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Informed consent for research in ICU obtained before ICU admission

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Abstract *Objective:* To analyze the procedure of the informed consent for ICU research obtained before ICU admission. *Design:* Prospective, open, observational study. *Setting:* 20-bed surgical ICU of a tertiary teaching university hospital and the ward before and after ICU. *Patients:* Patients, scheduled for elective cardiac surgery, who accepted to participate in a coagulation study. *Interventions:* Patients underwent the same informed consent procedure, including an oral presentation of the coagulation study and an informative leaflet the day before surgery on the ward. *Measurements and results:* Between January and August 2001, we included 38 patients; 36 survived ICU. Ten to 12 days after surgery, 8/36 (22%) patients did not know they had participated in a study, and 9/36 (25%) could not recall the study purpose and the related risk. Patients with incomplete recall stayed longer in ICU [median (range): 4 (3–6) vs 3 (1–5) days; $p = 0.004$]. None of these patients (0/9 vs 10/27; $p < 0.04$) had read the informative leaflet AND asked at least one question during the informed consent procedure. *Conclusions:* Even when the informed consent is obtained in the most optimal conditions for ICU research, its ethical value remains questionable. Indeed, a substantial number of patients were unaware of their study participation, or of the related purpose and risks. When the ICU stay is prolonged, we should at least repeatedly and actively (re)-inform patients about their study participation.

Introduction

Research is essential for the progress of medicine. Since the declaration of Helsinki, international guidelines require that informed consent be obtained from any human research subject for his enrollment in a clinical trial [1, 2]. The concept of informed consent includes three essential rules that must be respected. First, the patient has to receive adequate information about the study, with a complete disclosure of the risks and benefits from the investigator (disclosure) [3]. Second, the patient should be able to understand the implications of this research and the potential consequences of his decision to participate (decision-making capacity) [4]. Third, the patient should be able to decide freely to participate without any external pressure and to resign from the study at any time without any consequences on his care (voluntariness) [5]. In order to respect this third principle, the patient has to be aware of his study participation at any time. If these three criteria are not fulfilled, we may question the ethical value of the informed consent.

In recent years, especially after the publication of the European Directive, the informed consent for research in ICU has been repeatedly discussed [6, 7, 8]. Indeed, in ICU patients, the severity of illness, multiple treatments, the psychological burden and stressful environment may interfere with any of the three criteria and, therefore, may call into question the ethical value of the informed consent given. Many ICU patients may fail to understand the infor-

mation delivered [9, 10], or may be impaired in decision making [11, 12].

Obtaining informed consent before the patient's admission to ICU, whenever possible, may improve the procedure and increase respect of the patient's autonomy and liberty to accept or decline. Thus, the elective surgery with planned admission to ICU would be an ideal situation to obtain informed consent for research in ICU.

Our hypothesis was that, even in this potentially ideal situation, the ethical value of this informed consent may be questionable. In order to test this hypothesis, we sought to investigate whether patients would be able to mention having participated in a study and to recall the essential study components after inclusion. We further assessed the factors associated with the capacity to completely recall the study information.

Materials and methods

Patients

The investigation about informed consent was part of a study about coagulation in the surgical ICU after heart surgery. This study consisted in assessing a new coagulation management using a bedside analysis of activated prothrombin time. Patients scheduled for elective coronary artery bypass grafting or valvular surgery were eligible. Those who refused to participate or had exclusion criteria for the coagulation study were not considered for the present study. Incompetent or non-French-speaking patients, those with psychiatric disorders, senile dementia or other intellectual disabilities were not included. To give their consent to participate in the coagulation study, patients needed a Glasgow coma scale (GCS) of 15, and to be fully oriented and judged competent by the investigator.

Setting

The coagulation study was performed in a 20-bed general surgical ICU of a tertiary teaching, university-affiliated hospital, receiving 1,600 patients/year for a total of 6,000 hospital days/year and on the cardiovascular surgery ward.

The informed consent procedure

All patients underwent the same informed consent procedure, performed by the same investigator, on the ward the day before surgery. The information was given during a 20-min individual oral presentation, in accordance with a protocol. The investigator explained the study, insisting on two study components: the purpose and the risk for the patient. The defined keywords for the study purpose were "coagulation" and "coagulation management." The study risk was of being anti-coagulated according to the new coagulation-management strategy. We told the patient that, if he was in the study group, he would be treated according to the results of the new bedside analysis. The risk was minimal, because, if the result of the new bedside analysis seemed incoherent, his doctor could refer to the usual laboratory test.

