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Article *in* Journal of Perinatology · August 2004

DOI: 10.1038/sj.jp.7211142 · Source: PubMed

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Neonatal Research and the Validity of Informed Consent Obtained in the Perinatal Period

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BACKGROUND:
Consent for participation in clinical research is considered valid if it is informed, understood, and voluntary. In the case of minors, parents give permission for their child to participate in research studies after being presented with all information needed to make an informed decision. Although informed consent is a vital component of clinical research, there is little information evaluating its validity in neonatal intensive-care populations. The objective of this project was to determine the validity of informed consent obtained from parents of infants enrolled in the multicenter randomized research study, neurologic outcomes and pre-emptive analgesia in the neonate (NEOPAIN).

DESIGN/METHODS:
Parents of infants who survived to discharge and had signed consent for their newborn to participate in the NEOPAIN study at the University of Kentucky were asked 20 open-ended questions to determine their level of understanding about the NEOPAIN study. The NEOPAIN consent form, which had been approved by the University of Kentucky Medical Institutional Review Board (IRB), was used to formulate these questions. Questions addressed the timing of consent, parental understanding of the purpose, benefits, and risks of the study, the voluntary nature of the project, and their willingness to enroll in future studies if the opportunity presented. Answers were scored on a Likert scale, with 1 for no understanding and 5 for complete understanding.

RESULTS:
Five of 64 parents (7.8%) had no recollection of the NEOPAIN study or of signing consent. Of those who remembered the study, only 67.8% understood the purpose of the study, with a higher proportion of the mothers than fathers knowing the purpose of the study (73.3% vs 57.1%), ($p = 0.029$). Of those who understood the purpose of the study 95% were able to verbalize the benefits, but only 5% understood any potential risks. No parents reported feeling pressured or coerced to sign consent for the project and all parents reported they would enroll their child in additional studies if asked.

CONCLUSIONS:
Valid consent in the antenatal/perinatal population is difficult, if not impossible, to obtain. To maximize validity of consent in the antenatal/perinatal population every effort should be made to include mothers in the consent process. Additional attention during the consent process should be given to possible risks of the study.
Journal of Perinatology (2004) **24,** 409–415. doi:10.1038/sj.jp.7211142
Published online 20 May 2004

INTRODUCTION

Informed consent for participation in clinical research should follow guidelines set forth in the Belmont Report. [1] In order to give valid informed consent, research subjects must be competent, must have understanding of what they are being asked to do, and must be free from coercion.[2] Neonates, lacking competency, represent a unique group of research subjects. In the case of neonatal research, parents must give permission for their baby to participate in clinical research after being presented with all the information necessary to make an informed decision. Obtaining consent prior to delivery is further complicated by asking a member of one vulnerable population (the pregnant mother) to give consent on behalf of her unborn baby, who is also considered ''vulnerable''. Obtaining a valid proxy consent in this situation may be compromised by maternal illness, stress of labor, medication administration, and separation from the infant after birth.[3,4] Previous research has shown poor validity of consent obtained from adult populations consenting for themselves to participate in clinical research.[5–8] Little research, however, has been carried out on the validity of consent from parents of sick neonates. In this follow-up study, we investigated the hypothesis that most parents who signed permission for their newborns to participate in the neurologic outcomes and pre-emptive analgesia in the neonate (NEOPAIN) study had adequate knowledge of the project to provide valid informed consent.

PATIENTS AND METHODS

Subjects

The study population consisted of parents who had previously enrolled their newborn in the NEOPAIN study at the Neonatal

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Intensive Care Unit at the University of Kentucky study site from September, 1999 to December, 2001. Parents were eligible for participation in this study if they had signed informed consent for NEOPAIN and their infant had survived to discharge.

The NEOPAIN study evaluated the effect of continuous infusion morphine vs placebo on the neurologic outcome of premature infants. Inclusion criteria for NEOPAIN were 23 to 33 weeks estimated gestational age, need for mechanical ventilation, and <72 hours old at the time of enrollment. Infants with major congenital anomalies, severe birth asphyxia (5 minute Apgar ≤ 3, or cord pH <7.0), intrauterine growth retardation (birth weight <5 percentile for gestational age), or infants born to a narcotic-addicted mother were excluded. All parents were approached for consent by NEOPAIN study investigators and/or the certified clinical research coordinator (CCRC) assigned to the study. All individuals obtaining informed consent for NEOPAIN had completed an educational program on human subjects protection and had undergone orientation to this project by the site principal investigator (PI). After enrollment of the baby into the NEOPAIN study all patients were contacted at least once by the CCRC or PI to address any ongoing questions or concerns.

