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Neonatal Monitoring Technologies: Design for Integrated Solutions

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PAIN MONITORING IN NEONATES

By

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Conflict of interest: Hanne Storm is coowner and CEO of Med-Storm Innovation, Gimle terrasse 4, Oslo, Norway, that is developing the Skin Conductance Algesimeter to monitor pain.

When writing this chapter it was impossible to not use the already written “Bible” as background information, Anand KJS, Stevens BJ, and McGrath; “Pain in neonates and infants”, chapter 6; “Assessment of pain in neonates and infants” written by Stevens BJ, Pillai Riddel RR, Oberlander TE and Gibbins S (Anand KJS Elsevier 2007). Additionally, I have tried to add some data from adults to discuss against the findings in infants and also looked deeper into the physiological ways to assess pain.

ABSTRACT

In US it is mandatory to monitor and treat pain. Italy, France and Russia are establishing standards which require pain assessment and treatment. Physiological, behavioural and biochemical tools have been used for pain assessment but no golden standard is available. These tools have limits and benefits. The topic of this chapter is to discuss these tools for different infant groups and try to conclude if these tools can fulfill the golden standard for pain assessment that should be independently of the infant’s immaturity and level of illness, in real time, have accuracy for pain, react immediately, and have an index valid for all infants.

INTRODUCTION

In US inadequate analgesia in hospitalized patients in 2001 prompted the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), to introduce standards which require pain assessment and treatment (Vila H et al 2005, http://www.jointcommission.org/SentinelEvents/SentinalEventAlert/sea_32.htm). Pain was defined as the fifth vital sign (Vila H et al 2005). This directive has led to increased patient satisfaction with pain

management, but also an increased incidence of opioid associated adverse drug reactions that have the potential for fatal outcome (Overdyk F 2006). In France and Italy, from 2010, the Governments have made similar new guidelines for the importance of monitoring and treating pain. These requirements may be mandatory in EU countries and Russia in the next years to come.

The International Association for the Study of Pain (ISAP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”. Further, “the inability to communicate verbally does not negate the possibility that an individual is experiencing pain, and is in need of appropriate pain relieving treatment” (ISAP Task Force on Taxonomy from 2003). The Association also affirms pain to be of subjective character, each individual learning the application of the word through experiences from early life. Pain is a subjective experience. When pain is reported from a patient, acknowledging the reported pain, the site, nature and severity of pain, is strongly advocated (Agency for Health Care Policy & Research 1992).

To report pain requires a certain ability to communicate and is generally not applicable in children below three years of age. When ISAP emphasise the importance of pain treatment in non-verbal patients, the need of assessing pain in this patient group is emphasized as well. The perception of pain is an inherent quality of life that is developed to protect against tissue damage (Anand and Craig 1996). The intensity and duration of pain is dependent on the significance of pain for the individual (Stevens et al 2000, Stevens, Gibbins 2002, Guinsburg et al. 2003, O’Rourke 2004). The integration of non-verbal pain assessment tools in preterm infants has to take into account the infants developmental immaturity, physical and psychological, and the level of illness. To develop such pain assessment tool should be based on knowledge about how the developing brain filter, process and modulate pain.

The optimal pain assessment tools should therefore be developed so they can be used independently on the infant’s immaturity and level of illness. Further goals to head for; the pain assessment tools should show pain in real time, have accuracy for pain, react immediately, and have an index valid for all infants. The infant’s perception and expression of pain are influenced by how the caregiver assesses and manages the pain of the infant. It is of crucial importance that the caregivers understand how the infants communicate the pain.

BACKGROUND

ASSESSMENT OF ACUTE OR CHRONIC PAIN?

The tools that are available to assess pain in infants are mainly focusing on acute pain, specific nociceptive event that is self limited (American Pain Society 2001). Examination of behavioural changes like facial expression, body movement, flexion reflex, cry, and / or physiological indicators like heart rate, respiratory rate, blood pressure, oxygen saturation and palmar sweating, are the basis for acute pain assessment scores. Duhn and Medeves published a systematic review including a huge number of univariate, multivariate and composite measures for assessing acute pain in infants (2004). The focus on developing such tools emphasizes the demand to end up with a gold standard for pain management. In infants, physiological, biochemical and / or behavioural indicators are surrogates for self reporting of pain.

Chronic pain has been defined as a pathological pain state without apparent biological value that has persisted beyond the normal tissue healing time (i.e. usually 3 months) (Bonica 1953, Jovey 2002). The change of pain threshold has been associated with previously number of painful procedures (Graunau et al 2000, Holsti et al 2004) and may therefore be a potential first sign of the development of chronic pain. The last years there have been a lot of attention on how acute postoperative pain may develop into chronic pain in adults (Kehlet et al 2006). Interestingly, the prevalence of chronic pain after thoracotomy is lower if surgery is performed in childhood. When examining children it seems that infants are protected against development of chronic pain lasting into childhood (Kristiansen AD et al 2010). The suggested lower prevalence of chronic pain after surgery in childhood may be related to both physiological and psychological factors. An immature peripheral and central nervous system combined with an enhanced neuronal plastic capacity in the child's brain may contribute to a lower risk of developing chronic pain (Florence SL et al 1996). Bones, tendons, and ligaments are more indulgent and flexible in children, and therefore, thoracotomy, including the use of rib retractors, may be less harmful in children than in adults. Furthermore, the chronic post-thoracotomy pain in children is found to be mainly of neuropathic origin (Kristiansen AD et al 2010).

