Neonatal pearls : safety and efficacy of medication use in fetus and neonate

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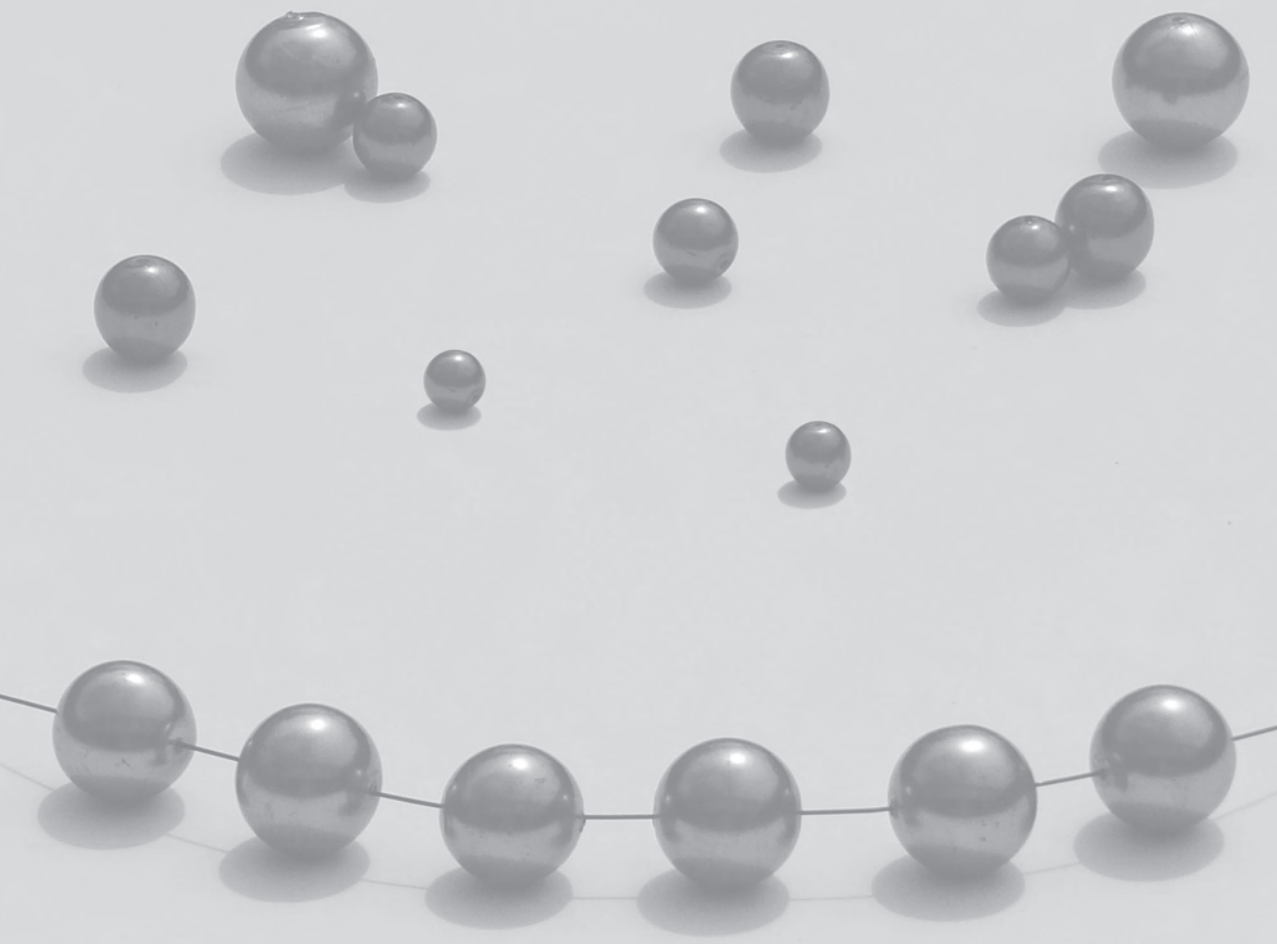
Chapter 9

Summary



Summary

Chapter 1 - General introduction.

