TREATMENT REGIMEN FOR CELPHOS POISONING

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ABSTRACT

Celphos poisoning is a major cause of mortality largely due to non-availability of its antidote, due to delay in appropriate management and skepticism amongst physicians regarding the outcome. Although different trials has been tried to counter its irreversible toxic effects but hardly with any concrete success. Here we report novel intervention, the protocol of which we have formulated and standardized for last 1.5years, for Celphos poisoning which aims to diminish the production and absorption of phosphine, enhance its excretion and prevent any organ toxicity with appropriate supportive therapy. The management plan involves gastric lavage with an aliquot of coconut oil mixed with NaHCO3 followed by KMNO4 in Normal saline as an essential step in the initial stage. In addition the plan involves appropriate supportive measures that were taken which include Inj. NS-4 units (500ml each) Iv. over 6hrs, inj. Citicholine 500mg Iv. BD (antioxidant to prevent neuronal toxicity), Tab.N-Acetyl cysteine (dispersable) 600mg 1 tab PO BD (antioxidant, replenishing cellular glutathione), broad spectrum antibiotics eg. Inj. Monocef 1gm Iv. BD and inj. Metronidazole 500mg Iv. TID, Magnesium (inj MgSO4 (50%))(4 ampules in 500ml of NS) as cell membrane stabilizer to prevent arrhythmias, dopamine for inotropic support, if required and inj. Pantop -40mg Iv. BD to decrease HCl production and for symptomatic relief. The survival rate of this novel intervention turns out to be 91%(10/11). Early arrival, history of vomiting, early diagnosis, resuscitation, decreasing formation and absorption of phosphine (by gastric and retrograde lavage with coconut oil
followed by KMnO₄), intensive monitoring and supportive therapy were associated with good outcome. We, therefore, recommend the use of this regimen /protocol by all the intensivists and physicians especially in rural and suburban areas in developing countries with limited resources like India where instruments like gastroscope to remove undissolved pellets, or intra-aortic balloon pump (IABP), ECMO (extracorporeal membrane oxygenation) as a supportive measures, to provide prompt and adequate cardiovascular support till toxin is removed, in health care divisions are hardly available.

**KEYWORDS:** Celpho, gastric lavage.

**Abbreviations:** AlP=aluminium phosphide, NS =normal saline

**INTRODUCTION**

Pesticide poisoning, whether due to self, accidental, occupational or for homicidal purpose, is a global public health problem, and self-poisoning accounts for one-third of the world's suicide rate.[1] Each year around 300,000 deaths occur worldwide due to pesticides.[2] Since the first available report of Celphos,(trade name for aluminium phosphide (AlP), poisoning in the early 1980s from India, it is now one of the most common causes of poisoning among agricultural pesticides.[3,4] Most cases of Celphos poisoning are reported from northwest, central India, some others from countries like Iran and Jordan, Sri Lanka and Morocco, with few case reports from many developed countries. In a recent scenario AlP also poses as a threat for chemical terrorism due to the immediate release of lethal phosphine gas.[5]

