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글라이포세이트 중독 환자에서 포함된 염의 종류에 따른 예후의 차이

정민규 · 금경탁 · 안성준 · 김용환 · 이준호 · 조광원 · 황성연 · 이동우

성균관대학교 의과대학 삼성창원병원 응급의학과

The Prognosis of Glyphosate herbicide intoxicated patients according to their salt types

Jeong Min Gyu, M.D., Kyoung Tak Keum, M.D., Seongjun Ahn, M.D., Yong Hwan Kim, M.D., Jun Ho Lee, M.D., Kwang Won Cho, M.D., Seong Youn Hwang, M.D., Dong Woo Lee, M.D.

Department of Emergency Medicine, Samsung Changwon Hospital, Sungkyunkwan University, School of Medicine, Changwon, Korea

Purpose: Glyphosate herbicide (GH) is a widely used herbicide and has been associated with significant mortality as poisoned cases increases. One of the reasons for high toxicity is thought to be toxic effect of its ingredient with glyphosate. This study was designed to determine differences in the clinical course with the salt-type contained in GH.
Methods: This was a retrospective study conducted at a single hospital between January 2013 and December 2017. We enrolled GH-poisoned patients visited the emergency department. According to salt-type, patients were divided into 4 groups: isopropylamine (IPA), ammonium (Am), potassium (Po), and mixed salts (Mi) groups. The demographics, laboratory variables, complications, and their mortality were analyzed to determine clinical differences associated with each salt-type. Addtionally, we subdivided patients into survivor and non-survivor groups for investigating predictive factors for the mortality.
Results: Total of 348 GH-poisoned patients were divided as follows: IPA 248, Am 41, Po 10, and Mi 49 patients. There was no difference in demographic or underlying disease history, but systolic blood pressure (SBP) was low in Po group. The ratio of intentional ingestion was higher in Po and Mi groups. Metabolic acidosis and relatively high lactate level were presented in Po group. As the primary outcome, the mortality rates were as follows: IPA, 26 (10.5%); Am, 2 (4.9%); Po, 1 (10%); and Mi, 1 (2%). There was no statistically significant difference in the mortality and the incidence of complications. Additionally, age, low SBP, low pH, corrected QT (QTc) prolongation, and respiratory failure requiring mechanical ventilation were analyzed as independent predictors for mortality in a regression analysis.
Conclusion: There was no statistical difference in their complications and the mortality across the GH-salt groups in this study.

Key Words: Glyphosate, herbicide, poisoning, isopropylamine, ammonium

INTRODUCTION

Glyphosate herbicide (GH) products have been widely used in recent years[1]. Glyphosate is a glycine derivative, and directly work to block the shikimic acid pathway essential for protein synthesis of plant. Due to the absence of this pathway in mammals, glyphosate is anticipated to be less toxic in humans. However, with the increase in the use of GH, the number of human poisoning cases is increasing, and the reported toxicity is unexpectedly higher. According to a study, the fatality rates of the GH-poisoned patients were reported to be approximately 3.2-29.3%[2].

The mixture of various supplements and glyphosate is considered one of the reasons for the relatively high toxicity of GH poisoning[3]. Glyphosate cannot be used alone as a herbicide, and it is mixed with several substances, such as various salts and surfactants, in formulated products. So, depending on the type and amounts of mixed supplements,

책임저자: **이 동 우**
경상남도 창원시 마산회원구 팔용로 158
삼성창원병원 응급의학과
Tel: +82-55-233-6140
Fax: +82-55-233-6134
E-mail: calmriver@daum.net

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the toxicity of GH may increase. A study reported that a higher toxicity of GH was observed when mixed with a polyethoxylated tallow amine (POEA), which is one of the most well-known surfactant in GH intoxication[4].

Glyphosate is poorly soluble in water, and some salts are required for liquefaction for its use as a herbicide. These salts include isopropylamine (IPA), ammonium (Am), potassium (Po), and trimesium, etc. Among them, glyphosate trimesium was withdrawn from the market due to its high toxicity[5]. On the other hand, IPA and ammonium are mainly used salts for mixing with glyphosate. A previous study published by Moon et al.[6] reported that the toxicity of IPA salt was more severe than that of ammonium.

We conducted a study to verify the effect of the salt type mixed with glyphosate on the prognosis and the differences in the toxicological characteristics of GH-poisoned patients visited the emergency room.

METHODS

This was a retrospective cohort study approved by the institutional review board of this hospital (IRB No. SCMC 20121-05-009).

1. Study design and enrollment

We enrolled GH-intoxicated patients aged ≥18 years who visited this emergency department (ED) between January 2013 and December 2017. The ED is a regional emergency medical center with an annual average volume of 45,000 emergency visits. GH intoxication in this study was confirmed from the history provided by the patients, their family, emergency medical personnel or the container label showing the toxic product information. No serological screening test was performed for diagnosis. In this study, oral ingestion was the only route of GH poisoning. The exclusion criteria were as follows: (1) unavailable clinical data, (2) co-intoxication with other pesticides, (3) patients who were discharged against medical advice or transferred to other facilities. However, if alcohol was ingested together with GH, those patients were enrolled in the study.

