Conditioning and Hyperalgesia in Newborns Exposed to Repeated Heel Lances

Anna Taddio, PhD
Vibhuti Shah, MD
Cheryl Gilbert-MacLeod, PhD
Joel Katz, PhD

Context Hospitalized infants undergo repeated invasive procedures. It is unknown whether cumulative experiences with pain lead to anticipatory pain behaviors and hyperalgesia.

Objectives To determine whether newborns who are born to mothers with diabetes and undergo repeated pain learn to anticipate pain and exhibit more pain during a painful procedure than normal infants.

Design, Setting, and Participants Prospective cohort study of 21 full-term newborns born to mothers with diabetes and 21 born to mothers with uneventful pregnancies, at a university teaching hospital between August 1999 and October 2000. Infants of diabetic mothers underwent repeated heel lances in the first 24 to 36 hours of life for monitoring of blood glucose concentrations. Pain responses of all infants undergoing a venipuncture on the dorsum of the hand to obtain blood for the newborn screening test after the first day of life were compared. In addition, from September through November 2001, 12 infants of diabetic mothers and 12 normal infants were compared for pain reactions to intramuscular vitamin K injection after birth.

Main Outcome Measures Percentages of time observed grimacing and crying and visual analog scale (VAS) scores.

Results Raters were blinded to exposure group. Median baseline scores for grimacing, crying time, and VAS did not differ significantly between groups ($P=.27$, $P=.32$, and $P=.32$, respectively). Median scores (interquartile range) for grimacing during skin cleansing were higher in infants of diabetic mothers (22.2% [77.5%] vs 0% [15%]; $P=.03$). The VAS scores for both groups were zero, but the distribution of the scores was significantly different (86% of normal infants vs 52% of infants of diabetic mothers had scores of zero) ($P=.04$). During venipuncture, infants of diabetic mothers had higher median scores for grimacing (81.7% [32.5%] vs 40% [73.4%]; $P=.01$), VAS (69% [27.5%] vs 5% [60.5%]; $P=.002$), and crying (40.2% [77%] vs 0% [54.8%]; $P=.03$) compared with normal infants. There were no differences between groups on any pain measure in response to intramuscular injection.

Conclusions Newborns who had diabetic mothers and were exposed to repeated heel lances in the first 24 to 36 hours of life learned to anticipate pain and exhibited more intense pain responses during venipuncture than normal infants.

TEN PERCENT TO 15% OF NEWborns require hospitalization after delivery for medical reasons including prematurity, congenital anomalies, sepsis, jaundice, and feeding difficulties.[1] Hospitalized newborns are subjected to many invasive procedures as part of their medical care. There are anecdotal reports of infants learning to anticipate pain and exhibiting altered pain responses as a consequence of their cumulative exposures to pain.[2]

The objective of this study was to prospectively examine the hypothesis that infants who undergo repeated painful procedures as part of their medical care learn to anticipate pain and exhibit more intense pain during a subsequent painful procedure compared with control infants.

METHODS

This was a prospective cohort study conducted in the postnatal ward of a university-affiliated hospital. The study was approved by the local ethics board, and written consent was obtained from parents of all participating infants. There were 2 groups of full-term neonates: those born to mothers with diabetes (type 1, type 2, or gestational) and those born to mothers with uneventful pregnancies. We excluded infants who were admitted to the neonatal intensive care unit, those receiving intravenous or intramuscular antibiotics, or those who were scheduled for circumcision during the study. Posters were placed in the delivery suite, and nurses and ward clerks were asked to contact the investigator on call when a potential study participant was admitted in labor.

Infants of diabetic mothers underwent repeated heel lances in the first 24 to 36 hours of life for monitoring of blood glucose concentrations. When the study was conducted, the clinical guidelines for glucose concentration monitoring involved obtaining a blood sample within the first hour after delivery and then every 2 to 4 hours during the first 24 hours

Author Affiliations: Department of Pharmacy, The Hospital for Sick Children, Graduate Department of Pharmaceutical Sciences, University of Toronto, Toronto (Dr Taddio), Department of Paediatrics, Mt Sinai Hospital, Toronto (Dr Shah), and Department of Anesthesia and Pain Management, Toronto General Hospital and Mt Sinai Hospital, Departments of Public Health Sciences and Anesthesia, University of Toronto (Dr Katz), Ontario; and Maritime Psychiatry, IWK Grace Health Centre, Halifax, Nova Scotia (Dr Gilbert-MacLeod).
Corresponding Author and Reprints: Anna Taddio, PhD, Department of Pharmacy, The Hospital for Sick Children, 555 University Ave, Toronto, Ontario, Canada M5G 1X8 (e-mail: anna.taddio@sickkids.on.ca).

of life. The frequency of blood sampling was conditional on prior glucose concentration readings and infant symptoms of hypoglycemia. Blood was collected for glucose monitoring by heel lance with automated Microtainer Safety Flow lancets (Becton, Dickinson and Co, Franklin Lakes, NJ). Normal infants were matched to those of diabetic mothers on birth weight (±500 g), sex, vaginal or cesarian delivery, and anesthesia (yes or no) during labor and delivery.

