

Clinical Study of Gamdutang Complex Formula on Patients of Acute Renal Failure due to Paraquat Intoxication

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Paraquat, one of the potent herbicides, causes fatal damage to many vital organs, when orally ingested, resulting in circulatory failure, respiratory distress syndrome, and a few other serious problems, but there is no known specific antidote against it. Of the possible problems related to paraquat intoxication, oliguric acute renal failure, which has been known to develop within 24 or 48 hours after intoxication, are notoriously life-threatening. So we attempted to investigate the clinical characteristics and progress of paraquat-induced acute renal failure and the therapeutic possibilities of herbal medicines. All of the fifteen subjects were treated with intravenous fluid injection of 5% dextrose saline or 10% dextrose water in conjunction with herbal medicines which were used for oral administration or gargling. Gamdutang, a decoction of Semen Glycin(黑豆 200g) and Radix Glycyrrhizae(甘草 100g) with addition of other herbs when necessary, was administered orally. At the same time, gargling fluid, consisted of Chinese ink(墨汁), char-frying powder of Rhei Rhizoma(大黃炒炭末), Succus phyllostachyos(竹瀝), was used to detoxify the oral cavity. Serum levels of Blood Urea Nitrogen(BUN) and Creatinine reached its peak on the third day of hospitalization, but then decreased and fell within the normal range on the 7th day and remained there. Serum levels of Na⁺ and K⁺ decreased down below the lower limits of normal range on the 7th day and on the 3rd day, respectively. Then they returned back within normal limits. Mean urine output on the 1st day of hospitalization was 1,050ml and it continuously increased to reach more than 2,000ml on the 14th day. From that day on, it stayed over 2,000ml. Fifteen cases of acute renal failure caused by paraquat intoxication were treated with combined treatments of oriental and western medicine in our hospital. However, we think that it is necessary to study further about the way to combine oriental and western medicine, to find out a more effective treatment method.

Key words : Gamdu-tang(甘豆湯), paraquat, Acute Renal Failure(ARF), Glycin(黑豆), Radix Glycyrrhizae(甘草), Chinese ink(墨汁), Char-frying powder of Rhei Rhizoma(大黃炒炭末), Succus Phyllostachyos(竹瀝)

Introduction

Paraquat is one of very potent herbicides which can lead to a fatal result when ingested and there is no specific antidote against it. It induces acute renal failure, hepatic dysfunction and progressive respiratory failure with high mortality rate. Clinical investigation and medical treatment were carried out on fifteen cases of patients with acute renal failure caused by paraquat intoxication who were admitted to the department of internal medicine, cheonju oriental medical hospital of wonkwang university. Commonly used agricultural chemicals in south korea in these days are organic phosphates, chlorinated organic insecticides, heavy metal salts, carbamate,

and germicides such as organic mercury fungicides, herbicides, and rodenticides. Chemical poisoning due to the use of these agricultural chemicals is one of the serious social problems in south korea¹⁾. Paraquat(1,1'-dimethyl 4,4'-bipyridylum dichloride : Gramoxone[®]) was developed in England in 1958. In south korea, it has been one of the frequently used herbicides since 1970s. Paraquat intoxication has a high mortality rate. Ingestion of paraquat in a very little amount in cases of suicidal attempts or negligence would cause many symptoms of intoxication, mainly involving gastrointestinal tract, lung, kidneys, liver, and central nervous system(CNS)^{2,3)}. It may specifically damage the epithelial lining of proximal tubules of nephrons of kidneys, causing a reversible acute renal failure which could be very fatal⁴⁾. The present methods of treatment of paraquat intoxication involve induced vomiting and gastric lavage immediately after ingestion, followed by administration of absorbents, such as fuller's earth, to reduce the amount of

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paraquat or to inactivate paraquat in gastrointestinal tract system. In addition, to eliminate paraquat in blood circulatory system, potent diuretics, dialysis, or charcoal hemoperfusion are used^{5,6}. However, the mortality rate of patients with paraquat intoxication remains very high. This study was carried out at cheonju oriental medical hospital of wonkwang university with fifteen patients with paraquat intoxication who developed acute renal failure. During the treatment, both oriental and western therapeutic modalities were employed. In addition to above mentioned methods, administration of diuretics and fluid therapy of western method were included. Oriental method contained oral administration of Gamdutang, Chinese ink, char-frying powder of Rhei Rhizoma. From this clinical observation, it is found to be effective to combine treatment method from both oriental and western medicine in treating acute renal failure due to paraquat intoxication.

