Major Surgery Within the First 3 Months of Life and Subsequent Biobehavioral Pain Responses to Immunization at Later Age: A Case Comparison Study

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ABSTRACT. *Objectives.* **Pain exposure during early infancy affects the pain perception beyond infancy into childhood. The objective of this study was to examine whether major surgery within the first 3 months of life in combination with preemptive analgesia alters pain responses to immunization at 14 or 45 months and to assess whether these alterations are greater in toddlers with a larger number of negative hospital experiences.**

Methods. **Two groups of 50 toddlers each were compared: index group and control group. All index toddlers had participated within the first 3 months of their life in a randomized, clinical trial that evaluated the efficacy of preemptive morphine administration for postoperative analgesia. The controls were matched by type of immunization and community health care pediatrician. Pain reactions were recorded at routine immunization at either 14 (measles-mumps-rubella immunization) or 45 months (diphtheria-tetanus-trivalent polio immunization) of age. Outcome measures were facial reaction, coded by the Maximum Discriminative Facial Movement Coding System; heart rate (HR); and cortisol saliva concentration. Negative hospital experiences included number of operations requiring postoperative morphine administration, cumulative Therapeutic Intervention Scoring System scores, and length of stay in the intensive care unit or total hospitalization days.**

Results. **No differences were found between the index and control groups in the facial display of pain, anger, or sadness or in physiologic parameters such as HR and cortisol concentrations. Intragroup analyses of the index group showed that after measles-mumps-rubella vaccination, the number of negative hospital experiences correlated positively with the facial responsiveness and negatively with HR responses. No effect was seen after diphtheria-tetanus-trivalent polio immunization.**

Conclusions. **Major surgery in combination with preemptive analgesia within the first months of life does not alter pain response to subsequent pain exposure in childhood. Greater exposure to early hospitalization influences the pain responses after prolonged time. These responses, however, diminish after a prolonged period of nonexposure.** *Pediatrics* **2003;111:129–135;** ***prospective study, newborn infant, repetitive pain, biobehavioral pain response, analgesia.***

ABBREVIATIONS. NICU, neonatal intensive care unit; ELBW, extreme low birth weight; HR, heart rate; MMR, measles-mumps-rubella; DTT, diphtheria-tetanus-trivalent polio; MAX, Maximum Discriminative Facial Movement Coding System; AC, appearance change; FEN, forehead/eyebrows/nasal; ENC, eye/nose/cheek; MLC, mouth/lips/chin; TISS, Therapeutic Intervention Scoring System; CNS, central nervous system.

It has been well established that the nociceptive pathways, (sub)cortical centers, and neurochemical systems necessary for pain perception and transmission are intact and functional from an early stage of fetal development.[1] However, in newborns, this neural system is still very immature and matures within the first year of life.[1] Experiments in animals suggest that during this "critical period of immaturity," alterations in normally occurring activity patterns, eg, as a result of frequent pain exposure, make this system more susceptible to perturbation than at any other time of life.[2–5]

Newborns who are admitted to neonatal intensive care unit (NICU) will be exposed to noxious interventions associated with life-saving high-technology care.[6] In neonates, both mature and premature, this may result in hypersensitivity to tissue damage, ie, decreased pain threshold.[7–11] This coincides with clinically significant biobehavioral changes in pain reaction, ie, facial reaction, cardiovascular response, and saliva cortisol response.[12–16]

Emerging evidence suggests that these biobehavioral changes will persist after discharge from the hospital. At corrected ages of 4 and 8 months, premature infants who were born with extreme low birth weight (ELBW) and perinatally subjected to pain show less facial activity but higher heart rate (HR) in response to subsequent pain than infants without any history of hospital exposure.[17,18] These effects were most pronounced in the infants who seemed to be sicker at birth, stayed longer in the NICU, experienced more NICU-related procedures, and received greater amounts of morphine.[17] Par-

