

Karolinska Institutet, Stockholm, Sweden

**PROCEDURE RELATED
PAIN AND ANXIETY
DURING BONE MARROW
ASPIRATION**

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ABSTRACT

Bone marrow aspiration/biopsy (BMA) is a common procedure used to diagnose and follow up treatment in patients with haematological disorders. Procedures in these patients are often associated with some pain, discomfort and anxiety. However, there is only sparse data on the characteristics and determinants of procedural pain during BMA. In addition, little is known concerning the level of agreement between patients' and health care professionals' ratings of the formers' experienced pain and anxiety. The overall aim of this study was to increase knowledge about pain and anxiety in adult haematological patients undergoing BMA, and about how health care professionals estimate patients' pain and anxiety during BMA.

Two-hundred-and-thirty-five adult patients (109 female and 126 male, median age 62 years, range 20-89) scheduled consecutively for BMA at the Division of Haematology, Karolinska University Hospital Solna, (Study I and II) were included, Nine attending haematologists and seven haematology fellows who performed the BMA, and nine registered nurses (RNs) who assisted the physicians (Study II) were also included. Self-administered questionnaires with questions regarding patient characteristics such as age, gender, pain in daily life, pre-existing pain, anxiety, employment status, previous BMA, pain during and after BMA) were used to assess patients before-, 10 minutes post and 1-7 days post BMA. The RNs and physicians filled in questionnaires regarding patients' pain and anxiety immediately after each BMA. Factors associated with BMA-related pain and anxiety was examined using univariate and multivariate logistic regression analysis. Seventy percent of haematological patients undergoing BMA reported procedure related pain, one-third of them severe. Pre-existing pain OR 2.60, anxiety about diagnostic outcome OR 3.17 or needle-insertion OR 2.49, and low employment status OR 3.14 were independent risk factors (Study I).

The level of agreement between patients and health-care professionals (Study II) was evaluated by calculating proportions of agreement, Cohen's unweighted kappa coefficient (κ) and intra class correlations (ICC). The results showed fair agreement regarding the occurrence of pain between RNs and patients and physicians (κ 0.33 and 0.37), and moderate agreement for intensity of pain (ICC 0.42 and 0.44). RNs and physicians underestimated severe pain and overestimated mild pain. There was slight agreement between patients and RNs and physicians regarding occurrence of anxiety about BMA outcome and needle-insertion (κ 0.14-0.21). The ICC showed poor agreement between patients and RNs and physicians for anxiety about BMA outcome

and needle-insertion (ICC 0.13-0.36). In conclusion, procedure related pain was common in these adult patients undergoing BMA, and was often accompanied with pre procedural anxiety and pain. Health-care professionals underestimated patients' pain and anxiety during BMA.

LIST OF PUBLICATIONS

- I. Lidén Y, Landgren O, Arnér S, Sjölund KF, Johansson E.
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LIST OF ABBREVIATIONS

BMA	Bone marrow aspiration/biopsy
CI	Confidence interval
ICC	Intra class correlation
mm	Millimetre
κ	Cohen's unweighted kappa coefficient
NRS	Numeric Rating Scale
OR	Odds ratio
P(A)	Proportion of agreement
RN(s)	Registered nurse(s)
STAI-S	Stait trait anxiety scale-state
STAI-T	Stait trait anxiety scale-trait
VAS	Visual Analogue Scale
VRS	Verbal Rating Scale

BACKGROUND

Haematopoiesis and haematological disorders

Haemopoiesis is the formation of blood cellular components [1]. In adults, the active haemopoietic bone marrow is mainly limited to the pelvis, cranium, vertebrae, and sternum [2]. A common primitive stem cell in the marrow has the capacity to self replicate, proliferate and differentiate to increasingly specialized progenitor cells which after many divisions within the marrow form mature cells (red cells, granulocytes, monocytes, platelets and lymphocytes) of the peripheral blood. Stem and progenitor cells cannot be recognized morphologically but can be identified by certain surface antigens and functional cell colony formation experiments [3, 4]. The bone marrow stroma contains fibroblasts, endothelial cells, macrophages, adipocytes, osteoblasts and osteoclasts which can produce factors stimulating hematopoiesis. In the bone marrow there are also mesenchymal (or stromal) stem cells which under proper stimulation can differentiate into osteoblasts, chondrocytes, myocytes, and many other cell types. They also function as “gatekeeper” cells of the bone marrow [5]. Haemopoiesis is assessed clinically by performing a full blood count on peripheral blood and by examination of bone marrow aspiration/core biopsies. There is a wide range of benign hematologic diseases most often giving rise to anemia, neutropenia, thrombocytopenia or combinations of these.

Malignant haematological disorders

Haematological malignancies originate in blood forming organs (bone marrow or lymphoid tissue). In Sweden, approximately 3700 adult patients are annually diagnosed with a haematological malignancy [6] including acute and chronic leukaemias, multiple myeloma, lymphomas, myelodysplastic syndromes and chronic myeloproliferative neoplasms [7]. Chemotherapy remains the cornerstone of treatment in most haematological malignancies. Treatment may also consist of radiation therapy, surgery, immunotherapy or molecular-targeted therapy [8-10].

Bone marrow aspiration/biopsy (BMA)

Aspiration/biopsy of the bone marrow is one of the most valuable diagnostic tools to evaluate haematological disorders [11]. Indications for BMA include the diagnosis, staging of disease and therapeutic monitoring of the disease [11]. Most patients must undergo repeated BMAs during their disease trajectory. Bone marrow samples can be

obtained, from the posterior iliac crest, and sometimes from the sternum, by needle aspiration or percutaneous trephine biopsy; and sometimes the test includes both an aspirate and a biopsy. The aspirate yields cells and particles of bone marrow, which are spread on slides for microscopic examination. Trephine biopsy is a more invasive procedure, using a larger needle with which a solid piece of bone marrow is obtained. This is then fixed in formalin and cut in sections. Trephine biopsy assesses the overall architecture and cellularity of the bone marrow [11]. Typically, the patient lies prone or on one side during the procedure, which is performed under local anaesthesia such as lidocaine 1% to numb the area. Sometimes the patient is pre-treated with analgesics and/or tranquillisers [12-15]. The entire procedure, from meeting the physicians to walking away, takes approximately 15 minutes.

