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Abstract 247

Information pamphlet given to relatives during the end-of-life decision
in the ICU:

An assessor-blinded, randomized controlled trial

Running head: Pamphlet and end-of-life decision

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Abstract

Background: Symptoms of post-traumatic stress disorder (PTSD) are common in family members of patients who have died in the intensive care unit (ICU).

Research question: Could a pamphlet describing the role of relatives in the end-of-life decision decrease their risk of developing PTSD-related symptoms?

Study design and Methods: In this assessor-blinded, randomized controlled trial, 90 relatives of adult patients for whom an end-of-life decision was anticipated were enrolled. Relatives were randomly assigned to receive, in addition to oral information, an information pamphlet explaining that the end-of-life decision is made by physicians (Group 1; n=45), or oral information alone (Group 2; n=45). PTSD-related symptoms were blindly assessed at 90 days after the patient's death using the Impact of Event Scale (IES; scores range from 0, indicating no symptoms, to 75, indicating severe symptoms). Anxiety and depression symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS) score (range 0–21; higher scores indicate worse symptoms).

Results: On day 90, the number of relatives with PTSD-related symptoms was significantly lower in Group 1 than in Group 2: 18/45 versus 33/45 ($P=0.001$). The risk ratio of having PTSD-related symptoms in Group 2 compared with Group 1 was 1.8 [95% confidence interval, 1.2 to 2.7]. The mean IES and HADS scores were significantly reduced in Group 1 compared with Group 2: 28 ± 10 versus 38 ± 14 ($P<0.001$) and 13 ± 5 versus 17 ± 8 ($P=0.023$), respectively.

Interpretation: An information pamphlet describing the relatives' role during end-of-life decisions significantly reduced their risk of developing PTSD-related symptoms.

Clinical Trial Registration: NCT02329418

Keywords: end-of-life; family; intensive care; pamphlet; stress disorders, post-traumatic; treatment, withdrawing; treatment, withholding

End of life in the intensive care unit (ICU) is a particularly stressful event for family members. Adequate communication, respect, and compassion shown to both the dying patient and their family are elements known to improve family satisfaction ^{1,2}. Meanwhile, the desire for close communication between the ICU medical team and relatives means that family members may be increasingly involved as surrogate decision-makers ³. Both family members and ICU staff are supportive of family participation in patient care as their participation may reduce the symptoms of anxiety and depression in family members ⁴. However, this increased participation may expose family members to the risk of psychological consequences, particularly following end-of-life procedures. Indeed, symptoms of post-traumatic stress disorder (PTSD) were found in 50% of family members of patients dying in the ICU, reaching 82% in family members who shared in end-of-life decisions ⁵. Major depressive disorder was found in 27% of next of kin who served as primary surrogate decision-makers before the death of their loved one in the ICU ⁶. Families of dying patients identified insufficient support for family as decision-makers as the most negative aspect of the ICU experience ⁷. In a systematic review including 40 studies, at least one third of surrogates experienced a negative emotional burden as the result of making treatment decisions ⁸.

In this context, a proactive communication strategy was found to be effective in reducing negative consequences on relatives of patients who were dying in the ICU ⁹. In this strategy, a 30-minute end-of-life conference was conducted according to specific guidelines and concluded with the delivery of a 15-page bereavement information leaflet. Although the leaflet detailed all aspects relating to the organization of care for patients at the end of life in the ICU and after their death, the role of relatives in the process of end-of-life decisions was not discussed. To address this point, we conducted a randomized, controlled study to evaluate the impact of a structured communication that included an information pamphlet describing the role of relatives and explaining that family members do not share responsibility for end-

of-life decisions according to the French Leonetti law enacted on April 22, 2005 ¹⁰. We hypothesized that specifying that point in a written document could decrease PTSD-related symptoms, along with symptoms of anxiety and depression, among relatives 90 days after the patient's death.

