Effect of N-acetylcysteine on pain in daily life in patients with sickle cell disease: a randomised clinical trial

The hallmarks of sickle cell disease (SCD) include the acute vaso-occlusive, painful crises (VOC), associated with frequent hospitalizations. SCD-related pain is reported on 17% of observed days, significantly hampering patients in their daily lives (van Tuijn et al, 2017).

Oxidative stress has been demonstrated to play a pivotal role in the pathophysiology of SCD, generated by factors such as haemolysis and ischaemia-reperfusion injury. Reactive oxygen species promote a vicious circle of additional haemolysis, inflammation, hypercoagulability and endothelial dysfunction. (Nur et al, 2011) Therefore, antioxidants may be of great therapeutic potential in SCD, by simultaneously affecting multiple pathophysiological processes.

The antioxidant N-acetylcysteine (NAC) has been demonstrated to exert a broad range of beneficial effects in SCD, improving markers of oxidative stress and haemolysis, and possibly even the VOC rate (Pace et al, 2003; Nur et al, 2012; Özpolat et al, 2014).

NAC is a safe, inexpensive drug that has been used for years for various indications, making it an accessible treatment for the majority of SCD patients in the developing world. We here report the results of an investigator-initiated, randomised, placebo-controlled, double-blind trial (NAC trial), which aimed to evaluate the effect of NAC on the frequency of SCD-related pain in daily life in patients with SCD (NCT01849016).

This study was initiated in four centres in the Netherlands in 2012, and expanded to six centres in Belgium and one centre in the United Kingdom in 2015. Patients were eligible for participation if they were ≥12 years old, had either HbSS, HbSC, HbSβ⁰ or HbSβ⁺ disease, and a history of ≥1 VOC per year. Patients using hydroxycarbamide were eligible to participate (see Table SI for complete criteria). Upon randomization, patients were randomly assigned to receive either oral NAC 600 mg twice daily or placebo. Total treatment duration was 6 months.

The primary end point was the rate of SCD-related pain days per patient year, as measured by a daily pain diary. Secondary outcomes included the rate per patient year of days with VOC, admission days for VOC, hospitalizations for VOC and days with home analgesic use.

The primary analysis of this study was limited to patients with a minimal completed study observation time of 110 days within the total follow-up of 6 months [modified intention-to-treat analysis (mITT)]. An additional, pre-specified per-protocol analysis was performed on a subset of patients with ≥110 study observation days available, N = 67. Additional baseline characteristics are shown in Table SIII.

Table I. Baseline characteristics of SCD patients in the modified intention-to-treat population. SCD patients with ≥110 study observation days available, N = 67. Additional baseline characteristics are shown in Table SIII.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo group (N = 40)</th>
<th>NAC group (N = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years – mean ± SD</td>
<td>28.4 ± 8.9</td>
<td>29.6 ± 8.4</td>
</tr>
<tr>
<td>Age category – n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12–17 years</td>
<td>6 (15)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>≥18 years</td>
<td>34 (85)</td>
<td>25 (93)</td>
</tr>
<tr>
<td>Female sex – n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>26 (65)</td>
<td>14 (52)</td>
</tr>
<tr>
<td>Haemoglobin genotype – n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbSS/HbSβ⁰</td>
<td>29 (73)</td>
<td>17 (63)</td>
</tr>
<tr>
<td>HbSC/HbSβ⁺</td>
<td>11 (28)</td>
<td>10 (37)</td>
</tr>
<tr>
<td>Ethnic origin – n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latin-America/Caribbean</td>
<td>17 (43)</td>
<td>12 (44)</td>
</tr>
<tr>
<td>Africa</td>
<td>23 (58)</td>
<td>15 (56)</td>
</tr>
<tr>
<td>Consent for text message service – n (%)</td>
<td>34 (85)</td>
<td>20 (74)</td>
</tr>
<tr>
<td>Use of hydroxyurea – n (%)</td>
<td>16 (40)</td>
<td>12 (44)</td>
</tr>
<tr>
<td>Clinical history over past 3 years – median (IQR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of VOC</td>
<td>11 (6-20)</td>
<td>8 (5-15)</td>
</tr>
<tr>
<td>Number of hospital admissions for VOC</td>
<td>3 (1-6)</td>
<td>3 (1-6)</td>
</tr>
</tbody>
</table>

IQR, interquartile range; NAC, N-acetylcysteine; SCD, sickle cell disease; SD, standard deviation; VOC, vaso-occlusive crisis.
patients with ≥80% adherence to the assigned study medication, as checked by tablet counts.

