40 is the new 50: reducing the need for platelet transfusions prior to lumbar puncture in adults with hematologic malignancies

Patients with hematologic malignancies frequently require lumbar punctures (LP) for administration of intrathecal chemotherapy. With myelosuppressive chemotherapy, thrombocytopenia is common and patients often require platelet transfusions in order to minimize the risk of bleeding during invasive procedures. Guidelines from the American Association of Blood Banks (AABB) recommend a minimum platelet count of 50x10^3/μL, but this is based largely on expert opinion.[1] As there are few objective data to support a specific platelet threshold, transfusion parameters prior to LP vary from country to country. In accordance with AABB recommendations, the current standard platelet count for adults undergoing LP in the USA is 50x10^3/μL. However, in the UK the standard pre-LP platelet count is 40x10^3/μL.[2] Platelet transfusion is associated with risks of transfusion reaction, alloimmunization, and transfusion-associated infection.[3] Furthermore, repeated platelet transfusions cause increased healthcare expenses and may delay important procedures.

Arguably, the most significant risks of LP are hemorrhagic complications, including subarachnoid hemorrhage, subdural hematoma, and epidural hematoma. These complications are rare, and while their incidence following diagnostic or therapeutic LP is not well documented, the incidence of spinal hematomas following spinal anesthesia is estimated to be between 1:3,600 and 1:220,000.[4-6]

Given the lack of consensus on a safe pre-LP platelet count and the need to allocate donor platelets appropriately, Froedtert and the Medical College of Wisconsin changed its institutional guidelines to recommend a minimum platelet count of 40x10^3/μL prior to performing LP for oncology patients on November 1, 2017.

After obtaining approval from the Institutional Review Board and the Medical College of Wisconsin Department of Medicine QI committee, we retrospectively analyzed the medical charts of adult oncology patients who underwent diagnostic or therapeutic LP between November 2016 and March 2019 at Froedtert and the Medical College of Wisconsin. To be included in the analysis, patients had to be at least 18 years of age with a platelet count measured ≤24 hours prior to the procedure. The patients' baseline characteristics, details regarding the LP, and laboratory data were obtained by review of electronic health records. The initial platelet count, post-transfusion platelet count, and the number of platelet transfusions were recorded. All platelet transfusions were single transfusion episodes with one unit of single-donor apheresis platelets.

Outcomes measured included incidence of hemorrhagic complications (i.e., spinal subdural, subarachnoid or epidural hematomas) and incidence of traumatic taps. Traumatic taps were defined as >10 red blood cells/μL cerebral spinal fluid. Hemorrhagic complications were identified by reviewing results of computed tomography and magnetic resonance imaging of the spine and by chart searches for "hematoma" and "hemorrhage". Overdispersed Poisson regression via generalized estimating equations was used to compare the number of units transfused per patient before and after the policy change. An independence working correlation structure was selected based on the QIC statistic. Logistic regression via generalized estimating equations was used to compare the likelihood of traumatic tap between tiers of pre-procedure platelet count.

From November 1, 2016 to March 1, 2019, 345 oncology patients underwent a total of 1,251 LP. Of those, 534 LP were completed prior to the change in platelet transfusion policy on November 1, 2017 ("50group"), and 717 occurred after the guideline change ("40group"). The median age of patients undergoing LP was 56 (range, 18-88), and 45% were female. The diagnosis was acute lymphoblastic leukemia in 39.4%, acute myelogenous leukemia in 21.6%, non-Hodgkin lymphoma in 23.7%, other hematologic malignancies in 8.6% and solid tumor in 6.8% of the LP. The LP was performed in the inpatient and outpatient setting in 64.5% and 35.5% of cases, respectively. LP was done under ultrasound guidance (55.8%), fluoroscopy (25.8%), or using a landmark-based approach (18.4%) (Table 1). The International Normalized Ratio had to be <1.5 for the procedure to be performed.

The average initial platelet count obtained within 24 hours of the procedure and prior to any platelet transfusions was 140x10^3/μL in the 50group and 133x10^3/μL in the 40group (*P*=0.584). The mean pre-procedure platelet count (obtained immediately before the procedure and after any transfusions were given) was 152x10^3/μL and 143x10^3/μL in the 50group and the 40group, respectively (Table 2). The pre-procedure platelet count was less than 40x10^3/μL in 39 (3.1%) procedures, between 40-50x10^3/μL in 120 (9.6%), and 50x10^3/μL or greater in 1,073 (85.8%) procedures. The average number of units of platelets transfused per LP decreased significantly from 0.6 in the 50group to 0.4 in the 40group (*P*=0.04).

