Role of Hypouricemic Agents in Tumor Lysis Syndrome: A Meta-Analysis

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Authors’ contributions

This work was carried out in collaboration among all authors. Author WA designed the study. Authors AA and RA performed the statistical analysis. Authors HA, AA and JAA took part in literature survey. Authors AA, OA, AB and FA managed the data extraction and Interpretation of data. Authors WA and MA wrote the original draft. Authors HA, SA, AA, MA wrote, reviewed and edited the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Objective and background: Tumor lysis syndrome (TLS) is a life-threatening emergency and demands emergency care of effective outcome with minimal or no side effects. The Hypouricemic agents, including Rasburicase, Allopurinol and Febuxostate used for the management of TLS. This

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study was designed to evaluate the Role of Hypouricemic agents by analyzing TLS development rate, control of uric acid, and Creatinine levels.

**Methods:** An extensive electronic data search was conducted by using all leading scientific databases. Twenty-six studies were selected to conduct this study, as per the inclusion criteria.

**Results:** The Odd ratio of TLS development rate was 4.06, 1.24, and 1.49 by Rusbricase, Allopurinol & Febuxostate administration respectively. 95% confidence interval was reported by selected studies against TLS development rate, Uric acid, and Creatinine levels by administrating Rusbricase, Allopurinol & Febuxostate.

**Conclusion:** All Hypouricemic agents, including Rasburicase, Allopurinol and Febuxostate, are effective to manage Tumor lysis Syndrome. However, a suitable and most effective intervention dose needs to identify with better efficacy and minimal side effects both in Adults and Children.

**Keywords:** Tumor lysis Syndrome (TLS); hypouricemic agents; rusbricase; allopurinol; febuxostate.

### 1. INTRODUCTION

Tumor lysis syndrome (TLS) is a frequently reported urgent care emergency of cancer healthcare facilities that mostly required hospital admission. TLS turn up by expeditious leakage of cell components by multiplying cancer cells. Due to the technology advancements and management strategies, more efficient therapies are available to control TLS and its consequences. TLS mostly seen in hematologic and solid malignancies, and identified by certain biochemical indicators; such as hyperuricemia, hyperkalemia, hypocalcemia etc. [1-3]. These biochemical indicators released from the cell because of cell lysis. Uric acid nephropathy or acute urate nephropathy (AUAN) is the most common associated characteristic of TLS [1-3].

TLS appeared after administration of cytotoxic drugs or chemotherapeutic agents, used in blood malignancies like acute lymphoblastic leukemia (ALL), acute myeloid leukemia, B-cell non-Hodgkin lymphoma (NHL) or Burkitt’s lymphoma [1-4]. TLS can also see if chemotherapeutic drugs used for other life-threatening conditions or often be seen without any history of chemotherapeutics, called as spontaneous TLS [3,4]. The conventional therapeutics used to increase chances of TLS formation are; dexamethasone, bortezomib, thalidomide, and rituximab; radiotherapy in case of solid cancers and total-body irradiation (TBI) [4].

TLS have different diagnostic features and categorized on the basis of diagnostic and clinical features into different groups. Clinical TLS based on clinical features and laboratory TLS based on laboratory identification are the two broad categories of TLS. The most adapted criteria was defined by Cairo & Bishop [1,2], which was amended by Howard in the ten years ago in 2018 [3]. Due to cell lysis in TLS, lactate dehydrogenase (LDH) was released, identified by simple blood testing and considered as one of the salient identification marker of disease progression. Tumor cells also have high phosphorus content [1,5], and the increased levels of biomarkers including calcium, which accumulates in the human body to promote nephrocalcinosis. TLS used to treat by continuous monitoring, hydration therapy, and administration of hypouricemic agents [1]. However, Hypouricemic agents specifically including allopurinol & Rasburicase and biomarkers accumulation responsible for the acute renal disorder [1,6,5]. Therefore, hypouricemic agents must be used after complete risk assessment. The recommended dose of allopurinol for adults is up to 800 mg daily and up to 300 mg daily in children. The recommended dose of Hypouricemic agents administered in every 8hours a day and also according to the patient’s body weight [1]. Rasburicase is the second most commonly used Hypouricemic agent, mostly used in critical patients. The recommended treatment dose is 0.2 mg/kg per day for almost a week, and continuation of treatment depending on the patient’s response. Febuxostat, is a new therapeutic recommended in patients with allopurinol allergy or intolerance [1].

