Procedural Pain in Newborn Infants: The Influence of Intensity and Development

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ABSTRACT. *Objective.* **Previous reports have shown that pain is managed inadequately in newborn infants. Ironically, clinicians believe that infants can experience pain much like adults, that infants are exposed daily to painful procedures, and that pain protection should be provided. In adults, a close relationship has been shown in how adults behave in response to pain, how painful they sense the stimulus to be, and physical measurements of the intensity of the stimulus. Whether similar parallels exist in newborn infants has not been examined. If these parallels do not exist in infants, it may help explain why clinicians fail to manage procedural pain in infants more effectively. The objective of this study was to determine whether the magnitude of infants' responses to nursing/medical procedures: 1) differs as a function of the invasiveness or intensity of the procedure; 2) differs as a function of intrauterine (gestational age at birth) and/or extrauterine (conceptional age) development; and 3) parallels the subjective pain ratings of clinicians for those procedures.**

Methods. **A broad developmental and clinical range of newborn infants was studied shortly before (baseline and preparatory periods), throughout, and shortly after (recovery period) required nursing/medical procedures during hospitalization. Heart rate, oxygen saturation, mean arterial pressure, and behavioral state (percentage of time spent in sleep or in agitation) were measured, and the magnitude of change in each in response to procedures was calculated. Procedures were categorized as mildly, moderately, and highly invasive to examine differences in response magnitude as a function of procedural invasiveness. Responses were compared as a function of prematurity and postnatal age. Clinicians' procedural pain ratings were compared with the magnitude of infants' responses.**

Results. **Of the original 152 infants, 135 were studied at least two times (range 2–27). Significant changes occurred in physiologic and behavioral measures in response to procedures indicative of pain responses. The magnitude of response generally increased with increased procedural invasiveness although there was considerable overlap of magnitude with invasiveness. Both premature and full-term infants differentiated procedural invasiveness. Very premature infants (<28 weeks' gestational age) exhibited increased increments in response magnitude with increasing postnatal age. Clinician's ratings of procedural painfulness were correlated with and predicted the magnitude of heart rate response to individual procedures.**

Conclusions. **Similar to what has been shown in adults, newborn and developing infants show increased magnitude physiologic and behavioral responses to increasingly invasive procedures, demonstrating that even very prematurely born infants respond to pain and differentiate stimulus intensity. However, the considerable overlap of magnitude with invasiveness suggests that there is not a physiologic or behavioral threshold that clearly marks the presence of pain. Inconsistencies in physiologic and behavioral responses make reliance on a pain index difficult. The best approach may be one of universal precaution to provide pain management systematically to reduce the acute and long-term impact of early procedural pain.** ***Pediatrics*** **1999;104(1). URL: http://www.pediatrics.org/cgi/content/full/104/1/e13;** ***development, stimulus intensity, pain response.***

ABBREVIATIONS. IVH, intraventricular hemorrhage; BASE, undisturbed baseline; PREP, preparatory procedures; PROC, actual procedure; REC, undisturbed recovery; MAP, mean arterial pressure.

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As part of their required clinical care in a hospital nursery setting, infants, whether healthy or sick, can be exposed to procedures that adults consider to be painful. Some of these procedures are more invasive and presumably more painful than are others. A recent survey showed that clinicians (ie, physicians and nurses) who are at the bedside of newborn infants on a daily basis believe that infants are capable of experiencing pain much like adults and that they are exposed routinely to moderately to very painful procedures.[1] Despite these beliefs, clinicians perceive the current use of both pharmacologic and nonpharmacologic pain management for procedures to be uniformly low.[1] They also believe that pharmacologic pain-relieving agents should be provided for the most painful procedures and that nonpharmacologic comfort measures (eg, pacifiers, swaddling) should be provided regardless of the painfulness of the procedure.[1]

In adults, a close relationship has been demonstrated in reflex response thresholds, pain sensation thresholds, and stimulus intensity[2–4] Therefore, there is a close relationship among how adults behave in response to pain, how painful they report the stimulus to be, and physical measurements of the intensity of the stimulus. This relationship can be modified by many factors such as psychologic or sociocultural influences.[5,6] However, even this basic relationship has not been demonstrated among infants, because laboratory-induced pain is unethical and self-reported ratings are not obtainable. Nevertheless, if, as clinicians believe, the experience of infants in pain is relatively similar with that of adults, we would hypothesize that the magnitude of infants' responses would parallel increases in the intensity or invasiveness of the stimuli. If these parallels do not exist, this may help explain why clinicians fail to manage infant pain more effectively.[1,7]

The present cross-sectional and longitudinal study was conducted to determine whether the magnitude of infants' responses to nursing/medical procedures: 1) differs as a function of the invasiveness or intensity of the procedure; 2) differs as a function of intrauterine (gestational age at birth) and extrauterine (conceptional age) development; and 3) parallels the subjective pain ratings of clinicians for those procedures. Because the literature suggests that developmental and clinical status may influence the magnitude of infants' responses to pain,[8,9] a broad developmental and clinical sample of infants was studied. In the absence of a single validated parameter to index infant pain, multiple indices, including both physiologic and behavioral parameters, were used to characterize the infants' responses.

METHODS

Subjects

On recruiting days, admission logs and medical charts were reviewed to identify potential subjects. Eligible infants included healthy and sick, full-term, and premature infants who had been admitted to a normal newborn, premature, or intensive care nursery. Recruitment was stratified by specific gestational age groupings (ie, <28 weeks, 28–32 weeks, 33–36 weeks, >36 weeks) in an attempt to achieve an even developmental distribution. Infants with major congenital anomalies or cardiac defects were not eligible for recruitment to avoid confounding. Informed consent was obtained from the mothers of eligible infants shortly after nursery admission to participate in studies conducted during the neonatal hospitalization.

Nursery and Medical Procedures

Each subject was studied longitudinally during their neonatal hospitalization while undergoing required nursing or medical procedures. Scheduling of studies was accomplished through an interface of research and nursery personnel. All subjects were studied initially during a routine physical examination. This included placement of a room temperature (cool to cold) stethoscope to the chest. Then, subjects were studied during additional procedures as they were required clinically and as often as research resources would allow. These procedures were categorized subjectively as being mildly, moderately, or highly invasive. In the absence of a conventional method of quantifying the invasiveness of various medical nursery procedures, categorization was based, in part, on the general duration (eg, very brief vs very long) and site of the procedure (eg, heel vs penis) and the depth and extent of tissue damage, as with methods used previously to describe the invasiveness of circumcision and surgical procedures.[10–12] All procedures were performed by nursery personnel with the exception of heelsticks and physical examinations which were performed by the research nurse.

