Hydrochlorothiazide and kidney stone recurrence; an in-depth analysis of the NOSTONE trial

Mohammad Zakeri Ghazaani1, Fatemeh Sadat Damanpak Rizi1, Elena Malekpour2, Elham Momeni3, Fatemeh Abbasi4*

1School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
2School of Health, Isfahan University of Medical Sciences, Isfahan, Iran
3Shahid Beheshti Hospital, Isfahan, Iran
4Department of Obstetrics and Gynecology, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

*Corresponding author: Fatemeh Abbasi, Email: fateme.abbassii@gmail.com

A B S T R A C T

Kidney stones constitute a distressing and often recurring condition with increasing prevalence in the last decades. Despite successful outcomes following kidney stone treatment, the recurrence rate remains notably high. Thiazides have conventionally been the mainstay for preventing kidney stone recurrence, with studies exploring their efficacy at various doses. The NOSTONE study is an exceptional placebo-controlled randomized controlled trial on the effectiveness of different doses of hydrochlorothiazide in preventing kidney stones. Notably commendable for its methodological rigor and comprehensive approach, the study serves as a noteworthy contribution to advancing our understanding of kidney stone prevention strategies. Our study provides a critical evaluation of the NOSTONE study's investigation into the effectiveness of hydrochlorothiazide in preventing the recurrence of kidney stones, with a primary emphasis on the statistical flaws identified within the NOSTONE study.

Implication for health policy/practice/research/medical education:

Kidney stones represent a disease with a rising prevalence and a notable recurrence rate. Thiazides have long been prescribed to mitigate recurrence; however, studies assessing their effectiveness in varied doses for preventing kidney stone recurrence have consistently faced limitations. The NOSTONE study has numerous strengths, but some limitations warrant scrutiny, particularly in analysis and statistical outcomes. Such examination can significantly contribute to refining future recommendations to prevent kidney stone recurrence.

Please cite this paper as: Zakeri Ghazaani M, Damanpak Rizi FS, Malekpour E, Momeni E, Abbasi F. Hydrochlorothiazide and kidney stone recurrence; an in-depth analysis of the NOSTONE trial. J Renal Inj Prev. 2024; x(x): e32279. doi: 10.34172/jrip.2024.32279.
effectiveness of hydrochlorothiazide at various doses in preventing the recurrence of kidney stones (8). This double-blind, placebo-controlled, randomized clinical trial (RCT) entailed a relatively prolonged treatment period and follow-up, meticulously examining over 400 patients. Despite the study's numerous strengths and the commendable efforts of those involved, it is essential to acknowledge that certain constraints exist, particularly in statistical analysis and the formulation of definitive conclusions. Despite commendable aspects, Dhayat et al.'s study has some statistical inadequacies that limit the results. Reporting P-values solely for the primary endpoint and not properly comparing study groups. Furthermore, the statement “There was no relationship” in the results is incorrect; a P value≥0.05 must be interpreted as “no significant relationship”. Using logistic regression, a more flexible analysis rather than the test for trend could have yielded different results. The results obtained through logistic regression are summarized in Table 1.

The 50 mg group had the lowest incidence of kidney stones in primary and symptomatic secondary endpoints. In the secondary radiological endpoint, the 25 and 50 mg groups showed a lower incidence of kidney stones than the other groups. In other cases, the groups had no notable differences based on effect size. Therefore, high-dose hydrochlorothiazide reduced the recurrence of kidney stones in the study population, which is consistent with previous studies. However, due to the study’s small population and low post-hoc power, the results have limitations in terms of generalizability.

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Endpoint</th>
<th>RR*, 95% CI (Minimum-Maximum)</th>
<th>Post Hoc Power</th>
<th>Minimum Sample Size (per group)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.5 mg</td>
<td>Primary endpoint</td>
<td>1.00 (0.58-1.75)</td>
<td>3%</td>
<td>950,000</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td>Secondary endpoint (Symptomatic)</td>
<td>1.21 (0.67-2.15)</td>
<td>9%</td>
<td>2259</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>Secondary endpoint (Radiologic)</td>
<td>0.85 (0.48-1.50)</td>
<td>8%</td>
<td>2443</td>
<td>0.57</td>
</tr>
<tr>
<td>25 mg</td>
<td>Primary endpoint</td>
<td>0.90 (0.52-1.57)</td>
<td>6%</td>
<td>4261</td>
<td>0.73</td>
</tr>
<tr>
<td></td>
<td>Secondary endpoint (Symptomatic)</td>
<td>1.27 (0.72-2.22)</td>
<td>14%</td>
<td>1015</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>Secondary endpoint (Radiologic)</td>
<td>0.48 (0.27-0.86)</td>
<td>68%</td>
<td>130</td>
<td>0.015</td>
</tr>
<tr>
<td>50 mg</td>
<td>Primary endpoint</td>
<td>0.66 (0.38-1.15)</td>
<td>30%</td>
<td>778</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>Secondary endpoint (Symptomatic)</td>
<td>0.73 (0.40-1.33)</td>
<td>15%</td>
<td>932</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>Secondary endpoint (Radiologic)</td>
<td>0.55 (0.30-0.99)</td>
<td>54%</td>
<td>168</td>
<td>0.047</td>
</tr>
</tbody>
</table>

*Dosage of hydrochlorothiazide, **Reference: Placebo group.

Conflicts of interest
The authors declare that they have no competing interests.

Ethical issues
Ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

Funding/Support
The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

References
Kidney stone recurrence


Copyright © 2024 The Author(s); Published by Nickan Research Institute. This is an open-access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.