After the first 24 hours of life, all infants underwent a venipuncture to obtain blood for the newborn screening test. Venipunctures were performed in the treatment room on the postnatal floor. The infants were optimally positioned for the procedure (ie, swaddled and lying supine on the examination table). The site chosen for all venipunctures was the dorsum of the hand. A 23-gauge butterfly needle was used. Venipunctures were performed by a variety of nurses who were unaware of the study hypothesis. To standardize observations, the procedure was divided into 3 phases: baseline, skin cleansing and preparation, and needle puncture and collection of the blood sample. Infants' faces were videotaped for the entire procedure.

Pain was rated later from videotapes by using 3 validated behavioral measures: grimacing (based on the Neonatal Facial Coding System),[3] visual analog scale (VAS), and crying time percentage. Three trained research assistants who were unaware of infant exposure group viewed the videotape and rated infant pain by using 1 of the 3 pain measures. The order in which infants appeared on the videotape was random. The videotape contained no information or features that could identify an infant as belonging to either group.

Grimacing has undergone extensive validity testing and is considered the gold standard for assessment of pain in infants.[4,5] For the grimacing scores, we used 3 facial actions that are particularly sensitive for indicating pain: bulging the brow, squeezing the eyes closed, and furrowing the nasolabial area.[6] Each facial action was scored as present or absent in 2-second intervals for the first 20 seconds of each phase of the procedure (or less if the phase lasted fewer than 20 seconds). The percentage of the total time that each facial action was observed during each of the 3 phases was calculated. An overall grimacing pain score was computed for each phase by summing the individual facial action scores and dividing by 3. Interrater reliability was assessed for each facial action in 19% of participating infants; the κ values ranged from 0.86 to 0.91.

Pain ratings using the VAS were based on global facial actions as well as other observable signs of pain, such as body movements and crying. Visual analog scale pain scores were rated on an unmarked 100-mm pain ruler, where 0 was no pain and 100 was the worst possible pain, expressed as a percentage. The VAS was scored across the same period as the grimacing scores. Crying time percentage was calculated across the entire period for the baseline and cleansing phases and across the first 2 minutes after venipuncture.[7] Crying and VAS pain ratings correlate with grimacing ratings and provide social validation of the pain scores obtained from the grimacing scoring system for infant caregivers,[8,9] allowing the pain scores to be understood in common terms.

To rule out the possibility that the infants exposed to multiple heel lances may react differently to venipuncture as a consequence of their medical condition and not repeated experience with pain, we compared the responses of a separate cohort of infants of diabetic mothers with those of a group of normal infants during intramuscular vitamin K injection, which is the first painful procedure performed on all newborns. This protocol was carried out in the same institution, with ethical approval and informed parental consent. Infants were matched on type of delivery.

Rating of pain in response to the intramuscular vitamin K injection was done from videotaped records and was divided into 3 phases: baseline, skin cleansing and preparation, and needle puncture and injection. Grimacing, VAS scores, and crying were calculated as described for venipuncture: during baseline, skin cleansing, and the first 20 seconds after vitamin K injection.

Statistical Analyses

There were no studies on which to base a sample-size calculation. In a study of venipuncture pain in neonates, we observed a mean pain score of 3 (SD, 1) on a behavioral scale that ranges from 0 to 7.[10] A sample size of 20 infants per group was chosen because it was feasible and large enough to achieve a difference of 0.8 in the pain score, assuming an SD of 1 (ie, moderately large effect size), with 70% power and $\alpha = .05$.

Demographic data were compared between groups with the Fisher exact test (categorical data) or t test (continuous data). Pain scores were compared between groups by using the nonparametric Mann-Whitney test because of the distribution characteristics of the data. Linear regression analysis was used to determine the difference in venipuncture scores between groups after adjustment for the cleansing phase. $P \leq .05$ was considered significant, and there was no adjustment for multiple comparisons. All analyses were performed with Statistical Package for the Social Sciences version 10 (Chicago, Ill).