2. Patient characteristics and clinical courses

The demographic data, history, vital signs, laboratory blood test results, and clinical courses of the patients were obtained from the electronic medical records. A standardized clinical profile of the intoxicated patients was used with the toxicology registry form of our ED. The ingested volumes of GH were also recorded and quantified based on suggestions of a previous study as follows[7]: "a spoon" as 5 mL, "a mouthful" as 25 mL, "a cup" as 100 mL, and "a bottle" as 300 mL. The amount claimed by the patient or guardian or the remaining amount in the bottles presented was recorded. As an important factor during the clinical course, the in-hospital mortality rate and the duration of the intensive care unit (ICU) stay were recorded.

In addition, the following cases were defined as having complications of the relevant organ in this study. Pneumonia was diagnosed by the presence of consolidated lung parenchymal lesions on chest radiography, and the patients had respiratory symptoms or fever. Acute respiratory failure was defined as a case requiring mechanical ventilation if the patient did not respond to normal oxygen breathing therapy (type I respiratory failure) or not adequately cleared exceed carbon dioxide (type II respiratory failure). Rhabdomyolysis was diagnosed by a creatine phosphokinase concentration of 〉1,000 IU/L. Acute kidney injury (AKI) was defined as an elevated serum creatinine concentration of 〉0.3 mg/dL or 1.5 times the previous or initially recorded baseline creatine concentration[8]. Ventilator-free day (VFD) was defined as the interval days from the time which patient was weaned from mechanical ventilation to the hospital discharge. In this study, since the primary end point was set as in-hospital mortality, we set the criteria for calculating VFD as the date of patient's discharge. For example, if the mechanical ventilation is maintained continuously until the discharge, VFD was counted as 0 day.

In addition, although the standard criteria for the corrected QT interval (QTc) prolongation can change with age and sex, 500 or more milliseconds (ms) of prolongation, which may cause significant cardiac arrhythmia in intoxicated patients, was used in this study[9]. The QTc interval was measured using Bazett's formula (QT interval/root RR).

The glyphosate salts were divided into the IPA, ammonium, potassium, and mixed salts (Mi) groups according to the salt mixed with glyphosate. The type of salt mixed with glyphosate was identified from the brand name of the ingested herbicides using the toxicological information established in the pesticide safety information system of the Rural Development Administration. The patients who ingested GH formulations containing two or more salts, rather than a single salt such as IPA, etc, were classified as the mixed salts group.

No specific treatment protocol was applied to the GH-intox-

icated patients who visited the hospital during the study period, and each treatment was performed individually according to the judgment of the medical staff in charge of the poisoned patients.

3. Statistical analyses

Nominal data were expressed as frequency and percentages. Continuous or ordinal variables were expressed as median with interquartile range or mean with standard deviation, depending on their normality after the Kolmogorov-Smirnov test. Pearson' s Chi-squared test or Fisher' s exact test for categorical variables and one-way analysis of variance test (Student' s t-test for post-hoc test) or Kruskal-Wallis test (Mann-Whitney U test for post-hoc test) were used to compare the four salt groups depending on the normality test. Regression analysis was performed to determine factors the effect on the in-hospital mortality if there was a statistically significant variable after analyzing the above-mentioned tests. The variables with statistically significant differences between the four groups and the variables with an area under the curve (AUC) of at least 0.8 for in-hospital mortality through the analysis of the receiver operating characteristic (ROC) curve were selected and analyzed for binary logistic regression. All the significant variables from the univariate analysis were used for multiple logistic regression analysis. Among these, some variables seemed to have collinearity, such as pH and bicarbonate, aspartate aminotransferase (AST) and alanine aminotransferase (ALT). These were inputted by only one variable at a time for logistic regression. As a logistic regression method, the Backward Elimination (Wald) was used. A *p*-value of 〈0.05 was considered statistically significant and all statistical analyses were performed with the PASW Statistics ver. 24.0 (IBM Corp., Armonk, NY, USA).

RESULTS

1. Demographics of patients and comparison of laboratory measurements

The total number of patients included in this study was 348 (Fig. 1). Each group of GH-intoxicated patients according to their salt was as follows: IPA Group (248 patients), Am group (41 patients), Po group (10 patients), and Mi group (49 patients). The median age of the four groups was 50 to 60 and the males accounted for more than 60%; these were not significantly different in the groups. In addition, there was no statistical difference related to the underlying diseases of the four groups. In the case of Glasgow Coma Scale (GCS), the median value of the Po group was 12, which was lower than those of the other groups, but there was no statistical significance. blood pressure (BP) and HR (heart rate), among the vital signs, showed a *p*-value of less than 0.05. The Po group had the lowest SBP of 100 (75-120) mmHg and the highest HR of 99 (78.25-111.25) beats/min. But, difference of HR was not statistically significant in the post-hoc analysis. There was no difference in the time from GH ingestion to the ED arrival, the estimated amount of ingestion, and the alcohol co-ingestion. However, the proportion of the main glyphosate component mixed with GH and whether GH was intentionally ingested showed significant differences across the groups. The number of cases of intentional poisoning in the Po and Mi