Data Collection Protocol

Before performing any procedure, three electrodes were placed in a conventional pattern on the chest if electrodes were not already in place. In addition, a pulse oximeter sensor and a cuff for noninvasive blood pressure measurements were placed. Signals from the neonatal heart rate monitor (Seimens Sirecust 404, Erlangen, Germany) and pulse oximeter/blood pressure monitor (Dinamap Plus, Critikon, Tampa, FL) were input to a personal computer at the bedside using data acquisition software (LabView, National Instruments, Austin, TX). Simultaneous keyboard entries were used to annotate the timing of procedures and to record comments.

Physiologic data were input continuously to the computer. Data collection was defined by four distinct sequential periods regardless of the clinical procedure. These included a baseline during which the infant was undisturbed in the isolette, a preparatory period during which the subject was prepared for the required procedure (eg, foot swabbed in preparation for a heelstick, infant restrained and genital area cleansed in preparation for a circumcision), the procedure itself, and a recovery period during which the infant was undisturbed in the isolette. Videotapes of each study were made and the behavioral state[13] of the infant during each of the four procedural periods was coded continuously by one of two trained coders using a 6-state scheme. A form was completed by the research nurse to include the infant's birth date and time, birth weight, gestational age, initial diagnoses, and Apgar scores. At the time of each study another form was completed to include the date and time of study, type and time of last feeding, presence of intraventricular hemorrhage (IVH) and current medical interventions (eg, oxygen, ventilation, and bilirubin lights). Current medications received by the subject were documented. These included local anesthetics, caffeine, opiates, diuretics, bronchodilators, pressers, steroids, anticonvulsants, antiarrhythmias, and neuromuscular agents. Sequential medical chart reviews were conducted to document the number and type of all procedures required during each 24-hour period throughout hospitalization and a running total for days on oxygen and on assisted ventilation. All demographic and clinical data were computer-entered.

Clinicians' Beliefs About Infant Procedural Pain

In a previous study,[1] 374 neonatal clinicians (327 nurses and 47 physicians) completed a questionnaire about infant pain and pain management. Using a 5-point Likert scale, they rated the painfulness of 12 bedside nursery procedures. These included five of the procedures (ie, gavage tube insertion; intravenous insertion; percutaneous central venous catheter or venipuncture; arterial puncture; lumbar puncture; and circumcision) that subjects had undergone as part of the current study. For the current analyses, the clinicians' ratings for these specific procedures were compared with the magnitude of the infants' actual physiologic and behavioral responses to those procedures to determine how closely the two paralleled.

Data Quantification and Analysis

Only subjects who had undergone two or more studies were included in the current sample although only one of their studies may have been included in the present analysis because of uninterpretable or missing data. Physiologic data were reviewed for nonphysiologic artifact and algorithms were applied to reject artifact,[14] producing an analysis dataset. A mean and SD for each physiologic parameter were computed for each of the four periods. For behavioral state, the percentage of time spent in each of the six behavioral states was calculated for each subject for each period during each study. To simplify, the percentage of time spent in state 1 (quiet sleep) and state 2 (active sleep) was used to represent the time spent in sleep, and the percent time spent in state 5 (fussy) and state 6 (crying) was used to represent the time spent agitated during each of the four periods. The difference in undisturbed baseline values (BASE) and values during preparatory procedures (PREP), actual procedure (PROC), and undisturbed recovery (REC) for each physiologic and behavioral parameter was computed to create an index of response magnitude. The Student's t tests examined whether these differences were equal to zero.

To determine the influence of subject characteristics on base values, correlations and the Student's t tests were performed for each physiologic parameter. Then, a repeated measures ANOVA model (PROC MIXED; SAS Institute, Cary, NC) was created to examine the influence of procedural invasiveness and development on response magnitude. These analyses were restricted for simplicity to one physiologic parameter, heart rate, and behavioral state, including both sleep and agitation. Intrauterine development was categorized as gestational ages of <28 weeks, 28–31 weeks, 32–36 weeks and >36 weeks at birth. Responses were compared among these four groups at two time points: studies conducted within the first week of life and studies conducted at >36 weeks' conceptional age (gestational age plus postnatal age). Each analysis model included base values, procedural invasiveness (mild, moderate, and high), gestational age category, and the interaction of gestational age category with invasiveness. (Analyses of behavioral state during the first week of life and >36 weeks' conceptional age include only two levels of procedural invasiveness [mildly and moderately invasive procedures] because of a paucity of usable data for those infants born >36 weeks' gestational age). To increase precision, the models also included whether supplemental oxygen, mechanical ventilation, and/or medications were provided at the time of study, as well as data on race, gender, and severity of IVH. To examine the effects of extrauterine development, a repeated measures ANOVA compared the heart rate and behavioral state responses of infants born at <28 weeks' gestational age during four conceptional age time periods: <28, 28 to 31, 32 to 36, and >36 weeks' conceptional age. These analysis models included the same covariates as in the previous analyses but substituted conceptional age for gestational age categories. Mean procedural pain ratings by clinicians extracted from our previous study were compared with the subjects' physiologic and behavioral responses (difference scores) to those same procedures using correlation analyses. A regression analysis model (PROC REG; SAS Institute, Cary, NC) was used to examine whether clinician's procedural pain ratings predicted the magnitude of physiologic and behavioral state responses. All statistical analyses were performed with SAS.

RESULTS

Subject Characteristics

A total of 152 subjects were recruited as newborns. Of these, 135 underwent at least two studies during the neonatal period and were included in the current analyses. Thirteen subjects underwent no studies before discharge (n = 6) or death (n = 7), and 4 subjects underwent only one study and were not included in the current analyses. Subject characteristics are shown in Table 1.

