Posttest can be found on page 137.

Determinants of Premature Infant Pain Responses to Heel Sticks

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The exposure of premature infants to stressors, such as pain intended to ensure their survival, may instead alter their brain development and contribute to several learning and behavioral difficulties observed in later childhood. The objective of this descriptive, cross-sectional study was to compare the pain responses of 72 preterm infants to a heel stick procedure taking into consideration a variety of factors, including the use of opioids and sedatives. The pain scores assessed on the Preterm Infant Pain Profile (PIPP) scale were highest for the lowest gestational age (GA) group. Multiple linear regression analysis with the four predictor variables noted to be correlated with the PIPP scores (GA, type of needle, severity of illness, and behavioral state) indicated a significant overall relationship (F [5/66] = 5.62, $p < 0.01$) and accounted for 44% of the variance. All but severity of illness did not add significantly to the variance. Gender, postnatal age, amount, opioids, and sedatives used were not correlated to the PIPP scores. It was concluded that sick premature infants and those who have been exposed to a variety of painful procedures may not manifest behavioral or physiological signs of pain, but may be the most to benefit from precise pain assessment and prudent management.

Preterm infants emerge from a safe uterine environment to a noisy, chaotic, stressful, and painful environment. Whereas the mature infant is better equipped to handle stressful experiences, the preterm infant lacks the autonomic and functional maturity to do so. The exposure to stressors and noxious stimuli intended to ensure the survival of preterm infants may instead alter their brain development and contribute to several learning and behavioral difficulties observed in later childhood (Abdulkader, Freer, Garry, Fleetwood-Walker, & McIntosh, 2007; Anand, 2000; Grunau, Oberlander, Whitfield, Fitzgerald, & Lee, 2001; Grunau, Holtsi, & Peters, 2006; Mainous & Looney, 2007). A recent study in France reported that on average, infants in the neonatal intensive care unit (NICU) experience 115 painful procedures in a two-week period (Lenclen & Carbajal, 2007). Researchers have noted that premature infants exposed to repeated painful experiences may either manifest more heightened responses to pain or may be desensitized to pain (Anand et al., 2005; Grunau, Whitfield, & Petrie, 1998). Whether responses of preterm infants are heightened or desensitized, there seems to be an agreement among researchers that there are permanent adverse consequences to pain due to an altered hypothalamic-pituitary-adrenal axis (Grunau et al., 2005).

Several studies over the last decade have contributed to the satisfactory, albeit not the precise, assessment of pain in the premature infant (Abu-Saad, Bours, Stevens, & Hamers, 1998; Anand, 2007a; Hummel, Lawlor-Klean, & Weiss, 2009). The appraisal of factors that could increase or decrease premature infants' response to pain has also been a subject of great interest (Holsti, Grunau, Whitfield, Oberlander, & Lindh, 2006; Johnston et al., 1999). Despite growing scientific evidence, several gaps in the research remain. For example, it is not yet clear whether repeated exposure to pain in preterm infants intensifies or diminishes their behavioral and physiologic responses, nor is it ascertained which factors heighten or dampen their responses. It is thus imperative to consider all possible contextual factors that could modulate the infant's responses to pain.

The effect of contextual factors in the responses to pain has been documented by several research studies (Ahn, 2006; Bartocci, Bergqvist, Lagercrantz, & Anand, 2006; Johnston et al., 1999) and are based on a hypothesis by Melzack and Wall (1970) – responses to painful stimuli vary in the context in which they are experienced. Therefore, the aims of this study were to compare preterm infant responses to a heel stick procedure taking into consideration a variety of factors: gestational age (GA), postnatal age at time of study, newborn complications, type of needle used, state of the infant before the procedure, gender, and the administration of opioids, sedatives, and steroids.