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ents' reports suggest that ELBW neonates at 18 months' corrected age are less reactive to everyday pain than peers without any history of perinatal pain exposure.[19] At the age of 8 to 10 years, ELBW children rated pictures of medical events as more painful than pictures of psychosocial pain events, unlike term-born peers.[20] At the age of 12 to 16 years, however, no differences could be demonstrated between adolescents with and without a history of perinatal pain exposure.[21]

The few reports on healthy full-term-born infants showed that these alterations in pain threshold are not restricted only to premature-born infants. Neonatal circumcision without any form of analgesia increased the infants' biobehavioral pain responses to subsequent immunization at the age of 4 to 6 months.[22–24] Also, stressful conditions at birth, eg, assisted delivery versus elective caesarean section, were associated with increased salivary cortisol responses to vaccination at 2 to 6 months of age.[25,26]

The effects of major surgery on the immature nervous system and subsequent pain response in childhood are unknown. In contrast with a decade ago, neonates nowadays receive preemptive analgesia for postoperative pain relief.[27] Experiments in animals suggest that appropriate doses of morphine may prevent the development of an altered pain threshold.[2] In humans, however, it is unknown whether effective dosages of morphine diminish these iatrogenic effects of pain.

This is why we examined whether major surgery in the first 3 months of life, under the condition of preemptive analgesia, alters the pain response to immunization at toddler age. We were also interested in whether the number of negative hospital experiences during infancy negatively affects pain responses to immunization at toddler age, because infants who are born with congenital abnormalities often undergo more than 1 surgical intervention and are hospitalized for a relatively prolonged period during which they are subjected to many noxious procedures. In contrast with pain after major surgery, many noxious procedures are still conducted without any form of analgesia.[28]

METHODS

Design and Subjects

A prospective matched-control study in a number of community health care centers in the Netherlands was undertaken. This study includes part of a cohort of (young) children who participated in a large double-blind, randomized, clinical trial that was conducted at the ICU of the Sophia Children's Hospital, the Netherlands, between April 1996 and August 1999. The aim of that trial was to assess the efficacy of preemptive continuous versus intermittent morphine administration after major abdominal or thoracic surgery. Evidence shows that both forms of morphine administration provided adequate pain relief as assessed by validated behavioral pain measures and hormonal stress responses.[29] Moreover, no differences were found in efficacy between the 2 forms of morphine administration.[29]

The inclusion criteria of these children to be included in this underlying matched-control study were as follows: having participated in the above-mentioned trial within the first 3 months of life and having received either routine measles-mumps-rubella (MMR) or diphtheria-tetanus-trivalent polio (DTT) immunization between January 1998 and July 2000. The immunization was given at each toddler's own community health care center.

At each center, a matched control toddler was selected. The match variables were community health care pediatrician and type of immunization. For preventing selection bias, the toddler closest in time to the immunization of the index child was selected. When parents refused consent, the toddler next in time was selected.

Inclusion criteria for the matched controls were no history of abdominal or thoracic surgery and undergoing either MMR or DTT vaccination. Exclusion criteria for the index as well as the control group were 1) mental retardation, 2) deafness, 3) blindness, and 4) overt signs of illness on the day of vaccination. According to routine schedules for immunization in infancy and childhood, the MMR was given at the age of 14 months and the DTT at the age of 45 months. The Medical Ethical Committee of this hospital approved this study, and informed parental consent was obtained.

Assessment Measures

Alterations in pain responses were assessed from a biobehavioral perspective. The behavioral response to immunization was assessed by the Maximum Discriminative Facial Movement Coding System (MAX).[30,31] This is an anatomy-based facial coding system that focuses on movements/appearance changes (ACs) in the face. These ACs are served by 3 separate branches of the facial nerve and by 3 relatively independent sets of muscles in 3 regions of the face: the forehead/eyebrows/nasal root (FEN region), eye/nose/cheek root (ENC region), and the mouth/lips/chin root (MLC region). The FEN region has 6 ACs, the ENC region has 7 ACs, and the MLC region has 17 ACs. Combinations of these ACs represent the presence of pain/distress or discrete emotions, eg, anger, sadness, fear.[32] Thus, the MAX yields data not only about the occurrence of pain but also about the affective aspects of the pain experience.

