CHAPTER 1

Introduction

This chapter presents several topics including the background and significance of the study, research objectives, research questions, and definition of the terms.

1.1 Background and Significance of the Study

A preterm neonate is a newborn infant who was born before 37 weeks of gestation with immaturity of many organ systems, especially the respiratory system. Consequently, most of these infants need intensive care for survival. Preterm neonates can be classified into extremely low gestational age (ELGA, ≤ 28 weeks), very low gestational age (VLGA, 29 to 32 weeks), and late preterm infant ($34^{0/7}$ to $36^{6/7}$ weeks) (Francis, 2012; McCort, 2014; Medlock, Ravelli, Tamminga, Mol, & Abu-Hanna, 2011). However, there was not a standard accepted definition of the category of infants (Behrman & Butler, 2007). Currently, Glass and colleagues (2015) defined the terms of subdivided preterm birth group including extremely preterm (< 28 weeks), very preterm (28 to < 32 weeks), moderate preterm (32 to < 34 weeks), and late preterm (34 to < 37 weeks). The survival rate of preterm neonates has increased dramatically for each additional week of gestation because of improvements in prenatal and obstetric care and neonatal intensive care units (NICU) (Beck et al., 2010; Blencowe & Cousens, 2013; Chawanpaiboon & Kanokpongsakdi, 2011). The trend of lower gestational age of infant survival has improved over the past decade (Kyser, Morriss, Bell, Klein, & Dagle, 2012). With increasing gestational age, rates of survival to discharge increased, while rates of survival with morbidity decreased (Stoll et al., 2010). The lower the gestational age of preterm neonates, the more invasive procedures were required for their survival (Carbajal et al., 2008). Therefore, ELGA and VLGA infants who require invasive procedures are commonly clients in the NICU.

Preterm neonates are exposed to early and repeated pain resulting from numerous diagnostic and therapeutic procedures which are essential for their survival. Invasive procedures, such as heel stick and insertion of intravenous and arterial lines, are essential for monitoring and intensive care management. The average number of painful procedures for preterm neonates in NICU was approximately 14 procedures per neonate per day, not including the high number of failed attempts (Carbajal et al., 2008; Chen et al., 2012; Cignacco et al., 2009). Within the first two weeks of life, the average number of painful procedures in neonates was 134 procedures (Stevens et al., 1999). The maximal number of painful procedures counted per one neonate during hospitalization varied from 249 (Chen et al., 2012) to 488 procedures (Barker & Rutter, 1995). This means that after birth the younger preterm neonates are more likely to have early, repeated and prolonged exposures to unavoidable painful procedures. Due to receiving early repeated painful procedures and not having vigorous responses, these infants suffer more pain than older neonates because clinicians might have the potentially erroneous conclusion that they are not experiencing pain (Grunau et al., 2005; Morison et al., 2003).

For vulnerable infants who cannot verbally share their pain, Anand and Craig (1996) pioneered the explanation that pain perception is an inherent quality of life that appears early in development to serve as a signaling system for tissue damage. Therefore, a procedure is considered as painful if it invades the neonate's bodily integrity, causing skin injury or mucosal injury (Carbajal et al., 2008). In addition, the neurologists also specifically confirmed conclusion that preterm neonates have all the anatomical and functional requirements for pain perception based on nociception (Fitzgerald, 1991, 2005; Fitzgerald & Walker, 2009). Nociception is the detection and transmission of painful stimuli from the site of the stimulus to the brain (Fitzgerald & Beggs, 2001). However, pain perception in neonates, especially preterm neonates, that involves functional pathways is not found in the mature nervous systems in older infants. During the developmental transition, unique structure and function in the neonatal nociceptive circuit will generally enhance and prolong the effects of both noxious and tactile stimulation leading this population to be more vulnerable than older infants and adults.

Unravelling the unique development of nociception is a key to understand pain behavior development in preterm infants. Based on experimental research involving rodent

models, the understanding of developmental neurobiology of pain and supraspinal processing has recently improved (Anand, 2008; Bartocci, Bergqvist, Lagercrantz, & Anand, 2006; Eiland, 2012; Fitzgerald, 2005, 2015; Pattinson & Fitzgerald, 2004; Slater et al., 2006), but how the whole process develops in the newborn is not completely understood (Fitzgerald, 2005, 2015; Verriotis, Chang, Fitzgerald, & Fabrizi, 2016). The pain mechanism of preterm neonates should shed light on the context of the developmental plasticity of nociceptive pathways which are characteristics of the immature pain system in fetuses.

