Follow-Up Study on Management of Tumour Lysis Syndrome with Single Low Fixed Dose (1.5 mg) of Rasburicase - A Tertiary Cancer Centre Experience from India

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ABSTRACT

BACKGROUND

Rasburicase (recombinant urate oxidase) has been proven to be an effective therapy for prevention of tumour lysis syndrome (TLS). The recommended daily dosing regimen of rasburicase is 0.2 mg/kg/day for 5 days which is expensive and unaffordable to many patients in the developing countries. The purpose of the present study was to evaluate the effect of single 1.5 mg dose rasburicase in the management of tumour lysis syndrome.

METHODS

This is a follow-up study done at our institute. Fifty (50) patients with tumour lysis syndrome who received rasburicase from August 2015 to January 2020 were enrolled in this study.

RESULTS

Single dose of rasburicase is effective in decreasing serum uric acid level in significant number (N = 41) of patients. Percentage of patients having uric acid less than 7 mg after single dose of rasburicase in 48 hours - 82.9 % (N = 34) while 17 % (N = 7) were found to have uric acid levels of more than 7 mg/dl. The percentage of patients with uric acid levels more than 7 mg/dl reduced from 36.5 % after 24 hours to 17 % after 48 hours. This indicates that the uric acid levels show a declining trend even after 24 hours without giving an additional dose of rasburicase. There was no relationship between uric acid levels at 24 hours and percentage change in creatinine level from baseline to 24 hours (correlation coefficient (r) = -0.047, P = 0.770. Patients who required additional dose (N = 9) had high base line value of uric acid and their high value was maintained over the follow up period of three days. Patients with pre exiting kidney disease and high level of baseline uric acid also needed dialysis (N = 3).

CONCLUSIONS

In majority of patients, a single 1.5 mg dose of rasburicase is an effective way to reduce raised uric acid in appropriate circumstances.

KEYWORDS

Single Dose, Recombinant Urate Oxidase, Uric Acid, Leukemia, Tumour Lysis Syndrome, Rasburicase

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DOI: 10.18410/jebmh/2021/403

How to Cite This Article:
Ranjan A, Khanna N, Ranjan V, et al. Follow-up study on management of tumorlysis syndrome with single low fixed dose (1.5 mg) of rasburicase- a tertiary cancer centre experience from India. J Evid Based Med Healthc 2021;8(25):2149-2154. DOI: 10.18410/jebmh/2021/403

Submission 06-01-2021,
Peer Review 17-01-2021,
Acceptance 04-05-2021,
Published 21-06-2021.

BACKGROUND

Tumour lysis syndrome is one of the most common cancer therapy-related complications with high morbidity and mortality. It results due to the abrupt release of intracellular metabolites after tumour cell lysis which causes the release of potassium, phosphate, uric acid, proteins and other purine metabolites leading to hyperkalaemia, hyperuricemia, hyperphosphatemia, and secondary hypocalcaemia. Uncontrolled TLS progresses to lactic acidosis and acute renal failure (ARF) resulting in multi-organ damage such as acute kidney injury (AKI), cardiac arrhythmias, and seizures or sudden deaths (Alakel et al.).[1] Rasburicase (recombinant urate oxidase) has been proven to be an effective therapy for the prevention of TLS. The recommended daily dosing regimen of rasburicase for five days is unaffordable to many patients in developing countries such as India. It is administered as an intravenous (IV) infusion over 30 min and should never be given as a bolus. The reconstituted solution can be stored at 2 – 8°C for 24 hours. Repeated use of rasburicase increases risk of hypersensitivity reactions.[2] Herein, we report a case series of 50 patients, including children and adults with malignancy, wherein TLS was managed by a single dose of rasburicase.

METHODS

This is a follow-up study done at our institute. Fifty (50) patients with tumour lysis syndrome who received rasburicase are enrolled in this study. Our study included patients of all age group who received rasburicase during the study period from August 2015 to January 2020. Any patient whose laboratory test or medical history suggested glucose-6-phosphate dehydrogenase deficiency and thus should not receive rasburicase was not included in our study.