Pain

Pain is a complex interaction involving sensory, emotional and behavioural factors; hence its definition and treatment include all of these aspects. According to the international Association for the Study of Pain (IASP), pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” [16]. It may be affected by emotional, social and spiritual components [17]. The sensitivity to pain differ from person to person and the perceptions of the intensity of pain are not proportional to the type or the extent of the tissue damage [17-19]. Pain can result in mental suffering and it may also affect the sufferer’s overall activity and function negatively [20]. Thus, the pain threshold (the least experience of pain which a subject can recognize) and pain tolerance (the greatest level of pain which a subject is prepared to tolerate) may differ between individuals [16].

Pain is temporally classified as acute or chronic. Acute pain can be defined as “pain of recent onset and probable limited duration. It usually has an identifiable temporal and causal relationship to injury or disease”[21]. Chronic pain “commonly persist beyond the time of healing of an injury and frequently there may not be any clearly identifiable cause [21]. Pain can also be divided into nociceptive and neuropathic, and can be a mixture of these two types. Nociceptive pain is “defined as is pain arising from activation of nociceptors”. Neuropathic pain is defined as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system” [22].

The experience of pain may be influenced by different factors such as recurrence and chronicity, gender, foreign background and sociodemographic factors [23-28].

Pain in patients with haematological disorders

Pain is a common symptom affecting about 52% of patients with haematological malignancies [29-31]. It can arise from the underlying malignancy (bone pain, postherpetic neuralgia or peripheral neuropathy), diagnostic procedures (e.g. bone marrow aspiration/biopsy (BMA) or lumbar puncture), side effects of treatment (radiation or cytotoxic medication, long-term steroids or bone marrow transplantation) or may be unrelated to the malignancy and its treatment [29]. The major types of pain syndrome in patients with haematological malignancies are nociceptive pain (continuous and break-through), neuropathic, or mixed nociceptive and neuropathic. The most frequent pain syndromes are bone-marrow expansion, osteolysis, mucosites, neuropathies and headache [30].

Procedure related pain

Hospitalised patients undergo frequent non-invasive and invasive procedures which may cause more or less pain, for example when turning over, on the insertion of central venous catheters, removal of wound drains, dressing changes, trachea suction and removal of femoral sheaths [32, 33]. Common invasive procedures are BMA, lumbar puncture, biopsies and cystoscopy [34]. Procedure related pain prompts an acute or sudden onset of pain for a brief duration [35]. In many cases the pain is acute but transitory [12, 36, 37], however procedure related pain can result in chronic pain [38]. The procedure may also cause the patient to feel anxious [39, 40]. Patients repeatedly subjected to painful procedures without adequate analgesia may also anxiously anticipate procedural pain [15, 35].

Assessment of pain

Measurement is important for determining the intensity, quality and duration of pain, to aid diagnosis, and to help choose therapy. An adequate assessment of pain is also necessary for effectual pain management. As pain is subjective, patients' own reports are the most valid measure of the experience. A frequently used self-rating scale for measuring the intensity of pain in the clinical and research setting is the visual analogue scale (VAS). The VAS is reliable for both acute and chronic pain [41, 42]. The VAS scale consists of a 100 mm horizontal or vertical line with one statement at each end: 0

mm = no pain and 100 mm = worst possible pain. Patients mark the point on the line that corresponds to the intensity felt at that moment. The VAS scale is also reliable for measuring other domains than sensory intensity, such as anxiety [43-45]. Verbal rating scales (VRS) consist of verbal pain descriptors ranging from no pain, to mild, moderate and severe pain [46]. Patients choose the word that best describes the present intensity of their pain. If this descriptor is converted to a VAS scale for acute pain, > 30 mm is considered to equal moderate pain and > 54 mm severe pain [47]. A further instrument, the numerical rating scale (NRS) consists of a series of numbers ranging from 0-10 or 0-100, with the endpoints representing 0 = no pain and 10 or 100 = worst possible pain [42]. However the VAS, VRS and NRS describe pain solely in terms of intensity. To specify the quality of pain; pain questionnaires covering various aspects of pain and its functional consequences are often used.

Patients' satisfaction with pain management

Pain relief can be defined here as the therapeutic relief of clinical pain whereas patient satisfaction is the "consumer's" personal evaluation of health care services and providers [48]. Patient satisfaction relates to psychosocial aspects of care such as communication and personal preference, and cultural aspects; whereas a patient's pain rating reflects more technical aspects of care [48]. Some studies have found that patient satisfaction with pain management correlates poorly with VAS pain score: patients report moderate- to-severe pain but are still satisfied with their pain management [49-51]. Factors possibly influencing this could be; communication to patients that pain management is a high priority, whether or not it was effective [52]. Perhaps the pattern of pain relief, rather than its severity, is a critical determinant of satisfaction [52]. Other research suggests that one reason for the incongruity between patient satisfaction and pain relief is that patients have low expectations of pain relief [53]. Other aspects of the interaction such as empathy and explanation may also be more important contributors to satisfaction than the provision of analgesia [54].

Anxiety

Anxiety is an emotional state that we all experience to some degree with symptoms including, nervousness, sweating, rapid heartbeat and dizziness [55]. Like pain and fear plays anxiety an adaptive role as an alarm that responds to danger and harm [56]. Spielberger describes anxiety as either as general proneness to anxiety or as situation-

related feelings such as apprehension, tension, nervousness and worry [57]. He distinguishes conceptually between chronic or trait anxiety (a general propensity to be anxious) and temporary or state anxiety (a temporary state varying in intensity).

Anxiety before pain predicts evaluated pain intensity during acute pain perception [58, 59]. In patients with chronic pain, psychological disorders such as depression and anxiety often coexist [60-62]. Patients with greater pain-related anxiety tend to over-predict a new pain experience [18]. Patients with diagnosed cancer can often experience worries about cancer treatment effects: fear of recurrence, fear of cancer progression and death, guilt, and spiritual questioning [63]. Fear about pain is also common in patients with cancer [64-66]. Fear of recurrence can be described as “the degree of concern reported by subjects about the chances of cancer returning” [66, 67].

Needle phobia is defined as an intense and persistent fear of injections [68]. Less severe fear of injections is known as needle anxiety and is frequent among patients in health-care settings [68]. It affects approximately 10% of a normal population, with varying severity [69]. Patients with malignancies experience increased exposure to needles during assessment, procedures and treatment [70].

