Intensive Care Med (2005) 31:880–884
DOI 10.1007/s00134-005-2647-8

PEDIATRIC BRIEF REPORT

Jessie M. Hulst
Jeroen W. B. Peters
Ada van den Bos
Koen F. M. Joosten
Johannes B. van Goudoever
Luc J. I. Zimmermann
Dick Tibboel

Illness severity and parental permission for clinical research in a pediatric ICU population

Received: 30 November 2003
Accepted: 8 April 2005
Published online: 13 May 2005

J. M. Hulst · J. W. B. Peters · A. van den Bos · D. Tibboel (✉)
Department of Pediatric Surgery,
Erasmus MC, Sophia Children's Hospital,
P.O. Box 2060, 3000 CB Rotterdam,
The Netherlands
e-mail: d.tibboel@erasmusmc.nl
Tel.: +31-10-4636567
Fax: +31-10-4636288

J. M. Hulst · K. F. M. Joosten · J. B. van Goudoever · L. J. I. Zimmermann
Department of Pediatrics,
Erasmus MC, Sophia Children's Hospital,
P.O. Box 2060, 3000 CB Rotterdam,
The Netherlands

L. J. I. Zimmermann
Department of Pediatrics,
Division of Neonatology,
University Hospital Maastricht,
P.O. Box 5800, 6202 AZ Maastricht,
The Netherlands

Abstract *Objective:* Research in child subjects requires parental permission. We examined whether parental authorization of involvement in a clinical study is influenced by the child's severity of illness at the time of the consent decision. *Design and setting:* Observational study in a multidisciplinary tertiary pediatric and neonatal intensive care. *Patients and participants:* Parents of 421 children (age range from preterm to 18 years) were asked to consent for participation in a study focusing on measuring their child's nutritional status within 24 h after admission to the ICU. Over 20% of the parents (n=88) refused consent, most of them because they expected the study to be too burdensome for their child. *Measurements and results:* Patient and disease characteristics were comparable in the children for whom consent had or had not been obtained. A higher illness severity score did not decrease the probability of obtaining informed consent, but parents of children with a history of disease were 3.2 times less likely to consent. *Conclusions:* Parents of children with higher illness severity scores are not more likely to decline permission to include their child in clinical observational research on the ICU. History of disease and subjectively perceived burden to the child are important factors that must be considered.

Keywords Clinical research · Informed consent · Proxy consent · Severity of illness · Intensive care · Children

Introduction

Consent to participate in research is obligatory, as has been clearly recognized by the World Medical Association in the Declaration of Helsinki [1]. When the subject is a minor, permission by a responsible relative can replace that of the subject. For parental or proxy consent to be valid, four essential components of the informed consent process must be fulfilled: the person granting permission must be mentally competent, have received appropriate information about the purpose and duration of the study and its risk and benefits, understand the information, and give consent voluntarily without coercion [2]. Previous studies have addressed these components [3, 4, 5] and factors associated with the decision to consent [3, 6, 7, 8, 9, 10].

To our knowledge, no studies have yet addressed the relationship between obtaining informed consent and factors associated with the severity of illness among a group of critically ill children admitted to a neonatal and pediatric intensive care (ICU). Our study examined whether parental authorization of involvement in a clinical study is influenced by the child's severity of illness at the time of the consent decision. Part of this work has previously been published as an abstract in the 43rd An-

nual Congress of the ESPR in Utrecht, The Netherlands, on 4–9 September 2002 [11].

Materials and methods

The study population included parents or legal representatives of children who were approached for consent to enroll their child in a nutritional assessment study. Children from the age of 12 years were asked for consent themselves at the same time as their parents, provided their condition permitted this. Informed consent was requested within 24 h following ICU admission and was obtained by any of the members of the research team according to international guidelines [12]. Parents received the outline of the study in an informative document which adhered to the guidelines of the Central Committee on Research Involving Human Subjects [13] and had been approved by the institutional review board of our hospital. Eligible children were all those admitted to our ICU during 2001, from preterm neonates to 18-year-olds. Exclusion criteria were treatment with extracorporeal membrane oxygenation, withholding/withdrawing of treatment, and inclusion into an ongoing nutritional intervention study. Of the 421 cases informed consent was provided in 333 (79%). Of the 21 children aged 12 years or older 11 could be involved in the consent process; the other 10 were under sedateion and/or mechanical ventilation. Table 1 lists the reasons for the 88 refusals (5 in line with the child's decision), with the most frequent reason (n=59) being that the proposed research to be too burdensome for their child; all refusers spontaneously expressed the reason for refusal.

