Successful implementation of a watchful waiting strategy for children with immune thrombocytopenia

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ABSTRACT

INTRODUCTION: Treatment of newly diagnosed immune thrombocytopenia (ITP) is controversial and guidelines vary internationally. At the Paediatric Department, Aalborg Hospital, a "watchful waiting" approach was adopted in the early 2000s. We aimed to investigate whether this change in strategy had any adverse effects on the subsequent clinical outcomes.

MATERIAL AND METHODS: Medical records were reviewed for children with ITP presenting with a platelet count < 30 × 10^9/l in the 1990s (n = 22) and in the 2000s (n = 47). Management during the initial admission and events during the first 12 months after diagnosis were recorded.

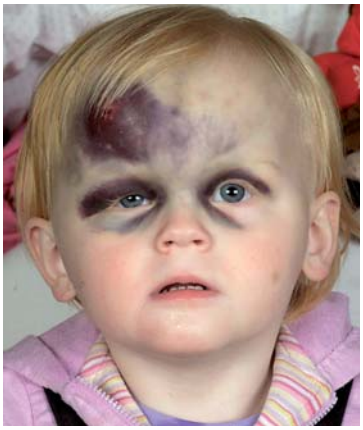
RESULTS: The rate of initial treatment with immunoglobulin or steroids was reduced from 64% in the 1990s to 15% in the 2000s. The percentage of children with ITP lasting more than three months did not increase (30% versus 32%). Nor did the occurrence of ITP lasting > 12 months (15% versus 27%). The proportion of children requiring readmission (19% versus 27%) or receiving therapy during follow-up (19% versus 23%) was unchanged. Serious bleeding requiring immediate intervention was equally rare (one episode in the 1990s, two in the 2000s). Cusum plots usefully depicted the changes in management and confirmed that the rate of adverse events did not increase.

CONCLUSION: A watchful waiting strategy for children with newly diagnosed ITP has been implemented without adverse effects on the duration or the morbidity of ITP.

Immune thrombocytopenia (ITP) is an acquired bleeding disorder characterized by immune-mediated destruction of platelets. In children, the primary form without an underlying disease occurs with an incidence of 4-5/10^5 per year, in Denmark corresponding to 40-50 cases per year [1, 2]. Most children recover within a few months without significant bleeding episodes, but approximately 25% develop chronic ITP (conventionally defined as a duration > 6 months) and a few experience serious bleeding episodes [1, 3]. Intracranial haemorrhage (ICH) is the most dreaded complication, albeit only occurring in approximately 0.1% [4, 5].

The variable and unpredictable course of the disease fuels an ongoing controversy regarding the management of newly diagnosed ITP [6]. Several therapies are available that effectively raise the platelet count: intravenous immunoglobulin (IVIG), corticosteroids (CS) or intravenous anti-D. "Interventionists" advocate their use to minimize the risk of serious haemorrhage. "Non-interventionists" advise to await spontaneous remission and reserve treatment for clinically significant bleeding episodes. The controversy is reflected in the varying international guidelines: In the US, an active approach based on the platelet count (PLC) is recommended; in the UK and in a recent consensus report, a conservative strategy is advised [7-9]. Clinical practice varies widely between nations and between centres [3, 10]. Evidence for the relative merits of the two approaches is lacking, and comparative trials that might resolve the controversy are difficult to design and conduct, given the low incidence of serious events.

The outcome of a "watchful waiting" approach has currently only been described in one German series that included 55 children [11]. In our Department, this restrictive approach was implemented soon after 2000. The introduction followed an early analysis of Nordic experience which suggested that the morbidity and the burden of disease were lower at centres with a low initial treatment rate [12]. At the time, an active policy was in place at most centres in Denmark [13]. In this study, we compare the clinical outcome in the first 12 months after diagnosis in the cohorts of children diagnosed in the 1990s and the 2000s, respectively. Cusum plots are used to describe the implementation of the new strategy and to investigate whether the conservative ap-



Haematoma after fall on a tiled floor. The platelet count was 9 × 10^9/l at the time.

ORIGINAL ARTICLE

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proach increased the occurrence of adverse events later in the course. In addition, the utility of a prognostic score in predicting brief duration is assessed retrospectively [14].