Study Protocol

IRB approval was obtained prior to beginning the study. After obtaining informed consent, the parents who signed permission for their infant to participate in the NEOPAIN study were interviewed by the investigators, either by phone or in the NICU follow-up clinic. Parents who consented to the interview were asked a set of questions regarding their understanding of the NEOPAIN study. Maternal medical history and demographic information was obtained from the NEOPAIN database. Five attempts were made to contact parents before they were considered lost to follow-up. The time interval from signing the NEOPAIN consent to completion of the questionnaire ranged from 3 to 28 months.

The study questionnaire consisted of 20 open-ended questions developed by the investigators[9] which the parents were required to answer in their own words without prompting. The questions were designed to address key features from the IRB-approved NEOPAIN consent form. A Likert-scale from 1 to 5 was used to score answers, with $1 =$ no understanding and $5 =$ full understanding with the correct responses being obtained from the NEOPAIN consent form. In order to score the Likert scale reliably investigators developed a priori standards for rating responses to each question (see Appendix A.) The first 10 parents interviewed were scored separately by two investigators to assess reliability. There was 100% scoring agreement between investigators ($p = 1$).

Questions addressed the parent's memory of signing the consent, feelings about the adequacy of explanation, adequacy of time given to consider participation, whether they felt pressured or coerced, and whether they had outside help in making the decision to participate. Six questions were used to evaluate validity. These questions required the parents to describe their understanding of the purpose of the study as well as benefits and risks of the study. They were also asked to describe what the NEOPAIN investigators were asking to do to their baby and whether they had the option to withdraw their infant from the study.

Data Analysis

All answers and patient/parent information were entered into Microsoft Excel®. Data was analyzed on SAS.JMP® using χ^2- and Fisher's exact test to determine significance. The α-error was set at 0.05.

RESULTS

There were 92 eligible subjects, of which 64 were located and interviewed (70%) (Table 1). In all, 28 parents were lost to follow-up. Consent for NEOPAIN was signed by the mother 35 times, by the father 21 times, and by both parents eight times. Parents were questioned about when they were asked to sign consent for their infant to participate in NEOPAIN. Five of 64 (7.8%) had no recollection of the NEOPAIN study or of signing consent for this study. Three of the five parents who had no recollection of NEOPAIN signed consent before delivery and the consent was reviewed with them again after delivery, before enrolling their infant. The other two parents were consented after delivery of the infant. Parents who remembered signing consent could accurately remember whether they signed consent before or after delivery, with 90% correctly recalling the timing of the consent ($p = 0.005$).

Table 1 Demographic Data

NEOPAIN consent signed by: (n)	
Both parents	8
Mother	35
Father	21
Maternal age (years)	
Mean (range)	26.3(16–43)
Ethnicity (n)	
White	58
Non-white	6
Married (*n*)	37
Birth location (*n*)	
Inborn	53
Outborn	11
Mode of delivery (n)	
C-section	43
Vaginal	21
Gestational age (weeks)	
Mean (range)	26.7 (24–32)
Singleton (n)	46
Twin (*n*)	18

Table 2 Comparison of Each Parents Contributions to the Understanding of the Consent in the NEOPAIN Study

	Consent form signed by mother ($n = 30$)	Consent form signed by father ($n = 21$)	Consent form signed by both parents ($n = 8$)	p-value
Understood the purpose (n) (%)	22 (73)	12 (57)	6 (75)	0.02
Knew risk (n) (%)	2 (7)	1 (5)	0 (0)	0.81
Knew benefits (n) (%)	21 (70)	12 (57)	6 (75)	0.07
Knew they could withdraw (n) (%)	22 (73)	13 (61)	5 (62)	0.65
Coerced (n) (%)	0	0	0	1

Of the 59 parents who remembered the NEOPAIN study, 40 recalled the purpose of the study (68%). Most parents (95%) who knew the purpose of the study could also verbalize potential benefits of the study, but only two of these parents (5%) remembered the potential risks. Overall, regardless of knowledge about the purpose of the NEOPAIN study, 64% (41 of 64) could name at least one potential benefit. Only three of 64 (5%) could name at least one potential risk. A total of 14 parents (37.5%) did not know that they had the right to withdraw their infant from the study at any time.