The proposed prospective nutritional assessment study [14] monitored the nutritional status of critically ill children by various means from admission to 6 months after discharge, including repeated antropometry (weight, length, circumferences of head, arm, and calf, and skinfolds), knemometry (measuring lower leg length), bioelectrical impedance analysis, indirect calorimetry, blood sampling, and stable isotope studies. Blood sampling was carried out only if arterial or venous access was already available (no additional vena puncture). The stable isotope studies required oral administration of the isotope (deuterium labeled water) and urine collection.

Clinical and demographic data were obtained both from children who participated in the nutritional assessment study and from those whose parents withheld permission to the proposed study. Severity of illness was assessed by means of validated scoring systems: the Pediatric Risk of Mortality score (PRISM) [15] and the Clinical Risk Index for Babies (CRIB) [16]. Furthermore, the Therapeutic Intervention Scoring System (TISS) score [17] was used to estimate the extent of interventions for each child during the first 24 h. Children were classified into three age groups: preterm neonates (gestational age <37 weeks), term neonates (0–30 days) and older children (>30 days). Since children aged 12 years or over are involved in the consent process, we also looked at this subgroup.

Data are expressed as median and range except when indicated otherwise. Parametric data were analyzed using Student's t test. Nonparametric data were analyzed using Pearson's χ^2 test or Fisher's exact test, and the Mann-Whitney U test. To adjust for the effect of other factors stepwise multivariate logistic regression analysis with backward elimination (likelihood ratio, $p<0.1$ for entry, $p<0.05$ for elimination) was carried out to examine which variables affected parents' decision at the time of request. In the preterm and term neonates we checked birth weight, postconceptional age at admission, illness severity score, TISS score, and whether undergoing surgery. In the older children additional factors were previous health status and acute/elective admission. A two-tailed p value less than 0.05 was considered to indicate statistical significance.

Table 1 Reasons for declining informed consent (n=88)

Reason	n	%
Too much (additional) burden on child	59	67
Too sick or too small	11	12
Child unwilling to participate, parents went along[a]	5	6
Too much to consider for parents	4	4
Against research	4	4
Infection risk	2	2
Do not see the importance	2	2
Bad experience with previous participation in another clinical study	1	1

[a] Children aged 12 years or over who were able to decide together with their parents

Results

Patient and disease characteristics and factors associated with the disease severity are shown in Table 2 for the children with and children without consent. There was a significantly higher percentage of children aged at least 12 years in the nonconsent group, and a significantly higher proportion of older children without consent had a history of underlying disease. All five children aged 12 years or over who declined to participate had a history of chronic disease and several hospital admissions. Median PRISM and TISS scores were similar in both groups, but the median CRIB score and length of stay of the preterm neonates in the consent group was significantly higher than in the nonconsent group. Among the older children the nonconsent group had a higher proportion of deaths during admission, but their PRISM scores were not significantly higher (median score 21.5 vs. 19, p=0.829).

In logistic regression analyses among term neonates none of the predefined variables explained parent's decision whether to give informed consent, whereas among the preterm neonates a significant model was found using all five predefined factors accounting for 17% of the variation (p=0.025). Birth weight and postconceptional age were significant contributors. A post-hoc analysis carried out in the preterm neonates without a CRIB score (n=41, admission later than 12 h after birth), using the variables TISS score, postconceptional age, and birth weight revealed no significant factor explaining parent's decision whether to give informed consent.

In the older children, no significant model was found using all six predefined factors. Following backward elimination three variables remained in the model (p=0.017) accounting for 12% of the variation: previous health status, undergoing surgery during admission, and PRISM score. This model suggests that parents of children with underlying disease were 3.2 times less likely to give informed consent for participation in the study, independent of the PRISM score or whether the child had to undergo surgery.

Table 2 Patient and disease characteristics and factors associated with illness severity (*PRISM* Pediatric Risk of Mortality, *CRIB* Clinical Risk Index for Babies, *TISS* Therapeutic Intervention Scoring system)