The patient then received a one-page informative leaflet. At the end of this procedure, the investigator invited the patient to read the leaflet before signing the informed consent form and to ask the investigator any question the patient might have about the study. The investigator noted whether the patient asked any question and/or if he read the informative leaflet in his presence.

Because the information procedure was based on a protocol, and because of the inclusion criteria of the patients, the disclosure of the information and the patient decision-making capacity were assumed to be as optimal as possible in the ICU environment.

Data collection

Age, gender, educational status, history of daily alcohol intake, GCS and laboratory values (glycemia, creatinine, bilirubin) upon admission to the ward, as well as medication during the 24 h before surgery (sedatives, analgesics, other psychotropic drugs) were recorded.

Upon ICU admission, the type of cardiac surgery, the durations of extracorporeal circulation and of aortic cross clamping, and the Simplified Acute Physiological Score second version (SAPS II) [13] were noted. The doses of sedatives and analgesics used during the ICU stay, and the lengths of mechanical ventilation and ICU stay, were recorded.

Ten to 12 days after surgery, the same investigator assessed, during an interview, whether the patient could recall his study participation and the study components. For this interview, the patient had to present a Glasgow coma scale (GCS) of 15, to be fully oriented and judged competent by the investigator.

Patients who could report their participation in the coagulation study, the study purpose and the related imposed risk were assigned to the "complete recall" group. Patients lacking one or more components were assigned to the "incomplete recall" group.

Ethics issue

The coagulation study was approved by the ethics committee for human research of our institution, as was the patient informative leaflet and the consent form. A specific informed consent was not sought for the study about the informed consent itself.

Statistical analysis

For statistical analysis, StatView for Windows version 5.0.1 (SAS Institute, Cary, NC, USA) was used. Results of patients with complete recall or with incomplete recall were first compared separately with the two-tailed Fisher's exact test, the unpaired *t*-test or the Mann-Whitney U-test, as appropriate. All tests were two-tailed, and a *p* value less than 0.05 was considered significant. We further assessed the sensitivity, specificity, positive predictive value, and negative predictive value to predict the complete recall of the study for particular factors.

Results

Between January and August 2001, we included 38 patients. Two patients died during the ICU stay (Fig. 1). Consequently, we analyzed 36 patients who signed the informed consent and were alive at day 12 after surgery. Of the 36 patients, eight (22%) did not know they had participated in a study at all. Among the 28 patients who could report their study participation, 27 (75% of all patients) could recall the essential study components, i.e., the study purpose and the related risk (Fig. 1).

Patients with complete recall did not differ from patients with incomplete recall regarding their history and demographic characteristics (Table 1). At the time of the informed consent procedure, the laboratory values and data regarding the current medication did not differ between the two groups. Data regarding the cardiac surgery were similar in both groups. Data at ICU admission or during the ICU stay did not differ between the two groups, except for their length of ICU stay. Patients with complete recall stayed less time in ICU than patients with incomplete recall [median (range): 3 (1–5) vs 4 (3–6) days; $p = 0.004$]. The doses of morphine per day, according to patient weight, and use of fentanyl and benzodiazepines during the ICU stay were similar in the two groups (Table 1).

More patients with complete recall had "read the informative leaflet AND asked at least one question" during the informed consent procedure [10/27 (37%) vs 0/9 (0%); $p = 0.04$] (Table 2). The sensitivity, specificity, positive predictive value, and negative predictive value of reading the leaflet AND asking questions to detect patients with complete recall were 37%, 100%, 100% and 35%, respectively.

Discussion

As many as 22% of ICU patients who had consented to participate in a study were unable to recall their study participation, although they had given their informed consent before the surgery and outside the stressful ICU environment. This high rate is surprising. Indeed, patients before an elective surgery were shown to feel less under pressure and anxious and more likely to understand the informative leaflet than patients before an emergency surgery [14]. The most appropriate moment to obtain an informed consent for clinical research in ICU patients seemed to be before an elective ICU admission. Although the patients in our study met this rare condition, the