In India, AlP is marketed as an food grain fumigant formulated in the form of 3g tablet consisting of AlP (56%) and carbamate (44%), in the names of Celphos, Alphos, Quickphos, Phosfume, Phostoxin, Talunex, Degesch, Synfume, Chemfume, Phostek or Delicia.[6,7] Celphos toxicity is due to the phosphine gas generated as a result of chemical reaction of AlP with moisture or acid in the stomach \[\text{AlP}+3\text{H}_2\text{O}=\text{Al(OH)}_3+\text{PH}_3\text{ or }\text{AlP}+3\text{HCl}=\text{AlC}_1_3+\text{PH}_3\]. Once generated, phosphine(\text{PH}_3) gas is rapidly absorbed throughout the gastrointestinal tract, leading to systemic toxic effects involving the heart, lung, kidney, liver with manifestation of serious cardiac arrhythmias, intractable shock, acidosis and pulmonary edema. After absorption, phosphine is oxidised to oxyacids. Phosphine is excreted in the urine as hypophosphite and also through the lung in the unchanged form. At cellular level phosphine causes cellular hypoxia due to the inhibition of mitochondrial respiratory
After ingestion, toxic features usually develop within few minutes. In mild poisoning nausea, repeated vomiting, diarrhea, headache, abdominal discomfort or pain and tachycardia are common clinical features, and these patients usually show recovery. On the other hand, in moderate to severe ingestional poisoning, the signs and symptoms of the gastrointestinal, cardiovascular, respiratory and nervous systems appear initially and, later on, features of hepatic and renal failure and disseminated intravascular coagulation may also occur. The toxicity of AlP particularly affects the cardiac and vascular tissues, which manifests as profound and refractory hypotension, congestive heart failure, electrocardiographic (ECG) abnormalities, myocarditis, sub endocardial infarction or pericarditis. ECG abnormalities include rhythm disturbances, ST-T changes and conduction defects. Temporal correlation in ECG changes showed that during the initial 3–6 h, sinus tachycardia is predominant, in the 6–12 h period ST-T changes and conduction disturbances appear, while in the later period, arrhythmias occurred.

Celphos poisoning has always been a big headache and menace for the intensivists throughout the world probably due to nonavailability of its antidote and 100% mortality. The literature is full of different drugs and trials to counter its irreversible toxic effects, but hardly with any concrete success. Here we report the novel combo intervention which we have formulated and standardized over last 1.5 years on celphos patients admitted to ICU of Maharishivalmiki hospital, Govt of NCT of Delhi. The present study aimed at evaluating the effectiveness of this novel intervention in decreasing the very high mortality and morbidity that occur as a result of celphos poisoning.

MATERIALS AND METHODS
In total eleven patients got admitted to ICU of Maharishi Valmiki Hospital, Govt of NCT of Delhi over the last 1.5 year period between June 2013-Nov. 2014 with a definite history of intake of celphos (AlP) poison. Most of the patients were young (<42Yrs), male, married, and literate. Most of them had taken 1-3 tablets of AlP (each 3g while 0.5g dose is lethal) and were brought less than an hour of intake of poison. In most cases there had been legal evidence (catridge containing AlP) of deliberate celphos intake. None of them had any history of mental illness, or hypotension, Diabetes mellitus, Koch or bleeding. After ingestion, nearly half of them had features of cardiogenic shock, hypotension and...
arrhythmias, mild respiratory distress, menthol like cooling upon breathing, and mild GI symptoms like nausea, vomiting, gastric pain while only one of them who reached hospital with delay of 2 hours and had taken alcohol also, had features of combined respiratory/CVS/CNS involvement. The approval of Ethical Committee of the institute had already been taken for all poisoning cases. The reason for pre-approval of this treatment regimen for celphos poisoning was that in such cases mortality is 100% with out any specific treatment and no time should be lost in resuscitating such patients.

On admission to ICU, the patients were made comfortable on the bed, monitoring gadgets were attached for Heart Rate (HR), Non-Invasive Blood Pressure (NIBP), ECG, Pulse Oximetry (SpO₂) and End-tidal carbon dioxide (EtCO₂) and Ryle's tube was inserted through nasal route. Novel combo intervention for celphos poisoning was initiated which included.

2.1 Gastric Lavage with 100ml of
Solution (A): 500ml of coconut oil mixed with 3 ampules of NaHCO₃(7.5%,25ml vial).
Solution (B): 2 pinches of KMNO₄ in one liter of normal saline (≈1:10,000 dilution).

Gastric lavage was done in three cycles via Ryles tube. Each cycle consisting of initially giving 100ml of solution A which was suctioned back within 5 seconds up to the maximum possible quantity without harming the patient followed by 100 ml of solution B which was given, kept and suctioned back in similar manner. The time gap between successive lavages was three minutes. In this procedure 50ml sterile syringes were used and all antiseptic precautions were taken.

