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Risk of bleeding after ultrasound-guided jugular central venous catheter insertion in severely thrombocytopenic oncologic patients

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ABSTRACT

Introduction: We sought to assess the incidence and risk factors of bleeding after ultrasound-guided internal jugular (USGIJ) catheter insertion in severely thrombocytopenic cancer patients, as safe platelet (PLT) count threshold remains controversial.
Methods: Retrospective study of 52 patients with hematologic malignancies and severe thrombocytopenia who underwent USGIJ catheter insertion between 2014 and 2016. Group A included patients with prophylactic PLT transfusion and Group B without. Statistical analysis was performed.
Results: Group A included 28 patients and Group B 24. Baseline characteristics were equally distributed. Median catheter size was 12 Fr and tunneled in 20/52 patients. Median PLT count was not statistically different between the groups, before transfusion and after the procedure. Postoperative minor bleeding occurred in 10/52 patients, similar between groups. Lower PLT count, larger catheter caliber and trend for AML diagnosis were identified as risk factors for bleeding. Age, gender, BMI, renal dysfunction and tunneled insertion were not significant.
Conclusion: Incidence of minor bleeding is low in severely thrombocytopenic patients after USGIJ catheter insertion. Prophylactic platelet transfusion may be reserved for patients with identified risk factors.

Introduction

Bleeding due to thrombocytopenia is a common problem in patients with malignancy undergoing chemotherapy and especially in hematologic malignancies. The association between thrombocytopenia and increased risk of bleeding has clearly been established and platelet (PLT) transfusions have been reported to decrease the risk of bleeding risk and therapy-related mortality in thrombocytopenic patients.[1] PLT transfusions are currently used in cancer patients either prophylactically to reduce the risk of bleeding or therapeutically to control active bleeding[2] with more than 70% of transfusions being prophylactic.[3] Patients with hematologic malignancies often require placement of central venous catheters, which could be needed either short or long term and for variety of reasons such as chemotherapy, stem cell therapy, plasmapheresis, dialysis or resuscitation. Due to the perceived risk of bleeding in patients with profound thrombocytopenia, a large number of physicians are often hesitant to perform these procedures without prophylactic PLT transfusions. The platelet count threshold recommended prior to central venous catheter (CVC) insertion varies significantly in the literature, However, a recent clinical practice guideline from the American Association of Blood Banks recommends a threshold 20×10^9/L or less for prophylactic transfusion.[4] Ultrasound-guided access has been widely adopted as a safer technique, even in patients with normal PLT counts.[10] The goal of the current study is to address the existing discrepancy related to the incidence of bleeding after ultrasound-guided internal jugular (USGIJ) CVC insertion in severely thrombocytopenic cancer patients, with and without PLT transfusion, and also identify potential risk factors for procedure-related bleeding.

Methods

This is a retrospective study of consecutive cancer patients with severe thrombocytopenia (PLT count $<50 \times 10^9$/L) who underwent USGIJ CVC insertion (December 2014–September 2016) in single

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tertiary referral cancer center. The study was approved by the Institutional Review Board. Demographics, clinical and laboratory data were collected retrospectively from the institution's electronic health record.

All CVCs were inserted using modified Seldinger technique under ultrasound guidance in the internal jugular vein with range of one to four lumen catheters. CVCs were inserted by experienced vascular surgery staff as an outpatient or inpatient procedures. Fluoroscopy or post procedure chest x-ray was used to confirm correct location of placed catheter.

The cohort was divided into two groups based on whether patients received prophylactic platelet transfusion, either prior or during the procedure or did not receive such transfusion. The decision to administer prophylactic platelet transfusion in preparation for CVC insertion was made by the primary oncology service. The choice between the two types of platelet products transfused, platelet concentrate (Pooled platelets) versus apheresis platelets (single donor platelets), was determined according to availability of the institution's blood bank. For the study analysis, both types of platelet transfusions were adjusted into units, based on count and volume. Pre and post-procedure platelet counts were collected retrospectively. Platelet transfusion prior to procedure was at the discretion of the treating primary oncology physician. The hemoglobin (Hgb) values before and after the CVC insertion and the requirement for post-procedure packed red blood cell (PRBC) transfusion were also recorded.

All patients in the cohort had normal or corrected coagulation parameters prior to CVC placement per institution protocol. Post-procedure bleeding was classified based on the definition of US DHHS Common terminology criteria for adverse events (CTCAE) (5) (Table 1).

Endpoints

The primary endpoint was identification of the rate and grade of post-procedure bleeding, evaluated by clinical examination of the insertion site and recorded daily in all cases by a registered nurse and the physician that placed the CVC.

