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Hydroxyurea lowers the frequency of sickle cell vaso-occlusive crises

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Hydroxyurea lowers the frequency of sickle cell vaso-occlusive crises

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ABSTRACT A critical appraisal and clinical application of Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. *N Engl J Med* 1995;(332):1317-1322 doi: 10.1056/nejm199505183322001

Keywords: *hydroxyurea, sickle cell vaso-occlusive crisis*

Clinical Context

M.W. is a 23-year-old African American male, with a history of multiple vaso-occlusive crises due to sickle cell hemoglobinopathy (SS), who presented to the emergency department (ED) with a three-day history of bilateral upper and lower extremity pain, sternal pain, and lumbar pain. He had a history of dactylitis, acute chest syndrome, and many sickle cell vaso-occulsive crises. During these crises, he was typically treated with oxygen, analgesics, hydration, and blood transfusions when indicated. He denied shortness of breath, sputum production, fever, chest pain and changes in vision. His sternal pain prompted a chest x-ray in the ED, which showed no acute cardiopulmonary process and helped to rule out acute chest syndrome. A complete blood count and comprehensive metabolic profile were obtained to help rule out other causes to his pain, and did not show any significant changes from his baseline levels. His hemoglobin was 6.5 (Baseline 6.9), a reticulocyte percentage of 18.4%, a white blood cell count of 17,400 (Baseline 15,000), and creatinine of 1.3 (Baseline 1.1). Of note, this was his tenth admission in the last six months for sickle cell vaso-occulsive crises. He followed regularly with a hematologist at an outside hospital, who treated his chronic pain with opioid analgesics and recommended he start hydroxyurea. However, when asked about hydroxyurea use, he did not wish to start it because he did not think that it would help reduce the frequency of his crises.

Clinical Question

Does daily administration of hydroxyurea reduce sickle cell vaso-occulsive crises in adults with sickle cell hemoglobinopathy?

Research Article

Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. *N Engl J Med* 1995;(332):1317-1322 doi: 10.1056/nejm199505183322001

Related Literature

A search for original research in PubMed and Google Scholar using the keywords “hydroxyurea,” “sickle cell crisis,” and “adult” yielded twelve publications that addressed the effect of hydroxyurea on the frequency of sickle cell vaso-occlusive crisis in adults

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with sickle cell hemoglobinopathy. Two of the articles were multi-year observational studies that followed patients of a previous study and focused primarily on the morbidity and mortality of patients using hydroxyurea, which fell out of the scope of the clinical question.[1,2] Seven were observational studies, and only "Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH): effect of hydroxyurea on the frequency of painful crises in sickle cell anemia" was a double-blinded randomized controlled trial[3-9]. The remaining article was a systematic review article written by Lanzkron et al.[10]

A decision was made to clinically appraise the MSH trial because it directly addressed the clinical question at hand, and it is a high-impact study that is still often cited today for the quality of evidence and clinical relevance it produced. The seven observational studies agreed with the MSH study that hydroxyurea reduced the frequency of sickle cell vaso-occlusive crises in sickle cell patients. The MSH study was chosen over the observational studies because of the strength of evidence that the MSH study achieved by its design: a multicenter double-blind clinically controlled trial.

Critical Appraisal

The Multicenter Study of Hydroxyurea in Sickle Cell study (MSH) is a double-blind randomized clinically controlled trial that researched the effect of hydroxyurea on the frequency of painful sickle cell crises in adult sickle cell anemia patients with three or more vaso-occlusive crises in a year. It took place at 21 centers throughout the United States; to be eligible for the study patients had to have sickle cell disease, be over 18 years of age, and report at least three sickle cell vaso-occlusive crises a year. Our patient fits these criteria. He is similar to the study population aside from the fact that the average hemoglobin levels of the experimental and control group were 8.4 and 8.5, respectively, whereas his baseline level is 6.9. The study design included a treatment group of 152 individuals assigned to daily hydroxyurea administration, and 147 patients assigned to the placebo group. The two groups were randomized so that there were no significant differences between the groups with regards to race, age, sex, number of alpha globin genes, beta globin haplotype, blood counts, average number of crises per year before the study, and complications from sickle cell anemia. The randomization was effective as the groups were similar. Patients were started out on 15 mg/kg of hydroxyurea or placebo, which was titrated up every 12 weeks by 5 mg/kg, unless bone marrow toxicity was observed. If marrow toxicity was observed in patients, hydroxyurea or placebo was stopped until blood levels stabilized, and then they were restarted on a lower dose of hydroxyurea or placebo. Patients were asked to keep daily records of their pain, analgesic use, and their visits to medical facilities. Every two weeks the patients had their blood drawn, and their journals were reviewed and crosschecked with monthly telephone questionnaires. Painful crises were defined as a visit to a health care facility for greater than four hours for acute sickle cell associated pain that required IV administration of analgesics. Acute chest syndrome, priapism, and hepatic sequestration were also considered crises.