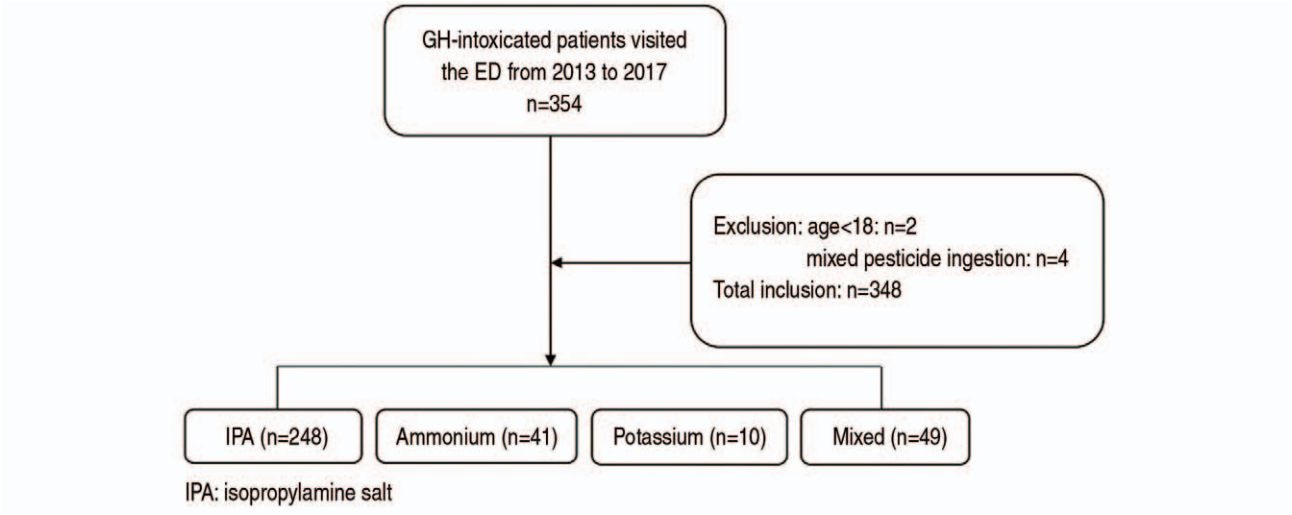

Fig. 1. Study flow diagram, GH (Glyphosate-herbicides), ED (Emergency department)

groups was 8 (80%) and 33 cases (67.3%), respectively, which were higher than those of the other two groups. The proportion of the main component of GH was also lowest than those of the other three groups at 18% (17.57-41%) in the Am group.

In addition, the laboratory blood tests of the four salt groups that showed statistically significant differences were as follows: white blood cell count (WBC, $p<0.001$), hematocrit (Hct, $p=0.001$), blood urea nitrogen (BUN, $p=0.043$), albumin ($p=0.031$), aspartate aminotransferase (AST, $p=0.007$), alanine aminotransferase (ALT, $p=0.004$), total bilirubin ($p=0.025$), potassium (K^+, $p<0.001$), pH ($p=0.019$), partial pressure of carbon dioxide (pCO_2, $p=0.007$), bicarbonate (HCO_3^-, $p=0.002$), and lactate ($p=0.008$). Among these variables, the values of K^+, pH, HCO3, and lactate are particularly noteworthy. These values showed high K^+, low pH, low HCO3, and high lactate tendencies in the po group, and relatively high pH, high HCO3, and low lactate level in the Mi group. There were no statistically significant differences in the other blood test variables across the four groups. In the case of serum ammonia level, the median value of the Am group was 21.5 mmol/L, which showed a higher trend compared to the other three groups. There were no differences between the four groups related to the use of gastric lavage and activated charcoal. All detailed numerical values and *p*-values for the above-mentioned variables are provided in Table 1.

2. Comparison of clinical courses between the four salts groups

The total number of deaths observed was 30, and the in-hospital mortality rate for GH poisoning in this study was 8.6%. Among the four groups, the Mi group had the lowest mortality rate (1 patient; 2%). The other groups had the following mortality rates: 26 patients (10.5%) in the IPA group, 2 patients (4.9%) in the Am group, and 1 patient (10%) in the Po group. However, the difference was not statistically significant ($p=0.177$). The *p*-values for the mortality rates of the groups are as follows: IPA vs. Am ($p=0.394$), IPA vs. Po ($p=0.978$), IPA vs. Mi ($p=0.061$), Am vs. Po ($p=0.488$), Am vs. Mi ($p=0.59$), and Po vs. Mi group ($p=0.313$).

In addition, there were no significant differences in the incidence of pneumonia, rhabdomyolysis, acute renal injury, complications of respiratory failure, the frequency of hemodialysis and application of intralipid emulsion (ILE) infusion. However, the median durations of stay in the ICU and VFD were statistically different: IPA, 2 (1-3), 0 (0-8.25); Am, 2 (1-4.75), 9 (3-20.25); Po, 3 (3-6), 4 (2-33.5); and Mi group, 2 (2-4), 5 (3-12) days, respectively ($p=0.042$, $p=0.018$). But, among these, the only *p*-values that were statistically significant were 0.014 for the comparison of the IPA and Po groups in case of ICU stay and 0.01 for the comparison of the IPA and Am groups in case of VFD.