The uniqueness of nociceptive pathways during developmental transition includes a greater density per area skin, a slow conduction speed of C-fibers, and immature descending inhibition. By 24 gestational age, preterm neonates have receptors as much as in adults, thus they contain large peripheral fields leading to overlapping receptive field and generating more electrical activity to brain (Hall & Anand, 2005; Simon & Tibboel, 2006). However, the peripheral fields decrease in size with maturation over the first two postnatal weeks (Eiland, 2012; Fitzgerald & Jennings 1999). Pain or nociceptive information in preterm neonates is transmitted primarily through the C-fibers, which are unmyelinated fibers, rather than through the A-delta myelinated fibers, occuring in older individuals (Fitzgerald & Walker, 2009; Walden, 2014). The underdeveloped myelination and slow synaptic transmission causes sensory and motor neurons in the central nervous system (CNS) to respond at longer and more variable latencies. Less precision also occurs in pain signal transmission in the spinal cord, and descending inhibitory neurotransmitters are lacking (Fitzgerald & Walker, 2009; Hall & Anand, 2005; Walden, 2014). The lack of descending inhibition in the neonatal dorsal horn means that it limits their ability to modulate the experience. As a result of painful procedural experiences during the first postnatal days and weeks, abnormal nociceptive input experiences leads to alterations in pain signal processing (Fitzgerald, 2005). The pain stimulus, prolonged exposures to noxious stimuli, and lack of positive feedback can cause neuronal excitotoxicity (Anand & Scalzo, 2000) and also alter the hardwiring of the neuronal organization of the brain (Marko & Dickerson, 2017). Thus, pain in early development should be managed to limit neuronal excitotoxicity and prevent a chain of adverse experiences in preterm infants leading to short and long term effects.

Pain can serve as a warning of injury, but it can also evoke negative physiologic, metabolic, and behavioral responses in infants. Preterm infants can demonstrate the following

negative physiological effects in response to potentially painful stimuli: (a) increase or decrease in heart rate, and or blood pressure and respiratory rate; (b) increased intracranial pressure; and (c) long-term alterations in neuro-pathway development (Anand, 1998; Anand & Scalzo, 2000; Badr, 2013; Fitzgerald & Beggs, 2001). The immediate pain responses are an increase in heart rate, a rise of heart rate variability, a decrease in oxygen saturation, and blood pressure fluctuations (Badr, 2013; Walden, 2014). Immature autoregulation of cerebral blood flow in the preterm neonates may be one of the contributing factors, rendering these infants vulnerable to various degrees of intraventricular hemorrhage (Anand, 1998; Anand & Scalzo, 2000). Pain during many weeks or months in the NICU might be one of the contributing factors to permanently altered pain sensitivity and neurodevelopment of preterm neonates and contribute to the overall energy expenditure of preterm neonates affecting postnatal growth (Bouza, 2009; Grunau, 2013; Grunau, Holsti, & Peters, 2006).

Pain in preterm neonates must be accurately identified and treated with optimal pain management. During the developmental transition, the challenge for all health care professions is to care for these surviving infants with understanding of the pain signals and their responses. This is crucial for improving the situation in the clinical setting by reducing exposure to pain, assessing accurately and improving pain relieving interventions for this vulnerable patient population. Anand (2001) stated that ability to recognize sources of pain and the routine use of pain assessment scales could help avoid repeatedly painful stimuli and increase the use of specific pain reduction interventions. Pain assessment is the key component of optimal pain management for preterm infants. Appropriate pain assessment is essential, since it is the trigger for interpretation and decision making, mainly concerning the implementation of analgesic measures or interventions (Schollin, 2003). On the other hand, failure to use a pain scale appropriately matched to the patient population or lack of knowledge in concerning the respondents' perceptions of premature infants' ability to sense pain and means of expressing pain may result in ineffective pain management (Byrd, Gonzales, & Parsons, 2009; Pölkki et al., 2010).