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Statement of Disclosure: *The authors reported no actual or potential conflict of interest in relation to this continuing nursing education article.*

Literature Review

Gestational Age and Pain Responses

Some researchers found that immature preterm infants have lower pain thresholds, and thus, they manifest greater physiological responses following a painful procedure (Anand, 2007a; Anand et al., 2005; Chimello, Gaspardo, Cugler, Martinez, & Linhares, 2009). Others, however, dispute this notion and report that immature infants lack the ability to respond appropriately to pain (Bartocci et al., 2006; Evans, McCartney, Lawhon, & Galloway, 2005; Johnston et al., 1999). Most researchers tend to agree that more mature infants respond more vigorously to invasive procedures, indicating that maturation is important, especially in the manifestation of visible behavioral responses (Gibbins et al., 2007; Goubet, Clifton, & Shah, 2001, Johnston, Stevens, Yang, & Horton, 1996; Mainous & Looney, 2007; Porter, Wolf, & Miller, 1998). One study found that infants who are 32 weeks GA and who have been in the NICU for four weeks had significantly greater heart rate, significantly lower oxygen saturation (O_2), and fewer upper facial expressions to pain compared to newly born, 32-week gestation infants (Johnston & Stevens, 1996). These findings suggest that prior experience with pain and not GA heightens the cardiac autonomic responses.

Likewise, when infants with different GAs were observed in the NICU at 36 weeks conceptual age, infants born closer to 36 weeks displayed the least heart rate increases to procedures compared to other GA groups (Porter et al., 1998). This finding also supports the notion that preterm infants who stay longer in the NICU and who are exposed to painful or noxious stimuli are more likely to react more vigorously to pain. In contrast, higher numbers of skin-breaking procedures were associated with dampened behavioral and autonomic responses to pain for premature infants born between 23 to 32 weeks (Grunau et al., 2001) and for infants less than 28 weeks gestation (Evans et al., 2005). It seems that very immature infants may not manifest "specific" behavioral responses to invasive, skin-breaking procedures (Johnston et al., 1999) and that GA should be assessed along with other factors, such as prior exposure to painful procedures and post-conceptual age at the time of the study, to distinguish the effects of these various factors (Porter et al., 1998).

Grunua and colleagues (2001) suggest that very small preterm infants may be in a state of constant autonomic arousal, while Als (1991) argues that premature infants become disorganized with increasing stress. More recently Ranger, Johnston, and Anand (2007) suggested that after repeated unanswered attempts to communicate pain, small GA infants become exhausted and may not manifest overt signs of distress. To give further credence to this latter argument, the use of near-infrared spectroscopy has demonstrated that infants as young as 25 weeks of gestation have a clear evoked activity of the cortex in response to pain. Even though this activity is less pronounced than older infants, it clearly demonstrates activation of the cortex following pain (Bartocci et al., 2006; Qui, 2006; Slater, Boyd, Meek, & Fitzgerald, 2006).

Prior Exposure to Painful Procedure and Pain Responses

Most researchers agree that multiple exposures to pain and stress in the NICU alter the responses of premature infants (Bhutta & Anand, 2002; Goubet et al., 2001). However, disagreement remains about the direction of these changes and behavioral versus physiologic responses. This may be due to the varied GAs of infants and the range of painful procedures in the published studies. The number of painful experiences premature infants are subjected to is inversely related to their pain scores in some studies (Evans et al., 2005; Grunau et al., 2001), while in others, the number of invasive procedures or the days spent in the NICU seem to make preterm infants respond more vigorously (Johnston & Stevens, 1996; Porter et al., 1999).

Still others report no relationship between exposure to pain and reactivity (Goubet et al., 2001). Fitzgerald, Millard, and McIntosh (1989) noted that the flexion reflex threshold of the foot where the heel-sticks were done was lower than the threshold of the other intact foot, indicating sensitization after repeated experience with painful procedures and possibly altered excitability of the spinal cord. Johnston and colleagues (1996) assessed the reaction of preterm infants to the heel-stick procedure over an eight-week period and found no significant change in heart rate or oxygen saturation over time, but they did find an increase in the facial expression to pain. In contrast, Goubet et al. (2001) noted no significant changes in facial or physiologic reactions for preterm infants when observed five times over a period of two weeks while undergoing heel-sticks. These conflicting results may reflect various sample sizes, the complex nature of assessing pain in preterm infants, the difficulty in differentiating between physiologic maturity and prior exposure to pain, and the impossibility of assessing all the stressful events premature infants are exposed to in the NICU.