Time intervals from signing of NEOPAIN consent to completion of the questionnaire were assessed. Intervals of <6 months ($n = 16$), 6 to 12 months ($n = 20$), and >12 months ($n = 23$) were analyzed. Time interval did not significantly affect understanding of purpose ($p = 0.26$), knowledge of benefits ($p = 0.41$), knowledge of risks ($p = 0.27$), or understanding of the voluntary nature of the study ($p = 0.95$).

Mothers were more likely than fathers to understand the purpose of the study ($p = 0.02$), and tended to remember more about potential benefits ($p = 0.07$). There was no difference between mothers and fathers regarding potential risks and right to withdraw. Involving the father in the consent process did not improve the overall understanding of the NEOPAIN study or its risk and benefits (Table 2). A total of 22 parents signed consent before delivery and were reconsented after delivery but before enrollment of the infant. This second consent process did not improve parental understanding of the study ($p = 0.86$).

Medication effects on memory were also evaluated. The medication given most frequently in the study population was magnesium sulfate. At the time they signed NEOPAIN consent 37 of 43 mothers were being treated with magnesium sulfate. Despite known adverse effects of magnesium on mentation and memory, the administration of magnesium sulfate appeared to have minimal effect on the mother's recall of the study.[10] Although all five mothers who had no recall of the NEOPAIN study were on magnesium sulfate, χ^2- analysis comparing ability to recall the study and exposure to magnesium sulfate therapy showed poor correlation ($p = 0.28$). Magnesium did not affect understanding of the study in mothers who remembered the study ($p = 0.45$).

Table 3 Parental Reasons for Enrolling in the NEOPAIN Study

Reason for enrollment	Number of parents ($n = 59$)
Help infant (n) (%)	21 (36)
Decrease pain (n) (%)	21 (36)
Altruism (n) (%)	4 (7)
Decrease IVH (n) (%)	2 (3)
Other (n) (%)	11 (19)

Others include: risks were minimal; explanation at the time of study; take advantage of study; felt it was safe; because she was premature; would receive morphine anyway; comfortable with study.

Table 4 Parental Fears Regarding the NEOPAIN Study

Parental fears	Number of parents ($n = 59$)
None (n) (%)	36 (61)
Addiction to morphine (n) (%)	9 (15)
Side effects of morphine (n) (%)	7 (12)
Becoming ventilator Dependent (n) (%)	2 (3)
Other (n) (%)	5 (8.5)

Other fears include: afraid in general; possible harm to their baby; becoming ventilator dependent; did not understand study completely.

Additional questions addressed why parents chose to enroll their infant in clinical research, which has been the focus of recent investigations in older children.[11] The vast majority of parents enrolled their infants in the hope of helping their baby in some way (Table 3). Fewer than half of the parents expressed any fears (Table 4). Despite significant gaps in knowledge about the study, all parents reported that they would enroll their child again if given the opportunity. Remarkably, very few parents remembered visits from the RC or PI after the baby was enrolled.

To have provided valid informed consent parents need to understand the purpose of the study as well as its benefits and risks. They also need to understand the voluntary nature of the study and to feel free from coercion. When all 5 points were analyzed together, only two of 64 (3%) parents met all criteria for giving valid informed consent. More than 55% of parents understood the

purpose, knew benefits, were aware of their right to withdraw, and did not feel coerced (Table 2). When evaluating the five key features of informed consent, only 3% of the parents met this criterion, with more than 90% failing because of inability to name a specific risk.

