bjh short report

The immune thrombocytopenic purpura (ITP) bleeding score: assessment of bleeding in patients with ITP

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Summary

A method for objective quantification of bleeding symptoms in immune thrombocytopenic purpura (ITP) has not been established. The ITP Bleeding Scale (IBLS) is a novel bleeding assessment system comprising 11 site-specific grades. Implementation of the IBLS on 100 patient visits revealed that although platelet count and large platelet count correlated well with bleeding symptoms overall, this relationship disappeared in marked thrombocytopenia. The IBLS is a useful clinical tool for monitoring bleeding and may be used to aid the development of laboratory parameters that correlate with underlying bleeding propensity in thrombocytopenia.

Keywords: platelets, bleeding scale, platelet function, wet purpura, intracranial haemorrhage.

This pilot study used an immune thrombocytopenic purpura (ITP)-specific bleeding score, the ITP Bleeding Scale (IBLS) to analyse the correlation of clinical and laboratory platelet variables with bleeding.

Methods

A prospective Institutional Review Board-approved study was conducted on 100 visits for 65 consenting patients with ITP (30 on one and 35 on two visits) from December 2004 to December 2005. The patients were primarily adults with chronic ITP; a minority were children or adults with acute ITP.

The IBLS (Table I) comprised 11 grades from 0 (none) to 2 (marked bleeding) assessed at nine anatomical sites by history over the previous week (Hx). In addition, two of these sites, skin and oral, were also assessed by physical examination (PE). The 'worst ever' bleeding experienced at each site was graded using the same system.

Blood counts were analysed by using the Bayer-ADVIA^{TM} 120(Giacomini *et al*, 2001). Large platelets (20–60 fl) were examined as they were reported to be more haemostatically active (Karpatkin, 1978; Michel *et al*, 2005).

Analysis focused on the six grades with most bleeding – skin and oral (Hx and PE), epistaxis and gynaecological (GYN) (Hx). Insufficient haemorrhages occurred at the other sites to enable inclusion in the analysis. Means, medians, ranges, the Kruskal–Wallis, Fisher's exact and chi-squared tests, and the Kappa statistic to establish inter-observer reliability (for 63/100 visits) were calculated. *P*-values $<0{\cdot}05$ were considered significant.

Results

The median age was 31·5 years; 20 patients were under 18 and eight over 65 years. Forty-two were female, 23 of reproductive age and assessed for GYN bleeding on 36 visits. Eighty-eight per cent had chronic ITP (median duration 6 years) and 40% were splenectomised. No correlation between IBLS and age, sex, duration of ITP or splenectomy status was found.

The IBLS grades on the 100 study visits are presented in Tables II–IV. Seventy-two per cent of grade 1 haemorrhages occured in the skin. Grade 2 bleeding was more heterogeneous (28% skin, 46% oral, 13% GYN and 10% epistaxis). Patients with more skin bleeding also had more oral bleeding (PE and Hx, all *P*-values $<0{\cdot}026$).

The median platelet count for all visits was $39{\cdot}5 \times 10^9$/l (range: $6–623 \times 10^9$/l). Twenty-five visits had a platelet count $\leq 20 \times 10^9$/l and 46 visits had a platelet

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Table I. The immune thrombocytopenic purpura bleeding score assessment.

	Bleeding grade		
Site	0	1	2
Skin [physical examination (PE)]	None	1–5 bruises and/or scattered petechiae	>5 bruises with size >2 cm and/or diffuse petechiae
Oral (PE)	None	1 blood blister or >5 petechiae or gum bleeding that clears easily with rinsing	Multiple blood blisters and/or gum bleeding
Skin (Hx)	None	1–5 bruises and/or scattered petechiae	>5 bruises with size >2 cm and/or diffuse petechiae
Oral (Hx)	None	1 blood blister or >5 petechiae and/or gum bleeding <5 min	Multiple blood blisters and/or gum bleeding >5 min
Epistaxis	None	Blood when blowing nose and/or epistaxis <5 min (per episode)	Bleeding >5 min (per episode)
Gastrointestinal (GI)	None	Occult blood	Gross blood
Urinary (U)	None	Microscopic (+ve dipstick)	Macroscopic
Gynecological (GYN)	None (normal period)	Spotting not at time of normal period	Bleeding >spotting not at time of period or very heavy period
Pulmonary	None	N/A	Yes
Intracranial haemorrhage	None	N/A	Yes
Subconjunctival haemorrhage	None	Yes	N/A