Psychological aspects may also play an important role. In adults psychological aspects such as fear of surgery have been found to be associated with more acute postoperative pain (Peters ML 2007). Children may not worry about the risk of having thoracotomy to the same extent as adults. Today there are no working definitions and/or validated assessment tools designed specifically to assess chronic pain in infants. The closest way to describe the development of chronic pain in infants may be by using the von Freys hairs or filaments to the sole of the foot and recording the force of the stimulus required to elicit the withdrawal response. The flexion withdrawal reflex shows how the central nervous system reacts to nociceptive stimuli similar to perceived pain in adults. Infants have lower threshold and more forceful response compared to adults (Fitzgerald et al 1998, Anand and Carr 1989). This threshold and response may change after increasing number of acute painful procedures (Hermann 2006). Interestingly, infants have increased wound sensitivity measured by the need of analgesic after surgery (Andrews and Fitzgerald 2002). Furthermore, early tissue damage from surgery raises demand for higher intraoperative fentanyl, and shows higher Comfort score (Peters et al 2005) and higher plasma levels of catecholamines when the surgery again affects the same dermatome as prior surgery (Peters et al 2005). Prospective studies with a long-term follow-up, including quantitative sensory testing including flexion withdrawal reflex, are needed in order to improve our knowledge about the prevalence of chronic pain after surgery and painful procedures in infants and children.

DEVELOPMENT OF PAIN PROCESSING MECHANISMS IN NEONATES

Due to neurological immaturity, it was long believed that neonates did not perceive pain (McGraw 1943). As a consequence of this, newborns often did not receive analgesic or anaesthetic medication during invasive procedures, including surgery (Lippmann et al 1976, Rees 1950, Inkster 1978, Norman 1986, Hatch 1987). When the foetus start to feel pain is still discussed. First from 26 weeks of gestational age structural integration of peripheral nerves, spinal cord, brain stem, thalamus and cerebral cortex, develop. Before integration of cerebral cortex with the peripheral nervous system, some researchers claim that noxious stimuli can only initiate stress responses, but no pain perception (Wise 1997). Pain-

induced stress responses in fetuses have been observed from 18-20 weeks of gestational age (Giannakoulopoulos et al 1999, Giannakoulopoulos et al 1994, Gitau et al 2001). Stressful stimuli in utero may induce expression and release of neuromodulators. Corticotrophin-releasing hormone (CRH) is such a neuromodulator which can result in impaired neuronal function (Avishai-Eliner S et al 2002). Knowledge about the infants' anatomical and functional structure to transmit ascending pain signals is available (e.g. Anand and Hickey 1987, Fitzgerald 1991). The brain's ability to modulate pain is limited due to limited cognitive capabilities and immature pain descending pathway (Mitchell and Boss 2002). Lower pain thresholds in preterm infants, as compared to older children and adults, have been observed as a consequence of the absence of inhibitory descending spinal thalamic fibres (Fitzgerald et al 1988, Anand and Carr 1989, Hermann 2006). Today it is thought that preterm infants are able to perceive pain, although their ability to perceive pain might be immature at birth.

THE IMPORTANCE OF PAIN MANAGEMENT IN NEONATES

Inadequate treatment of pain in neonates has several influences on short- and long-term outcomes (Grunau 2002, Witfield et al 2000). Furthermore, increase in behavioural, hormonal, metabolic and other physiological changes occur in infants after exposure to noxious stimuli (Anand et al 1985, Craig et al 1993, Rawlings et al 1980).

Surgical stress in neonates shown by increased level of stress hormones, have also shown associations with increased incidence of postoperative complications and even deaths (Anand et al 1992, Anand et al 1987, Anand et al 1988). By reducing the stress response to surgery in one group of newborns by giving deeper anaesthesia compared to a group receiving lighter anaesthesia, severity of outcomes such as sepsis and mortality was reduced (Anand et al 1992). Tracheal suction and routine procedures in respiratory distressed neonates resulted in prolonged hypoxemia compared to neonates exposed to the same procedures after receiving pain relief (Pokela 1994). It is reported that neonates receiving morphine are long term protected against cardiac reactivity to pain (Grunau et al 2001, Peters et al 2005). Other consequences of insufficient pain therapy are hemodynamic instability, hypoxemia or increased intracranial pressure, the latter potentially triggering brain haemorrhage. Painful procedures may increase intracranial pressure in premature infants (Bellieni et al 2003, Stevens et al 2003, Stevens et al 1994, Raju et al 1980) and there is also evidence that this could result in severe intraventricular haemorrhage (Anand KJS et al 1999). Neonates without anaesthesia during circumcision had elevated plasma cortisol during and after the intervention (Talbert et al 1976, Gunnar et al 1981). The circumcised boys were tested months afterwards and showed a stronger pain response during routine vaccination. This may be due to a sensitization to pain from circumcision (Taddio et al 1997).

Neonates find also non-invasive routine procedures stressful (Holsti 2004, Hellerud 2002, Lagerkrantz 1986). Other stressful procedures should also be monitored because in preterm infants similar side effects as for painful procedures may occur.