Secondary endpoints were identification of new onset post-procedure anemia and potential risk factors for bleeding, including baseline active and chronic diagnoses, demographics, pertinent laboratory parameters and procedural characteristics.

Statistical analysis

All data was managed and retained at institutional database. The medians and proportions were calculated for descriptive statistics. Mann-Whitney *U* test was used for continuous variables and Fisher's exact test for categorical variables. Univariate analysis was used to preselect possible risk factors for bleeding in the patient cohort. Those variables were then used as candidates for a multivariate logistic regression model to calculate the predictors for bleeding, reported as odds ratios (OR) with confidence intervals (CI). Spearman rank correlation was applied to evaluate the association between two variables. Reported P values were two-sided and a value $P < 0.05$ was considered statistically significant. Statistical analysis was performed using STATA/IC 14.2 (StataCorp, College Station, TX).

Results

We identified 52 patients who underwent USGIJ CVC placement procedure.There were no patients with post-procedure bleeding of grade 2 or higher in the cohort. The overall incidence of post procedure grade 1 bleeding was 19% (10/52), none of which required revision, application of manual pressure or blood product transfusion. The median platelet count at the time of CVC insertion for all patients was 24×10^9/L (IQR:12–33). The median age of cohort was 56.5 years old (IQR:41–65.5) and body mass index (BMI) was 25.3 (IQR:23.1–29.3). The median CVC size was 12 F (IQR:8–14). 38% of patients (20/52) had tunneled catheter placed. Acute myelogenous leukemia (AML) was the primary diagnosis in 29/52 (56%) patients while the rest 23/52 (44%) had the diagnosis of other hematologic malignancies.

Patients were divided into two groups based on whether they received prophylactic platelet transfusion (group A) or no transfusion (group B). Demographics, baseline comorbidities and procedural characteristics were equally distributed between the two groups (Table 2).

The median platelet count before the procedure was lower in group A patients 19.5 (IQR:11–28.5) $x10^9$/L versus 29.5 (IQR:20–34) $x10^9$/L in group B, but not significantly ($P = 0.091$). After the procedure, the platelet count was 27.5 (IQR:16–45) $x10^9$/L in group A, and 26.5 (IQR:18–35) $x10^9$/L in group B, ($P = 0.44$) (Fig. 1). There was a mild trend towards prophylactic platelet transfusion in patients with lower baseline platelet count (Spearman's rho $= -0.237$, $P = 0.091$). In regard to the rate of post-procedure bleeding, there was no significant difference between the two groups (21% in group A vs. 17% in group B, $P = 0.736$) (Fig. 2). The median platelet count of patients with post-procedure bleeding in the cohort was lower, but not statistically significant, 18 vs 27.5×10^9/L, $P = 0.358$.

Seventeen patients (32.7%) of the cohort received PRBC, which correlated mainly with pre-procedure lower hemoglobin (rho $= -0.596$, $P < 0.01$) rather than post-procedure bleeding (rho $= 0.283$, $P < 0.05$). Adjusted multivariate regression analysis showed that higher platelet count was protective (OR, 0.85 [95%CI 0.74–0.98], $P < 0.03$) against post-procedure bleeding. In addition,

Table 1
Classification of procedural bleeding by CTCAE.

Procedural complications					
Grade					
Adverse event	1	2	3	4	5
Postoperative hemorrhage	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; radiologic, endoscopic, or operative intervention indicated	Transfusion indicated of ≥ 2 units (10 cc/kg for pediatrics) pRBCs beyond protocol specification; urgent radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

CATCAE; Common Terminology Criteria for Adverse Events.
CTCAE 4.03 - June 14, 2010: Injury, poisoning and procedural complications.

Table 2
Characteristics of thrombocytopenic patients who underwent USGIJ CVC placement procedures.

	Group A (n = 28)	Group B (n = 24)	P value
Demographics			
Age, years	58.5 (40–63)	54.5 (43.5–66)	0.748
Male gender	13 (46.4)	13 (54.2)	0.391
BMI, kg/m2	24.7 (22.9–27.8)	26.7 (23.6–29.6)	0.295
Clinical data			
AML diagnosis	15 (53.6)	14 (58.3)	0.475
Other hematologic malignancies	13 (46.4)	10 (41.7)	0.475
CRF	12 (42.9)	8 (33.3)	0.339
Tunneled catheter	10 (35.7)	10 (41.6)	0.776
CVC french size	12 (8–13.75)	12 (8–14)	0.748
Internal Jugular Access			
Right	25 (89.3)	21 (87.5)	0.588
Left	3 ((10.7)	3 (12.5)	0.588

