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Moral Distress: Its Manifestations in Healthy Donors during Peripheral Blood Hematopoietic Stem Cell Harvesting

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A B S T R A C T

Hematopoietic stem cell donors (HSCDs) may have ambivalent feelings about donation. These feelings are related to moral obligation to help a sick relative and/or fear about the donation procedure. This ambivalence can produce moral distress (MD) and anxiety, which are usually unnoticed by the treating physician. The aim of this study was to evaluate the incidence of MD and anxiety in a group of related HSCDs for allogeneic transplantation. In this prospective observational study, to assess MD and anxiety, we applied 3 self-answered questionnaires—a questionnaire developed to assess MD (MDQ), State Trait Anxiety Index (STAI), and Edmonton Symptom Assessment System (ESAS)—before, during, and after hematopoietic stem cell donation. A total of 60 consecutive related HSCDs with a mean age of 38.2 years were included. Thirty-six were male. Hematopoietic stem cell collections were done by apheresis, performed as an outpatient process in all cases. The incidence of MD during the donation process was 56%. The proportion of HSCDs with moderate to high state anxiety decreased significantly from before donation (63%) to after donation (30%). Higher scores for MD correlated with higher scores on the STAI questionnaire ($r = 0.448$; $P < .005$). Thirty-seven donors (62%) had at least 1 physical symptom even before the stem cell mobilization process started, mainly anxiety (33%), difficulty sleeping (33%), and fatigue (30%). The number of symptomatic donors increased during donation (100%) and decreased after the procedure (80%). We conclude that MD and anxiety symptoms experienced by HSCDs are very common and can be explained by mixed feelings about the donation process. Providing comprehensive psychological support before starting the donation process and guaranteeing respect for the donor's autonomy are needed to decrease the negative impact of the donation experience.

INTRODUCTION

In the 1980s, the number of allogeneic hematopoietic stem cell transplantations (allo-HSCTs) performed was low; however, by the end of the 1990s, a sustained increase was observed. In 2016, 8539 cases of allo-HSCT were reported by the Center for International Blood and Marrow Transplant Research (CIBMTR) [1]. Many changes have occurred for the benefit of patients undergoing allo-HSCT, including better antibiotics, antifungals, and immunosuppressants; however, there have been few changes in the area of hematopoietic stem cell donors (HSCDs) during this period. Owing to the severity of the patients' illness, donors are generally given less attention than patients.

When HSCs are obtained from peripheral blood by apheresis, many donors experience physical symptoms [2]. Moreover, donors frequently suffer from anguish and feelings that are unnoticed by the treating physician and often their relatives as well. The origin of this discomfort is multifactorial, including fear of pain, fear of the procedure or of the side effects of the growth factor, feeling responsible for the success of the transplantation, family pressure, and other factors. [3,4]. Moral distress (MD) is a concept that has been investigated in health care workers, mainly in nurses and physicians [5]; however, HSCDs also may have ambivalence about the donation. A donor may be aware of a moral obligation to help a family member, but fear of

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the procedure or an adverse family environment can result in mixed feelings, including anxiety and MD.

MD manifests when the person knows how to act according to what is morally correct but for some reason does not want to or cannot do it, giving rise to physical, mental, and spiritual consequences [6]. Physical and psychological manifestations of MD include anger, frustration, shame, sleeplessness, anguish, sorrow, anxiety, sweating, headaches, and gastrointestinal discomfort [5,7,8]. The origin of anxiety and MD in HSCDs can be related to the fear of pain, fear of the unknown, or the presence of family conflicts. Because the MD concept has been little studied in the field of HSC donation, the present study was conducted with the aim of evaluating its incidence and observing its relationship with the presence of anxiety in a group of related donors for allo-HSCT.

METHODS

In this prospective observational study, a survey was conducted of related HSCDs at 3 different times during the HSC donation process. The study was carried out at the Hematology Service of the University Hospital of the Universidad Autónoma de Nuevo León from April 2014 to January 2017. The protocol was approved by the university's Institutional Ethics Review Committee (HE14-004). HSCD eligibility criteria included age >15 years and no previous HSC donation. Donors with active psychiatric illness who were receiving treatment with antidepressant medications or who could not answer the questionnaire for some reason (eg, insufficient Spanish language skills) were excluded.

