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A Single Arm Trial in Treatment of CKD Patients with Sodium Copper Chlorophyllin Formulation

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Abstract In a prospective, single arm study of 34 Chronic Kidney Disease (CKD) patients in a trial of 90 days wherein patients got standard-of-care treatment and liquid composition containing Sodium Copper Chlorophyllin, the Investigational Product (IP), as add-on treatment for first 60 days and patients were 'off' the IP for last 30 days. Significant reduction in serum creatinine, Blood Urea and Uric acid level and significant improvement in estimated Glomerular Filtration Rate (eGFR), and Health related criteria for quality of life were observed in 60 days' period of administration. eGFR remained significantly higher on 90th day than 0 day despite withdrawal of IP after 60 days. These observations suggest partial/limited reversal of lost kidney function as a lingering effect of the IP. Both these are first observations opening up new avenues for improving life of CKD patients. This is first clinical trial report of an orally consumed product that decreases serum creatinine and also actually improved health related quality of life within 60 days and a surprising evidence that suggests significant degree of restoration of kidney function in the progressively degenerative disease CKD. This clinical trial opens opportunities for managing CKD that were never available so far.

Keywords: *chronic kidney disease, copper chlorophyllin, creatinine, blood urea, quality of life*

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1. Introduction

Sodium Copper Chlorophyllin is sodium copper derivative prepared from chlorophyll extracted from the plants. Chlorophyll is present abundantly in the plant kingdom. Plants used for preparing Sodium Copper Chlorophyllin on commercial scale are Alfalfa, Spinach, and Mulberry etc. The chlorophyll extracted from the plant is not stable at room temperature; hence, it has to be converted to its salts, such as Sodium-Copper derivative or Potassium-copper derivative.

In foods, these salts are used as a natural colorant in various food preparations.

Sodium Copper Chlorohyllin in powder form, liquid form or capsules is being marketed in USA, Australia, and Singapore for non-specified and undefined highly general purposes such as detoxification, alkalizing the body and as an antioxidant by healthy people for anecdotal experience of "freshening effect".

Sodium copper chlorophyllin has been first used for a therapeutic purpose around 1950. In the late 1950s, chlorophyllin was added to papain and urea-containing ointments used for the chemical debridement of wounds in order to reduce local inflammation, promote healing, and control odor [1]. Several studies have reported that such ointments are effective in wound healing [2]. Recently a spray formulation of the papain/urea/chlorophyllin therapy has become available [3]. A recent study showed that human colon cancer cells undergo cell cycle arrest after treatment with chlorophyllin [4]. Several studies on complexes between chlorophylls and mutagens or carcinogens have been reported [5-10]; protective effect of chlorophyllin and lycopene from water extract of spinach has been shown on cytotoxicity and oxidative stress induced by heavy metals in human hepatoma cells [11]. It has been shown that Sodium Copper Chlorophyllin might be associated with diminished absorption of metal ions by chelating and blocking metal-mediated generation of Reactive Oxygen Species.

US FDA (United States Food and Drug Administration) has published a monograph on chlorophyllins for internal use for human being (19862 Federal Register / Vol. 55, No. 82 / Friday, May 21, 1990 / Rules and Regulations 21

CFR Part 357 [Docket No. 81N-0064] RIN 0905-AA08 Deodorant Drug Products for Internal Use for Over-the-Counter Human Use; Final Monograph) and on safety of their use. Accordingly, it is regarded that chlorophyllin as OTC deodorant drug product for internal use are generally regarded as safe for human being above 12 years of age in dosages ranging from 100-300 mg per day in as much divided dosages as possible.

The analysis of the therapeutic effect of sodium copper chlorophyllin tablet has been shown in treating 60 cases of leucopenia [12].

WO2016116950 [13] reported that when, in case studies, this Investigational Product (IP), was administered to patients diagnosed for Chronic Kidney Disease (CKD), it resulted in disappearance of edema, nausea and starting of routine work by the patients concurrent to statistically significant decrease in serum creatinine level over a three months' period of administration when compared with serum ceratinine level on the day of start of administration. In view of the well-known nature of CKD as progressively degenerative disease wherein there are no known treatments for improvement of Quality of Life (QOL) this is a surprising invention. In some patients increase in hemoglobin was also noted.