count $\geq 51 \times 10^9$/l. For visits without bleeding, the median platelet count was 61×10^9/l. The median platelet count was $11{\cdot}5 \times 10^9$/l for visits with 1 or more grade 2 haemorrhage(s) (Tables II–IV). At each visit, the number of sites of grade 1 bleeding inversely correlated with the platelet count ($P = 0{\cdot}003$).

The platelet count and large platelet count significantly correlated with bleeding grade for the 5/6 sites with frequent bleeding for all 100 visits. However, when the 38 visits with platelet counts $<30 \times 10^9$/l were evaluated separately, the platelet count and large platelet count were poorly associated with bleeding events (Tables II–IV), even though these visits accounted for 79% of all grade 2 haemorrhages.

Bleeding grades at the same anatomical site were different when determined by Hx and PE for 24% visits for skin and 19% for oral, 4/19 of which were grade 2 by Hx but Grade 0 on PE. 'Worst ever' bleeding was recorded for 53/65 patients. Eight per cent of subjects had never had a grade 2 haemorrhage, 83% had grade 2 at either skin and/or oral cavity, and 72% at other sites. Patients with previous grade 2 skin (Hx), oral (PE and Hx) and GYN, or any pulmonary symptoms, had more bleeding at these sites on current study visits than other patients (all $P \leq 0{\cdot}03$). Notably, the four patients who had had an intracranial haemorrhage (ICH) experienced significantly more oral cavity bleeding (wet purpura) during the study than the

Table II. Number of visits divided by bleeding grade for 11 sites.

	All 100 visits			38 visits with platelet count $<30 \times 10^9$/l		
	Bleeding grade			Bleeding grade		
Site	0	1	2	0	1	2
Skin by physical examination (PE)	37	57	6	5	29	4
Oral cavity by PE	83	9	8	25	5	8
Skin by Hx	44	51	5	6	28	4
Oral cavity by Hx	79	11	10	23	8	7
Epistaxis	81	15	4	27	9	2
Vaginal (GYN)	26	5	5	12	1	5
Gastrointestinal (GI)	99	0	1	37	0	1
Urinary (U)	100	0	0	38	0	0
Pulmonary	97	N/A	3	35	N/A	3
Intracranial haemorrhage (ICH)	100	N/A	0	38	N/A	0
Subconjunctival haemorrhage	100	0	N/A	38	0	N/A
Total number of bleeding scores of 0, 1 and 2	846	151	39	284	83	31
% of the total amount of bleeding scores	82%	14%	4%	71%	21%	8%

Table III. Platelet parameters for all study visits.

	Median platelet count ($\times 10^9$/l) on all 100 visits				Median large platelet count ($\times 10^9$/l) for 99 visits (not available on one visit)			
	Bleeding grade				Bleeding grade			
Site	0	1	2	*P*	0	1	2	*P*
Skin by physical examination (PE)	94	29	22	<0·0004	5	2	2	<0·0009
Oral by PE	56	27	10	<0·0001	4	4	1	<0·0063
Skin by history	67	27	18	<0·0001	4	2	2	<0·0002
Oral by history	56	23	15	<0·0006	4	2	1	<0·009
Epistaxis	53	25	30·5	NS	4	2	3	NS
Gynaecological	32	87	9	<0·0259	3	4	0	<0·0095

NS, not significant.

Table IV. Platelet parameters for the 38 visits with platelet counts of $\leq 30 \times 10^9$/l.