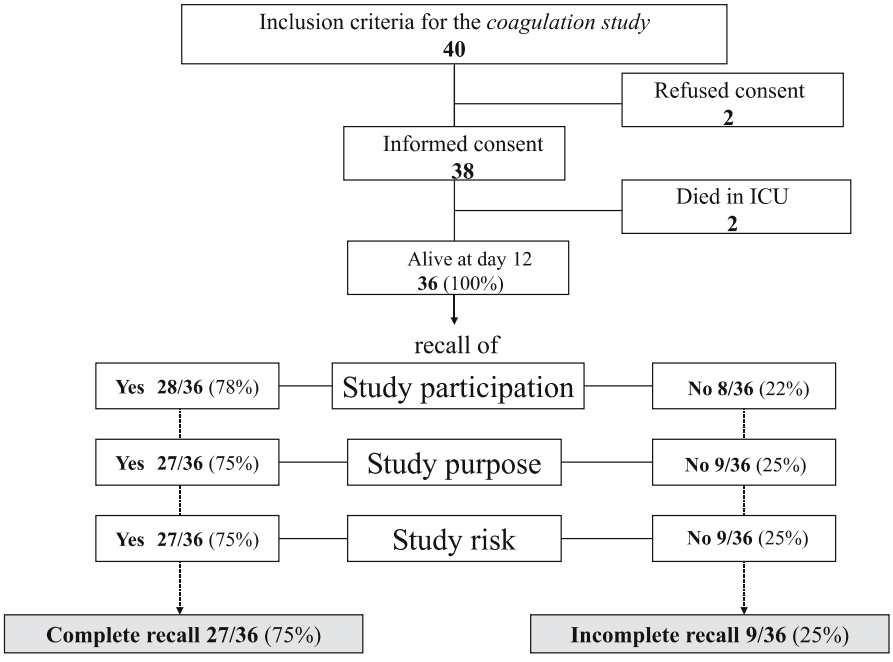

Fig. 1 Distribution of patients included in the coagulation study according to their outcome (survived ICU or not) and their ability to recall the study participation and the study components (purpose and risk)

Table 1 Patients demographic, surgical and ICU data according to complete vs incomplete recall of the study (*CABG* coronary artery bypass graft, *ICU* intensive care unit, *SAPS II* Simplified Acute Physiology Score)

	Complete recall of the study ($n = 27$)	Incomplete recall of the study ($n = 9$)	p value
Demographic and anamnestic data			
Age, years, mean ± SD	62 ± 10	68 ± 12	0.11 [a]
Male / female, *n*	24 / 3	6 / 3	0.15 [b]
Educational status:			
Up to junior high school, *n* (%)	6 (22)	4 (44.5)	0.14 [c]
Intermediate (High School), *n* (%)	14 (52)	4 (44.5)	-
University level or higher, *n* (%)	3 (11)	1 (11)	-
Not available, *n* (%)	4 (15)	0 (0)	-
Daily alcohol intake, *n* (%)	12 (44)	3 (33)	0.70 [b]
Surgery data			
CABG, *n* (%)	25 (93)	8 (89)	> 0.99 [b]
Valvular surgery, *n* (%)	2 (7)	1 (11)	> 0.99 [b]
Duration of extracorporeal circulation, min, mean ± SD	120 ± 32	133 ± 37	0.29 [a]
Duration of aortic cross clamping, minutes, mean ± SD	75 ± 26	88 ± 33	0.20 [a]
ICU data			
SAPS II, mean ± SD	23 ± 6	27 ± 9	0.10 [a]
Length of mechanical ventilation, (h) median (range)	9.5 (6–31.5)	9.5 (4–20)	0.21 [d]
Length of ICU stay, (days) median (range)	3 (1–5)	4 (3–6)	0.004 [d]
Morphine total dose, mg, mean ± SD	23 ± 13	32 ± 20	0.12 [a]
Morphine dose/ weight /day, mg/kg/24 h, mean ± SD	0.11 ± 0.61	0.11 ± 0.08	0.82 [a]
Administration of fentanyl, *n* (%)	1 (4)	0	> 0.99 [b]
Administration of midazolam, *n* (%)	6 (22)	3 (33)	0.66 [b]

Complete recall of the study: patients able to mention their study participation and study components
Incomplete recall of the study: patients not able to mention their study participation and study components
[a] Student's *t*-test, [b] Fisher's exact test, [c] X^2test, [d] Mann–Whitney *U*-test

Table 2 Data at the time of informed consent and the attitude of the patients

	Complete recall of the study ($n = 27$)	Incomplete recall of the study ($n = 9$)	p value
Data at the time of informed consent			
Glycemia, mmol/l, mean ± SD	7 ± 2	6 ± 2	0.32 [a]
Creatinine, μmol/l, mean ± SD	84 ± 17	87 ± 67	0.71 [a]
Bilirubin, mmol/l, mean ± SD	11 ± 4	11 ± 5	0.92 [a]
Medication last 24 h			
Benzodiazepines, *n* (%)	4 (15)	2 (22)	0.63 [b]
Morphine/ opioids, *n* (%)	0	0	> 0.99 [b]
"Attitude" of patients			
Read leaflet before consent, *n* (%)	16 (59)	3 (33)	0.26 [b]
Asked at least one question before consent, *n* (%)	17 (63)	3 (33)	0.14 [b]
Read AND asked, *n* (%)	10 (37)	0 (0)	0.04 [b]
Did not read nor ask, *n* (%)	4 (15)	3 (33)	0.33 [b]

