

Prognostic Factors in Metformin Intoxication; A Case Control Study

Lida Shojaei Arani^a, Shahin Shadnia^a, Hoorvash Faraji Dana^a, Kiumars Bahmani^b, Nasim Zamani^a, Hossein Hassanian-Moghaddam^a, Mitra Rahimi^a, Nami Mohammadian Khonsari^c, Peyman Erfan Talab Evini^{a*}

a. Department of Clinical Toxicology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

b. PhD student of Toxicology, Department of Pharmacology and Toxicology, School of Pharmacy, Shahid Beheshti University of Medical Science, Tehran, Iran.

c. Department of Forensic Medicine and Toxicology, Alborz University of Medical Sciences, Karaj, Iran.

Article Info:

Received: April 2021

Accepted: April 2021

Published online: May 2021

* Corresponding Author:

Peyman Erfan Talab Evini

Email:

peyman1346erfan@gmail.com

Abstract:

Introduction: Metformin is one of the most used oral antidiabetic agents. Intentional and unintentional overdose of metformin can be associated with life threatening condition. In this study we evaluate prognostic factors for metformin intoxication.

Methods and Results: This case-control study was performed on patients referred to Loghman Hakim toxicology emergency department due to metformin intoxication. The patients' information and lab data were subsequently extracted from their medical file and data processing and analysis performed. There was a significant difference between two groups in multiple items, patients who died had older age, higher blood sugar, BUN, Cr, PT, INR, and WBC, on the other hand this group had lower blood pressure, O₂ saturation, pH, HCO₃ and PTT. Receiver operating characteristic curve showed that five items including: Bp, O₂sat, pH, HCO₃ and Cr had the ability to predict the risk of mortality in patients with metformin poisoning. Univariate as well as multivariate analysis showed that factors including: BP<95 (P=0.0184), O₂sat<93 (P=0.0094), pH<6.94 (P=0.0032), HCO₃<17.25 (P=0.0302), and Cr>1.15 (P=0.0216) were related to patient's mortality.

Conclusion: Our study showed that mentioned clinical and laboratory findings may have an important role in determining the prognosis of patients with metformin poisoning. Extracorporeal treatments may be considered sooner in those who have poor prognostic factors since admission.

Keywords: Metformin; Prognosis; Mortality; Hyperglycemia; Metabolic acidosis

Please Cite this article as: Shojaei Arani L., Shadnia Sh., Faraji Dana H., Bahmani K., Zamani N., Hassanian-Moghaddam H., Rahimi M., Mohammadian Khonsari N., Erfan Talab Evini P., Prognostic Factors in Metformin Intoxication; A Case Control Study. Int. Pharm. Acta. 2021;4(1):e5

DOI: <https://doi.org/10.22037/ipa.v4i1.34565>

1. Introduction

Metformin, a member of the biguanide family, is one of the most used oral antidiabetic agents and the first-line treatment of type 2 diabetes mellitus (DM) [1]. Metformin reduces microcirculatory complications in type 2 diabetic patients and is widely used around the world [2]. Metformin promotes euglycemia but it is unlikely to cause hypoglycemia when used alone [3]. It can enhance the suppression of gluconeogenesis without increasing insulin secretion, reduce glucagon-stimulated gluconeogenesis, and increase uptake of glucose by

muscle and adipose cells [4]. Metformin is a first-line treatment for diabetes that is used alone or in combination with other anti-diabetic medications [3]. The most important toxicity of metformin is lactic acidosis [5]. metformin promotes the conversion of glucose to lactate in the splanchnic bed of the small intestine, and it also inhibits mitochondrial respiratory chain complex 1, leading to decreased hepatic gluconeogenesis from lactate, pyruvate, and alanine [6]. Although in the absence of acute overdose, metformin-associated lactic acidosis (MALA) is very rare, but it has a high mortality rate [7, 8]. In overdose conditions, this

complication can occur with more incidence and severity [9, 10]. The aim of this study was to evaluate the prognostic factors of patients with accidental or intentional metformin poisoning.

2. Materials & Methods

This case-control study was performed in two phases; retrospective and prospective. In the retrospective section (which was a 5-year period), all patients who had referred to the Loghman Hakim toxicology emergency department due to metformin intoxication between April 2014 and April 2019 have been enrolled. In the prospective section, all metformin-poisoned patients who have been referred to Loghman Hakim toxicology emergency department between April 2019 and April 2020- with the history of metformin intoxication and signs and symptoms including hypoglycemia, lactic acidosis, and a rise in blood urea nitrogen were included in the study. Patients with previous acute or chronic renal dysfunction, and those who took other life-threatening drugs along with metformin were excluded from the study. Then patients were followed to see their final outcome (death versus complete recovery). The patients' information and lab data were subsequently extracted from their medical file and a specific code was assigned to each patient. Data were collected in excel file and divided into two subgroups: survived group and non-survived group.