There were no differences between those subjects included (n = 135) and those not included (n = 17) in the current analyses with respect to gestational age (32 ± 5 vs 33 ± 7 weeks; P = .42), birth weight (1920 ± 1024 vs 2432 ± 1360 g; P = .18), gender (61/74 vs 8/7 girls/boys; P = .72), and race (71/63 vs 9/8 white/black; P = .87). The total number of studies analyzed was 678 and the number of studies per subject included in the current analyses is shown in Fig 1.

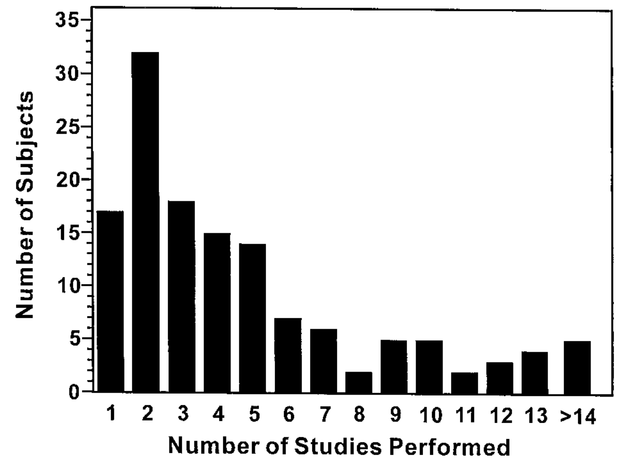


Fig 1. Number of studies analyzed per subject.

Physiologic Changes Within Procedures

The mean values (± SE) for each physiologic parameter during each of the four procedural periods during all studies are shown in Fig 2A–C. There were significant increases in mean heart rate from BASE to PREP, PREP to PROC, and BASE to PROC; and there were significant decreases from PROC to REC although heart rate remained elevated during REC over base levels (all P values = .0001). Mean oxygen saturation fell significantly from BASE to PREP and from BASE to PROC (P values =.0001) and remained lower during REC than during BASE (P = .001). Mean arterial pressure (MAP) was elevated significantly from BASE to PREP and from BASE to PROC but was significantly lower during REC than during BASE (all P values = .0001).

Behavioral Changes Within Procedures

As expected, infants became more agitated in response to procedures (Fig 2, D). From BASE to PREP and from PREP to PROC, there were significant decreases in sleep and significant increases in agitation (all P values = .0001). From PROC to REC, sleep

TABLE 1. Subject Characteristics

	Gestational Age at Birth				
	<28	28–32	33–36	>36	Overall
No. of subjects	33	42	30	30	135
Mean birth weight (g)	851 ± 223	1419 ± 410	2253 ± 378	3449 ± 438	1920 ± 1024
Mean 5-minute Apgar	6.7 ± 2.2	7.5 ± 1.6	7.8 ± 1.2	8.0 ± 1.1	7.5 ± 1.6
No. girls/boys	18/15	18/24	15/15	10/20	45/55%
No. white/black	14/19	29/13	15/14	13/16	53/47%
No. with IVH (none/grades I–II/grades III–IV)	15/12/6	23/10/9	28/2/0	28/1/1	70/19/11%
Mean days on oxygen	71 ± 49	20 ± 29	3 ± 6	3 ± 5	25 ± 40
Mean days on mechanical ventilation	39 ± 29	10 ± 17	2 ± 4	1 ± 4	13 ± 23
No. studies conducted with opiates (yes/no)	25/297	23/182	1/76	6/63	8/92%
No. studies conducted with caffeine (yes/no)	63/259	33/172	0/77	0/69	14/86%
Mean length of stay	82 ± 40	39 ± 26	14 ± 8	8 ± 5	37 ± 38
No. of studies performed	323	205	81	69	678
Mean no. of procedures* during stay	766 ± 648	223 ± 344	56 ± 71	44 ± 72	279 ± 471

* Procedures included aerosol rx, arterial stick, c-pap bagging, broviac, bath, cardiac catheterization, circumcision, code, chest tube insertion, physical exam, extubation, eye exam, gavage tube insertion, injection, intubation, intravenous insertion (IV), lumbar puncture (LP), nose culture, percutaneous cerebral venous catheter, postural drainage, arterial catheterization, heelstick, suctioning, surgery, urine catheterization, ultrasound, venipuncture, and wound care.

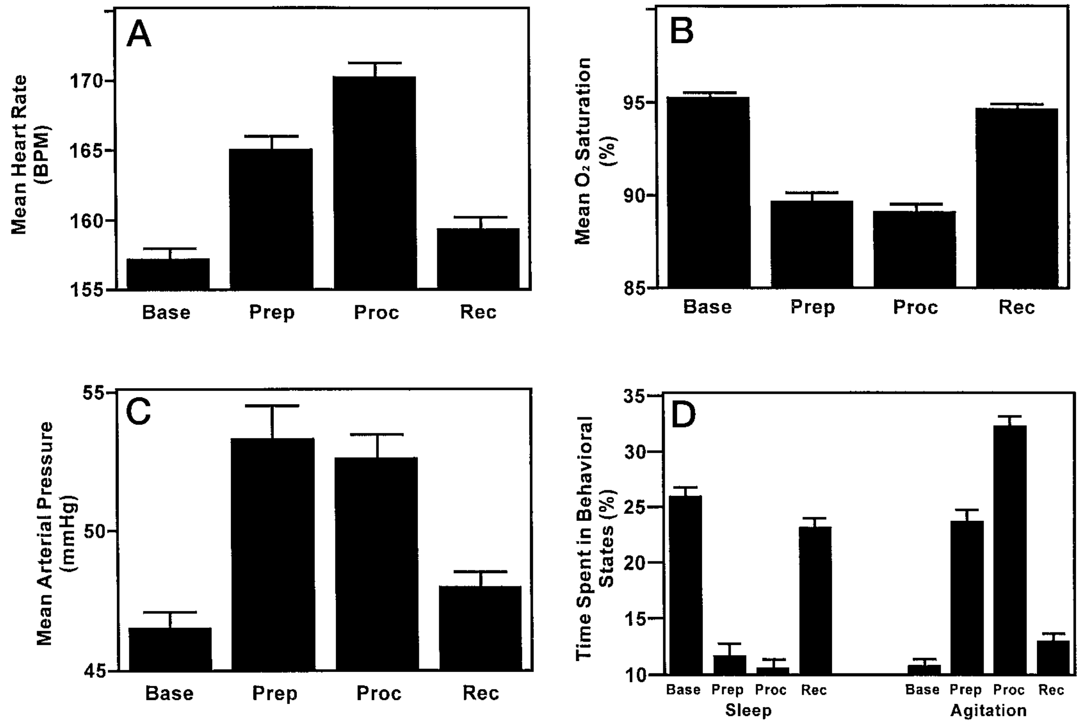


Fig 2. Physiologic and behavioral measures (mean ± SE) during BASE, PREP, PROC, and REC for all procedures. A indicates mean heart rate; B, mean oxygen saturation; C, MAP; and D, mean percent time spent in sleep (left) and agitation (right).

increased and agitated behavior decreased (*P* values = .0001).