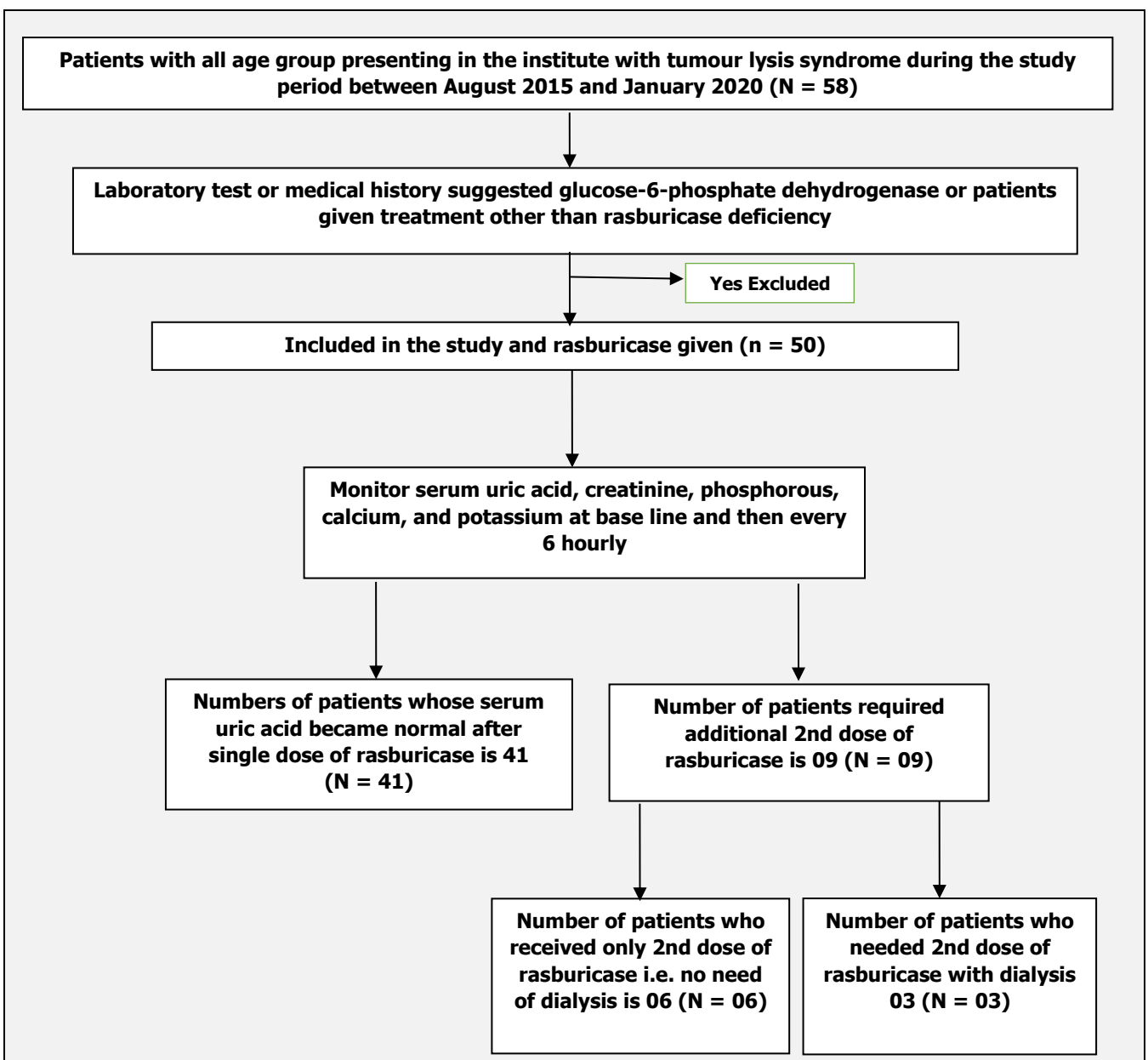

Figure 1. Flow Chart Indicating Recruitment and Follow-Up of Study Objects

In this study, we administered a single dose of 1.5 mg rasburicase with redosing, if indicated. Supportive therapy included hydration, urinary alkalinization, diuretics, and allopurinol depending on the clinical status. Subsequent TLS laboratory monitoring over three days after initial dosing was recorded. Data collection included patient demographics, cancer diagnosis, rasburicase time(s) of administration, baseline and daily uric acid, serum creatinine (S.Cr), and phosphorus concentrations, baseline potassium, white blood cell count (WBC), and lactate dehydrogenase (LDH). Day zero was defined as the day of rasburicase administration. Haemoglobin, white cell count, differential count, serum electrolytes, serum calcium, phosphorous, uric acid, and creatinine tests were done at the time of admission and they were monitored every six hours till the resolution of TLS.