Neonatal health care is provided with medication and protocols for almost all morbidities. Before the use of these medicines is allowed, they are extensively studied and tested for efficacy and safety. As patient population and knowledge on specific diseases changes with time, repeated evaluation of efficacy and safety of current used policies is of paramount importance. The most suitable study design for such evaluations is a retrospective overview, through which incidence and accompanying comorbidity can be surveyed. Results can possibly lead to adjustments of the protocol or be an incentive for new randomized controlled trials (RCT). RCTs are, however, only ethically justified once retrospective evidence is sufficient to suggest advantages of a possible new intervention.
Another great benefit of retrospective studies is their usefulness in investigation of rare diseases, which are common in neonatology. Designing prospective studies for possible new interventions in rare conditions, is extremely difficult.
Both above named reasons make retrospective studies indispensable in medical research.
In this thesis six 'Neonatal Pearls' are presented: six relatively rare clinical conditions, of which a retrospective study evaluates the efficacy, safety and/or long term consequences of the current protocol. Despite their retrospective design and relatively small sample size, they are all of significant value and may serve as potential foundations for future protocol adjustments and randomized controlled trials.

The general aim of this thesis was to emphasize the importance retrospective studies and evaluation of already existing protocols. Six retrospective studies investigating effectiveness, safety and/or long term consequences of different medicines in neonates are described.

Chapter 2 – Fetal, neonatal and developmental outcomes of lithium-exposed pregnancies.

Many women with a bipolar disorder are of reproductive age and will need to continue lithium treatment during pregnancy, as risks for relapses are high when discontinuing

lithium. The teratogenic and perinatal effects of lithium are slightly known, in contrary to the long-term effects of lithium on neurodevelopmental outcome of these children. In chapter 2 we investigated growth, neurological, cognitive and behavioral development of children exposed to lithium in utero in an observational retrospective cohort study. Of the 30 infants who were exposed to lithium in utero, 15 were available for follow-up and were investigated at 3-15 years of age. Only one child had signs of a minor neurological dysfunction, but without further clinical implications. Cognitive tests scores were within normal limits, although most children had lower scores on the performance IQ subtest. Growth, behavior and general development were all within the normal range. According to our results continuing lithium therapy during pregnancy seems not to cause adverse effects on growth, neurological, cognitive and behavioral development of exposed children.

Chapter 3 – Favorable neonatal outcome in allo-immune thrombocytopenia treated with antenatal intravenous immunoglobulin.

Fetal and neonatal allo-immune thrombocytopenia (FNAIT) is the most common cause of severe thrombocytopenia in neonates. Weekly maternal intravenous immunoglobulins (IVIG) is the cornerstone in antenatal treatment for already known cases of FNAIT. Nowadays, most centers prefer a non-invasive approach without fetal blood sampling (FBS) and intra-uterine platelet transfusions (IUPT). In chapter 3 we described a retrospective overview of 23 neonates treated antenatally between January 2006 and January 2012 with weekly maternal administration of IVIG. Twelve neonates (52%) had platelet counts <50 x 10^9/L, of which 3 had spontaneous rise, 8 received 1 matched platelet transfusion and 1 needed 2 matched transfusions. Three neonates had petechiae and hematomas, without clinical consequences. Only 1 neonate, without a sibling with intracranial hemorrhage (standard risk), had an intracranial (ICH) just before the start of antenatal IVIG at 28 weeks. Neurodevelopmental follow-up at two years of age was normal. The results of this study suggest that antenatal treatment with weekly maternal IVIG and postnatal matched platelet transfusion are effective and safe for the management of FNAIT.

Chapter 4 – Repeated courses of ibuprofen are effective in closure of a patent ductus arteriosus.

Patent ductus arteriosus (PDA) is a frequent complication in preterm infants. Ibuprofen and indomethacin (both COX-inhibitors) are used for pharmacological closure of PDA. In most centers a failed second course of COX-inhibitors is followed by possible harmful surgical closure. In chapter 4 we described a retrospective study to estimate the closure rate of clinically significant PDA after second and third courses of ibuprofen and record possible side effects. A total of 164 preterm infants, admitted between November 2005 and September 2011, with PDA were included. The closure rate was similar after the first (109/164), second (24/43) and third (6/11) course of ibuprofen (X^2=2.1, p=0.350). Late start of the first course of ibuprofen was a predictive factor for increased need of a second course (X^2=4.4, p=0.036). No additional side effects of multiple courses of ibuprofen were detected. Based on this study we conclude that repeated courses of ibuprofen are an effective and safe alternative for surgical closure and should be considered after failure of the first course of ibuprofen

Chapter 5 – Use of rifampin in persistent coagulase negative staphylococcal bacteremia in neonates.