	Informed consent (*n*=333)	No informed consent (*n*=88)	*p*
Gender: M/F	57%/43%	58%/42%	NS
Age (days; maximum)	2 (0–16.9 years)	2 (0–16.3 years)	NS
Preterm neonates	113 (34%)	38 (43%)	NS[a]
Gestational age (weeks)	31.3 (25–36.7)	31.1 (25–36.7)	NS
Birth weight (g)	1520 (530–3160)	1600 (650–3205)	NS
Postnatal age (days)	0 (0–83)	0 (0–58)	NS
Term neonates	106 (32%)	24 (27%)	
Gestational age (weeks)	39.7 (37–42.1)	39.4 (37–41.9)	NS
Birth weight (g)	3305 (1765–5855)	3608 (2470–4475)	NS
Postnatal age (days)	1 (0–30)	1 (0–30)	NS
Older children	114 (34%)	26 (30%)	
Age (years)	1.4 (0.1–17.0)	1.4 (0.1–16.3)	NS
Age >12 years	13 (4%)	8 (9%)	0.047
Ethnic background			NS
Caucasian	254 (76%)	71 (81%)	
Indo-Mediterranean	41 (12%)	12 (14%)	
African	30 (9%)	3 (3%)	
Asian	8 (2%)	2 (2%)	
Elective admission, n (%)	28 (25)	6 (23)	NS
Previous health status: healthy/underlying disease[b]	57/57 (50%/50%)	7/19 (27%/73%)	0.033
Surgery during admission	103 (31%)	20 (23%)	NS
Diagnostic category[c]			NS
Prematurity/dysmaturity	90 (27%)	28 (32%)	
Congenital anomalies requiring surgery	73 (22%)	14 (16%)	
Postnatal problems[d]	26 (8%)	10 (11%)	
Postoperative monitoring	49 (15%)	8 (9%)	
Sepsis or meningitis	26 (8%)	8 (9%)	
Respiratory illness[e]	48 (14%)	9 (10%)	
Other	21 (6%)	11 (13%)	
PRISM (range)[f]	11 (0–38)	11 (0–33)	NS
CRIBrange[g]	3 (0–16)	1 (0–10)	0.029
TISSrange[h]	13.9 (1–47)	13.7 (1–44)	NS
Length of stay (days)	7 (1–314)	6 (1–99)	NS
Preterm neonates (range)	12.5 (2–151)	6 (1–99)	0.028
Term neonates (range)	6 (1–314)	6.5 (1–67)	NS
Older children (range)	5 (1–138)	8 (2–88)	NS
Death during admission	19 (6%)	9 (10%)	NS
Preterm neonates	6 (5%)	3 (8%)	NS
Term neonates	6 (6%)	0 (0%)	NS
Older children	7 (6%)	6 (23%)	0.016

[a] Indicates the significance of the difference in age distribution between the groups with and without consent
[b] Only the older children (*n*=140)
[c] Most prominent diagnoses
[d] Examples: asphyxia, meconium aspiration, infection
[e] Examples: pneumonia, RS bronchiolitis
[f] In term neonates and older children together (*n*=270), also no significant difference found within the two age groups
[g] In preterm neonates (*n*=110, 41 missing)
[h] In all age groups together (19 missing values); also no significant differences within age groups

Discussion

Our study showed, contrary to our hypothesis, that a higher degree of current illness as determined by objective scores did not negatively influence parents' willingness to give informed consent for participation of their critically ill child in a clinical study. In the preterm neonates the illness severity scores were even found to be higher in the group of children for whom consent was obtained. Logistic regression analyses revealed some significant child-related factors that influenced parental decision. Since these factors explained only 12–17% of the variation in the decision regarding consent, we conclude that parents also base their decision on factors other than factors related to illness severity, the child, or its disease. Children aged 12 years or over should be involved in the consent process when considering participation in research [13, 18, 19]. In our study nearly half of these children (5/11) who could be involved in the consent process did not want to participate, and each had a

history of chronic disease. It seems that both in parents and children this factor is important in contemplating participation in research. We found no differences between the neonates in the consent group and in the nonconsent group concerning illness severity score, other clinical factors and illness severity perceived by parents which is in accordance with a previous study of newborn infants [6].

Concern has been expressed that many parents consenting to research do not understand the information or are too intimidated to refuse. We did not investigate the integrity of the consent process [3, 6], parental educational background, social economic status or personality; however, previous studies concerning these issues have been inconclusive [4, 5, 8, 20, 21]. We believe that a short general informative document explaining the nature of research being performed at the unit would help to prepare parents for the specific research that will be proposed.

Our study can be seen as nontherapeutic interventional research with minimal risk, but moderate burden on the child [12, 22], and it is debatable whether our results can be extrapolated to other types of studies, with different risks and benefits or lower burden. In this context, Pierro and Spitz [10] observed an increasing rate of parental refusal for nontherapeutic studies from 30% for performing anthropometric measures to 70% for stable isotope intravenous infusion, gas exchange measurements and blood sampling. A blinded randomized placebo controlled study conducted in our hospital investigating the analgesic effect of routine morphine infusion in preterm ventilated neonates had an inclusion rate of 71% [23]. This rate is comparable to the hypothetical 78% inclusion rate for studies involving moderate risk but possible major benefits, as reported by Singhal et al. [24] among parents with a child admitted to a neonatal ICU.

We conclude that the severity of illness as determined by objective scores did not differ between children whose parents consented and those whose parents did not consent. This suggests that parents are not influenced by the illness severity of their child in the decision to allow their child to participate in clinical observational research.

Acknowledgements The authors acknowledge the research nurses Annelies Bos, Marianne Maliepaard, Marjan Mourik, and Ineke van Vliet for their help in data collection. The authors thank Ko Hagoort (Erasmus MC, Rotterdam) for his careful editing.