Subjects and Methods, Treatment

1. Subjects

Fifteen subjects were selected from the patients admitted to cheonju oriental medical hospital of wonkwang university due to paraquat intoxication from June 1993 to May 2001, who developed acute renal failure and survived after treatments. The average time taken in arrival to hospital from the onset was 16.00 ± 3.74 hours and mean volume taken was 11.60 ± 3.37 ml. Nine cases were males and six cases were females with average age of 22.14 ± 2.41 years old (Table 1).

Table 1. Characteristic of Subjects

| Sex | male | 9 |
|--------------------|------------------|---|
| | female | 6 |
| Age(year) | 22.14 ± 2.41 | |
| Amount(ml) | 11.60 ± 3.37 | |
| Arrival time(hour) | 16.00 ± 3.74 | |

2. Methods

Once patients arrived hospital, we initially carried out urine test, blood test, X-ray, EKG, abdominal ultrasound and gastrofiberscopy after thorough history taking and physical examinations. During hospitalization, we examined serum BUN/Creatinine, sodium and potassium levels subsequently on 1st, 3rd, 7th, 14th, 21th, 28th day for close observing renal function, electrolytes and fluid balances. And we tried to keep balance between oral and parenteral intakes and outputs of urine and feces on daily basis.

3. Treatment

All fifteen patients were transferred from other hospitals,

which they first visited, after emergency-therapies such as gastric lavage and hemodialysis being done. And we started immediate oral and parenteral administrations based on above-mentioned examinations. Oral medications included two oriental herbal medicines; first, Gamdutang, a decoction of Semen Glycin(黑豆) 200g and Radix Glycyrrhizae(甘草) 100g, in some cases, with addition of Junci Medulla(燈心), Stigmata Maydis(玉蜀黍), Rhei Rhizoma(大黃). They were decocted with 3000ml of water until 2000ml of solution was collected. This was packed into 200ml pouchs which was administered orally more than three times a day. Second, gargling fluid consisted of 200ml of Gamdutang, 37.5g char-frying powder of Rhei Rhizoma(大黃炒炭末), and 10ml of Succus phyllostachyos(竹瀝). Patients were advice to gargle with this fluid as frequently as possible and generally about one to two liters were used a day. At the same time 5% dextrose saline and 10% dextrose water, or mixed with KCL or NaCl were administered intravenously and sometimes diuretics (furosemide) were added if needed to keep the urine output more than 1000ml a day.

Result

1. Symptoms and signs

Initially there were signs and symptoms of inflammatory reaction such as pain, swelling, erythema, erosion in the area where the chemical was contact when swallowed and it made oral intakes difficult. Other symptoms and signs were nausea, vomiting(12 cases), epigastric pain and burning sense(14 cases), hematochezia and bloody saliva(13 cases), dyspnea(9 cases), jaundice(7 cases), tachycardia(12 cases), diarrhea(11 cases), skin rash(2 cases).

2. Gastrofiberscopic examination

Of all fifteen patients, seven cases were examined within 24 hours after ingestion of paraquat which showed erosion in pharynx, esophagus, and non specific finding in stomach. and eight cases were examined after 24 hours which showed erosive esophagitis and acute erosive gastritis in the area of fundus and body of stomach.

3. Biochemical examination

1) Serum BUN level

Serum BUN was checked 28.40 ± 12.35 mg/dl on the 1st day, and on the 3rd day it was increased to 36.00 ± 8.36 mg/dl, but following this it was decreased to 17.40 ± 5.11 mg/dl, 14.40 ± 4.36 mg/dl, 9.60 ± 1.69 mg/dl, 9.20 ± 2.30 on the days 7th, 14th, 21th, and 28th respectively(Fig. 1).