Blood samples were preserved on ice by the personnel handling the specimens to avoid falsely low uric acid levels that may occur because of ongoing uric acid degradation in the blood taken for analysis. When creatinine or uric acid level was measured more than once close to the time of interest (for example 24 or 48 hours after therapy), the highest value was used in the analysis. All procedures performed in the study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants prior to starting the treatment.

Statistical Analysis

The data was collected in the Microsoft Access database and analyzed using statistical package for social sciences (SPSS) for Windows, version 20.0 (IBM Corporation, Armonk, NY). The qualitative variables were expressed as counts and percentages, while the quantitative variables were expressed as means and standard deviations or interquartile range.

Comparisons between means were performed using the Student's t-test for independent samples or the Mann–Whitney U test or one-way analysis of variance (ANOVA) for variables that did not meet the criteria of normality. The chi-square or Fisher's exact test was used for comparisons of proportions. $P < 0.05$ indicate significant differences. The correlation coefficient was obtained by Pearson's method.

RESULTS

Fifty (50) patients with tumour lysis syndrome who received rasburicase are enrolled in this study. The mean age duration of patients was found to be 27.22 ± 17.95 years ranging from 2 years to 65 years out of which 31 were males (62 %) and 19 females (38 %). The male to female ratio was 1.63 : 1. Among the malignancies, four patients (8 %) had diffuse large B-cell lymphoma, seven (14 %) had Burkitt lymphoma, fifteen (30 %) patients were suffering from B cell acute lymphoblastic leukemia (ALL), twelve (24 %) had T Cell ALL, two (4 %) had CLL, 2 (04 %) had CML, two (04 %) had AML and six (12 %) patients had solid tumours. After treatment with rasburicase, serum uric acid declined from 17.14 ± 5.38 mg/dL at baseline to 4.25 ± 2.82 mg/dL at 72 hrs which was statistically significant ($P < 0.0001$).

Statistical analysis was done between the patients who received a single dose of rasburicase and those who required the second dose with or without dialysis. (Table 1 and Table 2)

Variables		Patients who Received only Single Dose (N = 41)	Patients who Received Second Dose (N = 6) (No Dialysis)	Second Dose + Dialysis Patients (N = 3)	P - Value
	Weight	40.95 ± 14.95	51.66 ± 11.96	48.33 ± 11.59	0.201
	TLC	86917.1 ± 106673.9	45850 ± 56749.6	256433 ± 182179.2	0.022
	LDH	1416.53 ± 1506.41	946 ± 429.10	3067 ± 3368.21	0.156
Uric Acid	Baseline	16.32 ± 4.55	20.98 ± 8.30	20.58 ± 6.78	0.070
	24 hrs	6.16 ± 2.71 (-62.2 %)	13.25 ± 2.56 (-36.8 %)	12.46 ± 6.07 (-39.45 %)	<0.0001
	48 hrs	4.42 ± 2.24 (-72.9 %)	10.65 ± 3.51 (-49.2 %)	13.36 ± 8.05 (-35.08 %)	<0.0001
S. Creatinine	Baseline	1.56 ± 1.29	2.21 ± 1.45	1.96 ± 1.20	0.486
	24 hrs	1.13 ± 1.06 (-27.6 %)	1.75 ± 0.49 (-20.81 %)	2.7 ± 2.02 (+40.30 %)	0.036
	48 hrs	1.28 ± 1.24 (-17.9 %)	2.2 ± 0.98 (-0.45 %)	3.1 ± 0.75 (+58.1 %)	0.018