3. Binary multiple logistic regression analyses for the mortality

To verify the factors affecting in-hospital mortality, we subdivided the patient group into non-survivor (30 patients) and survivor (318 patients) groups and performed the same analysis as in the previous paragraph. The variables with significant *p*-values below 0.05 were obtained from the demographic and laboratory test results. ROC curves were drawn for the variables showing statistical differences for each group. Thereafter, the variables with AUC values of 0.8 or higher that increase the predictability of mortality include the following: age (0.804), SBP (0.857), GCS (0.832), creatinine (0.841), amylase (0.856), pH (0.925), HCO_3^- (0.801), lactate (0.832), and ventilator-free days (0.811).

The variables with *p*-values of <0.05 in the univariate logistic regression analysis were as follows: age ($p=0.001$), SBP ($p<0.001$), GCS ($p<0.001$), Cr ($p=0.005$), pH ($p<0.001$), HCO_3^- ($p<0.001$), lactate ($p<0.001$), QTc interval ($p<0.001$), VFD ($p=0.007$), respiratory failure ($p<0.001$), pneumonia ($p<0.001$), AKI ($p<0.001$), and rhabdomyolysis ($p<0.001$).

In addition, the *p*-value for each type of salts, which was the main variable in this study, was 0.282 in the univariate regression analysis. The univariate logistic regression analysis of the four groups was performed for various complications other than the mortality, and the *p*-values for the complications were as follows: respiratory failure ($p=0.764$), pneumonia ($p=0.628$), AKI ($p=0.321$), and rhabdomyolysis ($p=0.465$). Eventually, the clinical courses according to the salts group in the GH-poisoned patients did not affect their complications and in-hospital mortality.

The univariate logistic regression analyses showed that age, initial GCS, SBP, Cr, pH, HCO_3^-, lactate, QTc interval, VFD, complications of respiratory failure, pneumonia, AKI, and rhabdomyolysis were significant variables. Also, since there was no standardized protocol for the treatment of GH poisoning, specific treatments such as hemodialysis (HD) or ILE infusion were performed at the discretion of the attending physician. Therefore, we used these two treatment modalities to analyze the regression model as its variables. However, the analysis showed no effect on the mortality applying these two treat-

Table 1. Characteristics and laboratory findings of glyphosate-poisoned patients group according to the salts