State and Responses to Pain

Studies have reported that the responses of infants to pain are greatly determined by their state prior to the procedure. Pain scores increase when the infant is more alert and active (Fitzgerald et al., 1989; Stevens, Johnston, Petryshen, & Taddio, 1996). Ahn (2006) found a strong correlation between behavioral states and pain scores, indicating that when infants are awake, their pain responses are more intense. This finding is supported by Stevens, Johnston, and Horton (1994), and Grunau and Craig (1987), who also noted that infants in the awake states have significantly more behavioral changes than infants in the sleep state during the heel stick phase.

Severity of Illness and Pain Responses

Severity of illness is related to pain responses in some studies but not in others. For example, in a study of 81 premature infants between 28 to 33 weeks gestation, Evans and colleagues (2005) found that sicker preterm infants have less pain responses than healthier preterm infants. This is in contrast to the findings reported by Stevens et al. (1994), who reported no significant differences in facial actions of 124 preterm infants between 32 and 34 weeks post-conceptual age according to severity of illness. Discrepancy in results may be attributed to the different gestational ages assessed, as well as the different tools used to assess severity of illness.

Gender and Pain Responses

Another area of debate is the gender of the infant. Some studies report that gender has a bearing on pain responses of preterm infants, and others argue that such a relationship does not exist (Grunau & Craig, 1987; Guinsburg et al., 2000; Stevens et al., 1994).

Opioids/Sedatives and Pain Responses

Although preterm infants have been observed to be subjected to an average of 14 to 25 procedures day, mostly painful procedures (Badr & Balian, 1995; Simons et al., 2003), sedation for pain varies from one institution to the other. In some NICUs, 60% to 74% of infants receive opioids or sedatives before painful procedures (Lenclen & Carabjal, 2007; Walter-Nicolet et al., 2007), while in others, sedation is minimal (15%) or not used at all (Carbajal, Eble, & Anand, 2007; Prestes et al., 2005). Furthermore, morphine – the most commonly used narcotic in the NICU – has been investigated recently with evidence that it may not be effective against acute pain in preterm infants (Anand, 2007b; Bellù, de Waal, & Zanini, 2008; Carbajal et al., 2005; Cignacco et al., 2008). Early exposure to morphine predicted more "normalized" cardiac (but not behavioral) pain response in one study (Grunau et al., 2001), while higher morphine exposure was associated with lower facial activity in another (Grunau et al., 2006). The discrepancy in these studies was attributed to the relatively high doses of dexamethasone administered to infants in the earlier study.

Table 1.
Characteristics of the Sample (*N* = 72)

Variable	Number (Percent)
Apgar Score	
Greater than 5 at 5 minutes	41 (57%)
Less than 5 at 5 minutes	31 (43%)
Heel stick needle	
27-gauge	43 (60%)
21-gauge	29 (40%)
Gestational age	
36 weeks and more	15 (21%)
32 to 35 weeks	37 (51%)
26 to 31 weeks	20 (28%)
Steroid use	
Yes	5 (7%)
No	67 (93%)
Opiate use	
Yes	9 (13%)
No	62 (87%)
Sedative use	
Yes	6 (8%)
No	66 (92%)
Gender	
Female	37 (51%)
Male	35 (49%)

Methods

Design

A descriptive, cross-sectional, correlational study was used to assess the relationship between several background and contextual variables and the pain responses of preterm infants.

Setting

Two tertiary-level NICUs in two university hospitals in Beirut, Lebanon, one with 20 beds and one with 15 beds, were selected for the purposes of this study. These hospitals were selected because they have similar staffing and similar patient care protocols. There are no protocols in either hospital for sedation or for developmental or supportive care. Thus, none of the infants received any form of sedation for the heel stick. One difference between the hospitals is the heel prick procedure; one hospital used a 21-gauge needle while the other used a 27-gauge needle.

