Research in Neonatology: Improved Ratio of Risk to Benefit Through A Scientifically Based Alteration in Research Design*

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The ethical and moral issues encountered in the design of studies involving healthy adult subjects are relatively clearly defined. Voluntary and informed consent must be obtained from the subject indicating willingness to participate with a clear understanding of the purpose of the investigation, possible risks, and inconveniences which might occur. A full knowledge and acceptance of the inherent risk/benefit ratio are essential to informed consent.

Since very young children cannot consent to research, proxy informed consent must be obtained from their parents or legal guardians. When the subject to be studied is an infant, although the proxy consent cannot reflect the infant's actual opinion, it is nonetheless valid because parents are naturally and legally responsible for all decisions made on behalf of the dependent child. In addition to the parents there are a number of other advocates of the infant whose concurrence must be obtained before an investigation can be carried out. These advocates include the *researcher*, who is both advocate and adversary of the infant. To the extent he (or she) intends to impose risk on the infant he may be considered the adversary; because he must also demand maximum benefit to the infant, he is an advocate. Further, the investigator's *peers* in science and medicine—especially other pediatricians—are professionally committed to the role of advocate of the infant. Finally, the professional nurse responsible for its care has an intimate relationship to the helpless infant. These advocates, in addition to the *parents*, must all agree that there is an acceptable risk/benefit ratio before ethical research can be carried out.

In this paper we will discuss how we modified the design of a research proposal to meet the concerns and objections raised by all advocates of the infant. By scientifically approaching a solution to their objections, we significantly improved the risk/benefit ratio to the satisfaction of all advocates without loss of the original research objectives.

The Proposed Study

Research on adult volunteers has yielded a large body of knowledge of human physiology which has, in turn, been applied to the understanding of diseases. Previously, physicians caring for neonates were unaware of their fundamental physiologic differences and therefore treated sick infants as if they were simply small adults. They applied the principles of adult pathophysiology to understand the infant's diseases and administered proportionately smaller doses of medications. In-depth studies of normal neonates have generally met with considerable resistance. Such research is nontherapeutic, but, because it contributes to the advance of scientific knowledge and ability to help others who are sick, it should be ethically justifiable.

The pediatric subspecialty of neonatology has grown with the recognition that there are not only fundamental physiological differences between infants under one month of age and other children, but also differences within the group when comparing infants of one hour, one day, and one week of age. These differences are based primarily on the infant's gradual adaptation from fetal or dependent intrauterine life to extrauterine or relatively independent life. This adaptation requires a transitional stage of functional adaptation and maturation of major organs and systems. An example of this adaptation is the development of

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thermal homeostasis. Contrary to popular opinion, the fetus *in utero* is not warmed by the mother's body heat. Rather, the fetus' own metabolic processes generate heat which must be dissipated by the mother's body. Hypothermia occurs at birth when the infant is delivered into an environment where its moist skin and the significantly lower ambient temperature cause a rapid loss of body heat.[1-3] The chilled newly born infant is dried, wrapped in a blanket, and placed in a prewarmed incubator. Although the ambient air temperature in the incubator (approximately 32 C or 90 F) is below the body temperature of the infant, the narrow gradient minimizes heat loss from the infant to the environment. The result is that the body temperature is raised gradually to normal through endogenous heat production. Thus, in an incubator the infant must actually rewarm itself through energy-consuming processes. This rewarming usually requires between four and eight hours for moderately chilled full-term infants.[4] Although this early period of hypothermia does not appear to have an adverse effect on the normal infant it poses considerable stress on the sick neonate who, owing to debilitation, may not be able to generate adequate heat. As a result, hypothermia may aggravate the combined metabolic and respiratory acidosis most neonates experience at birth.[5,6] This combined stress results in a number of disturbances of physiologic and metabolic processes.[7-16]

In 1967 the first open bassinet infrared warmer was developed. In contrast to the incubator, radiant warming units direct infrared radiation from a source suspended overhead to the exposed skin of the infant. Although infrared radiant warmers have gained wide acceptance, their primary use has been to maintain already normal body temperature while allowing complete accessibility to the nude infant in an open bassinet.

