

The role of hydroxyurea to prevent silent stroke in sickle cell disease

Systematic review and meta-analysis

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Abstract

Background: Chronic blood transfusions are standard of care for stroke prevention in sickle cell disease but is not cost effective and not without risks. Hydroxyurea has emerged as an option in the prevention of silent stroke in sickle cell disease.

Objective: To evaluate the role of hydroxyurea in preventing silent strokes in a systematic review by adhering to the Cochrane guidelines.

Methods: PubMed, EMBASE, Web of Science Core Collection, and Cochrane Central Register of Controlled Trials were searched for the related articles. Eligibility criteria included randomized controlled trials (RCTs) comparing the use of hydroxyurea vs blood transfusions and observational studies evaluating the role of hydroxyurea to prevent stroke and silent stroke in patients with sickle cell anemia or sickle cell β thalassemia. The meta-analysis was conducted using STATA software version 13.

Results: We included 10 single arm observational studies with 361 participants, and one RCT study with 60 participants receiving hydroxyurea, respectively. There were no deaths attributed to hydroxyurea. The results revealed that 1% (95% CIs 0.0 to 0.05) of patients receiving hydroxyurea had stroke. 18% (95% CIs 0.03 to 0.4) of the hydroxyurea patients had silent stroke. 24% (95% CIs 0.02 to 0.57) of the hydroxyurea patients had adverse events attributed to hydroxyurea.

Conclusion: Our findings suggest that hydroxyurea is safe and may prevent silent stroke and stroke in sickle cell disease. More high-quality studies including RCTs are needed.

Abbreviations: CI = confidence interval, RCT = randomized clinical trial, RR = relative ratio, SCD = sickle cell disease, SCI = silent cerebral infarct, TCDI = transcranial Doppler imaging.

Keywords: hydroxyurea, meta-analysis, sickle cell disease, silent stroke, stroke

1. Introduction

Neurological complications are a major cause of morbidity and mortality in sickle cell disease. Silent strokes, defined as ischemic changes in brain tissue visible on imaging without overt physical signs or symptoms of a stroke, are more common than overt

strokes and are more likely to occur with increasing age. In children with sickle cell disease (SCD), silent cerebral infarct (SCI) occurs in 27% before the age of six years and 37% up to the age of 14 years, and approximately 11% of children with SCD will experience an overt stroke with the highest prevalence before the age of 6 years.^[1] The prevalence of SCI in adults is not well studied.^[2] Children who have SCIs are more likely to experience further neurological events, including stroke, than children without evidence of SCIs. This often results in lifelong neuropsychological effects, including lower intelligence quotients and poorer processing speeds compared to children without SCD and its complications. Children with SCD and SCI have higher global intellectual functioning scores than children who have had overt strokes; however, their scores are significantly lower than those of children without the disease.^[3] Although SCIs may not have obvious clinical symptoms, there are clearly neurocognitive consequences.

Chronic blood transfusions are the standard treatment for stroke prevention, but this method is not cost effective and not without risks, including iron overload and alloimmunization.^[3] Hydroxyurea, first tested in sickle cell anemia in 1984, has emerged as a vital therapeutic option. It is used as therapy for the prevention of complications of SCD, including pain and decreased organ function and it may be indicated to prevent stroke in patients with sickle cell disease.^[3]

The goal of this systematic review is to summarize the available data on the use of hydroxyurea for the prevention of SCI in patients with sickle cell disease.

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2. Materials and methods

2.1. Search strategy and study identification

This systematic review was conducted according to the Cochrane guidelines. Randomized controlled trials (RCTs) comparing the use of hydroxyurea vs blood transfusions or observation alone to prevent stroke and silent stroke in patients with sickle cell anemia or sickle cell β thalassemia were eligible for inclusion. Ethical approval by an institutional review board was waived as this was a systematic review. Observational studies evaluating the role of hydroxyurea to prevent stroke and silent stroke in patients with sickle cell anemia or sickle cell β thalassemia were eligible for inclusion. Our primary outcome was silent stroke, secondary outcomes included stroke and adverse events attributed to hydroxyurea.