Sample

The original study sample was composed of 76 clinically stable premature infants admitted to either one of the two NICUs. Four infants were excluded from the analysis due to incomplete PIPP and Neonatal Acute Physiology (SNAP-II) data. Using conventional parameters for sample size estimates (5% false-positive rate and a power of 80%, 2-sided), and a significance level of 0.05, sample size calculations were based on earlier studies using the PIPP scale. A sample size of 50 was considered more than sufficient to assess significant relationships between the study factors and the scores on the PIPP. Infants were between 27 to 40 weeks gestation, with a mean birth weight of 1742.6 g (SD $\pm$ 287.2), their hospitalization days ranged from 5 days to 59 days at the time of the heel stick (postnatal age), and 37 were girls and 35 were boys. Infants with major congenital anomalies, intraventricular hemorrhage (IVH grade III or IV), and/or parenchymal brain injury (periventricular leukomalacia) were excluded, as well as any infants who had received any sedatives or opioides within 72 hours of data collection (Scott et al., 1999). Only 5 of the 72 infants (7%) had received postnatal steroids, 9 out of the 72 (13%) had received opioids (fentanyl or morphine were used with dosages based on infant weight), 6 (8%) had received sedatives (midazolam or valium), and 3 (4%) had used a combination of sedatives and opioids during their NICU stay. See Table 1 for characteristics of the sample.

Measures

Three measures were used.

Infant Characteristics

Information was collected by prospective chart review. Data collected included birth weight, GA at birth, postnatal age, Apgar score at 5 minutes, illness severity using the SNAP-II, opioid and sedative administered as well as Dexamethasone used since birth.

The Score of Neonatal Acute Physiology (SNAP-II)

The SNAP-II is a standardized, clinically validated, and widely used scale to predict the outcome of preterm infants (Soraisham et al., 2009). It is obtained within 12 hours of admission to a NICU and quantifies six physiologic variables: temperature, blood pressure, PaO_2/fraction of inspired oxygen ratio, serum pH, the presence of seizures, and urine output. The total score can range from 0 to 115; higher scores reflect more disturbances in neonatal physiologic condition. The SNAP-II was re-validated in 2001 on a sample of 25,429 premature and full-term infants in 30 NICUs, and was found to have high predictive (0.91) and criterion validity (0.90) (Richardson, Corcoran, Escobar, & Lee, 2001). Based on earlier research and for the purposes of this study, the SNAP-II scores were dichotomized into two scores: a low severity illness for a score of less than 15 and a high severity illness scores above 15 (Lam, Claydon, Mitton, & Skarsgard, 2006; Lee et al., 2003; Skarsgard et al., 2005).

Pain Responses

The PIPP was used to measure the pain responses of infants to the heel stick (Stevens et al., 1996). The PIPP is a 7-indicator pain measure that includes three behavioral responses (brow bulge, eye squeeze, and nasolabial furrow), two physiologic responses (heart rate and oxygen saturation), and two contextual responses (gestational age and behavioral state). Each indicator is scored on a 4-point scale (0 to 3) to give a maximum total score of 21. The internal consistency, inter-rater reliability, and face validity of the PIPP scale have been well documented (Belleini et al., 2007; Stevens et al., 1994, 1996). The mean score on the PIPP scale for all infants in this study was 7.74 + 4.08, with a range between 2 and 18.

Procedure

Infants were recruited by one of two NICU research nurses. Written informed consent was not necessary or obtained because the heel stick procedure was part of the daily routines in the NICU. Oral consent was obtained from mothers according to a protocol approved by the Institutional Review Board (IRB) of the American University of Beirut. The heel stick procedure was selected to assess pain because it is a commonly occurring procedure in the NICU.

When a heel prick was necessary to obtain blood, it was taken using the following protocol. Infants were lying in an incubator in an open crib undisturbed for a minimum of 30 minutes before the recording. Physiologic recordings were carried out continuously; heart rate and respiratory rate were collected by attaching the existing leads to a cardiac monitor, while O_2 saturations were obtained by recording the values displayed on the pulse oximeter (both hospitals used Hewlett Packard neonatal monitors for heart rate and respiratory rate, and Nellcor for O_2 saturations). The data collection process was divided into two consecutive periods: 1) a baseline heart rate and O_2 saturation and behavioral state (15 seconds observation), and 2) a "heel stick" period, where the infant is observed during the heel stick procedure and where the PIPP score was obtained. During the procedure period, the nurse performing the heel stick opened the incubator doors, exposed the legs and feet, cleaned the heel with an alcohol swab with three circular swabs, pricked, then squeezed the heel to collect the required sample of blood. Following this, a cotton wool ball was placed on the injury site until bleeding ceased. If the infant was in an open crib, the same procedure was carried out except for "opening the incubator doors."