USGIJ CVC, Ultrasound guided Internal Jugular Central Venous Catheter; BMI, Body Mass Index; AML, Acute Myelogenous Leukemia; CRF, Chronic Renal Failure (eGFR <60 mL/min/1.73 m^2); IQR, interquartile range.
Continuous variables are reported as median (IQR). Categorical variables are reported as number (percentage). P values from continuous variables were derived from Mann-Whitney *U* test. P values from categorical variables were derived from Fisher's exact test.

a larger CVC French size predicted higher risk of bleeding (OR, 1.86 [95% CI 1.01–3.39], $P < 0.05$). Although not significant, there was a trend towards bleeding with acute myelogenous leukemia (AML) diagnosis (OR, 9.97 [95% CI 0.92–107.51], $P = 0.058$). We did not find that age, gender, BMI, renal dysfunction, baseline anemia and tunneled insertion were significant predictors (Fig. 3).

Discussion

Patients with hematologic malignancies often develop severe thrombocytopenia as a consequence of either the disease or the treatment, including stem cell transplant and chemotherapy. Usually, platelet transfusions are implemented to raise the platelet count and reduce the risk of clinical bleeding (prophylaxis) or stop active bleeding (therapy). Many studies have shown that prophylaxis from bleeding is the most common indication for administration of platelet transfusions to thrombocytopenic patients with hematologic malignancies,[3,4] with central venous catheter insertion being the most common intervention that requires prophylactic platelet transfusions.[8] In a review of literature, it was found that recommendations regarding prophylactic platelet transfusion guidelines have varied significantly.[3,6–9] Many institutions agree that a prophylactic platelet transfusion is beneficial in patients with platelet counts less than 20×10^9/L prior to CVC placement and that a platelet transfusion is not needed for patients with a platelet count greater than 50×10^9/L, but there is controversy regarding the need for pre-procedural platelet transfusions in patients with platelet counts between 20×10^9/L and 50×10^9/L. In the past, most guidelines recommended a pre-procedural platelet transfusion threshold prior to CVC placement to be 50×10^9/L, but more recent guidelines recommend a threshold of 20×10^9/L.[5] However, those are graded as weak recommendations based on low-quality evidence.

A large retrospective study evaluated the risk of bleeding with placement of 604 central venous catheters (CVC) in 193 patients with leukemia that had severe thrombocytopenia. The study did not have severe bleeding in any of the patients after CVC placement, and if there was any bleeding it was predominately Grade 1 bleeding (96%) and a small number of Grade 2 bleeding (4%). The classification of bleeding was based on US DHHS Common

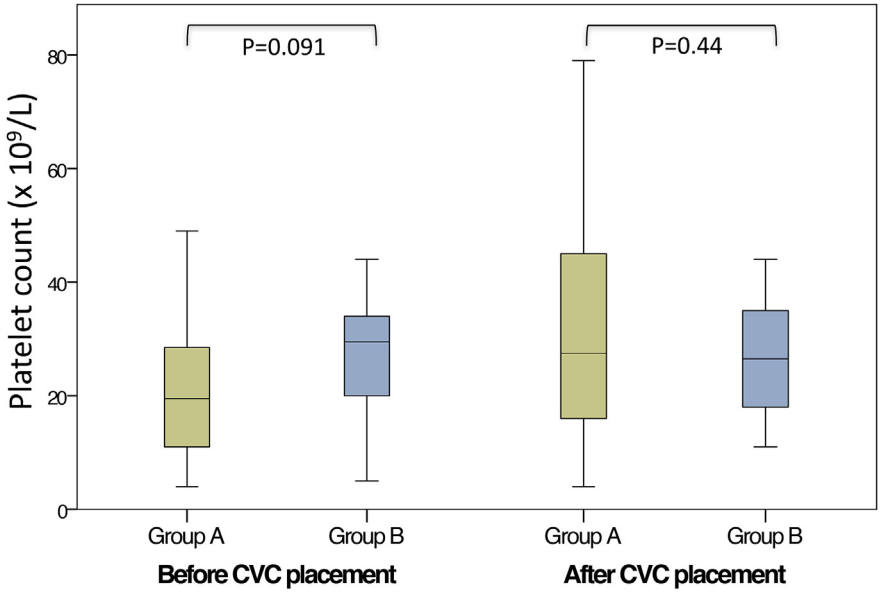

Fig. 1. Median platelet counts before and after the CVC procedure between the patients that received (Group A) and did not receive (Group B) prophylactic platelet transfusion. P values for continuous variables were derived from Mann-Whitney *U* Test. CVC, Central Venous Catheter.

