Translational approach for new therapeutic targets to prevent severe neonatal morbidities

Chapter 10

Valorization

This valorization chapter describes how the outcomes of this thesis contribute to neonatal units, parents, society as well as research and industry. The results described in this thesis enable new treatment and prevention modalities in both term and premature infants.

Societal Importance

Preterm birth is a very important public health priority worldwide; approximately 15 million babies are born preterm every year and preterm birth complications are the leading cause of death among children under 5 years of age (Liu et al., 2016). In addition, preterm birth is also associated with increased morbidity as well as with increased health care costs because of longer hospital stays and a greater need for intensive care due to medical care related to morbidities of prematurity. In a study from the US, the disproportionate share of neonatal care was highlighted (Barradas et al., 2016). Although 9.1% of all hospitalizations were associated with preterm birth, these hospitalizations accounted for 43.4% of total costs. In addition, 5.9% of the same cohort required re-hospitalization, the costs of which accounted for 22.6% of all costs. Therefore, we need evidence-based strategies to prevent prematurity and prematurity-related morbidities. As more immature infants survive due to the advances in neonatal care, the incidences of bronchopulmonary dysplasia (BPD) and necrotizing enterocolitis (NEC) do not decrease (Stoll et al., 2015). Hence, it is reasonable and also cost-effective to develop targeted therapies against morbidities such as BPD and NEC.

In addition to prematurity, neonatal hypoxic ischemic encephalopathy (HIE) presents also a significant clinical burden with its persistent high mortality and morbidity rates. Worldwide, four million newborn infants experience birth asphyxia each year, accounting for an estimated one million deaths and 42 million disability-adjusted life years (Nair, J., and Kumar, V.H.S., 2018). Although therapeutic hypothermia has been accepted as the standard of care for infants with moderate to severe HIE, it has not definitively changed overall outcomes in severe HIE. HIE has a multifactorial pathogenesis and multiple cellular events including excitotoxicity, inflammation and oxidative stress lead to cellular damage. Due to this complex events cascade, combination therapies acting on different stages of hypoxic ischemic injury were suggested as a novel approach to reach different targets in the setting of HIE. These therapy targets in HIE include prevention of acute lesions, increase in size of the therapeutic time window for protection, and enhanced repair in the long term (Cilio, M.R. and Ferriero, D.M., 2010). Therefore, development of alternative therapies, especially the combined use of neuroprotective agents, were suggested to provide more benefit for prevention of HIE-related devastating neurological disability (Douglas-Escobar, M., and Weiss M.D., 2015).

Since prematurity, prematurity-related morbidities and HIE contribute to a significantly higher burden of neonatal mortality and morbidity globally, there is a need

for alternative and supplementary therapeutic agents. In order to have global applicability, therapies need to have low costs and should be easily and readily available (Costa et al., 2018). However, research involving critically ill neonates is very hard to perform due to some unique ethical concerns. The design of trials, the informed consent process, and the implementation of studies in critically ill neonates is very difficult because these subjects are vulnerable and critically ill, have a significant risk of dying or a poor prognosis when surviving. Despite these ethical concerns, it is very crucial to perform research trials for introduction of new drugs, devices, and interventions and to develop the necessary evidence of efficacy and toxicity to support the use of these medications (Fleischman, A.R., 2016). It is also important to establish the safety and efficacy of such drugs in preterm infants, especially in the hospitalized population with lower birth weight and gestational age who are actually on multiple drugs (Costa et al., 2018). The drug-drug interactions in these patients are not well studied and may be further complicated by prematurity as such. From the ethical side, the main problem is to increase the effectiveness and to improve short- and long-term effects of these promising modalities in preterm infants while conducting drug studies in neonates within the ethical framework of respect for persons, justice, and beneficence (Ward, R.M., and Sherwin, R.C., 2015). To bypass these ethical problems related to clinical studies, we can perform experimental studies in the preclinical stage, the results of which can be translated into clinical usage. The experimental studies for prevention and treatment of important prematurity-associated neonatal morbidities and HIE that were reported in this thesis showed promising results for the possible therapeutic usage of some agents such as valproic acid, CDP-choline, melatonin, prostaglandin E1, uridine and topiramate. After those encouraging results from our experimental studies, the efficacy and safety of these therapies should be evaluated in this vulnerable group with further clinical studies. In accordance with this idea, limited number of clinical studies that evaluated the use of melatonin in HIE and neonatal sepsis in newborns have been published (Aly et al., 2015 and El Frargy, et al. 2015). Similarly, the safety and efficacy of topiramate was also evaluated in a recent feasibility study (Filippi et al., 2018). Therefore, I suggest that these preliminary studies may work as a pioneer for planning further larger clinical studies that may result with translation of our experimental results to clinical usage for these agents.

