Sodium thiosulfate ameliorates atopic dermatitis symptoms via inhibiting inflammatory infiltration and restoring skin barrier function

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Research Article

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Abstract

Background

Atopic dermatitis (AD) is a common disease with a considerable impact on the affected individual's quality of life and has limited treatment options. Sodium thiosulfate (STS) is a traditional medicine used in the rescue of cyanide poisoning, and some pruritus dermatosis. However, the exact efficacy and mechanism of its application with AD are not clear.

Patients and Methods:

We reviewed the records of patients with moderate to severe AD treated in the department of dermatology, the Third Xiangya Hospital, between January 2020 and July 2021. The change of Eczema Area and Severity Index (EASI), Scoring of Atopic Dermatitis index (SCORAD), Atopic Dermatitis Control Tool (ADCT), Patient-reported outcomes (PROs), skin barrier indexes and serum biochemical indicators were recorded.

Results

A total of 60 moderate to severe AD patients were enrolled, 20 in the STS 0.64g once daily + conventional therapy (STS QD) group, 20 in the STS 0.64g twice daily + conventional therapy (STS BID) group and 20 in the conventional therapy (control) group. Conventional therapy consisted of intravenous fluids of calcium, vitamin C and oral antihistamines rupatadine and bepotastine. Treatment with STS led to greater improvement with higher proportion of EASI50 and EASI75 and lower ADCT index compared to the control group. After treatment, greater improvement in PROs, skin barrier indexes were also observed in the STS treatment group than in the control group. To further study the underlying mechanism of STS, we analyzed the serum biochemical indicators. STS downregulated IgE by 4.12- and 7.26-folds (P = 0.0006 and P < 0.0001, respectively) and eosinophils by 2.24- and 5.28-folds (P = 0.0205 and P < 0.0001, respectively) in STS QD and STS BID group. In addition, STS downregulated interleukin-13(IL-13) by 2.86- and 3.16-folds (Both P < 0.0001) and interleukin-4 (IL-4) by 2.42- and 4.68-folds (Both P < 0.0001) in STS QD and STS BID group.

Conclusion

STS in combination with conventional therapy improves the signs and symptoms of AD by improving skin barrier function and downregulating concentrations of IgE, eosinophils and release of IL-4 and IL-13.

Introduction
Atopic dermatitis (AD) is a systemic, chronic, recurrent inflammatory skin disease with a prevalence of 15%-20% among children and 10% among adults worldwide[1]. It is characterized by itchiness, xerosis, eczematous lesions, and sleep disturbance, which always causes anxiety and depression and increases the burden of health care [2–5]. A complex etiology including genetic factors, immune dysfunction, environmental and microbiome factors that cause skin barrier abnormalities and the occurrence of AD, in which immune dysfunction predominantly type-2-skewed immune dysregulation is regarded as crucial to the pathogenesis of AD[6]. Cytokines and chemokines, including interleukin-4 (IL-4), interleukin-13 (IL-13), and interleukin-3(1IL-31), and thymic stromal lymphopoietin (TSLP), are increased in AD patients. The serum IgE and peripheral eosinophil levels also upregulated in AD patients[7]. Clinical stage, the severity of pruritus, age, and the goals of patients are the accordance to select the appropriate therapy for AD patients. Itching-control is the core of AD treatment. Adequate use of moisturizer products is fundamental in the treatment of AD, since it repairs and maintains skin barrier functions, thus preventing allergen invasion and relieving itching[8]. Topical anti-inflammatory drugs, such as topical corticosteroids (TCS) and tacrolimus ointments (topical calcineurin inhibitor) respond well in most patients. Systemic corticosteroids and cyclosporin (a kind of immunosuppressor) are used in patients with severe AD who do not respond to conventional treatments[9]. In recent years, the treatment of AD with biological agents like the IL-4 antibody dupilumab and the JAK inhibitor abrocitinib has shown bright prospects. However, the side effect of corticosteroids, immunosuppressor and the high cost of biological agents limited the long-term use of them. Thus, it is necessary to find cheaper and useful treatment.