Methods

This assessor-blinded, randomized controlled trial was conducted between October 2014 and March 2018 in three ICUs of the Grenoble Alpes University Hospital: a multiple trauma ICU (19 beds), a cardiac surgery ICU (20 beds), and a neurosurgical ICU (13 beds). The study was approved on July 9, 2014 by the Institutional Review Board of Sud-Est II (Chairperson Pr. B Kassai-Koupai, Lyon, France) (Ref#2014-014-2) according to the French law ¹¹. For each patient, written informed consent was obtained from one relative designated by family members. The study was registered with clinicaltrials.gov, identifier NCT02329418.

* Participants

Consecutive relatives (or person of trust) of adult patients for whom a decision to withhold and withdraw life-sustaining therapies in the ICU was anticipated were approached by the in-charge physicians. Relatives were included if they were ≥ 18 years of age, selected by all other family members, gave his or her written informed consent to participate, and had sufficient French-language skills for follow-up telephone interviews. Relatives were not included if the patient stayed in the ICU for less than 48 hours, might be discharged alive from the ICU, or had no social security.

* Study intervention

The intervention tested was a structured communication with an information pamphlet given to relatives of patients in the ICU. The pamphlet presented: i) the objective of care management in the ICU; ii) a summary of the French Leonetti law of April 22, 2005 on end-of-life care; iii) the role of family members in reporting any prior information about the

patient's wishes while not having responsibility for the end-of-life decision; and iv) the modalities of palliative care during the end-of-life process. The information pamphlet was written by Dr. Robin, anesthetist and intensivist, and Dr. Baro, psychiatrist (Grenoble Alpes University Hospital) (see the **Supplementary Appendix** for the original French version of the leaflet and a translated version). The intervention group (Group 1) was given both the pamphlet and oral information related to the decision to withhold and withdraw therapies during the first meeting with the in-charge nurses and physicians. The control group (Group 2) received the usual oral information by one or two designated doctors in each site, including the content of the pamphlet, with no written support. In both groups, medical team received dedicated training prior to start the study, and subsequent meetings between family members and the medical team could be held on the family's request.

* Randomization

The relatives were randomized in a 1:1 ratio into two groups, stratified by ICU, using a secure web-based random number generator to select permuted blocks, with a block size of four, and sequentially numbered, opaque, sealed envelopes: Group 1 (with pamphlet) versus Group 2 (without pamphlet). Because participants allocated to Group 2 could be disappointed by not getting the pamphlet that could, in theory, alter their outcome, we used the Zelen's design for randomization^{12,13}: the randomization was performed before giving relatives informed consent forms that had been adapted for the allocated group.

* Outcomes

Primary and secondary outcomes were measured at 90 days after the patient's death during a telephone interview with his or her relative conducted by two trained medical outcome assessors. The assessors were not involved in the care management of the patient, and they were blinded to the allocated group. To promote adherence to the interview, each relative received the IES and HADS questionnaires a few days before the scheduled date.

The primary outcome was the proportion of relatives with PTSD symptoms as assessed of the Impact of Event Scale (IES) questionnaire ¹⁴. This scale had good psychometric properties after a range of traumatic events ¹⁵. IES scores range from 0 (no PTSD) to 75 (severe PTSD). Significant PTSD symptoms were defined as an IES score greater than 30 ⁵.

Secondary outcomes included anxiety and depression symptoms assessed using the Hospital Anxiety and Depression Scale (HADS) score (range 0–21 for each subscale; higher scores indicate worse symptoms) ¹⁶. Significant anxiety and depression symptoms were defined as a score greater than 8 for both the anxiety and depression subscales. The number of relatives who asked for a psychiatrist/psychologist, and the duration and modalities of end-of-life processes were also reported.

* Data sources/measurements

In each participating ICU, data were collected and entered into the web-based electronic case report form (eCRF) (LimeSurvey 2.0 GmbH, Hamburg, Germany) by trial or clinical monitors (clinical research associates). Data included the patient's characteristics prior to ICU admission, the relative's characteristics, ICU stay details, and modalities of the withhold and withdraw process.

