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ORIGINAL ARTICLE

Bone marrow examination: a prospective survey on factors associated with pain

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Abstract Bone marrow examination (BME) represents an essential tool for diagnosis and monitoring of haematological disorders. It remains associated with morbidity and discomfort; repeat examinations are frequent. We made a single-centre prospective survey on 700 BME between July 2007 and July 2008 with a structured anonymized questionnaire for patients undergoing and physicians performing BME, which includes at our institution always aspiration and trephine. All procedures were performed according to institutionalised standard operating procedures; 412 patients' (58.9%) and 554 physicians' (79.1%) questionnaires were returned. Pain was the only procedure-related complication; no pain was reported in 149 (36.7%), bearable pain in 242 (59.6%) and unbearable pain in 15 (3.7%) cases. Premedication associated complications were reported by 110 (32.7%) of the 336 (65.4%) patients with premedication before BME. None of these were > WHO grade 2; most frequently reported were tiredness (76 patients; 22.6%), dizziness (19 patients; 5.7%) and nausea (15 patients; 4.5%). Only two factors were significantly associated with unbearable pain: "pain during prior BME" (seven of 94 with versus one of 198 without previous pain; $p<0.01$) and "information before BME" (four of 11 without versus 12 of 372 with adequate information before BME; $p<0.01$). Inadequate information at any time showed a trend towards an association with unbearable pain ($p=0.08$). No other factor was associated with unbearable pain. Good and adequate information appears to be the best way to reduce pain, even for a future BME.

Keywords Bone marrow examination · Complication · Pain · Information

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Introduction

Examination of the bone marrow is a central element for the diagnosis of haematological disorders and the management of these patients. Bone marrow aspirations and biopsies provide material for essential cytological, histological, cytogenetic, immunphenotyping or molecular analyses which cannot be obtained by other methods than bone marrow aspiration and trephine. In experienced hands, bone marrow examination (BME) is associated with low morbidity and mortality and is considered as an established method [1–4]. Still, some side effects are known and well described. The best investigated and most frequent complication is pain [5, 6]. It has been reported as moderate to severe in about one third of the patients in a recent study. In the same study, age of the patient and duration of the procedure were reported as key factors associated with more severe pain [6]. For many investigators, pain is considered as inacceptable for patients and at least some form of anaesthesia or premedication is suggested in order to reduce pain during BME. Multiple studies have shown good effects and low morbidity with the commonly used opioids and benzodiazepines [6–15].

Still for most patients, BME is considered as an unpleasant painful procedure with possible complications.

Many are afraid of BME, in most cases without any knowledge about the exact details of the diagnostic procedure. Studies so far have primarily focussed on incidence and severity of complications or side effects and on methods to prevent them. Little is known, in contrast, about factors associated with the subjective and objective experience of pain. This study was initiated in order to close this gap and to hopefully identify factors associated with pain experienced during BME through a prospective survey of patients and physicians. The primary endpoint was subjective unbearable pain.

Patients and methods

Study design

This was a prospective single centre survey-study at the University Hospital Basel. All patients undergoing a BME in the haematology in- or outpatient unit by a staff member of the haematology team between 1st of July 2007 and the 31st of July 2008 were included. All were given a questionnaire and asked, to return it the next day in a self addressed envelope. A separate questionnaire was given to the physician performing the BME with a self addressed envelope. Only the primary investigator (C.D.) was able to match the patients' and physicians' questionnaire by a numbering code.

The questionnaires for patients did include ten questions relating to their subjective experience of the procedure, on the information and assistance before, during and after the procedure, the experienced side effects and complications. The questionnaire for physicians did include 17 questions relating to objective observation of the procedure including disease, coagulation status, premedication, local anaesthesia, the numbers of necessary biopsies and aspirations, the observed side effects and complications and, the qualification of the staff member (junior, senior staff).

A total of 700 BME were included and 700 questionnaires distributed. Of these, 554 (79.1% return rate) questionnaires from physicians and 412 (58.9% return rate) questionnaires from patients were sent back. From 370 BME, corresponding questionnaires from both, patients and physicians were obtained.

The study was approved by the ethics committee of the cantons Basel-Stadt and Basel-Landschaft.

