

## Original Article

# Procedural Pain and Serious Adverse Events Following Bone Marrow Aspiration and Biopsy: Analysis from an Academic Center in India

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## Abstract

**Background:** The Bone Marrow Aspiration and Biopsy (BMAB) is an important and frequent investigative procedure for hematological diseases. Although thought to be safe and well tolerated; data is limited on the complications and degree of pain experienced by patients undergoing BMAB. Further scarce is data from India and other regions from the developing world especially given the evidence that cultural factors that could shape pain perception. Adverse events following bone marrow biopsy are rare but poorly documented.

**Aims:** To estimate the level of pain and frequency of serious adverse events experienced by patients undergoing BMAB at our center. We also attempted to identify factors associated with increased pain perception.

**Study Setting:** This study was conducted at a tertiary level teaching hospital, the Christian Medical College & Hospital, Ludhiana. Ethics approval was obtained from the Institutional research committee (CMC/1495).

**Study Period:** 01 April 2015 through 30 Nov 2019

**Study Design:** This is a comparative cross sectional study where comparison of those with relatively more pain to those with less was done to elicit the factors associated with pain perception.

**Results:** A total of 942 BMAB procedures were performed in this period (Table 1). The major serious adverse event was hemorrhage, which comprised 2 of the 9 serious adverse events. Those with prior BMAB had very low odds of pain (OR (95% CI): 0.23 (0.15–0.37)). However, when more than one attempt of biopsy was made the odds of pain was much higher (OR (95% CI): 1.62 (1.29–2.05)).

**Conclusions:** In our analysis BMAB is safe and associated with a low level of perceived pain. Serious adverse events following BMAB are rare, but can have considerable impact on the individual patient.

**Keywords:** Bone marrow biopsy; Pain; Complications; Bleeding

## Background

Bone Marrow Aspiration & Biopsy (BMAB) is an integral element in the management of most diseases of the blood and marrow [1]. The procedure is typically performed by primary providers and trained assistants at the bedside or in day care centers [2]. Vital information that predict prognosis and diagnosis like histopathological, cytogenetic, immunophenotyping or molecular results are best obtained by BMAB. Though occasional serious complications have been reported following the procedure; BMAB is associated with low morbidity and mortality and is considered safe [3-6]. The most frequent and reported complication is pain which could be influenced by ethnicity and is derived from reports from the western world [7]. Limited data exists from India and other regions in the developing world regarding pain and its perception. Available reports suggest that among ethnic groups; Indians have the highest

mean pain score and need the most medicines for pain control [8]. Further scarce is data on complications from these regions where procedural fear often discourages patients from pursuing treatment and diagnosis [8]. This study was initiated to address this gap and to identify factors associated with pain experienced during BMAB through a prospective survey of patients presenting to our academic center.

## Patients and Methods

### Study Setting

This study was conducted at a tertiary level academic hospital, the Christian Medical College & Hospital, Ludhiana. Ethics approval was obtained from the Institutional research committee (CMC/1495).

### Study Period

01 April 2015 through 30 Nov 2019.

## Study Design

This was a comparative cross sectional study where comparison of those with relatively more pain to those with less was done to elicit the factors associated with pain perception.

## Study Population

All consecutive patients who underwent a BMAB and provided informed consent which was taken pre-procedure were included. We excluded patients who underwent the procedure under general anesthesia.

## Data Sources and Variables

Information regarding age at diagnosis, address and sex, indication to perform the BMAB, coded as malignant and non-malignant was collected from each patient. Number of previous procedures and details regarding food intake were collected as recalled by the patient. Level of pain was noted soon after the procedure using the Wong-Baker grimace scale by the patient themselves.

## Statistical Analysis

Descriptive statistics were used to characterize variables. Multivariate Logistic Regression was used to evaluate factors associated with higher pain severity (Score >3).

## Bone Marrow Aspiration & Biopsy (BMAB)

The BMAB procedure was performed by variable operators namely; Consultant Physicians, Trainee Physicians and Physician assistants/extenders. All procedures were performed according to the Standard Operating Procedure (SOP) for BMAB of the Hospital. All Trainee Physicians and Physician assistants were trained for the procedure by the Consultant Physicians. The patient lies on an examination bed and a physician and a specially trained nurse was present. Lignocaine as a local anesthetic agent was infiltrated into the overlying skin and the periosteum of the biopsy site. All patients were pre-medicated with tramadol intravenous pre procedure and the preferred approach was from the Posterior crista iliaca (PSIS) through a left lateral approach. They were observed in the day care setting for up to 60 minutes prior to being sent home. The aspirations are done with 10-ml syringes. A serious adverse event was considered as one requiring a prolonged observation beyond routine practice or leading to or extending of admission to manage adverse events following and related to the BMAB.