Assessment of anxiety

An adequate assessment of anxiety is important for determining and evaluating its presence or the effectiveness of interventions reduce its occurrence. There are numerous rating scales for measuring anxiety and anxiety disorders [71]. A well-validated instrument is the State Trait Anxiety Inventory (STAI), developed by Spielberger [57, 72]. *State anxiety* is defined as a transitory emotional response involving unpleasant feelings of tension and apprehensive thoughts, while the *personality traits of anxiety* refers to individual differences in the likelihood that a person will experience state anxiety in a stressful situation [57]. The total score for each form ranges from 20 to 80 points; a higher score indicates greater anxiety. The VAS has been validated for measuring preoperative anxiety and it is a pertinent tool for assessing patient anxiety [43] [44]. The anxiety VAS consists of a 100 mm line with the two endpoints labelled “no anxiety” and “worst possible anxiety”. Participants mark the point on the line that best reflects their present anxiety.

Health-care professionals' opinions of patients' experience of pain & anxiety

In general, health-care professionals underestimate the level of pain that patients report, especially when pain is severe [37, 73, 74]. Grossman et al compared patients' ratings of their pain intensity to the assessments by attending nurses, house officers and oncology fellows. At all intensity levels, care-givers consistently rated the patients' pain experience lower than the patients did [75]. Discrepancy between patient and physician in their estimates of pain intensity is one of the most important predictors of under-treatment of cancer-related pain [73]. Under-treated pain is still common [29, 30, 51, 76, 77] and may depend on poor communication between patient and staff leading to inadequate pain assessment [78]. There is also strong evidence that many health-care professionals lack adequate knowledge of the nature of pain, pain physiology, different pain types and pain management [79-82]. Several studies have shown discrepancies between patients' and health-care professionals' ratings of patients' anxiety [83-85]. In general, the professionals tend to overestimate patients' emotional distress [83, 84]. However, there is also evidence that individual cancer patients' emotional problems are underestimated [85, 86]. The explanation may be that health-care professionals have their own views of how the patient probably feels. This in turn leads to the belief that patients have more anxiety than they actually have [85, 87, 88], or that patients deny or do not voice their anxiety [89, 90]. Health-care professionals' experience of care and time spent with the patient are also important factors [91]. Lack of time spent with patients may reduce the professionals' scope for understanding patients' situations [91, 92].

AIM OF THE STUDY

The present studies investigated aspects of pain and anxiety in adult patients with haematological disorders undergoing BMA.

Specific aims were:

1. to evaluate the frequency of pain during BMA
2. to evaluate the intensity of pain during BMA
3. to evaluate the duration of patients' experience of BMA-related pain post BMA
4. to identify factors related to patients' pain experience during BMA, and
5. to compare the level of agreement between patients' and health-care professionals' ratings of patients' pain and anxiety during BMA.

Formaterade: Punkter och numrering

MATERIAL AND METHODS

Patients (Studies I and II)

The studies included 263 consecutively recruited haematological patients, scheduled for BMA at the outpatients' clinic at the Division of Haematology, Karolinska University Hospital, Solna. Of these 33 were excluded due to difficulties in understanding the Swedish language (n=13), unwillingness to participate (n=7), late arrival (n=5), sedative medication (n=2) or a faint (n=1) before BMA (Figure 1). Of the remaining 235 patients, 168 (71%) patients had a haematological malignancy and 67 (29%) had other haematological disorders or non-haematological disease. Patients could only be enrolled once. The BMA was performed under local anaesthesia (Figure 1).

Health-care professionals` (Studies I and II)

Nine attending haematologists and seven haematology fellows performed the BMAs (Figure 1). Twenty-six percent of the BMA were performed by the haematologists and 74% by the haematology fellows. Seventy-three percent of the attending haematologists and 95% of the fellows had performed more than 100 BMAs previously.