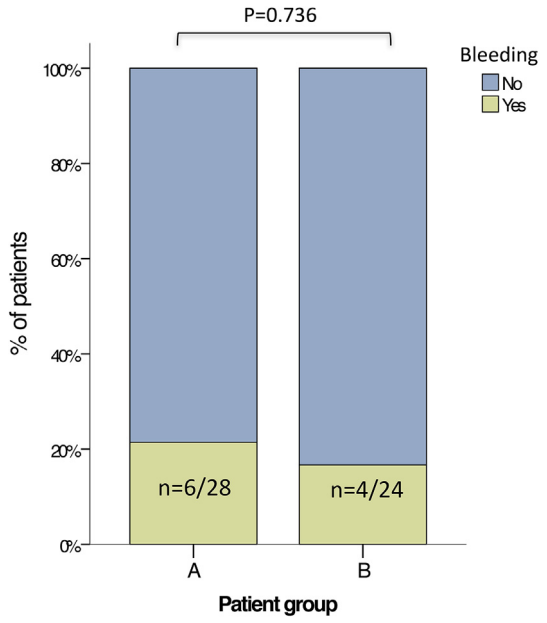

Fig. 2. Rate of post-procedure bleeding between the patients that received (Group A) and did not receive (Group B) prophylactic platelet transfusion. The P value for categorical variables were derived from Fisher exact test.

Terminology Criteria for Adverse Events (CTCAE).[5] The authors also found that patients with platelet counts less than 20×10^9/L benefited from platelet transfusions prior to the procedure since this group was found to have a higher risk of non-severe bleeding post CVC placement.[9]

Several other non-randomized retrospective studies have demonstrated the safety of performing invasive procedures, including central venous catheter placement, without clinically significant bleeding in patients with thrombocytopenia who did not receive prophylactic platelet transfusions.[11–13] The implementation of a platelet count threshold above which a platelet transfusion is required prior to central venous catheter insertion is therefore debatable. There is great uncertainty whether platelet transfusions are effective at preventing bleeding in patients with thrombocytopenia undergoing an invasive procedure, especially since these transfusions are not without associated adverse events. The most common reactions are mild to moderate and include rigors, fever, and urticaria.[16] Rarely, more serious sequelae include anaphylaxis, transfusion-transmitted infections, transfusion-related acute lung injury and immunomodulatory effects.[8,16–18] The requirement to administer platelet transfusions to correct thrombocytopenia prior to central line insertion may additionally delay the start of treatments, which may be time-critical especially in a patient in an intensive care unit. In addition, prophylactic utilization of limited blood bank resources such as platelets, is costly and could decrease the availability for patients with active bleeding in the operating room or the wards. In thrombocytopenic patients with hematologic malignancy, especially acute leukemia, platelet counts maybe refractory to transfusion as shown in literature.[9] In the current study, we did not evaluate the platelet counts after administration of platelets but after the procedure, which allowed us to compare the primary outcome in the two groups based on whether they received platelet transfusion.

Regardless of the platelet threshold for transfusion, many studies have shown that the risk of bleeding after a central venous catheter insertion appears to be low if an ultrasound-guided technique is used.[10,14] A systematic review showed that ultrasound guidance significantly reduced the failure rate of internal jugular vein cannulation (RR 0.14, [CI 0.06 to 0.33]) compared to using an anatomical landmark method.[14] In one retrospective study by Cavanna et al., 1978 ultrasound-guided CVC procedures were

