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# 응급실 초기에 다량의 글라이포세이트 중독과 관련된 예측인자: QTc 간격 연장

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# Predicting Factors Associated with Large Amounts of Glyphosate Intoxication in the Early-Stage Emergency Department: QTc Interval Prolongation

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**Purpose**: Taking large amounts of glyphosate is life-threatening, but the amounts of glyphosate taken by patients for suicide are not known precisely. The purpose of this study was to find the predictors of large amounts of glyphosate ingestion.
**Methods**: This retrospective study analyzed patients presenting to an emergency department with glyphosate intoxication between 2010 and 2019, in a single tertiary hospital. The variables associated with the intake amounts were investigated. The parameters were analyzed by multivariate variate logistic regression analyses and the receiver operating characteristic (ROC) curve.
**Results**: Of the 28 patients with glyphosate intoxication, 15 (53.6%) were in the large amounts group. Univariate analysis showed that metabolic acidosis, lactic acid, and corrected QT (QTc) interval were significant factors. In contrast, multivariate analysis presented the QTc interval as the only independent factor with intoxication from large amounts of glyphosate. (odds ratio, 95% confidence interval: 1.073, 1.011-1.139; $p$=0.020) The area under the ROC curve of the QTc interval was 0.838.
**Conclusion**: The QTc interval is associated significantly with patients who visit the emergency department after being intoxicated by large amounts of glyphosate. These conclusions will help in the initial triage of patients with glyphosate intoxication.

**Key Words**: Glyphosate, Emergencies, Herbicides, Triage

## INTRODUCTION

Suicide is a major public health problem, and the annual global age-standardized suicide rate was 10.5 per 100,000 in 2016[1]. In South Korea, it is a more serious problem, with the standardized suicide rate of 23.0 in 2017, the second-highest among OECD countries, and the fifth leading cause of death in South Korea in 2018[2,3]. In South Korea, more than half of the suicide methods were intoxication and 18% of attempted suicides through poisoning were attempted with pesticides[4,5].

Glyphosate is the most commonly used low-toxicity pesticide in the world these days[6]. However, if a large dose of glyphosate is taken for suicide, it is known that the mortality rate is 8 to 16% although there are some differences depending on the doses and the character of the patient[7]. Factors associated with mortality and severity in glyphosate poisoning patients are age, intake amount, vital signs, metabolic acidosis, hyperkalemia, QT interval, renal function, elapsed time, and lactate[8-11]. But, it is often difficult to know about the amount of intake glyphosate which is most important factor

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of severity, for many patients visits emergency department (ED) with confused mentality with alcohol ingestion or refuses to talk about intake volume.

In this study, we tried to identify factors predicting the amount of intake glyphosate in patients who attempt suicide including the characteristics at the time of presentation to the ED.

## STUDY DESIGN AND SEARCH STRATEGY

In this retrospective study, all adult glyphosate intoxication patients (aged≥18 years) were included, who visited an ED at the tertiary medical center from January 1, 2010, to December 31, 2019. We used the hospital's electronic medical record system to obtain medical records of patients who were candidates for study. The study protocol was approved by the Institutional Review Board (DSMC 2020-07-058) and exempted from prior consent requirements due to the retrospective nature of the study. Patients who took other pesticides and overdose-medication or unknown glyphosate amounts were excluded. Glyphosate was known to be the less toxic in does of 5000 mg/kg body weight or less when ingested orally[7]. When the average adult body weight was 60 kg, it was possible to classify the approximate severity of toxicity based on the intake of 300 g. Patients were categorized into large and small amount groups based on glyphosate intake amounts of 300 ml.

Demographic and clinical characteristics, including age, sex, comorbid diseases, mental change, vital signs, laboratory, ECG (electrocardiogram) findings were retrieved. It was confirmed whether continuous renal replacement therapy (CRRT) or ventilator was applied, and the sequential organ failure assessment (SOFA) score was calculated. Other variables related to the glyphosate ingestion event about the intake amount of glyphosate, the elapsed time from glyphosate ingestion to arrival at the ED, and co-ingestion of alcohol were obtained.

## STATISTICAL ANALYSIS

Continuous variables were reported as mean±standard deviation (SD) or median and inter-quartile range (IQR), with parametric data compared using Student's t-tests and non-parametric using the Mann-Whitney U test. Categorical variables were reported as number (percentage) and compared using the $\chi^2$ test with Yates correction or the Fisher's exact test, as warranted. Variables with statistical significance were tested by binary logistic regression analysis, and its odds ratio (OR) and 95% confidence interval (CI) were calculated. The area under curve (AUC) value, optimal cutoff value, sensitivity, and specificity were determined using receiver operating characteristic (ROC) curve. All statistical analyses were performed using SPSS 21 (SPSS IBM, Chicago, Illinois, USA), with a two-sided P-value〈0.05 considered statistically significant.