HR and salivary cortisol concentration were the biophysiologic pain indicators. HR was registered by pulse oximeter (Ohmeda Biox 3700; Ohmeda, Boulder, CO). Cortisol in saliva was assessed using a coated-tube radioimmunoassay method supplied by Diagnostic Products Corporation (Los Angeles, CA).[33]

Negative hospital experiences are understood to be total number of minor surgical procedures (ie, not requiring morphine for postoperative analgesia), major operations (ie, requiring morphine postoperatively), amount of illness as evaluated by the Therapeutic Intervention Scoring System (TISS),[34] length of stay in the NICU, and length of hospital stay. TISS is a well-established and validated parameter that can be regarded as a measure of the care and treatment given to patients.[34–36] TISS scores are determined daily by the nurses. For the purpose of this study, for each patient, all TISS scores were summed up into an index of illness.

Procedures and Apparatus

Immunization

The child was put backward on the parent's lap. The parent was instructed to hold the child in a "tight hug." The immunization was then given by the pediatrician, according to a protocol standardized for all participating community health care centers. The protocol did not allow for pain interventions of any kind such as eutectic mixture of local anesthetics (EMLA), distraction, or giving the toddler control over the situation.[37]

Data Sampling

The facial response to immunization was recorded by an 8-mm video camera (Hitachi VM-H90E, Tokyo, Japan). This camera was handheld to get a close up of at least two thirds of the children's face. The same type of camera was put on a tripod to record the display of the pulse oximeter. For getting an impression of each toddler's neutral face, video recordings of at least 60 seconds were made before immunization.

Two saliva samples were taken: one before and one 20 to 30 minutes after immunization.[13,38] To stimulate saliva flow, 0.3 mL of a citric acid solution (1.5%) was administered orally. The saliva was sampled with a cotton-bar on which a nonwoven swab was fixed. At least 0.5 mL of saliva was collected during a maximum period of 5 minutes. After swabbing, saliva was squeezed from the nonwoven swab in a syringe and stored in a vial at −20°C. A duplicate analysis of cortisol was done in each saliva sample. For

avoiding interassay variation, samples of 1 individual were analyzed in the same assay.

Video Analysis

MAX and HR were coded by 1 of the 2 coders (J.W.B.P. or J.B.d.M.). With respect to the MAX, video playbacks were used to code separately the brow, eye, and mouth regions of the face. One specific code was given for each AC. Coding of the face spanned the period from needle insertion up to 60 seconds thereafter. Several measures as a reaction to immunization were created: 1) sensory reaction, ie, time of presence of pain/distress expression, and 2) affective reactions, ie, time of presence of anger, sadness, or fear expression.

HR data were coded from the videotapes on a second-by-second basis starting from 60 seconds before to 60 seconds after immunization. These data were used to calculate HR before (HR before; ie, average HR of the 30 seconds before insertion of the needle) and HR after immunization (HR response; ie, average HR of the 60 seconds after immunization).

Apparatus

For marking onset and offset of the ACs in a chronological order and registering HR response with exact 1-second intervals, a copy was made of each videotape and a Vertical Interval Time Code was added (Adrienne Electronics Corporation; Las Vegas, NV). This means that each video frame (picture) was marked with a unique format frame (hours: minutes: seconds: frames), enabling selection and coding of various segments of the tape. A videotape analysis system was used, which included a computer with a vertical time code reader (16-bits ISA-board), the Observer 3.0 Base Package for Windows and the Observer 4.0 Software Package for video analysis (Noldus, Wageningen, the Netherlands), a videocassette recorder (Panasonic AG 5700, Yokohama, Japan) with remote control and stop action and slow motion feedback, and a 50-Hz monitor.

Reliability

Interobserver reliability had previously been obtained by using the MAX manual and training videotape. Each coder coded independently the training tape. Interobserver reliability was assessed with the master code and was computed following Izard's[32] indications in the MAX manual: agreements/(agreements + disagreements). The interobserver reliability was above the required 80% (86% and 88% for the 2 coders).

Data Analysis

To find out whether there was a difference between the index and control groups, we conducted 2 different statistical techniques.

