Does treatment of newly diagnosed idiopathic thrombocytopenic purpura reduce morbidity?

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Aim: To explore whether early treatment of children with idiopathic thrombocytopenic purpura (ITP) with immunoglobulin and/or corticosteroids reduces subsequent morbidity.

Methods: Centres participating in a Nordic ITP study were divided according to whether they had treated more than 2/3, from 1/3 to 2/3, or less than 1/3 children within 14 days of diagnosis. The course of disease from 15 days to 6 months after diagnosis was compared for children managed at the three centre categories. The comparison was restricted to children in whom at least one platelet count $<20 \times 10^9/l$ was measured, numbering 156, 143 and 84 in the three different categories, respectively.

Results: The three groups of children were clinically similar but were managed with initial treatment rates of 89%, 57% and 14%, respectively. By day 15, the platelet count had stabilised to $>20 \times 10^9/l$ in 67%, 67% and 52% ($p < 0.05$) and to $>150 \times 10^9/l$ in 38%, 29% and 29% ($p < 0.20$). At 1 month after diagnosis there was no difference in recovery rates. Chronic ITP developed in 27%, 22% and 25% in the three groups. During follow-up, one or more disease-related events occurred in 23%, 22% and 19%, with no difference in the average numbers of episodes with mucosal bleeding. Treatment courses were administered to 19%, 13% and 11%, respectively.

Conclusion: Active treatment policies accelerated platelet recovery in children with short-lasting ITP but did not avert the development of chronic ITP and did not cause a reduction in morbidity during follow-up.

The management of children with newly diagnosed idiopathic thrombocytopenic purpura (ITP) remains a topic of controversy. A division persists between interventionists aiming to eliminate any risk of life-threatening bleeding and non-interventionists trying to avoid unnecessary treatment. Guidelines have been published in both the UK and the US^{1–4} but with different recommendations, fuelling further debate. Trials showing the platelet-enhancing effects of different modes of therapy abound,⁵ but trials with clinical endpoints addressing the most important question – whether to treat or not – are non-existent, being difficult to design and conduct.

A Nordic study of childhood ITP described morbidity in the first 6 months after diagnosis.^{6,7} As part of the study, initial management was recorded in detail. The use of intravenous immunoglobulin (IVIG) or corticosteroids (CS) at the time of diagnosis showed national differences and varied considerably between centres within each country.⁸ Thus, the data provided the opportunity to compare the course of disease in children managed at centres with high, intermediate or low initial treatment rates.

METHODS

In the 3-year period 1998–2000 a total of 506 children with newly diagnosed ITP were prospectively registered by 98 centres in the five Nordic countries. The study was approved by national ethics committees and data authorities. Briefly, presenting features, management and treatment response were recorded at the time of diagnosis. During follow-up in the first 6 months after diagnosis, all disease-related events eliciting medical attention were recorded, and the times between diagnosis and the last platelet counts <20 , <50 and $<150 \times 10^9/l$ were determined.

Overall, 57% (287 of 506) children received therapy with IVIG and/or CS within 14 days of diagnosis, but treatment rates differed widely between centres. For the purposes of the present

study, centres were grouped in three categories with high (H), intermediate (I) and low (L) initial treatment rates:

- 43 H-centres treated more than 2/3 newly diagnosed children, with a pooled treatment rate of 87% (170 of 196 children)
- 31 I-centres treated from 1/3 to 2/3 children, with a pooled treatment rate of 53% (104 of 196)
- 24 L-centres treated less than 1/3 children, with a pooled treatment rate of 11% (13 of 114).

Analysis has been restricted to children in whom at least one platelet count $<20 \times 10^9/l$ was measured and with complete follow-up data. There were 383 such children: 156 at H-centres (group H), 143 at I-centres (group I) and 84 at L-centres (group L).

For each child the time from diagnosis until the last platelet count $<20 \times 10^9/l$ (all subsequent counts remaining above this level) was determined. This can be considered a risk period during which intracranial or major haemorrhages may occur.^{9–11} The time from diagnosis until the last platelet count $<150 \times 10^9/l$ was defined as the duration of thrombocytopenia. The number of reported disease-related events (bleeding episodes, drops in platelet count, trauma) and the number of interventions (hospitalisations, courses of therapy, bone marrow examinations) during follow-up were taken as measures of morbidity or burden of disease. Events occurring during the risk period potentially evolving into major haemorrhage were classified as risk events, and episodes with oozing mucosal bleeding as “wet” events.