Two research assistants were first trained to an inter-observer reliability of 90% on the PIPP scale with the principal investigator (PI) and then carried out the observations separately at the two time periods (baseline and during the heel stick) as described above.

Statistical Analysis

For statistical analysis, SPSS 16.0 was used. Results were expressed either as a Mean + SD, or as a percentage of the total number of infants. Physiologic and behavioral responses on the PIPP scores were compared before and during the heel stick using the paired *t*-test. Physiologic and behavioral responses were also compared based on needle type, GA, and SNAP-II scores before and during the heel stick. Analysis of variance (ANOVA) assessed the relationship between the different GAs and the PIPP. To assess the relationship between infant characteristics, opioids and sedatives used, type of needles, and the PIPP scores, Pearson product moment correlations and Spearman correlations were used for continuous and ordinal variables, respectfully, with significance set at $p < 0.05$. Because only five infants received dexamethasone after birth, this factor was not included in the analysis. The predictor variables were the type of needle used, GA, postnatal age, kind of opioids/sedatives used, gender, behavioral state before the procedure, and severity of illness. Finally, multiple linear regression models were used to evaluate the effect of the predictor variables combined on the PIPP scores.

Results

There was a significant increase in heart rate ($t = 8.27$, $p < 0.001$), a significant decrease in O_2 saturations ($t = 3.26$, $p < 0.01$), and significant changes on the three behavioral responses ($t = 4.78$, $p < 0.01$, $t = 7.03$, $p < 0.001$, and $t = 5.23$, $p < 0.01$), respectively, when comparing before and during scores on the PIPP. When changes in the physiological responses were observed based on type of needle, GA and the SNAP-II scores divided into two categories (less than 15 for the less severely ill infants and greater than 15 for the more severely ill infants), the same trend was noted (see Figure 1). As reflected in Figure 1, heart rate changes showed the most variations before and during the procedure, especially for the 27 to 32-week GA group ($t = 3.90$, $p < 0.05$). However, all changes in heart rate and O_2 saturations were significant for needle type, the three gestational ages, and the severity of illness.

To determine whether there were differences in the heel stick PIPP scores for infants at different GAs, mean PIPP scores were compared using ANOVA. The PIPP scores were highest for the lowest 27 to 32-week GA group (mean = 10.2 + 4.54) and lowest for the largest 36 to 40-week GA group (mean = 5.23 + 3.37); the 32 to 35-week GA group were in the middle (mean = 7.71 + 4.33, F [3/69] = 4.72, $p < 0.05$). Compared to earlier studies, these means are lower than most reported in the literature, especially for the older GA groups, indicting that preterm infants in the current study did not respond to pain similar to infants in earlier published studies (Evans et al., 2005).

There was a significant correlation between the total scores of infants on the PIPP and GA ($r = - 0.38$, $p < 0.05$), the type of needle used ($r = 0.43$, $p < 0.01$), severity of illness ($r = - 0.26$, $p < 0.05$), and the behavioral state of the infant before the procedure ($r = -0.41$, $p < 0.01$). Gender ($r = 0.15$), postnatal age ($r = -0.19$), and amount and kind of opioids/sedatives used ($r = -0.21$)