Four hemorrhagic complications occurred following LP. One subarachnoid hematoma occurred in the 50group at a pre-procedure platelet count of 165x10^3/μL. Three subdural hematomas occurred in the 40group at pre-procedure

Table 1. Demographic and clinical characteristics of patients and lumbar puncture episodes.

Variables	Total N=1,251	50group N=534	40group N=717	*P*
Age in years				0.92
Mean ± SD	53±16	53±15	53±16	
Median (range)	56 (18-88)	58 (18-84)	56 (20-88)	
Gender, N (%)				0.15
Female	418 (33.4)	151 (28.3)	267 (37.2)	
Male	833 (66.6)	383 (71.7)	450 (62.8)	
Diagnosis, N (%)				0.98
ALL	493 (39.4)	200 (37.5)	293 (40.9)	
AML	270 (21.6)	127 (23.8)	143 (19.9)	
NHL	296 (23.7)	123 (23.0)	173 (24.1)	
Other hematologic disorder	107 (8.6)	47 (8.8)	60 (8.4)	
Solid tumor	85 (6.8)	37 (6.9)	48 (6.7)	
Hospital setting, N (%)				0.17
Inpatient	802 (64.2)	361 (67.7)	441 (61.5)	
Observation	4 (0.3)	0 (0.0)	4 (0.6)	
Outpatient	444 (35.5)	172 (32.3)	272 (37.9)	
Missing	1	1	0	
Procedure method, N (%)				0.23
Fluoroscopy	323 (25.8)	136 (25.5)	187 (26.1)	
Landmark-based approach	230 (18.4)	79 (14.8)	151 (21.1)	
Ultrasound-guided	697 (55.8)	318 (59.7)	379 (52.9)	
Missing	1	1	0	

SD: standard deviation; ALL: acute lymphoblastic leukemia; AML: acute myelogenous leukemia; NHL: non-Hodgkin lymphoma.

Table 2. Initial and pre-procedure platelet counts.

Platelet counts	Total N=1,251	50group N=534	40group N=717	*P*
Initial platelet count, x10^9/L				0.64
Median (range)	111.5 (5.0-821.0)	119.0 (5.0-661.0)	108.0 (5.0-821.0)	
Mean ± SD	135.9±118.6	139.3±120.9	133.4±116.8	
Missing	3	3	0	
Pre-procedure platelet count, x10^9/L				0.45
Median (range)	114.5 (19.0-821.0)	120.0 (26.0-661.0)	111.0 (19-821.0)	
Mean ± SD	147.1±110.3	151.8±111.4	143.5±109.5	
Pre-procedure platelet count, x10^9/L, distribution, N (%)				
<40	39 (3.2)	12 (2.3)	27 (3.8)	
40-49	120 (9.7)	43 (8.2)	77 (10.9)	
50-59	137 (11.1)	62 (11.9)	75 (10.6)	
60-69	109 (8.8)	57 (10.9)	52 (7.3)	
70-79	62 (5.0)	19 (3.6)	43 (6.1)	
80-89	49 (4.0)	20 (3.8)	29 (4.1)	
90-99	39 (3.2)	16 (3.1)	23 (3.2)	
≥100	677 (55.0)	294 (56.2)	383 (54.0)	
Missing	19	11	8	
Traumatic tap, N (%)				0.77
No	664 (53.1)	287 (53.7)	377 (52.6)	
Yes	587 (46.9)	247 (46.3)	340 (47.4)	

Table 3. Multivariate analysis of predictors of a traumatic tap.

Comparison	Odds ratio	95% lower confidence limit	95% upper confidence limit	*P*
Plt <40 *vs*. 40 - <50	1.17	0.61	2.24	0.64
Plt 50 - <60 *vs*. 40 - <50	1.36	0.80	2.30	0.25
Plt 60 - <70 *vs*. 40 - <50	1.18	0.62	2.27	0.61
Plt 70 - <80 *vs*. 40 - <50	0.77	0.39	1.52	0.46
Plt 80 - <90 *vs*. 40 - <50	0.87	0.45	1.68	0.68
Plt 90 - <100 *vs*. 40 - <50	1.12	0.50	2.48	0.78
Plt ≥100 *vs*. 40 - <50	0.65	0.41	1.03	0.07
Landmark-based approach *vs*. fluoroscopy	0.71	0.47	1.10	0.13
Ultrasound-guided *vs*. fluoroscopy	0.32	0.19	0.53	<0.0001
Outpatient *vs*. inpatient	0.24	0.14	0.41	<0.0001
AML *vs*. ALL	1.06	0.70	1.59	0.79
NHL *vs*. ALL	0.67	0.45	1.01	0.05
Other *vs*. ALL	0.39	0.23	0.66	0.0005
Solid tumor *vs*. ALL	0.30	0.16	0.55	<0.0001