RESULTS

The study was carried out in 2 phases. The first phase was conducted between August 1999 and October 2000. The investigator approached the parents of 66 infants eligible to participate: parents declined participation for 11 infants (6 infants of diabetic mothers and 5 normal infants). Thus, 55 infants were recruited into the study. Seven infants of diabetic mothers were excluded from the analysis because consent was later withdrawn by parents (n=2), the infant was admitted to a neonatal intensive care unit (n=2), the venipuncture was unsuccessful (n=2), or the infant was crying inconsolably before the procedure (n=1). In the normal infant group, 6 infants were excluded because of videotaping errors that prevented identification of infants or the procedure phases (n=3), the venipuncture was unsuccessful

(n=1), or the infant was crying before the procedure (n=2).

Data from the remaining 42 infants (n=21/group) who completed the study were included in the analysis (TABLE 1). In 1 infant of a diabetic mother–normal infant pair, there was a mismatch on infant sex and delivery; however, data from these infants were retained for analysis. Gestational age was statistically significantly higher in normal infants ($P=.006$). Ninety percent of mothers in both groups received epidural or spinal local anesthesia during delivery. The mean number of heel lances was 9.8 (SD, 2.1) for infants of diabetic mothers, and the last monitored mean blood glucose concentration before venipuncture was 65 (SD, 9) mg/dL (3.6 [SD, 0.5] mmol/L).

Videotaping errors precluded analyses of infant responses during the cleansing phase in one infant and during venipuncture in another infant in the infants of diabetic mothers. Median baseline scores for grimacing, VAS pain scores, and crying times did not differ significantly between groups ($P=.27$, $P=.32$, and $P=.32$, respectively) (TABLE 2). During the skin-cleansing phase, grimacing scores were significantly higher in the infants of diabetic mothers than in normal infants (22% vs 0%; $P=.03$). Although the baseline median scores for the VAS and crying time were 0% in both groups, the distribution of scores differed statistically for the VAS ($P=.02$). Eighty-six percent of normal infants had VAS scores of 0% compared with 52% of infants of diabetic mothers ($P=.04$). During venipuncture, the infants of diabetic mothers had significantly higher pain scores than the normal infants for grimacing (81.7% vs 40%; $P=.01$), VAS (69% vs 5%; $P=.002$), and crying (40.2% vs 0%; $P=.03$). Differences in venipuncture pain between groups remained significant for grimacing ($P=.05$) and VAS scores ($P=.007$) but not for crying ($P=.23$) after adjustment for pain scores during skin cleansing.

The second phase of the study was conducted throughout a 3-month period, September through November 2001. Thirty-one infants were eligible to participate: 15 infants of diabetic mothers and 16 normal infants. Two infants of diabetic mothers and 3 normal infants were excluded because their parents declined to participate. Data from 2 of the 26 infants who participated in the study were excluded from the analysis, leaving 12 infants in each group (TABLE 3). Reasons for exclusion included inconsolable crying (n=1) and venipuncture (n=1) before vitamin K injection. Infant characteristics and pain responses during vitamin K injection were not significantly different between infants of diabetic mothers and normal infants (TABLE 4).

COMMENT

In this study, newborns exposed to repeated heel lances in the first 24 to 36 hours of life learned to anticipate the pain of an impending venipuncture compared with normal infants who had not undergone repeated painful procedures. This finding was demonstrated by the significantly greater VAS and grimacing pain scores they exhibited compared with the normal infants during the skin-cleansing phase that immediately preceded the venipuncture. Without repeated exposure to painful procedures, skin cleansing in neonates is a nonpainful event and induces little response. However, after an average of about 10 heel lances (preceded by skin cleansing), infants responded to cleansing of the skin with behaviors indicative of pain. We suggest that throughout the course of repeated exposure to skin cleansing followed by heel lancing, skin cleansing became a conditioned stimulus, reliably signaling the impending painful event and inducing anticipatory pain behaviors and possibly even pain.

Not only did these infants learn to anticipate pain but also the intensity of the pain they experienced in response to venipuncture was greater than that

Table 1. Baseline Characteristics at Venipuncture for Newborn Screening Test

Characteristic	Infants of Diabetic Mothers (n = 21)	Normal Infants (n = 21)	*P* Value
Gestational age, mean (SD), d	268.0 (5.8)	276.0 (11.0)	.006
Birth weight, mean (SD), g	3539 (586.2)	3412 (511.9)	.46
Males, %	47.6	52.4	>.99
1-min Apgar score, mean (SD)	8.7 (0.5)	8.9 (0.5)	.33
5-min Apgar score, mean (SD)	9.0 (0.3)	9.0 (0.2)	.57
Vaginal delivery, %	61.9	57.1	.77
Postnatal age at venipuncture, mean (SD), h	37.6 (7.6)	38.3 (11.4)	.82
Maternal age, mean (SD), y	32.5 (6.6)	30.5 (5.8)	.30