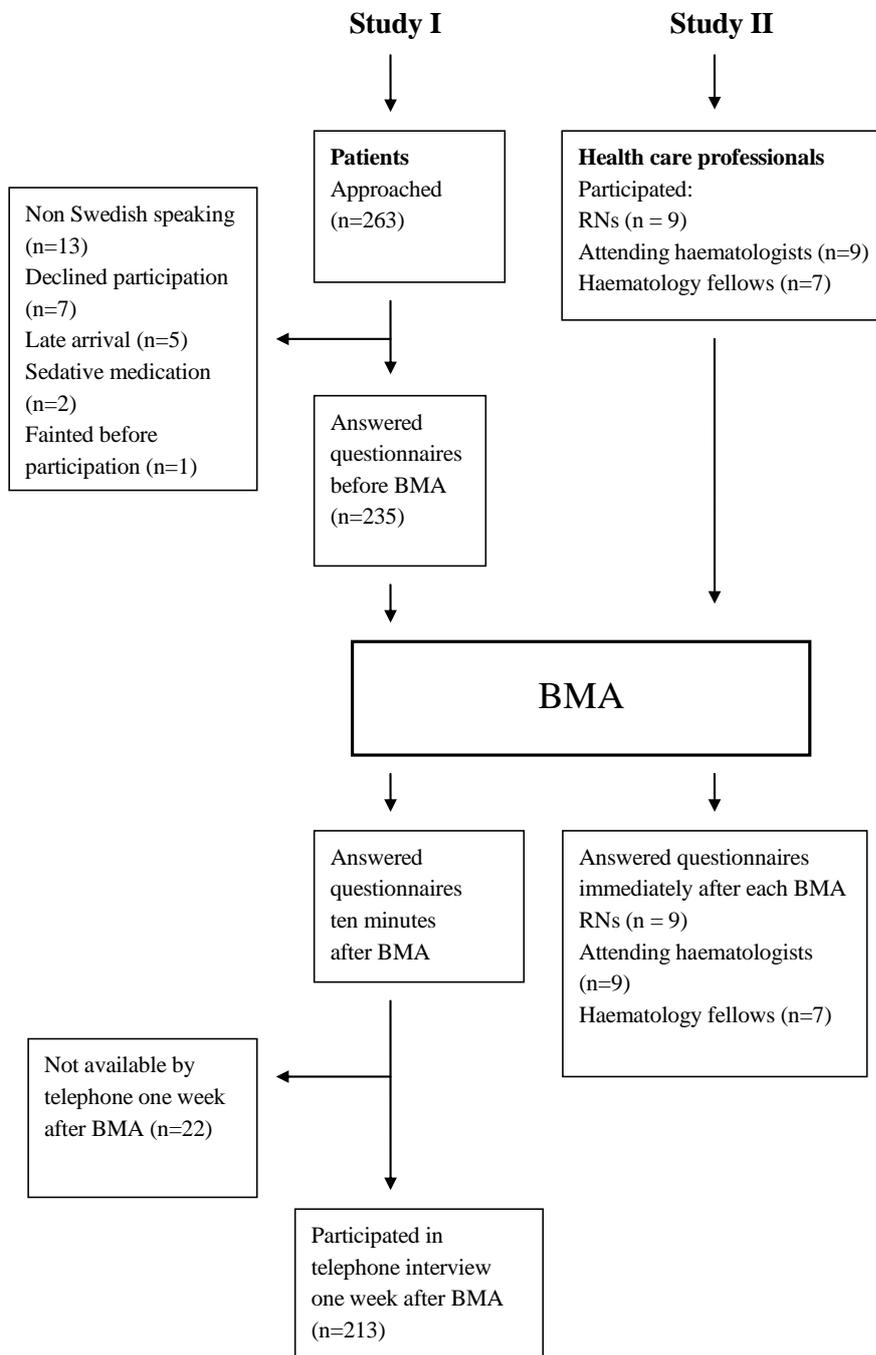


Figure 1. Inclusion of patients and health-care professionals.

Instruments

Questionnaires to the patients ten minutes before BMA

Patients answered questions concerning height and weight, pain in daily life (pre-existing pain), pain before BMA, whether pain medication was taken the same day as the BMA, anxiety about the diagnostic outcome of BMA and anxiety about BMA-needle-insertion. The questions regarding pre-existing pain were adapted from the Karolinska University Hospital Pain Questionnaire [38, 93] (Study I and II).

Demographic data were collected with a questionnaire [94] with items concerning gender, age, marital status, foreign background, employment status, education level and perceived economic status (Study I and II).

Anxiety was measured with the State Trait Anxiety Scale (STAI), a well-validated and reliability-tested instrument [57, 95]. STAI is composed of two forms, STAI-S and STAI-T, each with 20-item scales. STAI-S measures the subject's level or *state* of anxiety at a particular moment in time, whereas STAI-T refers to the *trait* or general feelings of anxiety-proneness. For respondents who omitted one or two items on either scale, the pro-rated full-scale score was obtained by the following procedure: the mean weighted score for the scale items to which the individual responded was determined; then we multiplied this value by 20; and rounded the product to the next higher whole number. If three or more items was omitted the data was excluded [72] (Study I).

Questionnaires to patients ten minutes after BMA

Patients answered questions regarding pain during the BMA, discomfort during the BMA, satisfaction with the pain management, whether information about BMA was received and whether the patient had undergone a BMA previously (Study I and II).

Telephone interview one week after BMA

Patients answered questions by telephone concerning occurrence of BMA-related pain and pain intensity at 1, 3, 6 and seven days following their BMA, and the use and type of medication for BMA-related pain (Study I).

Questionnaires to health-care professionals`

Immediately after each BMA, the performing physicians and the assisting RNs individually filled in a study-specific questionnaire. They recorded their assessment of patients' pain during the BMA, anxiety about their BMA outcome and anxiety about

needle-insertion, without knowing the patients' questionnaire responses. Physicians and RNs gender and the number of years working in the haematology were also recorded (Study II).

The patients were invited to participate in the study by the investigator (Y.L.) when they arrived at the outpatients' clinic at the Karolinska University Hospital, Solna Division of Haematology. Informed consent was obtained from all included patients before study enrolment and the patients received self-administered questionnaires. The participants also answered questions by phone one week after BMA (Figure 1). The investigator (Y.L.) attended during all the BMAs, and distributed and collected questionnaires.

Statistics and data analysis

The statistical methods used in Studies I and II and their functions are described in Tables 1 and 2. The level of statistical significance was set at $p < 0.05$. The statistical calculations were performed using the Stat View 5.0.1 and SPSS 14.0 software.

Study I

A power analysis was performed. A difference of 20% was considered as the smallest effect of clinical relevance to detect between the two variable groups: anxiety and pain during BMA vs. no anxiety and pain during BMA. α was set to 0.05. With a sample size of 93 persons in each group, the study would have a power of 80% to yield a statistically significant result. An attrition rate of 20% was estimated and an accrual of 233 patients was planned.

The ratings of pain intensity, anxiety and discomfort are presented with descriptive statistics. To estimate the probability of occurrence of pain related to known potential predictors, factors that could influence experience of pain were tested in univariate logistic regression. These were age [96], gender [23], prior BMA [97], pre-existing pain [98], pain before BMA [98], anxiety about BMA outcome and needle-insertion [58, 59], written and oral information received [99], pain medication taken same day as BMA [12], body mass index (BMI) [12], experience and training of physicians [37], type of BMA [37], economic situation, marital status [24], foreign background [100], employment status, education level [24], underlying diagnosis [66] and total STAI-S and total STAI-T [58]. Those variables with a p-value < 0.05 , i.e. age, prior BMA,

existing pain, pain before BMA, anxiety about result and needle-insertion, education level and employment status, were then included in a forward stepwise logistic regression. The Mann-Whitney *U* test or the Kruskal-Wallis test was used to investigate whether pain intensity was influenced by the same variables as above, except for total STAI-S and total STAI-T. Spearman's rank correlation was also employed to describe the relation between the STAI-S score and VAS scores for anxiety.

Study II

To estimate agreement regarding the occurrence of pain and anxiety between patients and health-care professionals, proportion of agreement (P/A) and Cohen's unweighted kappa coefficient (κ) were calculated. The ranges suggested by Landis and Koch were applied to interpret the magnitude of the κ values obtained ≤ 0 = poor, 0.01–0.20 = slight, 0.21–0.40 = fair, 0.41–0.60 = moderate, 0.61–0.80 = substantial, and 0.81–1.0 almost perfect agreement (ref). To evaluate the agreement between patients' and clinicians' ratings of intensity of pain and anxiety, single-measure intra class correlation (ICC) was used, interpreted as follows: < 0.4 = poor agreement, $0.4 - 0.74$ = moderate agreement, $\geq 0.75 - 1$ = good agreement [101, 102]. Patient-clinician agreement was sub-analyzed regarding patients' gender (female / male), age (≤ 60 years / > 60 years), foreign background (yes / no), type of BMA (bone marrow aspiration, bone marrow biopsy or both) and duration of BMA (≤ 15 minutes / > 15 minutes) (Table 2).