The three patient groups were compared for duration of risk, duration of thrombocytopenia, and occurrence of events and

Abbreviations: CS, corticosteroids; ITP, idiopathic thrombocytopenic purpura; IVIG, intravenous immunoglobulin

Table 1 Clinical characteristics and initial management of children admitted to centres with high (H), intermediate (I) and low (L) initial treatment rates

	Group H, n = 156	Group I, n = 143	Group L, n = 84
Clinical characteristics			
Boys	90 (58%)	77 (54%)	52 (62%)
Age 0–5 years	106 (68%)	91 (64%)	61 (73%)
Preceding infection	90 (58%)	78 (55%)	54 (64%)
Symptoms >14 days	30 (19%)	36 (25%)	18 (21%)
Wet purpura*	70 (45%)	64 (45%)	33 (39%)
Platelet count <10×10 ⁹ /l	93 (61%)†	94 (67%)‡	51 (61%)
Management			
Treatment§			
On day 1–14	139 (89%)	81 (57%)	12 (14%)
On day 1–2	108 (69%)	56 (39%)	9 (11%)
On day 3–14	31 (20%)	25 (17%)	3 (4%)
Immunoglobulin¶ (% of treated)	127 (91%)	76 (94%)	11 (92%)
Corticosteroids** (% of treated)	33 (24%)	13 (16%)	2 (17%)
Platelet transfusion	30 (19%)	8 (6%)	2 (2%)
Red cell transfusion	9 (6%)	3 (2%)	0 (0%)
Bone marrow examination	53 (34%)	50 (35%)	38 (45%)
One or more interventions††	147 (94%)	102 (71%)	48 (57%)

*Purpura with oozing mucosal bleeding; †platelet count at diagnosis missing in four cases; ‡platelet count at diagnosis missing in two cases; §a course of therapy with IVIG and/or CS initiated; ¶immunoglobulin therapy: two infusions of 1.0 g/kg or one infusion of 0.8 g/kg in most cases; **corticosteroid therapy: prednisone 1–2 mg/kg for 1–3 weeks in most cases; ††therapy with IVIG and/or CS, blood product transfusion or bone marrow examination.

interventions. Morbidity was ascertained for children with acute ITP (lasting less than 6 months) and with chronic ITP separately. Data are reported descriptively, with selected differences being tested for significance (χ^2 test for 2×3 table, 2 df).

RESULTS

The three patient groups were clinically similar, but their initial management differed markedly (table 1). H-centres treated 89% of the newly diagnosed children, I-centres 57% and L-centres 14%. Higher treatment rates were associated with more frequent use of blood product transfusions and with less frequent performance of bone marrow examination. Overall, the H-, I- and L-centres performed therapeutic and/or diagnostic interventions in 94%, 71% and 57% of the children.

Recovery from thrombocytopenia is compared in fig 1. An impact of therapy is discernible in the first month after diagnosis. By day 14, complete recovery rates at H-, I- and L-centres were 38%, 29% and 29% ($p<0.20$), respectively and the risk period was over in 67%, 67% and 52% of children ($p<0.05$). By 1 month, the recovery rate was close to 50% in all three groups, increasing to approximately 75% after 6 months, chronic ITP occurring in 27%, 22% and 25% of children, respectively. For children with acute ITP, the average duration of the risk period was 10, 12 and 14 days, and of thrombocytopenia 30, 35 and 34 days.

Close to 90% of children with acute ITP had an uneventful course, but H- and I-centres reported more events and more interventions than L-centres (table 2). Half of the children with chronic ITP experienced one or more events during follow-up in all three groups. "Wet" bleeding episodes occurred in similar numbers (averages 0.36, 0.38 and 0.38 per child with chronic ITP) and at similar rates (0.11, 0.12 and 0.10 per month at risk). Compared to L-centres, however, H- and I-centres reported a greater number of other events and also performed more interventions (average number of interventions of 3.10, 1.50 and 1.05 per child).

Figure 1 Recovery from thrombocytopenia at centres with high (black), intermediate (grey) and low (white) initial treatment rates. The curves show the percentages of children in whom the last platelet count <20×10⁹/l (◇, risk period ended) or the last platelet count <150×10⁹/l (○, complete recovery) has been measured, all subsequent counts being higher without any therapy.