Table 1. Statistical Analysis of Patients Who Received First and Second Dose (with or without Dialysis) of Rasburicase

Forty-one patients received a single 1.5 mg dose of rasburicase. Nine patients received an additional dose of 1.5 mg, 24 hours after the first dose. Based on biochemical assessment (persistent hyperuricemia) three patients required dialysis. In the present study, it was found that 24-hour uric acid was statistically significant between patients who needed a single dose (6.16 ± 2.71); Second dose (13.25 ± 2.56); Second dose + dialysis (12.46 ± 6.07) ($P < 0.0001$). 24-hour creatinine level was statistically significant between patients who needed single dose (1.13 ± 1.06); Second dose (1.75 ± 0.49); Second dose + dialysis (2.7 ±2.02 mg/dl) ($P = 0.036$).

Variables		Patients Who Received Only Single Dose (N = 41)	Patients Who Received Second Dose (with or without Dialysis) (N = 9)	P-Value
	Weight	40.95 ± 14.95	50.55 ± 11.21	0.0763
	TLC	86917.1 ± 106673.9	116044.4 ± 146275.3	0.4918
	LDH	1416.53 ± 1506.41	1653.2 ± 2019.07	0.6899
Uric Acid	Baseline	16.32 ± 4.55	20.85 ± 7.39	0.0205
	24 hours	6.16 ± 2.71 (-62.2 %)	12.98 ± 3.67 (-37.7 %)	<0.0001
	48 hours	4.42 ± 2.24 (-72.9 %)	11.55 ± 5.07 (-44.6 %)	<0.0001

Table 2. Statistical Analysis of Patients Who Received First and Second Dose (with or without Dialysis) of Rasburicase

The baseline uric acid levels for patients who needed only a single dose of uric acid were 16.32± 4.55 mg/dL which was significantly lower ($P = 0.0205$) than the levels in those who needed second dose 20.85 ± 7.39 mg/dL. Patients who needed the second dose also had a higher value of 24 hours of uric acid levels (12.98 ± 3.67) as compared to patients who needed a single dose (6.16 ± 2.71) ($P < 0.0001$). The mean weight of patients who need

an only single dose of uric acid is 40.95 ± 14.95 kg in those who needed the second dose is 50.55 ± 11.21 kg (P = 0.0763). The percentage of patients having uric acid less than 7 mg/dl after a single dose in 24 hours was 63.4 % (N = 26) while 36.5 % (N = 15) were found to have uric acid levels more than 7 mg/dl. Percentage of patients having uric acid less than 7 mg after a single dose of rasburicase in 48 hours was 82.9 % (N = 34) while 17 % (N = 7) were found to have uric acid levels more than 7 mg/dl. The percentage of patients with uric acid levels more than 7 mg/dl was reduced from 36.5 % after 24 hours to 17 % after 48 hours. This indicates that the uric acid levels show a declining trend even after 24 hours without giving an additional dose of rasburicase.

Summary of Results

- Single dose of rasburicase is effective in decreasing serum uric acid level in significant number (N = 41) of patients. Decreased value of uric acid is maintained over follow up period of 3 days (P < 0.0001).
- The baseline uric acid levels for patients who need only single dose of uric acid is 16.32 ± 4.55 mg/dL were significantly lower (P = 0.0205) than the levels in those who needed second dose (N = 9)20.85 ± 7.39 mg/dL.
- Patient who needed second dose also had higher value of 24 hour of uric acid level 12.98 ± 3.67 vs 6.16 ± 2.71 (P < 0.0001).
- Percentage of patients having uric acid less than 7 mg after single dose of rasburicase in 48 hours - 82.9% (n = 34) while 17% (n = 7) were found to have uric acid levels more than 7 mg/dl.
- The percentage of patients with uric acid levels more than 7 mg/dl was reduced from 36.5% after 24 hours to 17% after 48 hours.
- This indicates that the uric acid levels show declining trend even after 24 hours without giving an additional dose of rasburicase.
- Patients required additional dose (N = 9) had high base line value of uric acid and their high value was maintained over follow up period of three days.
- Patients with pre-existing kidney disease and high level of baseline uric acid also needed dialysis (N = 3).
- Tempo of decreasing uric acid level is also an important factor for deciding the need of additional treatment.

