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URINE PH MODULATION OF PATIENTS OF UROLITHIASIS WITH NIGHT TIME DOSE OF ALKALI CITRATE - A PILOT STUDY

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KEYWORDS :

INTRODUCTION

Incidence of upper urinary tract disease is increasing worldwide mainly due to life style changes and environmental factors. Wide geographic variations in prevalence across the globe is noted (1-20%).**1** Urolithiasis remains a common urological problem throughout the world. Recurrence is its most troublesome feature . The rate of recurrence is almost 50% in 5-10 years and is dependant on the stone composition and its underlying cause.**2** This poses a challenge to the treating physician as it is associated with significant acute and chronic morbidities. Since , the most affected age group is 30-50 years , the high recurrence rate causes a massive financial burden on the individuals as well as the healthcare system .**3**

Rapid development in technology , minimal access and miniaturization of instruments in the recent years have made the treatment less morbid. However these newer technologies like , flexible ureteroscopy and lasers have also increased the cost of treatment and are not accessible to majority of the rural and low income population .

The pathophysiology of urolithiasis is multifactorial and still remains elusive.Despite several attempts at developing a successful targeted therapy , none have shown promising results or compliance due to the long term nature of the therapies. At present prevention

seems to be the best strategy and is aimed at altering the urinary biochemistry .

Progress has been made in understanding the complex mechanisms by which promoters (Calcium (Ca) , Oxalate (OX) , Phosphorus and Uric acid) and inhibitors (Citrate , Magnesium , Organic substances and Macromolecules) influence stone formation. **4** Along with these inhibitors urinary volume and pH have been found to significantly alter the environment for stone formation. **5** There is unanimity about the role of Supersaturation (SS) as the driving force in stone formation. **5-7** Stones tend to form only when there is high concentration of stone forming minerals that cannot be kept in dissolved state. For upper tract stones , the most common minerals are Ca , OX , Phosphate and urate.

SS depends on increased excretion of stone constituents , urine volume and alteration of pH or the combination of these factors.**8** pH influences the ionic concentration of mineral content of the fluid . Hence it is an important modulator of SS Index .

Over the years , definative role for fluid , diet and alkaline citrate for Ca stones has been established. Diet seems to play a crucial role in urolithiasis.The dietary metabolism and mechanism that control saturation and crystallization in urine are extremely complex and can not be completely addressed by restrictive diet alone**. 9,10** Hence, there is necessity of drugs like alkaline citrate. Alkaline citate has shown favourable effects on urine composition in relation to the risk factors of Calcium Oxalate(CaOX)crystallization. Various dosages of alkaline citrate have been studied. But most authors have used the drug two or three times a day . **11-13** However, considering increased SS for CaOX and low urinary pH during night and early morning hours , single night time dose of alkali citrate can be an attractive option. Night time dose of citrate has been tried previously with good changes in urinary parameters , with the effect of night time dose lasting till 10 AM **.14-15** These studies have paved the way for such an approach. SS and pH are interrelated . SS can not be monitored on day to day basis . However pH can be easily monitored and is cost effective . This study was undertaken to evaluate the effect of a single night time dose of alkali citrate on pH . The main objective of this study was to achieve early morning pH between 5.8 to 6.5 .

METHOD :

We conducted a pilot study of 40 cases in a single institute,low resource set up from August 2019-Jan 2021.Patients were enrolled after written informed consent and approval of Ethics committee.The authors confirm the availability of,and access to, all original data reported in this study**.**

Patients in the age group of 20-60 yrs, with CaOx stone disease(stone analysis by Fourier Transform Infrared Spectroscopy(FTIR) method), in postoperative period and after removal of stent were included. Patients with active UTI , diabetes , uric acid , cystine and infection stones or stones with specific etiology or with anatomical defects, presence of renal or hepatic dysfunction , patients on drugs affecting citrate levels such as Acetazolamide , Topiramate , Ace Inhibitors and pregnant females were excluded .

Detailed history of family diet was taken so as to get information about salt intake . Dietary counselling formed important part of the study.

Protocol for urinary pH recording :

The pH recording was done by a hand held pH meter (**HANNA** instruments from state Romania) by the patient . Correct use of pH meter was demonstrated in the outpatient department . pH was measured at home by the patient and wherever possible cross checked at the hospital. Calibration of pH meter for pH " 4 " and " 7 " was done before each stage.