The manuscript has been drafted and prepared according to the STROBE Statement.

Ethics approval and consent to participate:

This study was evaluated by the Shahid Beheshti University of Medical Sciences ethics committee and approved with IR.SBMU.RETECH.REC.1398.427 reference code. Written informed consent was obtained from the patients to use all the obtained data for research and publication purposes. For the deceased, written consent was obtained from their family to use all the obtained data for research and publication purposes.

Statistical analysis:

Statistical analysis was done by SPSS software version 22 (Chicago, Ill, USA). The data was expressed as mean \pm SD for continuous or discrete variables and as frequency and percentage for categorical variables. Chi-square test was used for statistical analysis of qualitative variables. The statistical comparison was done using independent student's t-test for comparison of the two groups (survivors and died). Logistic regression was used to evaluate the predictive factors of mortality. The best cut off points were determined by calculating the

area under the receiver operating characteristics (ROC) curve. P values of 0.05 or less were considered to be statistically significant, and data was presented with a 95% confidence interval (CI).

Study limitation:

The most important limitation of this study was small sample size which can be a source of bias in the study.

3. Results

A total of 44 patients have been included in the study. Most of the patients were female and minority of them were male. There was not difference between survived and deceased groups in male to female ratio. There was a significant difference between two groups in multiple items, patients in deceased group had higher age, blood sugar, BUN, Cr, PT, INR, WBC, on the other hand this group had lower blood pressure, O₂ saturation, pH, HCO₃ and PTT (Table 1).

Receiver operating characteristic (ROC) curve showed that five items including: Bp, O₂sat, pH, HCO₃ and Cr had ability to predict the risk of mortality in patients with metformin poisoning (Figure 1), area under the ROC curve and the best cut off points was as following: BP<95 [AUC= 0.957 (95% CI: 0.885-1.000)], O₂sat<93 [AUC= 0.808 (95% CI: 0.478-1.000)], PH<6.94 [AUC= 0.812 (95% CI: 0.504-1.000)], HCO₃<17.25 [AUC= 0.974 (95% CI: 0.920-1.000)], and Cr>1.15 [AUC= 0.068 (95% CI: 0.000-0.177)].

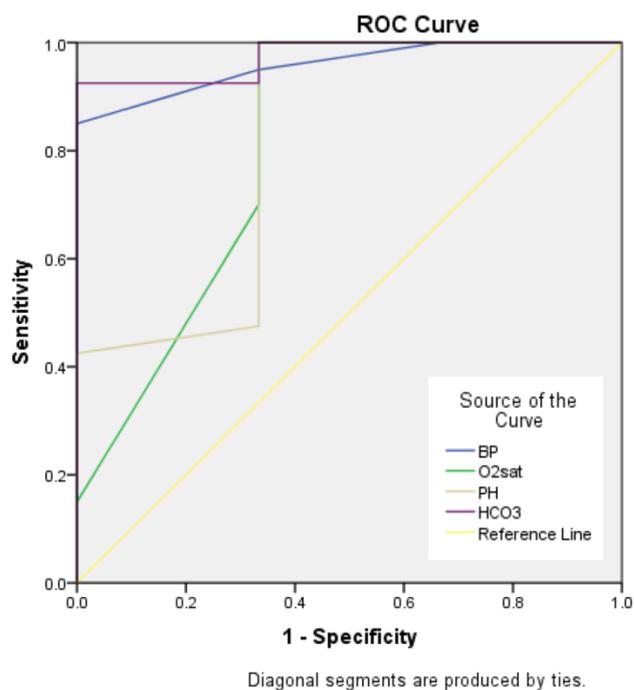


Figure 1. ROC curve of predictors of mortality.