DISCUSSION

There are several road blocks to researching the validity of informed consent in vulnerable populations. Many investigators are concerned about having their consent process evaluated. Finding high rates of nonvalid consent may be perceived as a risk to conducting future clinical research. In a litigious society and highly regulated research environment, investigators are fearful of liability if lack of validity is documented. These obstacles were overcome in this study by the willingness of the NEOPAIN study director and institutional PI to have their consent process scrutinized. Similarly, there are multiple obstacles to obtaining informed consent in the perinatal population. Investigators performing clinical research trials find the consent process to be quite cumbersome. Truog et al. suggest that there are many scenarios, particularly in neonatal clinical research, when informed consent should be waived.[12] He suggests that in clinical practice there are many situations in which no standard of care exists. Clinician should, therefore, be able to randomize to different therapies when clear clinical support for one therapy over another is lacking. This approach, although reasonable from a clinical perspective, is not acceptable from a regulatory and, possibly, an ethical standpoint.

Su Mason et al. in a study of 200 parents who had signed consent for their infants to participate in European clinical trials found that 70% had difficulty in one or more areas of the consent process.[13] With the exception of Mason's study there is little research evaluating the validity of informed consent obtained in the perinatal/neonatal period.

In our study, parents of surviving NEOPAIN subjects from the University of Kentucky were interviewed to determine validity of their consent. The finding that only 3% of parents who signed consent truly met criteria for validity was unexpected and quite concerning given a system of multiple checks and balances within the division of neonatology designed to assure that consent for clinical trials is performed correctly. All members of the division involved in clinical research, including faculty and fellows, are required to take and pass a continuing education course on protection of human subjects before they are allowed to participate in clinical research.[14] All key personnel who will be obtaining consent for clinical trials receive training from the institutional PI on the focus of the study and on the consent document and typically observe the PI obtain consent at least once before being allowed to obtain consent on their own. Additionally, a CCRC meets with parents before and after enrollment of infants in clinical trials to answer questions and make sure they have received copies of their consent forms. The CCRC is also present during the majority of consent procedures to make sure all areas of consent are covered. Finally, parents who signed consent before delivery of the infant were put through the consent process again before enrolling their infant. Despite all of these measures five parents had no recollection at all of the NEOPAIN study and most had no knowledge of risks. Those who were put through the consent process twice were no more likely to have given valid consent than those who were consented only once. The reason for this is not clear, but it is likely that the stress level of parents is not significantly lessened immediately after the birth of the infant. Our results, however, were not disparate from previously published results of informed consent in clinical research trials.[15,16]

An additional strength of our study was that only four neonatologists or neonatal fellows obtained consent, as opposed to 107 different individuals in the Mason study. Despite what should be a more consistent approach to obtaining consent, our rates of validity were still remarkably lower.

Part of the extreme difference in the rates of validity between the Mason study and ours may reflect a more stringent definition of validity or a different scoring approach used in our study. We theorize, however, that the population giving consent in the NEOPAIN study presented the largest hurdle to obtaining valid consent. Infants of the parents studied by Mason were relatively well and consent was not typically urgently required. In contrast, in the NEOPAIN trial infants were only hours old at the time of enrollment and were critically ill and on mechanical ventilation. Consent was almost always urgently needed and survival of the infant was far from assured. Mothers giving consent were frequently ill themselves, on medications, or gave consent in the time period immediately before or after delivery of a sick infant. Fathers giving consent were stressed by mother's hospitalization and the birth of a sick infant. Often infants required transport from outlying hospitals, requiring the father to choose whether to be with the mother or the infant during this initial critical time period.

Another interesting finding in our population was that maternal understanding was better than paternal, and that paternal involvement in the consent process added very little to the overall understanding of the NEOPAIN study. This finding was directly opposite our initial hypothesis that fathers would have better recall of the study and higher rates of valid consent. We assumed that the use of magnesium sulfate and the stress of labor would cause the mothers to have decreased short-term memory and affect their recall of the NEOPAIN study. In reality, the magnesium exposure seemed to have minimal if any affect. Although the reason for fathers having lower rates of validity than mothers is not clear, our results indicate that either our

perception of less stress for fathers is inaccurate, or that despite labor and medication exposure, mothers are able to handle stress better and process information more effectively. The question of magnesium interference, however, remains incompletely answered due to the small number of mothers not on magnesium sulfate at the time of consent.