The study was initially designed to follow patients for two years, but was stopped early at 21 months because interim analysis showed hydroxyurea administration to significantly decrease occurrence of vaso-occlusive crises. Of the 299 patients enrolled in the trial, 279 were being seen regularly when it was stopped. All patients were analyzed with the intention to treat principle. When compared to the placebo group the hydroxyurea group had significantly lower rates of vaso-occlusive crises per year (2.5 vs. 4.5, $p<0.001$), acute chest syndrome episodes (25 vs 51, $p<0.001$) and blood transfusions needed (48 vs 73, $p<0.001$). Time to first crisis (3.0 vs 1.5 months, $p=0.01$) and second crisis (8.8 vs 4.6 months, $p<0.001$) was significantly longer in the treatment group than in the placebo group. The lower rate of vaso-occlusive crises per year in the hydroxyurea group translated to a low number needed to treat of 2.27.

Many characteristics about this study contribute to its classification as a high quality study; one of these is the focus of the study. According to the Strength of Recommendation Taxonomy (SORT) criteria, MSH is a level 1 study because it is a randomized double-blind clinically controlled trial that focuses on a patient-oriented outcome.[11] By attempting to study the effects of hydroxyurea on the frequency of sickle cell vaso-occlusive crises, the researchers designed a primary outcome that was not focused on increasing laboratory values, but instead focused on the patients and their quality life. By doing this, they made sure that their study was going to be high-impact and clinically important.

Another redeeming aspect of the study was the ability to maintain blinding. This was done in a multitude of ways that included not revealing the treatment group to the researchers or patients unless a medical issue precluded it. Also, all laboratory values were sent directly to a central laboratory and not to the principal investigators in the study, so that the researchers were not made aware

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of the changes in hemoglobin F levels that occur with hydroxyurea administration. Furthermore, by using a low dose of hydroxyurea that was titrated up slowly, the side effects of hydroxyurea administration were minimized. Finally, by concurrently titrating the dose of the placebo in a similar manner, neither patients nor researchers were able to figure out what group patients belonged to. The study also utilized a blinded "crisis review committee" to classify adverse events in patients as crises or not. This created a standardized method of classification. By reducing the chance of introducing bias in these ways, the researchers gave more validity to their conclusions.

Finally, the study's stringent statistical parameters contributed to its excellence by giving strong evidence on which to base conclusions. Many of the conclusions in the study are based on a p value of 0.001, rather than the more commonly used 0.05. This greatly reduced the chance of making a type 1 error, and strongly suggests that the differences in vaso-occlusive crises per year, acute chest syndrome episodes, and blood transfusions needed between the hydroxyurea and the placebo are in fact true differences.

As noted above, there are many redeeming qualities to this study. However, no study is without its limitations. Firstly, although the researchers reviewed daily pain journals kept by patients, there is no mention of the difference between the treatment group and placebo group in reference to their pain level and quality of life. Although the investigators feel that a reduction from 4.5 to 2.5 crises per year in the treatment group may be important, the patients may not view this as a significant reduction. If there is no perceived difference in quality of life from those taking hydroxyurea, then its utility is diminished. The conclusions and clinical application of the study could have been strengthened had the investigators commented on the differences between the daily journals of the treatment and placebo groups. Additionally, the age and race distribution are not listed in the paper, which detracts from the study's clinical utility. It should also be mentioned that only 134 out of the 299 participants completed the full 2 years of the study due to the early termination. A total of 14 patients from the treatment group were discontinued from the study for safety reasons compared to 6 patients in the placebo group. Also, the doses of hydroxyurea in the treatment group were not standardized, which may have affected the results. Of the experimental group, 2% could not tolerate hydroxyurea whereas 21% received the maximum dose. The authors mention that 75% of the study population took 80% of their prescribed capsules. While this is an impressive percentage, it is still not perfect and leaves room for confounding factors. Finally, one must keep in mind that Bristol-Meyer Squib, the maker of hydroxyurea, helped fund the study. Whenever there is funding from a pharmaceutical company that could profit from the results of a study, one must critically analyze the results and see how they were obtained.

Overall, the MSH trial was a well-designed double-blind clinically randomized study that helped to establish the use of hydroxyurea to reduce the frequency of vaso-occlusive crises in sickle cell patients. It also helped to spur along many other studies that have since proven then safety and efficacy of using hydroxyurea. Even though the study was conducted nearly twenty-four years ago, its conclusions are still drawn upon to this day, which is a testimony to its quality.