There are some groups of hospitalized infants that need especially concern:

Low-birth-weight neonate/infants

Extremely low-birth weight infants (ELBW<1000g) experience hundreds of painful procedures during their hospitalization (Stevens et al. 2003). The long-term side effects from the management of these painful procedures are not well known, but will probably be improved if the caregivers are able to identify and manage safely and effectively the pain and other emotional stressors in these infants. The existing pain scores are not including ELBW infants. In this patient group, when they had reached 32 weeks corrected age, flexing and extending extremities, finger splaying, fisting and mouthing were movements consisting with pain, while startles, twitches, jitters and tremors are not associated with pain (Graunau et al 200, Holsti et al 2004). These authors discovered that the infants' responses to pain were affected by number of previously painful procedures, time since last painful procedures, duration of hospitalization and the use of analgesics during the neonatal period. Interestingly, when using the Skin Conductance changes and the Neonatal Pain, Agitation and Sedation Scale (N-PASS) to monitor pain in infants less than 28 weeks of gestational age, only Skin Conductance changes monitored the pain response during heel stick, not the N-PASS (Munster et al 2010). The N-PASS is developed for infants <28 – 35 weeks corrected age, and includes crying/irritability, behaviour state, facial expression, extremities/tone, and vital signs (heart rate, respiratory rate, blood pressure, oxygen saturation) (Hummel et al 2003). The reduced behavioural response to painful stimulus in ELBW infants or infants less than 28 weeks of gestational age may be due to the limited energy available to maintain a pain response as these infants are using their metabolic resources primarily for life supporting effort (Craig et al 1993). In these small infants physiological pain assessment tools may therefore be beneficially.

Pain Assessments in critically ill infants

Score for Neonatal Acute Physiology and SNAP Perinatal Extension (SNAP-II and SNAPPE-II) (Richardson et al. 2001) and Clinical Risk Index for babies (CRIB) (van Dijk et al 2002) are scores that are determining severity of illness. Furthermore, infants are defined to be severely ill when they are in intensive care environment requiring ventilation. In these infants the level of sedation (Ramsey 2000) has to be taken into account as well as behavioural state and physiological pain responses (Stevens 1994) that will be influenced from quiet sleep and severely illness. In these patients the composite pain measure, N-PASS (Hummel et al 2003), and behavioural indicators such as tears and high arousal (van Dijk et al 2002), have been used to assess pain. When these patients are exposed to pain agitation and different level of sedation, the especially pain part of these reactions may be difficult to interpret. When the infants additionally are exposed for muscle relaxation, physiological indicators may be useful to determine the pain. Infants who are critically ill may be unable to mount vigorous behavioural responses to pain and they may have a decreased level of consciousness as a result of their disease and/or analgesic and sedation medications. Since infants and young children do not verbalise their pain, pain is often poorly assessed and they are at particularly high risk for inadequate pain management. Although pain assessment in this group of patients is a challenge, it is important that assessments are performed on a regular basis using reliable and valid methods in order to ensure that pain is identified and treated.

In adults different findings have been reported from the intensive care units the last years; an intensive care unit patients can struggle with post-traumatic stress syndrome (PTSD) and depression after discharge (Nelson BJ et al 2000, Kress JP et al 2003, Jones C et al 2001, Osterman JE et al 2001). The chance to develop PTSD and depression increase by the number of days spent with sedation and neuromuscular blockade (Nelson BJ et al 2000). Daily interruption

in sedative medication may reduce the incidence of PTSD (Kress JP et al 2003) and lives can even be saved (Girard TD et al 2008). Memories of delusions from the ICU stay without any real event memories increase the chance to develop PTSD (Jones C et al 2001). Furthermore, withdrawal during drug weaning (Cammarano WB et al 1998), prolonged ventilation, delirium and death (Cammarano WB et al 1998, Pandharipande et al 2006) are associated to high daily doses of fentanyl equivalents, lorazepam equivalents and neuromuscular blockers. If similar findings as reported from adults are valid for children exposed to different painful procedures at the intensive ward when they were infants, need to be studied further.

Infants with neurological injury

Interestingly, infants with and without cerebral parenchymal infarction (grade 4 intraventricular haemorrhages) or cystic peri ventricular leukomalacia react similar regarding facial activity and cardiac autonomic reactivity after a painful event (Oberlander et al. 2002). An other group of patients to mention are infants with birth asphyxia. When they are on cooling therapy with some analgesics it is difficult to know if they perceive pain. The half time of analgesics is difficult to predict and they have not the normal muscle tone that gives them the possibility to show behavioural pain responses. Physiological pain indicators may be impaired because of hypothermia. Furthermore, from a theoretical point of view the origin of their asphyxia could be caused by impaired sympathetic outflow at birth since they possible had not the sympathetic drive to breath. The pain assessment on these infants is difficult and should be focused on in the future.

MAIN FOCUS OF THE CHAPTER

METHODS OF ASSESSING NEONATAL PAIN

The pain indicators most commonly used in infants are behavioural, physiological and biochemical. The different methods are systematically reviewed by Dunn and Medens (2004).

Behavioural pain indicators

It is important to be aware of that the pain expressed by the infants when using behavioural pain indicators has to be received by the caregiver in a proper way. It should therefore be focused on both the infants' capability to express pain but also the caregivers' capability to understand when the infant is communicating about the pain. Behavioural pain indicators are subjective and not real time pain indicators.

