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SERIES IN INTENSIVE MEDICINE: METHODOLOGICAL UPDATE IN MEDICINA INTENSIVA

Clinical research in critical care. Difficulties and perspectives☆

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Abstract In the field of Intensive Care Medicine, better survival rates have been the result of improved patient care, early detection of clinical deterioration, and prevention of iatrogenic complications, while research on new treatments has been followed by an overwhelming amount of disappointments. The origins of these fiascos are rooted in combined methodological problems – common to other disciplines, and in the particularities of critically ill patients. This paper discusses both aspects and suggests some options for the future.

PALABRAS CLAVE
Cuidados intensivos;
Ensayos clínicos;
Difusión de la innovación;
Medicina basada en la evidencia;
Medicina de precisión

Investigación en el enfermo crítico. Dificultades y perspectivas

Resumen En el ámbito de la medicina intensiva, el aumento de la supervivencia ha venido de la mano de la mejora de los cuidados, la detección precoz del deterioro clínico y la prevención de la iatrogenia, mientras que la investigación de nuevos tratamientos se ha seguido de una abrumadora serie de decepciones. Las raíces de estos fracasos hay que buscarlas en la conjunción de problemas metodológicos –comunes a otras disciplinas– y las particularidades de los pacientes críticos. En este artículo se exploran ambos aspectos y se sugieren algunas vías de progreso.

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Introduction

The ultimate goal of clinical research is to improve people's health. In order to achieve this goal, the studies on therapeutic and preventive interventions should be aimed at[1] obtaining a relevant goal for the clinical decision-making process[2]; be based on the appropriate methodology in order to minize random and systematic errors[3]; be exposed comprehensively and on the right format for the decision maker, and, eventually, wisely implemented toward patient care (Fig. 1).[4] Taking false stepts in any of these four (4) stages is a total waste of clinical research.[1–3]

According to available data, the volume of wasted clinical research is significant: between 30% and 50% of all randomized trials have important methodological mistakes[1,4]; the rate of non-replicated studies is above 50%[5–8]; most researches available cannot be used,[1,9–11] and, at one time or another, 40% of the patients receive therapies still not recognized as effective by the actual scientific standards.[2,12,13]

In the intensive care setting, important achievements have been made such as reducing the mortality rates associated with the acute respiratory distress syndrome (ARDS),[14] or sepsis.[15] However, these advances have been the result of improvements made in healthcare, early detection of clinical deterioration, and iatrogenia,[16,17] whereas a large number of randomized trials have turned out negative, or with an unexpected increase of mortality rates[18–23] (Table 1). This situation has made some influential researchers question the European regulations on clinical trials,[24] and even the suitability of randomized clinical trials in the intensive care setting.[17,25–28]

This first article from the series *Methodology of research in the critically ill patients*, discusses the deficiencies within the ''chain of research'' that may partly explain the fiascos resulting from the comparative effectiveness studies (CES) conducted in the intensive care setting; we will also be dealing with the particularities of clinical research in critically ill patients that may have contributed to these fiascos; finally, we will be taking a look at possible ways to improve the future of clinical research. Other methodological problems, big data research,[29] and ethical-legal aspects of clinical research will be discussed in future articles within this series.

Significant outcomes

Preclinical research is essential if we want to understand the physiopathology and development of effective therapies for the management of critically ill patients.[30] For instance, the confirmation of the acute pulmonary injury in ventilated animal models with high volumes[31] was successfully translated into the clinical practice and made up the foundation of the actual protective ventilation methods. However, up to 75–90% of all the results from preclinical research published in high profile scientific journals – usually of etiological and physiopathological type, are not reproducible[7] and, as of

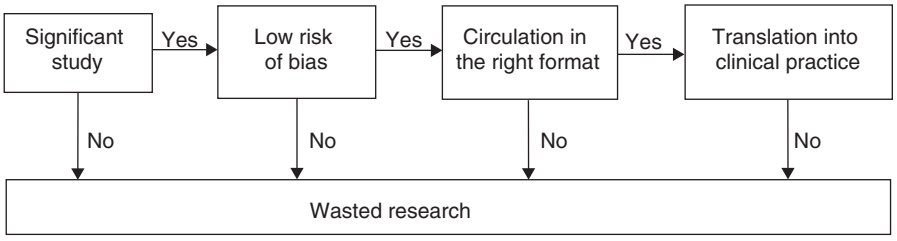

Figure 1 The chain of clinical research.

Table 1 Studies conducted in critically ill patients showing an increased mortality rate in the experimental group.

Study (year)	Intervention	Patients	Mortality RR
Hayes et al. (1994)[113]	Increased oxygen delivery	General critically ill patients	Hospital mortality RR 1.58 (95% CI 1.01, 2.56)
Takala et al. (1999)[19]	Growth hormone	General critically ill patients	Hospital mortality (multinational substudy) RR 2.4 (95% CI 1.6 to 3.5)
Finfer et al. (2009)[23]	Strict control of glycemia	General critically ill patients	Mortality at 90 days OR 1.14 (95% CI 1.02 to 1.28)
Gao Smith et al. (2012)[20]	β-2 antagonists	ARDS under mechanical ventilation	Mortality at 28 days RR 1.47 (95% CI 1.03 to 2.08)
Perner et al. (2012)[22]	Hydroxiethylal starch	Severe sepsis	Mortality at 90 days RR 1.17 (95% CI 1.01 to 1.36)
Ferguson et al. (2013)[21]	High frequency oscillatory ventilation	Moderate-serious ARDS	Hospital mortality RR 1.33 (95% CI 1.09 to 1.64)
Heyland et al. (2013)[73]	Glutamine	Critically ill patients with mechanical ventilation and multiple organ failure	Mortality at 28 days OR 1.28 (95% CI 1.0 to 1.64)

95% CI: 95 per cent confidence interval; OR: odds ratio; RR: relative risk; ARDS: acute respiratory distress syndrome.