Clinical Application

Although the study only commented on the effectiveness of hydroxyurea administration in adults with sickle cell disease, hydroxyurea administration has since been shown to be effective in children as young as nine months of age, and in other patients with other variants of sickle cell disease (HbS/beta(0)thalassemia, HbS/beta(+)thalassemia).[4,6,12] Other than the expected dose-dependent myelosuppression, the study did not find any major side effects associated with hydroxyurea. Although they do raise concerns about the potential for myleloproliferative neoplasms with long-term administration, subsequent studies have proven the treatment's safety in both adults and children.[1,2,13] This theoretical risk of myeloproliferative disorder has to be weighed against the harms of more frequent vaso-occlusive crises and hospitalizations. It is important to remember that, although hydroxyurea has shown to reduce vaso-occlusive crises experienced per year in sickle cell patients, it does not reduce this frequency to zero. Our patient was counseled on the risks and benefits of the drug and the likelihood of reducing painful crises, but he was still unconvinced. Patients like this one may not feel that the reduction in vaso-occulsive crises offsets the potential side effects of hydroxyurea administration. However, with upwards of ten vaso-occlusive crises within the previous six months causing significant morbidity, this patient would have been a good candidate to receive hydroxyurea. He would not elaborate further about what side effects worried him. His vaso-occlusive crisis was treated with adequate hydration and analgesics, and he was discharged with resolution of his pain.

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Take Home Points:

1. Sickle cell vaso-occlusive crises are a major cause of morbidity in sickle cell patients.
2. Hydroxyurea has been shown to reduce the frequency of sickle cell vaso-occlusive crises in sickle cell patients.
3. Hydroxyurea should be used in patients with more than three vaso-occlusive crises per year.

References

1. Steinberg MH, Barton F, Castro O, et al. Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. *JAMA*. 2003;289(13):1645-1651. doi: 10.1001/jama.289.13.1645
2. Steinberg MH, McCarthy WF, Castro O, et al. The risks and benefits of long-term use of hydroxyurea in sickle cell anemia: A 17.5 year follow-up. *American Journal of Hematology*. 2010;85(6):403-408. doi: 10.1002/ajh.21699
3. Ferguson RP, Arun A, Carter C, Walker SD, Castro O. Hydroxyurea treatment of sickle cell anemia in hospital-based practices. *American Journal of Hematology*. 2002;70(4):326-330. doi: 10.1002/ajh.10184
4. Ferster A, Tahriri P, Vermylen C, et al. Five years of experience with hydroxyurea in children and young adults with sickle cell disease. *Blood*. 2001;97(11):3628-3632. doi: 10.1182/blood.V97.11.3628
5. Italia K, Jain D, Gattani S, et al. Hydroxyurea in sickle cell disease—A study of clinico-pharmacological efficacy in the Indian haplotype. *Blood Cells, Molecules, and Diseases*. 2009;42(1):25-31. doi: 10.1016/j.bcmd.2008.08.003
6. Loukopoulos D, Voskaridou E, Stamoulakatou A, et al. Hydroxyurea Therapy in Thalassemiaa. *Annals of the New York Academy of Sciences*. 1998;850(1):120-128. doi: 10.1111/j.1749-6632.1998.tb10469.x
7. Vicari P, Barretto de Mello A, Figueiredo MS. Effects of hydroxyurea in a population of Brazilian patients with sickle cell anemia. *American Journal of Hematology*. 2005;78(3):243-244. doi: 10.1002/ajh.20293
8. Voskaridou E, Christoulas D, Bilalis A, et al. The effect of prolonged administration of hydroxyurea on morbidity and mortality in adult patients with sickle cell syndromes: results of a 17-year, single-center trial (LaSHS). *Blood*. 2010;115(12):2354-2363. doi: 10.1182/blood-2009-05-221333
9. Voskaridou E, Kalotychou V, Loukopoulos D. Clinical and laboratory effects of long-term administration of hydroxyurea to patients with sickle-cell/beta-thalassaemia. *British Journal of Haematology*. 1995;89(3):479-484. doi: 10.1111/j.1365-2141.1995.tb08352.x
10. Lanzkron SS. Systematic review: Hydroxyurea for the treatment of adults with sickle cell disease. *Annals of Internal Medicine*. 2008;148(12):939-955. doi: 10.7326/0003-4819-148-12-200806170-00221
11. Ebell MH, Siwek J, Weiss BD, et al. trength of recommendation taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *Am Fam Physician*. 2004;69(3):548-556.
12. Wang WC. Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). *The Lancet*. 2011;377(9778):1663-1672. doi: 10.1016/S0140-6736(11)60355-3
13. Wang WC, Wynn LW, Rogers ZR, Scott JP, Lane PA, Ware RE. A two-year pilot trial of hydroxyurea in very young children with sickle-cell anemia. *The Journal of Pediatrics*. 2001;139(6):790-796. doi: 10.1067/mpd.2001.119590

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