Patient population

The 527 returned questionnaires were answered by 128 (55.4%) male patients with a median age of 57.1 years, ranging from 20 to 95 years. Main disease indications for the BME were acute myeloid leukaemia with 96 (24.2%) patients, multiple myeloma with 60 (15.2%) patients and chronic myeloid leukaemia with 44 (11.1%) patients, reflecting primarily the population of a stem cell transplant unit. If a patient was undergoing a repeated BME in the study time, he was asked to fill in the questionnaire again. Thirty-eight patients were undergoing multiple BMEs in the study time. In 116 (22.0%) examinations, the investigated BME was the first one for this patient.

Bone marrow examination

All BME were performed according to a standard operating procedure (SOP) for bone marrow examinations of the University Hospital Basel. All junior staff members are trained for the procedure by a senior staff member. In every BME a physician and a specially trained nurse is present. The patient lies on a examination bed on his abdomen and the samples are taken standardly of the posterior crista iliaca. The aspirations are done with a 20-ml syringe with 2 ml Heparin and two 10-ml syringes each with 3 ml ethylenediaminetetraacetic acid (EDTA). While one EDTA syringe is filled with high pressure, the other two syringes are filled slowly with bone marrow. All in all 13 ml bone marrow is taken with the EDTA syringes and 15 ml bone marrow with the Heparin syringe. After the aspiration, the biopsy is taken and given in a container with SUSA. Afterwards the wound is coered sterile and compressed for half an hour in minimum. Immediately after the BME the biopsy and the aspiration are brought in the haematology labour for the asked investigations. During the study period, the haematology labour at the University Hospital of Basel performed 1,252 bone marrow samples. 376 (30.0%) were from another hospital. Liberal use of lidocain® 2% for local anaesthesia is part of the SOP. In our study, the median dose was 9.5 ml (range, 2–20 ml). Premedication with opioids or benzodiazepines were given liberally on patient's demand. Standard according to the SOP is a premedication with 25–50 mg Pethidinhydrochlorid (Pethidin®) i.v. and Midazolam (Dormicum®) 2-10 mg i.v. The side effects are discussed with every patient. In most cases, a compound of Midazolam i.v. (median, 3.36 mg; range, 1.0–12.0 mg) and Pethidinhydrochlorid i.v. (median, 30.69 mg; range, 10.0–75.0 mg) is used.

BME at the University Hospital of Basel includes always aspiration and trephine both are obtained during the same session with a *HS Hospital Service S.P.A, Trap System 11Gx100MM* bone marrow examination set.

Statistical analysis

The statistical analysis comparisons were made by the Omnibus-test and the Hosmer–Lemeshow test using the statistic software SPSS Ver. 12.

Because of low frequencies of some factors, exact significances (Fisher–Yates test in 2×2 tables or Freeman and Halton in 2×k tables) were calculated [16]. *P* values <0.05 were considered significant.

Results

Complications

The numbers of reported complications are summarised in Table 1. There were no bleeding or infectious complications observed or reported during this 13-month period of 554 BME. The only complication reported and directly related to the BME was pain; 406 patients mentioned pain in their response. Of these, no pain was reported by about one third; near 60% of the patients complained about mild to moderate pain, 15 patients (3.7%) about unbearable pain (Fig. 1).

More complications were reported as a consequence of premedication. A total of 336 (65.4%) patients had been given premedication before BME. One hundred ten of them (32.7%) reported at least one side effect; none was severe enough to require prolonged hospitalisation. The most frequent complications after the premedication were fatigue in 76 (22.6%) cases, dizziness in 19 (5.7%) cases and nausea in 15 (4.5%) cases. In contrast, 226 (67.3%) were satisfied and had no complications by their premedication.

Factors associated with pain

Questionnaires from physicians and patients did cover different topics; therefore, some factors associated with pain could only be looked at when both forms were returned (n=370). This explains the slightly divergent numbers for certain examinations.

For 82 patients (23.2%), the reported BME was their first examination; of these, 76 (92.7%) reported no to moderate pain. This number was slightly lower than those reported from patients with prior BME (265 patients; 97.4%; p=0.08).