Plt: platelet count (x10^9/L); AML: acute myelogenous leukemia; ALL: acute lymphoblastic leukemia; NHL: non-Hodgkin lymphoma; Other: other hematologic disorder.

platelet counts of 331x10^3/μL, 40x10^3/μL and 33x10^3/μL. Two patients had acute lymphoblastic leukemia, one had acute myelogenous leukemia, and one had non-Hodgkin lymphoma. Two hemorrhagic complications occurred in the inpatient setting and two occurred after an outpatient procedure. Two of these LP were done using a landmark-based approach, one with ultrasound guidance, and one under fluoroscopy. The International Normalized Ratio ranged from 1.0-1.1. Partial thromboplastin time was not measured in two patients and was 22.3 s and 22.4 s in the other two patients. Both patients who experienced a hemorrhagic complication with a platelet count less than 50x10^3/μL were receiving treatment with a tyrosine kinase inhibitor at the time of LP. The patient with a platelet count of 40x10^3/μL was on ponatinib and the patient with a platelet count of 33x10^3/μL was on dasatinib. Both dasatinib and ponatinib have been reported to impair platelet aggregation[7,8] and administration of dasatinib has been linked to an increased incidence of clinical bleeding.[9] Dasatinib was also associated with the occurrence of subdural hematoma following LP for administration of intrathecal chemotherapy in two patients without thrombocytopenia.[10] None of the patients who had a serious hemorrhagic complication was on any other antiplatelet or anticoagulant therapy at the time of LP. Given the low incidence of hemorrhagic complications, the study was not sufficiently powered to detect a statistically significant change in risk based on pre-procedure platelet count.

Traumatic taps, defined as >10 red blood cells/μL cerebrospinal fluid, occurred in 587 LP (46.9%). The incidence of traumatic taps did not differ significantly between groups (46.3% *vs*. 47.4%; *P*=0.68). Results of a multivariate analysis showed that significantly more traumatic taps occurred in patients who were inpatients compared to outpatients (*P*<0.0001) (Table 3). In the outpatient setting, LP done using a landmark-based approach did not carry an increased risk of traumatic tap compared to those done under fluoroscopy. In the inpatient setting, LP performed with ultrasound guidance had a significantly lower risk of traumatic tap than those done under fluoroscopy (*P*<0.0001). The risk of traumatic tap for LP done with a landmark-based approach could not be compared to the risk for those done under ultrasound guidance, as all LP done with ultrasound were performed in an inpatient setting and the vast majority of LP done using a landmark-based approach were performed in the outpatient setting. The average pre-procedure platelet count in patients who had a traumatic tap was 87x10^3/μL and was 144x10^3/μL in patients who did not have a traumatic tap. The risk of having a traumatic tap in patients whose pre-procedure platelet count was 50-59x10^3/μL was not significantly lower than that in patients whose pre-procedure platelet count was 40-49x10^3/μL (odds ratio=1.17; *P*=0.25). While no randomized, controlled studies have yet been performed, a handful of retrospective reviews have demonstrated similar findings with respect to both traumatic taps and serious hemorrhagic complications. In these studies of adult oncology patients, a higher incidence of traumatic tap was seen with platelet counts ≤50x10^3/μL, but no increase in the risk of serious bleeding events was reported.[11-14]

Although the risk of hemorrhagic complications following a traumatic tap has not been clearly defined, one study showed that traumatic LP was associated with a higher incidence of severe complications in both non-thrombocytopenic control patients and patients on heparin therapy.[15] In this study, the risk of a traumatic tap was not significantly

different between patients whose pre-LP platelet count was 40-49x10^3/μL *versus* 50-59x10^3/μL. However, the odds ratio trended towards significance when comparing the risk of traumatic tap with a pre-LP platelet count 40-49x10^3/μL compared to >100x10^3/μL.

In summary, decreasing the pre-LP platelet transfusion threshold from 50x10^3/μL to 40x10^3/μL was not associated with an increased risk of traumatic tap and has been adopted as our institution's standard of care. Four patients had a serious hemorrhagic complication following LP, but the incidence of these events was too low to determine whether platelet count had a significant impact on the risk. The influence of platelet count on the incidence of hemorrhagic complications after LP requires additional study.

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Contributions

KC collected data and wrote the manuscript. SA analyzed the data. AU provided input on the study and supervised the study from the procedure team. AT provided input on the study and supervised the study from transfusion medicine. LM, LR, SA, GSGM, KC, and EA provided input on the study and supervised the study from malignant hematology. LBK provided input on the study and supervised the study from classical hematology. EA was the principal investigator.

Data-sharing statement

Data on individual patients will not be shared. De-identified datasets can be made available to other investigators on request.

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