Behavioural pain indicators include facial activity, crying and body movements. Changes in facial expression comprise brow bulge, eyes squeezed shut, deepening of the naso-labial furrow, open lips, lip purse, chin quiver, curving of the tongue, and mouth stretched vertically and horizontally. Crying parameters include frequency, latency, duration, phonation and melody pattern. Gross motor movement and withdrawal from the pain stimulus are the body movements that best describe responses to pain in healthy infants. More details about the behavioural pain indicators are found under Uni- and Multi- dimensional pain scores.

Physiological variables of pain

Physiological variables have been validated as useful pain indicators despite that vital signs (heart rate, blood pressure, temperature, and respiration) are often misleading because they vary in response to illness. Hemodynamic changes are also strongly influenced by cardiovascular-active drugs, and they have a low specificity as a sign of adequate or inadequate anaesthesia or sedation. Interestingly, the Skin Conductance Algesimeter is not influenced from hemodynamic changes, environmental temperature, and respiratory rhythm ((Wallin et al 1975, Macefield et al 1996, Bini G et al 1980, Habler et al 1993, Hanada et al 2003).

Berde has suggested how the ideal physiological pain score should be defined (Berde 2009). In his appendix 1, Berde offers a provisional list of criteria that should be met for a candidate physiologic measure of pain intensity. In his appendix 2, Berde lists some no painful clinical conditions that may influence measurements based on sympathetic nerve activity. These conditions will potentially decrease the specificity to the physiological pain indicators and should therefore optimally be controlled for.

Berde's:

Appendix 1: Some Proposed Criteria for Ideal Physiologic Measures of Pain Intensity

1. Low cost, portable, reliable, easy to use, low risk.
2. Strong agreement with self-report pain scales in articulate subjects ages 4 yr and older. By strong agreement, we mean high sensitivity, high specificity and excellent positive and negative predictive value over the full range from mild to severe pain intensities. This should include strong agreement for patients/subjects with:
 - a. Experimental pain, including repetitive stimulation
 - b. Acute postoperative pain
 - c. Several distinct types of recurrent episodic pain and chronic persistent pain.
3. Strong agreement with self-report in subjects with experimental pain, acute pain, and chronic pain, under a range of situations such as those listed in appendix 2, items 1–3.

Berde's

Appendix 2: Test Situations for Candidate Physiologic Measures of Pain Intensity

1. Children and adults who are afraid or anxious but having no pain.
2. Adults and children ages 4 yr and older with low and high self reported pain scores with clinical conditions that affect sympathetic responses, *e.g.*, cold exposure, fever, anemia, hypovolemia, shock, congestive heart failure, autonomic neuropathies, sympathetic blockade associated with regional anesthesia, paraplegia with lower body stimuli that evoke autonomic hyperreflexia.
3. Adults and children ages 4 yr and older with low and high self-reported pain scores receiving medications with adrenergic agonist or adrenergic receptor blocking effects.
4. Infants, toddlers, and nonverbal adults with low and high previously validated behavioral pain/distress scores (*e.g.*, Children's

Hospital Eastern Ontario Pain Scale, Face, Legs, Activity, Cry, Consolability Scale, Premature Infant Pain Profile, or others, according to age and clinical context) over a range of clinical conditions such as those listed in 1–3 above.

Additionally to Berde's recommendations, an ideal physiological pain indicator should include real time analyses, fast reaction to painful stimulus, and a valid pain index that can be used for all infants based on low variation between infants when they are at the same pain/discomfort level. Physiological indicators of pain in preterm and full-term infants include increase in heart rate, changes in heart rate variability, respiratory rate, blood pressure, skin conductance (mirroring bursts in the skin sympathetic nervous system), as well as decrease in oxygen saturation. These variables are influenced from outflow in the sympathetic nervous system. It is therefore important to be aware of how the sympathetic nervous system out flow to the microcirculation or to the skin, is influenced from different stimuli or circumstances.

Of the pain assessments methods monitoring Sympathetic muscle outflow to the microcirculation, heart rate is the indicator most studied:

Heart rate studied at infants in sleep, behavioural state 1, ranged from 110-165 beats per minute (bpm), the mean was 137 bpm when 15 infants were studied 6 times during 48 hours (Røeggen et al 2010).

The variation was 80 % between infants, whereas the remaining 20% is estimated to be due to variation within infants. (Roeggen et al 2010). Heart rate is influenced from both sympathetic and parasympathetic nerve activity. In preterm infants, sympathetic control appears to be dominating, and the parasympathetic nervous system becomes more dominant near term and beyond. Heart rate variability (HRV) increases by age in preterm infants but is still lower and immature at term compared to term born infants (Spasov et al 1994). These results indicate that the maturation of cardiac autonomic control may be related to gestational age and level of neurologic maturity. An increasing HR response was also found in preterm infants with increasing gestational age (Craig et al 1993), contradictory results were found by Johnston et al (1996).

Furthermore, heart rate increased more in preterm infants born < 28 weeks of gestational age when they had lived for 4 weeks compared to newborn infants at 32 weeks of gestational during painful procedures. This finding indicates that heart rate is also influenced from postnatal age (Johnston et al 1996). Additionally to gestational age and postnatal age, also respiratory rhythm (including apnoea and hypoxia, use of mechanical ventilation, respiratory distress syndrome) (Habler et al 1993, Hanada et al 2003, Aarimaa et al 1998, Ravenswaaij-Arts et al 1995, Griffin et al 1994), changes in blood volume status (Wallin et al 1975, Macefield et al 1996), medication acting on blood circulation like beta blockers, environmental temperature (Bini G et al 1980), and emotional frightening or sudden situations, influence the heart rate (Hagbarth et al 1972, Wallin 1978). The huge variation of heart rate between infants when they are at behavioural state 1, makes it difficult to use heart rate as a score that will be valid for all infants, where a certain number define the pain stage. The influence from the circumstances as described above, make it not specific for emotional distress like pain. Even though these difficulties by using heart rate, typically heart rate, stress hormones or catecholamine have reduced response to painful stimulus

if the interventions are pre-treated by Embla or different levels of analgesia (Lindh et al 2000, Anand and Hickey 1992, Porges 1995).