Electronic searches were developed and performed by medical librarians (KS, RP) in PubMed, which includes Medline, EMBASE, Web of Science Core Collection, and Cochrane Central Register of Controlled Trials. All searches were executed on April 5, 2018, except for Cochrane Central which was run on May 1, 2018. The medical librarians developed a search strategy in PubMed and then translated that strategy using each database platform's unique controlled vocabulary, command language, and search fields. MeSH terms, Emtree terms, and keywords were used to search for the following concepts: hydroxyurea, sickle cell anemia, and stroke (see Appendix 1, <http://links.lww.com/MD/D500> for detailed search strategies). All retrieved citations retrieved were exported to EndNote software. The librarians performed a manual review for duplicates after using the duplicate finder in EndNote and 675 duplicates were identified and removed. After removal of duplicates a total of 1231 unique citations were yielded for inclusion/exclusion analysis. All searches were conducted without any language or time limits. All references from the obtained articles were manually scanned to identify additional studies missed in the original electronic database search.

2.2. Data extraction

Two review authors independently scanned the titles and abstracts of all studies for their eligibility for inclusion in the systematic review. If a decision on inclusion could not be made on the basis of the title and abstract, a full text of the manuscript was used to assess eligibility. Any inclusion or exclusion disagreements were resolved by consensus. A data extraction form was designed and pilot tested. The final data extraction form was used to extract data independently by two review authors.

2.3. Quality and bias assessment

The methodological quality of RCTs was assessed using the Cochrane risk of bias assessment tool.^[4] The review authors judged each quality domain based on the following three-point scale: "Yes" (low risk of bias: plausible bias unlikely to seriously alter the results if all criteria were met), "No" (high risk of bias: plausible bias that seriously weakens confidence in the results if one or more criteria were not met), or "Unclear" (uncertain risk of bias: plausible bias that raises some doubt about the results if one or more criteria were assessed as unclear).

The methodological quality of observational studies was assessed using the Downs & Black Checklist for Study Quality.^[5] Each domain within this checklist was attributed a value of one if it fulfilled that domain and the value of zero if it did not fulfill that

domain. A total score was calculated for this checklist for each included study with a maximum possible total value of 27.

2.4. Statistical analysis

For meta-analysis of data from observational studies without a control arm, proportion of patients experiencing each outcome was calculated and studies which were similar in terms of patients, intervention, control, and outcomes were included in the meta analysis.^[6] Methods by Stuart et al were used to transform the proportions into a quantity suitable for random-effects pooling.^[7] The pooled proportion was then calculated as a back-transform of the weighted mean of transformed proportions, using the random-effects model. Heterogeneity was calculated using the I^2 statistic. We considered $I^2 > 50\%$ to be indicative of significant heterogeneity. We conducted sensitivity analyses for the outcome of stroke based on overall methodological quality. The meta-analysis was conducted using STATA software version 13.^[8]

3. Results

3.1. Literature search results

We retrieved 1231 citations from our database search. Seventeen studies were marked for inclusion. After protocols, reviews, and duplicates were removed, 11 studies remained: 1 RCT^[9] and 10 observational studies^[1-3,10-16] (Fig. 1). One observational study was excluded from the meta-analysis because the treatment arm details were unclear.^[1]

3.2. Characteristics of included studies

The RCT by Ware et al^[9] enrolled 60 patients in the hydroxyurea arm and 61 patients in the chronic blood transfusions arm, administered 20 mg/kg/day of hydroxyurea. The RCT by Ware et al was of superior methodological quality and reported all relevant details and did not appear to suffer from any biases assessed via the Cochrane risk of bias assessment tool.