The donor selection process begins when the patient or their parents ask a relative whether he or she agrees to be the donor. If the potential donor agrees, then the attending physician provides information, obtains signed informed consent, and requests HLA typing. If the donor and recipient are nonmatched, the process is repeated with another family member until a matched-HLA donor is found. In the case of underage donors, in addition to the signed consent from their parents, the donor's assent is obtained.

In the present study, all HSCDs received information about the donation procedure and provided written informed consent for cell donation. Physicians responded to the donors' questions and then invited them to participate in the study. Donors (or their parents if the donor was a minor) who agreed to participate signed an informed consent form in accordance with the Declaration of Helsinki before the first questionnaire was delivered. The assent of minors was taken into consideration before signing by their parents.

Measuring Instruments

Participants were asked to complete 3 written self-answered questionnaires—a questionnaire to assess MD (MDQ), the State-Trait Anxiety Index (STAI) questionnaire, and the Edmonton Symptom Assessment System (ESAS) questionnaire—at 3 timepoints during the donation process: before initiating stem cell mobilization, before the apheresis procedure, and at 24 hours after the donation.

Because there is no validated instrument for measuring MD in HSCDs, a, the MDQ was developed containing questions that explore symptoms of MD, coercion by family or physicians to donate, and the donor's experiences during the donation process. The MDQ consisted of 20 items with responses rated on a 5-point Likert scale with the following options: in full agreement, in agreement, neither in agreement nor in disagreement, in disagreement, and in total disagreement, with a maximum possible total of 100 points. The MDQ was validated by 4 experts in HSCT and subsequently applied to 15 HSCDs to evaluate the homogeneity of the items. Interrater agreement according to the κ coefficient was 0.80. Donors with higher scores were arbitrarily considered to have higher MD. In addition, MD was considered significant when the donor's score exceeded the group's mean score.

Anxiety was assessed using a Spanish version of the STAI questionnaire [9]. The STAI questionnaire consists of 20 items for assessing "state anxiety" and 20 items for assessing "trait anxiety," with a raw score of 20 to 60 points for each scale. The state anxiety scale evaluates the current state of anxiety associated with a special situation, measuring subjective feelings of apprehension, tension, nervousness, worry, and activation of the autonomic nervous system, whereas the trait anxiety scale evaluates proneness to anxiety [9,10]. The level of anxiety was determined according to the percentile rank obtained using the raw score of each questionnaire and was classified as low anxiety (1st-23th percentile), moderate anxiety (25th-75th percentile) and high anxiety (77th-99th percentile) [9,11].

The ESAS questionnaire was used for distress screening in cancer patients in a previous study [12]. This questionnaire consists of a self-reported scale including 10 common symptoms in patients with cancer: pain, fatigue, nausea, depression, anxiety, drowsiness, appetite, well-being, shortness of breath, and sleepiness. The ESAS has been validated for use in the Spanish language and has been used for symptom screening in disciplines other than cancer or palliative care [13,14]. According to the score for each symptom assigned by the donor, the symptom can be classified as disabling or not disabling. An individual symptom score >7 was considered disabling [15].

In addition, the perceived quality of the family relationship between the donor and the recipient was investigated with questions asking about the family relationships with the transplant recipient, whether he donation process had improved or worsened their family relationship, and whether they would donate cells again.

HSC Mobilization and Collection

Peripheral blood was the HSC source, and collection by apheresis was performed as an outpatient process in all cases. HSC mobilization was done using granulocyte colony-stimulating factor (G-CSF) at a dose of 10 μg/kg body weight s.c. for 4 consecutive days starting on day 1 [16]. Before delivery of the first dose of G-CSF on day 1, donors completed the first 3 questionnaires (MDQ 1, ESAS 1, and STAI 1). On day 5, apheresis was performed, processing 4 donor blood volumes to obtain $\geq 2 \times 10^6$ $CD34^+$ HSCs/kg of recipient weight using Spectra Optia apheresis system (Terumo BCT, Lakewood, CO) or an Amicus separator system (Fresenius Kabi, Bad Homburg, Germany). Before apheresis collection, donors completed the second set of questionnaires (MDQ 2, ESAS 2, and STAI 2). The next day, the donor completed the third and last set of questionnaires (MDQ 3, ESAS 3, and STAI 3) of the study.