There are no data available, however, regarding the rate of infrared energy output which can be used safely to rewarm hypothermic infants. Since rapid rewarming would have profound significance for the management of chilled neonates, we decided that research to evaluate the optimal skin temperature set-point to achieve the most rapid rewarming of infants should be undertaken. In order to evaluate critically only the effects of rapid rewarming, the study was designed to investigate only the responses of chilled normal full-term rather than premature and sick neonates to rewarming with servocontrolled infrared heating units at each of four different temperature set-points between 35 and 38 C.

Our initial proposal was to chill healthy neonates and then to rewarm each of them at one of the four temperature set-points to determine which produced the most efficient exogenous rewarming to normal. A reduction in rewarming time would benefit hypothermic, premature, and sick infants. The healthy neonate would be exposed to controlled risks of chilling and rewarming for the benefit of the sick baby; it seemed to us that these risks were minimal. Furthermore, since the technology for rewarming was already at hand, the benefits could be realized promptly after the research was concluded. Thus it seemed that the proposal was ethically justified.

The Advocates

Peers: In view of the documented stressful effects of hypothermia as well as hyperthermia on newly born infants, responsible opinion of our scientific and medical peers was opposed to any intentional chilling or heat stress for the purpose of a nontherapeutic rewarming study.

Nurses: The nurse, constantly striving to humanize the impact of medical intervention, promotes and supports maternal-infant bonding. In caring for the infant she (or he) becomes a surrogate mother with all attendant emotions; accordingly, she opposes all potential harm to the infant. During the critical period of adaptation to extrauterine life, nursing care includes measures to safeguard the infant from exposure to potential thermal stress. The nursing personnel maintained that the standard care given every newborn infant in the delivery room precluded significant chilling. Thus, they opposed any variation in the procedure that would purposely allow chilling or subject the infant to heat stress.

Parents: Parents are understandably reluctant to consent to expose their children to risk. Proposing risk to an unidentified, unborn infant compounds their reluctance to consent. Both natural mothering instincts and the protective attitude of society toward the totally dependent infant contribute to a generally negative attitude toward even well-planned and safe investigations involving minimal risks.

To try to help his (or her) sick infant now with a new and potentially better therapeutic modality appeals directly to the best of parental motives: love and protection of the child. But, to put the healthy baby at risk now for the benefit of someone else's future unborn infant appeals only to a remote and abstract altruism: the possible advancement of scientific knowledge and the well-being of future generations. Thus, the difference between therapeutic and nontherapeutic research may be perceived by parents as a matter of present, concrete self-interest contrasted with remote, abstract altruism.

Re-evaluation of Study

Since our original proposal was unacceptable to the subject's advocates, our only options were either to discontinue our efforts, or to find some way to improve the risk/benefit ratio in order to gain their approval and support.

First, in response to the objections to intentional chilling of normal newborn infants, we conducted a retrospective examination of rectal temperatures as recorded on admission to the newborn nursery. A significant number of otherwise normal infants had rectal temperatures ranging from 34.5 C (94 F) to 36.1 C (97 F). Next, we conducted a prospective evaluation of infants admitted with rectal temperatures below 36.7 C (98 F) which revealed several variables in the "standard care" they were given in the delivery room. Individually and in combination these variations contributed directly to the unintentional lowering of body temperature.

The most significant among these variables was the time elapsed from the moment of delivery until the infant was handed to the delivery room nurse in charge of the infant's care. There was considerable variation in the time needed for adequate suctioning of fluid from the infant's mouth and nose, as well as in the interval between delivery and cutting of the umbilical cord. In addition, obstetricians frequently allow the mother to observe and feel her newly born infant resting wet and unclothed on her abdomen. Second, although the infant is wrapped loosely in a receiving blanket, the nurse may find it necessary to suction additional fluid from the infant's mouth and nose, listen to the quality of respirations, and count the infant's heart rate for 15 seconds using a stethoscope applied to the infant's exposed chest. Thereafter the infant is thoroughly dried and wrapped. After an interval of 5 to 15 minutes the infant is again unwrapped to expose the umbilicus for clamping and cutting to the appropriate length. Silver nitrate drops are placed in each eye and subsequently rinsed with copious quantities of saline solution at room temperature. Finally, the infant is rewrapped in a clean, dry receiving blanket and transferred to an incubator. Occasionally, owing to frequent use there is insufficient time for the incubator to rewarm to optimal temperature between infants.