As the facial response findings were highly skewed and could not be transformed to normality, polychotomous logistic regression analysis was conducted using the BMDP for DOS software package (SPSS, Inc, Chicago, IL). This technique computes the maximum likelihood estimates of parameters of logistic models for multinomial data, ie, nominal or ordinal data. For the purpose of this study, the facial responses were categorized into 4 categories: expression did not occur, duration of an expression lasted 0.1 to 10.0 seconds, duration of an expression lasted 10.1 to 20.0 seconds, or duration of an expression lasted >20.0 seconds. Each category contained at least 15% of the data. The following variables were considered to be of clinical interest and for this reason were entered as covariables: group, type of immunization, minor surgery, and hospitalization.

The HR and cortisol findings, on the contrary, could be transformed (natural log) to normality. For this reason, multiple regression analysis was conducted for these data. The following covariables were entered: group, type of immunization, minor surgery, hospitalization, and HR/cortisol before immunization. With respect to cortisol, the time of saliva sampling was also entered, to adjust for circadian rhythm effects on cortisol.

Spearman rank correlation was used to assess the association between negative hospital experiences and pain responses. Analysis of principal components was conducted before to find out which variables were interrelated and which could be clustered into 1 variable of adverse hospital events. This technique has the advantage that the number of independent variables can be reduced and hence reduces the risk at type I error. Missing values were replaced by predicted mean matching method.[39]

RESULTS

The index group consisted of 50 children. These toddlers were visited at their own community health care center, 44 in total, at which 50 matched controls were included. Patient characteristics are presented in Table 1. Overall, 28 children received MMR and 72 received DTT immunization. Gender did not differ significantly between the index and control groups. With respect to the index group, the median number of minor and major operations, ie, requiring morphine or not for postoperative pain relief, equals 1; the median number of days of hospitalization and NICU stay was 42 and 13 days, respectively; and the median total TISS score was 115. Of the children in the control group, 16 had stayed in a hospital. Nine of them spent several days in the hospital for observation purposes, mainly because of birth circumstances, eg, forceps delivery, vacuum extraction. The other 7 children had been admitted to a hospital because they had to undergo minor surgery in child

TABLE 1. Background Characteristics

	Index	Control
Immunization		
MMR	14	14
DTT	36	36
Gender		
Male	28	23
Female	22	27
Negative hospital experiences		
Surgery		
Major surgery*	1 (1–6)	
Minor surgery†	1 (0–14)	‡
Days hospitalized	42 (5–248)	§
Days at NICU	13 (2–248)	
Total TISS score	115 (24–2079)	
Days of mechanical ventilation	2 (0–26)	

* Opioids were administered for postoperative pain relief.
† No opioids were administered for postoperative pain relief.
‡ Seven children had undergone minor surgical procedures (eg, adenotomy, myringotomy).
§ Sixteen children had stayed in a hospital for observational purposes, mainly because of birth circumstances such as forceps delivery or vacuum extraction.

TABLE 2. Number of Subjects Who Showed Pain/Distress and Emotional Facial Expressions

	MMR		DTT	
	Index	Control	Index	Control
Pain/distress	12 (43%)	13 (46%)	13 (18%)	11 (15%)
Sadness	9 (32%)	11 (39%)	15 (21%)	18 (25%)
Anger	11 (39%)	12 (43%)	19 (19%)	17 (24%)
Fear	2 (7%)	0	0	1 (1%)

care, such as adenotomy or myringotomy. These surgical procedures all were conducted over the age of 18 months.

Age-Related Differences in Facial Responsiveness

The number of children who reacted with pain or emotion did not differ between the index and control groups (Table 2). The proportion of toddlers who reacted with a pain expression was greater after MMR than after DTT (89% and 33%, respectively). Anger and sadness were also more prominently present in the MMR group. Fear was not a common reaction as it was present in 3 children and therefore was excluded from additional analysis. In addition, the times of occurrence of each of these facial expressions were longer after MMR than after DTT immunization, except for fear (Fig 1).