Statistical Analysis

Quantitative and qualitative data were collected. Descriptive statistics were used to analyze the demographic and social characteristics of the participants, obtaining central tendency and dispersion measures for the numerical variables, while for the categorical variables, frequency, proportion, and percentage for the categorical variables. Normality for all the numerical variables studied was tested using the Kolmogorov–Smirnov test with Lilliefors correction. In the inferential analysis, when the assumption of normality was

met, parametric methodologies, including Pearson's correlation coefficient and the Student *t* test, were used, and when the variable under study showed a non-normal distribution, nonparametric testing with the Spearman or Mann–Whitney *U* test was used. The validity of the MDQ was tested using the κ coefficient. Statistical analyses were performed using SPSS version 20 (IBM, Armonk, NY).

RESULTS

Sixty donors (36 males and 24 females) were included in this study. Four donors were minors: 1 age 15 years, 1 age 16 years, and 2 age 17 years. The characteristics of the participants are shown in Table 1.

The 60 transplant recipients included 32 males (53%) and 28 females (47%), with a mean age of 33 ± 17.7 years. The most frequent diagnosis was acute lymphoblastic leukemia in 25 patients (42%), followed by acute myeloblastic leukemia in 12 patients (20%), chronic granulocytic leukemia in 5 patients (8%), aplastic anemia in 5 patients (8%), myelodysplastic syndrome in 5 patients (8%), Hodgkin lymphoma in 4 patients (7%) patients, and non-Hodgkin lymphoma in 4 patients (7%).

MD

On the first MDQ, most donors mentioned that they volunteered themselves as donors (75%), and the main reason was to help their sick relative (98%). Although most donors felt happy to be chosen as a donor (95%), 28% mentioned that they were not given the opportunity to accept or refuse to donate. Some of the participants agreed to be the donor because they were the only sibling that was HLA-compatible with the recipients (49%) or because they felt they had no choice (12%). In addition, 10% of donors mentioned that they would have preferred another family member to be the donor (Table 2). On the first MDQ, the mean score obtained was 33 points (range, 5 to 60), and 33 donors (55%) had a score exceeding the group's mean score.

Table 1
Characteristics of Participants (N = 60)

Characteristic	Value
Sex, n (%)	
Male	36 (60)
Female	24 (40)
Race/ethnicity, n (%)	
White/Latino	60 (100)
Age, yr, mean (SD)	38.2 (13.6)
Marital status, n (%)	
Married	38 (63)
Single	18 (30)
Other	4 (7)
Relationship to recipient, n (%)	
Brother	27 (45)
Sister	12 (20)
Mother	11 (18)
Father	6 (10)
Son	3 (5)
Daughter	1 (2)
Religion, n (%)	
Catholics	47 (78)
Non-Catholic Christianity	8 (14)
No religion	5 (8)
Level of education, n (%)	
University	24 (40)
Master's degree	3 (5)
Technical degree	3 (5)
High school	11 (18)
Middle school	13 (22)
Elementary school	6 (10)

On the second MDQ, most donors (85%) felt good or happy because they were chosen as donors (90%) and because they had the opportunity to help their sick family member (93%). However, 6 donors (10%) mentioned feeling that they had no other choice, and 5 donors (8%) would have preferred another family member to have been the donor. Ten donors (17%) mentioned being afraid of physical harm from donating HSCs. On the second MDQ, the mean score obtained was 19 points (range, 0 to 50), and 34 donors (56%) had a score exceeding the group's mean score.

On the third MDQ, completed at 24 hours after the donation process, an increase was observed in the percentage of donors who mentioned that they felt good (92%) or happy to have been chosen as a donor (97%), whereas the percentage of donors who felt obligated to donate decreased from 12% on the first MDQ to 5% on the third MDQ. This is reflected in the items "I'm the donor because I have no other option" and "I wish that another person had been the donor." On the third MDQ, the mean score obtained was 16 points (range, 0 to 47), and 35 donors (58%) had a score exceeding the group's mean score. Analyzing the scores obtained on the 3 MDQs together demonstrated that 33 donors (56.6%) had significant MD.

