# MEGA DOSE INTRAVENOUS METHYLPREDNISOLONE FOR TREATMENT OF MALIGNANT OSTEOPETROSIS

**SINASI ÖZSOYLU***

*SUMMARY: Two infants with recessive (Malignant) osteopetrosis were treated with intravenous methylprednisolone (daily, 30 mg/kg for 3 days, 20 mg/kg for 4 days, then subsequently 10,5 and 2 mg/kg a week) followed by 1/mg/kg till the hemoglobin level reached 11 g/dl for 34 and 62 days. Treatment was continued with oral prednison (2.5 or 5 mg) for 37 and 34 months duration. The liver and spleen in both patients became almost normal in size with the elevation of the platelet count and hemoglobin level to normal with a decrease of reticulocyte count and normoblastemia, and needle aspiration showed their bone marrow to be normocellular. Plasma hemoglobin and alkaline phosphatase decreased to normal with the elevation of haptoglobin levels. Growth and development became fairly appropriate for their ages though both had macrocrania and there was exophtalmus in one. With the exception of Cushingoid appearance during mega dose administration they did not show any important side effects of corticosteroid such as hyperglycemia and growth retardation.*

*Key Words : Osteopetrosis, mega dose methylprednisolone.*

## INTRODUCTION

Malignant infantile osteopetrosis is characterized by densely opaque bones, associated with hepatosplenomegaly, anemia, thrombocytopenia, leukoerythroblastic blood picture, hypocellular bone marrow and neurologic findings such as severe intracranial hypertension, blindness and deafness. Although variations in clinical severity of this rare autosomal recessive disorder have been known (1) early death is generally expected (2). Recently a new form of this disease with carbonic anhydrase II deficiency associated with cerebral calcification and renal tubular acidosis has been reported (3).

Some therapeutic approaches have been attempted in the malignant form of osteopetrosis such as low calcium intake (4) and corticosteroid (4,5) administration. Bone marrow transplantation seems to be a new hope for this serious disorder, affecting hematologic findings, bony changes and also monocyte bactericidal activity (6). Since excellent results had been obtained with mega dose intravenous corticosteroid in childhood myelofibrosis (7) in which condition bone marrow is hypocellular, it was tried in two cases of infantile osteopetrosis after informed consent was obtained from the parents.

*From Department of Pediatrics, Hacettepe University, Faculty of Medicine, Hematology Unit and Hacettepe Children's Hospital, Ankara, Turkiye.

## MATERIALS AND METHODS

A four-month old girl and a 5-month-old boy, both products of first cousin marriage, were referred to Hacettepe Children's Hospital with diagnosis of chronic granulocytic leukemia and rickets respectively. Marked hepatosplenomegaly, exophtalmus, growth (height and weight about 3 percentile) developmental failure (both could not hold their heads or turn over). Stuffy nose, enlarged bulging fontanel and severe generalized osteosclerosis by X-ray examinations were detected (Table 1). Eye grounds indicated engorgement of veins and optic atrophy in these infants respectively.

Laboratory findings indicated marked anemia with reticulocytosis, normoblastemia, leukemoid reaction, thrombocytopenia and severe hypocellular bone marrow by needle aspiration (Table 2). Plasma hemoglobin concentration was found to be elevated with a decrease in haptoglobin level. 99m Tc sulphur colloid scanning showed no uptake in the long bones with increased uptake of liver and spleen. Complete blood counts, platelet counts, Coombs test, measurement of plasma hemoglobin, haptoglobin, calcium, phosphorus and alkaline phosphatase were performed by using standard laboratory methods. Helper (OKT), suppressor (OKT8) and IgG, IgM and IgA levels were obtained by using monoclonal technique and Behring-Werke plates respectively.

Both patients were started on intravenous methylprednisolone (daily, 30 mg/kg for 3 days, 20 mg/kg for 4 days, then subsequently 10, 5, 2 mg/kg a week each followed by 1 mg/kg) until the hemoglobin level reached 11 g/dl concentration.

