Kidney Protective Effects of Acetazolamide for Patients Receiving High Dose Methotrexate: A Systematic Review and Meta-Analysis.

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Characteristic table

BACKGROUND

- High-dose methotrexate (HDMTX) (1 to 12 grams per square meter of body-surface area (g/m2)) is frequently used in osteosarcoma, acute lymphoblastic leukemia.
- MTX is 90% cleared by the kidneys [2]. The incidence of Acute Kidney Injury (AKI) following HDMTX ranges from 2 to 12%
- Urine alkalization is one of the standard treatments to prevent AKI in patients receiving HDMTX.
- While sodium bicarbonate infusion has been used as the first-line strategy, carbonic anhydrase inhibitors is a promising adjuvant/substitute with advantages such as faster urine alkalization time and avoid fluid overload.
- However, there is limited and incongruent evidence of its efficacy and safety.

OBJECTIVES

- To compare the efficacy and safety of carbonic anhydrase inhibitors to standard treatments in adult patients receiving HDMTX.
- The primary outcome: Incidence of HDMTX-related AKI
- The secondary outcomes : Time to achieve urine pH goal, urine output and fluid balance, MTX clearance, liver toxicity rate, and cost effectiveness and length of hospital stay (LOS).

METHODS

- The protocol was registered at PROSPERO (CRD42022352802) in August 2021.
- We included randomized controlled trials or comparative observational studies that enrolled participants 18 years old or older receiving HDMTX.
- We excluded articles irrelevant to the topic and/or did not provide sufficient data regarding doses, recruitment criteria, and follow-up period.
- A comprehensive search was performed on June 27, 2022. Two authors performed the data extraction independently.

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RESULTS

- Among 198 articles retrieved, six observational studies met all eligibility criteria. Four studies with five datasets (totally 558 patients/cycles) had enough data to include their results in the meta-analysis.
- No significant difference between AZL versus standard treatment in AKI rate (OR=0.79, 95% CI 0.48–1.29, P=0.34, I2=0%).
- No significant time difference between the two groups regarding time to urine pH (MD =0.07, 95% CI −1.9 to 2.04, P = 0.95, I2 = 25%).
- AZL did not reduce LOS (MD = 0.75, 95% CI -0.8 to 2.31, P = 0.34, I2 = 0%).
- The only reported side effect of AZL: hypokalemia (nearly 50% in AZL group) in one study.
- The overall assessed risk of bias was moderate to high. due to the studies' designs, in variable definitions, doses as well as routes of medication administration

Figure 1: PRISMA flowchart

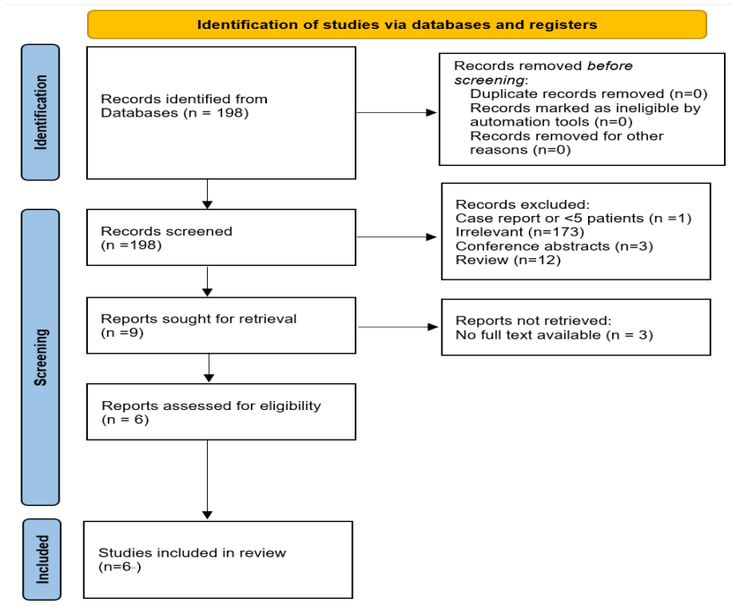
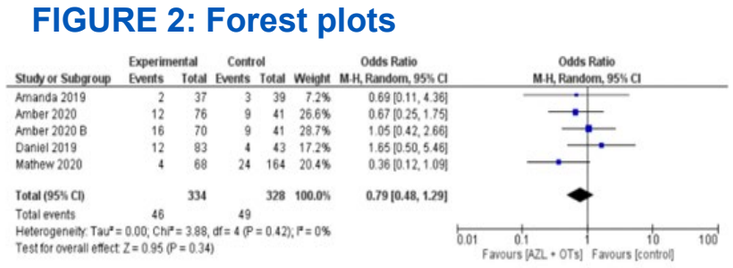
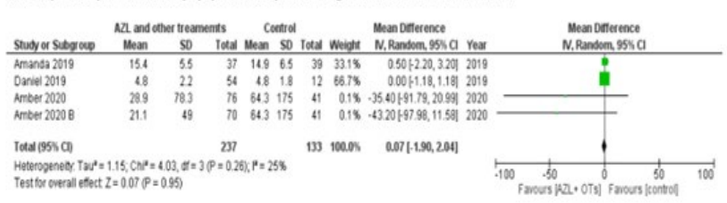


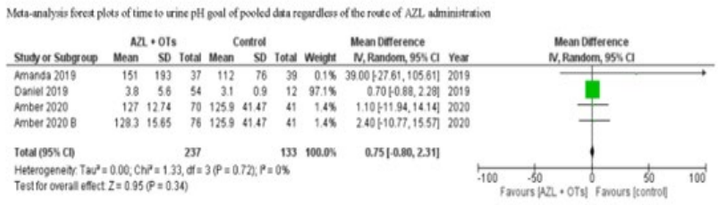
FIGURE 2: Forest plots



Meta-analysis forest plots of acute kidney injury incidence of pooled data regardless the route of AZL administration



Meta-analysis forest plots of time to urine pH goal of pooled data regardless of the route of AZL administration



Meta-analysis forest plots of the length of hospital stay from pooled data regardless of the route of AZL administration

DISCUSSION

- This systematic review and meta-analyses revealed that AZL, co-administered with other alkalization treatments or alone, was not less effective in preventing the toxicities related to HDMTX.
- Because some setbacks could underestimate AZL's protective effects and the evidence of AZL's effectiveness is still not concrete, the practice of using AZL in HDMTX patients need further assessment with a larger sample size. However, AZL is still a promising alternative for patients receiving HDMTX for many reasons.
- Most of the studies showed that AZL was a safe agent for patients receiving HDMTX, with a limited range of side effects such as hypokalemia which could be prevented by oral potassium supplementation

CONCLUSIONS

- This systematic review showed no significant difference between AZL and standard care treatment regarding urine alkalinization time and AKI rate in adult patients receiving HDMTX.
- We are unable to draw conclusions for practice on the use of carbonic acid inhibitors in patients receiving high doses of methotrexate.
- We suggest performing a large blinded, randomized, controlled trial to evaluate the potential benefits of this low-cost medication.

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