On days 1-3 , patients were not on any urinary prophylactic medicine or dietary restriction .Detailed dietery history was taken . On days 2 and 3 , the pH reading was done three times a day i.e. early morning (EM), two hours post lunch (PL) and post dinner (PD). From day 4 onwards, for 15 days patients were given 20 or 25 ml (depending on their weight , below or above 60 kgs respectively), diluted in 2 glasses of water, within one hour of dinner**.**

Dietary counseling was done and they were given dietary advice as described below. Interval between reading was always 15 days or more depending on patients work schedule. On days 18-20 detailed dietary history was taken . On days 19 and 20 , the pH reading three times a day as mentioned previously, was taken.

Brief dietary advice was given to all patients. A list of items with high OX , Phosphate , Magnesium ,Potassium , fibres , simple sugars ,Ca , proteins was given to patients . They were asked to avoid animal proteins specially red meat . They were allowed to consume other types of non vegetarian food only for breakfast or lunch. Legumes are to be considered in this category. Alongwith proteins plenty of salads to be consumed. Protein intake to be restricted to 0.8 to 1 gm/kg of body weight. Salt intake to be restricted to 100 to 120 gms per adult per

month. Here family dietary history is of help. Fluid intake advised was two and half to three liters per day and it has to be well distributed so as to achieve clear urine at all times. They were asked to avoid simple sugars. Dinner to be consumed two hours before bed time so as to achieve adequate fluid intake . Dinner should have more items containing magnesium , Potassium e.g. cooked vegetables , salad , banana , papaya , apple , potato with its skin . Vegetables when cooked show drastically reduced soluble Ox content. **16**

Statistical analysis was performed using SPSS 16.0 software . Paired t – test was used to analyse continuous data . Categorical data was compared using Chi – square test . $P < 0.001$ was taken as statistically significant .

RESULTS :

Table 1 Average of two readings of urine pH

Sr No	Morning		Afternoon		Evening	
	BM	N.T	BM	N.T	BM	N.T
1	5.15	5.85	5.6	5.8	5.9	5.9
2	5.3	5.9	5.8	6.0	5.7	5.8
3	5.2	5.85	5.5	5.8	5.3	5.8
4	5.5	5.95	5.85	6.0	5.5	5.7
5	5.55	5.85	5.4	6.1	5.6	6.0
6	5.2	5.8	5.6	6.0	5.1	5.9
7	5.1	5.85	5.9	6.2	5.55	6.0
8	5.0	5.85	5.9	6.1	5.6	5.8
9	5.25	6.0	6.0	6.05	5.55	5.9
10	5.2	5.9	5.6	6.0	5.6	5.8
11	5.1	5.8	5.8	6.0	5.0	5.8
12	5.3	6.2	6.25	6.3	6.0	6.0
13	5.2	5.85	5.9	6.0	5.7	5.8
14	5.2	5.8	5.8	6.1	5.6	5.8
15	5.3	5.9	5.8	6.0	5.4	5.8
16	5.2	6.0	5.8	6.0	5.5	5.8
17	5.35	5.9	5.45	5.9	5.6	5.85
18	5.4	6.15	5.9	6.0	5.3	6.0
19	5.3	5.8	6.0	6.1	5.8	5.6
20	5.5	6.2	6.1	6.3	6.0	5.9
21	5.25	5.85	5.8	5.9	5.8	5.9
22	5.0	5.45	5.5	5.55	5.5	5.6
23	5.5	6.0	5.65	6.0	5.75	6.0
24	5.0	5.8	5.6	5.9	5.7	5.8
25	5.05	5.75	5.6	5.8	5.6	5.7
26	5.1	5.8	5.65	5.7	5.5	5.7
27	5.0	5.8	5.3	5.7	5.2	5.6
28	5.0	6.0	5.45	5.7	5.45	5.6
29	5.0	5.6	5.9	6.0	5.6	5.6
30	5.1	5.7	5.6	5.8	5.6	5.8
31	5.3	6.0	5.9	6.0	5.8	6.0
32	5.25	5.9	5.8	6.0	5.7	5.9
33	5.05	5.4	5.6	5.8	5.55	5.8
34	5.0	5.9	5.45	5.8	5.35	5.8
35	5.2	6.0	5.65	5.8	5.7	5.8
36	5.25	6.0	5.65	6.0	5.7	6.0
37	5.05	6.0	6.0	6.0	5.8	6.0
38	5.6	6.0	6.0	6.0	6.0	6.0
39	5.55	6.1	5.8	6.0	5.7	5.8
40	5.55	6.0	5.6	5.8	5.7	5.8
Total	209.1	235.45	229.45	238.0	224.0	233.15
Mean	5.227	5.886	5.736	5.95	5.6	5.828
BM- Before Medication						
N.T – Alkali Citrate only at night						
S.D	0.18	0.17	0.21	0.16	0.22	0.13