## Results

### Patient Accrual and Baseline characteristics

Over the period of this study a total of 942 BMAB procedures were performed. The Mean  $\pm$  SD age of the patients was 47.1  $\pm$  19.1. Most of them were males (62.1%). The baseline demographic characteristics of these patients are summarized in (Table1). The most frequent indication for BMAB was for staging of lymphoma in 171(26.2%) patients.

### Pain Perception & Complications

The numbers of reported complications are summarized in (Table 1). The complications reported and directly related to the BMAB were pain, hemorrhage and vomiting. The Mean + SD pain score was only 2.7  $\pm$  1.4 and fourteen patients (1.48%) reported severe pain (>8). There was no difference in pain levels [3 (1-10)] or significant

**Table 1:** Baseline characteristics of patients who underwent BMAB.

Variable	Patients (N=942)	
	n (%)	Median (IQR)/Mean $\pm$ SD
Age	47	( $\pm$ 19.06)
Gender (male)	585	(62.1)
Procedural indication (malignancy diagnosis)	544	(77.38)
Pain score	2.7	( $\pm$ 1.39)
Duration of procedure (mins)	21.48	( $\pm$ 9.9)
Number of procedural attempts	2	(1)
Operator (Physician Assistant,%)	699	(68.05)
Prior BMAB experience (%)	112	(12.16)
Nil Per Oral, Pre procedure (%)	57	(6.68)
Pre-procedural Tea/Coffee (%)	269	(31.5)
Pre-procedural Meal (%)	517	(60.6)
Serious Adverse Event (%)	9	(0.96)

complications when performed by variable operators,  $P > 0.05$ . Sixteen patients (2.4%) did not report any pain. There were no infectious complications observed or deaths.

### Factors Associated with Pain

Univariate and multivariate analysis of clinical associations was performed. Food and drink intake prior to procedure was associated only at Univariate level. Those who did not take any food prior to procedure had very high odds of pain (odds ratio (OR) 1.81 (95% CI 1.01–3.22)). However, those who took juice had very low odds (OR (95% CI): 0.619 (0.43–0.90)).

The following risk-factors were associated with pain on Multivariate analysis: those with prior BMAB had very low odds of pain (OR (95% CI): 0.23 (0.15–0.37)). However, when more than one attempt of biopsy was made the odds of pain was much higher (OR (95% CI): 1.62 (1.29–2.05)). Having at least a snack or drinking juice pre-procedure could reduce pain perception.

### Serious Adverse Events

Nine serious adverse events were reported, representing 0.95% of total procedures. There were no deaths. The major serious adverse event was hemorrhage, which comprised 2 of the 9 serious adverse events. Both the hemorrhages were related to a posterior Iliac Artery pseudo aneurysm. One was managed conservatively while the second patient required surgical excision of the retroperitoneal hematoma and ligation of the right internal iliac artery. Both these patients with the hemorrhages had a myeloproliferative neoplasm. Other serious adverse events related to persistent vomiting and disabling aching pain in the ipsilateral leg.

## Discussion

This single center prospective study over a 4-year period illustrates the intensity of pain and incidence of serious adverse events following a BMAB from an academic center in India. Our study identifies pain intensity as low when performed in our hands. Though pain following BMAB has been reported as moderate to severe in up to one third of the patients; it is well recognized that sensitivity to and tolerance of pain differs amongst ethnic groups [9-11]. The mean pain score of 2.7 ( $\pm$  1.39) in our study reflects a low pain score and is similar to a

**Factors associated with higher symptom severity.**

	Point Estimate	95% Wald Confidence Limits	
Gender	1.155	0.833	1.602
Receiving chemotherapy	0.777	0.513	1.176
Nil per oral	0.715	0.387	1.322
Physician Extender Vs Consultant Physician	0.555	0.297	1.036
Physician Extender followed by consultant Vs Consultant Physician	0.87	0.391	1.937
Physician Trainee Vs Consultant Physician	1.229	0.627	2.408
Empty stomach Vs Post major meal	1.21	0.843	1.737
Light snack Vs Post major meal	1.805	1.011	3.223
Milk-based beverage Vs Non milk beverage	0.619	0.425	0.901
Milk-based beverage Vs No beverage	0.919	0.584	1.444
Fruit intake pre procedure Vs No fruits pre procedure	0.517	0.174	1.531
<b>Method</b>	<b>Variations</b>	<b>DF</b>	<b>t Value</b>
AGE	Unequal	278.16	1.65
ATTEMPTS	Unequal	232.82	-6.89
TIME	Unequal	303.48	1.29

recent Italian national survey [12] This is but in conflict to experience with other procedures that, amongst ethnic groups; Indians have a higher mean pain score and need more medications for pain control [10]. This could be because of our policy of premedication with tramadol. Opioids have been reported to reduce pain associated with the vacuum aspiration of bone marrow [9]. Intravenous tramadol is a safe agent and is known to reduce procedural pain when given pre procedure [13].