Influence of Subject Characteristics on Base Measures

Analyses that examined the influence of subject characteristics on BASE for each parameter revealed that gestationally younger and smaller birth weight subjects had, as expected, higher BASE levels of heart rate (*r* values >.51; *P* values = .0001). However, there was no relationship between gestational age or birth weight and BASE levels of oxygen saturation or MAP. Subjects who were conceptionally older at the time of the study had significantly higher MAP levels ($r = .32$; $P = .0001$) during BASE. Subjects with more severe grades of IVH had higher heart rates ($r = .21$; $P = .0001$) and MAP ($r = .20$; $P = .0001$) and lower oxygen saturation ($r = -.17$; $P = .0005$) levels during BASE, even after controlling for gestational age. Subjects who were receiving opiates at the time of study had lower BASE heart rates (151 ± 19 vs 158 ± 19; $P = .008$) and MAP (41 ± 13 vs 47 ± 12; $P <$ .01), whereas those subjects receiving the stimulant caffeine had higher BASE heart rates (170 ± 16 vs 155 ± 18; $P = .0001$). Subjects receiving supplemental oxygen at the time of study had higher BASE heart rates (161 ± 19 vs 152 ± 18; $P = .0001$), and those subjects being ventilated had lower MAP (42 ± 13 vs 48 ± 11; $P < .0001$). There were no physiologic differences during BASE as a function of race or gender. There were no physiologic differences during BASE among subjects about to undergo mildly, moderately, or highly invasive procedures when covariates that were shown to influence BASE (eg, birth weight effects on heart rate) were controlled for.

There were no systematic effects of gestational age or birth weight on behavioral state during BASE. However, conceptionally older subjects spent less time in sleep states ($r = -.23$; $P = .0001$) and more time in agitated states ($r = .19$; $P = .0001$) during BASE. Subjects with more severe grades of IVH also spent less time in sleep states during BASE ($r = -.14$; $P = .0007$). In contrast, ventilated subjects spent more time sleeping (31% ± 18 vs 24% ± 18%; $P < .0001$) and less time in agitated states (8% ± 12% vs 12% ± 12%; $P < .0006$). Similarly, subjects who were receiving opiates also spent more time sleeping (39% ± 15% vs 25% ± 18%; $P < .0001$) and less time in agitated states (4% ± 7% vs 12% ± 12%; $P = .0001$) during BASE. There were no race or gender effects on behavioral state during BASE. Subjects who were about to undergo mildly invasive procedures spent more time sleeping during BASE compared with those undergoing moderately invasive procedures (least-square means [SE] = 35 [3] vs 26 [3]%; $P =$ .0001), even after controlling for covariates (cited above). However, there were no differences in nonsleep behavioral states during BASE as a function of upcoming procedural invasiveness.

Physiologic and Behavioral Changes as a Function of Procedural Invasiveness

Insertion of a gavage tube ($n = 19$), physical examinations ($n = 248$), nose cultures ($n = 4$), and umbilical arterial catheter insertion ($n = 2$) were categorized as mildly invasive procedures; arterial punctures ($n = 9$), venous punctures ($n = 10$), and heelsticks ($n = 311$) were categorized as moderately invasive procedures; and circumcision ($n = 17$), lumbar punctures ($n = 10$), and eye examinations for retinopathy of prematurity ($n = 49$) were categorized as highly invasive procedures. The level of invasiveness significantly affected the magnitude of physiologic and behavioral change from BASE to PROC (Fig 3). A gradient in response magnitude was observed that increased from mildly to moderately to highly invasive procedures (all P values $< .01$). The only exceptions were that there was no difference in the magnitude of response for sleep between mildly and moderately invasive procedures and no difference for oxygen saturation and agitated behavior between moderately and highly invasive procedures. Despite the gradient in response magnitude with respect to procedural invasiveness, there was considerable overlap in response magnitude as shown in Fig 4 for the change in heart rate. For example, a 20- to 30-bpm change in heart rate from BASE to PROC could occur in response to mildly, moderately, and highly invasive procedures.

Effect of Gestational Age on Magnitude of Response

To determine the effect of gestational age on procedural responses early in life, the responses of the four gestational age groups to procedures conducted within the first week of life were compared (Fig 5). There was no primary effect as a function of gestational age; the four gestational age groups seemed to respond similarly for heart rate ($P = .22$), agitation ($P = .08$), and sleep behavior ($P = .60$) shortly after birth. However, there was a significant primary effect of procedural invasiveness. During the first week of life, the magnitude of the change in heart rate ($F = 12.45_{(2,84)}$; $P = .0001$), agitation ($F = 6.32_{(1,56)}$; $P = .01$), and sleep ($F = 7.94_{(1,56)}$; $P = .007$) was significantly different as a function of procedural invasiveness. Although changes in heart rate and behavioral state were always of less magnitude in response to mildly invasive procedures, increases in invasiveness did not always parallel increases in response, as seen in the heart rate responses of the 28 to 32 week group. There was no significant interaction between gestational age and procedural invasiveness for any measure. Thus, within the first week of life newborn infants differentiate the level of invasiveness of procedures regardless of differences in gestational age.