Table 1. Statistical methods used in study I.

<i>Method</i>	<i>Function</i>
Power analysis	Calculate minimum sample size required to accept outcome of a statistical test with a particular level of confidence.
Descriptive statistics: mean, median, range, percentage	Describe the characteristics of the study sample, e.g. gender, age and BMA duration.
Chi-square test (χ^2)	Test whether categorical variables differed from one other, e.g. type of BMA, anxiety and pain during BMA.
Mann-Whitney U-test	Compare medians of non-normal distributions in two groups.
Kruskal Wallis test	Compare medians of non-normal distributions in three groups.
Spearman's rank-order correlation coefficient	Describe association between two variables. A non-parametric measure of statistical dependence between two variables, e.g. STAI-S scores and VAS scores for anxiety.
Univariate logistic regression	Test a potential independent variable against a dependent variable, e.g. anxiety predicts pain. Estimates: Odds ratio (OR), and 95% confidence interval (CI).
Stepwise multivariate logistic regression	Test more than one independent variables towards a dependent variable, e.g. if pre-existing pain and anxiety predict pain. Estimates: Odds ratio (OR), and 95% confidence interval (CI).
Box-whisker plot diagram,	Graphically describe data. The median value is indicated by the central horizontal line while the lower and upper quartiles by the corresponding horizontal ends of the box. The shaded box itself represents the interquartile range, e.g. the intensity of BMA-related pain during and after BMA.

Table 2. Statistical methods used in study II.

<i>Method</i>	<i>Function</i>
Descriptive statistics: mean, median, range, percentage	Describe characteristics of study-sample, e.g. gender, type of BMA and number of RNs and physicians.
Proportion of agreement P(A)	Determine agreement between assessments among raters, e.g. occurrence of pain and anxiety between patients and health-care professionals.
Cohen's unweighted kappa coefficient (κ)	Correcting for eventuality that agreement between patient and health-care professionals could occur by chance.
Intra class correlation (ICC)	Assess the reliability of quantitative measurements made by different observers measuring the same quantity, e.g. agreement between patients and the health-care professionals scoring of intensity of pain and anxiety by using VAS.
McNemar test	Test the marginal homogeneity, e.g. between patient and health-care professionals. A non-parametric method.

ETHICAL CONSIDERATIONS

The studies were approved by the Regional Ethics Committee in Stockholm (Registration number: 041039/2).

Informed consent to participate was obtained from the patients and health-care professionals in these studies. When the patients were invited to take part in the study it was emphasized that participation was voluntary and that treatment would not be influenced by participation or not. Regarding questionnaires, there is always a risk that questions may constitute a risk to personal integrity. However, failure to ask how a person experiences pain and anxiety during a BMA might also constitute a violation of personal integrity. The researchers involved in these studies had no conflicts of interest.

RESULTS

Procedure related pain among adult patients with haematologic malignancies (Study I)

Patient characteristics

The study included 109 female and 126 male patients with a median age of 62 years (range 20-89 years). One hundred patients had no previous experience of BMA. BMA duration, pre-existing pain, previous BMA, type of examination, site of BMA and diagnosis (malignant or non malignant) are listed in Figure 2.

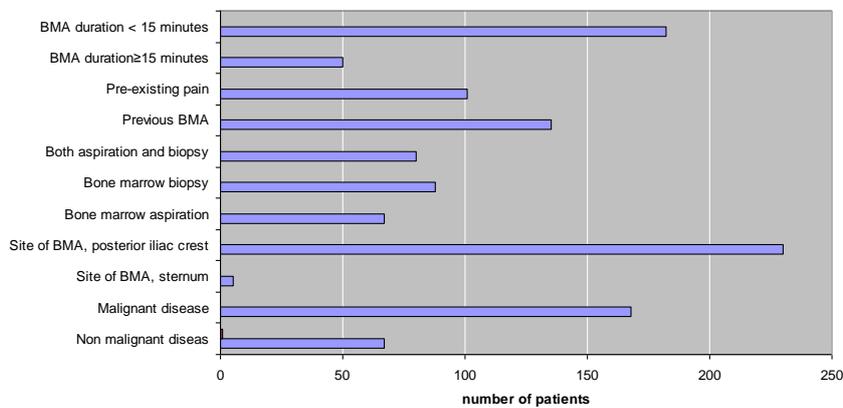


Figure 2. Characteristics of 235 patients undergoing BMA.

Pain during BMA

One-hundred-and-sixty-five of 235 patients (70%) reported pain during BMA, with a median VAS of 37 mm. Of these, 56% experienced moderate pain (VAS ≥ 30 mm), 32% reported severe pain (VAS ≥ 54 mm) and 3% experienced worst possible pain (VAS = 100mm). In the telephone interview, 64% reported BMA related pain on day one post BMA, median VAS 25 and a week post BMA pain was still present in 12% of the patients. Median VAS ranged between 15 and 30 mm. There was no difference in pain experience between patients with malignant diseases or non-malignant diseases.

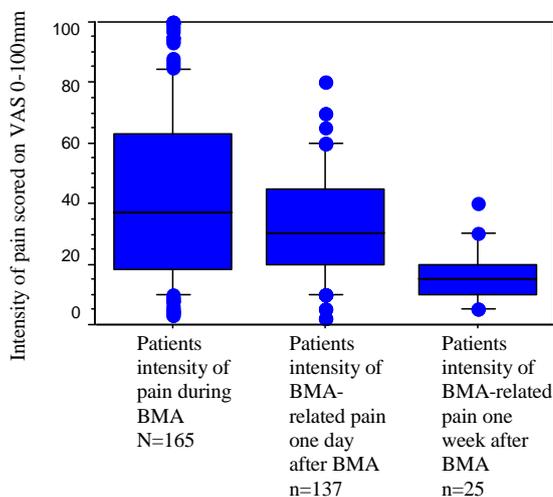


Figure 3. Intensity of BMA-related pain during BMA, one day and one week after BMA. Data presented as median visual analogue scale (VAS) with 25th and 75th percentile ranges in boxes. Whiskers represent 10th and 90th percentiles and dots are outliers.