Table 1. Clinical characteristics of patients with metformin poisoning, stratified by survived patients versus died patients

	SD ± All patients	SD ± Survived	SD ± Died	P value
Age	11.62 ± 29.39	12.33 ± 27.66	17.06 ± 53	0.0016*
Male/female	5/39	4/37	1/2	0.3100
Dose gr	15.65 ± 12.11	11.76 ± 12.16	0 ± 10	0.7545
PR	3.229 ± 89.48	89.93 ± 17.12	83.33 ± 7.572	0.5149
BP	0.3037 ± 115.2	117.3 ± 13.64	86.67 ± 15.28	0.0006*
RR	2.203 15.6 ±	15.49 ± 3.241	17.33 ± 3.055	0.3453
T	37 ± 29.5	36.98 ± 0.2509	37.27 ± 0.7506	0.1119
O2sat	97.16 ± 0.1271	97.5 ± 1.569	92.67 ± 4.619	<0.0001*
BS	103.1 ± 8.961	100.7 ± 26.79	136.3 ± 50.77	0.0419*
PH	7.304 ± 4.49	7.328 ± 0.06182	6.97 ± 0.3032	<0.0001*
PCO2	38.01 ± 11.02	38.48 ± 8.816	31.67 ± 10.37	0.2075
HCO3	19.54 ± 0.6984	20.3 ± 3.178	9.167 ± 7.63	<0.0001*
BUN	23.05 ± 2.746	22.12 ± 8.562	35.67 ± 29.77	0.0382*
Cr	1.188 ± 0.3699	1.06 ± 0.3395	2.9 ± 1.808	<0.0001*
Na	139.6 ± 95.65	139.7 ± 2.762	139.3 ± 3.055	0.8457
K	4.111 ± 15.4	4.09 ± 0.3534	4.4 ± 0.5568	0.1641
CPK	133.4 ± 14.82	132.9 ± 95.43	138.7 ± 119.6	0.9224
AST	28.67 ± 0.907	28.48 ± 15.91	31.33 ± 5.508	0.7606
ALT	25.53 ± 4.961	25.95 ± 15.26	20 ± 4.359	0.5089
PT	13.13 ± 0.1413	13.02 ± 0.7341	14.67 ± 1.724	0.0015*
PTT	35.37 ± 5.205	35.64 ± 4.836	31.8 ± 6.35	0.2002
INR	1.113 ± 0.3044	1.101 ± 0.1282	1.27 ± 0.2427	0.0446*
WBC	10.6 ± 1.407	10.08 ± 4.736	17.73 ± 7.222	0.0122*
RBC	4.392 ± 80.15	4.404 ± 0.3081	4.257 ± 0.2676	0.4290
HB	13.45 ± 35.26	13.46 ± 1.434	13.33 ± 1.21	0.8789
PLT	260.9 ± 11.62	263.2 ± 68.86	232.2 ± 200.7	0.5254
ALKP	187.2 ± 16.68	185.1 ± 35.77	211.5 ± 19.09	0.3192

Univariate analysis showed hypotension, low O2 saturation, acidosis, rise of Cr, older age, need for hemodialysis and need for bicarbonate therapy may be associated with poorer prognosis (Table 2). Multivariate analysis results strong association between five factor and mortality in patients with metformin poisoning which presented in Table 3.

Table 2. Variable that possible influence the survival of patients with metformin intoxication: univariate analysis.

Variable	Score	P value
BP<95	12.914	0.000
O2sat<93	18.151	0.000
PH<6.94	28.635	0.000
HCO3<17.25	12.914	0.000
Cr>1.15	7.677	0.006
Age	9.339	0.002
Underwent Extracorporeal removal	6.149	0.013
Underwent bicarbonate therapy	32.195	0.000

Table 3. Variable that significantly influence the survival of patients with metformin intoxication: multivariate analysis

Variable	OR	P value
BP	0.26 (0.0018 to 0.3570)	0.0184
<95	1	
>95		
O2sat<93	0.0125 (0.0008712 to 0.2377)	0.0094
>93	1	
PH<6.94	0.000 (0.000 to 0.1213)	0.0032
>6.94	1	
HCO3<17.25	0.04 (0.002702 to 0.4816)	0.0302
>17.25	1	
Cr>1.15	0.000 (0.000 to 0.4358)	0.0216
Underwent bicarbonate therapy	0.000 (0.000 to 0.1034)	0.0008
	1	

4. Discussion and Conclusion

Although metformin is considered a safe medication for the treatment of diabetes, overdose with metformin can be serious and fatal [11]. Every patient presenting to the

