Anticoagulation and bone marrow biopsy: is it safe to proceed?

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ABSTRACT

Background: Bone marrow (BM) biopsy is the most common diagnostic procedure in hematology. Bleeding is an expected complication, and its risk is assumed to be increased in patients on anticoagulants. However, the effect of anticoagulation on BM biopsy safety is unclear and guidelines are lacking robust data in this regard. As such, physicians use their clinical judgement to guide periprocedural management of anticoagulation.

Objective: To provide the best available evidence regarding management of anticoagulation in patients who need BM biopsy.

Methods: We reviewed and summarized available guidelines directing management of periprocedural anticoagulation for BM biopsy, and share our experience and practices with BM biopsy at our institution.

Results: The incidence of significant hemorrhage after BM biopsy is very low (0.007–1.1%). BM biopsy is classified as having a low to moderate bleeding risk. Interrupting anticoagulation is not consistently recommended. Strategies exist to minimize bleeding risk for anticoagulated patients. Patients with myeloproliferative neoplasms can develop an acquired von Willebrand syndrome which increases their risk for bleeding and therefore require extra vigilance to ensure appropriate hemostasis.

Conclusion: Withholding anticoagulation prior to BM biopsy is not routinely recommended. Instead, assessment and optimization of bleeding risk factors should be done on a patient by patient basis.

KEYWORDS

bone marrow biopsy; anticoagulation; bleeding; hemorrhage

Introduction

Bone marrow (BM) biopsy is a common and generally safe procedure. Complications are rare and the incidence of significant bleeding is very low. However, when bleeding does occur, it can be a catastrophic complication requiring emergent care. Quantifying bleeding risk is challenging given the low rate of events. Anticoagulants, including direct oral anticoagulants (DOACs), warfarin, heparin derivatives, and anti-platelet products, increase the risk of bleeding; however, the independent influence of anticoagulation on BM biopsy safety (in the context of other variables, e.g. operator error, coagulation defects, etc.) is unclear and guidelines directing periprocedural anticoagulation management are lacking robust quantitative data. We therefore summarize existing literature and share experience at our institution.

Bleeding after BM biopsy

Only a few studies have reported the incidence of bleeding following BM biopsy. In the prospective report by Bain [1], the one-year incidence of hemorrhage was 11 events in over 19 000 procedures (0.05%) with three patients needing hospitalization - two of which required blood transfusions. Retrospectively, Bain [2] reported an incidence of 14 hemorrhages in over 54,000 procedures (0.007%) over six years with six patients requiring blood transfusions and one death. Use of acetylsalicylic acid (ASA), acquired platelet dysfunction, interference with platelet function by fibrin-degradation products, and to a lesser extent, thrombocytopenia were possible risk factors for severe hemorrhage [2]. A similarly low incidence of five bleeding events in 1,252 procedures (0.4%) on 914 patients were reported by Patino, et al [3]. None of these patients were anticoagulated. Valebjorg reported two instances of severe bleeding (defined as >1 g/dL fall in hemoglobin concentration and/or requiring transfusion) in 182 patients (1.10%) [4]. Neither of these two patients were anticoagulated. Three cases of major bleeding due to gluteal artery injury after BM biopsy performed with powered bone marrow kits were reported. In all three cases, the coagulation parameters were normal [5]. Thus, the reported rate of major bleeding following BM biopsy is very low.

In addition to the aggregate studies described above, there were approximately 30 case reports that described severe bleeding following BM biopsy. Most (but not all) are summarized by Wojciechowski [6]. Of
the case studies, six reported the patient being anticoagulated. Myeloproliferative neoplasms (MPN) were overrepresented (10 cases) which is in keeping with observations by Bain [2]. This also reflects evidence of increased bleeding observed in MPN patients, especially those with thrombocyctosis [7]. Clinicians must be mindful of acquired von Willebrand syndrome (AVWS) in patients with MPNs. Prevalence rates of 12, 16, and 20 percent have been reported for Polycythemia Vera, Myelofibrosis, and Essential Thrombocyctemia, respectively [8]. In patients with Essential Thrombocyctemia, development of AVWS is associated with higher platelet counts, and those with platelet counts greater than $1,000,000 \times 10^9/L$ were observed to be at highest risk for bleeding [9].