The purpose of the trial was to find safety and efficacy of the Sodium Copper Chlorophyllin as an add-on supplement in syrup form for decrease in serum creatinine level as primary end point. Decrease in Blood Urea, increase in Hemoglobin level and control on uric acid levels, and effect of the administration of IP on DTP scan of kidney were made as secondary end points for the clinical trial .

2. Materials and Methods

The syrup is made of the active sodium copper chlorophyllin10mg/10 ml dose with sorbitol 7.49ml and glycerine 2.5ml as carriers.

2.1. Study Design and Conduct

This was a single arm, prospective study to determine safety and efficacy of the syrup with Sodium Copper Chlorophyllin as active agent in the IP. This trial (CTRI identifier: CTRI/2017/06/008870) was conducted in accordance with the ICH GCP guidelines for clinical trial. The study protocol was approved by Institutional Ethics Committee of the participating site. Those fulfilling inclusion and exclusion criteria and who were willing to participate in the study were given informed consent document and patient information sheet for reading. Patients were considered as enrolled only after consenting procedure was done.

The IP was administered three times a day, in morning, afternoon and evening. Advice was given to consume each dose on an empty stomach and without taking any food or drink at least 30 minutes after administration.

2.2. Eligibility Criteria

Adult patients diagnosed as having CKD but not on dialysis were enrolled in the clinical trial. Key inclusion criteria included age ≥18 and ≤70 years, serum creatinine level ≥1.8 mg/dL.

Patients who have had episode of dialysis in last 6 months; history of kidney transplant; pregnant or breast-feeding women; nephrotic syndrome; patients with uncontrolled diabetes, uncontrolled hypertension, gout or other illness and participant of other clinical trial were all not considered for enrollment.

Those fulfilling eligibility criteria and consenting in writing were enrolled in the study. In all 34 patients suffering from CKD with increased serum creatinine content were screened for this study. The patients received Syrup Urophyll, in addition to the medicines they were regularly taking for maintaining wellness. Their regular medicines were not stopped or altered during their participation in the study. No specific restrictions were placed on their diet as regards protein intake. Patients were to follow instructions given by her/his physician for diet. Total duration of the study was 3 months. The IP was administered for 2 months, while they did not receive it during third month.

At the time of Enrollment of patients, their medical examination was conducted. Approximately 5 ml blood was withdrawn on day 0 from suitable vein as 'baseline' and after 30, 60 days of administration of IP, and on 90th day i.e. 30 days after discontinuing IP. Following investigations were done: serum creatinine, serum blood urea, Complete Blood Count (CBC), Liver Function Test (LFT), Blood Sugar Level (BSL) (Random), Renal Function Test (RFT), and Serum Uric Acid. After enrollment (Day 0), there were three visits of patients to the site: first follow-up visit at day 30 (± 4 days), second follow-up visit at day 60 (± 4 days) and third follow-up visit at day 90 (± 4 days).Quality of Life was evaluated by using the questionnaire "Kidney Disease Quality of Life Short Form (KDQOL-SF^{TM}) Version 1.3" to assess and quantify the nature of life related parameters at day 0 day. It includes 43 kidney disease targeted items as well as 36 items that provide a generic core and an overall health rating item. Change in quality of life was also evaluated before starting of the IP and at day 60 after starting consumption of the IP.10ml of the IP was administered three times a day for 2 months i.e. up to 60 days.

The population of 34 subjects consisted 23 males and 11 females. The age of the patients ranged from 23 to 70 years. Out of the total patients, 24 patients were from urban area, while remaining 10 were from rural area. Most of them (29 out of 34 subjects) had either diabetes or hypertension or both, associated with anemia. About three fourth (76.5 %) subjects were well educated, i.e. studied up to above high school grade. Most of the patients (80 %) were non-smokers, while remaining 20 % subjects were smokers in the past. Only 4 subjects, out of 34, had history of chewing tobacco while one subject was current tobacco chewer.

Around 90% of the patients had anemia at the time of enrollment. As many as 13 patients, reported history of renal calculus or recurrent calculus. Four patients (11.8%) had a history of ischemic heart disease whereas one subject each reported history of stroke and of tuberculosis. At the end of the first and second months, 24 patients (70%) had good compliance with the IP. At the beginning as well as after 1, 2 and 3 months the subjects were clinically assessed by physical examination, biochemical

tests mentioned above and by questionnaire on quality of life.

