43	72.9	5	83.3	
Smoking	Non-smoker	26	44.1	2	33.3	0.8 NS
	Current smoker	15	25.4	2	33.3	
	Ex-smoker	18	30.5	2	33.3	
Alcohol	No	57	96.6	4	66.7	0.004 S
	On occasion	2	3.4	2	33.3	

NS: Not significant, S:Significant.

Table 6. Distribution of paracetamol characteristics according to outcome.

Variable		**Outcome**				***P. value***
		No complication		**Complications**		
		No.	**%**	**No.**	**%**	
Paracetamol type	Pure Paracetamol	21	35.6	4	66.7	0.1 NS
	Combined	38	64.4	2	33.3	
Recorded degree of toxicity	Toxic	4	6.8	0	0.0	0.01 S
	Overdose	40	67.8	1	16.7	
	Therapeutic	15	25.4	5	83.3	
Number of tablets	<5 tablets	2	3.4	0	0.0	<0.001 S
	5-10 tablets	22	37.3	0	0.0	
	11-15 tablets	21	35.6	0	0.0	
	16-20 tablets	8	13.6	0	0.0	
	>20 tablets	6	10.2	6	100	

Duration of poisoning before presentation (hour)	<1	20	33.9	1	16.7	0.4 NS
	1-2	17	28.8	1	16.7	
	3-4	9	15.3	1	16.7	
	>4	13	22	3	50	
Antidote needed	Yes	46	79.3	6	100	0.2 NS
	No	12	20.7	0	0.0	

Table 7. Distribution of management characteristics according to outcome

Variable		**Outcome**				***P. value***
		No complication		**Complications**		
		No.	**%**	**No.**	**%**	
Assessment	Vitally stable	49	83.1	0	-	**<0.001** S
	Unstable	10	16.9	6	100	
GCS	<8	1	1.7	0	0.0	0.5 NS
	8 - 12	9	15.3	0	0.0	
	13-15	49	83.1	6	100	
Admission to	ER	38	64.4	5	83.3	0.7 NS
	ICU	6	10.2	0	0.0	
	RCU	1	1.7	0	0.0	
	Ward	14	23.7	1	16.7	
N-acetyl cystine	Given	40	67.8	6	100	0.09 NS
	Not given	19	32.2	0	0.0	

Duration of hospital admission	6 hours	25	42.4	2	33.3	0.2 NS
	24 hours	13	22	1	16.7	
	48 hours	10	16.9	0	0.0	
	>48 hours	11	18.6	3	50	
Source of Admission	Relative	59	100.0	2	33.3	**<0.001** S
	Referral	0	0.0	4	66.7	

NS: Not significant, S:Significant

4. DISCUSSION

The paracetamol is a common analgesic and anti-pyretic drug all over the world although it has risk of poisoning and hepatotoxicity, when take in overdose [14]. However, the United State Food and Drug Administration approved the limitation of paracetamol doses either alone or in combination with other drugs to decrease risk of poisoning [17, 18]. This study is the first national study discussing the paracetamol poisoning and its outcome in emergency hospital. Present study showed that 90.7% of paracetamol poisoning patients were discharged without complications, while 9.3% of them were discharged with complications. These findings are close to results of Pajoumand et al[19] study in Iran which revealed that 93.5% of paracetamol poisoning patients were discharged free of complications, while 6.5% of them had complications. However, our study findings are better than results of Tan and Sklar study in Singapore which found that 16.7% of paracetamol poisoning patients developed complications [20]. The main complications of paracetamol poisoning detected in current study were liver failure (6.2%) and CNS complications (3.1%). This finding is similar to results of many literatures such as Yoon et al [14] study in USA and Tittarelli et al[21] study in Italy which stated that hepatotoxicity and subsequent hepatic failure are the outcome for many cases of intentional and non-intentional paracetamol poisoning. Despite these literatures, our study results are in general better than many American studies [22, 23] and this finding is attributed to many factors like higher public use of paracetamol in USA, higher rates suicidal attempts and alcohol consumption in USA as compared to our community in addition to limitation of paracetamol doses by Iraqi Health authorities. The paracetamol is known as the main agent that cause liver injury and about half of Americans' with acute liver injury is caused by paracetamol poisoning, while 20% of liver transplant is attributed to paracetamol poisoning [24, 25] and the mortality rates reached to 0.4% annually [26]. Paracetamol

poisoning hepatotoxicity resulted from noxious *N*-acetyl-para-benzo-quinone imine (NAPQI) metabolite that occurs in excessive amount, with glutathione (GSH) depletion, that leading to depletion in adenosine triphosphate (ATP) stores and hepatocyte damage[27,28]. Regarding CNS complications, our study finding is similar to results of Castanares-Zapatero et al [29] study in Belgium which found that two patients with paracetamol poisoning had neurological complications. The mental status remains normal even after paracetamol overdose, but altered consciousness and coma were reported after ingestion of high paracetamol doses [30].

In the current study, alcohol consumption was the significant risk factor for developing complications of paracetamol poisoning. This finding coincides with reports of Dart et al [31] study which documented that chronic alcoholism is related firstly to self-harm and secondly to potentiate the hepatotoxicity and liver failure if combined with paracetamol toxicity or overdose, but not with therapeutic dose. Our study found that therapeutic dose of PP was significantly related with poor outcome of PP patients. This finding indicates the urgent need for reviewing the national guidelines regarding dose of paracetamol alone or in combination with other agents as 83.3% of patients with poor outcome in our study had therapeutic dose of paracetamol. Our study also found a highly significant association was observed between increased number of Paracetamol tablets and poor outcome of PP patients. This finding is consistent with results of many previous studies which stated that paracetamol dose and time duration between ingestion of paracetamol to treatment with antidote were the common risk factors in predicting complications commonly the liver failure [32, 33]. In our study, there was a highly significant association between unstable PP patients on admission and poor outcome of PP patients. This finding is similar to results of Piotrowska et al [1] study in Switzerland. Current study showed a highly significant association between referred PP patients and poor outcome. Referred patients from other health institutes or hospitals were taken longer time that is accompanied with higher risk of complications than others [34]. Additionally, many treatment methods such as activated charcoal was not available in emergency department and low availability of N-acetyl cystine and other therapeutic techniques lead to current study paracetamol poisoning complications.

5. CONCLUSIONS

Our study concluded that proportion of paracetamol poisoning patients with complication is within international range although the facilities for management of cases are limited. The

main risk factors in developing complications of paracetamol poisoning are alcohol consumption, therapeutic dose, increased number of ingested tablets, unstable and referred patients. The main recommendation of this study are establishing updated national guidelines for intake of paracetamol alone or in combination with guidelines for diagnosis and management of poisoning in addition to arguing the availability of medicines and facilities for management of paracetamol poisoning in hospitals

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Ethical Clearance

Ethical clearance and approval of the study are ascertain by the authors, study protocol was approved by the Scientific Council and Ethical Committee at Kurdistan Board for Medical Specialties -Iraq. All ethical issues and data collection were in accordance with the World Medical Association Declaration of Helsinki 2013 for ethical issues of researches, verbal informed consent obtained from all patients and the data and privacy of patients were kept confidentially.

Conflict of interest: *Authors declared none*

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