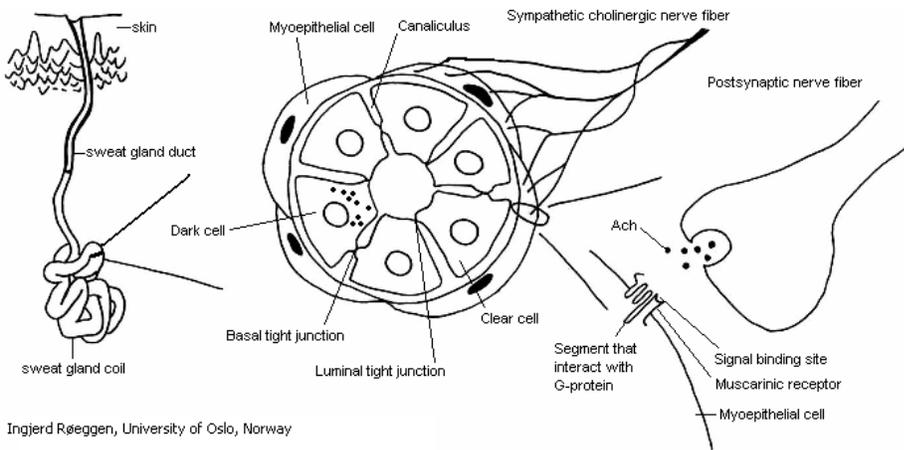
Oxygen desaturation is also used as a measure of pain in preterm infants:

When the oxygen saturation was studied at infants in sleep, behavioural state 1, it ranged between 91-100%, the median was 98%, when 15 infants were studied 6 times during 48 hours. The variation within infants was 41% and the variation between infants was 59%. (Røeggen et al 2010). Desaturation is both observed during stimuli that give arousal and frightening situations (tissue hypoxia due to vasoconstriction) as well as during general tissue hypoxia due to other causes. Oxygen saturation has therefore lack of specificity as a pain indicator.

Of the pain assessments methods monitoring Sympathetic outflow to the Skin, changes in skin conductance is the indicator most studied:

In Pubmed, “skin conductance” and “pain” give 165 hits. There have been about 50 studies on the Skin Conductance Algesimeter and 11 of them quantifies the levels and corresponding sensations of pain in neonates (Storm H 2000, Hellerud BC, Storm H 2002, Storm H, Fremming A 2002, Eriksson M et al 2008, Harrison D et al 2006, Munster JMA 2009, Pereira-da-Silva L et al 2009, Tristão R et al submitted, Kandamany N et al 2010, Gjerstad 2008). The system is based on changes in skin conductance induced by emotional sweating. Changes in Skin Conductance occur during emotional stressors like pain. Moreover, the Skin Conductance Algesimeter index reacts very fast, within 1-2 sec, to painful stimulus.

Skin Conductance activity, peaks per sec, studied at infants in sleep, behavioural state 1, ranged between 0.00 and 0.04 peaks per sec, median 0.00 SCRs/sec. 73% of the total variation was within-infant variation, with the remaining 27% of variation due to variation between infants when 15 infants were studied 6 times during 48 hours. When the Skin Conductance activity, peaks per sec, is used as a pain indicator the pain threshold has been defined to be reached at 0.21 peaks, 5 times the maximum value from when the patients are at behavioural state 1 (www.med-storm.com). Also when monitoring the skin sympathetic nerve activity between and within volunteers, the variation between and within individuals were similar (Kunimoto M et al 1992). Skin Conductance activity is mirroring the skin sympathetic nerve activity. Gestational age was found not to influence the skin conductance activity, peaks per sec (Storm 2002, Munster 2010, Silva 2010, Roeggen 2010), and postnatal age was not found to influence the skin conductance, peaks per sec, in three of these studies (Storm 2002, Munster 2010, Roeggen 2010), but weakly in the fourth (Silva 2010 et al). Since the Skin Conductance activity is induced by acetyl choline acting on muscarine receptors, changes in blood volume status (Wallin et al 1975, Macefield et al 1996), medication acting on blood circulation like beta blockers, environmental temperature (Bini G et al 1980), and neuro muscular blockers, do not influence the Skin Conductance activity. Furthermore, changes in respiratory rhythm do not influence the Skin Conductance activity (including apnoea) (Habler et al 1993, Hanada et al 2003), see figure:



Emotional frightening or sudden situations influence the skin conductance activity (Hagbarth et al 1972, Wallin 1978). Interestingly, when studying postoperative pain in children, two studies showed that anxiousness did not influence the Skin Conductance Algesimeter (Choo et al 2010, Hullett et al 2009). Since the variation between and within infants are low at patient in behavioural state 1, and that the values for infants at behavioural state 1 are 5 times lower than the pain threshold has been defined to be, and that only emotional stress influence the skin conductance as a pain indicator, it seems that skin conductance is better to monitor pain stimuli than heart rate and oxygen saturation in neonates. Furthermore, when studying postoperative pain in children, the accuracy to discover no pain was 97% and the sensitivity to discover moderate and severe pain was 90%. The specificity to discover moderate pain was 67% (Hullett et al 2009). The Skin Conductance Algesimeter did not show any correlation with the reported pain in children (Choo et al. 2010), the reason why can be the low specificity of the Skin Conductance Algesimeter to discover moderate pain. When the Skin Conductance Algesimeter increases it may also be because of other emotional stressors like intellectual tasks, nausea or vomiting etc.