Event rates per treatment arm were compared by Poisson regression analysis.

Additional information on the study methods is available in the online supporting information.

A total of 96 patients were randomised (Fig S1) between April 2013 and November 2015. Of the 90 patients, 40 in the placebo group and 27 in the NAC group were included in the mITT analysis (≥110 observation days, Tables I, SII, and III).

In the mITT population, the rate of SCD-related pain days per patient year was comparable between both treatment arms (Table II). In addition, NAC had no effect on the secondary outcomes of this study (Tables II and SIV–VI). This was consistent in sensitivity analyses in the total study cohort (Table SVII) and patients with ≥80 observation days (data not shown).

Only 70% of patients in the placebo group, and 56% in the NAC group returned all study medication bottles for tablet counts. Of these, the percentage of patients that were adherent to the study treatment (≥80% tablets used) was similar in both treatment arms (50% in placebo, 53% in NAC group). A per-protocol analysis was performed on this adherent subset (N = 27, Table SVIII). Here, we observed a significantly lower rate of VOC days in the NAC arm as compared to placebo: 20 vs. 40 events per patient year (Table SIX, rate ratio 0.50, 95% CI 0.27–0.94). The rate of hospital admission days per patient year and the risk of a first VOC appeared to be lower in the NAC arm, but this did not reach statistical significance (Tables SIV and SIX). In addition, haemoglobin and erythrocyte levels increased significantly after 3 months of study treatment (T3) in the NAC arm as compared to placebo (Table SX).

Significantly more patients in the NAC group reported gastro-intestinal events, including nausea, diarrhoea or abdominal discomfort (Table SXII, P = 0.006). All serious adverse events are listed in Table SXII.

In conclusion, treatment with oral NAC was not of clinical benefit over placebo in the mITT analysis of this study. These findings are in contrast with previous studies with NAC, and trials evaluating other antioxidants (Daak et al, 2013; Nihara et al, 2014). Importantly, adherence was poor in this study—a notorious issue in SCD (Walsh et al, 2014).
Per-protocol analysis in adherent patients did suggest a reduction of days with VOC in the NAC treatment arm, and trends of improvement in other parameters.

Various lessons can be learned for future studies. By including patients with only 1 VOC per year, a subgroup with relatively mild disease may have been less inclined to maintain good adherence. In retrospect, the patient-centred primary endpoint of SCD-related pain in daily life may not have been the most sensitive outcome for this study, as this definition may include chronic pains. (van Tuijn et al., 2017)

Significantly more patients in the NAC arm reported gastrointestinal adverse events, possibly adding to the higher dropout rate here. Notably, one patient experienced a gastrointestinal perforation after 2 weeks of NAC use. As NAC has proven to be safe in many clinical studies, it is most likely that this patient suffered from gastro-intestinal, vaso-occlusive ischaemia (Gardner & Jaffe, 2016). Lastly, the dosage of NAC in this study may have been relatively low to elicit strong clinical effects. Previous pilot studies with NAC appeared to demonstrate better effects at a higher dose, yet potentially also more adverse events. Individual dose escalation up to a highest tolerable dose could be a solution here.

These findings provide an important opportunity for further research. We are currently performing additional blood sample analysis of pathophysiological markers to corroborate our clinical findings. Encouragingly, the therapeutic potential of intravenous, high-dose administration of NAC during our clinical findings. Encouragingly, the therapeutic potential of intravenous, high-dose administration of NAC during VOC is currently being pursued (NCT01800526).

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Authorship contribution

J.W.R.S., K.F. and B.J.B. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. J.W.R.S. analysed the data and wrote the manuscript. J.W.R.S., K.F. and B.J.B. and C.A.B. interpreted the data. K.F. and B.J.B. supervised the study and edited the manuscript. K.F. and B.J.B. and C.A.B. designed the study, and K.F. and B.J.B supervised the interpretation and statistical analysis of the data. J.W.R.S. and M.B.B. collected data or assisted in data collection. All other authors enrolled patients in the study, assisted in data collection and revised and approved the final manuscript.

Disclosure of conflicts of interest

The authors declare no competing interests.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

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References


