

Evidence-based Medicine

Is inhaled nitric oxide therapy more effective or safer than the conventional treatment for the treatment of vaso-occlusive crises in sickle-cell anemia?

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INTRODUCTION

Sickle-cell diseases (SCD) constitute a group of hereditary anemias that occur together with chronic hemolytic anemia, vasculopathy, vaso-occlusive phenomena, and acute and generalized chronic organ lesion. One of these diseases is sickle-cell anemia, a recessive autosomal disease that results from a mutation in the beta (β) globin (chromosome 11), originating hemoglobin S, of which its homozygous form characterizes this pathology.

According to the World Health Organization (WHO), there are approximately 20 million individuals with sickle-cell anemia worldwide. Although SCD are more common in Africa, the migratory flows have disseminated the gene around the world¹.

Although the physiopathology of vaso-occlusion is not completely understood, it is known that the interactions between sickled red blood cells, endothelial alterations, vascular muscle tonus deregulation, activation of monocytes and adhesion molecules secondary to frequent hemolysis have an important role in the development of the disorder.

Certain complications such as cerebrovascular accident, pulmonary hypertension, priapism and leg ulcers are related to the intensity of hemolysis, whereas painful crises, acute chest syndrome (ACS) and osteonecrosis are associated with the high blood viscosity and the interactions between sickle cells, leukocytes and endothelium.

Due to the high morbidity and elevated complication treatment costs, there is an interest regarding the study of new therapies, such as the therapeutic use of inhaled nitric oxide.

Nitric oxide (NO) is a vasodilating substance, in addition to inhibiting platelet aggregation, decreasing cell adhesion molecules and also modulating ischemic lesions with reperfusion.

The objective of this systematic review was to evaluate the safety and effectiveness of inhaled NO to treat vaso-occlusive crises in sickle-cell anemia.

METHODS

A systematic review was carried out in the MEDLINE database using the following search strategy: (Anemia, Sickle Cell OR Acute Chest Syndrome) AND Nitric Oxide. The

filter “Therapy/Narrow” was used through the Clinical Queries interface. The authors analyzed the studies independently by title and summary of each recovered article and selected those that met the inclusion criteria: randomized clinical assay comparing the use of nitric oxide with placebo that had been written in Portuguese, English or Spanish.

After this initial selection process, the authors read the full text of the eligible articles and evaluated them critically. Only studies with a score ≥ 3 according to the criteria established by Jadad *et al.*² were included in the data analysis.

To evaluate effectiveness, we used the differences in mean time until crisis resolution between the groups and the decrease in the mean pain score according to the Visual Analog Scale (VAS), after 24 hours.

As a safety parameter, we used the difference between the frequency of adverse events and the acute chest syndrome (ACS) within 72 hours and the rate of return to the ER and re-hospitalization after 30 days. The measure used was the absolute risk reduction (ARR) with the corresponding 95% confidence interval (95% CI) and the number necessary to treat (NNT).

The *t* test was used to analyze the continuous variables (for difference of means), with the OpenEpi online tool and the Chi-square test was used to analyze dichotomous variables, with the Catmaker software.

RESULTS

The literature review was finished on March 07, 2011. A total of 124 articles were found, of which only three³⁻⁵ met the inclusion criteria. After careful reading and analysis of these three eligible articles, two were excluded for having losses to follow-up $> 20\%$ ^{4,5}. The only eligible article selected was the study by Gladwin *et al.*³, which had a score of 4 according to Jadad *et al.*².

The data of that study demonstrated there was no significant difference in resolution time of vaso-occlusive crisis between the two groups. The study *p*-value for the differences in medians was 0.87.

The study did not disclose the data on the time difference regarding crisis resolution as means and standard

deviations, as these data are usually expressed, but as medians with 95% CI, of which upper and lower limits were not equidistant from the median. Therefore, the authors calculated the one-sided p value in two different ways: using the upper limits and the lower limits of the 95% CI. The values obtained were 0.60 and 0.33, respectively.

All the other parameters (VAS mean score, adverse events, acute chest syndrome, return to the ER and re-

hospitalization) also demonstrated non-significant differences, as shown in Tables 1 and 2.

EVIDENCE SYNTHESIS

The use of inhaled nitric oxide for the treatment of vaso-occlusive crises in sickle-cell anemia does not demonstrate any significant differences regarding benefits or damages, when compared to the conventional treatment.

Table 1

Outcome	Nitric oxide	Placebo	p-value
Crisis resolution (hours)	73 (46.0 to 91.0)	65.5 (48.1 to 84.0)	0.60/0.33
VAS score 24 hours (cm)	6.1 (5.3 to 6.8)	6.0 (5.4 to 6.6)	0.92

Table 2

Outcome	Nitric oxide	Placebo	ARR (95% CI)	NNT
Adverse events	9	6	- 0.040 (-0.136 to 0.056)	-25
Return to the ER	8	11	0.04 (-0.066 to 0.146)	25
Rehospitalization	9	17	0.107 (- 0.013 to 0.227)	9
ACS	5	5	0	

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