Table 1: Some of the physical findings during treatment given chronologically.

| | Weight (g) | Height (cm) | Liver* (cm) | Spleen* (cm) |
|---|---|---|---|---|
| First case | | | | |
| 4 months of age | 5800 (3)** | 61 (10) | 5 | 6 |
| 6 months of age | 6700 | 64 | Just palpable | 2 |
| 8 months of age | 7000 | 66 | 1 | 1 |
| 10 months of age | 7850 | 79 | Non-palpable | |
| 15 months of age | 9550 (10) | 84 (>90) | Non-palpable | |
| Second case | | | | |
| 5 months of age | 5600 (3) | 61 (3) | 7 | 6 |
| 6 months of age | 6000 | 62 | 5 | 5 |
| 9 months of age | 6900 | 62 | 5 | 5 |
| 11 months of age | 8080 | 64 | 4 | 4 |
| 14 months of age | 8500 | 68 | 2 | 2 |
| 15 months of age | 10000 (25) | 73 (<3) | 1 | 1 |

*: Palpable below of respective costal margin

**: Number in parenthesis indicate percentile for age.

Hemoglobin levels reached 11 g/dl at the 34th and 62nd days of intravenous methylprednisolone administration respectively. Since then the patients have been on oral Prednison (2.5 or 5 mg/daily) for 37 and 34 month duration with increase of bone marrow cellularity at about the 6th and 4th months of treatment, respectively.

In both patients plasma hemoglobin became normal (<5 mg/dl) with elevation of haptoglobin levels and almost complete disappearance of leukocytosis with leukoerythroblastic blood picture and thrombocytopenia was completely corrected in both patients in 2 weeks and 2 months, successively (Table 2).

A marked decrease in liver and spleen size was observed in both patients with intravenous methylprednisolone administration; some improvement also observed #2 during oral prednison administration. Some improvement also observed in height and weight but not in head size (Table 1).

Although improvement in X-rays of long bones was not

Table 3: Calcium, phosphate and alkaline phosphatase levels before and during treatment.

| | Ca (mg/dl) | P (mg/dl) | Alkaline phosphatase (Bodansky Unit) |
|---|---|---|---|
| First case | | | |
| Initial | 9.8 | 3.8 | 44 |
| After treatment | | | |
| 3 months | 10 | 3.6 | 36 |
| 4 months | 9.6 | 3.7 | 22 |
| 5 months | 10 | 4.2 | 18 |
| 7 months | 9.5 | 4.6 | 18 |
| 11 months | 10.6 | 4.6 | 15 |
| Second case | | | |
| Initial | ND* | ND | ND |
| Following treatment | | | |
| 1 month | 7.6 | 4.2 | 24 |
| 2 months | 10.8 | 5.7 | 13 |
| 4 months | 10.6 | 5.6 | 12 |
| 9 months | 11 | 5.9 | 11 |

*N.D.: Not determined

Table 2: Some of the hematological findings just before starting and during treatment.

| | Hb (g/dl) | Hct (%) | Retics (%) | Nor-moblastemia ( /μ) | VBC ( /μ) | Platelet (x103/μl) | Bone Marrow | Plasma Hb (mg/dl) (0.7-3) | Hp (mg) | HbF (%) | HbA2 (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| First case | | | | | | | | | | | |
| 4 months of age | 7.5 | 26 | 7.4 | 1750 | 17500 | 56 | Hypocellular | | | | |
| 4.5 months of age | 10.38 | 30 | 8.8 | 618 | 10300 | 205 | | 5.5 | 0 | 6.3 | 2.8 |
| 5 months of age | 11.5 | 34 | 5.2 | 78 | 7800 | plenty on smear | | 5.18 | 0.92 | | |
| 5.5 months of age | 11.82 | 35 | 0.2 | 61 | 6100 | plenty on smear | Hypocellular | | | 9.7 | 2.45 |
| 10 months of age | 10.02 | 34 | 1.4 | 0 | 6400 | plenty on smear | Cellular | | | 2 | |
| 15 months of age | 10.38 | 33 | 0.4 | 0 | 7900 | plenty on smear | | 25 | 1.8 | | |
| 16 months of age | 11.5 | 34 | 0.6 | 0 | 6200 | plenty on smear | | | | | |
| Second case | | | | | | | | | | | |
| 5 months of age | 6.79 | 22 | 7.2 | 4060 | 29000 | 60 | Hypocellular | 6 | 1.9 | 5.4 | 2.9 |
| 6 months of age | 8.55 | 25 | 4.2 | 16192 | 35200 | 96 | | | | | |
| 7 months of age | 11.5 | 36 | - | 396 | 19800 | | | | | 5 | 2.2 |
| 9 months of age | 12.46 | 37 | 1.4 | 0 | 10600 | | Cellular | | | 6.5 | 2.5 |
| 14 months of age | 11.82 | 35 | 0.8 | 66 | 6600 | 356 | | 2 | 2.11 | | |

marked, repeat 99m Tc sulphur colloid scanning in both cases showed normal marrow uptake. Elevated alkaline phosphatase levels became almost normal for the ages (<15 BU) without obvious changes in calcium and inorganic phosphate concentrations except early low calcium in case #2 (Table 3).