To design this systemic review meta-analysis, our aim was to identify and report the Role of Hypouricemic agents in Tumor lysis Syndrome based on scientific literature reported.

### 2. METHODS

#### 2.1 Literature Search Strategy

Data searching was processed from all pronounced scientific databases including Medline, Google Scholar, Scopus, Embase, and Cochrane up to April 2021. Three authors of the team were responsible to perform an extensive
searching of relevant scientific literature independently. A variety of keywords were defined to avoid any discrepancy and data loss. The defined keywords were; Hypouricemic agents, Tumor lysis; OR Hypouricemic agents, TLS; OR allopurinol, Tumor lysis; OR allopurinol, TLS; OR Rasburicase, Tumor lysis; OR Rasburicase, TLS; OR Febuxostat, Tumor lysis; OR Febuxostat, TLS; allopurinol, uric acid; OR allopurinol, creatinine; Rasburicase, uric acid; OR Rasburicase, creatinine; OR Febuxostat, uric acid; OR Febuxostat, creatinine. The reference section of screened studies was also analyzed to identify any missed literature during electronic search.

2.2 Inclusion Criteria

The defined inclusion criteria were: (1) All the published scientific literature reported the use of any of the Hypouricemic agents such as allopurinol, Rasburicase, and Febuxostat in Tumor lysis syndrome (2) Measurable effect of Hypouricemic agents should be reported (3) The criteria of TLS categorization should be clearly defined (4) Categorization of Tumor should be reported (5) No age criteria were imposed, both adult and Children studies are included (6) Reporting of Intervention dose and treatment duration of Hypouricemic agents (7) All full-text studies were included retrospective data review, randomized control trials, original research articles, descriptive and analytic studies (cohort or case-control) (8) No gender, ethnicity, and population, criteria were imposed (9) All studies were published in English language.

2.3 Exclusion Criteria

Studies were excluded from the study (1) won’t meet the inclusion criteria (2) Incomplete studies (3) Case reports, reviews, editorials, and meta-analysis (4) Conference Presentations

2.4 Outcome Measures

Primary: TLS development rate in response to Hypouricemic agents
Secondary: Evaluation of Uric acid and Creatinine after TLS development

2.5 Selection of Data

Two assigned authors of data extraction, process the data selection independently. Critically analyze the study titles, and Abstracts to identify if they fulfill the inclusion criteria. Full text, complete studies thoroughly analyzed to clear any selection doubts. The difference of study selection between the authors was discussed and mutually decides by consensus for inclusion.

The required data of MA was extracted including study design, Treatment duration, used therapeutic and intervention dose, population type, disorder diagnosed, primary & secondary outcome, and NOS score. Odd ratio (OR) and confidence interval (CI) was calculated from available quantitative outcome. Confidence Interval (CI) should be 95%.

2.6 Risk of Bias Assessment

Funnel plot was designed of selected studies and parameters to avoid publication bias.

2.7 Quality and Grading Assessment of Selected Studies

The Newcastle-Ottawa scale (NOS) was used to assess the quality of selected studies. According to NOS scoring, high quality studies graded >7 score, 5-7 for medium quality studies, and <5 for low quality studies.

2.8 Involvement of Patient and Public

It’s a systemic review meta-analysis, and neither required patient nor public involvement in this study.

2.9 Statistical Analysis

Statistical analysis was conducted by using Rev Man software. Forest plots were used to perform to conduct this meta-analysis. OR and its respective CI of each selected study were used to conduct forest plot presentation. The forest plots were drawn against the TLS development rate for Allopurinol, Rusbricase, and Febuxostat. Uric Acid and Creatinine levels against each drug were also determined by conducting forest plot drawing. Study heterogeneity was identified by using Chi² and I² tests. Funnel plot analysis was performed to identify publication bias.

3. RESULTS

The extensive data search ends up getting 26 studies fulfilling the inclusion criteria to conduct this systemic review meta-analysis. Selected studies were published from 1998 to 2017.
Twenty studies reported the use of Rasburicase whereas 06 studies were based on Allopurinol and Febuxostate. We did not filter the population group in this study, however; the adult population group was the most prevalent one among selected studies. Sixteen studies (61.5%) studies were based on the adult population group, children and adult and children population group were based on 05 (19.2%) studies of each group. Table 1 presented the overview of all selected studies.