Differences Between Index and Control Groups

No differences were found between the index and control groups in any of the biobehavioral pain responses. Thus, time of presence of the pain, sadness, or anger expression did not differ between the 2 groups. HR before and HR responses to immunization as well as cortisol concentrations before and after immunization were similar between the 2 groups.

Differences Between Type of Immunization

On the contrary, most of the biobehavioral pain responses did differ between the 2 types of immunization. As shown in Fig 1, the times of presence of the facial pain and anger expressions were significantly shorter in children of the DTT group ($P < .01$). The times of presence of the sadness expression did not differ between the MMR and DTT groups. As expected, HR before was significantly ($P < .01$) lower in children of the DTT group, which is explained by their higher average age. After immunization, the response in HR was lower in children of the DTT group (Fig 2), although it did not reach statistical significance ($P = .06$). Cortisol concentrations before and after immunization did not differ between the MMR and DTT groups (Fig 3).

Association Between Hospitalization and Minor Surgery

No association was found between hospitalization or minor surgery and times of presence of the pain, anger, or sadness expressions as well as with the physiologic values for HR before and after immunization and cortisol concentration before and after immunization.

Index Subgroup Analysis

Principal component analysis demonstrated that 3 of the 5 negative hospital experiences—major operations, total TISS score, and length of stay at the NICU—were closely interrelated. Therefore, these 3 variables were grouped together into a score of adverse hospital events. The other variables—minor surgery and days of stay in the hospital—were considered to be independent.

Spearman rank correlation coefficients between biobehavioral pain responses and adverse hospital events, minor surgery, and days of stay in the hospital are presented in Table 3. For the index children who received MMR, a greater number of adverse hospital events were associated with increased facial pain responses but with a diminished HR acceleration to immunization. Total days of hospitalization was also negatively associated with HR response. No association was found between the other biobehavioral pain responses and number of negative hospital experiences.

For the control children who received MMR, no association was found between the biobehavioral pain indices and number of days hospitalized or number of minor surgical procedures. For the control

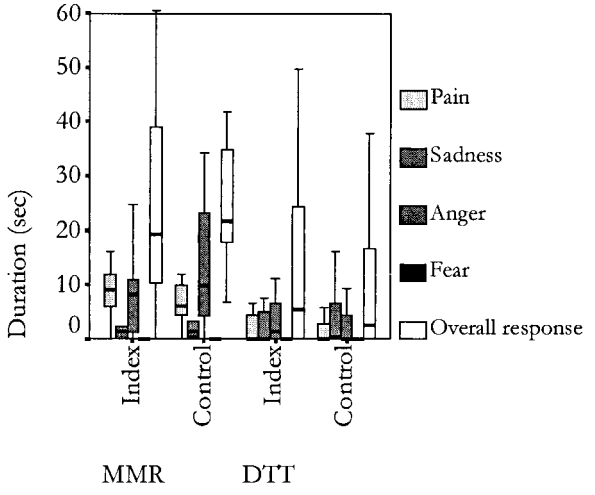

Fig 1. Times of presence of facial expressions.

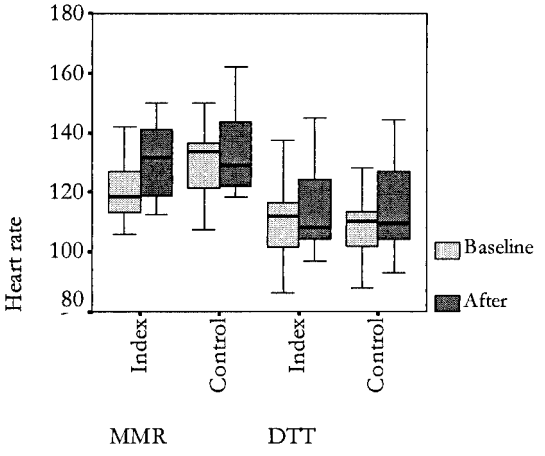

Fig 2. HRs at baseline and postimmunization.