No correlations were observed between the presence of MD and such donor characteristics as sex (0.161), education level (-0.248), occupation (-0.210), or marital status (-0.159).

Regarding the family relationship between the donor and recipient, 59 donors (98%) reported having a good family relationship with the recipient, 28 (48%) agreed that their HSC donation had improved their family relationship, and 56 (94%) stated that they would donate again if necessary. Only 3 donors (5%) indicated that the donation process had worsened their family relationship with the recipient and that they would not donate cells again if necessary.

Most of the donors (90%) indicated that they had received sufficient information from the treating physician, but donors noted other important sources of information as well, such as the patient (22%), other relatives (8%), and even the Internet (11%).

Anxiety

The majority of donors (63.3%) reported moderate to high state anxiety on the first STAI questionnaire. The frequency of moderate to high state anxiety progressively decreased in the second (48.2%) and the third STAI questionnaires (30%), while the frequency of moderate to high trait anxiety remained stable on the 3 STAI questionnaires (38%, 36%, and 30%, respectively) (Table 3). A higher score for anxiety in the donor correlated with a greater number of children (r = 0.336). In addition, a correlation between higher levels of anxiety and higher MD was observed between STAI 1 and MDQ 1 (r = 0.339; P = .024), between STAI 2 and MDQ 2 (r = 0.448, $P <$ .005), and between STAI 3 and MDQ 3 (r = 0.278; P = .013).

Physical Symptoms

Frequently, physical discomfort related to the donation of HSCs is attributed to the use of G-CSF; however, by analyzing the first ESAS questionnaire, we found that 37 donors (62%) already had at least 1 symptom before the use of G-CSF (Table 4). The 3 most frequent symptoms reported by donors

Table 2
First Moral Distress Questionnaire Applied before Performing any Procedure on the Donor

Option	Strongly disagree, n (%)	Disagree, n (%)	Neither agree nor disagree, n (%)	Agree, n (%)	Strongly agree, n (%)
The transplant recipient asked me to be the cell donor.	20 (33)	6 (10)	10 (17)	8 (13)	16 (27)
Another relative of mine asked me to be the donor.	35 (58)	11 (18)	9 (15)	2 (3)	3 (5)
The physician asked me to be the donor.	33 (55)	3 (5)	11 (18)	5 (8)	8 (13)
From the beginning, I offered to be the donor.	6 (10)	3 (5)	6 (10)	6 (10)	39 (65)
I feel pressured by family to be the donor.	54 (90)	5 (8)	1 (2)	0 (0)	0 (0)
I feel pressured by the physician to be the donor.	53 (88)	5 (8)	1 (2)	1 (2)	0 (0)
They gave me the opportunity to accept or refuse to be the cell donor.	14 (23)	3 (5)	12 (20)	11 (18)	20 (33)
The main reason why I decided to be a cell donor was to help my sick family member.	0 (0)	1 (2)	0 (0)	0 (0)	59 (98)
The main reason to be a cell donor is to please my family.	29 (48)	8 (13)	10 (17)	1 (2)	12 (20)
The main reason to be a cell donor is to be useful to others.	16 (27)	8 (13)	8 (13)	8 (13)	20 (33)
The main reason why I decided to become a cell donor is because I was the only one compatible with the patient.	13 (22)	8 (13)	10 (17)	7 (12)	22 (37)
I am happy to be the cell donor.	1 (2)	1 (2)	1 (2)	8 (13)	49 (82)
I feel nervous about being the cell donor.	20 (33)	9 (15)	5 (8)	16 (27)	10 (17)
I am the donor because I have no other option.	44 (73)	8 (13)	1 (2)	3 (5)	4 (7)
I am donating because it is a great opportunity to help my family member.	22 (37)	5 (8)	1 (2)	5 (8)	27 (45)
I wish that another person had been the donor (brother or sister).	33 (55)	10 (17)	11 (18)	2 (3)	4 (7)
I am afraid that something will happen to me because I am the cell donor.	35 (58)	10 (17)	4 (7)	6 (10)	5 (8)
I do not feel anything regarding being the cell donor.	21 (35)	11 (18)	16 (27)	5 (8)	7 (12)
In general, I feel good right now.	2 (3)	5 (8)	2 (3)	15 (25)	36 (60)
In general, I feel bad right now.	40 (67)	11 (18)	2 (3)	5 (8)	2 (3)