To determine the effect of gestational age on responses later in development, the same four gestational age groups were compared, using only study subjects >36 weeks' conceptional age (Fig 6). There was a primary effect of gestational age on the magnitude of change in heart rate in response to procedures ($F = 3.36_{(3,66)}$; $P = .02$). Two of the groups (<28 weeks and 32–36 weeks) exhibited equivalent magnitude responses (16 ± 3 bpm [least square means ± SE]), whereas the 28–32-week group exhibited the largest response (23 ± 4 bpm) and the >36-week group exhibited the smallest response (7 ± 3 bpm). Each of the groups was significantly different from the full-term group with respect to the magnitude of the heart rate response (P values $< .04$). There was no primary effect of gestational age on the magnitude of change in the percentage of time spent in sleep ($P = .10$) or agitated ($P = .23$) behavior during procedures. There was a significant primary effect of procedural invasiveness on the magnitude of change in heart rate ($F = 14.86_{(2,121)}$; $P = .0001$) and in agitated behavior ($F = 4.49_{(1,68)}$; $P = .04$); the increase from BASE to PROC was significantly greater with each

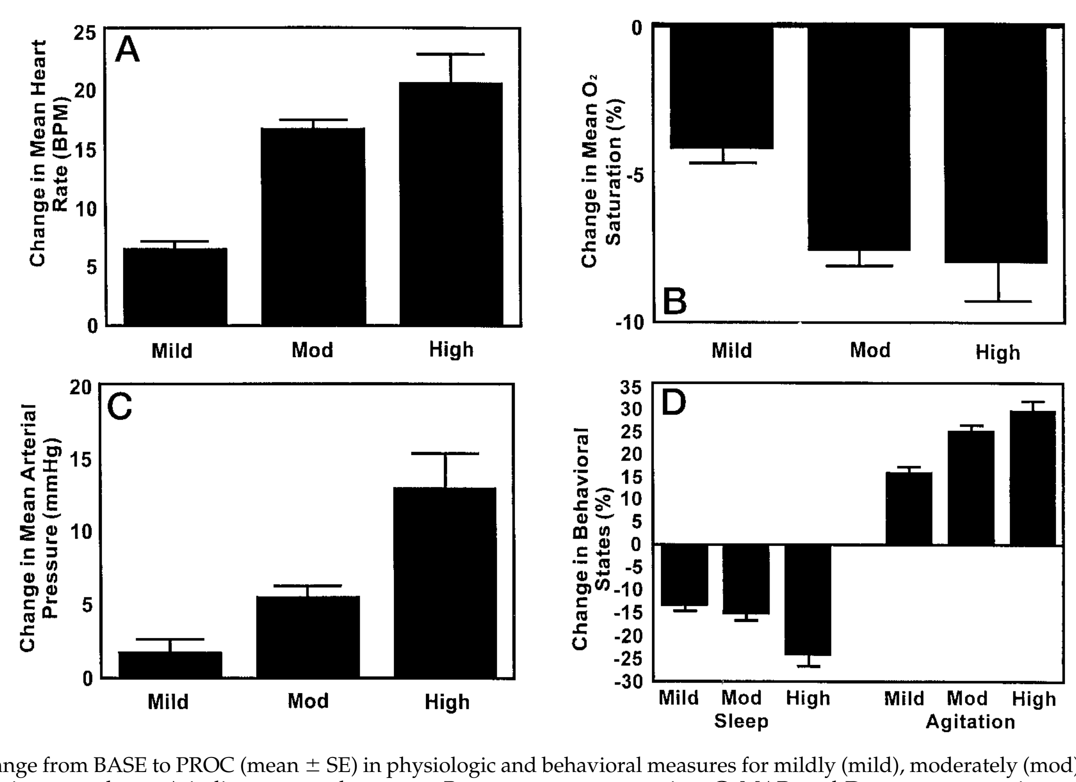


Fig 3. Change from BASE to PROC (mean ± SE) in physiologic and behavioral measures for mildly (mild), moderately (mod), and highly (high) invasive procedures. A indicates mean heart rate; B, mean oxygen saturation; C, MAP; and D, mean percent time spent in sleep (left) and agitation (right).

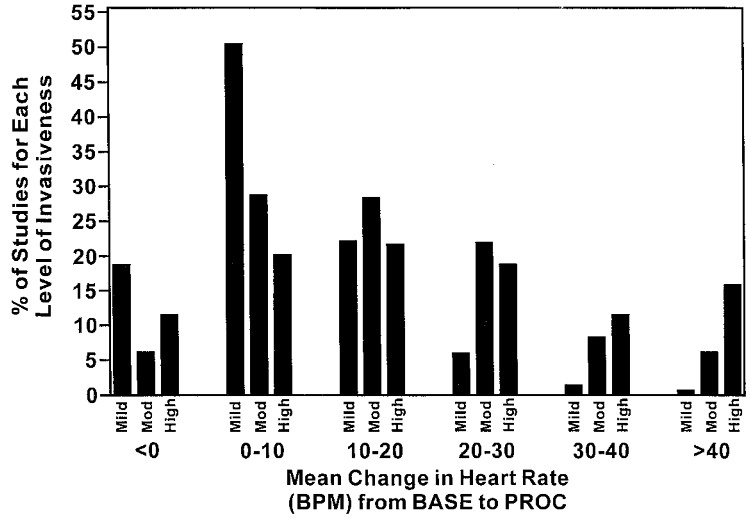


Fig 4. Percentage of studies for each level of procedural invasiveness in which the mean change in heart rate from BASE to PROC was negative (<0 bpm), 0 to 10 bpm, 10 to 20 bpm, 20 to 30 bpm, 30 to 40 bpm, or >40 bpm.