Presently, from literature review, there are thirteen pain assessment scales available for preterm neonates which can be classified into two groups including uni-dimensional and multi-dimensional scales (de Melo, Lélis, de Moura, Cardoso, da Silva, 2014). However, no gold standard scale for clinical practice exists (Anand, 2007; Fitzgerald & Walker, 2009;

Gibbins, Stevens, Beyene et al., 2008). Three limitations of existing pain assessment scales for preterm neonates included lack of incorporated developmentally important behaviors of preterm neonates, failure to include factors affecting intensity of the pain reactions in previous scales, and complex scoring leading to low utilization of validated pain scale in preterm neonates at the bedside (Anand, 2007; Bellieni & Buonocore, 2008; Fitzgerald & Walker, 2009).

Lack of incorporated developmentally important behaviors of preterm neonates causes the issue of difficulty in recognizing pain responses for preterm neonates. The individual behaviors in many previous pain scales used with preterm infants were originally derived from observations of term born infants who most likely had a vigorous magnitude of pain behavior (e.g. Neonatal Facial Coding System [NFCS] and Neonatal Infant Pain Scale [NIPS]). Although term and preterm infants have similar patterns of pain response in general, pain response in preterm infants may be less noticeable or completely absent. Existing evidence suggested that only four of ten facial expressions (brow bulge, eye squeeze, nasolabial furrow, and vertical mouth stretch) of NFCS were sensitive indicators of pain in preterm neonates (Gibbins, Stevens, Beyene et al., 2008; Gibbins, Stevens, McGrath et al., 2008; Holsti, Grunau, Oberlander, Whitfield, & Weinberg, 2005). In addition, the same four of ten facial expressions of NFCS were used in several studies (Ramenghi, Wood, Griffith, & Levene, 1996; Rushforth & Levene, 1994). Moreover, the knowledge related to a neurodevelopmental approach to pain in preterm neonates is growing. The clear evidence for anatomic developments supporting the preterm neonates' capacity for nociception and the key sites of developmental transition in preterm neonate pain pathways have emerged (Bouza, 2009; Eiland, 2012; Fitzgerald, 2005; Fitzgerald & Walker, 2009).

Failure to include factors affecting the intensity of the pain reactions in previous scales causes consistent underestimation of pain in preterm neonates. Anand (2007) insisted that preterm newborns who were more immature, asleep, or exposed to previous painful procedures were less likely to demonstrate specific responses to pain. It means that there are many factors affecting pain reactivity in preterm neonates. Concerning those factors, the Premature Infant Pain Profile revised (PIPP-R) which included the gestational age and behavioral states as contextual factors in scoring was used in NICUs (Stevens et al., 2014). However, PIPP's scores have not been clearly explained in some circumstances. For example,

the PIPP-R scores in ELGA infants of 7.8 (*SD* = 2.8) was interpreted as pain (Gibbins et al., 2014), while the PIPP-R score of 8.3 (*SD* = 2.9) (Steven et al., 2014) and 11.64 (*SD* = 3.2) (Vederhus, Eide, & Natvig, 2006) were the mean scores during non-painful procedures.

The mean of pain scores might be affected by other factors. In addition, the PIPP-R scores were poorly correlated with exposure to pain-associated procedures (Rohan, 2014). The result of low pain scores while having high frequency exposures to pain clearly shows the limitation of application of these instruments at the bedside. Due to the complexity of pain in preterm infants, the importance of measuring pain multi-dimensionally including factors associated with pain responses are suggested (Sellam, Engberg, Denhaerynck, Criag, & Cignacco, 2013; Walden, 2014). An empirical study concluded that the number of skin breaking procedures since birth predicted dampened facial responses to a heel stick (Grunau et al., 2005). It can be explained that the exposure to repetitive pain may cause excessive N-methyl-*D*-aspartate (NMDA)/excitatory amino acid activation resulting in an excessive amount of calcium entry into the cell, which can initiate excitotoxic cell death (Anand, 2008; Anand & Scalzo, 2000). The excitotoxic damage to developing neuron might alter pain pathway during developmental transition period. However, factors affecting pain reactivity in preterm neonates (e.g. previous pain exposure) have not been examined and included in any of existing scales. Thus, previous pain exposure and other factors need to be explored.