We also included 10 observational studies which were without a control arm.^[1-3,10-16] The study by McMahon et al^[1] enrolled 17 patients in the hydroxyurea arm and did not report dosing/frequency. This retrospective study evaluated 351 children, median age 6.7 years, with sickle cell disease who were treated with hydroxyurea and chronic blood transfusions and followed from 2003 to 2009. The study by Rigano et al^[2] enrolled 104 patients and administered 10–35 mg/kg/day of hydroxyurea. This retrospective study evaluated the incidence of cerebrovascular events in 104 adults, median age 41 years (range: 20–76 years), with HbS β^0 thalassemia who were treated with hydroxyurea and followed for a mean of 11 years. The study by Nottage et al^[3] enrolled 50 patients in the hydroxyurea arm and administered 20 mg/kg/day of hydroxyurea. This prospective cohort study evaluated children, median age 9.4 years (range: 1.1–17.3 years), with sickle cell anemia or HbS β^0 thalassemia who began hydroxyurea therapy and were followed from 2010 to 2016. The study by Bernaudin et al^[10] enrolled 46 patients in the hydroxyurea arm and administered 24.6 (+/- 2.1) mg/kg/day of hydroxyurea. This study evaluated a cohort of 92 children, median age 3.7 years (range: 1.3–8.3 years), with sickle cell anemia and abnormal Transcranial Doppler Imaging (TCDI) who were followed from 1992 to 2016. The study by Hankins et al^[11] enrolled 11 patients in the hydroxyurea arm and

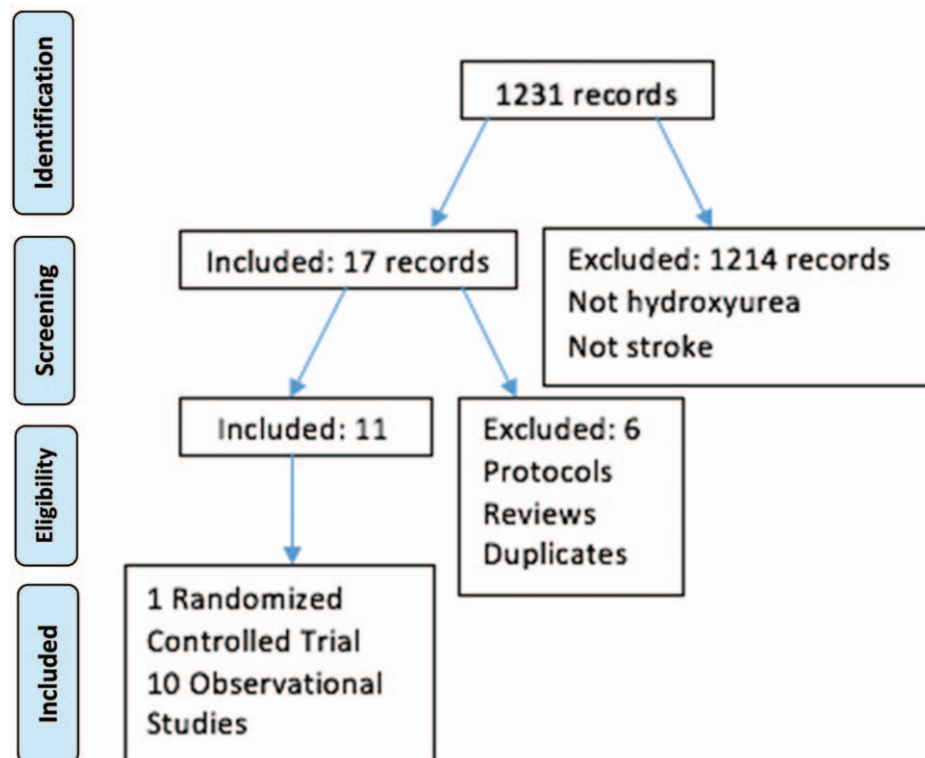


Figure 1. Flow diagram of study selection. We retrieved 1231 citations from our database search. Seventeen studies were marked for inclusion. After protocols, reviews, and duplicates were removed, 1 RCT and 10 observational studies remained.

administered 26.6 mg/kg/day of hydroxyurea. The study evaluated 8 patients, median age 17.1 years (range: 16.4–17.8 years), with sickle cell anemia who had been treated with hydroxyurea for a minimum of 15 years. The study by Maggio et al^[12] enrolled 42 patients in the hydroxyurea arm and administered about 15 mg/kg/day of hydroxyurea. The study evaluated 42 patients, mean age 36 years (range: 18–53 years), with sickle cell anemia or HbS⁰ thalassemia who were treated with hydroxyurea and were followed for a mean of 6.6 years. The study by Rothman et al^[13] enrolled 37 patients in the hydroxyurea arm and administered 25.2 (+/– 5.6) mg/kg/day of hydroxyurea. This retrospective study evaluated 37 children, mean age 6.8 years (range: 1.8–14.8 years), with sickle cell anemia and abnormal Transcranial Doppler Imaging (TCDI) who were followed from 2000 to 2009.