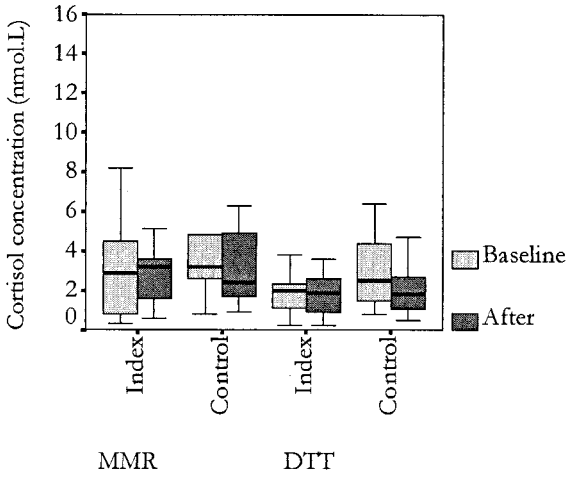

Fig 3. Salivary cortisol responses to immunization.

children who received the DTT, there was only a negative association between HR response and history of minor surgery. However, HR before immunization was also lower in these children.

DISCUSSION

We found that major surgery in combination with preemptive morphine administration within the first 3 months of life does not alter the behavioral and physiologic pain response to intrusive immunization at the age of 14 or 45 months. However, in the index group, negative hospital experiences, as evidenced by higher number of major surgical procedures, higher TISS scores, and longer stays in the NICU, were positively associated with greater facial pain but with a reduced HR response to immunization at the age of 14 months but not at 45 months.

Experimental studies in animals have demonstrated that nociception during a distinct period of life changes the neuroanatomical architecture and decreases pain thresholds.[3,4,40] It has been suggested that these alterations may be maximal when 6- to 9-day-old rats are exposed to pain.[5] No alterations are seen when pain is induced in 14-day-old rats.[3] The central nervous system (CNS) of a 7-day-old rat functions like that of a full-term human neonate, and that of a 14-day-old rat corresponds to that of an infant 1 year of age.[1] The specific mechanisms by which these alterations in neuroanatomy and hypersensitivity to pain are induced have not fully been established. It is assumed that activation of the N-methyl-D-aspartic acid receptor ion complex produces an increase in intracellular calcium and other second messengers, which stimulate protein kinases and new gene expression.[2,5,41] On this basis, we theorized that major surgery in early infancy induces structural alterations in children's CNS and reduces their pain threshold. It was assumed that alterations in pain threshold were paralleled by alterations in biobehavioral responses to pain.[22,23,25,26]

In this study, no differences were found in the biobehavioral pain responses between the index and control groups, suggesting that appropriate pain relief after major surgery prevents the development of alterations in pain threshold in the long term. Others found that preemptive application of the analgesic EMLA cream prevents young infants from developing lower pain thresholds after repeated heel sticks[7] but not after neonatal circumcision.[42] EMLA, however, has only mild to moderate analgesic properties for circumcision.[43] Findings in animals also have demonstrated that judicious use of pain relief prevents the development of altered pain threshold.[2]

On the contrary, Oberlander et al[17] found that infants who had received greater amounts of morphine during their stay in the NICU were more sensitive to pain. It is unclear from that study whether judicious dosages of morphine were administered. Inadequate doses of morphine (too low or too high) also induce neuroanatomical changes, which may give the same outcome as nociception.[2]

For practical reasons, we were not able to select control children without any history of minor surgery; however, surgeries were conducted after 18 months of age. All of these children received relief for postoperative pain. According to the findings of Ruda et al,[3] we did not expect that minor surgery would have any effect on pain thresholds as no alterations in neuroanatomy of the dorsal horn or in pain thresholds were found in adult rats that were exposed to pain at the age of 14 days. This was confirmed by our statistical analyses.

Subgroup analysis of the index group shows that negative hospital experiences such as major surgical procedures, higher TISS scores, and longer stays in the NICU affect pain thresholds at 14 months of age. These alterations, however, are not permanent as there was no association between the number of these negative hospital experiences and biobehavioral pain responsiveness at the age of 45 months. Experimental studies in animals also suggest recovery over time as the altered pain thresholds return to normal values at adult age.[40,44] A possible explanation is the plasticity of the CNS; besides pain in early infancy, daily experiences in infancy and childhood form and reform neuronal pathways. These "learning effects" may eventually influence children's neural processing of nociception, even in the presence of CNS alterations. This seems to be evident for the children who had few negative hospital experiences and received MMR and for all who received DTT immunization. Additional research, however, is necessary.