**Periprocedural management of anticoagulation: guidelines**

Recommendations for anticoagulation management are summarized in Table 1. Firstly, we found that there is a dearth of empiric prescriptive literature directing anticoagulation management specific to BM biopsy. Only eight secondary sources were readily identified that specifically referenced BM biopsy. In general, these guidelines categorize bleeding risk by weighing bleeding potential (i.e., procedure type) against clotting risk (e.g., atrial fibrillation). These recommendations appear largely consensus driven, and with respect to BM biopsy, based on extrapolation from other minor procedures. This is understandable given that the low incidence of bleeding makes identifying a risk association challenging.

These guidelines signal that BM biopsy is safe without altering anticoagulation but there is no consensus. A survey of 104 hematologists in Australia and New Zealand further highlights practice variability with 13 percent performing the biopsies irrespective of the INR, 51 percent performing the biopsy if the INR was not above the therapeutic range, 18 percent performed the biopsy if the INR was $<2.0$, and 18 percent stopping warfarin or reversing anticoagulation before performing the biopsy [10]. Without a consensus, physicians must therefore use their clinical judgment to interpret bleeding risk associated with anticoagulation.

**Our practices**

To assess bleeding after BM biopsy at our institution, we reviewed electronic medical records and surveyed all current and former physicians who have performed BM biopsies from January 2010 to December 2020. Major bleeding was defined as: (1) fatal bleeding; and/or (2) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome; and/or (3) bleeding causing a fall in hemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red cells [11]. In total, 3,552 BM biopsies were performed. Forty-two percent of patients were males, and forty-eight percent females. Thirteen percent of patients were taking anticoagulants (warfarin, low molecular weight heparins, and DOACs), 32% of patients were taking antiplatelet drugs (ASA, clopidogrel), and 5.5% of patients were on both anticoagulants and antiplatelet agents. Only one incident of major bleeding (0.03%) was reported. This was a 65-year-old female patient with new Essential Thrombocyctemia and extreme thrombocyctosis (platelet count $>1,200,000 \times 10^9/L$) and AVWS. She had post-procedure hemorrhage for three days. There was a drop of hemoglobin of $>20$ g/L, requiring

| Table 1. Bleeding risk assessment and anticoagulation management recommendations for bone marrow biopsy |
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| **Guideline** | **Bleeding risk category** | **Recommendations** |
| Thrombosis Canada: NOACs/DOACs preoperative management [15] | Moderate | Stop NOAC/DOAC one day prior to procedure. |
| Thrombosis Canada: Warfarin Perioperative Management [16] | Low/Moderate | Selected procedures with large-bore needles (e.g., bone marrow biopsy) may need Warfarin interruption. Stop warfarin five days before procedure and consider bridging for high-risk groups. |
| MD Anderson Periprocedure Management of Anticoagulants [17] | Low | Do not interrupt anticoagulation. |
| 2016 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation [18] | Low | Low risk procedures are generally safe to perform without interrupting antithrombotic therapy, provided the INR is not supratherapeutic in the case of warfarin. Do not withhold anticoagulation. Target INR $<3.0$. Consider bridging for high thrombosis risk cases. Exception: Withhold glycoprotein IIb/IIIa inhibitors 4–8 h before procedure. |
| Society of Interventional Radiology Consensus Guidelines for the Periprocedural Management of Thrombotic and Bleeding Risk in Patients Undergoing Percutaneous Image-Guided Interventions – Part II: Recommendations [19] | Low | |
| The manuals from the Canterbury District Health Board - Protocol for Bone Marrow Aspirate and Trephine Biopsy [12] | Not specified | Warfarin interruption not required. |
| Bleeding risk assessment for bedside and interventional radiology guided procedures: Consensus guidelines and beyond [20] | BM aspiration without biopsy is low risk. BM biopsy is moderate to high risk | Stop DOAC one to two days prior to the procedure. Target INR $<1.8$ for high risk procedures. |

Abbreviations: BM, bone marrow; DOAC, direct oral anticoagulant; INR, international normalized ratio; NOAC, novel oral anticoagulant.
hospitalization, desmopressin, tranexamic acid, and urgent initiation of cytoreductive therapy with hydroxyurea. No blood transfusions were necessary. Hemorrhage resolved with a decrease in platelet count to below 800,000 × 10^9/L.