DISCUSSION

Hande and Garrow[3] classified TLS as laboratory TLS (LTLS) or clinical TLS (CTLS). Cairo and Bishop[4] modified these criteria to formulate a commonly used classification system for TLS.

According to this system LTLS defined when two or more of the following criteria are met within 3 days before or 7 days after the commencement of chemotherapy in spite of adequate hydration and use of uric acid reducing agent:

1. 25 % decrease from baseline in serum calcium, and/or
2. 25 % increase from baseline in the serum values of uric acid, potassium, or phosphorous.

CTLS is defined as LTLS accompanied by one or more clinical manifestations such as cardiac arrhythmia, AKI, seizure, or death with an elevated serum creatinine > 1.5 ULN (upper limit of normal) (Sevinir et al.).[5]

TLS requires early intervention with proper hydration and anti-hyperuricaemic drugs being the key in the management of TLS. Delay in treatment of laboratory TLS may lead to clinical TLS which further delay the definitive treatment and lead to poor outcomes.

Our data demonstrate the effectiveness of a single 1.5 mg dose of rasburicase, repeated if required, in lowering serum uric acid levels in patients with TLS due to various malignancies. Many published studies support the low and single dose of rasburicase. (Table 3)

Reference	Patients (N)	Study Design	Type of Malignancy Included	Dose/Duration	Uric Acid Response
Hutcherson (2006)[6]	11	Retrospective	AML, MM, BL, MDS, CLL, adenocarcinoma, lung cancer	6 mg x 1 (0.045 – 0.1, mg/kg)	Decreased to < 8 mg/dL within 12 – 18 h in 10 pts.
Trifilio (2006)[7]	43	Retrospective	Plasma cell dyscrasias, NHLAML, CLL, MDS	3 mg x 1 (average 0.035 mg/kg)	Median decrease of 43 % in 24 h; 37 pts received 1 dose
McDonnell (2006)[8]	11	Retrospective	NHL, AML, CMML, ALL, MDS, BL, CML	6 mg x 1 (0.023 – 0.136 mg/kg)	Median decrease of 83 % (11.7–2 mg/dL) in 10 pts. within 24 h
Campara (2009)[9]	21	Retrospective	Acute/chronic leukaemias, NHL, MM, PCL, myelofibrosis	0.15 mg/kg average x 1 (0.11 – 0.24 mg/kg)	Decreased by 89.7 ± 9 % for all pts. within 24 h (P < 0.001)
Knoebel (2010)[10]	48	Retrospective	Leukemia/lymphoma > $50x10^9$/ L, LDH > 2 ULN, S.Cr > 1.5 mg/dL	0.05 mg/kg x 1	Maintained <8 mg/dL in 40 pts. (P < 0.001)
Antony R (2015)[11]	55	Retrospective	High risk haematological and solid tumours	Single 1.5 mg dose	52 patients UA levels reduced with 24 h, and by day 3. All patients UA levels reduced to normal after administration.
Jayabose (2014)[12]	41	Retrospective	Acute leukemia, NHL	Single dose 0.15 mg/kg	Twenty-seven needed only one dose; 12 needed 2 or 3 doses; and two needed 5 doses each. One child required dialysis
Kukkar (2016)[13]	15	Retrospective	Hematologic malignancies at risk for TLS	Single dose 0.15 mg/kg	Single dose of rasburicase produced a rapid and sustained therapeutic effect of lowering the plasma UA levels in all the 15 patients
Present study	50	Follow-up Study	ALL Burkitt's Lymphoma Solid Tumours DLBCL, ALL, CML, AML, CLL	1.5 mg single dose	Median decrease of 62.2 % (6.16 ± 2.71) in 41 patients within 24 hours (P < 0. 0001)

Table 3. Comparison with Various Studies of Low Dose Rasburicase

ALL- acute lymphoblastic leukemia; AML- acute myeloid leukemia; CLL- chronic lymphocytic leukemia; CML- chronic myeloid leukemia; CMML-chronic myelomonocytic leukemia; LDH - lactate dehydrogenase; MDS - myelodysplastic syndrome; NHL- non-Hodgkin's lymphoma; NR - not reported; S. Cr - serum creatinine; ULN - the upper limit of normal; WBC - white blood cells. BL- Burkitt's lymphoma; MM- multiple myeloma.