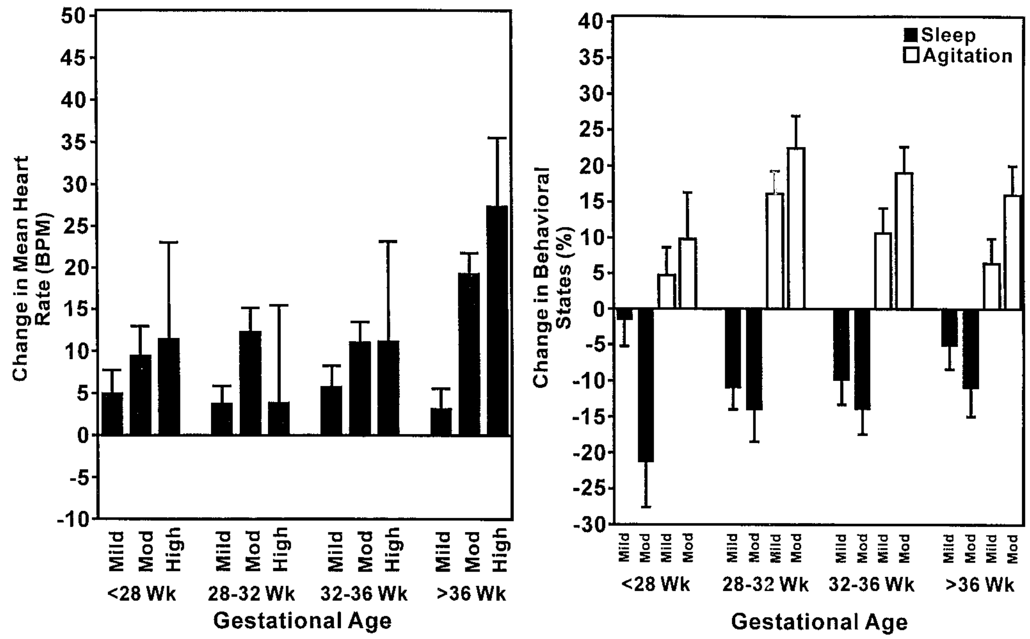


Fig 5. Mean (least square mean ± SE) change in heart rate and behavioral state from BASE to PROC for each level of procedural invasiveness for infants <28, 28 to 32, 32 to 36, and >36 weeks' gestational age studied within the first week of life. Behavioral state data are not shown for highly invasive procedures because of paucity of behavioral data for those infants born >36 weeks' gestational age.

increase in procedural invasiveness. There was also a significant interaction between gestational age and procedural invasiveness for heart rate ($F = 2.13_{6,121}$; $P = .05$); infants born at <28 weeks and at >36 weeks showed equal magnitude responses to moderately and highly invasive procedures, whereas infants born between 28 and 36 weeks' gestational age showed a more linear response with increasing invasiveness.

The Effect of Conceptional Age on Magnitude of Response

To determine whether newborn infants' responses to painful procedures change over time, the responses of infants born at <28 weeks were compared as they progressed through four sequential conceptional ages: <28 weeks, 28 to 32 weeks, 32 to 36 weeks, and >36 weeks (Fig 7). The magnitude of heart rate change from BASE to PROC increased with increasing conceptional age ($P = .005$). A similar trend was seen for agitated behavior ($P = .06$). Procedural invasiveness had a statistically significant effect for all measures (P values $< .03$); responses to mildly invasive procedures were consistently different than were responses to both moderately (P values $= .05$) and highly (P values $< .03$) invasive procedures, but responses to moderately and highly invasive procedures were not different. There were no significant interactions between conceptional age and procedural invasiveness.

Relationship Between Clinician's Pain Ratings and Infants' Procedural Responses

Figure 8 shows the mean change from BASE to PROC in heart rate and percent time spent in agitation for each procedure studied. Sleep is not shown,

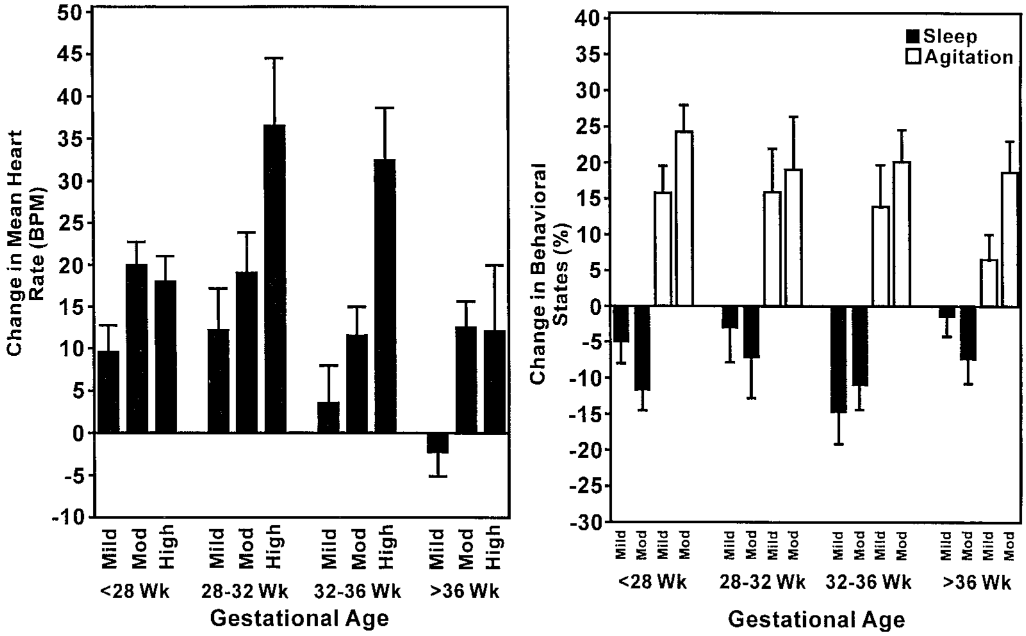


Fig 6. Mean (least square mean ± SE) change in heart rate and behavioral state from BASE to PROC for each level of procedural invasiveness for infants <28, 28 to 32, 32 to 36, and >36 weeks' gestational age studied at >36 weeks' conceptional age. Data for behavioral state are not shown for highly invasive procedures because of paucity of information for those infants born >36 weeks' gestational age.