Sodium thiosulfate (STS), an inorganic agent with antioxidant, anti-inflammatory and vasodialatory properties, has been used for the treatment of cyanide poisoning. It is also used for off-label application in calciphylaxis and cisplatin-induced hearing loss[10]. Although the possible mechanism remains unclear, the effect of STS on some pruritus dermatitis has also been reported in some Chinese studies. Several Chinese researchers suggest that STS improves the anti-inflammatory, anti-allergic, and neutralizing acid effects of eczema in the body[11]. A recent study showed that STS could improve uremic pruritus, and the authors speculated that the underlying mechanism of STS may be attributed to stimulating the production of nitric oxide, which could then lead to vasodilation and reduce local inflammation and pruritogen[12].

In this observational study, we analyzed the records of 60 moderate to severe AD patients and found that treatment with STS significantly reduced the severity of AD. It’s function in downregulating indicators that reflect skin barrier condition and reducing the release of Th2 cytokines revealed the underlying mechanism of STS on treating AD.

Patients And Methods

2.1. patients involved in this study

This retrospective, observational, single-center study undertaken at the department of dermatology, Central South University Third Xiangya Hospital, analyzed the data of all patients diagnosed with
moderate to severe AD between January 2019 and July 2022. The diagnosis of AD was based on established Williams’s criteria\[^{13}\]. We included 40 patients treated with conventional therapy plus with STS and 20 patients treated only with conventional therapy. Exclusion criteria for this study included age < 18 years old, Pregnant or lactating women, patients with cardiovascular and other systemic diseases and patients who had received glucocorticoids or immunosuppressants in the last month. This study was approved by IRB of The Third Xiangya Hospital of Central South University (Rapid 22168), and the requirement to obtain informed consent was waived.

2.2. Drugs involved in this study

Conventional therapy consisted of intravenous fluids of calcium, vitamin C and oral antihistamines rupatadine and bepotastine. STS was diluted with 0.9% normal saline and administered intravenously once or twice daily. The STS dosage selection was based on the initial severity of symptoms.

2.3. The indicators recorded in this study

The severity of AD was assessed by the Eczema Area and Severity Index (EASI), Scoring of Atopic Dermatitis index (SCORAD) \[^{14,15}\]. 50% and 75% improvement of EASI (EASI50/EASI75) score, decreasing amplitude of EASI and SCORAD and the change of Dermatitis Control Tool (ADCT) from baseline to the date of discharge were involved to analyze the efficacy of STS. We also recorded the patient-reported outcome (PROs) including Dermatology Life Quality Index (DLQI), Peak Pruritus Numerical Rating Scale (PP-NRS), Patient-Oriented Eczema Measure (POEM) and time required to attain itching relief to assess the change of the symptoms of AD more specifically. To explore the underlying mechanism of STS on treating AD, the skin barrier indicators like water content of stratum corneum (WCSC), PH value, and trans-epidermal water loss (TEWL) detected through non-invasive skin test methods (German CK MPA10 multifunctional skin tester) were recorded. Moreover, the serum total IgE, peripheral blood eosinophil counts before and after treatment were also recorded.

2.4. ELISA assay for cytokines

Cytokine levels of IL-4 and IL-13 before starting and at the end of the therapy were detected by the IL-4 and IL-13 ELISA kits (Elabscience, China) based on the manufacturer’s instructions.

3. Statistical Analysis

Statistical analysis was performed with SPSS version 26.0 (IBM, Armonk, USA) and GraphPad Prism version 8.1.0 (La Jolla, CA). All data were expressed as mean ± standard derivation (SD). Statistical significance was determined by one-way analysis of variance (ANOVA), followed by Dunnett’s multiple comparison test, and a P < 0.05 was considered statistically significant.

