Selected Summaries

Intravenous Magnesium Sulfate: A New Weapon Against Acute Asthma?

[Ciarallo L, Saucer AH, Shannon MW. Intravenous magnesium therapy for moderate to severe pediatric asthma: Results of a randomized, placebo-controlled trial. J Pediatr 1996, 129: 809-814.]

Intravenous magnesium sulfate (IVMg) has shown beneficial effects in acute asthma in adults because of its potential to reverse the bronchospasm. The results are however, not consistent in all studies. With this background the present randomized, placebo-controlled trial was conducted in children of 6-18 years age. The cases in study and control groups (15 and 16 patients, respectively), selected on the basis of peak expiratory flow rate (PEFR) less than 60% of predicted after 3 nebulizations of (3_2 agonists, were matched for mean age, sex ratio, respiratory rate, PEFR, PEFR (% predicted), forced vital capacity (FVC), home treatment, emergency room visits in the past and baseline serum magnesium levels. Only forced expiratory volume in one second (FEV_1) differed in two groups (33.1 ± 11.4 and 45.1 ± 12.2% of predicted in study and control groups, respectively). The study group received IVMg (25 mg/kg magnesium sulfate, maximum 2 g in 100 ml saline) as infusion over 20 minutes.

Pulmonary functions and vital signs were monitored upto 110 minutes after the infusion. The magnesium group showed significant improvement from baseline PEFR, 80 minutes after initiation of IVMg (46% *vs* 16%; p = 0.05). This difference was maintained at the end of study at 110 minutes. At this time only 4 (27%) of the study group had PEFR less than 60% of predicted compared to 11 (69%) in the control group (p=0.02). FEV_1 improvement from baseline was also significant in favor of study group (34% *vs* 1%, p=0.05) at 50 minutes and more noticeable at 80 minutes (p=0.01) and 110 minutes (p=0.01). Improvement in FVC was less pronounced.

At the end of the study, review of patients' clinical condition snowed that 4 patients in the magnesium group did not require hospitalization while improvement in none of the placebo group was such that hospitalization could be avoided. The authors point out that in 1 out of 4 cases treated with IVMg in addition to the usual treatment of acute asthma, hospitalization and its inherent social and economic problems can be avoided. No significant side effects of therapy with IVMg were noticed.

Comments

It was in 1938 that Haury in his animal experiments showed that magnesium (Mg) has smooth muscle relaxation potential and relieves histamine induced bronchospasm. In his subsequent work, he demonstrated that 50% of a small group of asthmatics had hypomagnesemia. However, this finding was not substantiated by other workers(l).

The mode of action of Mg appears to be through certain mechanisms which decrease the uptake and release of calcium in bronchial smooth muscles. It may also inhibit degranulation of mast cells, thus decreasing the release of mediators for bronchoconstriction(2).

Bronchodilation by Mg and its probable role in management of acute severe asthma

has been the subject of various studies during the last 10-15 years. In a meta-analysis of the earlier work on this aspect, a significant improvement in clinical score of asthma and various pulmonary functions was documented(3). Magnesium has been found useful only when administered intravenously. Intramuscular injections are painful and aerosolized forms are ineffective. The usual recommended dose is 30-70 mg/kg of magnesium sulfate. At this dose the drug appears quite safe. The side effects of facial flushing and warmth and malaise are infrequent and well tolerated.

Nebulized p-2 agonists and intravenous corticosteroids form the first line therapy of acute asthma at the present time(l,3). Ipratropium has limited role in very young children. Intravenous administration of theophylline, which was frontline drug before P-2 agonists were introduced, has fallen into disrepute. It does not appear to offer any added advantage over fJ-2 agonists and corticosteroid therapy(l). At this stage, availability of a safe and effective therapy in the form of IVMg holds promise. In the study under consideration, the reported improvement is of such magnitude which is not commonly documented even with combination of drugs. This makes the case of using IVMg in larger number of cases. However, before IVMg becomes a regular drug for acute severe asthma, further studies should be carried out address-ng the precise place of this therapy in avoiding hospitalizaing, minimizing hospital stay and its role in status asthmaticus.

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Bone Marrow Transplantation for Sickle Cell Anemia: Is it the Right Choice?

[Walters MC, Patience M, Leisenring W, Eckman JR, Scott JP, Menter WC, et al. Bone marrow transplantation for sickle cell disease. N Engl J Med 1996, 335: 369-376.]