Pain during a prior BME had an impact on pain during a subsequent examination. From 199 patients who had no pain in prior examinations, only one (0.5%) did report unbearable pain. In contrast, seven of 94 patients with pain during a prior BME reported unbearable pain during their subsequent BME (p<0.01).

Numbers of attempts to obtain sufficient material from the BME was not significantly associated with pain. This related to attempts for biopsy as well as for attempts to obtain adequate aspiration material. In 487 (90.9%) examinations, the biopsy was successful with one attempt; maximum was five attempts. In 475 (88.8%) examinations, the aspiration was successful with one attempt; maximum were six aspiration attempts. The proportion of patients with unbearable pain was 3.3% for the 320 patients with one attempt for a biopsy compared to the higher proportion of 5.9% for the 32 patients with repetitive BME attempts (p=0.62). This was comparable with the aspiration attempts, with unbearable pain for 3.1% of the 313 patients with one attempt for a biopsy compared to 7.1% of the 39 patients with repetitive aspiration attempts (p=0.18).

Age had no impact on severe pain. Four percent of the 75 patients below age 60 years complained about unbearable pain, 5.8% of the 103 patients older than 60 years (p=0.74).

Three hundred ten (89.9%) bone marrow examinations were done by a physician with more than ten BMEs experience; 298 (96.1%) patients had bearable pain like 34 (97.1%) which were examined by a physician with less than ten bone marrow examinations experience. The experience of the physician had no impact on pain (p=1.00).

Body weight had no impact on severe pain; 3.9% of the 279 patients with body weight within normal range complained about unbearable pain, compared with 2.4% of the 83 adipose (p=0.74).

Table 1 Complications in 554 bone marrow examinations

			Number of patients	Percent
Procedure-related complications	Pain	No	149	36.7
		Bearable	242	59.6
		Unbearable	15	3.7
	Serious bleeding	Yes	0	0
		No	554	100.0
	Infection	Yes	0	0
		No	554	100.0
Premedication-related complications		No	226	67.3
		Dizziness	19	5.7
		Nausea	15	4.5
		Fatigue	76	22.6

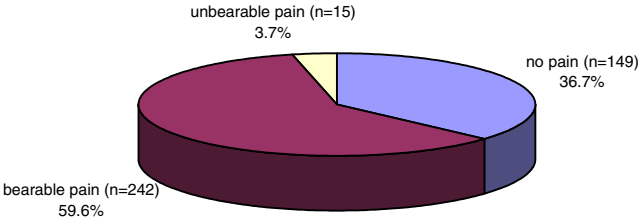

Fig. 1 Proportions of patients with pain during bone marrow examination

Quality of information was in general good. In their response, 393 (96.8%) reported to be satisfied with the information obtained, prior, during and after the BME. Of these, 13 patients complained about unbearable pain (3.3%); in contrast, two of 11 patients with unsatisfactory information complained about unbearable pain (18%; $p=0.08$).

In 405 examinations, the patients were satisfied with the assistance during the procedure and 14 (3.5%) patients complained about unbearable pain. Of the five patients who were not satisfied with assistance, only one suffered unbearable pain ($p=0.17$).

Two hundred seventy-eight (61.0%) patients had a prior premedication, primarily with Midazolam and Pethidinhydrochlorid in an adequate dose. Premedication did reduce pain but not prevent unbearable pain. The proportion of patients with unbearable pain was similar in patients with or without premedication (3.0% versus 2.8%; $p=0.56$). These results are summarised in Table 2.

Discussion

This prospective study, performed at the University Hospital of Basel, a tertiary centre for severe bone marrow disorders, identified pain in previous bone marrow examinations and inadequate information during the procedure as the main and significant factors associated with unbearable pain during bone marrow examination. The study confirmed the safety of the procedure with no complications associated with BME except pain, if indeed BME is performed in experienced hands with adequate training and according to standard operating procedures. Prolonged bleeding, infectious complications or prolonged pain, reported complications in the context of BME by others were not observed [1–4]. The only complications besides