Six included studies have reported the effect of both Allopurinol and Febuxostate. The NOS score was calculated individually for these studies to evaluate the better quality outcome. Six studies scored 8, and 04 scored 9, categorized as high quality. Twelve studies scored between 5-7 and referred to as medium quality, whereas six studies scored <5 and categorized as low quality. NOS score was not available for 04 studies.

3.1 Analysis of Primary and Secondary Outcomes

We evaluated TLS development rate, Uric acid levels, and creatinine levels against each of the Hypouricemic agents including Allopurinol, Rusbricase, and Febuxostate. Twenty studies evaluated against Rusbricase and six each for Allopurinol and Febuxostate. 95% confidence interval was calculated against each parameter, see Figs. 1-3.

3.2 Analytical Outcome of Rusbricase Administration

Rusbricase administration was evaluated from our first selected study from 1998 to 2011. The overall effect of Rusbricase TLS development rate, uric acid level, and creatinine level was p=<0.0001. The heterogeneity was Chi² 7.80, 477.91, and 600.63 for TLS development, Uric acid level, and Creatinine level, respectively. The calculated odd ratio of the TLS development rate by the Rusbricase administration was 4.06, see Figs. 1a, 2a, & 3a.

3.3 Analytical Outcome of Allopurinol and Febuxostate Administration

Among the included studies, the Allopurinol and Febuxostate administration was reported from 2014 to 2017. The overall effect was p=<0.12, of TLS development rate evaluation, and p=<0.00001 for uric acid and creatinine level. The Odd ratios of TLS development rate were 1.24, and 1.49 for Allopurinol & Febuxostate, see Figs. 2b,c & 3b,c.

Funnel plot was calculated against each parameter to rule out any risk of bias.

4. DISCUSSION

The current study reported the Role of Hypouricemic agents, including Rasburicase, Allopurinol, and Febuxostate in Tumor lysis Syndrome. To the best of our knowledge, this is the first meta-analysis to analyze all three Hypouricemic agents in TLS management. TLS is a fatal pathological condition that needs emergency management, otherwise leads to life-threatening consequences.

The first included study of Rasburicase administration was reported by Lascomb et al. in 1998 of kidney failure in response to TLS management [7]. Later on, many studies and trials were conducted to execute a more refined outcome. Included studies used different intervention doses and duration and monitor the outcome with the help of Uric acid and creatinine levels. Intervention dose of 0.045 mg to 6 mg/kg were used depending on the number of shots per day and treatment duration. Based on the control trial, a single dose of 6 mg/kg rasburicase able to correct uric acid levels in adults, with apparently no adverse events reported [15]. However, another study warns against the administration of 6mg/kg rasburicase due to the high risk of TLS development [12]. Low-dose rasburicase is also effective in most patients and also has less possibility of TLS development. The only concern is that not all patients respond to low-dose rasburicase and took a long time to correct biochemical markers [23]. Campara et al. evaluated another approach and concluded that a low dose of 0.15 mg/kg rasburicase able to correct uric acid levels for 48 hours to control and maintain uric acid levels [21]. A dose of 0.4 mg/dl to 4.8 mg/dl rasburicase were used in Children [8]. Adverse events were not reported in all studies and we also not outline it as Outcome measure. However, few studies reported the withdrawal of patients because of adverse events reporting [19,12,19,21,22,25].
### Table 1. Overview of selected studies