Factors associated with BMA-related pain

Regarding potential predictive factors associated with the occurrence of pain during BMA, there was statistical significance for younger age, prior BMA, pre-existing pain, pain before BMA, anxiety about needle-insertion and the diagnostic outcome of the BMA, high education level, low employment status (sick-leave or unemployed) and high STAI-S and STAI-T levels. Results for STAI-S and STAI-T are shown in Table 3. In a multivariate logistic regression, the contribution of significant variables demonstrated that pre-existing pain (OR = 2.60 95% CI 1.26-5.36), anxiety about the needle-insertion OR = 2.49 95% CI 1.22-5.10), anxiety about the diagnostic outcome (OR = 3.17 95% CI 1.54-6.52) and low employment status (OR = 3.14 95% CI 1.31-7.55) were significantly related to the likelihood of pain during BMA.

Table 3. Anxiety in relation to pain during BMA, measured with the Spielberger Stait Trait Anxiety Inventory scale.

Characteristic	Pain during BMA median (range) n = 165	No pain during BMA median (range) n = 70	p-value
STAI-S*	43 (23-74)	37 (27-68)	0.0005
STAI-T**	42.5 (28-69)	29 (25-54)	0.0041

*Internal attrition, n = 13 **Internal attrition n = 19

Patient satisfaction

In total, 216 patients (93%) reported that they were satisfied with the pain management during BMA. Of those patients who reported pain during BMA, 91% were satisfied with the pain treatment (VAS median 30mm). However those who were dissatisfied with the pain management scored VAS median 80 mm (Figure 4).

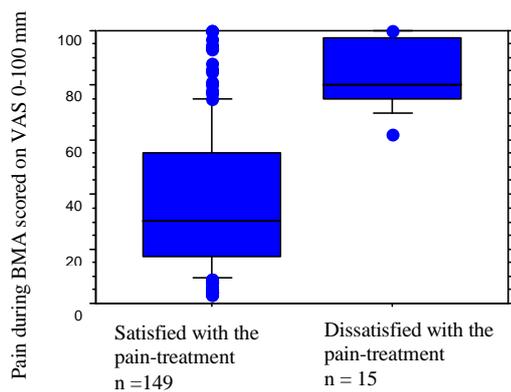


Figure 4. Intensity of bone-marrow-aspiration/biopsy (BMA)-related pain during BMA among patients satisfied or not, respectively, with the pain management. Data presented as median visual analogue scale (VAS) with 25th and 75th percentile ranges in boxes. Whiskers represent 10th and 90th percentiles and dots are outliers.

Poor congruence between haematological cancer patients and health-care professional's ratings of patients' pain and anxiety during bone marrow aspiration (Study II)

Agreement between patients and health-care professionals regarding occurrence and intensity of pain

The P(A)s for occurrence of pain during BMA between patients and RNs and physicians were 73% and 70% respectively. The corresponding κ 's were fair (0.33 and 0.37). In the sub-analysis κ was slight to moderate (Table 4).

Table 4. Level of agreement between patients and RNs and physicians (n = 235) regarding occurrence of pain, from sub-analysis.

Level of agreement	Patients' and RNs' agreement on pain during BMA	Patients' and physicians' agreement on pain during BMA
Poor ≤0	-	-
Slight 0.01-0.20	Female patients Bone Marrow Aspiration	Foreign background
Fair 0.21-0.40	Age < 60 years Age > 60 years No foreign background Foreign background Bone Marrow Biopsy BMA-duration < 15 minutes	Age < 60 years Age > 60 years No foreign background Bone Marrow Biopsy Bone Marrow Aspiration Both Biopsy and Aspiration BMA-duration < 15 minutes Female patients Male patients
Moderate 0.41-0.60	BMA-duration > 15 minutes Male patients Both Biopsy and Aspiration	BMA-duration > 15 minutes
Substantial 0.61-0.80	-	-
Almost perfect 0.81-1.0	-	-

Agreement between patients and RNs and physicians regarding intensity of pain was moderate (ICC; 0.42 and 0.44). In the sub-analysis the agreement was poor-to-moderate. Severe pain (VAS > 54) reported by patients was identified by RNs and physicians in 34% and 35% of cases, respectively.

Agreement between health-care professionals on occurrence and intensity of anxiety about BMA outcome and needle-insertion

The P(A)s between patients and RNs and physicians for anxiety about BMA outcome and needle-insertion were 56% and 55% respectively vs. 53% and 59% respectively.

The corresponding κ was slight (0.19 and 0.14) for anxiety about BMA outcome and fair (0.24 and 0.36) for anxiety about needle-insertion. In sub-analysis κ was slight-to-fair (Table 5).

Table 5. Level of agreement between patients and RNs and physicians (n = 235) regarding occurrence of anxiety, from sub-analysis.

Level of agreement	Patients' and RNs' agreement on anxiety about BMA outcome	Patients' and physicians' agreement on anxiety about BMA outcome	Patients' and RNs' agreement on anxiety about needle-insertion	Patients' and physicians' agreement on anxiety about needle-insertion
Poor ≤ 0	-	-	Foreign background	-
Slight 0.01-0.20	Age ≤ 60 years Age > 60 years Female Male No foreign background Foreign background Bone marrow biopsy Bone marrow aspiration BMA duration ≤ 15 minutes	Age ≤ 60 years Age > 60 years Female Male No foreign background Foreign background Bone marrow biopsy Both biopsy and aspiration BMA duration ≤ 15 minutes BMA duration > 15 minutes	Age ≤ 60 years Age > 60 years Female Male No foreign background Bone marrow biopsy Bone marrow aspiration BMA duration ≤ 15 minutes BMA duration > 15 minutes	Age ≤ 60 years Female Male Foreign background Both biopsy and aspiration BMA duration ≤ 15 minutes
Fair 0.21-0.40	Both biopsy and aspiration BMA duration > 15 minutes	Bone marrow aspiration	Both biopsy and aspiration	Age > 60 years No foreign background Bone marrow biopsy Bone marrow aspiration BMA duration > 15 minutes
Moderate 0.41-0.60	-	-	-	-
Substantial 0.61-0.80	-	-	-	-

Almost perfect 0.81-1.0	-	-	-	-
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Agreement between patients and RNs and physicians was poor regarding intensity of anxiety about BMA outcome and needle-insertion (ICC; 0.13 and 0.30 vs. 0.24 and 0.36). In the sub-analysis, agreement was poor-to-moderate. The patients expressed a higher degree of anxiety about the BMA result and needle-insertion than the RNs and physicians were able to identify (Figure 5).