Characteristics of the groups	IPA (n=248)	Am (n=41)	Po (n=10)	Mi (n=49)	*p* value
Age (years)	61 (49-72)	57 (47.75-67.75)	53 (48.25-61.25)	55 (44.5-62.5)	0.127
Male	171 (69.2%)	32 (76.2%)	9 (90%)	37 (75.5%)	0.43
Underlying disease					
Hypertension	41 (16.6%)	7 (16.7%)	2 (20%)	16 (32.7%)	0.075
Diabetes mellitus	35 (14.2%)	8 (19%)	1 (10%)	7 (14.3%)	0.845
Other illness	60 (24.3%)	6 (14.3%)	0 (0%)	10 (20.4%)	0.181
Vital signs					
SBP (mmHg)	110 (96-140)	120 (100-142.5)	100 (75-120)	120 (100-140)	*0.041
HR (beats/minute)	84 (72-100)	92 (78.25-100)	99 (78.25-111.25)	78 (67.5-95.5)	*0.044
RR (breaths/minute)	18 (18-20)	18 (18-20)	20 (18-24)	18 (16-20)	0.149
BT (˚C)	36.5 (36-36.8)	36.35 (36-36.73)	36.1 (33.25-36.58)	36.5 (36-36.65)	0.395
GCS	15 (12-15)	15 (14-15)	12 (3-15)	15 (12-15)	0.052
Estimated ingestion time (minutes)	120 (68.25-180)	137.5 (90-214.25)	72 (60-198)	103.5 (60-213.25)	0.336
Amount (ml)					0.392
5	24 (9.7%)	3 (7.3%)	0	5 (10.2%)	
25	42 (16.9%)	9 (22%)	2 (20%)	9 (18.4%)	
100	111 (44.8%)	18 (43.9%)	1 (10%)	19 (38.8%)	
300	71 (28.6%)	11 (26.8%)	7 (70%)	16 (32.7%)	
Intentional poisoning	86 (34.8%)	18 (42.9%)	8 (80%)	33 (67.3%)	*<0.001
Glyphosate percentage	41 (41-41)	18 (17.57-41)	44.75 (44.75-44.75)	39 (30.15-39)	*<0.001
Co-ingestion with alcohol	58 (23.5%)	8 (19%)	4 (40%)	18 (36.7%)	0.117
Gastric lavage	157 (63.6%)	23 (54.8%)	6 (60%)	25 (51%)	0.328
Activated charcoal	200 (81%)	32 (76.2%)	8 (80%)	43 (87.8%)	0.535
Laboratory findings					
WBC (cells/ml)	8,050 (1200-13400)	4,865 (1175-9325)	8,000 (7500-30000)	5,001 (2460-17500)	*<0.001
Hct (%)	40.75 (35.8-44.1)	44.35 (40-46.25)	45 (42.3-45)	42 (36.75-45)	*0.001
Hb (g/dl)	14.4 (12.48-15.6)	14.6 (12.6-15.5)	14.7 (12.6-15.5)	14.7 (12.9-16)	0.708
Platelet (×1,000 cells/ml)	205 (27.1-266.25)	284.5 (22.175-291.25)	263 (237-315)	136.4 (120-240.5)	0.068
BUN (mg/dl)	13.6 (10.4-17)	16.75 (11.85-22.48)	14 (9.5-17.7)	13 (10-17)	*0.043
Cr (mg/dl)	0.9 (0.7-1.2)	0.9 (0.7-1.2)	1.2 (0.75-1.6)	0.9 (0.7-1.1)	0.133
Albumin (g/dl)	4 (3.6-4.4)	4.1 (3.95-4.5)	4.8 (3.75-4.85)	4.15 (3.73-4.48)	*0.031
AST (IU/L)	30.5 (24-44.25)	32.5 (25-47.25)	52 (31-64)	27 (21-36.5)	*0.007
ALT (IU/L)	21.5 (16-33)	22 (16.75-36.5)	39 (29.5-53)	17 (13-24.5)	*0.004
Total bilirubin (mg/dl)	0.7 (0.5-1)	0.9 (0.6-1)	0.7 (0.5-0.85)	0.6 (0.4-0.9)	*0.025
Glucose (mg/dl)	135 (111-180)	145 (110-195)	198 (106-229.5)	127 (112.5-155.5)	0.327
PT (INR)	0.98 (0.92-1.09)	0.98 (0.94-1.06)	0.96 (0.93-1)	0.98 (0.93-1.05)	0.828
aPTT (sec)	26.9 (24.9-30.3)	28.3 (26.1-30.2)	30.25 (27.55-32.9)	27.3 (25.6-31.3)	0.128
Na (mmol/L)	140 (137-143)	140 (137-143)	142 (137-146)	140 (137.3-142.5)	0.765
K (mmol/L)	3.78 (3.41-4.3)	3.8 (3.5-4.6)	6.5 (5.05-7.89)	3.7 (3.55-4.45)	*<0.001
Amylase (IU/L)	113 (68-181)	83.5 (55.25-158.75)	99 (64.5-181)	77 (57-133.5)	0.064
Lipase (IU/L)	41.5 (30-60.75)	33 (23.5-47)	62 (43.5-85.5)	32 (24.25-54.75)	*0.003
CRP (mg/L)	5 (1.29-5.25)	5 (4.25-5.75)	3.5 (0.25-5.75)	5 (2.63-5)	0.617
Ammonia (mmol/L)	10 (10-35)	21.5 (10-37.75)	10 (10-17)	10 (10-33)	0.156
CPK (IU/L)	112 (72-188)	119 (81.5-202)	150 (104.5-279.5)	126 (78-244.5)	0.63
LDH (IU/L)	219.5 (190-282)	266.5 (201-307)	312.5 (213.75-373)	215 (173.5-285)	0.267
CK-MB (ng/ml)	1.9 (1.2-4.1)	2.3 (1.83-3.53)	2.35 (1.35-4.18)	1.65 (1-3.53)	0.304
TnI (ng/ml)	0.01 (0.01-0.02)	0.01 (0-0.02)	0.01 (0-0.03)	0 (0-9.01)	0.13
pH	7.35 (7.27-7.4)	7.33 (7.19-7.4)	7.27 (6.99-7.35)	7.37 (7.31-7.42)	*0.019
PO_2 (mmHg)	87 (70-100)	91 (74.5-99.25)	83 (60.5-94)	84 (72.25-98.5)	0.832
PCO_2 (mmHg)	34 (28-38)	33 (26.75-36)	37 (34-45.5)	37.5 (32-40.75)	*0.007
HCO_3^- (mmol/L)	18.6 (14.7-22.2)	17.6 (13.2-21.85)	14.5 (6.75-22.7)	21.25 (18.65-23.6)	*0.002
Lactate (mmol/L)	3.1 (1.63-5.2)	2.25 (1.3-3.65)	2.9 (2.05-7.35)	2.15 (1.125-4.275)	*0.008

All variables were expressed as median value (interquartile range)

IPA: isopropylamine, Am: ammonium, Po: potassium, Mi: mixed salts, SBP: systolic blood pressure, HR: heart rate, RR: respiratory rate, BT: body temperature, GCS: glasgow coma scale, WBC: white blood cell count, Hct: hematocrit, Hb: hemoglobin, BUN: blood urea nitrogen, Cr: creatinine, AST: aspartate aminotransferase, ALT: alanine aminotransferase, PT: prothrombin time, INR: International Normalized Ratio, aPTT: activated partial thromboplastin time, CRP: C-reactive protein, CPK: creatine phosphokinase, LDH: lactate dehydrogenase, CK-MB: creatine kinase MB isoenzyme, TnI: troponin I

* *p* value<0.05 is statistically significant

ments. Finally, the multiple binary logistic regression showed that age, SBP, pH, QTc interval, and respiratory failure were statistically significant predictors for in-hospital mortality. The characteristics of this regression model were the Hosmer-Lemeshow statistic 0.354 and the Nagelkerke R square 0.838. The odd ratio with 95% confidence interval and the *p*-values for all the other variables are provided in Table 3.

DISCUSSION

In this study, there were no statistical differences in the complications and in-hospital mortality across the IPA, Am, Po, and Mi groups of the GH-intoxication. In addition, the factors that affected the mortality of patients in this study were age, SBP, pH, QTc interval, and respiratory failure complication.