2.2 Retrograde lavage: Ryles tube was inserted via rectum after properly lubricating it with lidocaine jelly (2%), taking all precautions not to perforate the gut, up to the length so that only 15cms of ryles tube were kept outside the anal verge. Then retrograde lavage was done in similar manner with 100ml of solution A and solution B as in gastric lavage. Retrograde lavage was done only after completion of three cycles of gastric lavage.

2.3 Supportive therapy: included
- Inj. NS-4 units(500ml each) Iv. over 6hrs
- Inj. Citicholine 500mg Iv. BD
- Tab. N- Acetylcysteine (dispersable) 600mg 1 tab PO BD
- Inj. MgSO₄ (50%)--4 ampules in 500ml of NS Iv over 24 hrs.
• Inj. Monocef 1gm Iv. BD
• Inj. Metronidazole 500mg Iv. TID
• Inj. PANTOP -40mg Iv. BD

Symptomatic treatment was initiated on a patient to patient basis. During this period, strict and vigil monitoring of all vital organs and important parameters like SaO2, Electrocardiogram was done and treatment regimen were titrated according to the clinical condition of the patients. Gastric lavage and retrograde lavage was again performed after 3 hours of admission with the same solution only once.

After admission in the ICU, all baseline routine and specific investigations were carried out including arterial blood gas analysis (ABG), CBC, KFT/LFT/Electrolytes, chest x-rays, urine examination, input/output monitoring, PT/INR after every 12hrs period. At the end of the study period, all the data were arranged systematically and were subjected to statistical analysis using non-parametric tests. Value of $P<0.05$ was taken as significant value.

RESULTS

In the last 1.5 years, 11 patients got admitted in ICU of Maharishi Valmiki Hospital, Govt of NCT of Delhi, with an alleged history of Celphos intake. The demographic profile of these patients is shown in Table 1. The age of 11 patients who got admitted in ICU ranged from 23 to 48 years, with a mean and standard deviation of 35.97±4.02. There was significant difference on the gender basis as 81.8% (9/11) admitted with Celphos consumption were males. The incidence of poisoning was surprisingly high with a significant proportion in the more literate class (91%)(10/11). The incidence was significantly higher in the families of low income 72.7% (8/11), especially among the married young members 81.8%)(9/11). The incidence of poisoning was higher among the rural 63% (7/11) as compared to sub-urban population. The maximum number of patients 45.5% (5/11) presented clinically with cardiovascular instability, either in the form of hypotension or arrhythmias which was clinically quite significant ($P<0.05$) [Table 2]. Mild GI symptoms in the form of nausea, vomiting occurred in 45.5% (5/11)) which was again quite significant ($P<0.05$). Also, 36.3% (4/11) of the patients presented with mild respiratory distress while only 9.1% 1(1/11) of the patients had symptoms like altered sensorium or combined symptoms related to respiratory, CVS or CNS [Table 2]. Significantly high 54.5% (6/11) no. of patients had two organs, liver and kidneys, mildly affected by the poison.
Further, 45.5%(5/11) of the patients required ionotropic support for maintaining stable hemodynamic parameters which was again quite significant ($P<0.05$). The mean stay in ICU varied from 2 to 7 days, with a mean stay of 4.2days with an SD of 1.3. The survival rate after following this combo intervention was 91% (10/11) while only 9%(1/11) succumbed to Celphos poisonings which again is quite significant [Table 2]. The lone mortality was due to delay in the hospitalization (>2hrs) and the use of agents that increases the solubility of AIP pellets like in our case the patient that died was alcoholic.