In adult patients that are anaesthetised, both the sensitivity and specificity to pain were 86% when compared to a surgical stress score (Storm H et al 2005). At patients in anaesthesia, when a standardized painful stimulus was given, the response measured by changes in skin conductance, peaks per sec, was statistical significant associated to genes that are associated to pain perception (Storm et al 2010). Furthermore, when studying functional MR of brain activity during acute painful procedures, the results show increase in both skin conductance activity and brain areas associated to pain perception (Dubé AA et al 2009). Moreover, both during deep and superficial painful stimuli, the skin conductance activity and the reported pain from the volunteers increased similarly (Burton AR et al 2009).

This table summarize the different responses to stimuli of the sympathetic nervous system to the microcirculation and to the skin, and how these stimuli influence the oxygen saturation.

	Hypoxia measured by oxygen desaturation	Sympathetic muscle outflow (microcirculation / vasoconstriction)	Sympathetic skin outflow (increase in skin conductance peaks)
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Emotional stress without arousal		No influence	yes
Arousal stimuli like sudden inspiration, chest compression, sudden electrical skin shock.	Desaturation without general hypoxia	Vasoconstriction	yes
Frightening situation	Desaturation without general hypoxia	Yes (cold sweat)	Yes
Cooling		Yes	No influence
Warming		Inhibited outflow (vaso dilatation)	No influence
Respiratory rhythm		Influence	No influence
Apnea	Desaturation with general hypoxia	Influence	No influence
Hypoxia	Desaturation with general hypoxia	Yes	Not studied
Baroreflex control		Yes	No influence
Valsalva manoeures		yes	No influence
Carotid sinus nerve stimulation		Inhibited outflow (vaso dilatation)	No influence

Physiological measures available to be used as pain indicators today in infants are, heart rate, oxygen saturation, and then Skin Conductance Algesimeter, when taking Berde's criteria into account, the conclusions should be:

Equipments already existing in the Neonatal wards like oxygen saturation and heart rate are today associated to lower expenses compared to the Skin Conductance Algesimeter that at most places have to be purchased since it is of new origin. The equipments have the same feasibility when they are used. The Skin Conductance Algesimeter had stronger association with the self-report pain scales in articulating children compared to heart rate in the postoperative period (Hullet et al 2009).

The Skin Conductance showed high sensitivity, 90%, to discover moderate and severe pain different from heart rate, and if the reported pain was treated with pain killers, the Skin Conductance Algesimeter index decreased when pain killers were given, different from the heart rate (Ledowski et al 2006). The negative predictive value to discover no pain in children was 97% when the Skin Conductance Algesimeter index was used. The specificity, to pain, was 67% for children to discover moderate and severe pain. Furthermore, during acute pain in volunteers, The skin conductance activity and pain-evoked brain responses increased (Dube AA 2009). Also superficial and deep pain increased the Skin Conductance Activity and the reported pain of the patients (Burton AR et al 2009). When discussing the Berde Appendix 2, it has to be taken into

account the nature of the sympathetic nervous system; none of the suggested physiological pain indicators may differ between different emotional stressors that give arousal but anxiousness was found to not influence the Skin Conductance Algesimeter postoperatively. The caregiver's clinical judgment has therefore to be used. Other clinical conditions that affect sympathetic responses, *e.g.*, cold exposure, fever, anemia, hypovolemia, shock, and congestive heart failure will influence the oxygen saturation and heart rate but not the Skin Conductance Algesimeter (Wallin et al 1975, Macefield et al 1996, Bini G et al 1980, Habler et al 1993, Hanada et al 2003). If the skin sympathetic nerves are injured or blocked at the extremity where the skin conductance electrodes are fastened, the Skin Conductance Algesimeter will not react to painful stimuli, then it may be better to use the heart rate as a pain indicator or fasten the Skin Conductance electrodes on the extremity with intact nerve system. Furthermore, different from heart rate, the Skin Conductance Algesimeter will not be influenced from adrenergic agonist or adrenergic receptor blocking effectors because acetyl choline acts on muscarine receptors. Additionally to Berde's recommendations, an ideal physiological pain indicator should include real time analyses, and fast reaction to painful stimulus that is valid for both the heart rate, oxygen saturation, and Skin Conductance. So far it seems that the variation between and within infants, when they are at the same discomfort level, are very low for the Skin Conductance Algesimeter different from the heart rate and oxygen saturation (Røeggen et al 2010). The Skin Conductance Algesimeter has therefore the potential to be used as a valid pain indicator valid for all infants, but other emotional stressors have to be taken into account.