The study by Schmutge et al^[14] enrolled 27 patients in the hydroxyurea arm and administered 10 to 30 mg/kg/day of hydroxyurea. The study evaluated 27 children, median age 10.5 (range: 3.8–19 years), with sickle cell disease who were followed for a mean of 47 months. The study by Solomou et al^[15] enrolled 24 sickle cell disease patients, mean age 38.4 years (range: 20–59 years), and included 16 patients who were treated with hydroxyurea but the dosing/frequency was not reported. The study by Thornburg et al^[16] enrolled 14 patients in the hydroxyurea arm and administered about 28 (+/– 4) mg/kg/day of hydroxyurea. The study evaluated 14 children, mean age 35 months (range: 18 months to 5 years) with sickle cell anemia who were treated with hydroxyurea and followed for a mean of 25 (range: 22–28 months) months. Please see Table 1 for characteristics of included studies.

Table 1

Characteristics of included studies.

Study	Study Design	Number of Patients Receiving Hydroxyurea	Hydroxyurea Dose, mg/kg/day	Methodological Quality Score
Ware, 2016	Randomized controlled trial	60	20	NA
Nottage, 2016	Prospective cohort study	50	20	18
Bernaudin, 2016	Cohort study	46	24.6 +/- 2.1	16
Hankins, 2014	Cohort study	8	26.6	16
Solomou, 2013	Prospective cohort study	16	NR	14
Rigano, 2013	Cohort study	104	10 to 35	14
Rothman, 2010	Cohort study	37	25.2 +/- 5.6	13
McMahon, 2009	Retrospective cohort study	17	NR	15
Thornburg, 2007	Cohort study	14	28 +/- 4 avg	11
Schmutge, 2005	Cohort study	27	10 to 30	10
Maggio, 2004	Cohort study	42	15 avg	12

Each study's design, the number of patients receiving hydroxyurea, the dose of hydroxyurea, and the methodological quality score out of 27 is shown. NA and NR indicate the measure was not applicable or reported, respectively.

3.3. Quality of studies

Overall, the methodological quality of observational studies was moderate. The median total score for methodological quality was 14 (range: 10–18). Specifically, 40% (4/10) of studies reported important adverse events that may be a consequence of the intervention. Eighty percent (8/10) of studies provided estimates of the random variability in the data for the main outcomes. Eighty percent (8/10) of studies reported actual probability values for the main outcomes, except where the probability value is less than .001.

3.4. Overall incidence of stroke, silent stroke, and treatment related adverse events and death

The RCT^[9] comparing hydroxyurea and chronic blood transfusions enrolled 121 participants. There were no strokes, silent strokes, or deaths reported in either arm. There was no difference between hydroxyurea and chronic blood transfusions (RR 1.52, 95% CI 0.57 to 4.02, $P = .394$, 121 participants) for the outcome of treatment related adverse events.

There were no deaths attributed to hydroxyurea among 10 observational studies. Approximately 1% (95% CI 0.0 to 0.05, 314 participants, 7 comparisons, $I^2 = 48\%$) of the hydroxyurea patients had stroke (Fig. 2). Approximately 18% (95% CI 0.03 to 0.4, 266 participants, 6 comparisons, $I^2 = 91\%$) of the hydroxyurea patients had silent stroke (Fig. 3). Approximately 24% (95% CI 0.02 to 0.57, 91 participants, 4 comparisons, $I^2 = 88\%$) of the hydroxyurea patients had adverse events attributed to

hydroxyurea (Fig. 4). Our findings for the outcome of stroke did not change based on the methodological quality of included studies.

4. Discussion

Our findings suggest that hydroxyurea may prevent stroke. Overall included studies suggest that hydroxyurea was well tolerated and may prevent silent stroke. However, there was inconsistent and unclear reporting on cerebrovascular outcomes in the included observational studies. The overall methodological quality was moderate. Nonetheless, we believe that these findings are relevant to clinicians who prescribe hydroxyurea to patients with sickle cell disease, and may serve as a call to action for other researchers.