2) Serum Creatinine level

Serum creatinine was checked 2.56 ± 0.61 mg/dl on the 1st day, and it was increased to 3.08 ± 1.09 mg/dl on the 3rd day, but slowly decreased to 1.91 ± 0.44 mg/dl on the 7th day, 1.28 ± 0.04 mg/dl on the 14th day, 1.10 ± 0.03 mg/dl on the 21th day, 1.11 ± 0.04 mg/dl on the 28th day(Fig. 1).

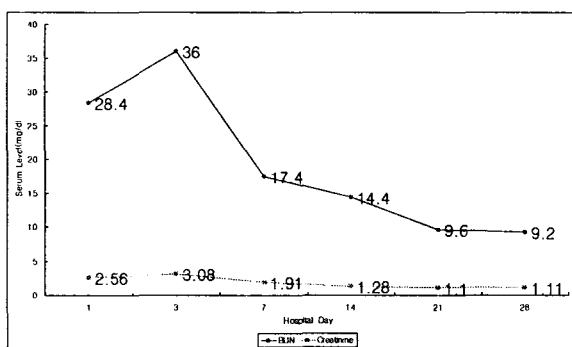


Fig. 1. Change of Serum Level of BUN and Creatinine

3) Serum Na⁺ level

Serum sodium was checked 140.25 ± 1.58 mEq/dl on the 1st day, and persistently decreased to 135.50 ± 0.69 mEq/dl on the 3rd day, 134.73 ± 2.98 mEq/dl on the 7th day, 132.85 ± 2.25 mEq/dl on the 14th day, which is the lowest. On the day 21th and 28th it was increased to 144.00 ± 1.02 mEq/dl and 145.50 ± 1.94 mEq/dl but within normal range(Fig. 2).

Table 2. Serum Chemistry Results

| | 1 | 3 | 7 | 14 | 21 | 28(day) |
|-----------------------------|---------------|---------------|---------------|---------------|---------------|---------------|
| Na ⁺ (mEq/dl) | 140.25 ± 1.58 | 135.50 ± 0.69 | 134.73 ± 2.98 | 132.85 ± 2.25 | 144.00 ± 1.02 | 145.50 ± 1.94 |
| K ⁺ (mEq/dl) | 3.60 ± 0.34 | 3.22 ± 0.29 | 3.66 ± 0.47 | 3.70 ± 0.40 | 4.30 ± 0.03 | 4.31 ± 0.35 |
| BUN (mg/dl) | 28.40 ± 12.35 | 36.00 ± 8.36 | 17.40 ± 5.11 | 14.40 ± 4.36 | 9.60 ± 1.69 | 9.20 ± 2.30 |
| Creatinine (mg/dl) | 2.56 ± 0.61 | 3.08 ± 1.09 | 1.91 ± 0.44 | 1.28 ± 0.04 | 1.10 ± 0.03 | 1.11 ± 0.04 |

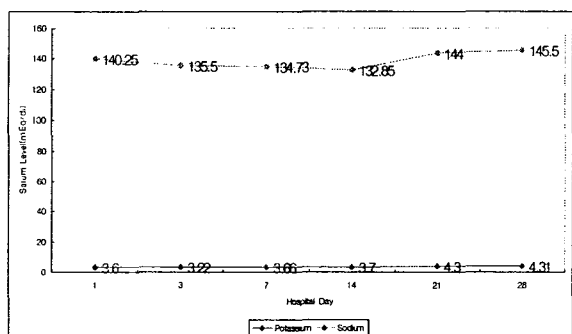


Fig. 2. Change of Serum Level of Sodium and Potassium

4) Serum K⁺ level

Serum potassium was checked 3.60 ± 0.34 mEq/dl on the 1st day, 3.22 ± 0.29 mEq/dl on the 3rd day, which was below the normal range. But after this it was increased within normal

range to 3.66 ± 0.47 mEq/dl on the 7th day, 3.70 ± 0.40 mEq/dl on the 14th day, 4.30 ± 0.03 mEq/dl on the 21th day, 4.31 ± 0.35 mEq/dl on the 28th day(Table 2)(Fig. 2).