Table 2 Factors associated with unbearable pain during BME

Factors examined		Bearable pain	Unbearable pain	*P* value
Prior bone marrow examination	Yes	265	7	0.085
	No	76	6	
Pain during prior examination	Yes	94	7	0.002[a]
	No	198	1	
Number of attempts for biopsy	1	320	11	0,620
	>1	32	2	
Numbers of attempts for aspiration	1	313	10	0.179
	>1	39	3	
Age of patient	1990–1950	72	3	0.736
	1950–1910	97	6	
Physicians experience	1–10	34	1	1.000
	>10	298	12	
Adipositas	Yes	81	2	0.740
	No	268	11	
Quality of information overall[b]	Satisfactory	380	13	0.079
	Unsatisfactory	11	2	
Quality of information before examination[b]	Satisfactory	372	11	0.002[a]
	Unsatisfactory	12	4	
Quality of assistance[c]	Satisfactory	391	14	0.171
	Unsatisfactory	4	1	
Premedication	Yes	268	10	0.560
	No	173	5	

Numbers refer to patients reporting pain in association with the specific factors. Hence, numbers do not add up to the same numbers for all factors alike

[a] Identifies significant factor

[b] "Unsatisfactory" refers to patients, who were unhappy with the information either before, during or after the examination

[c] "Unsatisfactory" refers to patients, who were unhappy with the assistance either before, during or after the examination.

pain, fatigue, dizziness and nausea, were reported as secondary to the premedication.

The incidence of 3.7% severe pain, reported on a subjective scale by the patients as unbearable, was low compared with reports from the literature where, in a recent survey from 2003, 15.9% of the patients complained about severe pain [6]. This difference could be due to the study design, the standardised approach by using a SOP or, by different cut-offs for unbearable pain. Still, 3.7% of patients with unbearable pain could be considered as too high and as an argument for standardised routine application of premedication. In contrast to the literature [6–15], we did not find a significant correlation between the use of premedication and serious pain; a similar proportion of patients with and without premedication complained about unbearable pain (p=0.56). These results differ with the observation of Vanhelleputte et al. who showed, that patients in the Tramadol group had significantly less pain during bone marrow aspiration then patients given placebo (VAS 16.5 versus VAS 28.8; p=0,003) [6]. An explanation could be that Vanhelleputte did look at the mean VAS reports only, not at the proportion of patients with "unbearable" pain. Even though most reports of randomised controlled trials report a reduction of pain with premedication, our results are compatible with other observations. Wolanskyj et al. did not see a significant pain reduction by Lorazepam and Morphin in their study in 2000 (p=0.21) [7]. Giannoutsos et al. showed in a retrospective study in 2004, that 76 from 112 patients did choose not to have a premedication before BME and that 74 of this 76 were happy with their decision [8]. The reported side effects of premedication and its morbidity and mortality in general are very low. Reduction of pain has to be balanced by the patient and the treating physician with the potential side effects, such as prolonged nausea, fatigue and dizziness, which might be more important in the outpatient clinic, where patients might need to drive back home or have to stay longer.

The key findings of our study were the factors identified with an association to severe pain. Neither age, sex, body mass index, premedication, number of attempts, nor experience of the examining physician or quality of assistance during BME were found to be significantly associated. These observations are in part in line with previous reports, except the premedication, experience of the physician and even though age was found important in one study, while it seems to play a minor role in another study [5, 6]. The main findings were pain during a prior BME and inadequate information. The factor "good information" showed a trend when analysed as overall factor. It was found significant when the information before BME was considered separately with significantly more serious pain in patients who were unhappy with their information prior the BME (p<0.01). These findings can easily be explained. Well-informed patients can arrange a mental strategy and have less often serious pain. Patients with serious pain generally had a worse image about the examination and concerning the physician. Patients with severe pain might no longer remember the quality of the information. Probably, serious pain might reflect a marker for a physician, who is also not that careful in giving for example the local anaesthesia. This might specifically relate to the first examination in order not to traumatise the patient for future examinations. This fits with the report from Park et al. who showed in 2008 that patients, who had Lorazepam before the examination, were significant more often ready to accept a future BME [9].

What are the consequences of this report? The data clearly show the big influence of good information by the physician to reduce pain during invasive examination. It is probable that these results apply for all sorts of invasive examinations, not just bone marrow examinations. This fact is often underestimated in clinical daily routine but could be an effective simple way to reduce pain during examinations. The data as well suggest, in line with the literature, that advantages and disadvantages of premedication should be discussed with the patients and that the approach should integrate patients' preferences.

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