Biochemical responses to pain

Biological responses to pain in infants have been carefully reviewed in previously publications (Goldman and Koren 2002, Overlander and Saul 2002). An indication of pain may be when stress hormones such as rennin, aldosterone, catecholamine, cortisol, endorphins, growth hormone and glucagon increase in plasma, and when insulin, contrarily, is suppressed (Anand et al 1987, Anand and Hickey 1992, Goldman and Koren 2002). The biochemical changes might be sensitive markers of pain, but the invasiveness of determining blood levels of these hormones, as well as the time it takes to analyse these changes, makes them less useful in clinical practice. Hence, biochemical responses should not routinely be used for assessment of pain.

Pain scoring systems

Pain scoring systems are based on either behavioural changes, physiological changes, or a combination of physiological and behavioural changes. A multidimensional approach for assessing pain has been recommended. A systematic integrative review of infant pain assessment tools found 35 pain measures; 18 of which were one-dimensional and 17 were multidimensional (Duncan 2004). However, when tested for reliability, validity, clinical utility and feasibility, none of the existing instruments fulfilled all the criteria for an ideal measure.

One dimensional behavioural pain scores

One-dimensional pain scores for preterm and term born infants include one indicator (cry) or multiple indicators from one domain (body movement). Even though low specificity to distinguish between pain and agitation caused *i.e.* by hunger, behavioural indicators are still validated to be the best indicator of pain for preterm, term and older infants (Hudson-Barr et al 1998). Neonatal Facial Action Coding system (NFCS) has now been simplified, fewer indicators, and is therefore less time consuming for clinicians but still with high levels of reliability,

construct validity and concurrent validity (Grunau et al. 1998, Pereire et al 1999). It has been reported that facial expression diminishes after time in immature infants if the infant has been exposed to many prior painful procedures (Grunnau et al 2001, Johnston and Stevens 1996, Holsti et al 2004). This makes the facial expression less valid after long hospitalization period. Cry analyses have been performed to distinguish between hunger, procedural pain, and postoperative- or chronic pain (Kiriya and Werthermann 1978, Benini et al. 1993), but may be difficult to handle in a clinical setting. Both facial expressions and cry may be influenced by behavioural state, severity of illness, gestational age, postnatal age and neurological impairment (Johnson and Strada 1986, Grunau and Craig 1987, Hadjistavropoulos 1997). Body movements, reflex movement in preterm infants developing into movement by purpose in older infants, have also been used as pain indicators (Franck 1986, Craig et al 1993). The quality and quantity of movements are depending on both gestational and postnatal age. Extremely immature infants who are experiencing many painful procedures may become limp and flaccid when painful stimuli are repeated and the Infant Body Coding System will not work properly as a pain indicator.

One-dimensional physiological pain indicators

Physiological responses to pain are now accepted as indicators of pain (Anand and Craig 1996). Whatever the physiological response come from, the expression should be sufficient to be an indicator of pain. The specificity to pain still needs further investigation; see physiological variables to monitor pain above.

Multidimensional pain indicators

Because of the complexity of pain responses and the limits of most of the one-dimensional indicators, multiple dimensions may be warranted. The low correlation between the behavioural (subjective) and physiological (objective) indicators (Stevens et al 1994, Johnston et al 1995, Barr et al 1998), indicate that using two systems measuring the same phenomena from two different angles may be beneficial. For term and preterm infants, the Premature Infant Pain Profile (PIPP) that includes three behavioural (facial action: brow bulge, eye squeeze) and two physiologic (hear rate, oxygen saturation), and two contextual (gestational age, behavioural state) has been used to validated pain responses (Stevens et al 1996). The PIPP has been carefully validated and moderate internal consistency, high interrater and intrarater reliability, construct validity have been reported (Stevens et al 1996, Ballantyne et al 1999, McNair et al 2004). In a previous study, the use of PIPP scale has demonstrated a great sensibility in discrimination between tactile and painful stimulation. When using the PIPP score, wide individual variation in both the physiological and behavioral measures were found, and some infants did not show any increase at all. This would speak in favor of a composite method that would increase the chance of detecting signs of pain, compared to a one-dimensional measure. PIPP is also one of the most frequently used scales in neonatal pain research (Stevens et al, 1996).

Modifying factors to pain assessment

Age dependent changes influenced from maturation or previous pain exposes

There has been developed assessment tool for pain in infants with carefully validation (Stevens et al 1996, Ballantyne et al 1999, McNair et al 2004). Even though it is crucial to be aware of the

rapid maturation of the biological substrates underlying emotions, cognition, language and social relations (Craig 2002). Porter et al (Porter et al 1999b) also found that the nervous system is under transformation when exposed to painful procedures. Interestingly, infants that have been exposed to more extensive pain experiences had less facial action (Johnston and Stevens 1996). Premature infants appear to have a dampened response to painful procedures later in infancy, whereas full-term infants exposed to extreme stress at an early stage exhibit heightened responses to painful procedures. Caregivers have to be aware of that the pain responses in infants change not only by age but also by severe and repetitive painful stimuli. Pain assessment tools may be selected by cautious for the different age groups and for the different illnesses of the infants.