In GH poisoning, it is thought that the toxicity in humans,

Table 2. Complications and outcomes of glyphosate-poisoned patients group according to the salts

Characteristics of the groups	IPA (n=248)	Am (n=41)	Po (n=10)	Mi (n=49)	*p* value
Respiratory failure requiring ventilator care	26 (10.5%)	3 (7.1%)	1 (10%)	3 (6.1%)	0.764
Pneumonia	50 (20.2%)	11 (26.2%)	3 (30%)	9 (18.4%)	0.628
Acute kidney injury	34 (13.8%)	10 (23.8%)	2 (20%)	7 (14.3%)	0.321
Hemodialysis	4 (1.6%)	1 (2.4%)	1 (10%)	2 (4.1%)	0.124
ILE infusion for Tx	34 (13.8%)	10 (23.8%)	2 (20%)	13 (26.5%)	0.071
Rhabdomyolysis	37 (15%)	10 (23.8%)	2 (20%)	8 (16.3%)	0.465
QTc prolongation	45 (18.2%)	2 (4.8%)	2 (20%)	5 (10.2%)	0.073
Total admission length (days)	4 (3-7)	4 (2-5)	5.5 (2.8-7.3)	4 (2.5-6)	0.278
ICU admission length (days)	2 (1-3)	2 (1-4.75)	3 (3-6)	2 (2-4)	*0.042
Ventilator-free days	0 (0-8.25)	9 (3-20.25)	4 (2-33.5)	5 (3-12)	0.018
In-hospital mortality	26 (10.5%)	2 (4.9%)	1 (10%)	1 (2%)	0.177

IPA:isopropylamine,Am:ammonium,Po:potassium,Mi:mixedsalts,QTc: corrected QT, ICU: intensive care unit, ILE: intralipid emulsion, Tx: treatment

* *p* value<0.05 is statistically significant

Table 3. Univariate and multivariate logistic regression analysis for the in-hospital mortality

Predictors of the mortality	Unadjusted OR (95% CI)	*p* value	Adjusted OR (95% CI)	*p* value
Age (years)	1.05 (1.021-1.08)	*0.001	1.079 (1.014-1.148)	*0.017
SBP (mmHg)	0.948 (0.931-0.965)	*<0.001	0.967 (0.939-0.986)	*0.026
GCS	0.751 (0.688-0.82)	*<0.001	1.26 (0.973-1.585)	0.058
Amount of ingestion (ml)	1.002 (1-1.005)	0.065	-	-
Cr (mg/dl)	1.717 (1.18-2.5)	*0.005	1.345 (0.762-2.129)	0.165
Amylase (IU/L)	1.001 (1-1.003)	0.122	-	-
pH	0 (0-0)	*<0.001	0.001 (0-0.021)	*<0.001
HCO_3^- (mmol/L)	0.819 (0.756-0.888)	*<0.001	-	-
Lactate (mmol/L)	1.422 (1.254-1.613)	*<0.001	0.94 (0.749-1.178)	0.523
QTc interval (ms)	1.044 (1.029-1.059)	*<0.001	1.035 (1.026-1.055)	*0.002
Ventilator-free days	0.817 (0.705-0.947)	*0.007	0.889 (0.716-1.104)	0.286
Respiratory failure	22.76 (9.462-46.021)	*<0.001	26.265 (17.789-48.691)	*<0.001
Pneumonia	10 (4.429-22.577)	*<0.001	1.176 (0.798-3.614)	0.235
Acute kidney injury	3.215 (1.013-6.080)	*<0.001	6.143 (0.744-66.943)	0.161
Rhabdomyolysis	18.278 (7.778-42.954)	*<0.001	7.419 (0.651-72.31)	0.175
Hemodialysis	0.904 (0.702-1.191)	0.379	-	-
ILE infusion	0.736 (0.247-2.193)	0.582	0.58 (0.033-10.265)	0.71
Each salt type				
Isopropylamine	Reference	0.282	-	-
Ammonium	0.438 (0.1-1.92)	0.273	-	-
Potassium	0.949 (0.116-7.791)	0.961	-	-
Mixed salts	0.178 (0.024-1.343)	0.094	-	-

SBP: systolic blood pressure, GCS: Glasgow Coma Scale, WBC: white blood cell count, AST: aspartate aminotransferase, Cr: creatinine, QTc: corrected QT, ILE: intralipid emulsion, OR: odds ratio

* *p* value<0.05 is statistically significant

including mammals, is caused by the supplements, such as salt and surfactants, mixed with glyphosate rather than the toxicity of glyphosate itself[3,10]. This has been reported in several studies previously. In this study, the glyphosate proportions of each GHs ranged from 13% to 44%. We determined the effect of the proportion of glyphosate in the GH products on in-hospital mortality. There was no effect on the mortality in the two groups: 41% glyphosate (39.5-41%) of the survivors and 41% glyphosate (38.29-41%) of the non-survivors (p=0.936). In particular, the median glyphosate proportions for the Am and Mi groups were 18% and 39% glyphosate, and these groups recorded 2/41 and 1/49 deaths, respectively. This emphasized that the ratio of glyphosate in their products has little effect on the overall toxicity of the GH.