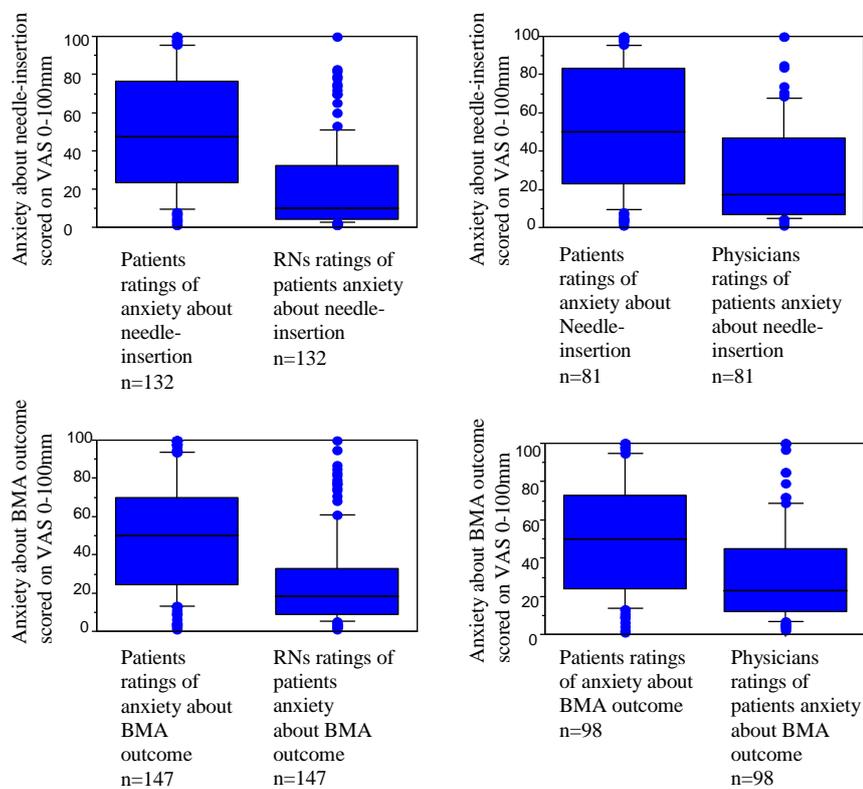


Figure 5. Intensity of anxiety about needle-insertion and BMA outcome where both patients, RNs and physicians scored anxiety. Data presented as median visual analogue scale (VAS) with 25th and 75th percentile ranges in boxes. Whiskers represent 10th and 90th percentiles and dots are outliers.

RESULT DISCUSSION

Procedure related pain after BMA is often described as a temporary and transitory experience. However this study shows that it is common and severe and may sometimes be long-lasting. Further, the congruence between patients' and the health-care professionals' ratings of the formers' pain and anxiety during BMA is poor. In this study one-third of the patients experienced severe pain (VAS >54 mm) and three percent scored worst possible pain, which tallies with previous studies where 16-33% of the patients report severe pain during BMA [12, 37, 103]. As did Kuball et al [37], we found that the duration of BMA was associated with intensity of pain during BMA. Pre-existing pain (chronic pain) was an independent risk factor associated with BMA-related pain. Patients with pre-existing pain also experienced higher intensity of pain, which is in line with the increasing evidence that chronic pain before surgery predicts increased intensity of post-operative pain [98]. In addition, chronic pain is common in patients with cancer [77, 104]. It is well known that patients and clinicians do not agree regarding patients' experience of pain and anxiety. The present study showed fair agreement between patients and health-care professionals regarding the occurrence of pain during BMA. RNs and physicians underestimated severe pain (>54 mm on VAS) and overestimated mild pain (VAS < 30 mm). These results agree with other investigators' in a variety of patient-care settings [37, 51, 75, 82, 105-107]. Different explanations of incongruity have been reported: thus, RNs and physicians with greater experience seem to underestimate the pain more frequently than do those with less experience [82, 108]. Patients and clinicians relate to different experience when scoring pain: thus patients might refer to personal experience whereas health-care professionals relate their experience of pain to the numbers of patients with pain whom they have cared for and therefore, perhaps unconsciously, base their scores on their experience of others' pain [109].

Potential explanations of patients' experience of pain during BMA have been that local anaesthesia alone does not abolish the pain [37] because patients are anxious and frightened before their BMA [13, 14, 110]. In this study, pre-existing anxiety about BMA outcome and anxiety about needle-insertion predicted occurrence of pain during the BMA. Pain is reportedly associated with patients' mood and anxiety before its onset and predicts greater intensity during acute pain perception [58, 59]. Anxiety about needle-insertion was also associated with higher intensity of pain. Patients with

malignancies experience extensive exposure to needles during assessment, procedures and treatment [70] and this may cause needle anxiety [111]. Anxiety is a common emotional symptom in patients with cancer, and fear of recurrence is significant for many cancer patients [63]. Patients who experienced pain during BMA also rated higher STAI-S and STAI-T scores than those who did not. This confirms the findings of Kain et al [58] that trait anxiety two weeks preoperatively correlated with patients' state anxiety and the state anxiety correlated with the patients' immediate postoperative pain. In Study II patients expressed anxiety about the BMA outcome and needle-insertion more frequently and much more intensively than the RNs and physicians were able to identify. Their poor identification of patients' anxiety may be related to lack of time to discern their emotional distress or to the fact that patients do not express their anxiety [112, 113].

Procedure related pain is often described as temporary and transitory [35]. However this study (1) shows that BMA related pain was still present one week after BMA. This result causes one to wonder whether BMA-related pain really is included in this definition, and if so maybe it should be treated more aggressively even post BMA.

As in other studies, patients' satisfaction with the management of their pain correlates poorly with VAS pain score [49, 52, 76]. One explanation could be that we only asked "are you satisfied with the pain management"? This could cover beliefs about the health-care professionals, e.g. "physicians and nurses have done all they can" or "I expected some pain and am satisfied with the care given". Patient satisfaction is not a clearly defined concept!