**Table 1: Demographic profile of Celphos poisoning patients.**

<table>
<thead>
<tr>
<th>Total Number of patients</th>
<th>11</th>
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<tbody>
<tr>
<td><strong>Age in years 23-48yrs</strong>&lt;br&gt;(mean± SD)</td>
<td>(35.97±4.02)</td>
</tr>
<tr>
<td><strong>Gender</strong>&lt;br&gt;Male:female</td>
<td>*9:2</td>
</tr>
<tr>
<td><strong>Location</strong>&lt;br&gt;Sub-urban:rural</td>
<td>4:7*</td>
</tr>
<tr>
<td><strong>Educational level</strong>&lt;br&gt;literate: illiterate</td>
<td>*10:1</td>
</tr>
<tr>
<td><strong>Marital status</strong>&lt;br&gt;married : unmarried</td>
<td>*9:2</td>
</tr>
<tr>
<td><strong>Family income</strong>&lt;br&gt;(&lt;Rs5000/month:&gt;Rs7000/month)&lt;br&gt;low : high</td>
<td>*8:3</td>
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*P<0.05

**Table 2 Clinical presentation and treatment pattern of celphos poisoning patients**

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>NO. Of patients</th>
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<tr>
<td>1.Clinical presentation in emergency ward&lt;br&gt;• GI symptoms : nausea, vomiting, abdominal pain</td>
<td>5/11(45.5%)*</td>
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<tr>
<td>• Respiratory distress, menthol like cooling effect upon breathing)</td>
<td>4/11(36.3%)*</td>
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<tr>
<td>• CVS instability/arrhythmias</td>
<td>5/11(45.5%)*</td>
</tr>
<tr>
<td>• altered sensorium</td>
<td>1/11 (9%)</td>
</tr>
<tr>
<td>• combined respiratory/CVS/ CNS involvement</td>
<td>1/11(9%)</td>
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• number of organs involved
  • two (liver, kidneys)
  • three (liver, kidneys, heart)

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<tr>
<td>6/11 (54.5%)*</td>
<td>5/11 (45.5%)</td>
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2. Treatment pattern and outcome
• Ionotropic support
• Stay in hospital (5-7 days)
• outcome (death/survival)
• post discharge complications observed during followup of one year

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<tr>
<td>5/11 (45.5%)*</td>
<td>4.2±1.3</td>
</tr>
<tr>
<td>1/10 (9/91*)%</td>
<td>0/10</td>
</tr>
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</table>