A few studies have reported the toxicity of surfactants among GH, but its reported toxicity associated with the salt type are relatively scarce. For example, the high toxicity of the POEA surfactant and the surfactant volume have been reported[4,11], whereas, the only study that reported the toxicity associated with the IPA versus ammonium salt was by Moon et al. as far as our authors know[6]. The study found that the cardiovascular complications of the IPA group were greater than those of the ammonium group; the mortality rate was also higher in the IPA group. The mortality of the IPA group was 10.3% (11 deaths/107 patients) in that study, which was close to the 10.5% in this study; however, no mortality was reported in the 40 poisoned patients of the ammonia group in Moon's study. The authors suggested the following were attributed to the greater cardiovascular complications associated with the IPA salt. IPA salt may cause intraventricular conduction disturbance by interfering with the uptake of calcium in myocardial cells in rats and rabbits[12]. The duration of vasopressor administration during shock in the IPA group was longer than that in the ammonia group. In addition, other experimental study has shown that the IPA salt can reduce the mean arterial pressure and cardiac index than glyphosate alone. Also, other study involving mammals also showed that the IPA salt caused vasorelaxation[13]. It was described that the major cardiovascular complications may be higher in the IPA group than in the ammonium group due to these factors.

However, in this study, there were no differences between the clinical complications in the IPA group and the Am group. The Am group in this study comprised 42 participants, and 2 (4.9%) of them died, unlike in the Moon's study. This was distinctly lower than the 26 mortality (10.5%) in the IPA group, but the difference was not statistically significant. In addition, the Po and the Mi groups were analyzed in this study, and there was no significant difference in the in-hospital mortality. However, in the Po group, the total enrolled patients were few (10 patients), and the statistical power would be not adequate to show sufficient clinical results. Although there was also no statistical difference in the Mi group, only one death (2%) occurred in this study, and the toxicity of the Mi group would be considered the lowest on data.

Salt is a substance for increasing water solubility by stabilizing GH, which has a weak acidity because of glyphosate. So, additional herbicidal efficacy was not expected for each salt material. However, contrary to the expectation of low toxicity of GH in humans, the GH containing trimesium (trimethylsufonium) salt showed very high toxicity[5]. However, because there are few studies on the toxicity of salt types, inevitably, we referred to the toxicity of each salt for plants reported so far. In the study reported by Li et al.[14], when IPA and ammonium salt-based GHs were applied to plants, it was showed that the absorption of GH after 2 hours was higher in the IPA groups. However, it was also reported that there was no difference in the overall efficacy of the GHs in plants regardless of this initial absorption difference. In a study comparing IPA, ammonium, and potassium salts in plants, it was reported that IPA had the shortest vaporization time compared with the ammonium and potassium salts[15]. Although this was the result of an experimental study on plants, if the IPA salt has high volatility, the risk of aspiration in human ingested case may be higher for IPA salt than for other salts. That study did not describe the herbicidal efficacy as a plant herbicide, and it was concluded that each composition of GH showed that the interaction with the target plant could be different.

Although the mentioned study results are discrepant, the results suggest that the toxic effect on the human body, just like on plants, may vary depending on the salt type. Although there was no statistical difference, the IPA-related mortality in this study was also the highest, just as the toxicity of IPA was higher than that of ammonium salt in Moon's study. On the other hand, no deaths were reported in the ammonium group in that study; however, it may be possible that the two deaths in this study were within the statistically insignificant range in a relatively small parameter of 42 patients. Conversely, it can be said that no deaths out of 40 patients reported in Moon's study may be within the range of expected deaths considered likely to occur if the population parameters are large. Meanwhile, there was a record that the LD_{50} of the IPA salt in rats was 5000 mg/kg or more, and the LD_{50} of the ammonium salt was 4613 mg/kg, both salts showed very low toxicity[16]. Based on this, the toxicity of the IPA and the Am groups

may be similar or possibly even a little higher for the Am group. Therefore, although this study showed that there was no statistically significant difference among the four salt groups, it seems difficult to deny or confirm the conclusion of Moon' s study that the IPA salt was more toxic than ammonium salt.

Due to the few enrolled patients in the Po group, the mortality rate was close to that of IPA at 10%. However, there is also the possibility that the mortality rate will decrease in the Po group if the parameter increases like as the IPA group. A study reported by Kamijo at al.[17] showed that the poisoned patients with GH-potassium salt had a mortality rate of 7.3% (4 deaths of 55 patients). In the study, accompanying hyperkalemia was also described as one of the reasons for the relatively high mortality. In this study, the K^+ value of the Po group was 6.5 (5.05-7.89) mEq/L, which was significantly higher than that of the other three groups. This was the same finding reported in that study described above. The potassium salt group showed an average K^+ concentration of 6.2 mEq/L. Thus, this elevation of the K^+ concentration externally administered may adversely affect cardiac function and increase the likelihood of fatal arrhythmia. For this reason, there is the possibility of a relatively high toxicity in the Po group. However, as mentioned above, it is necessary to confirm if such high toxicity occurs repeatedly in future studies involving larger samples of GH-potassium salts poisoned patients.