Our study also confirms the safety of the procedure with no infectious complications or death. Reported complications following BMAB include trauma to neighboring structures, infection and hemorrhage [14] Though it can be a potentially hazardous procedure; and deaths have been reported; serious complications have been rare [6,15,16]. In our series 2 (0.2%) patients had serious hemorrhage. Both these patients had retroperitoneal hemorrhage and needed transfusion. One was managed conservatively while the second one required surgical excision of the retroperitoneal hematoma and ligation of right internal iliac artery. This adverse event has been reported and both conservative and surgical approaches have been utilized to manage this complication [3,17-19]. Thrombocytopenia and anticoagulant therapy have been reported as potential factors for this complication. Both our patients had neither thrombocytopenia nor were on anticoagulant therapy. Both these patients had a myeloproliferative neoplasm. This is similar to the experience from UK where this diagnosis was associated with higher risk of bleeding during bone marrow biopsy [6]. The mechanisms that may be involved with the risk of bleeding in chronic myeloproliferative neoplasms include acquired Von Wille brand disease or an acquired platelet dysfunction and storage pool defects compounded by the hypersplenism [20].

Our final objective was to determine factors associated with lower pain perception that help improve the patient experience in our

population. A small proportion of patients experienced severe pain, but clearly the vast majority was comfortable with the procedure. Factors which have been previously explored in possible connection to pain in BMAB include gender, age, and level of education, information prior to procedure, Prior BMAB, indication, operator experience, duration, and difficulty of the procedure [9]. Though a prior BMAB has been associated with unbearable pain in an earlier report; in our experience this is associated with a lower pain score [21]. This possibly could be due to a more informed patient due to their earlier experience and also supported by the detailed explanation prior to each procedure. It has been observed that patients with information about the procedure or who had previous personal experience with bone marrow examination could arrange a mental strategy and experience lesser pain [21].

We found no relation to pain with operator experience or indication. In our study the number of attempts influenced pain. Higher number of attempts was associated with a higher pain score. This is likely due to an increase in anxiety or reflective of the observation that patients undergoing lengthy procedures( due to repetitive attempts) report higher pain scores than patients undergoing shorter uncomplicated procedures [22]. In our series patients who had a meal intake or a juice prior to the procedure reported lower pain scores. This is a novel association. Evidence does support an analgesic effect of sweet solutions for newborns and infants and has been explored in older children [23]. However, data is scarce on food intake and pre procedural pain in adults. A report on healthy volunteers showed a better pain threshold and tolerance in subjects after food intake as compared to before intake of food postulating that intake of food could stimulate the release of hormones and endorphins leading to the observed hypoalgesia [24]. This novel association needs to be explored since most patients who visit a clinic in India report empty stomach in anticipation of investigations.

## Strength & Limitations

We present some of the first information on procedural pain in BMAB and its complications from India. We were able to identify factors which might help improve the experience of the procedure and be alert to complications.

The findings of the study should be interpreted with several limitations in mind. We had a diverse group of patients who underwent a BMAB. We included patients with both malignant and benign diseases of the blood and marrow. We did not account for / have data on the baseline pain threshold from comorbidity prior to procedure, meaning that some patients may have had a higher threshold that contributed to varied pain perception. There is also likely to be significant heterogeneity in pain perception across the various ethnicities and a larger prospective study from multiple centers in India is required to conclusively state that our results are representative of the country.

## Conclusions

In our analysis BMAB is safe and associated with a low level of procedural pain. Serious adverse events following BMAB are rare but can have considerable impact on the individual patient. The procedure appears relatively safe and pain perception was not influenced by the

operator,  $P > 0.05$ . Factors associated with decreased pain perception were prior BMAB experience and completion of the procedure in fewer attempts. Having a meal or drinking juice pre-procedure could reduce pain perception.

## Ethics Declaration

The study received approval from the Research Ethics Board of Christian Medical College & Hospital, Ludhiana (CMC/1495). All procedures were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all individual participants included in the study.