Another explanation for the absence of associations between negative hospital experiences and biobehavioral pain responses at the age of 45 months is that these children can be instructed on what to expect and can be rewarded after good behavior.[45] Furthermore, their ability to cope with the situation and the pain are more extended compared with 14-month-olds. A third explanation might be that the DTT immunization is less painful than the MMR.

An unexpected finding was the diminution in HR accelerations when the number of negative hospital experiences increased. From a psychophysiologic perspective, HR deceleration can be regarded as a process that facilitates environmental intake; HR acceleration, on the contrary, filters out irrelevant stim-

TABLE 3. Spearman Rank Correlations Between Negative Hospital Experiences and Biobehavioral Pain Responses

	MMR			DTT		
	Adverse Hospital Events	Minor Surgery	Days Hospitalized	Adverse Hospital Events	Minor Surgery	Days Hospitalized
Pain	0.59	0.47	0.45	−0.25	−0.08	−0.10
P value	.03	.09	.11	.14	.63	.56
Sadness	0.45	0.39	0.38	−0.13	0.0	−0.03
P value	.11	.17	.18	.43	1.0	.87
Anger	0.33	0.43	0.42	−0.19	−0.13	0.04
P value	.25	.12	.14	.27	.46	.80
HR before	0.09	0.31	−0.02	−0.03	−0.17	0.0
P value	.79	.29	.93	.86	.29	.99
HR response	−0.65	−0.52	−0.70	−0.12	−0.18	−0.07
P value	.01	.06	.01	.48	.29	.67
Cortisol before	−0.27	−0.43	−0.20	0.14	−0.08	0.21
P value	.37	.14	.51	.49	.69	.29
Cortisol response	−0.13	−0.12	−0.06	−0.16	−0.22	−0.13
P value	.67	.69	.85	.41	.25	.50

uli (eg, nociception) that have distraction value for the performance of internalized cognitive elaboration.[46] From this perspective, it thus seems that with increasing number of negative hospital experiences, children become less effective in filtering nociceptive input. However, the less vigorous acceleration in HRs can also be regarded as an adaptive response of the body as it reduces among others overall oxygen consumption.

Experimental studies in animals show that repetitive neonatal pain may, apart from alterations in pain thresholds, lead to vulnerability to stress disorders and anxiety-mediated adult behavior.[40] Grunau et al[20] found, in ELBW-born children, that the duration of NICU stay after 8 to 10 years was related to small increases in pain affect ratings in recreational and daily living settings but not for medical and psychological pain. We therefore investigated whether major surgery or number of negative hospital experiences would alter the affective dimension of the pain experience. Anxiety was found in only 3 children, 2 of which had a history of major surgery. However, this emotion was fleeting, as the maximum time of occurrence was not more than 2 seconds. Moreover, no differences were found in the occurrence with the other affective pain reactions such as anger and sadness between the index and control groups. Neither was there a relation between these emotions and number of negative hospital experiences.

CONCLUSION

This is the first clinical study to demonstrate that major surgery in combination with an appropriate and standardized analgesic protocol within the first months of life does not result in an altered pain response to subsequent pain exposure in childhood. Prolonged exposure to early hospitalization contributes to an altered pain response, which seems to "recover" over time. Whether in humans structural neuroanatomical alterations are still apparent after a prolonged period is not known but seems highly likely. New achievements in neuroimaging, such as magnetic resonance imaging[47] or contrast positron emission tomography scan,[48] might give new clues to answer these intriguing questions.

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PURVEYORS OF DISASTER

"The pharmaceutical industry is, of course, in the business of inventing treatments. Some people wonder whether it may help invent diseases, too."

Groopman J. Hormones for men. *New Yorker Magazine.* July 29, 2002

Submitted by Student