* Statistical analysis

According to the available literature^{5,9}, the proportion of relatives of patients dying in the ICU expected to develop PTSD-related symptoms would be at least 70% in the control group. Assuming a two-sided alpha risk of 0.05 and a power of 90%, the enrolment of two equally sized groups (41 patients per group) could detect a 50% reduction in relative risk of PTSD at 90 days. To account for relatives lost to follow-up and patients surviving after the decision to withhold and withdraw therapies, a total of 90 patients was requested for the study. No interim analysis was performed. In case of missing data concerning the primary outcome, a logistic regression was applied from the characteristics of the relative and the duration of the respective patient's ICU stay. If the regression coefficient was >0.5 , the subject was imputed to have PTSD, otherwise he or she did not have PTSD.

Continuous data were expressed as mean (SD) or median (25–75th centiles), and categorical data were expressed as numbers and percentages with their 95% confidence interval (95% CI). Comparisons were conducted on an intention-to-treat basis using the Chi-square test, Student's t-test, or Mann–Whitney *U*-test. Primary outcome was shown with risk ratio, risk difference, and number needed to treat. The Cochran–Mantel–Haenszel test was used to search for associations between ICU sites and primary outcome. Statistical significance was declared when $P \leq 0.05$ (Stata 15.1, Stata Corporation, College Station, TX, USA).

Results

Of the 94 relatives who were randomly assigned to a study group, 90 were analyzed (**Fig.1**). There were three relatives of patients who survived after the end-of-life decision and one relative who subsequently withdrew consent. There was no crossover from one group to the other. In Group 1, there were five missing data points for the primary outcome: two relatives who were lost to follow-up and three relatives who refused to take part in the interview at 90 days without prior withdrawal of consent. According to the imputation procedure for missing data, three relatives were considered to have PTSD and two not to have PTSD. Baseline characteristics of patients and their relatives were similar between the two groups (**Table 1**). At the time of the end-of-life decision, 80 patients (89%) were mechanically ventilated and 55 patients (61%) were deeply sedated. Nurses and physicians in all three ICUs held regular meetings with relatives on end-of-life care. Before the study, no ICU provided relatives with written information about end-of-life decisions.

The number of relatives with IES scores greater than 30 was 18 of 45 (40%) [95% CI, 26% to 56%] in Group 1 versus 33 of 45 (73%) [95% CI, 58% to 85%] in Group 2 ($P=0.001$). There was no interaction between the proportion of relatives with PTSD and the ICU site (Cochran–Mantel–Haenszel test; $P=0.79$). The risk ratio of having an IES score greater than 30 in Group 2 compared with Group 1 was 1.8 [95% CI, 1.2 to 2.7], the risk difference was 0.33 [95% CI, 0.14 to 0.53], and the number needed to treat was 3. Similar results were found without imputation of the five missing data points (**Table 2**).

Regarding the secondary outcomes, the mean IES and HADS scores at 90 days were significantly reduced in Group 1 compared with Group 2 (**Table 3**). Group 2 included more relatives with symptoms of depression and presented a higher average anxiety score than did Group 1. However, the number of relatives who were seen by a psychiatrist or psychologist

within the 90 days was similar between the two groups (**Table 3**). The duration of the end-of-life process – that is, the time from decision to death – was comparable between the two groups of patients: 1.0 day (0.0–2.0) in Group 1 versus 1.0 day (0.0–2.0) in Group 2 (P=0.4). The modalities of the end-of-life process were comparable between the three sites: withdrawing (n=55/90 patients), withholding (n=35/90 patients), written notification of the decision in the medical file (n=89/90 patients), peer review procedure (n=90/90 patients), and involvement of an external third party (n=50/90 patients). There was no difference in these modalities between Group 1 and Group 2. The end-of-life procedure used did not significantly affect the proportion of relatives with IES scores greater than 30: withholding (n=35 relatives) 46% [95% CI, 29% to 63%] versus withdrawing (n=55 relatives) 64% [95% CI, 50% to 76%] (P=0.09).

Discussion

This randomized clinical trial of relatives of patients dying in the ICU showed that a structured, written communication with an information pamphlet detailing the role of relatives in decisions to withdraw and withhold life-sustaining therapies significantly reduced the risk of developing PTSD-related symptoms by 90 days after the patient's death. Specifically, written support presenting the legal framework of French law on the end-of-life process and detailing the role of family members in end-of-life decisions was associated with a reduction of this risk. In line with this finding was the positive impact of this written support on anxiety and depression scores. These results indicate that the written content of an information pamphlet plays a role in preventing the psychological consequences of end-of-life decisions among relatives.