## RESULTS

During the study period, 43 patients visited the tertiary medical center emergency department (ED) due to glyphosate intoxication. After excluding 15 patients by predetermined criteria, 28 patients were enrolled. Patients were divided into two groups based on the median ingestion value 300 ml. One group was thirteen patients with a small amount ingestion group (46.4%) and the other was fifteen patients with a large amount ingestion group (53.6%) (Fig. 1).

Total glyphosate intoxication patients including 18 (64.3%) men and 10 (35.7%) women of the mean age 64 years (range 51-77 years) were analyzed. A change in consciousness was observed in 11 patients (39.3%), and seven patients (25.0%) were taking alcohol together. The 28-day mortality rate was 14.3%, with 4 of the total patients. Leukocytosis (white blood cell, median, 15200/㎕, IQR, 8900-19200) was observed, lactate (2.5 mmol/L, 1.3-4.7 mmol/L) increased, and pH (7.39, 7.29-7.47) and $HCO_3$ (18.5 mmol/L, 15.7-22.8 mmol/L) decreased (Table 1).

On comparison of small and large amount glyphosate ingestion groups, the large ingestion group depicted lower $HCO_3$ levels (median, 20.0 mmol/L vs 16.5 mmol/L, $p$=0.039), whereas depicted higher creatinine (1.00 mg/dL vs 1.30 mg/dL, $p$=0.050), higher lactate level (1.4 mmol/L vs 3.9 mmol/L, $p$=0.006) and higher sequential organ failure assessment (SOFA) score (1 vs 2, $p$=0.037). ECG findings also showed that QTc (corrected QT interval) was longer in the large amounts intake group, significantly. (435 ms vs 480 ms, $p$=0.002) Multivariate analysis was performed by backward elimination and applying factors such as lactic acid, QTc interval, and $HCO_3$ that adjusted by a $p$-value of 0.1 or less, and age, sex and SOFA score which are basic patient factors. Prolonged QTc (OR 1.073, 95% CI: 1.011-1.139, $p$=0.020) was factors associated significantly with the prediction of the large amounts glyphosate ingestion (Table 2). Using the receiver operating characteristic curve, the area under the curve (AUC) representing QTc interval was 0.838 (95% CI: 0.685-992, $p$=0.002) (Fig.

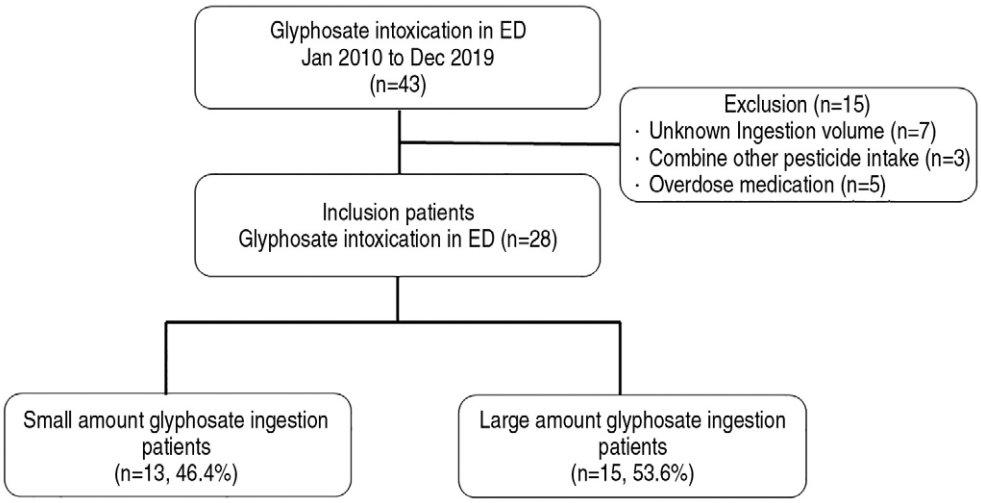


**Fig. 1.** Flowchart of the study patients. ED: emergency department

2 and Table 3).