| S. No. | Author & Reference no. | year | study design | Treatment duration | Drug | Intervention (mg/dl) n = no. of patients | Study group | Type of disorder | Primary outcome | secondary outcome | NOS score |
|--------|------------------------|------|--------------|-------------------|------|---------------------------------------|-------------|-----------------|-----------------|------------------|-----------|
| 1      | Lascomb [7]            | 1998 | Control trial| 7 days            | Rasburicase | Rasburicase 0.15 mg/kg/d (n 17)        | Children & adults | Risk of hyperuricemia with non-Hodgkin lymphoma, ALL, or nonacute lymphoid leukemia | WBC, LDH, UALs | UAL; Cr and phosphate | 4         |
| 2      | Bosly [8]              | 2003 | Control trial| 7 days            | Rasburicase | Rasburicase 0.2 mg/kg/twice daily for first 72 h (n 112) | Children | Cancer; risk for hyperuricemia | UALs | UAL | 6         |
| 3      | Coiffier [9]           | 2003 | Cohort       | 6 days            | Rasburicase | Rasburicase 0.2 mg/kg/d (n 100)       | Children | Risk of hyperuricemia | N/A | N/A | 5         |
| 4      | Poliesech [10]         | 2003 | Cohort       | 5 days            | Rasburicase | Rasburicase 0.2 mg/kg/d (n 5)         | Adults     | Hematologic malignancy; high risk of TLS | N/A | UAL; Cr | 4         |
| 5      | Pui [11]               | 2005 | Control trial| 7 days            | Rasburicase | Rasburicase 0.20 mg/kg; median of 3 d of dosing (range 1-7) (n 72) | Adults     | Patients with cancer; risk of acute hyperuricemia and TLS | Control of UALs during induction phase of chemotherapy | N/A | 9       |
| 6      | Mc Donnel [12]         | 2005 | Retrospective| 5 days            | Rasburicase | 6 mg (single dose) ALLO                | Adults     | hematological malignancy | UALs below reference values; AEs; AKI | AE | 5       |
| 7      | Wang [13] (Wrand)      | 2006 | Cohort       | 5 days            | Rasburicase | Rasburicase 0.2 mg/kg for 1-7 d; median of 4 d of treatment (range 2-6) (n 27) | Adults     | ALL; high-grade lymphoma; AML, multiple myeloma; hyperuricemia | N/A | 6         |
| 8      | Ho [14] (Hu)           | 2006 | Retrospective| 5 days            | Rasburicase | 0.15-0.2 mg/kg, subsequent doses given based on TLS parameters; ALLO was permitted after 24 h | Children | leukemia | N/A | AE; pts requiring HD; treatment duration | 4         |
| 9      | Hutcherson [15]        | 2006 | Retrospective| 2 days            | Rasburicase | 0.045-0.1 mg/kg ALLO 300 mg/d        | Children | high or potential risk for TLS | N/A | Evaluation of the renal protection | 4         |
| 10     | Llinares [16]          | 2006 | Retrospective| 2 days            | Rasburicase | Exposed: 6 mg                         | Children & | high or potential risk for | N/A | AE; pts | 5         |
| S. No. | Author & Reference no. | Year | Study design | Treatment duration | Drug | Intervention (mg/dl) | Study group | Type of disorder | Primary outcome | Secondary outcome | NOS score |
|-------|------------------------|------|--------------|-------------------|------|---------------------|-------------|-----------------|----------------|------------------|-----------|
| (Linare) | Lower fixed-dose group (n 7); nonexposed: 0.15 mg/kg/d for 5 d (weight-based dose group) (n 25) | | | | Rasburicase | Adults | TLS; | requiring dialysis | | | | |
| 11 | Steel [17] | 2006 | Retrospective | 6 days | Rasburicase | 0.05 mg/kg, 2nd dose given based on TLS parameters ALLO | Adults | leukemia | N/A | | 5 |
| 12 | Reeves [18] | 2008 | Retrospective cohort | 24 hours | Rasburicase | Rasburicase 7.5 mg, single dose (n 17) | Children & Adults | cancer/ chemotherapy | Normalization of UALs to 8 mg/dL | UAL | 5 |
| 13 | Ishizawa [19] | 2009 | Randomized control trial | 3 days | Rasburicase | Rasburicase 0.15 mg/kg, once daily for 5 consecutive d (n 25) | Children & Adults | high or potential risk for TLS; | Reduction of plasma UALs | | 8 |
| 14 | Chow [20] | 2009 | Retrospective | 2 days | Rasburicase | 0.15 mg/kg (single dose) ALLO | Adults | risk of urecemia | N/A | UA exposure; no. of doses required to maintain normal UAL; decreased kidney function; electrolyte abnormalities, clinical safety Hematologic and clinical chemistry; antirasburicase Abs; AEs | 6 |
| 15 | Campara [21] (Kompara) | 2009 | Retrospective | 6 days | Rasburicase | 6 mg (single dose) ALLO | Children | malignancy | N/A | | 4 |
| 16 | Cortes [22] | 2010 | Randomized control trial | 1 day | Rasburicase | Rasburicase (0.2 mg/kg/d) for 5 d (n 92); (2) | Adults | active leukemia/ lymphoma | Serum UA; Cr; Ca; P; sodium; K; LDH; CBC | | 6 |