The present study confirms that relatives of patients dying in the ICU are at risk of developing acute PTSD-related symptoms by 90 days after the patient's death, as detailed previously^{5,9}. PTSD is a syndrome lasting at least one month after a traumatic event and comprises three types of responses: unwanted recollection, strong avoidance of reminders of the trauma, and physiological hyperarousal, e.g. insomnia, difficulty concentrating, and irritability¹⁷. This disorder can develop after seeing a traumatic event, such as a loved one dying in the ICU. Numerous risk factors of acute stress disorder are present following the unexpected admission to the ICU of a patient at high risk of dying, such as the unfamiliar environment of the ICU for family members¹⁸, their being asked to assume the role of surrogate decision-maker¹⁹, and the complex communication related to the withdrawing and withholding procedure²⁰. More than half of family members have moderate-to-severe levels of traumatic stress symptoms as soon as 4 days after the patient's admission to the ICU¹⁸. For relatives of patients requiring end-of-life decisions, factors independently associated with the

risk of developing PTSD were receiving incomplete information and sharing responsibility for making end-of-life decisions ⁵. In the present study, we found no differences between the two groups of relatives regarding their characteristics at baseline (see Table 1).

The role of relatives as formal or informal surrogate decision-makers, while positive in situations where the patient is not dying, may have negative psychological consequences when it involves end-of-life decisions. Physicians may overestimate the extent to which stressed family members are able to make decisions based on understanding information given orally. Family members and ICU staff may differ in their perception of the quality of the discussion of the patient's end-of-life wishes ²¹. In addition, family members may experience doubt regarding whether they have made the right decisions if they have no experience as a surrogate or no prior dialogue with the patient about his or her wishes. These conditions could favor the development of feelings of guilt, leading to anxiety, depression, and complicated grief when relatives are given responsibility for making end-of-life decisions ²². The first and most frequently reported question from relatives involved in end-of-life decisions is "did I do right thing?" ²³. This experience of guilt and anxiety can continue for as long as 3.3 years after the patient's death ²⁴. On the other hand, knowledge of which treatment the patient would have wanted, at best with advance directives prepared by the patient, was significantly associated with subsequent reduced feelings of guilt among relatives ⁸.

In this context, the French Leonetti law enacted on April 22, 2005 introduced the notion of unreasonable persistence of treatments (i.e. medical futility) and delineated the framework for decisions about withholding or withdrawing life-sustaining therapies to be made within medical collegiality ¹⁰. This law was updated on February 2016 to reinforce the importance of advance directives prepared by the patient, the role of the designated relative, and the possibility of using continuous and deep sedation following an end-of-life decision ²⁵. The notions of a designated relative (or person of trust) representing a patient's wishes and of

advance directives specifying the patient's treatment preferences have been introduced. Moreover, the Leonetti's law states that family members have no explicit role with respect to the law in end-of-life decisions made for their loved one. Our study provides evidence about the impact of written support with specific statements to reduce the risk of PTSD-related symptoms.

Our study has several limitations. First, the study was conducted in three sites of one French university hospital. There is a large variability worldwide regarding decisions to withdraw/withhold life-sustaining therapies²⁶. Whether the contents of this pamphlet can be used at other sites warrants further investigation. However, the feelings of guilt for end-of-life decisions have been widely identified^{8,9,22}. Second, we did not assess IES and HADS scores in relatives at the time of inclusion. Although the characteristics of relatives were comparable (see Table 1), a possible difference regarding their IES and HADS scores at baseline cannot be excluded. However, the randomization process should ensure the equal distribution of potential psychological problems across the two groups. Third, blinding of the allocated group during the interview was a critical issue. Although formal questionnaires were sent to each relative a few days before the scheduled date to prepare him or her for a formal interview, and although the assessor was blinded to the allocated group, we cannot exclude the possibility of interactions between assessors and family members that might have influenced the scoring. Fourth, findings of this study were based on the reading of the pamphlet by each relative in the intervention group (Group 1). Although the medical team was at the disposal of families to further discuss the terms of the pamphlet, this opportunity was rarely used. We did not assess with relatives the quality of the pamphlet reading, for example by evaluating the time spent reading the leaflet, degree of understanding, interactions with other family members, or which specific elements of the pamphlet relatives considered to be critical. Fifth, patients experiencing cardiac arrest made up the largest group of all

patients admitted to the ICU (n=27/90 patients). Although causes of admissions were equally allocated between the two groups, we did not assess the impact of the pamphlet relating to the cause of ICU admission. Sixth, we were unable to determine how many relatives had been screened for our study and thus the rate of eligibility.