There are various limitations to the data that we analyzed. To date the only RCT we found that directly addressed the prevention of silent strokes is the Silent Cerebral Infarct Multi-Center Clinical Trial (SIT) which studied chronic packed red blood cell (PRBC) transfusions compared to observation in the secondary prevention of silent stroke.^[17] This study was outside the realm of our research question and was therefore not included in the analysis. The one RCT that we included addressed silent stroke. This RCT was a multicenter non-inferiority trial originally designed to study the use of hydroxyurea vs PRBC transfusions in the primary prevention of overt stroke in

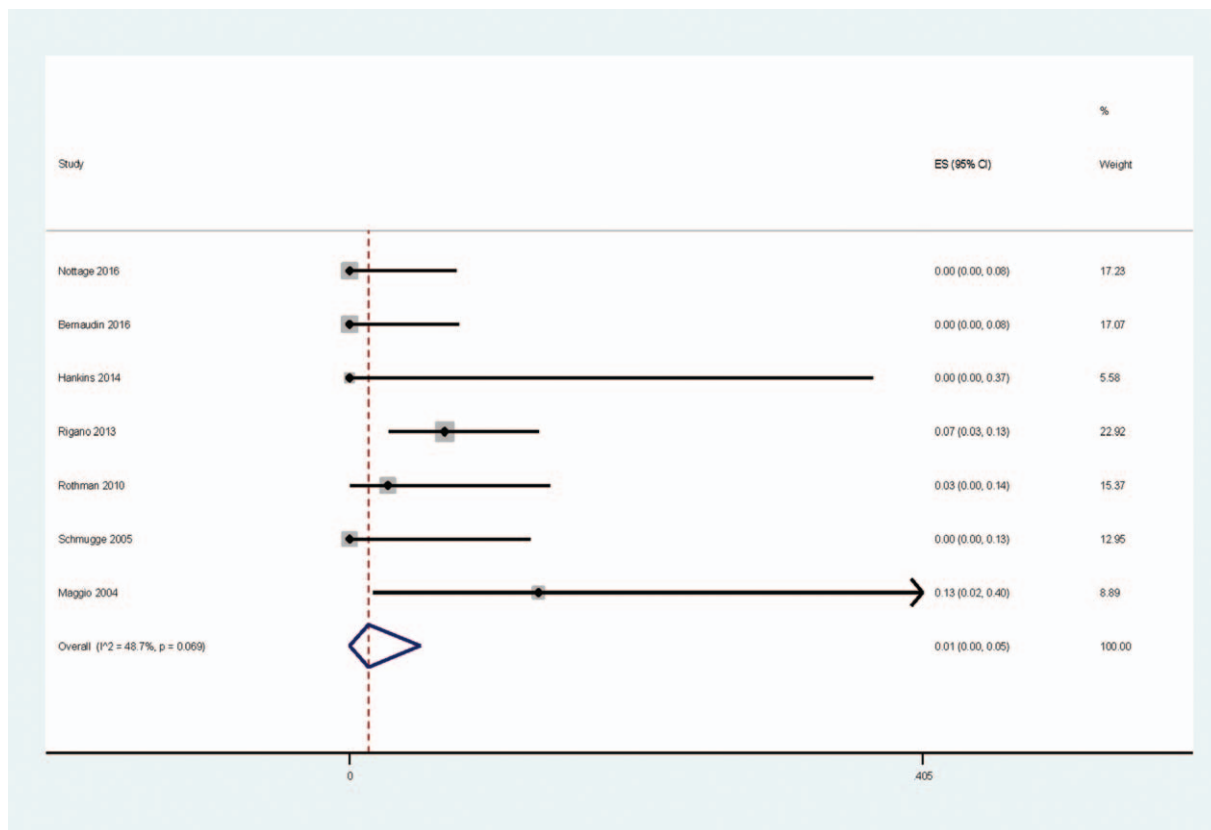


Figure 2. Pooled incidence of stroke in observational studies. The diamond in the figure reflects the pooled proportion of patients experiencing stroke in the studies included in the meta-analysis.