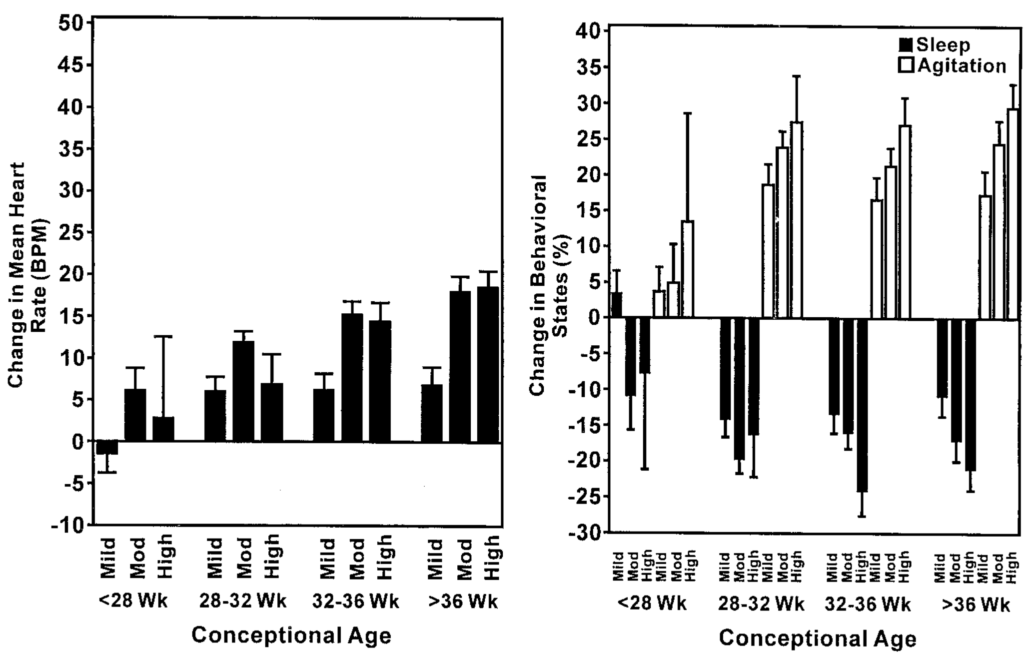
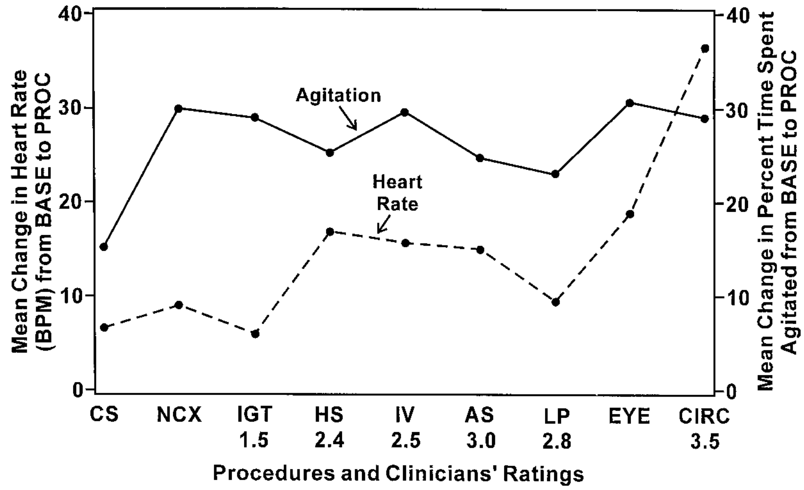


Fig 7. Mean (least square mean ± SE) change in heart rate and behavioral state from BASE to PROC for each level of procedural invasiveness for infants <28 weeks' gestational age studied at <28, 28 to 32, 32 to 36, and >36 weeks' conceptional age.

because it was generally inversely related to agitation. The procedures are displayed in the order of the originally proposed gradient of procedural invasiveness. The change from BASE to PROC for mean heart rate ranged from ~7 ± 9 bpm in response to a cold stethoscope to 37 ± 23 bpm during circumcision and for agitation, from an increase of 15 ± 16% to the cold stethoscope to 31 ± 14% to an eye examination. The clinicians' ratings for those procedures shared in common across this and the previous survey study[1] are shown along the x-axis in Fig 8. There was a low but significant correlation between the clinicians' ratings of painfulness and the magnitude of the heart rate response from BASE to PROC (r = .25; P = .0001). A regression analysis showed that clinicians' pain ratings significantly predicted the magnitude of heart rate changes from BASE to PROC (P = .0001), controlling for BASE levels, gestational age, day of life, and whether the infants' were ventilated at the time of study. For each 1-unit change in pain rating (on a 5-point scale), heart rate increased an average of 13 bpm from BASE to PROC.

Fig 8. Mean change from BASE to PROC in heart rate (bpm) and agitation (percent time spent) for each procedure. Clinicians' ratings of procedural painfulness[1] are shown along horizontal axis. CS indicates cold stethoscope component of physical examination; NCX, nose culture; IGT, insertion of gavage tube; HS, heelstick; IV, insertion of intravenous line; AS, arterial puncture; LP, lumbar puncture; EYE, eye examination for retinopathy of prematurity; and CIRC, circumcision.



DISCUSSION

The results of this study demonstrate that on average newborn infants differentiate the intensity or invasiveness of stimuli associated with their required nursing and medical care while in the hospital. Generally, the more intense the stimulation, the greater the magnitude of their physiologic and behavioral responses (Fig 3). This was observed both within procedures as each progressed from beginning to end (Fig 2) and across procedures that differed in level of invasiveness (Fig 3). These findings are generally consistent with those in adults, suggesting relatively parallel relationships among sensation, response magnitude, and stimulus intensity.

However, as in studies of adults, important modifiers of these relationships were observed in this sample of infants. Gestational age was one important modifier. When infants of varying gestational ages were compared within the first postnatal week of life, they clearly differentiated between mildly and more (ie, moderately and highly) invasive procedures. However, they did not differentiate between the more (ie, moderately versus highly) invasive procedures. Thus, early in their lives, infants seem to respond similarly to procedures that adults may perceive as being substantially different in terms of intensity. This was true for infants of very different gestational ages such that full-term infants did not differentiate invasiveness with greater resolution than did very premature infants during the first week of life. However, when these same infants were observed after they reached 36 weeks conceptional age, the magnitude of their physiologic responses now differed as a function of their prematurity. Infants born closest to full-term displayed the smallest heart rate increases to procedures compared with all other gestational age groups. This suggests lingering effects of a premature exposure to extrauterine life, reflected in greater lability in response to pain even 2 months after birth. However, it does not necessarily indicate that full-term infants are less sensitive to pain than are premature infants. In addition, at this later conceptional age, infants were now differentiating among all three levels of procedural invasiveness. However, this differentiation was accounted for by infants born between 28 and 36 weeks gestational age. The most (<28 weeks' gestational age) and least (>36 weeks' gestational age) prematurely born infants exhibited the same magnitude heart rate responses to both moderately and highly invasive procedures, whereas the 28- to 36-week gestational age infants showed a more linear response. It is not clear from our data what may account for these effects, but they did not seem to be attributable to differences in the distribution of gender, race, or illness (ie, those requiring ventilation, oxygenation, medication).