## DISCUSSION

This study was performed to evaluate the factors that associated with the intake amount in patients who took glyphosate for suicide. Eleven of the patients (39.3%) who took glyphosate had a change in consciousness, and seven patients took alcohol together, accounting for a quarter of the total patients. The SOFA score, which is an index of patient severity, was found to be significantly higher in patients who took large amounts[12]. The glyphosate intake amount is highly related to the severity, which means that it is important to know the amount in the early stage[11,13]. But if communication with the patient is restricted due to unconsciousness or uncooperativity, we will need some tools to know the dosage[11,13]. We found that QTc was prolonged in large amount glyphosate intake patients and the cutoff value was 463.5 ms, AUC 0.838, sensitivity 73.3 specificity 84.6.

There have been many reports of cardiovascular-related side effects which include tachycardia, bradycardia, hypotension, and various changes in ECG[13,14]. The QTc interval prolongation was the most representative ECG presented in patients with glyphosate intoxication, which was associated with the development of various complications as well as mortality[8,15]. QT prolongation is known for dangerous rhythms that can cause sudden cardiac death-arrhythmias like Torsades de pointes, which can bring a poor prognosis with or without previous heart disease[16,17]. According to the American College of Cardiology, a QTc-interval higher than 450 ms in males and higher than 460 ms in females is defined as prolonged[18]. Our findings show that 463.5 ms appears as a cutoff value for predicting the large amount to be taken, and it appears that 480 ms in the large amounts intake group. This is included within the prolongation definition of QTc, and then which will be an important index for the initial evaluation glyphosate intoxication amount.

Although there are various causes of elevated lactate, most are known to be mediated by anaerobic mechanisms due to tissue hypoperfusion and hypoxia[19]. Clinically, elevated lactate is widely used for diagnosis and prognosis evaluation of various diseases such as shock, post-cardiac arrest, regional tissue ischemia, mitochondrial disease, and drugs/toxins[19]. However, studies evaluating lactic acid in patients who took glyphosate are still insufficient, and the only one article was found that lactic acid was associated with 30-day mortality[11]. In this study, lactic acid showed a prominent elevation in the group that took large amount glyphosate, but no definite hypoxia or shock was observed. It is estimated that glyphosate acts as an independent factor that causes an increase in lactate due to cellular toxicity. Usually available as a mixture with glyphosate and surfactants, such products induce mitochondrial apoptosis and necrosis leading to cell death[20]. Mitochondrial damage occurs by reduced oxidative phosphorylation. That reduces adenosine triphosphate synthesis and increases NADH reoxidation[21]. As a result, pyruvate is accumulated but pyruvate dehydrogenase is blocked, the Krebs cycle, which is an aerobic pathway, is not activated, and lactic acid is increased in the activation of the anaerobic pathway[22].

Metabolic acidosis is known to be the most common complication, even though its definition is inconsistent[9-11]. Metabolic acidosis with pH〈7.35 was present in this study