In proposing to warm the skin to a maximum of 38 C (100.4 F) a temperature well above the manufacturer's suggested temperature setting, the objection was raised that we might produce thermal injury to the skin. However, a random sampling of water temperatures used for bathing neonates as prepared by our nursery personnel revealed that the temperatures ranged from 35 C (97 F) to 42 C (105 F), with an average temperature of 38 C (100.4 F). Moreover, a review of the literature indicated that the first minimal evidence of thermal injury to the skin is not observed until the temperature is greater than 44 C (111.2 F).[17] A number of our peers were opposed to undertaking a study of rewarming infants to maximal skin temperature of 38 C (104 F) because it might produce apnea. Indeed, there are brief anecdotal reports in the literature indicating that infants immersed in 37 C water baths in an effort to minimize heat loss in the delivery room frequently developed apneic episodes. Hence a strong caveat was issued against this procedure as early as 1966.[18] Other investigators studying the occurrence of unexplained apnea in premature infants housed in standard incubators demonstrated that incubator temperatures above 34 C (93.2 F) could also cause episodes of apnea.[29]

However, on further evaluation these two modalities were found to exhibit fundamental differences from infrared warmers. First, in a water bath approximately 85 per cent of the infant's skin is warmed compared to approximately 40 per cent under an infrared radiant heat source. Second, the infant inside the incubator breathes warmed air while the infant under the infrared warmer breathes cooler air at room temperature. This cooler air continuously stimulates the thermal receptors in the nasopharynx which, in turn, induce normal respirations. However, to ensure early

recognition and intervention in the event of apnea, the study was altered to provide for continuous observation by a physician in addition to electronic monitoring of respirations.

The Revised Protocol

With these scientifically based supporting data which gained the approval of all advocates, the protocol was submitted to the Clinical Investigation Committee of the Medical College of Pennsylvania. This committee has the responsibility to approve all research on human subjects in the institution. The Clinical Investigation Committee is also an advocate of the rights of the research subject, but in a special, corporate way. Through its deliberations it represents the concerns of each advocate and strives to attain the most acceptable risk/benefit ratio in the proposed investigation. After our modification of the study design met the concerns and objections of *all* advocates our research protocol was approved.

The study was completed in four months during which time a total of 42 chilled infants were rewarmed. A wide variety of clinical and laboratory parameters of thermal stress were measured at frequent intervals throughout the study of each infant. None of the infants became apneic or demonstrated evidence of thermal stress. Our results demonstrated the benefits of rapid rewarming of hypothermic infants at temperatures heretofore assumed to be unphysiologic and possibly even harmful.

Summary

The ethical issues encountered in the design and implementation of this study are typical of most investigations involving newborn infants. The objections and concerns raised on scientific and emotional grounds proved to be of objective value. Two potential stresses were originally proposed: intentional chilling and rapid rewarming. All advocates opposed as unacceptable the intentional chilling of infants when there was no direct therapeutic benefit. This opposition caused us to make a careful observation of current "standard care." When these observations discovered significant numbers of normal newborn infants already chilled, the need for intentional chilling was eliminated. What remained to be evaluated was rapid rewarming. However, this procedure was now to be applied *therapeutically* to hypothermic infants rather than intentionally chilled infants.

Data from earlier investigations of apnea occurring in premature infants were not applicable to the present study owing to the dissimilarity of environmental conditions and physiologic responses. The subsequent improvement in the risk/benefit ratio based on review of these data increased the incentive to participate. Now all advocates, including the parents, readily sought to participate in developing an improved standard of care for their infants. In neonatal research, the helpless, voiceless subject has numerous advocates in addition to the investigator: parents, surrogate parents, attending pediatrician, and society. All proposed investigations must bear the strictest scrutiny of all advocates to ensure that they are to cause the maximum future benefit at the least present risk. In this study the cooperation of all advocates resulted in an acceptable modification of the protocol.

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