Our results were similar to findings presented by Trifilio et al.[14] which included 247 patients in which a single dose of 3 mg rasburicase, was administered in 236 cases and repeated if required. Our data also supports the findings presented by Latha et al.[15] done at Sri Ramachandra Medical Centre, Chennai, Tamil Nadu, India. It was a retrospective analysis of case records of seven children with acute lymphoblastic leukemia (ALL) and TLS. Out of 7 children, 2 were females and 5 were males. Out of these 7, 3 had T-cell ALL and 4 had pre-B-cell ALL. At the time of admission highest and lowest uric acid levels were found to be 32.2 mg/dl and 9.7 mg/dl, respectively. In all seven patients a single dose of rasburicase resulted in a swift and sustained therapeutic effect of lowering the plasma uric acid levels.

Serum Uric Acid

Trifilio et al.[14] study included 247 patients in which a single dose of 3 mg rasburicase was administered in 236 cases (Table 4)

Parameter	Present Study	Trifilio et al.[14]
Percentage of the patient had uric acid less than 7 after a single dose in 24 hours	63.4 %	72 %
Percentage of the patient had uric acid less than 7 mg after a single dose of rasburicase in 48 hours	82.9 %	97 %
Less than 5 after a single dose in 24 hours	31.7 %	48 %
Less than 5 mg after a single dose in 48 hours	63.4 %	80 %
Baseline uric acid for patient not achieved level less than 7 after 24 hours	12.82-24.92 mg/dl	8.1-27.3 mg / dl
Baseline uric acid for patient not achieved less than 5 mg after 24 hours	11.78-22.76 mg/dl	7.2-27.3 mg / dl

Table 4. Comparison of Present Study with Trifilio et al.[14]

In Trifilio et[14] al. the percentage of patients with uric acid levels, less than 7 mg/dl after 24 hrs and 48 hrs and less than 5 mg/dl after 24 hrs and 48 hrs were 72 %, 97 %, 48 %, and 80 % while in this study these parameters were found to be 63.4 %, 82.9 %, 31.7 %, and 63.4 % respectively. The baseline uric acid levels for patients required only one dose were significantly lower than the levels in those who required additional treatment. Correlation between baseline and 24-hour uric acid in subjects who achieved valueless than 7 after 24 hours – correlation coefficient (r) = -0.181, P = 0.365. Correlation between baseline and 24 hour uric acid in subjects who achieved value less than 5 after 24 hours - correlation coefficient (r) = -0.246, P = 0.418.

Serum Creatinine

In the present study, it was found that though there were changes in creatinine after treatment by rasburicase from baseline 1.66 ± 1.29 mg/dL to 1.34 ± 1.25 mg/dL at 48 hrs it was statistically non-significant (P = 0.452). 41 patients required single dose of rasburicase. These patients had baseline creatinine of 1.56 ± 1.29 mg/dl which gradually decreased to 1.28 ± 1.24 mg/dl in 48 hours. Patients who required dialysis had higher baseline creatinine due to pre-existing renal disease and their creatinine increased from 1.96 ± 1.20 mg/dl at baseline to 3.1 ± 0.75 at 48 hours. There was no relationship between uric acid levels at 24 hours and percentage change in creatinine level from baseline to 24 hours (correlation coefficient (r) = -0.047, P = 0.770.

CONCLUSIONS

Single low dose of rasburicase is an effective way to correct raised uric acid in tumour lysis syndrome patients. We can repeat it when appropriate responses are not seen. This approach reduces the cost of treatment, hence very useful in developing countries.

Study Limitations

The present study included only patients who received low dose rasburicase, and controls were not included. The study included a sample of 50 patients only. Further research with larger sample size and including controls is needed to increase the power of the study.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.
The authors acknowledge the help and guidance of faculty and staff of the department of medical oncology of Gujarat cancer and research institute as well as co-operation received from patients.

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