4. Daily urine output

Total daily urine output was 1050.00 ± 34.87 ml on the 1st day, and was increased to 1391.67 ± 129.64 ml on the 3rd day, 1641.67 ± 187.26 ml on the 7th day, 2716.67 ± 152.27 ml on the 14th day, 2200.57 ± 157.73 ml on the 21th day, 2900.00 ± 88.19 ml on the 28th day(Fig. 3).

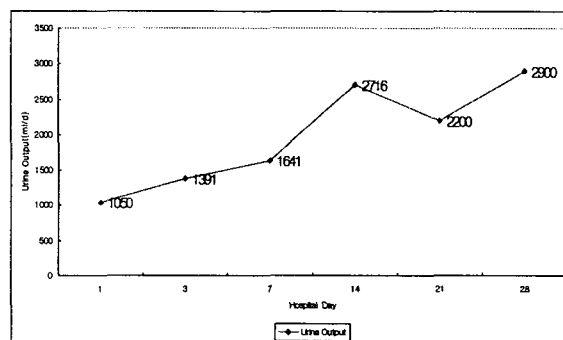


Fig. 3. Change of Daily Urine Output

Discussion

Paraquat was developed as a herbicide and it has been widely used in the world². It is known as Gramoxon[®] or Paraco[®], yet has different effects on the plants and animals. It is proven to have a selective toxicity on the plants and animals as it forms inert complex when in contact with clay mineral⁷. However, the toxicity of paraquat with even a low dosage of 10-15ml of 20% paraquat solution is very high with LD₅₀ of 40mg/kg. It can cause many signs and symptoms, mainly involving organs such as gastrointestinal tract, lung, kidney, liver, heart and CNS^{2,3,10}. Especially it could damage the epithelial lining of proximal tubules of nephrons in kidneys, resulting in fatal acute renal failure which may be reversible⁴. When it is consumed by human, less than 20% of ingested paraquat is absorbed in the gastrointestinal tract system and the rest is discharged with feces⁶. In normal kidney, 90-100% of the absorbed paraquat is eliminated as urine within 48 hours, but when there is a reduced function of kidney developed within 24 hours, the amount of paraquat elimination is reduced and accumulated in other organs¹¹. Within few hours or days, the absorbed paraquat usually causes signs and symptoms as mentioned above. Moon et al¹² reported that the oral ulceration caused by paraquat can occur within 1-3 days, abnormal functions of the kidneys within 2 days, the liver 3-5 days and the lungs with variable times. In

this study, average amount of orally taken paraquat in fifteen subjects was 11.60ml, and all of them had developed abnormal kidney functions, despite of gastric lavage within 12 hours before transferring to cheonju oriental medicine hospital. Hence it indicates that paraquat intoxication could still cause acute renal failure regardless of gastric lavage. The signs and symptoms in patients with paraquat intoxication were pain, redness, ulceration and difficulty in swallowing, which are identical to those reported by Yang et al³. Orepoulos et al¹¹ reported that signs of inflammation and hemorrhage was observed by autopsy of the esophagus and stomach in paraquat intoxicated patients. Ackrill et al¹⁴ also find a case of mediastinitis due to the ulceration of esophagus. It explains the destructive mechanism of paraquat. All of fifteen patients in this study experienced in difficulty in oral feeding due to oral ulcers and erosion in the gastrointestinal tract including mouth, and also the same in oral-taken herbal medicine. Anon et al¹⁵ stated on the biochemical mechanism of paraquat that acts as a catalytic agent which produces superoxide anions(O₂⁻) by transferring an electrons from NADH₂ to O₂ and destructs tissues caused by these superoxide anions. Fisher et al¹⁶ claimed that there is more production superoxide anions when a high concentration of oxygen is supplied to patients with paraquat intoxication. Therefore, the toxicity of paraquat is proportional to the concentration of oxygen. The tissue damage caused by the production of superoxide anions and peroxide radicals is promoted when they act as a medium for an electron transfer with the presence of oxygen, especially in the lung¹⁷. The pathological change of kidney is due to damage of epithelial lining of proximal tubules causing a abnormality of reabsorption of glucose, amino acids, phosphoric acid, etc and resulting in the symptoms and signs similar to Fanconi's syndrome^{4,18}. 11 cases reported by Young et al showed oliguria in 82% and proteinuria of greater than 2(+) in 89% of the patients¹³. The average of 89.9mg/dl of serum BUN showed in eight patients resulting in serious uremia. The level of serum BUN and serum creatinine of one patient who survived, returned almost to normal level showing that the kidney function is reversible which is identical to the report by Vaziri et al¹⁸. The general treatment for patients with paraquat intoxication, in order to inactivate or inhibit absorption of paraquat as early as possible, involves gastric lavage by fuller's earth or benotite, and gastrointestinal tract flushing with mixed solution of NaCl, KCl, and NaHCO₃^{22,35}. To promote the elimination of paraquat which is already absorbed, fluid infusion and diuretics are used^{6,19}. Recently, at the early stage of paraquat intoxication it is known to be effective to use hemodialysis and hemoperfusion for the elimination of