Table 3
Level of Anxiety According to the Percentile Rank Obtained Using the Raw Score of Each State-Trait Anxiety Index (STAI) Questionnaire

Anxiety Level	STAI 1 (N = 60), n (%)		STAI 2 (N = 60), n (%)		STAI 3 (N = 60), n (%)	
	State Anxiety	Trait Anxiety	State Anxiety	Trait Anxiety	State Anxiety	Trait Anxiety
Low (1st to 23th percentiles)	22 (36.6)	37 (61.6)	31 (51.5)	38 (63.3)	42 (70)	43 (71.6)
Moderate (25th to 75th percentiles)	32 (53.3)	22 (36.6)	25 (41.6)	20 (33.3)	16 (26.6)	16 (26.6)
High (77th to 99th percentiles)	6 (10.0)	1 (1.66)	4 (6.66)	2 (3.33)	2 (3.33)	1 (1.66)

Table 4
Number of Patients who Manifested Symptoms before Starting any Procedure (ESAS Questionnaire 1), Immediately before Donating Hematopoietic Cells (ESAS Questionnaire 2), and 24 Hours after Donating Hematopoietic Cells (ESAS Questionnaire 3)

Symptom	ESAS 1, Mean (SD)	ESAS 2, Mean (SD)	ESAS 3, Mean (SD)
Pain (bone)	1.07 (2.4)	3.67 (3.2)	2.37 (2.9)
Fatigue	1.47 (2.6)	2.97 (3.2)	2.0 (2.7)
Nausea	0.18 (0.8)	0.28 (1.1)	0.33 (1.4)
Depression	0.43 (1.4)	0.30 (1.2)	0.15 (0.65)
Anxiety	1.25 (2.1)	1.33 (2.2)	0.73 (1.9)
Drowsiness	1.42 (2.8)	2.2 (3.0)	1.10 (2.3)
Lack of appetite	1.67 (2.9)	2.9 (3.6)	2.05 (3.1)
Discomfort	1.03 (2.5)	2.88 (3.6)	2.33 (3.3)
Shortness of breath	0.48 (1.5)	0.78 (2.1)	0.27 (1.1)
Difficulty sleeping	1.50 (2.4)	2.78 (3.2)	0.97 (2.1)

before any intervention were anxiety (33%), difficulty sleeping (33%), and fatigue (30%). As expected, on the second ESAS questionnaire, after the donor received cell mobilization with G-CSF, a greater proportion of donors (100%) manifested at least 1 symptom. The 3 most frequent symptoms were bone pain (78%), fatigue (63%), and difficulty sleeping (55%). On the third ESAS questionnaire, completed at 24 hours after cell collection, all symptoms decreased in frequency and intensity, and 12 donors (20%) were asymptomatic. Table 5 presents the mean score obtained for each symptom, showing higher scores on the second ESAS questionnaire. The number of donors reporting at least 1 disabling symptom (ESAS >7) on the first,

Table 5
Mean Score Given to Each Symptom by the 60 Donors at 3 Different Times during the Hematopoietic Cell Donation Process, before Starting any Procedure (ESAS 1), Immediately before Donating Hematopoietic Cells (ESAS 2), and 24 Hours after Donating Hematopoietic Cells (ESAS 3)

Symptom	ESAS 1, n (%)	ESAS 2, n (%)	ESAS 3, n (%)
Pain (bone)	12 (20)	47 (78)	36 (60)
Fatigue	18 (30)	38 (63)	30 (50)
Nausea	3 (5)	7 (12)	4 (7)
Depression	6 (10)	5 (8)	3 (5)
Anxiety	20 (33)	21 (35)	11 (18)
Drowsiness	16 (27)	29 (48)	15 (25)
Lack of appetite	16 (27)	30 (50)	22 (36)
Discomfort	11 (18)	31 (52)	24 (40)
Shortness of breath	6 (10)	9 (15)	6 (10)
Difficulty sleeping	20 (33)	33 (55)	16 (26)

second, and third ESAS questionnaires was 16 (26.6%), 31 (51.6%), and 18 (30%), respectively.