Hypoimmunoglobulin G level (250 mg/ml) with normal 1 gM (160 mg/dl), I gA (38 mg/dl) concentrations, with low helper count case #1 on the 10th month of age which was also present at 15 months of age (IgG: 330 mg/dl; IgM: 90 mg/dl).

## DISCUSSION

Increased hemoglobin concentration and platelet count with decrease in splenic size and transfusion requirement in infantile osteopetrosis have been reported previously (2, 4, 5, 8). But, with tapering of the prednison dose below 1 mg/kg hematological improvement regressed in them with the appearance of hepatosplenomegaly (5). With mega doses of intravenous corticosteroid administration, not only clinical and hematological findings became normal, with the exception of mild exophthalmia, palpable spleen and very mild normoblastemia in case #2, but they stayed normal during a 12 and 10-month follow up period, with 0.25 or 0.50 mg/kg oral prednison which it was planned to discontinue in several months according to our experience with a plastic anemia, congenital pure red cell anemia and myelofibrosis (7, 9-11). Optic atrophy, present when case #2 was first seen, did not improve.

Repeated bone marrow scanning in both cases showed normal uptake as reported with conventional (2 mg/kg, oral) steroid treatment (5). Bone morrow needle aspiration became normocellular in both children with the disappearance of the leukemoid blood picture. With clinical and hemoglobin level improvement reticulocytosis decreased. Although hypersplenic hemolysis is accepted as the main contributing factor for severe anemia and thrombocytopenia in this disease (5, 12-14) elevated plasma hemoglobin with decrease haptoglobin levels, despite negative Coombs test in both patients, as reported previously (5), strongly suggests also intravascular hemolysis which could be an additional factor for the pathogenesis of anemia of malignant infantile osteopetrosis. The peripheral blood picture, including platelet count, became normal before improvement of bone marrow cellularity in these patients.

This was also observed in our patients with a plastic anemia. Idiopathic childhood myelofibrosis and paroxysmal nocturnal hemoglobinuria cases given mega doses of intravenous methylprednisolone (7, 9).

Since increased circulating myeloid and erythroid progenitor cells were shown in malignant infantile osteopetrosis (15), it is possible that those cells responded first to high dose intravenous methylprednisolone before bone marrow space became available in this disorder.

Mega dose intravenous corticosteroids stimulate erythropoiesis in congenital pure red cell anemia cases which become refractory (10) or resistant (17) to begin with to conventional steroid (2 mg/kg) therapy. It also stimulates all bone marrow elements in aplastic anemia (9), and idiopathic myelofibrosis (7). Although the specific mechanisms of mega dose corticosteroid in osteopetrosis are not known, its significant benefit in the management of this life-threatening disease, was marked compared to our previous 11 infants with this disorder who all died before one year of age with continued enlargement of liver and spleen with deepening anemia and thrombocytopenia which required frequent transfusions.

The side effects of this treatment, with the exception of Cushingoid appearance during high dose administration, were not observed, such as hypertension, hyperglycemia, hypercalcemia ( it be came 11 mg/dl only in case #2), and growth retardation. No infection was observed in this infants during the treatment period, though decreased bacterial killing was reported previously in infantile osteopetrosis (16). It should be noted that hypogammaglobulinemia was documented in one of these infants in whom helper T cells were also found to be low with decreased helper suppressor ratio.

Since mega dose intravenous methylprednisolone treatment is easier, cheaper and less dangerous than bone marrow transplantation, it should be started as early as possible; before any sequelae of the disease appear such as optic atrophy and marked macro crania which do not seem to be affected by this treatment as excepted.

Five to 10 mg/kg methylprednisolone has been called high dose (18, 19) therefore the doses they are not different than those of our previous studies (7, 9-11, 17).

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Correspondence:
Sinasi Özsoylu
Hacettepe University,
Faculty of Medicine,
Department of Pediatrics,
Hematology Unit and
Hacettepe Children's Hospital,
Ankara, TURKIYE.