paraquat from the body. Especially, as hemoperfusion shows 7-10 times more effective in paraquat elimination than hemodialysis, many research and cases studies recommend to use a method of hemoperfusion for reducing symptoms and signs of paraquat intoxication and for increasing the chance of survival²⁰. The aspect of oriental medicine of intoxication and the diagnosis and treatment were recorded and used in various ways since Jang^{21,22}. Especially, since Gamdutang(甘豆湯) was first recorded in 千金方 of Son(孫)²³, it has been known as a most effective antidote to toxins. The effectiveness of Gamdutang(甘豆湯) was reported by Park²⁴ in aconite toxin, by Lee et al²⁵ in acute intoxication of Radix Aconiti(附子), by Au²⁶ in subacute lead poisoning, and by Kim²⁷ in reducing damage to the liver and kidneys by the aconite main tuber(草烏) mix-fried with Gamdutang(甘豆湯). All fifteen patients were admitted to Cheonju Oriental Hospital after gastric lavage done in other hospitals. Treatment of Oriental Medicine was consisted of oral administration or oral flush with Gamdutang(甘豆湯) alone and with a mixture of Gamdutang(甘豆湯), Chinese ink(墨汁), char-frying powder of Rhei Rhizoma(大黃炒炭末), Fuller's earth and Succus phyllostachyos(竹瀝), with total minimum amount of 1000 ml per day. From clinical observation with the treatment, it can be proposed that paraquat has detoxicated by Gamdutang(甘豆湯), absorbed by Chinese ink(墨汁) and char-frying powder of Rhei Rhizoma(大黃炒炭末), and removed from gastrointestinal tract by char-frying powder of Rhei Rhizoma(大黃炒炭末). Moreover, Succus phyllostachyos(竹瀝) clear Heat and expel Dampness(清熱去痰). During the observation, the level of serum BUN and creatinine was reached its maximum at the 3rd day regardless of the treatment, but returned to the normal level on the 7th day and 14th day, respectively. It showed that creatinine took longer period to be normalized than BUN. Formula of Gamdutang(甘豆湯) consists of Radix Glycyrrhizae(甘草), Semen Glycin(黑豆), and sometimes Semen Mungo(綠豆) and Semen Lablab(白扁豆) are added²⁸. Wyang²⁹ said that Radix Glycyrrhizae(甘草) detoxifies by harmonizing the center(和中) and Semen Glycin(黑豆) by dissipating heat(散熱), thus Gamdutang(甘豆湯) can detoxify wide range of toxins. Radix Glycyrrhizae(甘草) consists of mainly glycyrrhizin of triterpenoid saponins³⁰. Ojima et al³¹ reported that glycyrrhizin and glycyrrhetic acid prolong the rate of elimination of cortisol and prednisolone in rat and bovine and increase biological half-life. Azimov et al³² also indicated that glyderrinine, which is a derivative of glycyrrhizic acid extracted from Radix Glycyrrhizae(甘草), has a stronger anti-inflammatory reaction than hydrocortisone. Active ingredients of Semen Glycin(黑豆) are daidzin and genistin³⁰.