Complexity of scoring of validated pain scales leading to little use at bedside remains a clinical issue. Most of the previous pain assessment scales have been developed mainly for research purposes, then clinical utility evaluation at the bedside in preterm neonates are rarely tested (Pölkki, Korhonen, Axelin, Saarela, & Laukkala, 2014; Stevens & Gibbins, 2002). Only PIPP and CRIES scales were tested for clinical utility and published (Schiller, 1999). Clinical utility can be conceptualized as a multi-dimensional judgment and can be measured from NICU nurses' perspectives about a pain assessment instrument for their working practice including appropriateness, accessibility, practicability, and acceptability (Smart, 2006). The pain assessment scales improve the communication of pain indicators among clinicians that can assist in better pain management practices for neonates in all levels of care. Recently, the validated pain scale for premature infants is the PIPP (Mitchell, Brooks, & Roane, 2000; Slater, Fitzgerald, & Meek, 2007). However, it still has some limitaions and is impractical to use (Badr, 2013). The review of the PIPP using studies from year 1996 to 2009

found that none of the studies reported how PIPP scores were used to make clinical decision (Stevens, Johnston, Taddio, Gibbins, & Yamada, 2010). In addition, nurses who used PIPP-R reported that they needed additional clarifications for how to use the scale and to calculate the total pain score; thus, further studies examining the clinical utility of the PIPP-R scale are needed (Gibbins et al., 2014; Steven et al., 2014). Complex scoring makes the instrument unfeasible to be implemented at the bedside, and limits nursing professions' ability to work as real-time instruments to improve pain management. This demonstrated that integration of pain assessment which is a prerequisite to pain management into daily practice remains problematic.

The major issues concerning existing pain assessment scales leave room for the improvement of clinical pain scales. Several literature reviews and expert opinions related to pain in preterm neonates also suggested the need for developing a new scale (Anand, 2007; Anand et al., 2006; Badr, 2013). Therefore, a new pain assessment scale for preterm neonates in the NICU concerning the developmental maturity of those infants and the factors affecting their pain responses is urgently needed. An improved and appropriate clinical pain assessment scale may increase an effectiveness of pain management because pain assessment is fundamental of pain management (Schollin, 2005). The purpose of this study, therefore, was to develop a clinical pain assessment scale for preterm neonates in the NICU and to examine its psychometric properties and clinical utility.

1.2 Research Objectives

Three objectives of this study were as follows:

1.2.1 To develop a clinical pain scale for preterm neonates in procedural pain the NICU

1.2.2 To test the psychometric properties of the developed clinical pain scale for preterm neonates in the NICU

1.2.3 To examine the clinical utility of the developed pain scale for preterm neonates in the NICU

1.3 Research Questions

Three research questions were stated as follows:

1.3.1 What are the characteristics of the clinical pain scale for preterm neonates in the NICU?

1.3.2 What are the psychometric properties of the developed clinical pain scale for preterm neonates in the NICU?

1.3.3 What is the clinical utility of the developed pain scale for preterm neonates in the NICU?

1.4 Definition of Terms

A preterm neonate was a newborn infant born at between $\geq 24^{0/7}$ and $36^{6/7}$ weeks of gestation based on early ultrasonogram or a New Ballard score who was hospitalized in the NICU at under the postmenstrual age of 36 weeks and receiving respiratory support.

Pain was defined as an acute unpleasant sensory and emotional experience associated with actual or potential tissue damage caused by medical or nursing procedures that invade the neonate's bodily integrity, causing skin injury or mucosal injury.

Psychometric properties referred to construct validity and reliability of the clinical pain scale for preterm neonates. In this study, construct validity was examined using content-related validity evidence, hypothesis testing, and convergence evidence. Reliability was examined using internal consistency testing and inter-rater reliability testing.

Clinical utility was the usefulness of the pain scale in clinical practice. It can be evaluated based on the users' judgment on its appropriateness, accessibility, practicability, and acceptability. Regarding those four aspects, the impact of the clinical pain scale for preterm neonates on pain management, availability, suitability for using in NICU environment, and the preference of users were examined.