Table 2 :- shows urine pH difference before and after alkali citrate dosage Difference Between Average pH reading

Sr No	Morning	Aftrenoon	Evening
	Difference Bet 1-2	DifferenceBet 1-2	Difference Bet 1-2
1	0.7	0.2	0
2	0.6	0.2	0.1
3	0.65	0.3	0.5
4	0.45	0.15	0.2
5	0.3	0.7	0.4
6	0.6	0.4	0.8
7	0.75	0.3	0.45
8	0.85	0.2	0.2
9	0.75	0.05	0.35
10	0.7	0.4	0.2
11	0.7	0.2	0.8
12	0.9	0.05	0
13	0.65	0.1	0.1
14	0.6	0.3	0.2
15	0.6	0.2	0.4
16	0.8	0.2	0.3
17	0.55	0.45	0.25
18	0.75	0.1	0.7
19	0.5	0.1	0.2
20	0.7	0.2	- 0.1
21	0.6	0.1	0.1
22	0.45	0.05	0.1
23	0.5	0.35	0.25
24	0.8	0.3	0.1
25	0.7	0.2	0.1
26	0.7	0.05	0.2
27	0.8	0.4	0.4
28	1.0	0.25	0.15
29	0.6	0.1	0
30	0.6	0.2	0.2
31	0.7	0.2	0.2
32	0.65	0.2	0.2
33	0.35	0.2	0.25
34	0.9	0.35	0.45
35	0.8	0.15	0.1
36	0.75	0.35	0.3
37	0.95	0	0.2
38	0.4	0	0
39	0.55	0.2	0.1
40	0.45	0.1	0.1
Total	26.35	8.55	9.55
Mean	0.659	0.214	0.239
SD + -	0.176	0.070	0.070

As shown in Table 1 , mean +/- SD of EM, PL , PD pH readings without medication was 5.23 +/- 0.18 , 5.74 +/- 0.21 and 5.60 +/- 0.22 respectively .

Mean SD of PM , PL , PD pH readings after night time dose of alkaline citrate was 5.89 +/- 0.17 , 5.95 +/- 0.16 and 5.83 +/- 0.13 respectively. The two –tailed P value is < 0.001. By conventional criteria , this difference in both situation , is statistically significant.

The total of difference in morning urine pH reading (26.35) was highest as compared to any other time interval .Total difference in afternoon pH reading was 8.55 and evening was 9.55 . The mean +/- SD of difference in morning pH reading was 0.659 +/- 0.176 , afternoon 0.214 +/- 0.07 and at evening 0.239 +/- 0.07. The two-tailed P value is less than 0.001 .By conventional criteria this difference is considered to be extremely statistically significant.

Before medication , all patients showed early morning pH between 5 to 5.5 . Increase in Post lunch & post dinner pH is also noted. Average early morning pH before medication was 5.23 while that after single night time dose was 5.89 i.e. a rise of about 0.66 (12.62 %). Rise in post lunch pH was 0.21 (3.65 %) and that for post dinner was 0.23 (4.10 %) . There was hardly any difference in rise in pH after 25 ml of alkaline citrate against 20 ml .

DISCUSSION :-

The pH of a solution is important modulator of supersaturation. Correction of pH during early morning hours is important to prevent Stone recurrence. This is because

1) CaOX stone formers show low pH during night and early morning hours and show rise in the day time pH. This explains the finding of

increase in pH in post lunch and post dinner period.
2) Though urine is always SS for CaOX , SS is maximum during night time. Highest crystallization risk for CaOX has been noted between pH 4.5 and 5.5 . Crystals formed in this pH range are that of thermodynamically stable COM form .[17] Hence correcting early morning pH beyond 5.8 is important as there is highest possibility of crystallization between 10 pm to 6 am .[18]
3) There is some role of post prandial alkalinity as a physiological response to diet.[19]

There are two mechanisms of nucleation homogenous and heterogenous.