Participants had three follow-ups as site-visits during the three months follow-up duration.

Clinical assessment was done; vitals were noted during these follow-ups. Blood investigations were done after enrollment and at each scheduled monthly follow-up.

Serum Creatinine, Serum Urea, Hemogram and Uric acid was assessed at days 0, 30, 60 and 90. To assess safety by laboratory test, liver function test was performed at day 0 and 60. From Serum creatinine value eGFR (estimated Glomerular Filtration Rate) was calculated.

The main objective of the study was to assess the level of serum creatinine and decrease in the same relative to the level of the same at the time of recruitment in the clinical trial as an effect of Syrup Urophyll. In addition, changes in Serum Urea, Hemoglobin and Uric acid were also assessed. The values of estimated Glomerular Filtration Rate (eGFR) were calculated by using the equation [14]:

$$eGFR\ for\ female = 144X\left(\ S_{cr}/0.7\right)^{-1.209}\ X\left(0.993\right)^{Age}$$

$$eGFR\ for\ Male = 141X\left(Scr/0.9\right)^{-1.209}\ X\left(0.993\right)^{Age}$$

wherein, S_{cr} is serum creatinine. The data were statistically analyzed for Analysis of Variance (ANOVA), and t test and correlation following standard methods of analysis.

2.3. Safety Analyses

At the beginning of the clinical trial, and after 60 days the liver function tests were conducted.

3. Results and Discussion

Observations on blood analysis of subjects at 0 day, 30 days, 60 days and 90 days is given in Table 1.

Table 1. Clinical parameters of CKD subjects on the day of recruitment (0 day) and at 30 days intervals thereafter up to 90 days

Parameter	Mean				Interpretation/Observation
	0 day	30 days	60 days	90 days	
Serum Creatinine (mg/dl)	3.85	3.36**	3.51*	3.64 NS	Difference in creatinine is significant. Rise in 90 days is evidence of IP: efficacy relationship
Serum creatinine as % of 0 day level	100	87.17**	90.71*	91.15*	Serum Creatinine as % of 0day, all treatments show significant decrease, including 90 days; which indicates a carryover effect of IP, suggesting partial restoration of kidney function in 2 months
Glomerular filtration rate , eGFR ml/min/1.73 m2	17.37	24.33**	21.60*	22.60**	Highly significant increase in eGFR even on 90th day is evidence of a carryover effect of IP, suggesting significant restoration of kidney function in 2 months
Blood Urea mg/dl	95.6	78.95**	77.27**	86.33*	Highly significant reduction in blood urea on 30 ,60 and 90 days confirms the efficacy as well as partial restoration of kidney function/partial rejuvenation
Uric acid mg/dl	5.24	5.13NS	5.56NS	5.21NS	Uric acid on 0 day itself is in normal range; hence lower than that is not expected to occur by treatment
Hemoglobin All subjects mg/dl	11.5	11NS	11NS	11NS	Many patients were being administered Erythropoietin; and none of them were receiving any iron supplement

Non-significant (NS) : Significant at p = 0.05, * : Significant at p = 0.01, **.