Sensitivity and specificity for pain assessment tools

Physiological and behavioural responses are sensitive indicators of pain but they have poor specificity. The non specificity is similar for both behavioural and physiological pain assessment tools (Craig et al 2000). The caregivers have therefore to use their clinical judgement to understand why is the infant in distress. If an ongoing stimulus occur, the response is high likely to be due to this stimulus. The treatment should focus on reducing the stimulus that induce distress or treat the symptoms according to the stimulus origin. The indicators available for pain should therefore be used as warning indicators for caregivers to know when to examine the infants for what sort of emotional stress that occur. It is important to remember that also other emotional stimuli than pain may be harmful (Holsti L 2004, Hellerud BC 2002, Lagerkrantz H 1986). When using heart rate or oxygen saturation also stress related to diseases like changes in blood volume or respiration, fever, and medication acting on blood circulation have to be taken into account. The physiological state (wakefulness/sleep, hunger) of the infant preceding the painful stimulus is also known to influence the responses (Ramsey 2000). Additionally, physiologic and behavioural indicators generally used to assess acute pain may be dampened in infants and children with chronic pain. To make an accurate assessment of pain based on observed behaviours, it is of crucial importance to consider the infant's circumstances and environment at the time of assessment. The most specific physiological indicators of pain may be the Skin Conductance Algesimeter that is only influenced from emotions (not influenced from changes in blood volume or respiration, fever, medication acting blood circulation, neuromuscular blockers, or gestational age).

Differences between the physiological and behavioural pain assessment tools

Interestingly, the findings from behavioural and physiological responses during painful responses have been reported to be either uncorrelated or weakly correlated. The reason why may be multiples; the caregiver may interpret the behavioural responses differently, the behavioural responses may be less reactive in very ill patients and small for gestational age infants, and for infants who have been exposed for severe and repetitive pain insults. Also different medication used for sedation may blur the behavioural pain response. The physiological response may be influenced from different circumstances, like changes in blood circulation, respiration, environmental temperature, or medication used for sedation. Interestingly, it has recently been shown that oral sucrose has sedative effect without influencing the pain perception (Schlater et al 2010). This is in accordance with the findings that oral sucrose decreases the response from heel stick when studying the behavioural response and crying time but not the

physiological responses like heart rate and skin conductance changes (Storm H, Fremming A 2002). It is also found that when the sound stimuli increase in the ward above 65dB, the physiological responses for discomfort increase but behavioural state does not increase (Haidet et al 2010). Moreover, the physiological pain assessment tools should be preferred to be used as pain assessment tools in very low birth weight infants (Munster et al 2010), critical ill infants with and without neuromuscular blockers (Stevens 1994), infants exposed to hypothermia, and infants exposed to many prior painful procedures (Grunnau et al 2001a, Johnston and Stevens 1996, Holsti et al 2004).

Because the different reactions from the behavioural and physiological measures it is concluded that pain assessment tools should be multidimensional to be able to pick up any distress. The high sensitivity may be on the expenses of the specificity to pain. By not being more focused for the patient's individual situation, there is a risk for even less specificity, and the chance of treating physiological or emotional stressors without pain with analgesics may increase.

FUTURE RESEARCH DIRECTIONS

The pain assessment tools should have clinical utility regards to time, cost, instructions, acceptability and format. The clinical utility has also to include the clinical significance for the patient's outcome.

When teaching caregivers about pain assessment tools their potential bias should be emphasized. When parents, nurses, and physicians are presented for exact the same infant pain behaviour, they interpret the behaviour differently (Pillai Riddel and Craig 2004). This indicates strongly the need of an objective pain indicator that works in real time that make the caregiver less responsible for their very difficult ambiguous situation where infants have to be evaluated about their pain situation. Furthermore, a proper educational task should be available for the caregivers to be more self-confident when they are validating the infant's emotional distress. Despite the abundance of pain assessment tools, specific, objective and effective methods of measuring pain and stress in infants with varying ages and severity of illness are still required. Recently, the Skin Conductance Algesimeter, a measurement of electrodermal activity, has been reported to be a valid, non-invasive, physiological measure of pain and stress in both preterm (from 22 – 24 weeks of gestational age) and term born infants. The Skin Conductance response, peaks per sec, is not influenced from gestational age and the variation between and within infants is very low when they are at the same pain / discomfort level different from heart rate and oxygen saturation. Changes in Skin Conductance occur during emotional stressors like pain. The Skin Conductance Algesimeter index mirrors directly bursts in the skin sympathetic nervous system. Skin conductance has acetylcholine as transmitter, acting on muscarine receptors. The Skin Conductance Algesimeter is therefore not being influenced by adrenergic receptor active agents, room temperature changes, apnea, or muscle relaxing agents. Moreover, the Skin Conductance Algesimeter index reacts very fast, within 1-2 sec, to painful stimulus. It is found that the response to painful stimulus is statistical significant associated to the genes believed to be influenced from pain perception (Storm 2010). Different from heart rate that is mainly influenced from the brain stem level, the SCA is influenced from higher brain areas associated to pain perception (Dube et al 2009). The Skin Conductance Algesimeter follows the NIDCAP nurses observation score and is more sensitive to pain than the N-PASS in infants less than 28 weeks of gestational age.

CONCLUSIONS

Physiological and behavioural pain assessment tools do not correlate, or correlate weakly. Both tools lack specificity to pain. The physiological pain assessment tools seem to be better than behavioural pain scores at least for some patient groups, and can be used to warn in real time when emotional stressors like pain occur. Then the caregivers should use their clinical judgement to find out if it is pain or other stressors that occur. If the physiological pain assessment tool is activated by other stimuli than emotions, a behaviour pain score could be beneficial to use together with the clinical judgement. The Physiological measures should ideally follow the guidelines from Berde (Berde 2010) and additionally include real time analyses, fast reaction to painful stimulus, and a valid pain index that can be used for all infants.

RECOMMENDED LITERATURE

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