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

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Patients with hematologic malignancies frequently require lumbar punctures (LPs) 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 50 x 10^3/µL, but this is based largely on expert opinion [1]. As there is little objective data to support a specific platelet threshold, transfusion parameters prior to lumbar puncture vary from country to country. In accordance with AABB recommendations, the current standard platelet count for adults undergoing LP in the United States is 50 x 10^3/µL. However the in UK the standard pre-LP platelet count is 40 x 10^3/µL [2]. Platelet transfusion is associated with risk 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 lumbar puncture are hemorrhagic complications including subarachnoid hemorrhage (SAH), subdural hematoma (SDH), and epidural hematoma. These complications are rare, and while the incidence following diagnostic or therapeutic lumbar puncture is not well documented, the incidence of spinal hematomas following spinal anesthesia is estimated between 1:3600 to 1:220,000 [4-6].

Given the lack of consensus on a safe pre-LP platelet count and the need to appropriately allocate donor platelets, Froedtert and the Medical College of Wisconsin changed its

institutional guidelines to recommend a minimum platelet count of 40 x 10^3/µL prior to performing lumbar puncture for oncology patients on November 1, 2017.

After obtaining approval from the IRB 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 lumbar puncture from November 2016 to 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. Baseline patient characteristics, details regarding the LP, and laboratory data were obtained by review of the electronic health record. The initial platelet count, post-transfusion platelet count, and the number of platelet transfusions were recorded. All platelet transfusions were single transfusion episodes with 1 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 (RBC) / µL cerebral spinal fluid (CSF). Hemorrhagic complications were identified by reviewing imaging results for CT and MRI of the spine and by chart search for "hematoma" and "hemorrhage". Overdispersed Poisson regression via generalized estimating equations (GEE) were 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 (GEE) was used to compare the likelihood of traumatic tap between tiers of pre-procedure platelet count.

From November 1st, 2016 to March 1st, 2019, 345 oncology patients underwent a total of 1251 lumbar punctures (LPs). Of those, 534 LPs were completed prior to the change in platelet transfusion parameters on November 1st, 2017 (50group), and 717 occurred after the guideline change (40group). The median age of patients undergoing LPs was 56(18-88), and 45% were female. The diagnosis was acute lymphoblastic leukemia (ALL) in 39.4%, acute myelogenous leukemia (AML) in 21.6%, non-Hodgkin's lymphoma (NHL) in 23.7%, other hematological malignancies in 8.6% and solid tumor in 6.8% of LPs. The LPs were performed in the inpatient and outpatient setting in 64.5% and 35.5% respectively. Lumbar punctures were done under ultrasound guidance (55.8%), fluoroscopy (25.8%), and by landmark based approach (18.4%) (Table 1). INR was required 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 140 x $10^3/\mu L$ in the 50group and 133 x $10^3/\mu L$ in the 40group(p = 0.584). The mean pre-procedure platelet count (obtained immediately before the procedure and after any transfusions were given) was 152 x $10^3/\mu L$ and 143 x $10^3/\mu L$ in 50group and 40group respectively. (Table 2). The pre-procedure platelet count was less than 40 x $10^3/\mu L$ in 39 (3.1%),between 40 - 50 x $10^3/\mu L$ in 120 (9.6%), and 50 x $10^3/\mu L$ or greater in 1073 (85.8%) procedures. The average number of units of platelets transfused per lumbar puncture significantly decreased 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 165 x $10^3/\mu L$. Three subdural hematomas occurred in the 40group at pre-procedure platelet counts of 331, 40 and 33 x $10^3/\mu L$. Two patients had ALL, one had AML, and one had NHL. Two hemorrhagic complications occurred in

the inpatient setting and two occurred after an outpatient procedure. Two of the lumbar punctures were done by the landmark-based approach, one by ultrasound guidance, and one under fluoroscopy. INR ranged from 1.0-1.1. PTT was not measured in two patients and was 22.3 and 22.4 in the other two patients. Both patients who experienced a hemorrhagic complication with a platelet count less than 50 x 10^3/µL were receiving treatment with a tyrosine kinase inhibitor at the time of lumbar puncture. The patient with a platelet count of 40 x 10^3/µL was on ponatinib and the patient with a platelet count of 33 x 10^3/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 has also been associated with the occurrence of subdural hematoma following lumbar puncture for administration of intrathecal chemotherapy in two patients without thrombocytopenia [10]. None of the patients who had a serious hemorrhagic complication were on any other anti-platelet or anticoagulant therapies 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 RBC's per µL CSF, occurred in 587 LPs (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 inpatient compared to outpatient (p < 0.0001) (Table 3). In the outpatient setting, LPs done by a landmark based approach did not carry an increased risk of traumatic tap compared to those done under fluoroscopy. In the inpatient setting, LPs 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 LPs done by the landmark based approach could not be compared to that for those done by ultrasound guidance, as all LPs done with ultrasound were performed inpatient and the vast majority of LPs done by a landmark based approach were performed in the outpatient setting. The average pre-procedure platelet count in patients who had a traumatic tap was 87 x 10^3/µL and was 144 x 10^3/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 - 59 x 10^3/µL was not significantly lower than in patients whose pre-procedure platelet count was 40 - 49 x 10^3/µL (OR 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 ≤ 50 x 10^3/µL, but no increase in risk of serious bleeding events was reported [11-14].

Although the risk of hemorrhagic complications following traumatic tap has not been clearly defined, one study showed that traumatic lumbar puncture 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 traumatic tap was not significantly different between patients whose pre-LP platelet count was 40-49 x 10^3/µL versus 50-59 x 10^3/µL. However, the odds ratio trended towards significance when comparing the risk of traumatic tap with a pre-LP platelet count 40-49 x 10^3/µL compared to > 100 x 10^3/µL.

In summary, decreasing the pre-lumbar puncture platelet transfusion threshold from 50 x 10^3/µL to 40 x 10^3/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 lumbar puncture, 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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Tables/Figures

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

Variables	Total N=1251	50group N=534	40group N=717	P Value
Age in years				*0.92*
Mean ± SD	53 ± 16	53 ± 15	53 ± 16	
Median (min; max)	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 heme 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	

ALL: Acute lymphoblastic leukemia, AML: Acute myelogenous leukemia, NHL: Non-hodgkin lymphoma

Table 2. Initial and pre-procedure platelet counts

	Total N=1251	**50group N=534**	**40group N=717**	**P Value**
Initial Platelet count x10^9/L				*0.64*
Median (min; max)	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				*0.45*
Median (min; max)	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	
<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 traumatic tap

Comparison	Odds ratio	95% lower confidence limit	95% upper confidence limit	p-value
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	<.0001
Outpatient vs Inpatient	0.24	0.14	0.41	<.0001
AML vs ALL	1.06	0.70	1.59	0.79
NHL vs ALL	0.67	0.45	1.01	0.05
Other heme disorder vs ALL	0.39	0.23	0.66	0.0005
Solid vs ALL	0.30	0.16	0.55	<.0001

Plt: platelet, ALL: Acute lymphoblastic leukemia, AML: Acute myelogenous leukemia, NHL: Non-hodgkin lymphoma