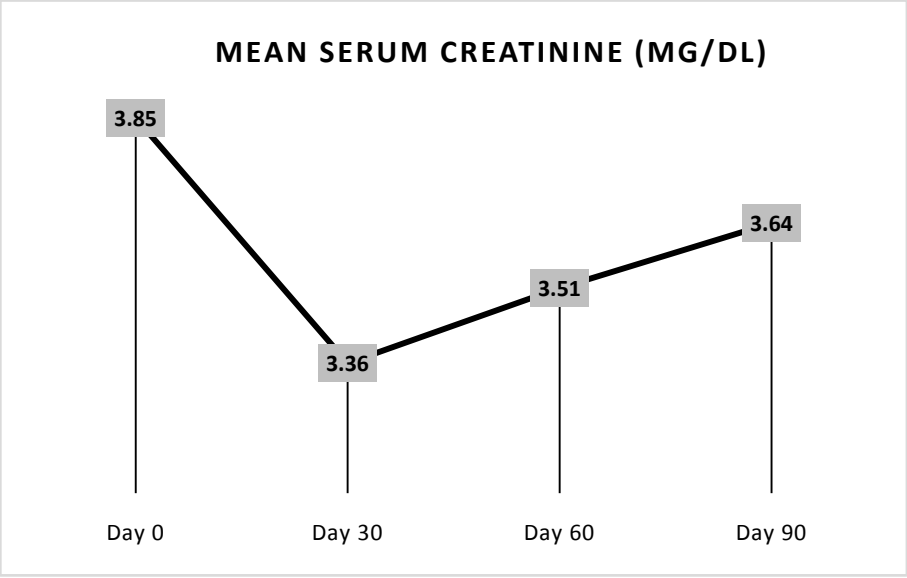

Figure 1. Reduction in serum creatinine level in period of 90 days

The ANOVA of the data indicated significant reduction at p = 0.01 in the creatinine content among the subjects, and at p = 0.05 between in the mean creatinine content amongst the days. Mean initial serum creatinine on Zero day was 3.85 ± 1.43. It significantly (p = 0.01) decreased to 3.36 ± 1.37 on 30th day. On 60th day, the mean increased to 3.51, however, remained significantly less than the initial value of 3.85 at p=0.05. The subjects did not receive the IP from 60 days onwards up to 90th day. On 90th day, the mean creatinine content further increased to 3.64 ± 1.99, which was at par with the initial value (3.85) (Figure 1).

Thus the creatinine content attained its original level, after withdrawing the IP for one month.

It was interesting to note that, when the relative values of creatinine content were considered rather than actual content of creatinine in serum, (i.e. difference in the observed creatinine level over the initial assumed level of 100), it was observed that the relative content of serum creatinine was significantly lower not only on 30th and 60th day but also remained so on 90th day at P=0.05 (Figure 2); indicating thereby the continuing/lingering effect of IP even 30 days after withdrawal of the IP.

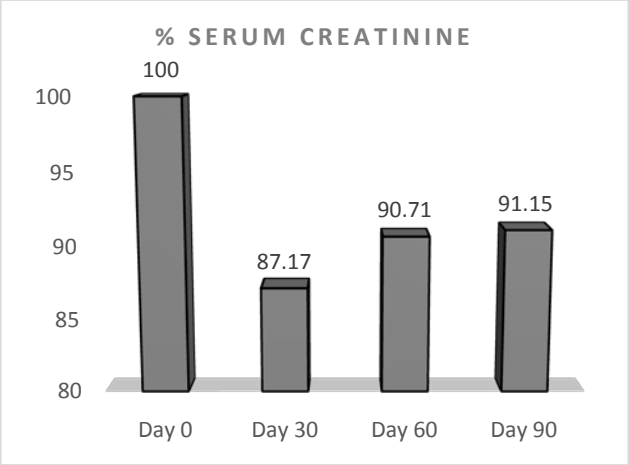

Figure 2. Relative reduction of serum creatinine over a period of 90 days

Similarly, the eGFR remained significantly improved even on 90th day over 0 day indicating continuing/lingering effect of IP even after its withdrawal for 30 days. However, the observations suggest that continued withdrawal further to 90 days may push the patient to the original clinical status at some time after 30 days' withdrawal. Thus, relationship of the cause of administration of Urophyll to the effect of remission in the clinical parameters of CKD is established. At the same time, continuing/lingering effect even after 30 days withdrawal is suggestive of reversion of at least some loss of function of kidney tissue, which is highly significant advance in the science in view of the observation so far that there is a progressive loss in kidney function in CKD and the only recourse available so far was to try and retard the progression of the CKD.