Figure 1.
Behavioral States of the Infants Before Heel Prick

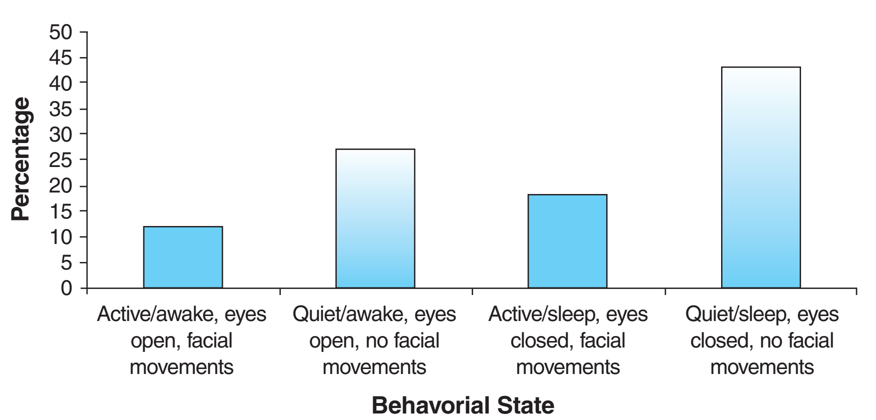


Table 2.
Determinants of the PIPP Scores (N = 72)

Variables	PIPP Scores		
	β	βSE	Beta
Gestational age	-0.032	0.015	-2.21**
Type of needle	-0.023	0.006	1.19*
			0.022*
Behavioral state	0.049	0.022	0.60*
SNAP - II	-0.016	0.012	-0.42
F			5.62**
R^2			0.443

* $p < 0.05$
** $p < 0.01$

were not correlated to the PIPP scores. Infants who had been in NICU for a longer period of time did not score any differently to pain than infants who had been in the NICU for a shorter period of time. Boys and girls did not respond any differently to the heel prick, and the use of opioids or sedatives had no bearing on their pain responses. Most infants in this study were in the quiet sleep state before the procedure (see Figure 1).

Multiple linear regression analysis for the four predictor variables noted to be correlated with the pain scores (GA, type of needle, severity of illness, and behavioral state) and the PIPP scores indicated a significant relationship overall (F [5/66] = 5.62, $p < 0.01$) and accounted for 44% of the variance. GA accounted for 19% of the variance, type of needle for another 14%, and behavioral state for another 11%. Severity of illness did not significantly alter the variance. Except for severity of illness, each step of the equation remained significant, indicating the partial contribution of each of these factors in predicting pain responses (see Table 2).

Discussion

The mean PIPP score in the current sample for all gestational ages was 7.74 ± 4.08, much lower than the published means in the literature for similar gestational ages that range between 7.65 and 12.9 (Evans et al., 2005; Gibbins et al., 2002; Stevens et al., 1996). One explanation is that Lebanon infants admitted to NICU may be exposed to many more painful and heel stick procedures than their counterparts in the United States (5 to 8 heel sticks a day in Lebanon compared to 1 to 2 in the U.S.), contributing to decreased sensitization and habituation to repeated pain exposure. Another explanation may be that few infants (25%) in this study received any form of sedation or opioids 72 hours before the heel stick (13% had received opioids, 8 had received sedatives, and 4% had used both), possibly making them habituated to pain. This finding is in contrast to a recent meta-analysis of opioids for neonates (Bellu et al., 2008), noting that infants given opioids had lower PIPP scores compared to infants who did not receive opioids. Another possible interpretation is that due to the low percentage of infants on sedatives or opioids, the significant effect of this variable was washed out statistically. Findings from this current study are supported by earlier research that documents sensitization to repeated exposure to the heel stick procedures and other noxious stimuli (Johnston et al., 1996; Pineles, Sandman, Waffarn, Uy, & Davis, 2007).

The fact that the lowest gestational age group had the highest PIPP scores is supported by some studies (Gibbins et al., 2007) and not others (Evans et al., 2005; Stevens et al., 1994). Both latter studies argue that neurological changes occur at 31 weeks, allowing infants to be more responsive. Conversely, the study by Gibbins and colleagues (2007) reported that infants between 28 to 32 6/7-weeks gestation had the greatest amount of change in O_2 saturation and heart rate compared to infants born after 36 weeks. The discrepancy in results could be explained by the various methods used to assess pain. Thus, while Gibbins and colleagues (2007) used the Neonatal Facial Coding System, other researchers have used the PIPP scale. It could also be because the NICU setting where Gibbins et al. (2007) conducted their study was similar to the setting in this current study; no policies for the use of sucrose or other standardized pain management policies were in place.