In conclusion, the provision of an information pamphlet during end-of-life decisions was effective in decreasing PTSD-related symptoms and symptoms of anxiety and depression 90 days after the patient's death. A structured communication with a pamphlet detailing the role of relatives may play a positive role in preventing psychological consequences of this traumatic event.

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Figure Legend

Fig.1. Study flow diagram of randomization of patients' relatives

Take Home Point

Question: Could an information pamphlet decrease the risk of developing PTSD-related symptoms among relatives in the end-of-life decisions in the intensive care unit? Does the description of the role of relatives in this process play a preventive role?

Results: In this randomized clinical trial, a structured, written communication with an information pamphlet significantly reduced the risk of developing PTSD-related symptoms by 90 days after the patient's death along with reduced anxiety and depression scores.

Interpretation: The written content of an information pamphlet plays a role in preventing the psychological consequences of end-of-life decisions among relatives.

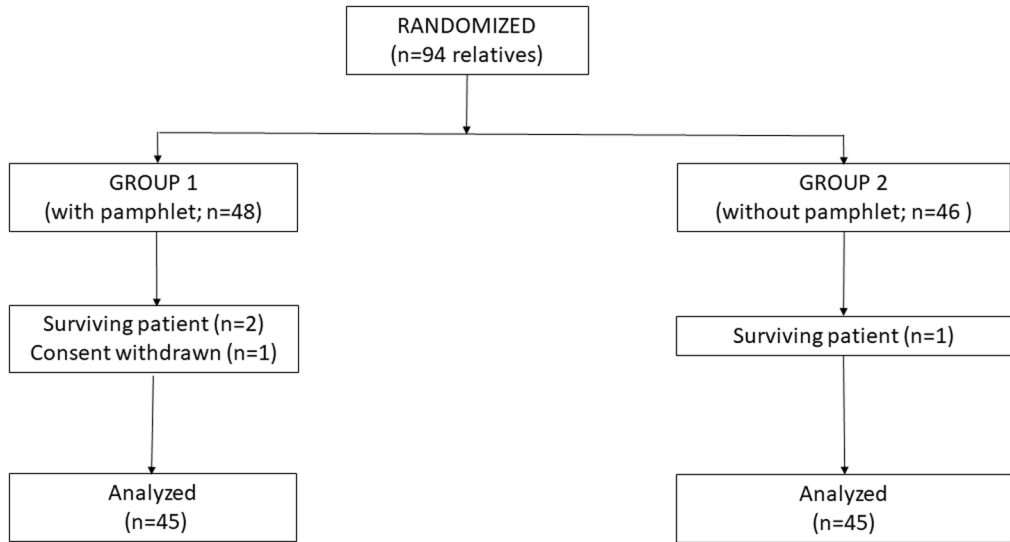


Table 1. Baseline characteristics of patients and their relatives according to the allocated group: Group 1 (with pamphlet) or Group 2 (without pamphlet). Data are expressed as median (25–75th centiles) or number (percentages).

