Onyalai — therapeutic effects of vincristine sulphate

A prospective randomized trial

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Summary

Twenty out of 40 patients with onyalai admitted to Rundu State Hospital, Kavango, SWA/Namibia, were randomized to receive a vincristine sulphate bolus of 1,5 mg/m² or an equivalent volume of normal saline intravenously on days 8 and 15 when haemorrhage or a platelet count of less than 50 x 10^9/l persisted for more than 1 week after admission. All patients were observed in hospital for at least 21 days. Five out of 10 patients who received vincristine achieved a platelet count in excess of 100 x 10^9/l on day 21 and only 2 out of 10 patients who received placebo achieved a similar rise in the platelet count. Two patients, neither of whom was treated with vincristine, died of cerebral haemorrhage.

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The management of onyalai, a form of immune thrombocytopenic purpura which occurs among certain black populations in southern Africa, presents a major problem.[1] The acute onset of episodes of severe bleeding with haemorrhagic shock and the risk of cerebral haemorrhage can cause early death in almost 10% of patients.[2] The active replacement of blood loss has reduced deaths due to haemorrhagic shock, but cerebral haemorrhage remains a real danger in the acute phase.

A randomized trial which compared the effects of corticosteroids, intravenous gammaglobulin and ascorbic acid (as placebo) on the platelet counts in patients with onyalai who had persistent thrombocytopenia or haemorrhage for more than 7 days after admission showed no difference in the three treatment groups.[3] A splenectomy may benefit patients with uncontrollable haemorrhage.[4]

Vinca alkaloids stimulate thrombocytopoiesis.[5] Bolus therapy with vincristine sulphate may improve the platelet count in more than 50% of patients with refractory idiopathic thrombocytopenic purpura, the response generally occurring within 1 week.[6,7]

A randomized trial was undertaken to assess the effect of bolus intravenous injections of vincristine sulphate on the platelet counts in patients with onyalai who were thrombocytopenic or still bleeding actively 1 week after the onset of an acute haemorrhagic episode. A quick rise in the platelet count in these patients would reduce the morbidity and mortality of the acute phase of onyalai.

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Patients and methods

Forty patients were entered into this trial between 20 January 1984 and 8 March 1985. Every patient presented with haemorrhagic bullae, a bleeding tendency and severe thrombocytopenia with no signs of underlying systemic disease. All were admitted to Rundu State Hospital for a minimum of 21 days. Twenty of the patients who had persistent haemorrhage or a platelet count of less than 50 x 10^9/l 7 days after admission were randomized, by the toss of a coin, to receive either 15 ml normal saline intravenously (treatment A; placebo) or vincristine sulphate 1,5 mg/m² (treatment B) as an intravenous bolus on days 8 and 15. Lactulose was given to each one who received vincristine to prevent constipation. All those in the trial received ascorbic acid 1 g 3 times a day. Fresh ABO-compatible blood was transfused whenever the haemoglobin dropped below 10 g/dl in the presence of active bleeding. Informed consent was obtained from every patient.

Blood counts were performed on admission and on days 8, 15 and 22 with a Coulter Model DN and a Coulter Thrombocounter. A malaria smear, urine and stool microscopy, and a pregnancy test in postpubertal female patients were performed routinely.

The Mann-Whitney *U*-test for signed-rank data was used to compare the platelet counts of treatment groups A and B.

Results

The age and sex distribution of the patients is shown in Fig. 1 and the clinical findings on admission are listed in Table I.

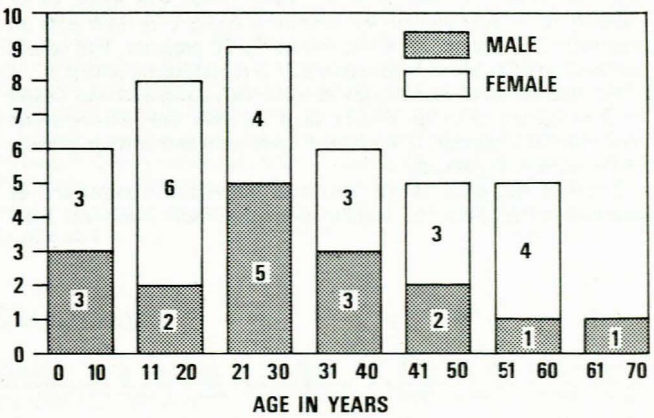

Fig. 1. Age and sex distribution of patients.

