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SERIES IN INTENSIVE MEDICINE: METHODOLOGICAL UPDATE IN MEDICINA INTENSIVA

Ethics research in critically ill patients☆

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Abstract Research in critical care patients is an ethical obligation. The ethical conflicts of intensive care research arise from patient vulnerability, since during ICU admission these individuals sometimes lose all or part of their decision making capacity and autonomy. We therefore must dedicate effort to ensure that neither treatment (sedation or mechanical ventilation) nor the disease itself can affect the right to individual freedom of the participants in research, improving the conditions under which informed consent must be obtained. Fragility, understood as a decrease in the capacity to tolerate adverse effects derived from research must be taken into account in selecting the participants. Research should be relevant, not possible to carry out in non-critical patients, and *a priori* should offer potential benefits that outweigh the risks that must be known and assumable, based on principles of responsibility.

PALABRAS CLAVE
Bioética;
Investigación;
Paciente crítico;
Consentimiento informado

Ética de la investigación en el paciente crítico

Resumen La investigación en el enfermo crítico es una obligación ética. Los conflictos éticos de la investigación en medicina intensiva provienen de la vulnerabilidad del enfermo, que en ocasiones ha perdido o visto reducida su capacidad de decidir, perdiendo así su autonomía. Debemos por tanto aunar esfuerzos para que ni los tratamientos, como la sedación o la ventilación mecánica, ni la propia enfermedad cercenen el derecho a la libertad individual de los participantes en la investigación, favoreciendo las condiciones en que hemos de recabar el consentimiento informado. La fragilidad, entendida como el compromiso de la capacidad para tolerar efectos adversos derivados de la investigación, ha de ser tenida en cuenta en la selección de los participantes. Esta ha de ser pertinente, imposible de aplicar en pacientes menos graves y ofrecer *a priori* unos beneficios potenciales que superen unos riesgos que han de ser conocidos y asumibles en función de una ética de la responsabilidad.

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Introduction

''Preserve health and cure diseases'', this is how Claude Bernard opens his master piece *Introduction to the study of experimental medicine*,[1] this set the starting point of medical research by promoting the application of the experimental method in this field. In his introduction, he says that, without a doubt, experimenting is harder in medicine than in any other science because, although medicine is an applied science, it is different from other disciplines in that the individual is the action subject.

The right clinical practice and, by definition, the ethical clinical practice, only acquires social legitimacy if it has been proven through clinical research. This change of mindset led us to relegate the practice of medicine doctrine based on benefit intention, to mainly base it on presumptions, personal experiences, and subjective criteria.

The decision-making process in critically ill patients is a complex one, consequently the research conducted in this field is complex too. We know that at the ICU, each patient is unique since his physiopathology, response to treatment, and prognosis are conditioned by several determinant factors; we do not deal with certainties as it happens in other sciences like mathematics, but rather we move forward by conducting estimates on individual patients based on researches conducted on groups of similar patients.

Therefore, we should understand clinical research as an ethical obligation for the sake of the scientific advancement for our future generations. But we should also take into consideration here that it includes risks for the subjects of research being mandatory to protect these individuals with special dedication.

The origin of modern bioethics and the atrocities of clinical research with humans

The need for an ethical regulation of research practices in medicine has its origin in historical aspects that we will develop now but is also justified by the scientific advances; the acquisition of new knowledge; and society having a more active and autonomous role in the management of healthcare. In Bernard's work[1] it is established that it is immoral to experiment with a person if his participation can be dangerous, even though the result may be beneficial for the rest of the society. This argument that seems undisputable today and has been widely legislated was not the rule of law in the unfortunate researches conducted in the 20th century that gave birth to modern bioethics, based on the patient's autonomy, and respect for his dignity and individual rights. Recently, we have come to know that clinical trials that were being conducted in India have been interrupted[2] after reports of individual rights violations, which eventually leads to the need for legislating research in an effort to protect its participants.

History has provided us with several examples of exploitation of human beings in researches being conducted during WWII in Nazi Germany that were described as crimes against humanity in the Nuremberg Trials.[3] The Nuremberg Code Decalogue is a set of ethical principles that, for the very first time, states that it is mandatory to obtain the voluntary consent from the individual who is going to participate in any kind of clinical research. Unfortunately, cruelty in experimentation with human beings was not limited to Nazi Germany and it is very likely that other experiments conducted with humans that violated the person's individual rights have never been made public. In Japan, the experiments conducted by Unit 731 during the first half of the 20th century consisted, among others, of studying the progress of lesions of bombarded prisoners. Living human beings were dissected, frozen, and the effects of inoculating toxic agents, toxins, and the exposure to radiation was studied. In the United States, barely a few decades ago, the experiments conducted at Willowbrook State School from 1958 through 1960 were made public and consisted of inoculating mentally handicapped children with the virus of hepatitis in order to study the effectiveness of treatment. During the early decades of the 20th century, experiments were conducted in the Hebrew Orphan Asylum of New York with children where they would be deprived from vitamins in order to study rickets and scurvy. There is no doubt that these events and their repercussion in the public opinion contributed to the development of bioethics. But if one experimentation with human beings was really something else generating a social debate that set a turning point in the development of ethics in research was the study on syphilis conducted in Tuskegee, AL (USA) from 1930 through 1972; in this research the evolution of syphilis was observed without offering the study subjects any of the available treatments in an effort to see how was the natural progression of the disease; during the aforementioned period of time, researchers published over ten papers in scientific journals.[4–10] Consequently, back in the year 1974, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was created. Its recommendations on clinical research appear in the Belmont report[11] published in 1978. Today it is an inescapable reference in clinical research and one foundational documents of modern bioethics. The Belmont report sets the basic principles that guarantee morally appropriate researches (Table 1); if we apply these principles to research with critically ill patients, we could say that the principle of respect to people sees that all patients should be treated like autonomous people, capable of deliberating based on their personal goals, and therefore making consistent decisions; if their autonomy has been compromised, they should be entitled to protection. The autonomy of critically ill patients needs to be protected because these are especially vulnerable patients who do not have absolute control of the situation, are not empowered, or see their own capabilities weakened.[12]

The benefit principle should be understood as maximizing any potential benefits while reducing as much as possible all possible damages; this is an important trait in critically ill patients, since their vital risk *per se* puts into question that research should ever be conducted exposing them to risks when no benefit is expected. This makes this population of

Table 1 Belmont report: ethical principles of clinical research.

Principle of respect for people
Benefit principle
Principle of justice