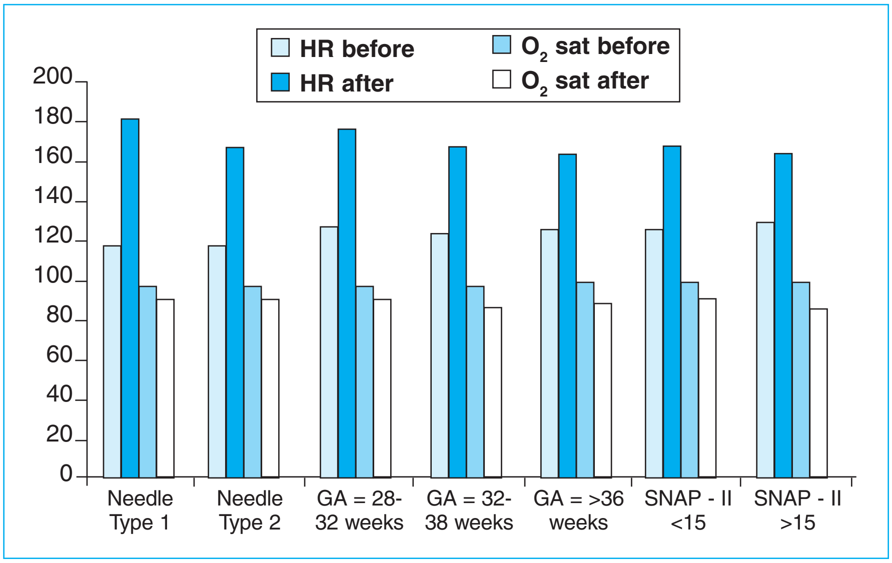
The PIPP scores for infants 32 to 35 weeks GA and those older than 36 weeks GA in this study were lower than most PIPP scores for similar GA infants (Evans et al., 2005; Stevens et al., 1999) and could again be explained by the excessive number of painful procedures to which infants in Beirut are exposed. Grunau and colleagues (2005) argue that infants who received more than 20 painful procedures (as did most of the infants in this study) may be "non-naive" responders to pain, an argument supported by this study's results and that warrant further investigation. The significant increase in heart rate and the decrease in 0_2 saturations and the significant changes on the three behavioral responses noted in this study are also supported by earlier studies (Grunau et al., 2005; McIntosh, Van Veen, & Brameyer, 1993; Stevens et al., 1994).

The higher scores on the PIPP for infants who were pricked with the larger 21-gauge needle compared to the 27-gauge needle is an expected finding and should alert nurses not to use the 21-gauge needle. Furthermore, results of this study imply that although repeated exposure to pain dampens the responses of preterm infants, it is not so when a large needle is used. Thus, the assumption that repeated exposure of infants to tissue breakdown decreases pain responses may only be applicable when using smaller needles. Grunua et al. (2005) had questioned whether a "cutoff" of 20 procedures exists after which pain responses are dampened; in this study, it is argued that not only the number of procedures but the intensity of pain may have a negative affect. This finding is supported by an earlier study that noted lower scores on the PIPP compared to previous studies when a Quick Heel™ 99 lancet (a smaller needle) was used (Evans et al., 2005).

The fact that sicker infants had lower PIPP is expected because those infants may have had more painful procedures, a finding supported by earlier studies (Evans et al., 2005; Stevens et al., 1994). It has been argued that acutely ill infants are less capable of manifesting behavioral responses to pain (Gibbins et al., 2007; Grunau et al., 2005). Although the severity of illness as measured on the SNAP-II was negatively correlated to the PIPP scores, it did not remain a significant factor in the multiple regression analysis, indicating that other factors entered into the equation. GA, type of needle, and the behavioral state of the infants before the heel stick were stronger predictors of the PIPP scores.