One of the risks in conducting any clinical research trial, regardless of age, is that the mere fact that research participation is being offered, means that some parents will interpret the research intervention as a true therapeutic option. This is commonly referred to as therapeutic misconception.[17] Therapeutic misconception is an obstacle faced by almost all clinical research and requires that the investigators and institutional review boards account for this common misconception.[18] Modifications to the consent process must ensure that patients understand risk and fully comprehend the nature of the research. In the situation where parents are faced with the potential death of a child, they are more likely to grasp at extraordinary measures and/or research to try to save their infant. This is reflected in the reasons given for participation as well as the near universal lack of recall of any potential risks. This is, in all likelihood, a normal tendency for any individual in a mentally and physically stressful situation to focus on the potential good and ignore the bad.

Overall, our findings suggest that our current approach to obtaining informed consent in this vulnerable population is, as suggested by others before us, an 'elaborate ritual' and a sham.[19] Our findings show that our current consent process in neonatal clinical research does not achieve the primary goal of valid informed consent. The major area that lacked validity was understanding of risk. Evaluation of our consent process points out the need to emphasize the presence of the risks associated with a study. Our results also indicate the need to involve the mother in the consent process whenever possible, and to include her in follow-up visits after enrollment of her baby. Viewing consent as a dynamic process with frequent question and answer sessions, as well as review of the study purpose, risks and benefits during the early days of the study will also potentially increase validity of consent. Making the consent process more interactive by requiring the consenting parent to verbalize to the investigators their understanding of purpose, risks, benefits, and voluntary participation may also possibly improve validity.

CONCLUSION

Overall, our study indicates that despite frequent lack of understanding of what we were asking them to consent to, parents are agreeable to having their infants participate in research. In view of the outcome of this study, as well as the Mason study, perhaps the best approach to obtaining improved rates of valid consent is an institution by institution review of consent process to determine individual institutional areas of deficiency. Additionally, we need to recognize that some populations, despite meeting a technical definition of competency, may not be able to give valid consent despite our best efforts.

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Appendix A: QUESTIONNAIRE TO DETERMINE VALIDITY OF INFORMED CONSENT

1.	Were you asked to allow your baby to participate in the study before or after the baby was born?	Before	After
2.	Did you sign the consent before the baby was born or after the baby was born?	Before	After
3.	Did you feel you got a complete explanation of the study?	Yes	No
4.	If you answered no to the last question, what other information would you like to have been given?		
5.	Did you get a copy of the consent form to review and keep?	Yes	No
6.	Did you feel you had enough time to review the consent and ask questions before enrolling your baby?		
7.	Can you tell us what the purpose of the study was?		
	1	3	5
	Don't know		Pain control in tiny babies. Better mental outcomes with pain control. Prevent death. Prevent brain bleeding. Prevent brain damage, or softening of brain tissue.
	Comments:		
8.	Do you remember what we were asking to do to your baby?		
	1	3	5
	Don't remember		Give morphine. Give pain medicine.
	Comments:		
9.	Were you told of any possible risks or danger to the baby from the study?		
	Yes	No	
10.	What risks do you remember being told about?		
	1	3	5
	Don't know		Breathing problems. Blood pressure problems. Vomiting. Urinary retention. Slower movement of the intestines. Higher level of jaundice. Seizures.
	Comments:		
11.	Do you remember what benefits your baby might get from being in the study?		
	1	3	5
	Don't know		Pain control in tiny babies. Better mental outcomes with pain control. Prevent death. Prevent brain bleeding. Prevent brain damage, or softening of brain tissue.
	Comments:		
12.	Did you ever feel pressured or forced to participate in the study?		
13.	If yes to #12, what in particular made you afraid not to enter your baby in the study?		
14.	Did you feel that all of the questions you had about the study got answered to your satisfaction?		

15.	Did you know whether you could take your baby out of the study or did the baby have to stay in the study until it was over?	
16.	Did anyone help you decide whether or not to enter the study?	
	Yes	No
	Who:	
17.	What in particular made you decide to enter your baby in the study?	
18.	Did you have any fears about entering your baby in the study?	
19.	Did anyone talk to you about the study after your baby was signed up?	
20.	Now that it is all done, if you had a chance to do it over, would you enter your child in the study?	