Table 2. Outcome Measures Used to Assess Pain During Venipuncture for Newborn Screening Test

	Median (25th, 75th Percentile), %		
	Infants of Diabetic Mothers (n = 21)	Normal Infants (n = 21)	*P* Value
Grimacing score			
Baseline	0 (0, 0)	0 (0, 1.7)	.27
Skin cleansing*	22.2 (0, 77.5)	0 (0, 15)	.03
Skin puncture*	81.7 (67.5, 100)	40 (13.3, 86.7)	.01
Visual analog scale			
Baseline	0 (0, 0)	0 (0, 0)	.32
Skin cleansing*	0 (0, 39.3)	0 (0, 0)	.02
Skin puncture*	69 (52.8, 80.3)	5 (0, 60.5)	.002
Crying time			
Baseline	0 (0, 0)	0 (0, 0)	.32
Skin cleansing*	0 (0, 42.2)	0 (0, 0)	.14
Skin puncture*	40.2 (15.2, 92.2)	0 (0, 54.8)	.03

*Number is 20 for infants of diabetic mothers.

of normal infants. The difference in venipuncture pain scores between the infants exposed to multiple heel lances and normal infants was maintained when we adjusted for pain response during skin cleansing. In addition, we chose a venipuncture site on the dorsum of the hand, in uninjured tissue, remote from the site of repeated heel lancing to avoid testing in a region that had been rendered hyperalgesic because of injury and inflammation.[11]

Conditioning and hypersensitivity responses have not been consistently demonstrated. In one study of the cortisol responses of newborns,[12] increased salivary cortisol concentrations were observed after a second heel lance. This result was in contrast to a second experience with a handling stressor (mock discharge examination), which produced a lower cortisol response than the first exposure. In another study,[13] infant crying response was not different during the preparatory phases of a heel lance when there was one previous experience with a heel lance.

Learning and memory have been demonstrated in preterm infants as young as 32 weeks of gestation by using paradigms of exposure learning, classic conditioning, and habituation.[14] The gestational age at which newborns can begin to learn the associations between events involved in painful procedures is unknown. In a study that assessed preterm and full-term infant responses during the phases of painful medical procedures,[15] the magnitude of heart rate change between the baseline and procedure phase increased significantly over time with increasing conceptional age. Investigators did not discuss whether there were similar changes in infant responses between the baseline and preparatory phases. Thus, whether conditioning contributed to the observed hyperalgesia is unknown.

We do not know the extent to which the anticipatory pain behaviors and heightened pain responses persist beyond the first days of life and what impact, if any, this early exposure might have on subsequent behavior, learning, and memory. Cumulative experience with procedural pain may have long-term effects. In a recent longitudinal investigation of preterm infants' responses to heel lance, differences were observed in behavioral and physiologic responses to pain at 32 weeks' postconceptional age that were correlated with the number of previous invasive procedures. Changes in pain reactivity were normalized if infants had received morphine, suggesting that analgesia ameliorated the effects of cumulative pain on later pain reactivity.[16] The number of invasive procedures in the preceding 24 hours significantly predicted grimacing in a separate study of very low-birthweight infants undergoing medical procedures.[17] However, in another study by the same group of investigators, only subtle differences in pain response lingered at 4 months' corrected age between former very low-birth-weight infants and full-term controls during finger-lance blood collection.[18] We previously showed that a single painful experience in the neonatal period was associated with long-term effects.[19,20] In 2 studies, neonatal circumcision was associated with increases in pain following routine 4- or 6-month vaccination. Preoperative treatment with a local anesthetic cream attenuated vaccination response, suggesting that vaccination pain response was affected by circumcision pain experienced months before.[19]

There are limitations to this study. Because the study could not be randomized, the differences in pain we observed between the groups may be explained by factors other than the effects of repeated exposure to painful procedures. We matched infants on birth characteristics. Infants of diabetic mothers were on average 1 week younger than normal infants. This difference in gestational age has not been associated with significant differences in pain response in full-term infants.[21] Moreover, we

Table 3. Baseline Characteristics at Intramuscular Injection of Vitamin K

Characteristic	Infants of Diabetic Mothers (n = 12)	Normal Infants (n = 12)	*P* Value
Gestational age, mean (SD), d	270.9 (10.2)	272.7 (8.2)	.65
Birth weight, mean (SD), g	3277 (719.5)	3376 (467.4)	.70
Males, %	58	33	.41
1-min Apgar score, mean (SD)	8.5 (1.4)	8.7 (0.5)	.71
5-min Apgar score, mean (SD)	9.1 (0.3)	9.0 (0.4)	.58
Vaginal delivery, %	58	58	>.99
Postnatal age at intramuscular injection, mean (SD), h	0.5 (0.2)	0.6 (0.4)	.47
Maternal age, mean (SD), y	36.4 (4.6)	33.6 (4.2)	.13