References

1. Declaration of Helsinki (2000) Recommendations guiding physicians in biomedical research involving human subjects. World Medical Association, Edinburgh
2. Mason SA, Allmark PJ (2000) Obtaining informed consent to neonatal randomised controlled trials: interviews with parents and clinicians in the Euricon study. Lancet 356:2045–2051
3. Mason S (1997) Obtaining informed consent for neonatal randomised controlled trials—an "elaborate ritual"? Arch Dis Child Fetal Neonatal Ed 76:F143–F145
4. Stuijvenberg M van, Suur MH, de Vos S, Tjiang GC, Steyerberg EW, Derksen-Lubsen G, Moll HA (1998) Informed consent, parental awareness, and reasons for participating in a randomised controlled study. Arch Dis Child 79:120–125
5. Tait AR, Voepel-Lewis T, Malviya S (2003) Do they understand? I. Parental consent for children participating in clinical anesthesia and surgery research. Anesthesiology 98:603–608
6. Zupancic JA, Gillie P, Streiner DL, Watts JL, Schmidt B (1997) Determinants of parental authorization for involvement of newborn infants in clinical trials. Pediatrics 99:E6
7. Harth SC, Thong YH (1990) Sociodemographic and motivational characteristics of parents who volunteer their children for clinical research: a controlled study. BMJ 300:1372–1375
8. Harth SC, Johnstone RR, Thong YH (1992) The psychological profile of parents who volunteer their children for clinical research: a controlled study. J Med Ethics 18:86–93
9. Harth SC, Thong YH (1995) Parental perceptions and attitudes about informed consent in clinical research involving children. Soc Sci Med 41:1647–1651
10. Pierro A, Spitz L (1997) Informed consent in clinical research: the crisis in paediatrics. Lancet 349:1703
11. Hulst JM, van den Bos A, Peters J, Mourik M, van Goudoever J, Joosten K, Zimmermann L, HA B, Tibboel D (2002) Severity of illness does not influence parental informed consent. Pediatr Res 52:800
12. McIntosh N, Bates P, Brykczynska G, Dunstan G, Goldman A, Harvey D, Larcher V, McCrae D, McKinnon A, Patton M, Saunders J, Shelley P (2000) Guidelines for the ethical conduct of medical research involving children. Royal College of Paediatrics, Child Health: Ethics Advisory Committee. Arch Dis Child 82:177–182
13. Central Committee on Research Involving Human Subjects (2002) Manual for the review of medical research involving human subjects. Central Committee on Research Involving Human Subjects,– The Hague
14. Hulst J, Joosten K, Zimmermann L, Hop W, Van Buuren S, Büller H, Tibboel D, Van Goudoever J (2004) Malnutrition in critically ill children: from admission to 6 months after discharge. Clin Nutr 23:223–232
15. Pollack MM, Ruttimann UE, Getson PR (1988) Pediatric risk of mortality (PRISM) score. Crit Care Med 16:1110–1116
16. The International Neonatal Network (1993) The CRIB (clinical risk index for babies) score: a tool for assessing initial neonatal risk and comparing performance of neonatal intensive care units. Lancet 342:193–198
17. Keene AR, Cullen DJ (1983) Therapeutic Intervention Scoring System: update 1983. Crit Care Med 11:1–3
18. Gill D, Crawley FP, LoGiudice M, Grosek S, Kurz R, de Lourdes-Levy M, Mjones S, Nicolopoulos D, Rubino A, Sauer PJ, Siimes M, Weindig M, Zach M, Chambers TL (2003) Guidelines for informed consent in biomedical research involving paediatric populations as research participants. Eur J Pediatr 162:455–458

19. Alderson P (1993) Children's consent to surgery. Open University Press, Buckingham
20. Tait AR, Voepel-Lewis T, Siewert M, Malviya S (1998) Factors that influence parents' decisions to consent to their child's participation in clinical anesthesia research. Anesth Analg 86:50–53
21. Simon C, Zyzanski SJ, Eder M, Raiz P, Kodish ED, Siminoff LA (2003) Groups potentially at risk for making poorly informed decisions about entry into clinical trials for childhood cancer. J Clin Oncol 21:2173–2178
22. Sauer PJ (2002) Research in children. A report of the Ethics Working Group of the CESP. Eur J Pediatr 161:1–5
23. Simons SH, van Dijk M, van Lingen RA, Roofthooft D, Duivenvoorden HJ, Jongeneel N, Bunkers C, Smink E, Anand KJ, van den Anker JN, Tibboel D (2003) Routine morphine infusion in preterm newborns who received ventilatory support: a randomized controlled trial. JAMA 290:2419–2427
24. Singhal N, Oberle K, Burgess E, Huber-Okrainec J (2002) Parents' perceptions of research with newborns. J Perinatol 22:57–63