| S.No. | Author & Reference no. | Year | Study design | Treatment duration | Drug | Intervention (mg/dl) | n = no. of patients | Study group | Type of disorder | Primary outcome | Secondary outcome | NOS score |
|-------|------------------------|------|--------------|-------------------|------|---------------------|-------------------|-------------|------------------|----------------|------------------|-----------|
| 17    | Knoebel [23]           | 2010 | Retrospective| 6 days            | Rasburicase | 4.5 mg (single dose) | Adults hematological malignancy | N/A         | UALs; % reduction of UALs; no. of patients requiring additional doses; changes in kidney function; costs | 6 |
| 18    | Yim [24]               | 2010 | Retrospective| 4 days            | Rasburicase | Exposed: 0.2 mg/kg/d for 1 d (n 6); nonexposed: ALLO (n 17) | Adults Hyperuricemia | N/A         | UALs; % reduction of UALs; no. of patients requiring additional doses; changes in kidney function; costs | 5 |
| 19    | Raj [25]               | 2011 | Randomized control trial | 2 days            | Rasburicase | Rasburicase, single dose, as needed (max 5 doses over 5 d) (n 40) | Adults Hematologic malignancies | Reduction of plasma UALs | Rate of UAL decline; urinary allantoin levels & excretion rate; kidney function (serum Cr, CCr, K and P or Ca levels), AEs | 5 |
| 20    | Tirifilio [26]         | 2011 | Retrospective| 3 days            | Rasburicase | 3 mg; subsequent doses were allowed | Adults hematological malignancy | N/A         | UALs; % reduction of UALs; no. of patients requiring additional doses; changes in kidney function; costs | 4 |
| 21    | Maie [27]              | 2014 | Retrospective cohort | 6 days            | Febuxostate | 40 mg/day | Adults hematological malignancy | N/A         | UALs; % reduction of UALs; no. of patients requiring additional doses; changes in kidney function; costs | 8 |
|       | Maie                   | 2014 | Retrospective cohort | 6 days            | Allopurinol | 300 mg/day | Adults hematological malignancy | Change in UALs | Normalization of UAL; laboratory | NA |
| S. No. | Author & Reference no. | year | study design | Treatment duration | Drug | Intervention (mg/dl) | n = no. of patients | Study group | Type of disorder | Primary outcome | secondary outcome | NOS score |
|-------|------------------------|------|--------------|-------------------|------|---------------------|---------------------|-------------|----------------|----------------|-----------------|-----------|
| 22    | Takai [28]             | 2014 | Prospective cohort | 6 days          | Febuxostate | 60 mg/day         | Adults              | hematological malignancy | N/A            | UAL; normalization of UALs; kidney failure | NA       |
|       | Takai                  | 2014 | Prospective cohort | 6 days          | Allopurinol  | 200 mg/day        | Adults              | hematological malignancy | Plasma UA response rate | N/A            | NA                   |          |
| 23    | Spina [29]             | 2015 | Randomized control trial | 6 days      | Febuxostate | 120 mg/day        | Adults              | hematological malignancy | N/A            | UAL; TLS clinical and laboratory parameters | 9        |
|       | Spina                  | 2015 | Randomized control trial | 6 days      | Allopurinol  | 600 mg/day        | Adults              | hematological malignancy | N/A            | _               | 8        |
| 24    | Sharma [30]            | 2016 | Randomized control trial | 3 days      | Febuxostate | 40 mg/day         | Adults              | CML                     | N/A            | _               | 8        |
|       | Sharma                 | 2016 | Randomized control trial | 3 days      | Allopurinol  | 200-300 mg/day    | Adults              | CML                     | Normalization of UALs | N/A            | _              | 9        |
| 25    | Tamuru [31]            | 2016 | Randomized control trial | 5 days      | Febuxostate | 60 mg/day         | Adults              | Any malignancy          | N/A            | Kidney failure; electrolytes; UAL; Ca | 8        |
|       | Tamuru                 | 2016 | Randomized control trial | 5 days      | Allopurinol  | 300 mg/day        | Adults              | Any malignancy          | N/A            | UAL UAL |          |
| 26    | Kishimoto [32]         | 2017 | Retrospective cohort | a dose/24 hour | Febuxostate | 10 mg/day         | Children & Adults | hematological malignancy | N/A            | _               | 9        |
|       | Kishimoto              | 2017 | Retrospective cohort | a dose/24 hour | Allopurinol  | 300 mg/day        | Children & Adults | hematological malignancy | N/A            | _               | NA       |