Transplantation of hematopoietic stem cells from HLA-identical siblings can be curative in several non-malignant hematologic disorders, including aplastic anemia, (J thalassemia major, congenital immunodeficiency disorders, and certain inborn errors of metabolism. The present multicentric study was taken up to explore the risks and benefits of allogenic bone marrow transplantation in young patients with symptomatic and complicated sickle cell disease.

Twenty two patients less than 16 years of age (median, 10.4, range 3.3 to 13.9 years) with symptomatic sickle cell disease

(hemoglobin genotype S/S, hemoglobin S/C disease or sickle cell-p thalassemia) and HLA identical sibling donors (hemoglobin genotype A/A or A/S) were considered for marrow transplantation. The indications for transplantation included debilitating clinical events, such as stroke (n=12), recurrent acute chest syndrome (n=5) and recurrent painful vaso-occlusive crises (n=5) which contribute to the high morbidity and early mortality in these patients. Those with extensive end organ damage *(e.g.* stage III or IV sickle lung disease, severe renal impairment or liver damage) were excluded. Patients were prepared for transplantation with busulfan, cyclophosphamide, and antithymocyte globulin. Patients received either a combination of methotrexate and cyclosporine (21 patients) or cyclosporine and prednisone (1 patient) for the prevention of acute graft-versus-host disease (GVHD). Kaplan-Meier method was used to estimate survival and event free survival (events included death, disease recurrence and graft rejection).

Twenty of the 22 patients survived, with a median follow up of 23.9 months (range, 10.1 to 51.0 months). Sustained engraftment with 85% or more donor-derived blood cells was demonstrated by tests for chimerism in 16 of the 20 surviving patients. In three patients, sickle cell disease recurred due to graft rejection; in a fourth patient graft rejection was accompanied by marrow aplasia. In 1 of the 16 patients with engraftment, there was stable mixed chimerism. Two patients died of central nervous system hemorrhage or graft versus host disease. Kaplan Meier estimates of survival and event free survival at four years were 91% and 73%, respectively; the cumulative incidence of graft rejection was 18%. Among patients with a history of acute chest syndrome, lung function stabilized; among patients with prior CNS vasculopathy who had engraftment, stablization of cerebrovascular disease was documented by magnetic resonance imaging. It was concluded that allogeneic stem-cell transplantation can be curative in young patients with symptomatic sickle cell disease.

Comments

Sickle cells, filled with hemoglobin S, occlude microcirculation resulting in vascular crisis in the spleen, brain, lung, kidney, eye and heart. The clinical manifestations vary from mild anemia to frequent pain crises and acute chest syndrome. These life threatening events are the main morbidity of the disease and share varying degrees of bone marrow ischemia, necrosis, embolization and inflammation(l).

The present multicentric collaborative trial suggests that bone marrow transplantation has the potential to cure all these patients. Fifteen out of 22 patients (68%) were cured. Though evaluation of the ultimate effect of transplantation on stabilization of end organ damage require longer follow up, yet it is suggested that these 15 children shall remain free of the sickle cell disease, associated pain, need for transfusions, complications and early death. However, these children are also likely to carry a risk of chemotherapy induced malignancy and infertility.

There was allograft rejection followed by a recurrence of sickle cell disease in 4 patients, a result similar to the 12% rejection rate reported among children with fJ thalassemia who received HLA matched marrow grafts from siblings(2). The data also suggests that patients who have not undergone long term transfusion therapy and do not have severe complications are optimal candidates for marrow transplant. However, the optimal timing of transplant remains uncertain. In the study under re-

view, the patients appeared to have a high risk of severe morbidity and early death. Marrow transplantation might be better if performed early in the course of sickle cell disease(3).

Deaths are unavoidable with current state of transplantation technology and the rate is unlikely to fall below 10%(4). On the other hand, the overall death rate in children with sickle cell disease during the first decade of life is near 1% only(5). This highlights the importance of predicting a patient who is likely to have a poor outcome and may benefit from early transplantation. A major drawback in this regard is unavailability of precise criteria which may help select an optimal candidate for marrow graft(6). Resorting to bone marrow transplantation with a liberal selection policy may expose a large number of patients to the risk of infertility, graft versus host disease, exacerbation of sickle vascular disease, complications related to the conditioning regimen and even death. An alternative strategy in the treatment of sickle cell disease has been the long term administration of oral hydroxyurea, an easily available cheap drug that stimulates the production of fetal hemoglobin(7). Clinicians have-to weigh the pros and cons of these two approaches. Whereas the former is associated with a definitive cure albeit at considerable risk, the latter approach ameliorates the disease with a limited risk of reversible short term complications. The two therapeutic options should be examined in light of their efficacy, feasibility and cost effectiveness, especially in a developing country like ours.

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