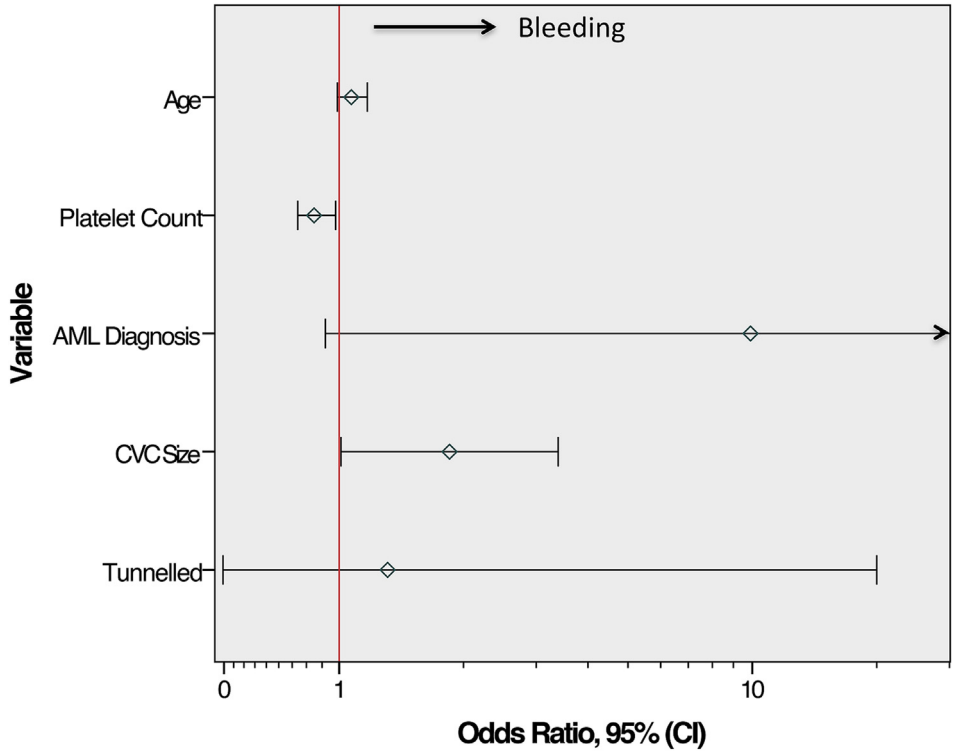

Fig. 3. The x-axis represents the Odds ratio on a log scale with the reference line (red), Odds ratios (diamond) and 95% CI (whiskers). AML, Acute myelogenous leukemia; CVC, Central venous catheter; CI, Confidence intervals. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.

performed in 1660 patients who had a solid or hematologic malignancy, of which 116 had a platelet count below 50×10^9/L, and 70 had a platelet count below 20×10^9/L. None of the patients experienced major bleeding.

Our study evaluated the risk of bleeding after placement of IJCVC in patients with and without prophylactic platelet transfusion. Clinically there was no major bleeding on either group and there was no difference in the incidence of minor bleeding, which was observed in less than one-fifth of the cohort. Blood transfusion was provided in approximately one-third of the patients, similar in both groups and it was mostly associated with baseline anemia rather than bleeding. These results correlate with other studies in the literature, which evaluated outcomes in patients with similar characteristics.[4,6,9–14] After adjusting for prophylactic platelet transfusion and other variables, lower platelet counts and large-bore CVC predicted minor bleeding. Although the post-procedure median platelet count was lower in patients that experienced postoperative bleeding (18 vs 27.5×10^9/L), it did not reach statistical significance possibly due to decreased number of patients in the entire cohort that had profound thrombocytopenia ($<20 \times 10^9$/L) after prophylactic platelet transfusion and also the potential contribution of other risk factors towards the occurence of bleeding. However, increasing platelet counts was found to be protective after accounting for other parameters. We also found there was a trend towards bleeding in patients with AML diagnosis rather than any other diagnosis, which might be attributed to a different platelet function and activity in AML versus other hematologic malignancies as reported in other studies.[15] Interestingly, we did not find that baseline renal dysfunction or tunneled CVC insertion to be significant predictors of bleeding in these patients, possibly due to the smaller sample size.

Despite the low degree and rate of bleeding following CVC placement, other technical factors may have significant role in the decision-making regarding prophylactic platelet transfusion. As many of those patients have multiple prior catheters, the risk of central venous stenosis or occlusion increases and thus the risk of intra-thoracic major vein injury. Although we did not encounter any patients in our cohort with suspicion of such injury, based on chest radiography, clinical examination and laboratory parameters, it is possible that it may occur with potentially serious complications in patients with severe thrombocytopenia.

This study has specific inherent limitations. Being a retrospective, single center and small cohort study, is subject to selection bias. Also, the decision for transfusion administration in patients with hematologic malignancy and severe thrombocytopenia was provider dependent although based on national guidelines. Also, despite the application of graded assessment of post-procedure bleeding, there can be a degree of subjectivity. Therefore, determination of the primary outcome was based on two clinical assessments.

In conclusion, our study demonstrates that ultrasound guided IJCVC placement in cancer patients with severe thrombocytopenia is relatively safe, as it can be associated with low risk of clinically insignificant bleeding. Prophylactic platelet transfusion prior to the procedure can be minimized and reserved mostly for patients with profound thrombocytopenia and specific risk factors, such as acute myelogenous leukemia and need for large-bore central venous catheter.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.amjsurg.2018.06.019.

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