The behavioral state of the infant was negatively correlated to the PIPP scores, indicating that when infants are awake, they are more likely to demonstrate behavioral responses to pain, a finding well supported in the literature (Johnston et al., 1999; Ranger et al., 2007; Stevens et al., 1994). Infants in the active awake states had the greatest proportions of behavioral changes in the study by Stevens et al. (1994), while preterm infants who were sleeping had dampened responses to the heel stick procedure (Johnston et al., 1999). The fact that the majority of infants in this study were in the sleep states prior to the heel stick procedure (see Figure 2) could further lend support to their lower PIPP scores compared to earlier studies. This finding should be interpreted with caution because it could translate to recommending that heel sticks be performed when infants are in the sleep states, a proposition unlikely to be supported by developmental specialists.

Figure 2.
Heart Rate and O_2 Changes Based on Needle Type, Gestational Age, and SNAP-II Scores



Type 1 needle: 21-gauge needle
Type 2 needle: 27-gauge needle

Similar to earlier findings, no correlation between the use of opioids and sedatives and pain reactions was found (Anand, 2007b; Carbajal et al., 2005, Cignacco et al., 2008). This is of paramount importance supporting new evidence that opioids given for older children and adults to relieve pain may be of no benefit for preterm infants, who may require other forms of sedation (Bellu et al., 2008). This conclusion should be interpreted with prudence because only 25% of the infants in this study had received opioids or sedatives. The low rate of opioid and sedative administration may reflect the apprehension of neonatologists in Beirut to sedate infants because it may "harm infants" or "depress their respiratory systems." It may even reflect the traditional myth that premature infants do not feel pain because their nerve pathways are not sufficiently myelinated. It is clear that more research is warranted to understand the attitudes of health professionals in developing countries regarding pain assessment and management for preterm infants. Clinical trials are also necessary to establish the short- and long-term safety and efficacy of opioids and sedatives in preterm infants, and to understand other factors that could contribute to pain responses in preterm infants, especially in terms of long-term neurodevelopment.

Clinical Implications and Future Directions

Pain and its management are of crucial importance to all concerned with the care of preterm infants. Although much has been achieved in the past few decades, there remains much more to be learned to achieve adequate pain control and management. A most remarkable clinical application for practitioners is that sick premature infants and those who have been exposed to a multitude of painful procedures may not manifest overt behavioral or physiological

Table 3.
Clinical Recommendations Based on Study Findings and Discussion

- Painful procedures should be avoided in preterm infants if possible because they are likely to be associated with an excessive stress response that may be harmful.
- Invasive procedures are frequently carried out in sick preterm infants without sedation, which pose a great threat to infants' physiological stability and possibly of negative, long-term outcomes.
- Repeated exposure to painful stimuli may dampen overt responses to pain but may be harmful in the long term.
- The use of morphine for analgesia in preterm infants is of questionable benefit for the relief of pain.
- Very small GA infants may not manifest behavioral responses to pain as much as older GA infants; however, their heightened physiological responses reflect the pain they are experiencing.
- The use of large needles for heel sticks is not recommended, and the use of newer devices, such as the spring-loaded or the Quick Heel™ lancets, are suggested.
- The use of indwelling arterial lines and central venous catheters can reduce the need for repeated heel sticks to obtain blood gases.
- More research is recommended to clarify the most appropriate medication for pain relief in preterm infants as well as dosing regimen.
- Practitioners should routinely adopt pain assessment measurement in their care of preterm infants in the NICU.

signs of pain, but may be those most in need for appropriate intervention. A recent study, albeit pilot, demonstrated that the pain from a heel stick could alter cerebral blood flow and cause intraventricular hemorrhage (IVH) (Manious & Looney, 2007). This raises even more serious concerns regarding the need to protect small premature infants who are at an increased risk for IVH hemorrhage and its disconcerting long-term consequences (Badr, 2006; Badr, Garg, & Kamath, 2006; Badr & Purdy, 2006). Table 3 provides a brief description of clinical application of the findings of this study.

Future research could assess the relationship between pain exposure for infants at different GAs, brain structure, and development. Another area of great concern is that while pain research has proliferated in the past 20 years and pain assessment tools are abundant, a majority of nurses and physicians working with preterm infants do not routinely assess pain, and pain management remains unsystematic and capricious (Bergqvist et al., 2007; Cignacco et al., 2007; Simons et al., 2003). Therefore, translating research findings to clinical practice is fundamental to the effective care of preterm infants.

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