Results

4.1. STS reduces the overall disease severity scores
A total of 60 patients were recorded in the study. 20 in the STS BID group, 20 in the STS QD group and 20 in the conventional therapy group. The baseline characteristics were similar among the three groups (p > 0.05) (Table 1). The results showed that compared to patients with conventional therapy, both STS BID and STS QD groups achieved higher proportion of EASI50 [12 (60.0%) in STS QD group, 18 (90.0%) in STS BID group and 5 (25.0%) in control group] and EASI75 responses [6(30.0%) in STS QD group, 14(70.0%) in STS BID group, and 1(5.0%) in control group] after treatment (Figure. 1A). Interestingly, changes of ADCT indexes showed the same tendency with 12.85 ± 0.81 in the control group, 10.35 ± 0.81 in the STS QD group, and 9.30 ± 1.26 in the STS BID group (Both P < 0.0001) (Figure. 1B). Compared to control group, SCORAD significantly decreased by 1.78- and 3.46-folds in STSQD and STSBID group retrospectively (P = 0.0025 and P < 0.0001 respectively). EASI decreased by 1.77- and 2.31-folds in STSQD and STSBID group retrospectively (Both P < 0.0001) (Fig. 1. C&D).
Table 1
Demographic and clinical characteristics of the AD patients at baseline

<table>
<thead>
<tr>
<th>Group</th>
<th>control group</th>
<th>STS QD group</th>
<th>STS BID group</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Number</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>0.552</td>
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<tr>
<td>Age</td>
<td>53.9 ± 11.3</td>
<td>44.8 ± 19.0</td>
<td>50.6 ± 17.9</td>
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<tr>
<td>Gender</td>
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<td></td>
<td></td>
<td>0.284</td>
</tr>
<tr>
<td>Female</td>
<td>12 (60.0%)</td>
<td>14 (70.0%)</td>
<td>16 (80.0%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8 (40.0%)</td>
<td>6 (30.0%)</td>
<td>4 (20.0%)</td>
<td></td>
</tr>
<tr>
<td>IGA score at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2 (10.0%)</td>
<td>1 (5.0%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>7 (35.0%)</td>
<td>4 (20.0%)</td>
<td>3 (15.0%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>11 (55.0%)</td>
<td>15 (75.0%)</td>
<td>17 (85.0%)</td>
<td></td>
</tr>
<tr>
<td>SCORAD</td>
<td>52.66 ± 10.21</td>
<td>56.62 ± 10.55</td>
<td>53.71 ± 10.34</td>
<td>0.100</td>
</tr>
<tr>
<td>EASI</td>
<td>13.83 ± 1.74</td>
<td>14.11 ± 1.75</td>
<td>13.72 ± 1.57</td>
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<td>PP-NRS</td>
<td>8.55 ± 0.94</td>
<td>8.60 ± 0.994</td>
<td>8.45 ± 1.05</td>
<td>0.889</td>
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<td>DLQI</td>
<td>12.80 ± 0.77</td>
<td>12.65 ± 0.75</td>
<td>12.75 ± 0.79</td>
<td>0.821</td>
</tr>
<tr>
<td>POEM</td>
<td>19.85 ± 2.01</td>
<td>20.20 ± 2.28</td>
<td>20.05 ± 2.58</td>
<td>0.891</td>
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<tr>
<td>IgE(IU/mL)</td>
<td>1583.0 ± 302.75</td>
<td>1571.2 ± 267.613</td>
<td>1628.0 ± 397.84</td>
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<tr>
<td>Eosinophil count (cells/µL)</td>
<td>1.35 ± 0.66</td>
<td>1.39 ± 0.74</td>
<td>1.33 ± 0.76</td>
<td>0.965</td>
</tr>
<tr>
<td>IL-13 (pg/ml)</td>
<td>35.21 ± 2.84</td>
<td>34.62 ± 2.91</td>
<td>35.09 ± 2.09</td>
<td>0.758</td>
</tr>
<tr>
<td>IL-4 (pg/ml)</td>
<td>15.54 ± 1.86</td>
<td>15.68 ± 2.10</td>
<td>15.59 ± 1.91</td>
<td>0.857</td>
</tr>
</tbody>
</table>

4.2. STS improves the scores of PROs

To further explore the efficacy of STS, we recorded the PROs including POEM, PP-NRS and DLQI. They are significantly reduced in both STS doses groups than control group. The baseline value could be found in Table 1 and the difference was not statistically significant. After treatment, the value of POEM downregulated to 10.35 ± 0.81 and 9.30 ± 1.26 in STS QD and STS BID group respectively, while 12.85 ±
0.81 in control group (Both $P < 0.0001$) (Fig. 2. C). PP-NRS and DLQI showed the same pattern. For PP-NRS, $5.2 \pm 0.77$ and $4.30 \pm 0.73$ in STS QD and STS BID group respectively versus $6.25 \pm 1.02$ in control group (Both $P < 0.0001$). For DLQI, $7.90 \pm 0.718$ and $6.85 \pm 0.875$ in STS QD and STS BID group respectively versus $9.25 \pm 0.851$ in control group (Both $P < 0.0001$) (Fig. 2. A&B).