There is no study on mechanism of Semen Glycin(黑豆) in detoxication, yet it has been used for the treatment of adverse effects by digitalis and aconitine in Oriental Medicine³³. Hence, more thorough research on this area is required. Based on the functions of ingredients of Gamdutang(甘豆湯), the aim of its use for paraquat poisoning is to detoxify the toxic effect of paraquat, protect the liver, promote elimination of paraquat, reduce inflammatory reaction, and to promote the recovery of ulcers in the upper gastrointestinal tract system. Chinese ink(墨), also known as 烏金, 陳玄, or 玄香, is made of a mixture of colloid solution and aromatic essence with the smoke of pine. It has therapeutic effects in coagulating blood, reducing inflammation, promoting urination and treating welling-abscess swelling(癰腫), according to 本草綱目30). Carbon, made by the smoke of pine, of Chinese ink(墨) may be responsible for its absorptive action. Rhei Rhizoma(大黃) consists of several types of glucoside and genin that is derived from anthraquinone³⁴. In recent study, it was suggested that the active compound, which is responsible for draining precipitation action(瀉下作用), is sennoside A which is degraded into sennidine by intestine flora. Sennidine stimulates intestines to induce fecal movement by increasing peristalsis³⁰. Succus phyllostachyos(竹瀝) treats heat, cough and phlegm accumulation(熱咳痰積) by sweetness cold and glossy moisten(甘寒滑潤) and clearing heat and loosening phlegm(清熱化痰)³⁴. Nephrotoxicity, caused by administration of various number of chemicals or poisons, produces toxic substances in large concentration, leading to ARF³⁵. For kidneys are supplied by 25% of cardiac output, they are easily damaged by accumulation and deposition of nephrotoxins in interstitium and medullary epithelium³⁵. ARF from paraquat poisoning produces toxins and ischemia. Under light microscopic examination, there was a marked sign of necrosis at proximal tubule, but at distal tubule^{4,18,26}. The proximal tubule of kidneys in a rat with paraquat pre-treated was investigated under electron microscopy, which has shown swelling of endoplasmic reticulum and lipidic lamellate cytosome. It might be caused by a combination of paraquat ion and acid lipoprotein in lysosome³⁷. Therefore, it was thought to be abnormality of proximal tubule as observed in light microscopy. Due to marked decrease in kidney function, ARF causes accumulation of fluid, solute, and nitrogen metabolite with clinical manifestations of increase of serum creatinine, azotemia, and oliguria where daily urine output is less than 400ml. When daily urine output is more than 400ml it is called non-oliguric ARF³⁸. Non-oliguric ARF is caused by injury, post-operation, hypotension, renal toxins, rhabdomyolysis, and all types of ARF and it was reported that it happens in 25-80% of ARF cases³⁹. Oliguria do no harm to patients of ARF nor

large urine output guarantee prompt prognosis, but, Non-oliguric patients are better than oliguric patients in management and treatment with better chance of survival³⁸. In a study done on patients with ARF40), out of 12 oliguric patients, there were 9 patients died or progressed into terminal stage renal failure whereas in 13 non-oliguric patients, there were 4 patients died or progressed to terminal stage renal failure. This suggests that transforming from oliguria to non-oliguria is one way to increase survival rate in ARF from paraquat intoxication. In this study, we provided enough fluids and small doses of diuretics, if necessary, based on daily inputs and outputs intending to protect the kidney from dysfunctioning, which made difficult to balance the fluid and electrolytes and clinically manifested by oliguria first of all.

Conclusion

ARF patients of paraquat intoxication at Chonju Oriental Hospital of Wonkwang University treated with fluid and lasix intravenously, a decoction of Gamdutang orally, a mix of Chinese ink(墨汁), Junci Medulla(燈心), char-frying powder of Rhei Rhizoma(大黃炒炭末), Succus phyllostachyos(竹瀝), Stigmata Maydis(玉蜀鬚) and Rhei Rhizoma(大黃) for gargling or oral administration. Paraquat intoxication results in high mortality rate. Until present, many patients of paraquat intoxication have given up hope or died due to unavailable antidote and there were not a clear treatment method of Oriental medicine. After the observation of fifteen ARF patients caused by paraquat intoxication, who were treated by combination of oriental and western medicine, it is necessary to research more systematically in this area.

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