Combining data for acute and chronic ITP, there was no difference in the three groups in the percentages of children with events (23%, 22% and 19%) or subjected to interventions (22%, 20% and 19%). The interventional activity, however, was considerably higher in group H (153 interventions in 35 children, average 4.4) than in group I (71 interventions in 28 children, average 2.5) or group L (30 interventions in 16 children, average 1.9). One or more courses of therapy were given to 19%, 13% and 11% of children.

DISCUSSION

This supplementary analysis of data from the Nordic study of children with newly diagnosed ITP has shown that centres with high or intermediate treatment rates increased the percentages of children with rapid termination of bleeding risk and of thrombocytopenia, but failed to reduce the percentages with ITP lasting more than 1 month or becoming chronic. They therefore also failed to reduce the morbidity from bleeding episodes and interventions during follow-up. It appears that early therapy can shorten the duration of thrombocytopenia only for children with ITP lasting less than 1 month, a group expecting very few disease-related events before recovery. Thus, our study provides no evidence that up-front treatment reduces later morbidity.

The findings must be interpreted with caution, however. The analysis is not a comparison of well-defined treatment policies established prior to data collection, but is based on an arbitrary categorisation of centres according to observed treatment rates. Follow-up is incomplete. Data reported from multiple centres may be of variable quality, and a grading system¹² ensuring uniform description of bleeding symptoms was not in use at the time of the study. In addition, the frequency of blood sampling probably varied considerably between centres, resulting in bias in the comparison of duration of risk and of thrombocytopenia since large sampling intervals will shorten these time periods as determined in this study. Finally, the endpoints used in the comparison do not include the all-important outcomes of life-threatening haemorrhages and mortality.

Nonetheless, the design defined three groups of children with equally severe disease and with similar percentages of insidious onset of symptoms, the most powerful predictor of chronic disease.⁷ A simple comparison of treated and untreated children across all centres would have yielded two clinically dissimilar groups. Also, the outcomes used for comparison are clinically important. Low platelet counts are associated with a perception

Table 2 Disease-related events and interventions during follow-up from 2 weeks to 6 months after diagnosis in children with acute ITP and with chronic ITP

	Group H	Group I	Group L
Acute ITP	n = 114	n = 111	n = 63
Risk period ended* by day 14	96 (84%)	89 (80%)	43 (68%)
Complete recovery† by day 14	59 (52%)	42 (38%)	24 (38%)
Sum of days at risk‡ during follow-up (average)	571 (5.0)	706 (6.4)	434 (6.9)
One or more events§	13 (11%)	14 (13%)	5 (8%)
All reported events (average)	17 (0.15)	18 (0.16)	7 (0.11)
Events during risk period (average)	13 (0.11)	14 (0.13)	4 (0.06)
Wet bleeding episodes (average)	2 (0.02)	0 (0.00)	0 (0.00)
One or more interventions¶	11 (10%)	11 (10%)	5 (8%)
Readmissions (average)	12 (0.11)	11 (0.10)	3 (0.05)
Treatment courses (average)	9 (0.08)	9 (0.08)	2 (0.03)
Bone marrow examinations (average)	2 (0.02)	3 (0.03)	3 (0.05)
Chronic ITP	n = 42	n = 32	n = 21
Risk period ended* by day 14	9 (21%)	7 (22%)	1 (5%)
Sum of days at risk‡ during follow-up (average)	4247 (101)	2969 (93)	2352 (112)
One or more events§	23 (55%)	17 (53%)	11 (52%)
All reported events (average)	72 (1.71)	36 (1.13)	20 (0.95)
Events during risk period (average)	65 (1.55)	32 (1.00)	19 (0.90)
Wet bleeding episodes (average)	15 (0.36)	12 (0.38)	8 (0.38)
One or more interventions¶	24 (57%)	17 (53%)	11 (52%)
Readmissions (average)	58 (1.38)	23 (0.72)	8 (0.38)
Treatment courses (average)	64 (1.52)	23 (0.72)	10 (0.48)
Bone marrow examinations (average)	8 (0.19)	2 (0.06)	4 (0.19)

*Platelet count remaining at $>20 \times 10^9/l$ without therapy; †platelet count remaining at $>150 \times 10^9/l$ without therapy; ‡sum of days from diagnosis to last platelet count $<20 \times 10^9/l$; §ITP-related episode eliciting medical attention; ¶hospitalisation, treatment with IVIG or CS, or bone marrow examination.

of risk that may be stressful to parents, and the interventions prompted by minor bleeding episodes cause discomfort to the children. The sum of events and interventions seems a relevant measure of the burden of disease and also reflects the cost of management. In spite of the stated limitations, we therefore consider that the analysis is both appropriate and informative.