Complete recall of the study: patients able to mention their study participation and study components
Incomplete recall of the study: patients not able to mention their study participation and study components
[a] Student's *t*-test, [b] Fisher's exact test

proportion of patients unable to recall their study participation was high compared with previous reports. In the HERO-2 consent sub-study, only a small minority of patients (6%) were unable to remember the consent process. This difference of rate of recall may be due to the different times elapsed between the consent process and the second interview of the studies [15]. In other studies including patients with acute myocardial infarction, the rates of lack of recall were similar to our rate. However, the informed-consent procedures were performed in

a more stressful and urgent condition than was our consent procedure [16, 17].

In our study, as many as 25% of patients had incomplete recall of the study components. Interestingly, almost all patients either were able to recall the entire study or did not recall the study at all. This finding led us to investigate the potential factors associated with the lack of recall. Indeed, it seems that the first step to improving the informed consent procedure would be to assess the factors associated with incomplete recall of the study and to act on them.

We found that age and educational status had no effect on recall of the study components, in contrast to previous studies where the rate of recall varied inversely with age and directly with educational level [18, 19]. The incomplete recall of the study was associated with a slightly longer ICU stay but not with the use of drugs. This finding suggests that, when a patient has a prolonged ICU stay, the investigators should periodically verify that the patient is aware of his participation in the study.

During this study, we found two relevant aspects that may help in increasing the ethical value of informed consent: interaction between the investigator and the patient, and the active participation of the patient during the consent procedure, by asking questions or by reading the informative leaflet. When the patient had read the informative leaflet AND asked at least one question, we found that he could always recall the complete information about the study, with a positive predictive value of 100%. This is in line with Flory's findings that showed that spending time to talk to the study participant appears to be the most effective way of improving his understanding [20].

Our study revives the debate about informed consent. Indeed, the coagulation study could be considered trivial regarding the risk for the patient, in the sense that the investigation was not invasive and the equipoise was obvious. In this case, we could question, as did Dreyfuss, whether informed consent is not more aimed at protecting the investigator than at protecting the patient [21]. Even if obtaining informed consent is, in most cases, an essential way to demonstrate respect for the patient's autonomy, it can lead, as suggested Truog, to some unnecessary and even silly practices [22].

In all cases, the ethics committee has to weigh, on one hand, the burden for the patient of the information obtained and, on the other hand, the protection offered to the patient by informed consent. This protection of autonomy is characterized by the possibility of refusing to participate in the study and to withdraw without penalty. This respect for potential and enrolled subjects is one of the seven requirements to make clinical research ethical [23]. In any case, informed consent is not sufficient for ethical clinical research.

There are some study limitations. First, we analyzed only a small number of patients, because this study was part of a parent study about coagulation management in ICU after cardiac surgery. This precluded the possibility of a multivariate analysis to define further whether some factors may predict independently the complete recall of the study 12 days after a major surgery. Second, we did not investigate the recall of the patients who refused to participate in the coagulation-management study. Since there was no consent in this case, we could not analyze the procedure. Third, we did not assess the patient's cognitive capacity. There is good evidence that, when tested, the cognitive capacity in ICU patients or sick patients is impaired [10, 11]. However, we performed our informed-consent procedure before admission to ICU. Our patients were undergoing an elective cardiac surgery, and they were not in an emergency situation, in contrast to other studies [9]. However, we cannot exclude that some cognitive impairment could have been totally overlooked in our patients by the investigator. Furthermore, spending more time with the patient to test his cognitive capacity and interacting with him much longer than for a "standard" informed consent procedure would have biased our results. For the same reason, we did not measure the patient's memory.

Conclusion

In order to respect the principle of autonomy for informed consent, the patient should be able to decide freely, without any external pressure, whether he or she agrees to continue to participate in the study at any time. Even in the present study, where the conditions of obtaining informed consent were considered ideal for ICU research, more than 20% of patients were not aware of their study participation. These findings suggest that we should encourage patients to ask questions and read the informative leaflet during the informed-consent procedure. In any case, especially when the ICU stay is prolonged, we should repeatedly and actively (re)-inform patients about their study participation, particularly if the study imposes some burden or risks over time. Whether such interventions may increase the ethical value of the informed consent in ICU research should be further investigated.

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