**Table 1.** Demographic and clinical characteristics of the glyphosate intoxication patients divided by intake amount

| Character | Total | Small (n=13) | Large (n=15) | *p*-value |
|---|---|---|---|---|
| Age (years) | 64 (51-77) | 67 (51-83) | 63 (50-73) | 0.273 |
| Sex, male | 18 (64.3) | 8 (61.5) | 10 (66.7) | 0.544 |
| Previous illness | | | | |
| Hypertension | 7 (25.0) | 2 (15.4) | 5 (33.3) | 0.258 |
| Diabetes | 9 (32.1) | 3 (23.1) | 6 (40.0) | 0.293 |
| Chronic kidney disease | 1 (3.6) | 0 (0) | 1 (6.7) | 0.536 |
| History of MI | 2 (7.1) | 0 (0) | 2 (13.3) | 0.278 |
| History of CVA | 2 (7.1) | 1 (7.7) | 1 (6.7) | 0.722 |
| Psychiatric disease | 5 (17.9) | 1 (7.7) | 4 (26.7) | 0.211 |
| Oncology disease | 4 (14.3) | 2 (15.4) | 2 (13.3) | 0.644 |
| Vital sign | | | | |
| SBP (mmHg) | 130 (110-140) | 140 (125-152) | 120 (100-140) | 0.040 |
| DBP (mmHg) | 80 (70-90) | 80 (70-98) | 80 (68-90) | 0.209 |
| Pulse rate (per minute) | 87 (82-106) | 96 (76-105) | 86 (83-108) | 0.401 |
| Body temperature (˚C) | 36.5 (36.0-37.2) | 36.5 (36.3-37.2) | 36.2 (36.0-37.2) | 0.138 |
| $O_2$ saturation | 98 (96-100) | 100 (93-100) | 97 (96-100) | 0.279 |
| Laboratory finding | | | | |
| WBC (×1000/㎕) | 15.2 (8.9-19.2) | 15.2 (7.9-19.1) | 15.2 (9.6-19.8) | 0.342 |
| Platelet (×1000/㎕) | 261 (207-287) | 254 (206-281) | 265 (207-293) | 0.363 |
| Hemoglobin (g/dL) | 13.8 (12.5-15.1) | 13.8 (12.7-15.7) | 13.7 (12.1-14.9) | 0.321 |
| Sodium (mmol/L) | 141 (138-144) | 140 (139-143) | 141 (135-146) | 0.345 |
| Potassium (mmol/L) | 4.1 (3.6-4.9) | 4.1 (3.8-4.5) | 4.2 (3.5-5.3) | 0.305 |
| Chloride (mmol/L) | 103 (99-107) | 105 (102-107) | 103 (98-108) | 0.243 |
| BUN (mg/dL) | 17 (13-27) | 17 (13-26) | 17 (13-27) | 0.486 |
| Creatinine (mg/dL) | 1.19 (0.95-1.50) | 1.00 (0.78-1.45) | 1.30 (1.06-1.50) | 0.050 |
| AST (U/L) | 29 (23-39) | 31 (22-39) | 27 (24-37) | 0.397 |
| ALT (U/L) | 22 (12-34) | 22 (12-27) | 20 (12-36) | 0.424 |
| Albumin (g/dL) | 4.3 (4.0-4.6) | 4.3 (3.9-4.6) | 4.2 (4.0-4.6) | 0.329 |
| Glucose (mg/dL) | 185 (119-226) | 132 (106-213) | 188 (136-239) | 0.137 |
| Total bilirubin (mg/dL) | 0.65 (0.40-1.02) | 0.70 (0.43-1.25) | 0.44 (0.31-0.74) | 0.102 |
| PT (INR) | 1.02 (0.95-1.09) | 0.99 (0.92-1.08) | 1.03 (0.96-1.12) | 0.152 |
| APTT (sec) | 24.4 (22.9-29.8) | 24.9 (23.3-31.5) | 24.2 (22.1-28.5) | 0.167 |
| CRP (mg/dL) | 0.4 (0.1-3.3) | 1.0 (0.1-11.5) | 0.4 (0.1-0.9) | 0.379 |
| CK-MB (㎍/mL) | 1.4 (0.6-2.9) | 1.6 (0.6-3.1) | 1.0 (0.5-2.3) | 0.227 |
| Troponin I (ng/mL) | 0.04 (0.03-0.16) | 0.05 (0.04-0.16) | 0.04 (0.02-0.12) | 0.148 |
| CPK (U/L) | 98 (68-183) | 91 (66-207) | 100 (67-165) | 0.487 |
| ABGA | | | | |
| pH | 7.39 (7.29-7.47) | 7.41 (7.32-7.48) | 7.34 (7.21-7.47) | 0.127 |
| $PCO_2$ (mmHg) | 31.6 (26.1-36.2) | 31.7 (30.0-37.4) | 31.0 (23.3-33.0) | 0.155 |
| $PaO_2$ (mmHg) | 82.1 (64.0-107.4) | 69.8 (63.0-89.5) | 86.5 (67.0-114.0) | 0.115 |
| $HCO_3$ (mmol/L) | 18.5 (15.7-22.8) | 20.0 (16.2-24.0) | 16.5 (14.8-19.4) | 0.039 |
| $SaO_2$ (%) | 95.9 (92.5-97.8) | 94.5 (92.7-97.0) | 97.0 (91.9-98.3) | 0.172 |
| Lactic acid (mmol/L) | 2.5 (1.3-4.7) | 1.4 (0.9-2.5) | 3.9 (2.6-6.4) | 0.006 |
| SOFA score | 2 (1-4) | 1 (1-3) | 2 (2-5) | 0.037 |
| CRRT | 1 (3.6) | 0 (0) | 1 (6.7) | 0.536 |
| Ventilator | 9 (32.1) | 4 (30.8) | 5 (33.3) | 0.604 |
| Mental change | 11 (39.3) | 3 (23.1) | 8 (53.3) | 0.106 |
| QTc interval (ms) | 459 (434-485) | 435 (416-459) | 480 (459-497) | 0.002 |
| Alcohol intake | 7 (25.0) | 3 (23.1) | 4 (26.7) | 0.588 |
| Ingestion amount (mL) | 300 (150-300) | 150 (75-150) | 300 (300-500) | <0.001 |
| Elapsed time (minute) | 183 (91-542) | 189 (134-764) | 131 (61-480) | 0.182 |
| 28-day mortality | 4 (14.3) | 2 (15.4) | 2 (13.3) | 0.928 |