Twenty patients were randomized to receive treatment A or B. Another 2 patients who qualified for randomization are included with the patients who did not receive treatment A or B because 1 of this pair died of cerebral haemorrhage on day 12.

The mean duration of clinical haemorrhage for all the patients before admission was 2,6 days (range 1 - 14 days). Haemorrhage

TABLE I. CLINICAL SIGNS ON ADMISSION

Signs	No. of patients
Haemorrhagic bullae in buccal cavity and skin	40
Epistaxis	22
Petechiae/ecchymoses	6
Melaena/haematemesis	10
Haematuria (bilharzia –ve)	4
Vaginal bleeding	3

TABLE II. MEAN PLATELET COUNTS (x 10^9/l) DURING THE TRIAL (RANGE)

Day	Whole group ($N = 40$)	Supportive therapy only ($N = 20$)	Vincristine ($N = 10$)	Placebo ($N = 10$)
1	15 (3 - 39)	12 (3 - 33)	17 (4 - 39)	22 (5 - 34)
8	64 (7 - 248)	96 (53 - 190)	23 (7 - 78)	14 (7 - 33)
15	124 (3 - 455)	151 (38 - 455)	98 (12 - 301)	34 (3 - 234)
22	158 (4 - 612)	206 (40 - 612)	118 (5 - 312)	67 (8 - 286)

persisted for an average of 5,8 days (range 1 - 19 days) after admission, giving a total mean duration of haemorrhage of 8,4 days (range 4 - 22 days) for this series. Twenty-two patients each received between 1 and 16 U of blood.

The mean platelet counts on days 1, 8, 15 and 22 for all the patients — 20 patients who did not receive treatment A or B and 20 patients randomized to receive either A or B — are listed in Table II.

No significant *P* values were obtained for the difference in platelet counts on days 15 and 22 for treatment groups A and B. Nevertheless 5 out of 10 patients who received vincristine had a rise in their platelet counts to $>$ 100 x 10^9/l on day 22, compared with 2 out of 10 in the control group who received placebo. On day 22 the platelet count exceeded 150 x 10^9/l in 4 patients who had received vincristine, and in 1 patient who had received placebo.

The mean haemoglobin value on admission was 10,8 g/dl (range 4,2 - 15,0 g/dl). A total of 92 U whole blood was given to 22 patients (11 U to 3 patients on treatment A, 26 U to 8 patients on treatment B, 55 U to 11 of the remaining 20 patients, 1 of whom received 16 U of blood before dying of cerebral haemorrhage).

On routine stool microscopy *Ancylostoma duodenale* was found in 13 patients, *Giardia lamblia* in 4 patients and *Strongyloides stercoralis* in 1 patient. *Schistosoma haematobium* ova were present in the urine of 6 patients.

None of the patients who received vincristine complained of neuromuscular pains or constipation and there were no local reactions at the site of injection. One 18-year-old man who had already been given 8 U blood within 3 days after admission suddenly complained of headache, became unconscious and died the same day. Another man, aged 23 years, who had persistent profuse bleeding was given 16 U fresh blood. On day 12 he complained of headache, developed hemiplegia, bcecame unconscious and died the next day. Although autopsies could not be performed, both these deaths appeared to be as a result of haemorrhage into the central nervous system. Neither of these patients had been treated with vincristine.

Discussion

The morbidity of the acute phase of onyalai, measured in terms of the need for blood transfusions in 22 patients, and cerebral haemorrhage in 2 patients, is once again clearly illustrated. Eight patients receiving vincristine required blood transfusions compared with 3 patients receiving placebo. The rise in the platelet count to $>$ 100 x 10^9/l in half the patients who received vincristine was a pleasing result. The fact that this was not statistically significant may perhaps be explained by the small number of pairs and the large variations in the platelet counts.

None of the complications associated with vincristine sulphate therapy occurred in these patients.

Onyalai occurs in rural, underdeveloped areas of Africa where medical services are often limited. We therefore believe that this relatively simple treatment should be given a trial in patients with onyalai who have persistent haemorrhage or thrombocytopenia (if facilities to measure the platelet count exist) for more than 7 days.

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