	Median platelet count ($\times 10^9$/l) for 38 visits				Median large platelet count ($\times 10^9$/l) for 37 visits (not available on 1 visit)			
	Bleeding grade				Bleeding grade			
Site	0	1	2	*P*	0	1	2	*P*
Skin by physical examination (PE)	14	17	19	NS	1·5	1	1	NS
Oral by PE	20	19	10	$P < 0{\cdot}0318$	1	2	1	NS
Skin by history	15	17·5	16·5	NS	2	1	2	NS
Oral by history	18	15	11	NS	1	1·5	0	NS
Epistaxis	15	23	20	NS	1	2	1	NS
Gynaecological	11·5	10	9	NS	1	0	0	$P < 0{\cdot}01$

Sites with less frequent bleeding (GI, U, Haemoptysis and ICH) are not included in this table. NS, not significant.

49 patients with no ICH ($P = 0.009$ for PE; $P = 0.014$ for Hx) (Crosby, 1975).

Inter-observer reliability was good, with 92% of sites graded identically. Kappa statistics was 0·71 for skin (Hx) and 0·66 for PE; 0·52 for oral (Hx) and 0·46 for PE; 0·58 for epistaxis; and 0·78 for GYN.

Discussion

Although almost all bleeding symptoms in ITP are relatively minor events (Bolton-Maggs, 2003), their accurate and objective description is important to enable more detailed study of the heterogeneity in bleeding propensity. Furthermore, in the evaluation of treatment protocols, quantification of changes in bleeding is as important as monitoring the platelet response.

Platelet function is difficult to assess at counts $\leq 30 \times 10^9$/l when platelet aggregation assays are not possible (Hayward *et al*, 2006). This study demonstrated that platelet count and large platelet count were also poor indicators of bleeding in marked thrombocytopenia (Tables II–IV). In the future, flow cytometry could be used to assess the function of individual platelets in thrombocytopenic states (Michelson, 2006). A standardised bleeding assessment system, such as the IBLS, is a prerequisite for examining the relationship between laboratory parameters and bleeding.

Comprising 11 site-specific distinct grades, the IBLS creates a denser picture of bleeding symptoms than previously published scales (Buchanan & Adix, 2002; Khellaf *et al*, 2005, National Cancer Institute (NCI) 2006). Incorporating both Hx and PE enabled the improved detection of rapidly fluctuating signs and symptoms. A summative system generating an 'overall' bleeding score would be highly desirable. However, in the absence of data from a larger trial (in progress), this would require arbitrary weighting of the significance of bleeding at each site.

The World Health Organization (WHO) Bleeding Scale, designed for use in chemotherapy, is the most commonly applied criteria in thrombocytopenia (NCI, 2006). The WHO system uses 'medical intervention' to distinguish between grade 1 and 2, and does not distinguish subtle symptom fluctuations that may be clinically significant in ITP. In contrast, the IBLS can capture such details, for example an increase in mucosal bleeding that may indicate impending ICH. In this study, 14% of IBLS grades were grade 1 and 4% grade 2, suggesting that further discrimination of higher grades was not required (the highest two WHO grades were not observed in these 100 study visits). Overall, this study

demonstrated the utility of the IBLS and its relationship to the platelet count. Formal comparison to the WHO system is currently underway.

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Contribution of authors

LKP helped in the final stages of the study design, executed the data collection, analysed the data and co-wrote the manuscript. BP participated in data analysis and interpretation and co-wrote the manuscript. DP was one of the two designers of the Bleeding Score tool, and reviewed and commented on the manuscript. JMH participated in writing the manuscript. JMJ helped with the design of the study and reviewed the manuscript. ASE participated in analysing the data. MLL performed critical components of the statistical analysis of the data for the manuscript. JBB was one of the designers of the Bleeding Score and of the study. Dr Bussel participated in executing the study, helped analyse the data, and co-wrote the manuscript.

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