MATERIAL AND METHODS

In the period from 1 January 1990 to 31 December 2009, a total of 78 children aged 0-15 years were admitted to the Paediatric Department, Aalborg Hospital with newly diagnosed ITP (29 in the 1990s and 49 in the 2000s). The diagnosis was based on conventional criteria, i.e. isolated thrombocytopenia without clinical or laboratory evidence of underlying disease. For this study, only children with at least one PLC < 30 × 10^9/l during the primary admission were included. This reduced the cohorts to 22 in the 1990s and 47 children in the 2000s.

Patient records were reviewed and the following data extracted: bleeding manifestations, PLC at diagnosis, lowest PLC during the primary admission, platelet-enhancing therapy (IVIG and CS), side effects of treatment, blood transfusions and bone marrow examination (BME). In addition, for the clinical course during the subsequent 12 months we recorded: date of measurement of the last PLC below 100 × 10^9/l, bleeding events, readmissions and therapy. Registration was anonymous, and informed consent or ethical approval was not required. All children diagnosed in 2009 who had remitted before termination of the study were included in the cohort.

In accordance with the new terminology, each case was categorized as brief (duration of thrombocytopenia < 100 × 10^9/l < 3 months), persistent (> 3 months) or chronic ITP (> 12 months [15]. The score predicting brief duration was calculated from six characteristics recorded at diagnosis [14]. The number of readmissions and subsequent treatments during the following 12 months was determined. Bleeding manifestations were graded on a modified version of Buchanan's scale: "wet" mucosal bleeding being (grade 3), bleeding requiring immediate intervention (grade 4), ICH or other life-threatening haemorrhage (grade 5) [16].

The cohorts of children from the two decades were compared regarding clinical characteristics at diagnosis, initial treatment rates and later clinical outcomes during follow-up, i.e. percentages with persistent or chronic ITP, readmission, subsequent treatment, occurrence of grade 4 or grade 5 events. Differences were compared using Fisher's exact test.

To describe the change in management, we used cusum graphs plotting the cumulated number of children who were treated or had a BME performed in the series of successive cases [17]. Days of primary admission were also cusum-plotted to describe changes in the duration of hospital stay. To investigate changes in the incidence of later adverse events, the number of children with persistent ITP, chronic ITP, one or more readmissions or secondary treatment were similarly cusum-plotted. Using the rates from the 1990s as a reference, the plots were adjusted to display the deviation of observed events from 1990 rates; these plots were used descriptively, without inserting statistical significance limits. Finally, the value of the prognostic score was tested by plotting the cumulated sum of individually predicted risks against the expected and observed occurrence of persistent ITP.

TABLE 1

Comparison of clinical characteristics, initial treatment, duration of disease and main endpoints during the first 12 months after diagnosis of newly diagnosed immune thrombocytopenia in the 1990s and 2000s, respectively. Average days of admission for the two groups were 7.0 and 4.0, respectively.

	n (%)		
	1990-1999 (n = 22)	2000-2009 (n = 47)	p
Boys	16 (73)	23 (47)	0.07
Age < 10 years	21 (95)	41 (87)	0.42
Post infection[a]	15 (68)	29 (62)	0.79
Wet purpura[b]	11 (50)	17 (36)	0.30
Abrupt onset of disease[c]	13 (59)	36 (77)	0.16
Platelet count < 10 × 10^9/l	19 (86)	32 (68)	0.15
Initial treatment[d]	14 (64)	7 (15)	0.0001
Platelet transfusion	1 (5)	1 (2)	0.54
BME during initial admission	7 (32)	0 (0)	0.0002
Persisting ITP[e]	7 (32)	14 (30)	1.00
Chronic ITP, old definition[f]	8 (36)	15 (32)	0.79
Chronic ITP, new definition[g]	6 (27)	7 (15)	0.32
Readmission[h]	6 (27)	9 (19)	0.53
Subsequent treatment[i]	5 (23)	9 (19)	0.76
Bleeding events grade 4 or 5[j]	1 (4.5)	2 (4.3)	1.00
Subsequent BME	4 (18)	3 (6.4)	0.20