The concentration of Blood Urea in the blood also varied in patients as well as time intervals i.e. 0, 30, 60and 90 days. The urea content decreased from 95.6 at the beginning to 78.95 and 77.27 at 30th and 60th days respectively. On 90th day it increased to 86.33, however, the value was significantly (p = 0.05) lower than that of zero day. Thus, it may be concluded that the IP under investigation was effective in reducing the level of urea in the blood, till the time it is being administered. After withdrawing the IP, the amount of Blood Urea tended to remain statistically lower at p = 0.05 level at least for 30 days. This does indicate carry over very effect of IP which is possible only if there is at least a significant level of revival of kidney function on account of revitalization of the kidney tissue. However, since the trend from 60th to 90thdays is suggesting of slow relapse to 0 day level, it can be reasoned that the revival is subject to continuation of Urophyll, which may hold the further progression at same level or the revival may progress further, and although at a significantly slow rate, it shall provide substantial benefit to the patient. The uric acid content also varied among the patients. However, the variation in uric acid under the influence of IP was statistically non-significant. On an average it had a mean of 5.24 and the values ranged from 5.12 to 5.56 without any effect of either IP or the time period .In human blood plasma, the reference range of uric acid is typically 3.4-7.2 mg/dL (200-430 µmol/L) for men (1 mg/dL=59.48 µmol/L), and 2.4-6.1 mg/dL for women (140-360 µmol/L). Hence, since the mean value at 0 day is within normal range, one would not expect any significant change in it by treatment. Hence, the result is not contrary to any expectation..

The results presented in Table 1 indicated that the IP Urophyll syrup was effective in decreasing Serum Creatinine and urea contents, and in increasing glomerular filtration rate. The effect of Urophyll was persistent till 90th day in case of relative decrease in creatinine level over 0 day, eGFR and Blood Urea, even after withdrawing the IP after 60th day onwards. Thus, it is clear that if serum creatinine level falls, blood urea nitrogen also falls and decrease in them is correlated with increase in eGFR and improvement in Quality of Life. With improvement in these clinical parameters, it follows that albuminuria, proteinuria and hematuria shall also decease and probability of final renal failure will also substantially decrease.

The summary of the results indicated positive and significant effect of Urophyll syrup in reducing the intensity of chronic kidney disease.

3.1. Effect of Urophyll Syrup on Quality of Life

In "Kidney Disease Quality of Life Short Form (KDQOL-SF^{TM}) Version 1.3" following areas were covered: Symptom / Problem (12 items), Effect of kidney disease on daily life (8 items), Burden of kidney disease (4 items), Work status (2 items),Cognitive function (3 items), Quality of social interaction (3 items), Sleep (4 items) and Social support (2 items).

The questionnaire also included a 36-item health survey (RAND 36-Item Health Survey 1.0 or SF-36^{TM}) as the generic core, consisting of eight multi-item measures of physical and mental health status as follows: Physical functioning (10 items),Role limitations caused by physical health problems (4 items), Role limitations caused by emotional health problems (3 items); Social functioning (2 items), Emotional well-being (5 items), Pain (2 items), Energy/fatigue (4 items) and General health perceptions (5 items). No patient attempted question on his/her sexual life, of questionnaire, hence was not analyzed.