Coagulase negative staphylococci (CoNS) are the most common cause of late onset sepsis in the Neonatal Intensive Care Unit (NICU). A minority of neonates does not respond to vancomycin therapy and develops persistent bacteremia, which may be treated with rifampin (originally an antibiotic against the tubercle bacillus). In chapter 5 we evaluated the use of rifampin in persistent CoNS bacteremia with a retrospective study of 137 neonates with CoNS bacteremia. Eighteen of these neonates were treated with rifampin, because of persistent bacteremia (3 positive blood cultures at least 48 hours apart with clinical symptoms) or (suspected) intravascular thrombus. Duration of bacteremia prior to rifampin therapy (8.0 ± 3.6 days) was positively correlated to the total duration of bacteremia (10.3 ± 3.7 days). The earlier rifampin was started, the earlier the blood culture became sterile. After starting rifampin therapy C-reactive protein (CRP) levels of all neonates declined and blood cultures became sterile after 2.3 ± 1.6 days. Vancomycin levels were not consistently measured in all neonates, sometimes resulting in late detection of sub-therapeutic trough levels. The results of this study indicate that rifampin is effective in the treatment of persistent CoNS

infections in neonates, but outcome may be more improved by adequate monitoring of vancomycin trough levels.

Chapter 6 – Outcome and management in neonatal thrombocytopenia due to maternal ITP.

Neonatal thrombocytopenia due to maternal idiopathic thrombocytopenic purpura (ITP) is not uncommon, but ICH is very rare(<1%). Postnatal neonatal treatment consists of platelet transfusions, IVIG and/or prednisone; however evidence about the preferred postnatal treatment is scarce. In chapter 6 we described a retrospective analysis of the 67 neonates born from 41 mothers with ITP during pregnancy. Severe thrombocytopenia occurred in 20/67 (29.9%) neonates; in one neonate unilateral polymycrogyria was detected on cranial imaging. In 3 neonates platelet count rose spontaneously, whereas 18 neonates received treatment (of which 1 due to persistent moderate thrombocytopenia). Postnatal treatment consisted of: platelet transfusions (n=3), prednisone (n=2), IVIG (n=1), platelet transfusions and IVIG (n=11), platelet transfusion and prednisone (n=1). Relapses of platelet counts after platelet transfusions were commonly seen. Risk factors for severe neonatal thrombocytopenia were delivery of a previous neonate with severe thrombocytopenia and low maternal platelet nadir during pregnancy.
The results of this study suggest severe thrombocytopenia in neonates from mothers with ITP occurs more frequently than previously reported. Treatment with multiple platelet transfusions and IVIG is often required to reach a platelet count above $50x10^9$/L. We propose starting IVIG, when platelet count falls quickly below 50 x 10^9/L after the first platelet transfusion.

Chapter 7 – Short and long term outcome of neonatal hyperglycemia in very preterm infants.

Hyperglycemia in preterm infants is associated with increased morbidity and mortality, but data on long-term outcome are limited. In chapter 7 we investigated the effects of neonatal hyperglycemia (blood glucose >10 mmol/l, treated with insulin for >12 hours) on growth and neurobehavioral outcome at 2 years of age in a retrospective follow-up study. Between January 2002 and December 2006 859 preterm infants (<32 weeks) were admitted, of which 66 (8%) developed hyperglycemia.

Hyperglycemia was significantly correlated to mortality, with 27/66 (41%) in the hyperglycemia group versus 62/793 (8%) in those without hyperglycemia. Mortality was predominantly observed in hyperglycemic infants with mean glucose values > 8.0 mmol/L or maximum glucose values > 9.5 mmol/L on days 3-4 after the diagnosis of hyperglycemia. Morbidity was also more common in infants with hyperglycemia and a birth weight of <1000 gram or a gestational age below 28 weeks.
Thirty-three survivors treated with insulin for hyperglycemia and 63 controls (matched for gestational age, birth weight, gender and year of admission) without hyperglycemia were evaluated for follow-up at a corrected age of 2 years. Growth was similar, but behavioral and neurological development were more frequently abnormal among those with hyperglycemia. We concluded that despite treatment with insulin, hyperglycemia has negative effects on mortality and neurobehavioral outcome. Therefore, more research to the pathophysiology of hyperglycemia-induced brain injury should be performed and better strategies to manage hyperglycemia are urgently required.

Chapter 8 – General discussion.

In the general discussion, the main results of this thesis were discussed for each chapter separately. A summary on 'what is already known' of each topic was given, underlining the weaknesses and contradictions in current evidence. Suggestions for further research were done, to improve our knowledge for optimization of treatment policies. Practical recommendations based on the current evidence, in combination with the results of the studies described in this thesis are proposed. We conclude by stating that evaluation and adjustment of medical interventions in neonates is a continuous process, which requires increased awareness from the medical community and well-designed studies.