Table 4. Outcome Measures Used to Assess Pain During Intramuscular Injection of Vitamin K

	Median (25th, 75th Percentile), %		
	Infants of Diabetic Mothers (n = 12)	Normal Infants (n = 12)	*P* Value
Grimacing Score			
Baseline*	0 (0, 0)	0 (0, 0)	.88
Skin cleansing†	19.5 (0, 33.3)	25 (0, 75)	.57
Skin puncture	56.3 (42.6, 70.5)	57.1 (42.6, 77)	.48
Visual analog scale			
Baseline*	0 (0, 0)	0 (0, 0)	.74
Skin cleansing†	4.5 (0, 10.8)	8 (0, 16)	.57
Skin puncture	46.5 (27.5, 66)	42.5 (36, 47.8)	.89
Crying time			
Baseline*	0 (0, 0)	0 (0, 0)	.53
Skin cleansing†	0 (0, 0)	0 (0, 66.6)	.32
Skin puncture	44 (33.6, 63.9)	58.9 (37.9, 73.9)	.35

*Number is 11 for infants of diabetic mothers.
†Number is 11 for normal infants.

matched on infant birth weight because weight (or size) of the infant may be related to the ease of venipuncture.

Because randomization was impossible, the results can possibly be explained by preexisting differences between infants of diabetic mothers and control infants, specifically with respect to their medical condition. To evaluate this possibility, glucose concentrations were monitored closely, and the value before venipuncture was in the normal range. It is therefore unlikely that low glucose concentrations (hypoglycemia), which may be associated with clinical symptoms such as jitteriness,[22] account for the observed differences in pain behaviors. To further evaluate this possibility, we compared pain responses during the first painful medical procedure performed after birth (intramuscular injection of vitamin K) in a different cohort of normal infants and infants of diabetic mothers. The latter did not demonstrate an increased response during either skin cleansing or intramuscular injection. Although the number of infants in this cohort was small and a significant difference may not have been detected, it is reassuring that on nearly every pain measure, infants of diabetic mothers scored lower than normal infants. Therefore, preexisting differences in pain responses between groups probably do not account for the significant differences we observed during venipuncture.

A final limitation is that parents and videographers were aware of infant exposure status. We attempted to minimize bias during data collection by ensuring that all infants were settled at baseline, using a variety of nurses to collect blood samples, and using raters who were unaware of infant exposure group to score pain from videotaped records. Videotaped records did not contain any information that could identify the infant's exposure group. Raters were unaware of any physical features that might have distinguished infants of diabetic mothers from normal infants, and since birth weight was similar in both groups, it is unlikely that infant appearance differed as a function of group. Furthermore, if parents were present during the venipuncture, they did not interfere with the procedure or speak about the study. In addition, we excluded infants who were admitted to the neonatal intensive care unit after delivery. All study infants stayed with their mothers, so separation from the mother could not explain observed differences between groups.

In summary, full-term infants exposed to repeated heel lances demonstrated heightened pain in response to skin cleansing and venipuncture compared with a group of normal infants. This finding has important implications. First, pain in hospitalized newborns may be classically conditioned by the unwitting pairing of a neutral stimulus with a painful procedure. Thus, pain and pain behaviors in neonates will be elicited by the previously neutral stimulus after conditioning has occurred. Second, previous pain experience may be important in determining analgesic efficacy. Because sick preterm and full-term infants are subjected to many invasive procedures as part of their medical care, there may be significant cumulative effects of pain that might lead to administration of higher-than-normal doses of analgesics.

Our data suggest that effective management of neonatal pain during invasive medical procedures might prevent the development of hyperalgesia, conditioned pain, and conditioned pain behaviors. Taken together, these data provide further evidence that infant pain is modulated by experiences with pain, as it is in children and adults.

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Acquisition of data: Taddio, Shah, Gilbert-MacLeod.
Analysis and interpretation of data: Taddio, Shah, Katz.
Drafting of the manuscript: Taddio, Katz.
Critical revision of the manuscript for important intellectual content: Taddio, Shah, Gilbert-MacLeod, Katz.
Statistical expertise: Taddio, Katz.
Administrative, technical, or material support: Taddio, Gilbert-MacLeod.
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