It is difficult to guess why the Mi group had the lowest mortality, but the following may be considered. First, this may be attributed to a lack of statistical power. The number of patients in the Mi group was higher than that in the Po group; however, it was still lower than that in the IPA group. If another patient died in the Mi group, the mortality rate doubled to 4%; this is comparable to the mortality rate of the Am group, which recorded 4.9%. Second, the types and component ratios of the salts in the Mi group could not be confirmed. In the GH with mixed salts, because the proportion of glyphosate was 39%, which was similar that of IPA and Po group, the volume of each salt may be lower than its dosage of single salt mixed with glyphosate. These lower volume of the salt in the Mi group may have accounted for the overall reduction in its toxicity if not considering the possibility of their interaction of salts each other.

The mortality rate of GH intoxication in this study was 8.6%, and it was similar those reported by previous studies[18-20], although some papers have reported lower (3.2%) or higher (13.7%) mortality rates[21,22]. This suggests that the poisoned patients enrolled in this study had common degrees of severity; they were neither mild nor severe. This may mean that the clinical courses of patients in this study may be generalized to other studies.

The predictors of mortality associated with GH poisoning in this study include advanced age, low SBP, low pH, QTc interval prolongation, and respiratory failure complications. The predictors for mortality associated with GH toxicity have been reported in several studies, and they include old age, large ingestion dose, low SBP, altered mental status, hyperkalemia, respiratory distress, prolonged QTc interval, high lactate level, metabolic acidosis, and elevated creatinine concentrations etc[7,19,23-26]. These are relatively comparable to the mortality predictors determined in this study. Although their statistical significance was lost in the multivariate regression analysis, GCS, Cr, and the lactate concentration, which were significant during the univariate analysis in this study, are consistent. In acute poisoning by some toxic materials, the intrinsic factors of the exposed patients are also important, so old age for severity predictor has been reported in several studies. In case of the ingestion doses, those of the survivor and non-survivor groups were significantly different (p=0.004) in this study, but the univariate analysis showed no significance. However, considering that it is difficult to accurately measure the volume of ingested toxic material in a toxicologic study, it can be inferred that the ingestion dose is related to the toxicity of GH, but the statistical significance may vary depending on the data of each study. The low SBP and altered mental status, metabolic acidosis, high lactate, and elevated creatinine, as mortality predictors, may be interrelated and have a causal relationship. First, low BP may be due to the direct cardiovascular toxicity of GH[12,27]. Then, due to the low perfusion caused by hypotension, a change in mental status occurred decreasing in cerebral blood flow, and lactic acidosis via tissue ischemia also occurred, which may have led to AKI, metabolic acidosis, and hyperkalemia consecutively. In addition, these may eventually lead to respiratory failure requiring mechanical ventilation, as shown in this study. However, in case of AKI, together with the indirect effects of low BP, the GH also showed direct nephrotoxicity[28]. In addition, there were also case reports of aseptic meningitis and reversible encephalopathy after GH intoxication, and there is a possibility that direct neurotoxicity of GH may result in altered mental status[29,30]. To put it all together, several predictors of mortality in this study were common, and they were consistent with those in previous studies.

There were some limitations to this study. First, this study was a retrospective study, and treatment was performed indi-

vidually for the GH-poisoned patients. As a result, mortality may vary from patient to patient. However, there is no specific treatment for GH intoxication, and the bias is thought to be limited. Second, since the accurate ingestion dose of the GH was not directly measured, there may be a bias associated with their actual poisoning dosage. Also, in case of estimating the ingestion dose of GH, patient's vomiting was not considered. Patients may vomit immediately after ingestion of poisonous substances, or may vomit over time, possibly resulting in less GH ingestion than initially estimated ingestion dosage. However, since it is clinically difficult to confirm the amount of GH removal due to vomiting, it would be the inevitable error factor in estimating the ingestion dose to some extent. Third, the types of GH salt were classified according to the testimonies of the patients, guardians, witnesses or information on the herbicide bottles. Therefore, the brand name of the toxic product may have been misleading if the patient ingest herbicide in bottle of contained other pesticides. However, this may be a common limitation of most studies for GH-intoxications because it is judged that there are still very limited facilities for laboratory testing to confirm the ingredients of a GH and their classifications. Fourth, there were fewer poisoned patients in the Am group than in the IPA group, and the statistical power may have been insufficient. In particular, the number of poisoned patients in the Po group was low, so, it is possible that their clinical characteristics were not reflected properly. Fifth, although patients who co-ingested alcohol were included in the study, the serum ethanol concentration could not be measured directly. The effect of co-ingesting the GH with alcohol on the toxic effect of GH has not been established; however, the inability to measure the serum concentration may make it difficult to accurately analyze its contribution to toxicity. But, in this study, the mortality rates of the survivor and non-survivor groups, as well as the salt groups, did not differ with co-ingesting GH with alcohol. Lastly, the individual proportions of the salts could not be determined in the Mi group, which had the lowest in-hospital mortality rate although this was not statistically significant. Due to this limitation, it was not possible to clearly explain the low mortality rate in the Mi group by dividing each salt.

CONCLUSION

In conclusion, the clinical courses associated with each of salt types in the GH intoxication were not significantly different. Further studies are needed to confirm this finding. It will also be necessary to determine the most toxic components of GH in the future.

ORCID

Dong Woo Lee (https://orcid.org/0000-0002-4571-9137)
Jeong Min Gyu (https://orcid.org/0000-0003-0762-3211)

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