MI: myocardial infarction, CVA: cerebrovascular accident, SBP: systolic blood pressure, DBP: diastolic blood pressure, WBC: white blood cell, BUN: blood urea nitrogen, AST: aspartate transaminase, ALT: alanine transaminase, PT: prothrombin time, APTT: activated partial thromboplastin time, CRP: C-reactive protein, CPK: creatinine phosphokinase, ABGA: arterial blood gas analysis, SOFA: sequential organ failure assessment, CRRT: continuous renal replacement therapy, QTc: corrected QT interval

**Table 2.** Multivariate logistic regression analysis of factors predicting large amount glyphosate intake

| | Odds Ratio | 95% confidence interval | *p*-value |
|---|---|---|---|
| QTc interval (ms) | 1.073 | 1.011-1.139 | 0.020 |

QTc: corrected QT interval

**Table 3.** Prediction value of QTc interval for large amount glyphosate ingestion

| | AUC | CI 95% | *p*-value | Optimal cutoff value | Specificity | Sensitivity |
|---|---|---|---|---|---|---|
| QTc interval | 0.838 | 0.685-0.992 | 0.002 | 463.5 | 84.6 | 73.3 |

QTc: corrected QT interval, AUC: area under curve, CI: confidence interval

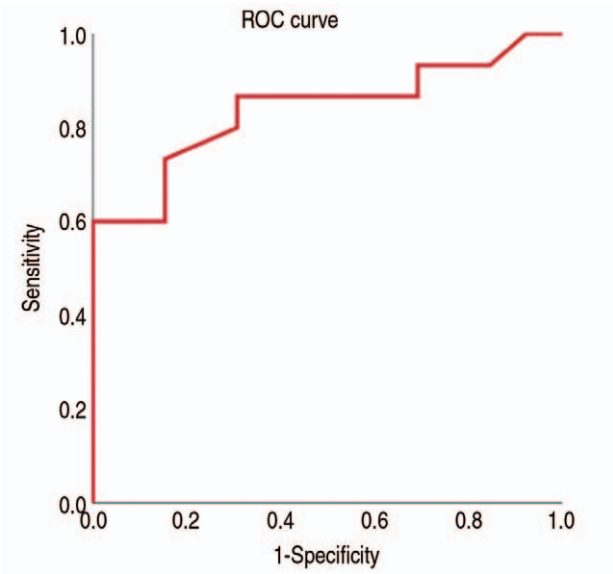


**Fig. 2.** Receiver operating characteristic curve (ROC) for prediction of large amount glyphosate intoxication based on the QTc prolongation.

in 13 patients, which was about half of total patients. The pathophysiology of metabolic acidosis has not yet been clarified and may require additional research. Hyperkalemia is also known to occur frequently in glyphosate patients[10,13]. It was generated by the shift of potassium outward of cells as metabolic acidosis progresses[23]. In this study, there were 7 patients with hyperkalemia, accounting for a quarter of the total.

Nephrotoxicity is a fatal complication in a glyphosate intoxication patient[13]. Menkes et al confirmed acute renal tubular necrosis via postmortem specimens from a patient who took glyphosate for suicide[24]. Glyphosate concentrations were higher in the kidneys than in any other organs such as the brain, liver, and blood[24]. In this study, creatinine increased significantly in patients with large amounts of glyphosate intoxication, and it is considered that it can be used as an important predictor for prognostic evaluation.

Respiratory failure was also observed to be a complication such as aspiration pneumonia or upper respiratory injury, often requiring tracheal intubation and mechanical ventilation[10,11,13]. There was a change in consciousness in a large number of patients who took glyphosate for the purpose of suicide, regardless of the amount, and nausea and vomiting were frequently accompanied together, which causes aspiration[13]. In this study as well, 11 patients (39.3%) had a change in consciousness and 9 patients (32.1%) needed mechanical ventilation. There was no difference depending on the intake amount.

This study had several limitations. First, the study was of single center retrospective design and included a relatively small patient sample. Second, only the initial condition of the patient was evaluated, and analysis of the progress and long-term outcome was not performed. Third, the diagnosis of glyphosate intoxication was not confirmed by laboratory test, only judged through the patient, guardian, or the rescue team statement[25,26]. Fourth, in this study, the standard for intoxication of a large amount was set to 300 ml, but there is a discussion about the amount of high risk on other studies. It also does not take into account the patient' s weight and does not consider any errors that could occur as a conversion of mass values to volume values[7-9].

In conclusion, a large amount of glyphosate intake has a poor prognosis. QTc interval is a good predictor of amount of intake glyphosate in initial evaluation at ED. These results will help in faster, more accurate triage and appropriate treatment accordingly in patients with glyphosate intoxication.

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