BME = bone marrow examination; ITP = immune thrombocytopenia.
a) Infection or vaccination < 1 month prior to onset of symptoms.
b) Bleeding event grade 3 or above graded on Buchanan's scale.
c) Symptoms < 14 days prior to diagnosis.
d) Immunoglobulin and/or corticosteroids.
e) Platelet count < 100 × 10^9/l > 3 months.
f) < 150 × 10^9/l > 6 months.
g) < 100 × 10^9/l > 12 months.
h) Six children were readmitted 19 times, nine children were readmitted 20 times.
i) Immunoglobulin, corticosteroid or anti-D (15 treatments for five children, 13 treatments for nine children).
j) Graded on Buchanan's scale.

RESULTS

The cohorts of children from the two decades were clinically similar with regard to presenting characteristics, although wet mucosal bleeding and PLC < 10 × 10^9/l were slightly more frequent in the 1990s (**Table 1**). Management during initial admission differed markedly, however. In the 1990s, 64% were given platelet-enhanc-

ing therapy, and 32% had a diagnostic BME performed. In the 2000s, only 15% were treated and none had a BME performed. IVIG was the preferred treatment throughout the period: 20 of the 22 treated children were given IVIG, 14 a single 1 g/kg infusion and six were given two infusions. Side effects of IVIG were noted in eight (36%) cases. They were usually mild and transient, but two children experienced an anaphylactoid reaction with chills and hypotension, and in two cases the infusion was terminated due to a febrile reaction.

The subsequent course of disease in the 12 months after discharge showed no significant differences between the two groups (Table 1). The development of persistent or chronic ITP did not increase in the 2000s. The percentages of children who needed readmission or treatment for bleeding episodes were also unchanged, but the use of subsequent therapy clearly became less frequent: In the 1990s, the average number of follow-up treatments was 3.0, in the 2000s it was 1.4. Serious grade 4 bleeding requiring immediate intervention was rare in both decades: one child had a severe gingival bleeding (1996), one a severe epistaxis (2004) and one experienced profuse haemorrhage following a dental extraction (2005). No life-threatening haemorrhage occurred. A delayed BME was performed in only a few children; in no case was the diagnosis revised.

Figure 1 describes the implementation of the watchful waiting strategy. BME became less frequent from the mid 1990s and the policy of restricted treatment was introduced early in the 2000s (Figure 1A). After implementation of the conservative strategy, the children were discharged more rapidly (Figure 1B); the average duration of hospitalization decreased from 7.0 to 4.0 days.

Figure 2 displays the occurrence of adverse events after the initial admission. Overall, the curves show no

FIGURE 1

Management of children with newly diagnosed immune thrombocytopenia in the 1990s (cases 1-22) and in the 2000s (cases 23-69). **A.** shows the cumulated number of children who received therapy (blue) and underwent bone marrow examination (green). **B.** displays the cumulated sum of admission days (blue) and the difference between actual admission days and the average number of admission days in the 1990s (green).