To our knowledge, this is the first study to compare the clinical outcome of different treatment strategies for children with newly diagnosed ITP. The risks and benefits of various approaches have been much debated but with little evidence to support different opinions. In most multicentre studies, approximately half the children are given therapy at the time of diagnosis,^{2 13 14} probably the mean result of diverse attitudes. A watch and wait policy has been found to be safe,¹⁵ and treatment guided by bleeding symptoms is recommended in the UK,⁴ but a risk avoidance strategy based on platelet count as in the US guideline³ is still widespread. We found no obvious benefit from high treatment rates, which were in fact associated with a greater tendency to specify events and intervene, increasing the burden of disease. Our data cannot exclude, however, that H-centres maintained safe platelet counts for longer durations in the risk periods and thereby offered better protection against intracranial haemorrhages.

In conclusion, the present study found high, intermediate and low treatment rates for newly diagnosed ITP to be equivalent regarding morbidity during follow-up. The analysis does not suggest an optimal management strategy, but it has defined some benefits and drawbacks associated with early therapy. Hopefully, this evidence will stimulate centres to review local practices critically.

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What is already known on this topic

- Published guidelines for managing children with ITP are essentially opinion based and offer different recommendations for management.
- Randomised trials have documented the platelet-enhancing effects of several therapies, but little is known regarding their impact on the later clinical course.

What this study adds

- The outcomes of high, intermediate and low initial treatment rates have been compared in clinical terms.
- Treatment of most children soon after diagnosis may hasten recovery of platelet counts in children with ITP lasting less than 1 month, but does not seem to avert longer-lasting thrombocytopenia or to reduce the number of disease-related events occurring during follow-up.

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Dyskinetic cerebral palsy

A Swedish study of children born between 1995 and 1998 showed a decrease in the prevalence of cerebral palsy as a whole but not of dyskinetic cerebral palsy. Now data have been presented for 48 children with dyskinetic cerebral palsy born in western Sweden between 1991 and 1998 (Kate Himmelmann and colleagues. *Developmental Medicine and Child Neurology* 2007;**49**:246–51; see also editorial, *ibid*: 244).

Out of a total of 202 095 live births, 55 children with dyskinetic cerebral palsy (13% of all children with cerebral palsy) were identified at 4–8 years of age, a prevalence of 0.27 per 1000. Data for births in 1959–98 showed no significant change in the prevalence of dyskinetic cerebral palsy. Forty eight of the 55 children took part in the follow-up study. They were 27 boys and 21 girls, 39 with dystonic and nine with choreathetotic features. At a mean age of 9 years commonly found neurological features included persistence of primitive reflexes and dystonia that was as severe, or more severe, in the arms compared with the legs. Thirty four children had oral dystonia causing feeding and speech problems. Thirty three had evidence of spasticity. Ten children were able to walk, four independently and six with the help of mechanical devices. Thirty five had learning disability, the likelihood increasing with increasing motor impairment, but six of the 38 children unable to walk did not have learning disability. Ten children could speak though dysarthric and the other 38 used alternative methods of communication; 11 used Blissymbolics. Eleven were visually impaired, all in the group of 28 children at gross motor function classification system (GMFCS) grade V. Thirty children had epilepsy. Eighteen children, all at GMFCS levels IV and V, had a gastrostomy tube; they were better nourished than children with the same levels of motor impairment who did not have a gastrostomy tube.

Thirty eight children had been born at term. Thirty four of 42 children born at or near term (at least 34 weeks' gestation) had perinatal or neonatal adverse events. Placental abruption or uterine rupture, low Apgar score, neonatal seizures, instrumental delivery and emergency caesarean section were all much more common among these children than among children with other forms of cerebral palsy born at the same gestational age. Neuroimaging (CT and/or MRI) was performed in 43 children. Thirty one of 39 children born at or near term had evidence of late third trimester lesions in the basal ganglia and/or thalamus. No child in this study had kernicterus.

Dyskinetic cerebral palsy occurs predominantly in term-born infants with perinatal events suggesting hypoxia and ischaemia. Kernicterus is no longer a significant cause in Sweden. The prevalence of dyskinetic cerebral palsy has not changed in four decades. Improvements in perinatal care may have reduced the rate of adverse events but increased survival among those affected.