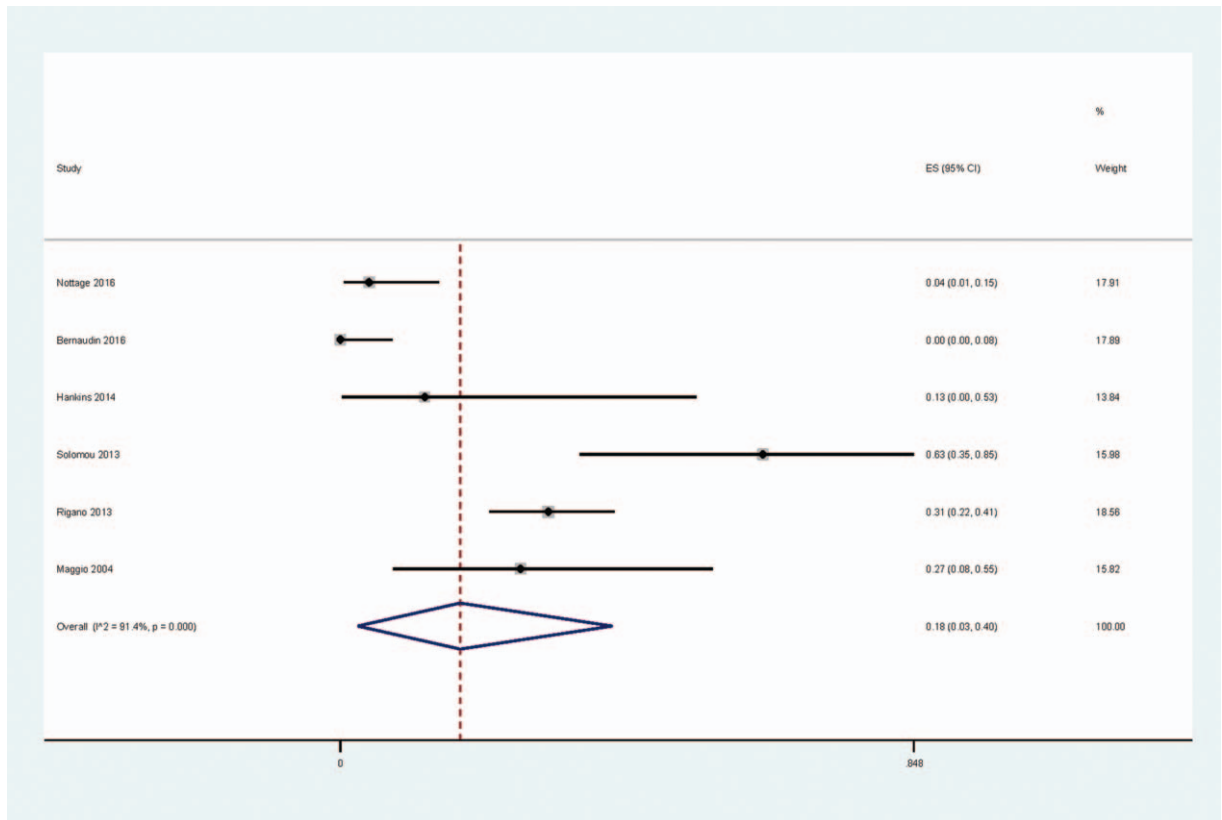


Figure 3. Pooled incidence of silent stroke in observational studies. The diamond in the figure reflects the pooled proportion of patients experiencing silent stroke in the studies included in the meta-analysis.