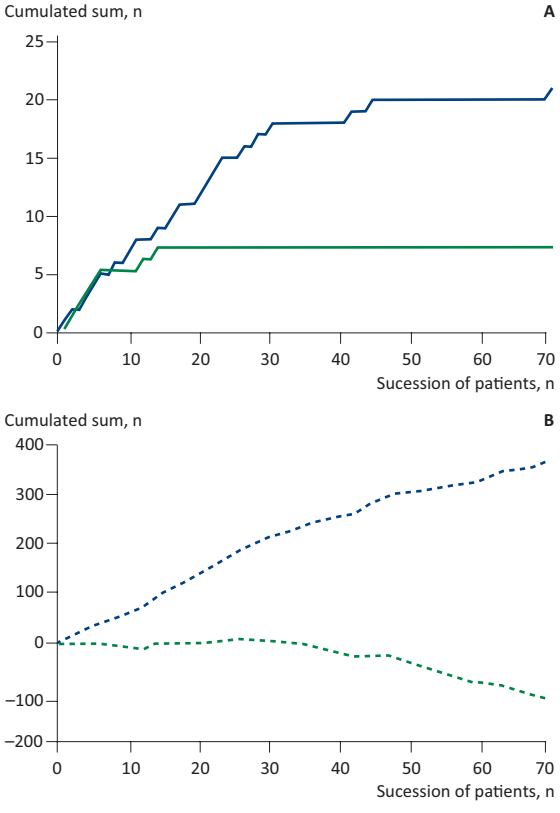
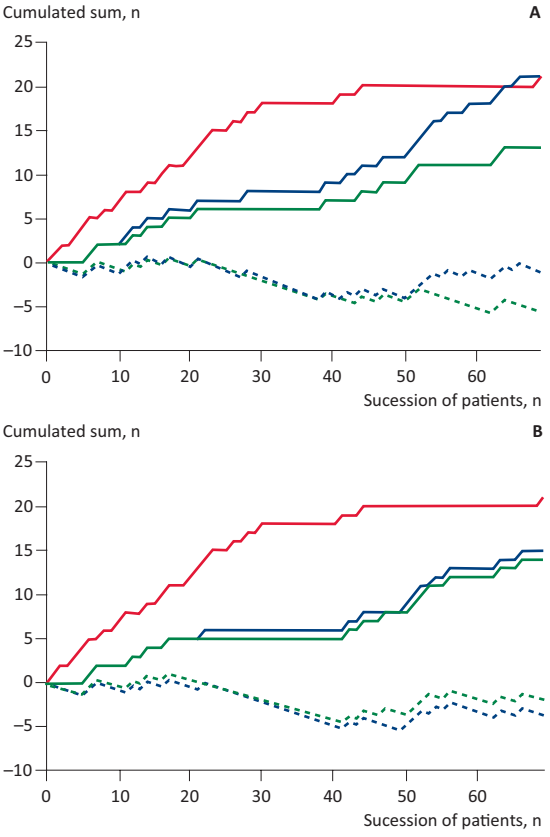


FIGURE 2

Course of disease in the first 12 months after diagnosis in 69 children with immune thrombocytopenia. The cumulated sum of treated children is inserted (red) to show relation to management changes. **A.** Cumulated number of children with persistent immune thrombocytopenia (blue curve) and chronic immune thrombocytopenia (green curve), and the difference between observed numbers and numbers expected from the rates of occurrence in the 1990s (dotter). **B.** Cumulated number of children who were readmitted (blue curve) or treated (green curves), and the difference between observed and expected numbers (dotted) relative to the 1990s.



evidence of an increase in the 2000s of the number of children with persisting or chronic ITP (Figure 2A) or the number needing readmission or treatment (Figure 2B). The curves show a run of cases in the early 2000s with brief duration and low morbidity, causing a downward displacement in the adjusted curves relative to the 1990s. Yet, thereafter the curves assumed a roughly horizontal course again. Thus, the curves are compatible with a fluctuating case mix without overall changes in composition.

A retrospective analysis confirmed the predictive value of the prognostic score: ITP lasted less than three months in 34 of 42 (81%) children with high scores (10-14), in 13 of 21 (62%) with intermediate scores (5-9) and in one of six (17%) with low scores (0-4). **Figure 3** compares the predicted cumulation of persisting cases with the expected and with the observed cases. Overall, the number of observed cases corresponded to expectation (32%) [14], but with fluctuations in case mix during the study period; the curve based on individual risk assignment from the score followed the observed curve more closely, indicating improved prediction.

DISCUSSION

This retrospective study shows that no untoward effects followed the implementation of a conservative management strategy for children with newly diagnosed ITP at our Department.

Apparently, the policy of treating only selected children during the initial admission did not increase the risk of adverse events later in the course or of chronic duration. Similarly, omission of a diagnostic BME has not resulted in misdiagnoses so far. Our findings, along with the report by Dickerhoff et al, support recent conservative treatment recommendations [10, 12].

The study is subject to the limitations of a retrospective, historical comparison of relatively small cohorts. In addition, the difference in size of cohorts suggests that hidden bias may be present. Much of the difference, however, can be explained by a 20% increase in childhood population, a 20% expansion in the uptake region in 2007 and a change in referral pattern within the region. Variation in case mix during the study period, with differing runs of patients, also impedes straightforward interpretation. Nonetheless, the two cohorts are clinically similar, and we find that the comparison is unlikely to be significantly biased.