Despite this event, we do not routinely interrupt anticoagulation for BM biopsy given that there is no clear independent association between bleeding and anticoagulation in the literature. We feel that while the thrombosis risk of a brief pause in anticoagulation is minimal, it is not non-existent. There is also a risk of miscommunication between patient and clinician regarding when to start and stop anticoagulation, potentially putting patients at further undue risk for thrombosis.

Instead, we recommend weighing the risks and benefits of stopping anticoagulation for each patient with special consideration paid to the following risk-reduction strategies:

1. Preferentially schedule BM biopsies prior to doses of heparin products to allow maximal clearance of the drug (i.e. trough levels). Heparin infusion should be consider for inpatients with significant thrombosis risk (e.g. acute or large burden thrombosis) who are deemed to be at highest risk for bleeding or have a reduced physiologic reserve to tolerate a bleed if it occurs. Warfarin dosing should be titrated to correct supratherapeutic levels prior to the procedure. It has been proposed that INR be checked seven days before the procedure. If it is within therapeutic range (INR <3.0) and the trend is stable, it is safe to proceed. If a patient has recently started warfarin, or they have unstable control, INR should be checked within 24 hours before the procedure [12].

2. Manage anxiety and pain to optimize patient positioning to improve accuracy and minimize trauma.

3. Monitor for and correct extreme thrombocytopenias (i.e. platelet count <10).

4. Ensure adequate post-procedure monitoring, educate patients regarding the signs and symptoms associated with hemorrhage, and provide instruction regarding how to seek medical attention should a hemorrhage occur. At our center, we apply pressure to the insertion site by placing a towel or pad under the iliac crest while the patient lies supine with their knees slightly flexed. Bleeding is assessed for at 10- and 20-min post-procedure.

5. Point of care ultrasound machines are becoming increasingly accessible and offer a tool to improve biopsy accuracy, reduce trauma, and presumably reduce the potential for hemorrhage especially in patients with challenging anatomy, large body habitus, or difficulty positioning [13]. We use ultrasound as an adjunct to standard landmarking by palpation of the iliact crest. Mapping boney anatomy and measuring subcutaneous tissue depth with ultrasound has anecdotally improved the accuracy of insertion and quality of sampling, and decreased patient trauma in the most challenging patients. More research is needed to quantify these benefits and identify any potential risks.

6. We pay special consideration to patients with MPNs. These patients are commonly on ASA which is an additional risk factor for bleeding. We do not routinely interrupt anticoagulation for MPN patients. Instead, we take a thorough history to screen for abnormal bleeding (especially in those with extreme elevations in cell counts), screen for AVWS when suspicious, and maximize the above strategies including copious post-procedure monitoring and education. Desmopressin, VWF-containing concentrates, recombinant factor VIIa, and antifibrinolytics can be used as a treatment for hemorrhage in these patients or prophylactically in those at highest risk of bleeding based on history of documented AVWS as described by Tiede et al. [14].

Conclusion

The incidence of significant hemorrhage after BM biopsy is very low and we propose that the risks of routinely withholding anticoagulation outweigh the benefits. Interrupting anticoagulation prior to BM biopsy is not routinely recommended. Instead, assessment and optimization of bleeding risk factors should be done on a patient by patient basis. All patients must be assessed for hemorrhage after the procedure and educated/instructed properly. Patients with MPN require extra vigilance and may need additional observation time to ensure appropriate hemostasis.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

Availability of data and materials

Data sharing is not applicable to this article.

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