*P<0.05

DISCUSSION
Celphos poisoning has always been a big headache and menace for the intensivists throughout the world probably due to non-availability of its antidote and 100% mortality which does not encourage the physicians to try whole heartedly to salvage the patients. The literature is full of different drugs and trials to counter its irreversible toxic effects, but hardly with any concrete success. Here we report combo intervention for Celphos poisoning with 91% survival rate and only 9% mortality. The management plan involves gastric lavage (with an aliquot of coconut oil mixed with NaHCO3 followed by KMNO4 in NS) as an essential step in the initial stage. The principles aim of our management plan was to sustain life with appropriate resuscitation measures until phosphine is excreted from the body. Although Gastric lavage with saline or sodium bicarbonate or potassium permanganate has been recommended by earlier studies[12] but not in the form of protocol (as discussed in material and methods section) which we have formulated and standardized over last 1.5 year. The rationale behind the use of a mixture of coconut oil and soda bicarbonate in our patients aimed to decrease the formation and absorption of phosphide (PH3) produced as a result of chemical reaction of AlP with moisture and/HCl [AlP+3H2O=Al(OH)3+PH3 or AlP+3HCl=AlCl3+PH3]. The mechanism by which coconut oil reduces the toxicity of phosphides is unknown but most probably it forms a protective layer around the gastrointestinal mucosa, thereby preventing the absorption of phosphine gas. Secondly, Soda bicarbonate mainly neutralizes the HCl in stomach and thus diminishing the catalytic reaction of phosphide with HCl, thereby inhibiting the release of phosphine from AlP pellets.[13] Further, use of KMnO4 in NS in non-corrosive conc. (<1:10,000 dilution) is guided by the fact that it provides alternative medium for AlP to react with, oxidising phosphine to non
toxic phosphate releasing Al(MnO4)3 and less toxic potassium phosphate instead (KPH2), [AlP +3H\textsubscript{2}O\textsuperscript{+} 3KMnO\textsubscript{4}=Al(MnO4)3 +3KPH\textsubscript{2}], Phosphine/ phosphide, if it does not induce emesis or eliminated completely by gastric and retrograde lavage, is rapidly absorbed from the gastrointestinal mucosa and once it gains access to bloodstream it reaches various tissues and at cellular level inhibits the mitochondrial respiratory chain and hence leads to cell necrosis and death. It has been suggested that phosphate leads to non-competitive inhibition of the cytochrome oxidase of mitochondria, blocking the electron transfer chain and oxidative phosphorylation, producing an energy crisis in the cells.[4,6] Recently, Chugh et al. found inhibition of catalase and induction of superoxide dismutase enzymes by phosphine in humans, leading to free radical formation, lipid peroxidation and protein denaturation of cell membrane, ultimately leading to hypoxic cell damage.[14] In our treatment regimen, novel therapies such as N-Acetyl cysteine (600mg tab BD) (antioxidant, replenishing cellular glutathione), and Inj. Citicholine (500mg Iv BD) (prevents neuronal injury) have been tried to reduce free radical damage to tissues and the results were excellent. The reason for oral delivery of N-Acetyl cysteine is to provide first line of protection to gastrointestinal mucosal cells from reactive oxygen species generated as a result of loss of antioxidant enzymes and secondarily, unlike glutathione, N-Acetyl cysteine is more permeable antioxidant.

All AlP poisoning require hemodynamic monitoring and early resuscitation with fluids and vasoactive agents. In our cases 4 liters of NS were administered within first 6hrs guided by Central Venous Pressure (CVP) (with an aim to keep CVP at around 8-10cm of water) in order to maintain adequate hydration and renal perfusion required for renal excretion of phosphine.. Further, cardiac dose of dopamine 2-5μg/kg/min was given to those patients who required ionotrope support. The proton pump inhibitors added in our protocol were given in order to decrease the production of HCl and for symptomatic relief.

Mild GI symptoms like nausea, vomiting, abdominal pain and diarrhea are usually the first to occur after exposure. 45.5% (5/11) patients in our study group came with these symptoms. However none of them reported to have GI bleeding as reported by various studies. Most of patients in our study group developed altered LFT and KFT profile (in the form of raised aspartate transaminase (AST) or creatinine), respiratory and metabolic acidosis (as depicted in ABG reports) which subsided within few days after appropriate measures were taken.
Furthermore magnesium (Inj. MgSO4 (50%) -4 ampules in 500ml of NS Iv over 24 hrs) has been added as a therapeutic option in our treatment plan. Magnesium acts as a cell membrane stabilising agent and prevents cardiac arrythmais induced by phoshine toxicity. Myocardial depression from Celphos toxicity is not uncommon and carries a very high mortality.[15,16] These cardiotoxic effects were quite marked in our patients as 45.5% (5/11) of the patients required ionotrophic support. Vascular changes may lead to marked low blood pressure that does not respond well to vasopressor agents. Cardiotoxicity/toxic chemical myocarditis is manifested as depressed left ventricular ejection fraction, ECG changes varying from ST segment elevation/depression, PR prolongation, broad QRS complexes, and right or left bundle branch block, supraventricular ectopics or fibrillation.[11,17]