emergency department after a suspected metformin ingestion should undergo cardiopulmonary monitoring for a minimum of 4 to 6 hours [12]. Determination of the patients' prognosis since presentation is a critically important factor in patient management in settings with limited ICU beds as the clinical toxicology setting [13]. Based on our findings, age had a significant prognostic value; patients with higher age had poorer prognosis, which is consistent with other studies [2]. In general, elderly patients has higher mortality in poisoning [14]. Higher blood pressure in the survived group and a significant difference with the non-survived group indicate the effects of hypotension on the poor prognosis of patients. Studies have not specifically addressed the prognostic effect of hypotension, but in case reports, cases with low blood pressure have a worse prognosis [15]. In this study, high blood sugar was associated with a worse prognosis that had not been studied in prognostic studies but in a review, patients with hyperglycemia after metformin intoxication also were more at the risk of death [16]. O₂ saturation in non survivors was significantly lower than survivors that could be because of severity in poisoning and impairment in global oxygen extraction [17]. Other factors including: blood pH, serum Cr, Prothrombin time and INR were significantly different between two groups which is consistent with other studies [2]. Interestingly there was no difference between two groups in serum potassium despite other studies [2]. In the study of univariate as well as multivariate showed, factors including: BP<95, O₂sat<93, pH<6.94, HCO₃<17.25, and Cr>1.15 were closely related to patient's mortality. Our study showed that a number of laboratory and clinical factors play an important role in determining the prognosis of patients with metformin poisoning. Extracorporeal treatments may be considered sooner in those who have poorer prognostic factors since admission. With the evaluation of the cut of points, it can be observed that any condition that increases acidosis, increases the risk of mortality, and any condition that reduces acidosis, such as high respiratory rates and more oxygenation and acid washout reduces the risk of mortality. In our evaluation, older age, mean blood pressures under 95, oxygen saturations below 93%, bicarbonate levels below 17.75 meq/L, creatinine levels higher than 1.15 mg/dL and levels under 6.94 were found to be associated with poor prognosis.

Conflict of interest

The authors declare that they have no conflict of interests.

Ethics

Ethics code: IR.SBMU.RETECH.REC.1398.427

Funding/ Support

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' ORCIDs

Peyman Erfan Talab Evini:
<https://orcid.org/0000-0002-0995-4973>

References

- Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). 2012;25(3):154-171.
- Seidowsky A, Nseir S, Houdret N, et al. Metformin-associated lactic acidosis: a prognostic and therapeutic study. 2009;37(7):2191-2196.
- Hermann LJD, *metabolisme*. Metformin: a review of its pharmacological properties and therapeutic use. 1979;5(3):233-245.
- Bailey CJ, Turner RC. *JNEJoM*. Metformin. 1996;334(9):574-579.
- Lalau J-D. Lactic acidosis induced by metformin. 2010;33(9):727-740.
- Vecchio S, Giampreti A, Petrolini V, et al. Metformin accumulation: lactic acidosis and high plasmatic metformin levels in a retrospective case series of 66 patients on chronic therapy. 2014;52(2):129-135.
- Eppenga WL, Lalmohamed A, Geerts AF, et al. Risk of lactic acidosis or elevated lactate concentrations in metformin users with renal impairment: a population-based cohort study. 2014;37(8):2218-2224.
- Richy FF, Sabido-Espin M, Guedes S, et al. Incidence of lactic acidosis in patients with type 2 diabetes with and without renal impairment treated with metformin: a retrospective cohort study. 2014;37(8):2291-2295.
- Lalau JD, Mourlhon C, Bergeret A, et al. Consequences of metformin intoxication. 1998;21(11):2036.
- Dell'Aglio DM, Perino LJ, Kazzi Z, et al. Acute metformin overdose: examining serum pH, lactate level, and metformin concentrations in survivors versus nonsurvivors: a systematic review of the literature. 2009;54(6):818-823.
- Stevens A, Hamel JF, Toure A, et al. Metformin overdose: a serious iatrogenic complication—Western France Poison Control Centre data analysis. 2019;125(5):466-473.
- Arroyo AM, Walroth TA, Mowry JB, et al. The MALAdy of metformin poisoning: is CVVH the cure? 2010;17(1):96-100.
- Alizadeh AM, Hassanian- Moghaddam H, Shadnia S, et al. Simplified acute physiology score II/acute physiology and chronic health evaluation II and prediction of the mortality and later development of complications in poisoned patients admitted to intensive care unit. 2014;115(3):297-300.
- Mühlberg W, Becher K, Heppner H-J, et al. Acute poisoning in old and very old patients: a longitudinal retrospective study of 5883 patients in a toxicological intensive care unit. 2005;38(3):182-189.
- Nisse P, Mathieu- Nolf M, Deveaux M, et al. A fatal case of metformin poisoning. 2003;41(7):1035-1036.
- Spiller HA, Quadrani DA. *JAOP*. Toxic effects from metformin exposure. 2004;38(5):776-780.
- Protti A, Fortunato F, Monti M, et al. Metformin overdose, but not lactic acidosis per se, inhibits oxygen consumption in pigs. *Crit Care*. 2012;16(3):R75-R75. doi: 10.1186/cc11332. PubMed PMID: 22568883; eng.