Another important modifier was conceptional age. Infants born very prematurely (<28 weeks' gestation) became more responsive to procedures as they progressed through their hospitalization. Therefore, very early in their hospital course, premature infants seem to respond in magnitude much like full-term infants, but as their extrauterine exposure proceeds, their responses become increasingly more vigorous. It is difficult to compare these findings with those of the existing studies, because the measures used are not directly comparable. For example, Johnston and Stevens[8] reported that the maximum heart rate during heelstick procedures for infants born at 28 weeks' gestational age was higher when they were studied 4 weeks later (at 32 weeks' conceptional age) than that of infants born and studied at 32 weeks' gestational age. This implies that the heart rate response increases with increased postnatal age, similar with what we observed. Yet in a separate study, Johnston[9] reported no change in the maximum heart rate during heelstick procedures for infants born at <30 weeks' gestational age and studied at 2-week intervals for 8 weeks. To what extent the higher resting heart rates of premature infants[15] may have contributed to these discrepant findings is not clear. Johnston and Stevens[8] also reported that infants born at 28 weeks and studied 4 weeks later displayed significantly less facial activity compared with that of infants born at 32 weeks. Thus, with increased postnatal age (and experience), the earlier born premature infants were less responsive behaviorally. However, in separate heelstick studies Johnston[9] and Craig[16] reported significantly increased facial activity among prematurely born infants as postnatal age increased. These conflicting reports underscore the complexities of characterizing specifically the impact of development on procedural pain responses, but suggest overall that premature and full-term infants sense and respond to pain and differentiate stimulus intensities to one extent or another.

Previously, we reported discrepancies between clinicians' beliefs regarding current and optimal pain management for newborn infants.[1] In that report, we showed that clinicians believe that the medical and nursing procedures they witness and/or perform are painful and that pain management should be used for these procedures. Yet they believe that procedural pain management is used rarely. Our current data suggest that clinicians would not observe small or sick newborns exhibiting well-differentiated responses to different stimulus intensities at least compared with those of more mature infants. This observation may be inconsistent with their own experience of pain such that more intensely painful stimuli should elicit more robust reactions. Clinicians also may not track developmental changes that suggest that over time the responses of these small, sick infants become more vigorous. These impressions may generalize to an assumption that infants do not require pain management, because early in their course, they did not seem to respond to pain. However, both the neuroanatomic and neurophysiologic basis for pain perception seems to be in place by 28 weeks' gestation; not only can pain signals reach the cortex by this gestational age, but there is sufficient cortical maturity to process the signals.[17] It is these premature infants who commonly require more procedures and potentially more invasive procedures during their hospital course. We found the average number of procedures for infants born at $<$28 weeks' gestation to be more than 700 during the course of their hospitalization. Many of these are invasive and would be considered painful by adults.

Although we could not, in a controlled manner examine the impact of different titrations of stimulus intensity on infants' responses, we did examine the relationships among a hypothetical gradient of pain, clinicians' ratings of procedural pain, and the infants' responses. We had hypothesized that circumcision would be at the most invasive end of the spectrum, and this procedure did elicit the most vigorous physiologic and behavioral reactions of those we studied. Similarly, clinicians rated circumcision as the most painful of 12 clinical procedures.[1] Thus, there was convergence in a hypothetical gradient of pain, a survey-based gradient of pain, and the infants' actual responses to one procedure, circumcision. However, we observed other, nonparallel relationships. For example, using the hypothetical pain gradient, we had ranked lumbar punctures as a highly invasive procedure and arterial sticks to draw blood as a moderately invasive procedure. Clinicians ranked lumbar punctures as slightly less painful than arterial sticks, and infants responded with greater heart rate increases to arterial sticks than to lumbar punctures, consistent with clinicians' ratings. Clinicians rated the insertion of a gavage tube as being one of the least painful procedures, similar with its placement along the hypothetical gradient. The increase in heart rate in response to this procedure was relatively small, but it provoked relatively large increases in agitation (29% $\pm$ 18%). These inconsistencies between behavioral and physiologic responses also may lead to confusion regarding the impact of pain on newborns, resulting in unsystematic and inadequate pain management.

These observations highlight the difficulties in developing a pain index for infants, an agenda that has received heightened interest in recent years.[18,19] First, there does not seem to be a physiologic or behavioral response threshold that clearly identifies the presence of pain. This is illustrated in Fig 4 in which similar magnitudes of infants' responses overlap a broad variety of stimuli types and intensities. Second, any index must account for developmental differences, both those attributed to gestational age and those attributed to postnatal age or experience, and there is not yet a consensus about how to characterize these best. Third, there is perhaps no reason to expect the organization of the newborn infants' physiologic and behavioral systems to be so coordinated as to present a unified picture for the caregiver, yet it is not yet clear how to best weight these two domains. In this and other studies, there are numerous instances in which physiologic and behavioral responses do not parallel. Two of the more highly regarded infant pain indices[20,21] that rely heavily on physiologic (eg, breathing patterns or requirement for increased supplemental oxygen) and behavioral (eg, crying, behavioral arousal, and limb movement) parameters are being studied extensively now to determine their validity, reliability, clinical validation, and utility. However, it is clear that inferring pain from a single parameter or an isolated response remains questionable.

As we continue to characterize and examine infants' responses in medical settings, we will hopefully narrow the gap among what clinicians perceive as currently suboptimal pain management for their patients, what they perceive as being desirable, and what is shown to be effective for the infants. In the meantime, the best approach may be one of universal precaution, to provide pain management systematically, not only for those individuals who, for whatever reason, seem to be more likely to respond acutely or to be at the greatest risk for adverse consequences of pain. However, it is also imperative to continue to identify which pain management interventions are more effective, which groups of infants are at highest risk for sequelae of pain, and whether any groups of infants seem to respond negatively to pain management. Nevertheless, with emerging reports that there may be permanent adverse consequences of early pain,[22–25] we should, to the best of our abilities, adopt approaches to provide the best protection against pain and help ensure healthy development for infants who require medical interventions early in life.

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