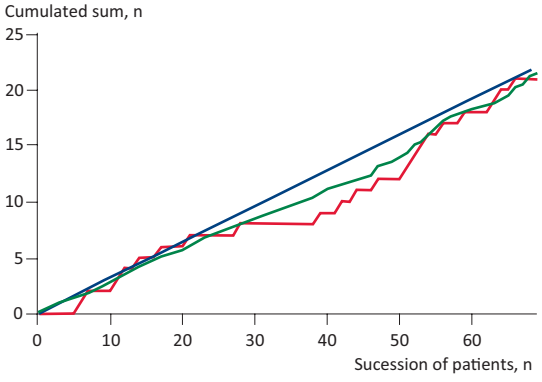
Furthermore, some of the inherent uncertainties have been overcome by cusum-plotting the chronological series of patients. The graphs were used retrospectively and descriptively to visualize change in clinical practice and to provide assurance that deleterious outcomes did not accumulate at an increasing rate after adopting the new approach. Notably, temporal fluctuations in case mix does not impede interpretation of the displays. We find that the cusum plot is a simple, versatile and useful tool for monitoring clinical practice and clinical outcomes. Used prospectively, statistical warning limits for deviations from expectation can be inserted [17], but for clinical purposes any trend becoming visually obvious as a change in slope provides early warning and should be investigated before statistical significance is reached.

While shedding light on several important issues, the study cannot answer the most important question of all: does a non-interventionist approach increase the risk of ICH before thrombocytopenia resolves? An ICH is fatal in approximately 50% of cases and leaves 20% of the survivors with some neurological deficit [5]. Given the low incidence, answering the above question would require an exceedingly large trial comparing the two strategies. We would expect, however, that an increased risk of ICH would be accompanied by an increased occurrence of other bleeding events, and we saw no evidence to this effect: Serious haemorrhages were equally rare in both decades. Risk factors predicting ICH would be useful, but they have been difficult to define, apart from PLC < 20×10^9/l [5]. A recent study identified trauma and haematuria as high risk factors requiring aggressive treatment [18]; the predictive value of haematuria, however, needs to be confirmed.

The risk of serious haemorrhage could be further reduced if a therapy reducing the duration of severe thrombocytopenia was available. It has been suggested that up-front treatment with IVIG may prevent the development of chronic ITP owing to its immune modu-

FIGURE 3

Evaluation of the score predicting recovery from immune thrombocytopenia within three months. The plot shows the observed cumulation of cases with persistent immune thrombocytopenia (red curve), the cumulation expected from a reference rate of 32% (blue line) and the cumulation predicted using the prognostic score (green curve) with rates 21% for high scores, 38% for intermediate scores and 77% for low scores [14].



latory effect [19]. Our data do not support this assumption; nor do the results of the prospective Nordic study [1]. The question needs to be settled by randomized trials. With the present conflicting evidence, we do not consider it justified to reintroduce an active therapeutic approach for newly diagnosed cases.

The watch-and-wait approach is not only less costly, but also less burdensome for the children, sparing them general anaesthesia for BME, side effects from treatment and long hospital stays. Parents, however, need detailed information on objective risks in order to establish confidence before discharge. Parental apprehension is based mainly on an undue fixation on the PLC and on the inherent uncertainties regarding the course of ITP. We believe that the prognostic score derived from the Nordic cohort, even if not used for decisions on therapy, may be helpful in this context [14]. The score has been validated in an Argentinian study [20] and our retrospective evaluation confirmed its predictive ability. The majority of children have high prognostic scores and their parents can be reassured that the condition will most likely resolve within a few months without significant events. Parents of children with low scores, on the other hand, should be prepared for a longer duration and instructed in relevant precautions.

In conclusion, this study provides evidence that a conservative approach to the management of children with newly diagnosed ITP is safe, does not result in higher rates of readmission or subsequent treatment, and does not increase the risk of persistent or chronic ITP. Consequently, we shall adhere to this approach even though definitive proof of a superior benefit:risk ratio is lacking. Our practice will be monitored with prospective cusum-plotting of significant bleeding events.

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