We also evaluated the time required to attain itching relief in each group as another criterion of efficacy, which suggests that STS shortened the course of treatment with $4.90 \pm 1.119$ days and $3.50 \pm 0.688$ days in STS QD and STS BID group respectively versus $5.595 \pm 1.731$ in control group ($P = 0.72$, $P = 0.0012$ respectively) (Fig. 2. D).

### 4.3. STS improves skin barrier function

To reveal the underlying mechanism of STS on treating AD, we recorded several indicators detected through non-invasive skin test methods that reflect the condition of skin barrier including WCSC, PH value, and TEWL of skin. The value of these indicators at baseline are listed in Table 1. After treatment, with the improvement of AD symptom, the value of WCSC in three groups were increased, and the change in STS group ($36.16 \pm 3.03$ for STS BID group and $31.05 \pm 1.63$ for STS QD group) were significantly greater than that in control group ($29.27 \pm 2.11$) ($P = 0.0485$ and $P < 0.0001$, respectively) (Fig. 3. A). Both PH value and TEWL were down to a relatively normal level. PH value were decreased to $4.68 \pm 0.19$, $5.42 \pm 0.29$, and $5.63 \pm 3.00$ for STS BID group, STS QD group, and control group, respectively ($P = 0.0342$ and $P < 0.0001$, respectively). As for TEWL, we observed the same tendency as the change of PH value with $14.94 \pm 0.59$ in STS BID group, $17.64 \pm 0.59$ in STS QD group, and $20.82 \pm 1.08$ (Both $P < 0.0001$) (Fig. 3. B&C). Images of RCM were also recorded. There are moderate counts of inflammatory cells in the dermal papilla of lesions of AD patients at baseline. After treatment, we found that there are fewer inflammatory cells in the papilla of the same lesion in STS groups than control group, which may reflect the underlying effect of STS (Fig. 3. D).

### 4.4. STS downregulates the release of cytokines and reduces inflammatory infiltration

Then, to further explore the molecular mechanism of STS, serum biochemical indicators including IgE, eosinophil, IL-13, and IL-4 concentrations of AD patients were recorded. The results showed that STS treatment was associated with significantly lower total IgE, eosinophil, IL-13, and IL-4 concentrations in the peripheral blood at the end of treatment than that at baseline. The baseline values were showed in Table 1. At the date of discharge, we found that STS downregulated IgE by $4.12$- and $7.26$-folds ($P = 0.0006$ and $P < 0.0001$, respectively) and eosinophils by $2.24$- and $5.28$-folds ($P = 0.0205$ and $P < 0.0001$, respectively) in STS QD and STS BID group (Figure. 4A&B). The data of IL-4 and IL-13 in the peripheral blood of each group showed that both cytokines presented an abnormal increasing trend in the AD patients of each group. More significantly reduction of STS therapy after treatment also been found. After treatment, STS downregulated IL-13 by $2.86$- and $3.16$-folds (Both $P < 0.0001$) and IL-4 by $2.42$- and $4.68$-folds (Both $P < 0.0001$) in STS QD and STS BID group respectively (Fig. 4. C&D).
Discussion

Atopic dermatitis (AD) is a multifactorial skin disease with clinical manifestation of recurrent eczematous lesions and intense pruritus. Therapy of AD is selected depending on the clinical stage, severity of pruritus, age, coexisting conditions and the goals of them[16]. STS, an inorganic compound, used in pruritus-control and dermatitis in several studies[17]. But the effect and underlying mechanisms of it are not fully understood. In this study, we found that STS combined with conventional therapy effectively relieved the symptoms of AD, shortened the duration of AD pruritus, improved the skin barrier function of AD patients, and reduced the release of Th2 cytokines and inflammatory infiltration.