	Group 1	Group 2	P value ^a
Characteristics of patients	(n=45)	(n=45)	
Age, years	69 (62–77)	71 (59–80)	0.8
Male, n (%)	28 (62)	29 (64)	1.0
SAPS II	59 (47–68)	61 (53–72)	0.4
History, n (%)			
Cardiovascular	17 (38)	16 (36)	1.0
Respiratory	4 (9)	5 (11)	1.0
Diabetes	9 (20)	10 (22)	1.0
Cancer	8 (18)	6 (13)	0.8
Other	15 (33)	12 (27)	0.6
Admission source, n (%)			0.09
Medicine	25 (56)	33 (73)	
Surgery	12 (27)	10 (22)	
Other	8 (18)	2 (4)	
Type of ICU, n (%)			1.0
Multiple trauma ICU	9 (20)	9 (20)	
Cardiac-ICU	25 (56)	27 (60)	
Neuro-ICU	11 (24)	9 (20)	
Cause of admission, n (%)			0.3
Cardiac arrest	13 (29)	14 (31)	
Cardiogenic shock	2 (4)	6 (13)	
Septic shock	4 (9)	4 (9)	
Acute respiratory failure	4 (9)	5 (11)	
Traumatic brain injury	3 (7)	2 (4)	
Intracerebral hematoma	7 (16)	6 (13)	
Post-operative	9 (20)	7 (16)	
Other	3 (7)	1 (2)	
Treatments at the time of end-of-life decision, n (%)			
Mechanical ventilation	40 (89)	40 (89)	1.0
Vasopressors	23 (51)	26 (58)	0.7

Renal replacement therapy	5 (11)	7 (16)	0.8
ECMO	3 (7)	5 (11)	0.7
Sedation	26 (58)	29 (64)	0.7
Time to end-of-life decision, days	5 (3–14)	10 (4–17)	0.3
Duration in the ICU, days	6 (4–15)	10 (5–18)	0.3
Characteristics of relatives	(n=45)	(n=45)	
Age, years	54 (47–65)	54 (47–66)	0.9
Male, n (%)	20 (44)	14 (31)	0.3
Relation to the patient, n (%)			1.0
Spouse	17 (38)	17 (38)	
Child	20 (44)	19 (42)	
Parent	1 (2)	2 (4)	
Other	7 (16)	7 (16)	
Known prior to the patient's admission ^b , n (%)	7/41 (17)	3/42 (7)	0.2

^a Fisher exact tests were applied for qualitative data; Wilcoxon / Mann -Whitney tests were applied for quantitative data.

^b There were 7 missing data.

ICU, intensive care unit; SAPS, Simplified Acute Physiology Score; ECMO, extracorporeal membrane oxygenation

Table 2. Proportion of relatives presenting with PTSD (i.e., an IES score greater than 30) according to the allocated group for relatives: Group 1 (with pamphlet) or Group 2 (without pamphlet). Results are shown with and without imputation of missing data, i.e, the two relatives who were lost to follow-up and the three relatives who refused to take part in the interview at 90 days (Group 1). Data are expressed as number (percentages).

	Group 1	Group 2	Risk ratio and risk difference	P value ^a
With imputation of missing data, n (%)	18 (40)	33 (73)	RR=1.8 (1.2–2.7) RD=0.33 (0.14–0.53) NNT=3	0.001
Without imputation, n (%)	15 (38) ^b	33 (73)	RR=2.0 (1.3–3.0) RD=0.36 (0.16–0.56) NNT=3	<0.001

^a Chi-square test

^b There are 5 missing data

IES, Impact of Event Scale; NNT, number needed to treat; PTSD, post-traumatic stress disorder; RD, risk difference; RR, risk ratio

Table 3. Secondary outcomes according to the allocated group for relatives: Group 1 (with pamphlet) or Group 2 (without pamphlet). Significant anxiety and depression symptoms were defined as a score greater than 8 on the anxiety and depression subscales. Data are expressed as mean (SD) or number (percentages) unless stated otherwise. The numbers of relatives are without imputation of missing data.

	Group 1 n=40	Group 2 n=45	P value
IES score, mean (SD)	28 (10)	38 (14)	<0.001
HADS score, mean (SD)	13 (5)	17 (8)	0.023
HADS anxiety subscale, mean (SD)	6 (3)	8 (5)	0.036
HADS depression subscale, mean (SD)	7 (3)	8 (5)	0.07
Individuals with anxiety symptoms, n (%)	10 (25)	20 (44)	0.06
Individuals with depression symptoms, n (%)	10 (25)	25 (56)	0.004
Individuals seen by a psychiatrist /psychologist, n (%)	11 (28)	13 (29)	0.9

HADS, Hospital Anxiety and Depression Scale; IES, Impact of Event Scale