DISCUSSION

MD, understood as the consequence of doing something owing to a sense of moral obligation even when against the person's own will, has been investigated mainly in health care professionals; however, this phenomenon is not limited to this group. In the field of HSC transplantation, MD is experienced by donors who want to do what they consider to be the right thing (donate) and feel obligated to do it, but fear the consequences of donation (eg, pain, G-CSF effects, transplant failure). The ambivalent feelings in the context of HSC donation have been explored in some previous studies [17-19].

Although short-term adverse effects of peripheral blood stem cell donation are infrequent (2%) and generally not serious, life-threatening donor complications have been described [20-22]. This can cause fear in the donor, manifesting as anguish, anxiety, and desire to not donate. In the present study, most donors (98%) reported feeling happy to be the donor and to help their sick family member (moral obligation); however, 17 (28%) felt that their family did not give them the opportunity to accept or refuse to be the donor, and thus they had no choice. This ambivalence could have been caused by a feeling of moral obligation to be the donor mixed with the fear of the unknown (the cell donation process), pain, or the long-term effects of donation. This was evidenced by the high number of donors (62%) who reported experiencing symptoms (eg, fatigue, anxiety, insomnia) before starting the stem cell mobilization process.

At our transplantation center, all potential donors received information and applied their right of autonomy to accept or reject being a donor; however, it is difficult for the physician to know how the family asked the participant to be the donor. Previous studies have described donors' feeling of being coerced by family or friends, and it has been observed that the donor can develop a feeling of abandonment by relatives, given that the transplant recipient is the sick person who requires more care [23-25]. In fact, on the first MDQ, 10% of donors mentioned that they would have preferred another family member to have been the donor; this percentage decreased to 6% on the third MDQ.

Previous studies have shown that MD can manifest with such symptoms as anxiety, sleeplessness, sweating, headaches, and gastrointestinal discomfort, as well as negative feelings such as anguish, anger, and frustration [5,7,26]. Through the MDQ, evaluating the donor's moral obligation against the present symptoms and his or her desire to not be a donor, we found that a high percentage (56.6%) of donors had MD. In addition, the MDQ scores decreased progressively over the 3 iterations, relating the presence of MD with the donation procedure and possibly a feeling of relief after going through this process.

Anxiety was one of the most frequent symptoms observed in this study, highest before starting the donation process and decreasing by 24 hours after donation (from 63% to 30%). This level of anxiety could be explained by the donor's fear of undergoing an unknown procedure. Similar data was reported by Münzenberg et al. [27]. In addition, we observed a higher score for anxiety in donors with higher score for MD. This was most evident in the STAI 2 questionnaire and the MDQ 2 ($r = 0.448$; $P < .005$).

Many HSCDs experience physical symptoms, such as myalgia (54%), headache (52%), malaise (49%), and bone pain, usually related to hematopoietic growth factors [2]. With the ESAS questionnaire, we found that 62% of the donors had symptoms before G-CSF administration, simply because they knew that they would be HSCDs. The frequency and intensity of symptoms were increased on the second questionnaire, probably related to the use of G-CSF, and decreased on the third questionnaire at 24 hours after donation, probably reflecting both relief from the moral and physical challenges of the donation and the reward of doing the morally right thing.

The presence of MD in a donor should be considered when there are indications of coercion for the donation, when the donor reports feeling that they have no other option, and when they present with such symptoms as anxiety, fear, lack of appetite, or insomnia even before starting the donation process. One limitation of this study is that manifestations of MD are subjective and their measurement is difficult, although it has already been analyzed in other areas. Another limitation of the study is the small number of pediatric donors, precluding generalization of the results to this group of donors. Strengths of the study include the prospective design and the correlation observed between the MDQ and the other 2 previously validated questionnaires used.

CONCLUSIONS

Our present results show that in the context of HSC donation, the presence of physical and psychological symptoms in the donor is related to feelings of ambivalence stemming from the moral obligation to help a sick family member and fear of the donation procedure. Providing comprehensive psychological support before starting the donation process and guaranteeing respect for the donor's autonomy are needed to decrease the negative impact of the donation experience on the donor's physical and mental well-being.

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