N/A: Not available, WBC: White blood cell, LDH: lactate dehydrogenase, UALs: Uric acid levels, Cr: Creatinine, Ca: Calcium, P: Phosphorus, K: Potassium, CBC: Complete blood count, AKI: Acute kidney injury, AE: Adverse events
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**Fig. 1(a).** TLS development rate for Rasburicase

**Fig. 1(b).** TLS development rate for Allopurinol

**Fig. 1(c).** TLS development rate for Febuxostate
### Uric acid level for Rasburicase

| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Mean Difference IV, Fixed, 95% CI | Mean Difference IV, Fixed, 95% CI |
|-------------------|------------------|----|-------|--------------|----|-------|-----------------------------------|-----------------------------------|
| Kishimoto (A)     | 70               | 25 | 100   | 20           | 10 | 100   | 12.6%                            | 60.00 [44.72, 55.28]              |
| male (A)          | 30               | 20 | 100   | 40           | 20 | 100   | 11.5%                            | -100.00 [-154.3, -142.2]          |
| Sharma (A)       | 30               | 15 | 100   | 45           | 10 | 100   | 29.2%                            | -150.00 [-214.3, -216.47]         |
| Spina (A)         | 20               | 20 | 100   | 50           | 15 | 100   | 14.7%                            | -300.00 [-349.9, -251.1]          |
| takai (A)         | 40               | 20 | 100   | 60           | 10 | 100   | 18.3%                            | -200.00 [-24.28, -15.82]          |
| Tamuru (P)        | 72               | 20 | 100   | 82           | 15 | 100   | 14.7%                            | -100.00 [-149.2, -51.02]          |
| Total (95% CI)    | 560             | 300 | 800   | 400          | 200 | 1000 | -8.59 [-10.47, -6.71]            |

**Heterogeneity:** $\chi^2 = 568.03, df = 5 (P < 0.00001); I^2 = 99%  
Test for overall effect $Z = 8.87 (P < 0.00001)$

### Uric acid level for allopurinol

| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Mean Difference IV, Fixed, 95% CI | Mean Difference IV, Fixed, 95% CI |
|-------------------|------------------|----|-------|--------------|----|-------|-----------------------------------|-----------------------------------|
| Kishimoto (A)     | 55               | 40 | 75    | 72           | 50 | 75    | 3.5%                             | -17.00 [-31.49, -2.51]            |
| male (A)          | 65               | 35 | 75    | 70           | 40 | 75    | 6.5%                             | -5.00 [-16.32, -6.32]             |
| Sharma (A)       | 50               | 20 | 75    | 69           | 30 | 75    | 12.4%                            | -100.00 [-27.16, -18.04]          |
| Spina (A)         | 45               | 10 | 75    | 60           | 30 | 75    | 22.4%                            | -200.00 [-25.00, -14.84]          |
| takai (A)         | 65               | 10 | 75    | 60           | 30 | 75    | 22.4%                            | 5.00 [4.99, 10.08]                |
| Tamuru (P)        | 50               | 20 | 75    | 65           | 30 | 75    | 12.4%                            | -150.00 [-23.16, -6.84]           |
| Total (95% CI)    | 450             | 100 | 450   | 450          | 100 | 4500  | -10.08 [-12.66, 7.20]            |

**Heterogeneity:** $\chi^2 = 55.51, df = 5 (P < 0.00001); I^2 = 91%  
Test for overall effect $Z = 6.86 (P < 0.00001)$

### Uric acid levels for Febuxostate

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Fig. 3(a). Creatinine levels for Rasburicase

![Creatinine levels for Rasburicase](image)

Fig. 3(b). Creatinine levels for Allopurinol

![Creatinine levels for Allopurinol](image)

Fig. 3(c). Creatinine levels for Febuxostate

![Creatinine levels for Febuxostate](image)
Six studies evaluated the management of Allopurinol and Febuxostate. The intervention dose of Febuxostate was 10-120mg/day and up to 300mg/day of Allopurinol was used among selected studies. Most studies that Febuxostate used in a low dose and a better option to manage Uric acid levels [28-30]. Tamura et al. reported similar efficacy outcomes of both therapeutics Allopurinol and Febuxostate to control uric acid levels [31]. A study by Kishimoto et al. concluded Febuxostat as a better option to control uric acid in Children. Only two studies reported serious adverse events [29,30], and three patients were managed by blood transfusion [30].

5. CONCLUSION

This meta-analysis concluded that all Hypouricemic agents are effective to control biochemical indicators, including Uric acid and Creatinine. However, correct and effective dose selection with minimal or no adverse effect outcome is critical. Further, trials are suggested to conclude the suitable dose of all these Hypouricemic agents both in Adults and Children resulted in better efficacy and minimal side effects.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.
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