In acute poisoning cases, death due to acute hepatocellular toxicity and fulminant hepatic failure can occur. Blood and protein in the urine, and acute kidney failure due to pHOSHINE toxicity and circulatory shock can occur. Also, there have been reports of significant hypomagnesemia and massive focal myocardial damage.[18,19] Chronic exposures to very low concentrations may result in anemia, bronchitis, GI disturbances, and visual, speech, and motor disturbances.[20] Severe exposure can cause accumulation of fluid in the lungs, pulmonary edema, which may have a delayed onset of 72 hours or more after exposure. Furthermore, this phosphine gas is eliminated through the lungs; hence, due to high concentration in the respiratory alveoli, it is responsible for direct alveolar damage.[21] Acute respiratory distress syndrome (ARDS) and exudative pleural effusions can develop. Studies in the past have shown increased levels of inflammatory markers (cytokines and interleukins) in ARDS, which increase the capillary permeability. This combined effect of increase in capillary permeability due to global hypoxia and ARDS could be responsible for the exudative effusion seen predominantly in the pleural cavity and not in other serous cavities.[22]

The findings of our study do correlate with various studies worldwide, as most of our patients presented with arrhythmias of varying nature, hypotension, altered LFT and KFT profile, respiratory and metabolic acidosis, mild respiratory and GI disturbances. However, only one of our patients developed multi-organ system failure and died. Rest of Patients (10/11) did not devoloped life threatening complications like acute hepatocellularae toxicity, massive focal myocardial damage, GI bleeding ,cardiac failure, non cardiogenic pulmonary edema(ARDS). This could be possibility due to early hospitalization, and immediate resuscitation of the
patients by our novel intervention which aimed to diminish the production and absorption of phosphine and enhance its excretion plus intensive monitoring and appropriate supportive therapy added in our protocol to prevent any organ toxicity.

The main principles of our novel intervention are the following.

• Diminishing the production and absorption of phosphine and accelerating its removal through GI tract as explained earlier
• Reduce organ toxicity with appropriate supportive measures like use of antioxidants to reduce free radical damage, magnesium supplementation as cell membrane stabilizer to prevent arrhythmias.
• Use of broad spectrum antibiotics as coconut oil used in lavage is non-sterile and proton pump inhibitors to counter acidic medium required for phosphine production.
• Phosphine is excreted through urine also. Therefore, adequate hydration and renal perfusion by low-dose dopamine 2–5 μg/kg/minute must be maintained. Diuretics are not useful in the presence of profound shock.
• Enhance phosphine excretion, especially through lungs, if required, by increasing the respiratory rate, which becomes easier when the patient is paralyzed, sedated and put on mechanical ventilation.

Improved intensive care, availability of gastroscope in far flung areas, social awareness regarding its toxicity, strict laws and legislations regarding the free sales of the chemical could further reduce the mortality due to AIP toxicity as there is no antidote available presently. In acute poisoning cases, advanced measures like use of intra-aortic balloon pump (IABP) to mechanically support the heart can be evaluated, in future, to reduce toxic myocarditis with refractory shock due to AIP poisoning. The possibility of a beneficial effect of extracorporeal life support (ECLS) as a supportive measure may prove a useful treatment modality, in future, as this device can maintain adequate tissue perfusion to prevent multiorgan failure and give time to recovery of myocardial tissue from phosphine-induced injury.

CONCLUSION
Due to no known specific antidote, management for celphos poisoning remains primarily supportive care. With the novel intervention we have formulated and standardized over last 1.5 years we were able to save 91% of our patients. Early arrival, diagnosis, history of vomiting after consumption of AIP, EARLY resuscitation and decreased formation and
absorption of phospine (by lavage with coconut oil and KMnO₄) intensive monitoring and supportive therapy were the core of our intervention that resulted in good outcome. We, therefore, recommend the use of this protocol by all the intensivists and physicians especially in rural and suburban areas in developing countries with limited resources like India where instruments like gastroscope, to remove undissolved pellets or intra-aortic balloon pump (IABP), extracorporeal life support (ECLS), as a supportive measures to provide prompt and adequate cardiovascular support till toxin is removed, in health care divisions are hardly available.

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