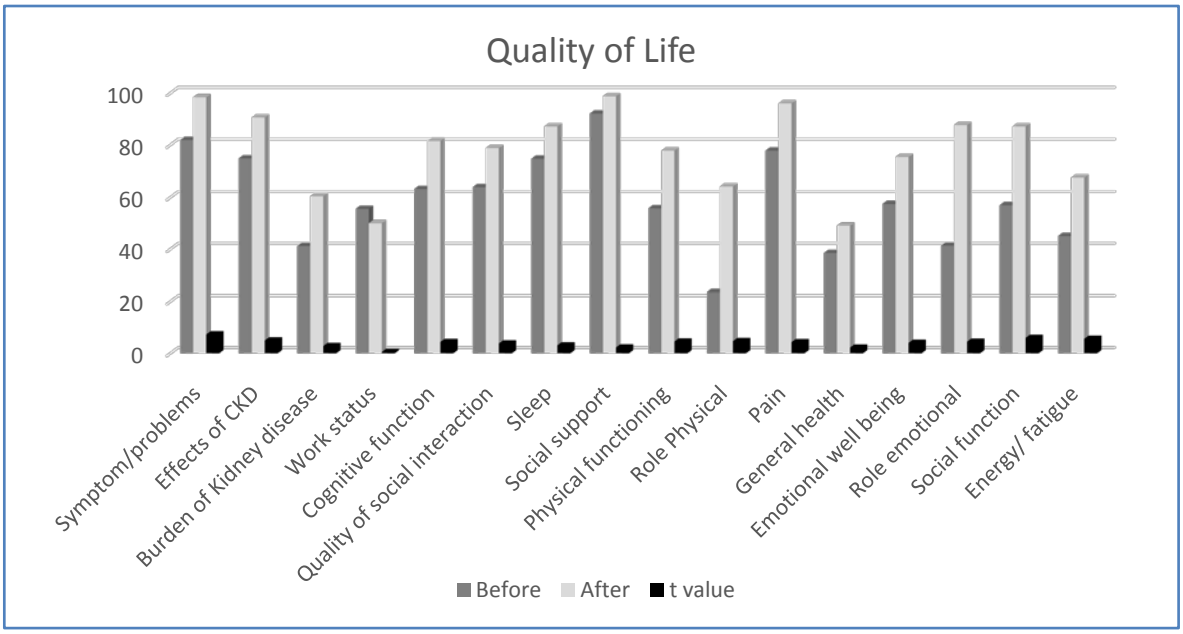

Figure 3. Parameters showing quality of life

The life style of the subjects were recorded before starting the treatment (0 day), as well as, on 60th day. The results obtained at both time periods were compared by employing paired t test. The results indicated that there was significant improvement in almost all parameters, except the work status. Thus, apart from giving relief from chronic kidney diseases, the IP also improved quality of the life among the patients suffering from CKD (Figure 3). Pre-coded numeric values for responses on some of the KDQOL-SF items were in the direction such that a higher number reflects a more favorable health state. However, pre-coded values for some of the items were in the direction such that a smaller number reflects a more favorable health state. The scoring procedure for the KDQOL- SF first transformed the raw pre-coded numeric values of items to a 0-100 possible range, with higher transformed scores always reflecting better quality of life.

Figure 3 shows that the IP effectively improved quality of life and social interaction apart from remission in symptoms of chronic kidney diseases.

This is first report of an orally consumed product which improves, in CKD patients, QOL based on health related criteria. Other methods known so far are management related. It has been stated that“ patient preferences into medical decision making ------QOL can be more important to patients than longevity. ------- There is also a need for clearer understanding of what, if any, interventions improve health related QoL in CKD.” [15]. This requirement is fulfilled for the first time by this investigational Product. A management approach [16] provided that “acceptance” had a significant positive contribution to the prediction of PHQL and MHQL (physical and mental health-related quality of life). Another management approach [17] acknowledges that “To find an equilibrium and improve his/her QoL, the patient should be active and positive regarding his/her own disease. The patient's disease profoundly affects the QoL of spouse and family.”

Improvement in QOL provided by this IP in 60 days is exceptional when compared to current Standard of Care therapy.

3.2. Side Effects

The only side effect observed during the clinical trial was loose motion or diarrhea in some patients. Four patients withdrew after experiencing diarrhea. Rest managed by reducing the dose of 10 or 5 ml per day or to two times a day until they got habituated to IP and reverted to prescribed dose.

4. Discussion

It may thus be concluded from the present study that the Urophyll Syrup seems to be safe particularly in case of the patients suffering from chronic kidney disease, although loose stools/diarrhea needs a little attention; which may be solved in case of patients who have shown that effect by reverting to a smaller dose until the patient gets habituated to the dose and then restoring it to the recommended 10 ml level. As far as efficacy of, Urophyll Syrup is concerned the results obtained on the patients were in favor of the IP, for the entire duration of two months of its administration, the effect of which has also shown to get carried over up to 90 days in case of relative decrease in serum creatinine, eGFR and Blood Urea mg/dl. It may be mentioned that rather than absolute figure of creatinine content, eGFR increase has been seen to remain statistically significant even on 90th day after the IP was discontinued between 60 and 90 days. This suggests some significant degree of reversion of the damage done by CKD to the kidney tissue. This is first report of a product that is directly targeting the kidney. Improvement in all clinical aspects of CKD is implied in achievement of statistically significant improvement in quality of life; which is the most important objective of a CKD treatment that is rarely achieved in currently known CKD treatments prior to the introduction of the IP.

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Statement of Ethics

Subjects have given their written informed consent. The study protocol has been approved by the research institute's committee on human research.

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