METHODOLOGICAL DISCUSSION

The prospective design, large sample size and high response rate, were strengths in these studies. The procedures of collecting data by the researcher (ten minutes before BMA and ten minutes after BMA) could have contributed to the very high response rate.

The variables considered for analyses, were mainly pain predictors reported in previously published studies. However, the analyses of several variables involves an increased risk of type I error, and our results may therefore require replication.

Although validated questionnaires sensitive for acute and chronic pain and anxiety were used [41, 42, 44], the questions about anxiety may have affected patients' reporting of this aspect; which may subsequently have affected reported pain negatively. If so, this effect was small, because our data on pain frequency are comparable to results from other studies on BMA-related pain where anxiety was not explored. The Visual Analogue Scale used for measuring anxiety correlated with STAI-S, indicating that STAI-S may not be essential in future studies of BMA-related pain. Among patients who reported no pain during BMA, 60% gave no VAS score and 40% indicated VAS 1-30 mm. These responses limited our ability to conduct a multivariate analysis of factors associated with BMA-pain intensity, and this may have influenced the internal validity. When pain intensity is analysed in all patients, reported pain intensity could be misleading. However, we report pain intensity among patients who reported pain during BMA.

One threat to the external validity is the characteristics of the sample. Highly homogeneous samples may limit generalization. To avoid this threat, we selected "typical" patients undergoing BMA (including age, gender, foreign background, disease etc). Also the health-care professionals were the usual staff members.

This is one of the first studies of the duration of procedural pain. Patients were interviewed by telephone about the occurrence and intensity of BMA-related pain, i.e. 1, 3, 6 and 7 days (same day as interview) following BMA. The retrospective data should be interpreted with caution, due to the risk of recall bias. However, Singer et al showed in a retrospective study that patients can recall the severity of an acutely painful episode for one week after its occurrence, and that retrospective pain assessment may hence be a valid design for pain assessment [114].

In study II, the RNs and physicians were blinded to the patients' ratings of pain and anxiety, which is strength in this study. However, we compared small staff samples with a larger patient sample. Personal differences between individual RNs and physicians may thus have influenced the result and consequently the internal validity. However, our intention was to investigate the overall agreement between patients, RNs and physicians, not how individual RNs and physicians assess patients' pain and anxiety during BMA. The timing of our questionnaires regarding anxiety differed between the patients and health-care professionals, in that patients answered questions

prior to BMA whilst RNs and physicians responded to these questions immediately after: this could have influenced the congruence regarding anxiety. However this was the only feasible way of distributing questionnaires since the health-care professionals first meeting with the patient was in the consulting room where the BMA was performed.

The kappa (κ) statistics are conventionally used to measure the degree of agreement between two independent judges. P(A) is the proportion of times that the observers agree and kappa (κ) is the measure of agreement corrected for chance agreement.

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When interpreting kappa, it is important to consider that kappa may not be reliable when the prevalence of a rating in the population is very high or low. The value of kappa may indicate poor reliability even with a high observed proportion of agreement [115].

The correlation (ICC) is the most common method for assessing reliability with continuous data. However one limitation is that it is strongly influenced by the variance of the trait in the sample/population in which it is assessed. Thus ICCs measured for different populations might not be comparable [101].

CONCLUSIONS AND CLINICAL IMPLICATIONS

Conclusions

The results of these studies demonstrate that:

1. The majority of the adult haematological patients reported pain during BMA.
2. Of those patients who experienced pain during BMA, one-third scored severe pain (VAS > 54mm) and 3% worst possible pain.
3. Pain related to BMA was still present in 64% of the patients one day after BMA and in 12% one week after.
4. Pre-existing pain, anxiety about diagnostic outcome and needle-insertion, and low employment status (sick-leave/unemployed), predicted pain during BMA.
5. Overall there was a fair agreement between patients' and health-care professionals' ratings of patients' pain. Health-care professionals significantly underestimated patients' severity of pain and when pain intensity was severe (VAS > 54). This pain was identified by RNs and physicians in one third of cases respectively.
6. There was slight-to-fair agreement regarding anxiety about BMA outcome and needle-insertion. Health-care professionals significantly underestimated patients' anxiety about needle-insertion and diagnostic outcome. At all intensity levels, health-care professionals rated the patients' anxiety lower than the patients did.

Clinical implications

Results from these studies emphasize the need for implementing new routines for patients undergoing BMA. An adequate assessment of pain is of major importance for effectual pain management. As pain is subjective, patients' own reports are the most valid measure of the experience. They can easily be obtained by asking patients to quantify their pain before and after the procedure using a pain-rating scale (VAS, VRS or NRS), so that appropriate steps can be taken if analgesia for BMA is inadequate. A protocol for managing procedure related pain during BMA, including identifying pre-existing pain and anxiety, could be developed. Evaluation and planning for pain management during BMA may start with the decision to perform BMA. The poor agreement between patients' and health-care professionals' ratings of patients' pain could depend on lack of practice in assessing pain. If patients are not asked to rate their pain intensity, "pain" is based on health-care professionals' assumptions. Time spent with the patient is short (15 minutes): more time spent with the patient before BMA

might reduce patients' anxiety and enable them to get answers to their questions about BMA. In summary: 1) identify patients who are at increased risk of pain during BMA, 2) assess, and document patients' pain and anxiety during BMA in their medical records, 3) develop routines for those patients who are at increased risk of experiencing BMA-related pain.

FUTURE RESEARCH

Results from these two studies imply future research. Patients with haematological disorders may undergo BMA several times. The procedure is often performed at the outpatients' clinic where the opportunity to sedate is limited on account of the necessity to involve additional staff or resuscitation for safe administration. One avenue is to investigate the administration and substance of the local anaesthesia. Maybe the time between giving a local anaesthetic and performing the BMA is too short, or maybe longer-acting anaesthesia is needed. This is focus for future research.

A few patients are bothered by remaining pain one week after BMA. The reason was not investigated in this study, but is also a high priority for future research.

Patients' satisfaction with pain management correlates poorly with VAS pain scores. Patients reported moderate-to-severe pain but were satisfied with their pain management. Satisfaction has multidimensional components and, regarding patients undergoing BMA, it would be important to explore the concept from the patients' point of view: what does satisfaction with pain management during BMA imply?

The goal of pain treatment during BMA must be to relieve pain and anxiety, with minimal side-effects, and to use a method that does not require additional staff or resuscitation facilities for safe administration.

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