Homogenous nucleation is influenced mainly by ionic concentration of a mineral . But ionic concentration of a mineral is controlled by pH.[20] In case of CaOX ionic concentration of Ca, Ox and citrate are important .
1)Urinary Ca excretion is inversely proportional to urinary pH.
2)Activity of many transport processes involved in handling of Ca , citrate and phosphate are sensitive to pH(e.g.NADC,TRPV5)[21]
3)In acidic pH , majority of citrate is in divalent form (when pH is less than 5.6) .[22]Divalent form gets reabsorbed.50% of the Citrate gets converted to Trivalent form at pH 6.4.[23] Infact pKa of Trivalent Citrate is 5.6 Trivalent form gets excreted in urine and prevents aggregation of CaOx crystals.Trivalent form is known to potentiate action of macromolecules.This way pH influences homogenous nucleation.

Heterogenous nucleation is around Uric acid crystals,Cell Debrie and Calcium phosphate crystal.
1)Acidic PH favours uric acid crystallization as pKa of uric acid is 5.5. Hence early morning pH has to be more than 5.8 to prevent uric acid crystallization and possible heterogenous nucleation of CaOx.
2)Acidic pH is also associated with tubular cell injury and enhanced adhesions of Calcium Oxalate Monohydrate (COM) crystals to tubular cells.Cell proliferation is better after pH6.[24] Debrie from injured cell may promote heterogenous nucleation of CaOx.
3)If pH increases beyond 6.5 it will increase chances of Calcium phosphate crystallization and favour heterogenous nucleation of CaOx.Hence postprandial pH should not increase beyond 6.5.

The main objective of this study was to achieve early morning pH between 5.8 to 6.5 by giving single night time dose of alkali citrate to counter acidic pH seen during night and early morning.

By increasing pH during this period,it is likely to reduce SS index of CaOx which is highest at night.Thus it becomes promising targeted therapy to decrease or possibly eliminate risk of crystallization.In our study rise in early morning pH after alkali citrate is expected as more than 95% of citrate gets absorbed within three hours .Post Lunch and Post dinner rise in pH could also be due to dietary modifications advised.Since rise in early morning pH is marked it cannot be ascribed to dietary modifications.

Due to diurnal variation[25] and postprandial alkalization, urine pH increases in day time as mentioned above.Hence additional daytime alkali Citrate dosage may be couynterproductive as it can increase pH beyond 6.5, giving rise to possibility of Calcium phosphate crystallization.Hence pH has to be maintained below 6.5.

In our study we observed rise in early morning pH of about 0.66(12.62%) after single night time dose.Previous study has observed rise in pH of about 0.6 in 24 hr urine sample.[26] This was noted after 7 days treatment with a night time dose of 20-25ml i.e.60-75mEq of citrate.In our study pH levels were measured after 15 days of treatment with a dose of 20- 25ml depending on patients weight.Rise in pH with 25ml dose(for those with more than 60kg Wt)was comparable to those with 20ml dose(Wt less than 60kg) as endogenous acid secretion increases with Weight.

Another important fact is for a given dose of alkali citrate one may show rise in pH rather than citrate levels while others will show the opposite. Hence dose will have to be ideally individualized by complete analysis of 24 hr urinary parameters. But this is not practicable and economical. pH monitoring is easy and hence practicable.

One may find comparable efficacy of pharmacological and dietary therapy in controlled clinical trial.But adherence to chronic dietary changes is difficult to achieve. Dietary changes will not be able to counter endogenous acid load completely.Hence addition of alkali citrate at right time and right dosage is important. Good compliance with long term therapy is expected since it is a single night time dose.

With promising results of this study ,larger multicentric study with long term follow up backed by 24 Urinary parameters will be of help.We did not analyse change in other urinary parameters as it was undertaken in low resourse setting.Measuring pH becomes feasible, cost effective alternative.

A major drawback is intolerance to alkaline citrate.In such situation we will have to fall back on rigid, restrictive ,individualized dietary regimen with Lemon juice.[27]

CONCLUSION

The pH of a solution is an important modulator of supersaturation . SS Index for CaOx is maximum during night and early morning hours. This needs to be countered with alkali citrate dose in that period , as diet alone will not be sufficient to counter it. Circadian variation of rising urinary pH along with physiological post prandial alkalinization of urine reduces the necessity of day time alkali citrate . Night time dose of alkali citrate thus becomes a promising targeted therapy to correct problematic urinary biochemistry at night .

Disclosures and declarations

Ethical approval : Ethical clearance was obtained from institutional ethics committee , for the study titled " Urine pH modulation of patients of urolithiasis with night time dose of alkali citrate – A pilot study " ; dated 23 /03/2018 proposal no : PGP/Ph.D/Syn – 01/2017. All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional ethics committee and with the 1964 Helsinki declaration and it's later amendments or comparable ethical standards .

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