Specifically, we analyzed the change of EASI SCORAD and ADCT scales, the world-recognized scales to assess AD severity and the efficacy of STS[18]. In our study, patients were mostly with a moderate to severe AD condition. STS significantly downregulated scores of these scales in a dose dependent manner, though the score of ADCT didn't get the threshold “≤7” in the short-term treatment. In addition, scores of PROs were also reduced much more significantly in both STS groups. PROs including DLQI, PP-NRS, POEM help health care providers know the changes in patients’ physical and psychological status, the severity of symptoms, and their impact on daily life during treatment efficiently[19]. Our study defined STS as a cheap and effective drug for AD to relieve pruritus and control symptoms.

Furthermore, we found that indicators reflecting the condition of skin barrier are in an abnormal level in AD patients. Skin barrier dysfunction, interacting with genetic and environmental factors, microbial imbalance and several other factors, has been proved to be one of the pivotal factors acting on the induction and development of AD[20]. After treatment, compared to control group, these indexes in STS groups get a much greater improvement and showed a dose-dependent effect. This result suggested that STS improves the skin barrier of AD patients.

Immune dysregulation is another critical etiology of AD pathology. Predominance of Th2 cytokines is the key Pathogenesis related to immune dysfunction in AD. Increased Th2 cytokines like IL-4, IL-13, and IL-31 released into the skin, which promote inflammation, pruritus, and the production of antigen-specific IgE by activating B cells and plasma cells[21]. In this work, These Th2 cytokines and eosinophils are all in a highly abnormal level. We also found that serum IgE, IL-4 and IL-13 levels positively correlated with the severity of AD, this is consistent with several previous studies [22, 23]. Our study suggests that STS decreases peripheral total IgE and eosinophil counts, reduced the release of Th2 cytokines, which may be one of the underlying mechanisms of this medicine on treating AD.

In a summary, our study showed that STS enhances the efficacy of AD by improving the skin barrier, reducing the release of Th2 cytokines and inflammatory infiltration, which provides a basis for the usage of STS in AD. It may be a potential treatment option in combination with the conventional therapy for long-term AD control.

Declarations
FUNDING
None

CONFLICT OF INTEREST
The author declares no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS
Declared none

References


**Figures**
Figure 1

STS improves the overall disease severity scores

After treatment, STS groups achieved significantly higher proportion in EASI50 and EASI75 respond (A), lower ADCT indexes (B) and greater decreasing amplitudes of SCORAD and EASI scores (C and D). ns, P>0.05, *P≤0.05, **P≤0.01, ***P≤0.001, ****P≤0.0001.
Figure 2

STS improves the scores of PROs

After treatment, greater improvement in PROs were observed in the STS treatment groups than in the control group (A-C). STS also shortened the time for patients to get itch relief (D). PROs, patient-reported outcome, DLQI, Dermatology Life Quality Index, PP-NRS, Peak Pruritus Numerical Rating Scale, POEM, Patient-Oriented Eczema Measure. ns, P>0.05, *P≤0.05, **P≤0.01, ***P≤0.001, ****P≤0.0001.
STS improves skin barrier function

Indicators that reflect the condition of skin barrier including WCSC, PH value, and TEWL of skin get much more improvement in STS groups than control group (A-C). Moreover, after treatment, there are fewer inflammatory cells in the papilla of patients in STS groups than in control group (D). WCSC, water content of stratum corneum, TEWL, trans-epidermal water loss. ns, P>0.05, *, P≤0.05, **, P≤0.01, ***, P≤0.001, ****, P≤0.0001. Red circles indicate the inflammatory cells in the dermis.
Figure 4

STS downregulates the release of cytokines and reduces inflammatory infiltration

After STS treatment, both IgE and eosinophils were significantly reduced than control group (A&B). Th2 cytokines including IL-13 and IL-4 also downregulated much more in STS groups compared to control group(C&D). ns, P>0.05, *P≤0.05, **P≤0.01, ***P≤0.001, ****P≤0.0001.