## References

1. Tomasian A, Jennings JW. Bone marrow aspiration and biopsy: techniques and practice implications. *Skeletal Radiol*. 2021; 51: 81-88.
2. Roldan CJ, Huh BK, Chai T, Driver LC, Song J, Thakur S. Sacroiliac joint pain following iliac-bone marrow aspiration and biopsy: a cohort study. *Pain Manag*. 2019; 9: 251-8.
3. Wojciechowski A, Duckert M, Hartmann J, Bullinger L, Matzdorff A. Retroperitoneal Hematoma after Bone Marrow Biopsy: The First Cut Should Not Be the Deepest - Abstract - *Oncology Research and Treatment*. 2019; 42: 283-288.
4. Bhootra BL. 1. Fatality Following a Sternal Bone Marrow Aspiration Procedure. *Med Sci Law*. 2004; 44: 170-2.
5. Martino M, Console G, Russo L, Messina G, D'Arro' BLG, Irrera G, et al. Internal Iliac Artery Perforation following Bone Marrow Aspiration in a Patient with No Previously Identified Risk Factors: A Case Report and Review of the Literature. *Acta Haematol*. 2012; 127: 23-5.
6. Bain BJ. Bone marrow biopsy morbidity: review of 2003. *J Clin Pathol*. 2005; 58: 406-8.
7. Degen C, Christen S, Rovo A, Gratwohl A. Bone marrow examination: a prospective survey on factors associated with pain. *Ann Hematol*. 2010; 89: 619-24.
8. Friedrich P, Lam CG, Kaur G, Itriago E, Ribeiro RC, Arora RS. Determinants of Treatment Abandonment in Childhood Cancer: Results from a Global Survey. *PLoS ONE*. 2016; 11: e0163090.
9. Vanhelleputte P, Nijs K, Delforge M, Evers G, Vanderschueren S. Pain during bone marrow aspiration: prevalence and prevention. *J Pain Symptom Manage*. 2003; 26: 860-6.
10. Tan E-C, Lim Y, Teo Y-Y, Goh R, Law H-Y, Sia AT. Ethnic differences in pain perception and patient-controlled analgesia usage for postoperative pain. *J Pain*. 2008; 9: 849-55.
11. Kuball J, Schüz J, Gamm H, Weber M. Bone marrow punctures and pain. *Acute Pain*. 2004; 6: 9-14.
12. Liptrott SJ, Botti S, Bonifazi F, Cioce M, De Cecco V, Pesce AR, et al. Management of Pain and Anxiety during Bone Marrow Aspiration: An Italian National Survey. *Pain Manag Nurs*. 2021; 22: 349-55.
13. Mohammad Faizan Zahid. Methods of reducing pain during bone marrow biopsy: a narrative review. The Aga Khan University. 2015; 4: 184-193.
14. Malempati S, Joshi S, Lai S, Braner D, Tegtmeier K. Bone Marrow Aspiration and Biopsy. *N Engl J Med*. 2009; 361: e28.
15. Bain BJ. Morbidity associated with bone marrow aspiration and trephine biopsy - a review of UK data for 2004. *Haematologica*. 2006; 91: 1293-4.
16. Patiño B. Morbidity and Mortality Associated with Performing Bone Marrow Aspiration and Biopsy. *Int Phys Med Rehabil J*. 2018; 3.
17. Jung IJ, Lim ST, Choi YS, Jang TS, Oh SH, Yuk HB, et al. Retroperitoneal Hemorrhage after Bone Marrow Aspiration and Biopsy in an Essential Thrombocythemia Patient. *Korean J Med*. 2015; 88: 598-601.
18. Mirtella D, Fedeli P, Cingolani M, Vacchiano G. Retroperitoneal hemorrhage caused by trephine biopsy. *Am J Forensic Med Pathol*. 2019; 40: 289-92.
19. Tsai H-L, Liu S-W, How C-K, Chern C-H, Yen DH-T, Huang C-I. A rare case of massive retroperitoneal hemorrhage after bone marrow aspiration alone. *Am J Emerg Med*. 2008; 26: 1070-e5.
20. Kaifia A, Kirschner M, Wolf D, Maintz C, Hänel M, Gattermann N, et al. Bleeding, thrombosis, and anticoagulation in myeloproliferative neoplasms (MPN): analysis from the German SAL-MPN-registry. *J Hematol Oncol J Hematol Oncol*. 2016; 9: 18.
21. Christian Degen, Susanne Christen, Alicia Rovo, Alois Gratwohl. Bone marrow examination: a prospective survey on factors associated with pain. *Annals of Hematology*. 2010; 89: 619-624.
22. Hjortholm N, Jaddini E, Halaburda K, Snarski E. Strategies of pain reduction during the bone marrow biopsy. *Ann Hematol*. 2013; 92: 145-9.
23. Harrison D, Yamada J, Adams-Webber T, Ohlsson A, Beyene J, Stevens B. Sweet tasting solutions for reduction of needle-related procedural pain in children aged one to 16 years. *Cochrane Database Syst Rev*. 2015; 2015: CD008408.
24. Anjana Y, Reetu K. Effect of food intake on pain perception in healthy human subjects. *J Evol Med Dent Sci*. 2014; 3: 7984-9.