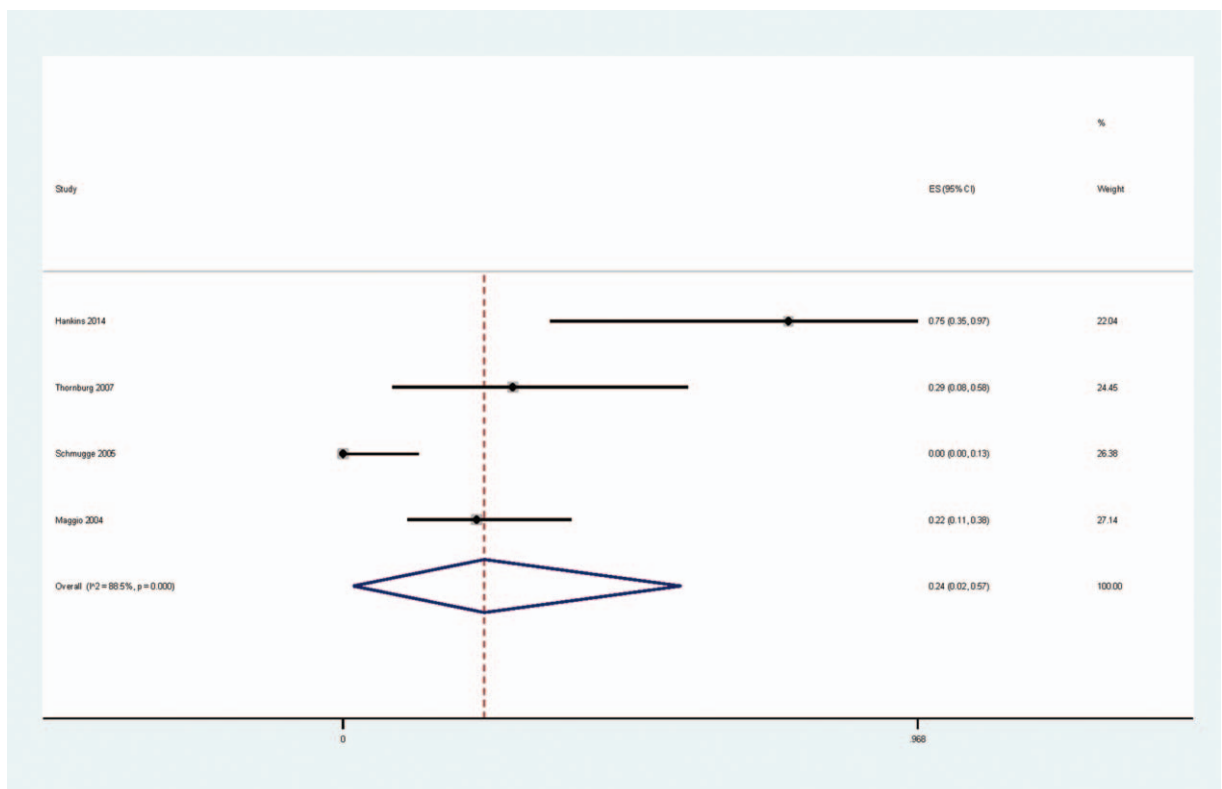


Figure 4. Pooled incidence of toxicity in observational studies. The diamond in the figure reflects the pooled proportion of patients experiencing hydroxyurea related adverse events in the studies included in the meta-analysis.

children.^[9] In this RCT, all children received before and after MRI of the brain with central review as surveillance for silent strokes. There was no progression of silent stroke in either the PRBC or hydroxyurea arm, but the RCT was not adequately powered to determine whether or not hydroxyurea is comparable to PRBC transfusion in the prevention of silent stroke. Due to this, we added observational studies addressing the use of hydroxyurea and silent stroke in our systematic review and meta-analysis.

To date, there is insufficient evidence to support or argue against the use of hydroxyurea in the prevention of silent stroke in sickle cell disease. The SIT trial demonstrated that PRBC transfusion is superior to observation in the secondary prevention of silent stroke and many would consider chronic PRBC transfusions the standard of care in the secondary prevention of silent stroke. Hydroxyurea potentially presents an option with considerable benefit in cost, resource utilization, time requirement for the patient, and reduction in side effect profile. While some of the studies included in our systematic review suggest a potential benefit, due to the paucity of data, no definitive conclusions could be made. In our literature review we found that there is currently only one RCT that is addressing role of hydroxyurea in the prevention of silent strokes in children with sickle cell disease.^[18] We did not find any addressing the same question in adults with sickle cell disease either. At the time of our review, there were no ongoing RCTs comparing Hydroxyurea to PRBC transfusions in the prevention of silent stroke. Perhaps future studies will better elucidate the efficacy of hydroxyurea in the prevention of silent strokes in sickle cell disease. Overall, based on one RCT and observational studies included in our systematic review, we believe hydroxyurea is safe and may prevent silent stroke and stroke in sickle cell disease. Future observational studies addressing this issue need to improve the methodological quality of conduct and reporting.

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