Contributions of this thesis to understanding of neonatal diseases and planning future studies for health professional societies

The findings in this thesis are of importance and of additional value for current understanding and further research in the prevention of prematurity related morbidities and HIE in term babies. Prematurity-related morbidities including BPD and NEC have multifactorial pathogenesis. Therefore, there is no single curative treatment for these

morbidities and new therapeutic agents are required to prevent and/or treat these morbidities.

Epigenetic mechanisms including DNA base modifications such as methylation, alteration of histones resulting in chromatin modification, as well as the actions of noncoding RNA are required for both lung modelling and remodeling. Recently, epigenetic regulation was also suggested to play an important role in development of chronic lung diseases including BPD (Merritt et al., 2011). In this thesis, valproic acid, which is a histone deacetylase inhibitor, was suggested as an alternative preventive treatment approach for neonatal hyperoxic lung injury in preterm infants due to its epigenetic effects. Since valproic acid was reported to be used as a therapeutic agent for treatment of severe neonatal seizures, its effectiveness against BPD in preterm infants should be evaluated in future clinical studies in the presence of the data provided by our preclinical study.

The complex multifactorial pathogenesis of NEC results in intestinal dysfunction, inflammation, injury and necrosis. All these events result in the disruption of cell membranes in all organ systems including lung and intestine. Therefore, restoration of cell membrane functions may provide benefits in these conditions. Herein, CDP-choline, an endogenous intermediate of major membrane phospholipids, was shown to reduce both hyperoxic lung injury and NEC by several different mechanisms of action. As CDP-choline was administered to preterm infants for treatment of respiratory distress syndrome, its usage for either prevention and/or treatment of both NEC and BPD in these infants may be evaluated by future clinical studies. As mentioned above, due to the complex pathogenesis of these morbidities, combinations of therapies instead of a single therapeutic agent should also be evaluated for both treatment and/or prevention of BPD and NEC in preterm infants. This combination therapeutic approach may also be tested for newer treatment strategies for HIE as mentioned in the thesis. Especially, combination of some inexpensive therapies such as magnesium sulfate and melatonin as mentioned in the thesis may enable neonatologists to provide an effective therapy in developing countries that lack therapeutic hypothermia. The results of this thesis will encourage clinical researchers to test therapeutic approaches best suited for the resources in their environment.

Contributions of this thesis to health economics and hospital costs

Preterm birth and prematurity represent a global economic problem due to longer hospitalization periods and re-hospitalizations after discharge. In addition, prematurity-related increased neurological and pulmonary conditions such as cerebral palsy, asthma and learning difficulties may lead to an economic burden due to the increased health costs. Therefore, the newer and inexpensive therapeutic approaches and the combination of therapies described in this thesis may help to decrease the health care

costs in these infants, which is important for both the family, and the society in a country. These experimental therapeutic approaches may offer new treatment strategies in the NICU perspective by either decreasing the duration of hospitalization or decreasing the incidence and/or severity of adverse outcomes associated with these morbidities. It may also reduce the need of re-hospitalization associated with the effects of abnormal lung injury or intestinal damage during hospitalization.

Contributions of this thesis to parents

Preterm birth has also been linked to increased parental stress, depression, and anxiety (Pace et al., 2016). Parental anxiety can be decreased by detailed discussion of expected prematurity-related issues and possible treatment strategies. Herein, the results of this thesis may offer understanding and hope for their infants to have a possible cure in the presence of risk factors for BPD or NEC development.

Future perspectives

This thesis provides a combination of several therapeutic approaches for the prevention of important neonatal morbidities in both term and preterm infants. The reported experimental studies justify clinical applications and translations. This translation must be done in carefully designed clinical trials, where not only the short-term benefit is tested, but also data on the long-term follow-up is collected. Therefore, the studies in this thesis serve both the pathophysiological understanding and the therapeutic innovation. All these improvements may guide clinicians to perform human studies with the idea in mind that it is more important to develop preventive strategies rather than treatment strategies for these morbidities.

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