Diploma thesis

Laser-acupuncture for neonatal abstinence syndrome -
A retrospective data analysis of developmental check-ups and comparison of the results between acupuncture- and control group

Submitted by
Ilona Paier

in order to attain the academic degree
“Doctor medicinae universae”
(Dr. med. univ.)

Division of Neonatology
Department of Paediatrics and Adolescent Medicine
Medical University of Graz
Graz, Austria

under the supervision of
Priv-Doz. Dr. med. univ. Wolfgang Raith
and
Dr. med. univ. Lukas Peter Mileder

Graz, 30 May 2017

Affidavit / Eidesstattliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe verfasst habe, andere als die angegebenen Quellen nicht verwendet habe und die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.

Graz, 30. Mai 2017 Ilona Paier eh.

Prologue

This diploma thesis was written during a period from October 2015 to May 2017 at the Medical University of Graz, Department of Paediatrics and Adolescent Medicine, Division of Neonatology.

Although the topic "Neonatal Abstinence Syndrome" is not commonplace in routine medical care, it caught my interest from the first day on. As I have been interested in the field of paediatrics from the beginning of my studies, I was glad to have the chance to work at the Department of Paediatrics and Adolescent Medicine.

The research project proved to be difficult and long-winded. I had to put in big intense to collect the data. Unfortunately not everything worked out as it was initially planned and I was not able to acquire data from all the subjects.

Nevertheless I am of the opinion that my efforts were worth it. With my diploma thesis I aimed at difficulties that may arise in the further care of infants with Neonatal Abstinence Syndrome.

By conducting a literature research, I put together suggestions and ideas, which may improve the encounter between families with drug-abuse issues and medical institutions.

Acknowledgement / Danksagung

Ein großes Dankeschön geht an meinen Betreuer Priv-Doz.Dr.med.univ. Wolfgang Raith für seine großartige Unterstützung bei der Erstellung dieser Diplomarbeit. Mit seiner Kompetenz, seiner Erfahrung und seinem Engagement begleitete er mich geduldig durch den gesamten Arbeitsprozess und war mir bei Fragen und Unklarheiten stets ein Ansprechpartner. Als nächstes möchte ich meinem Zweitbetreuer Dr.med.univ. Lukas Peter Mileder herzlich für seine Bemühungen danken! Durch seine ausgezeichneten Englisch-Kenntnisse konnte er mir bei der Verfassung dieser Diplomarbeit in englischer Sprache entscheidend weiterhelfen! Univ.-Ass.Mag.Dr.rer.nat Alexander Avian gebührt ebenso großer Dank für die Hilfe bei der Erstellung der Statistik und für wertvolle Hinweise zum Aufbau dieser Arbeit. Weiterer Dank gebührt all den niedergelassenen Kinderärzten, die mir bei der Datenerhebung geholfen haben. Ohne ihre Mithilfe wäre die Erstellung dieser Arbeit schwer möglich gewesen! Danke an Dr. Hans Jürgen Dornbusch, Dr. Peter Mileder, Dr. Olga Prehsfreund, Dr. Gertrude Kaltenbäck, Dr. Sonja Gindl, Dr. Max Haidvogl, Dr. Christian Moissier, Dr. Johann Stebbegg und Dr. Günther Krottmayer!

Ein ganz besonderer Dank gilt meinem geliebten Papa, Mag. Hubert Frisch, der mir das Studium ermöglicht hat! Er war auch in schwierigen Zeiten für mich da, hat mir immer Mut zugesprochen und an mich gelglaubt, danke! Meiner geliebten Mama, Liselotte Paier, möchte ich auch von Herzen für ihre Unterstützung während des Studiums danken! Sie hatte stets ein offenes Ohr für mich und konnte mich mit ihrer liebevollen und fröhlichen Art immer wieder aufheitern und motivieren! Ich bedanke mich auch besonders bei meinen lieben Großeltern Liselotte und Franz Paier für ihr Interesse, ihre Fürsorge und ihre Unterstützung! Auch meiner lieben Großmutter, Aloisia Frisch, möchte ich gerne für die familiäre Unterstützung während meiner Studienzeit danken! Dankbar bin ich auch meinem Freund, Martin Wiedenbauer, den ich während des Studiums kennen gelernt habe und der mich immer unterstützt hat! Zu guter Letzt möchte ich meiner Schwester und Studienkollegin Ursula Paier danken! Liebe Ursi, danke, dass du das Medizin-Studium mit mir gemeinsam bestritten hast! Du warst eine große Stütze für mich! Die wunderbare, gemeinsame Studienzeit wird mir immer in Erinnerung bleiben!

Abbreviations and their definitions

AG = acupuncture group

BSID II = Bayley Scales of Infant Development II

CG = control group

DA = developmental age

DDST = Denver Developmental Screening Test

DQ = developmental quotient

f = female

GA = gestational age

GMDS = Griffith Mental Development Scales

HT7 = acupuncture point Heart 7 chin. *Shenmen*

KI3 = acupuncture point Kidney 3 chin. *Tai Xi*

LI4 = acupuncture point Large Intestine 4 chin. *He Gu*

LOS = length of hospital stay

LR3 = acupuncture point Liver 3 chin. *Tai Chong*

m = male

MIDD = minor developmental delay

MODD = moderate developmental delay

NAS = Neonatal Abstinence Syndrome

nc = no comorbidities

NDD = no developmental delay

SDD = severe developmental delay

SSRI = selective serotonin reuptake inhibitor

Glossary

Illustration listing

List of tables

Abstract

Introduction: Neonatal Abstinence Syndrome (NAS) is a drug withdrawal syndrome caused by abrupt discontinuation of chronic foetal exposure to opioids. The study of Raith et al. investigated the benefits of laser-acupuncture as a supplementary treatment option in new-borns with NAS. In this diploma thesis we examined the further development of these study participants.

Methods: The developmental outcome of 28 infants (acupuncture-group [AG]: n=14, control-group [CG]: n=14) was examined by conducting a retrospective data analysis. The data, originated from an investigation period of 2009 - 2014, were primarily derived from electronic health records from the University Hospital of Graz. Additionally practising paediatricians were surveyed using a standardized questionnaire. We investigated the developmental outcome at 12 and 24 months and compared the results of the AG and the CG.

Results: We were able to acquire developmental data from 22 out of 28 subjects (78.6%, AG: n=10, CG: n=12). The two groups did not significantly differ in their developmental outcome at 12- ($p = .594$) and 24 months ($p = 1.000$).

Discussion: As a result of these findings, non-invasive laser acupuncture had no significant effect on the developmental outcome of our subjects.

Zusammenfassung

Einleitung: Das Neonatale Abstinenz Syndrom (NAS) tritt nach in-utero-Exposition mit Opioiden oder anderen legalen / illegalen Substanzen auf. Es handelt sich dabei um Entzugserscheinungen, die auf das abrupte Abbrechen der Substanzexposition nach der Geburt zurückzuführen sind.
Die Studie von Raith et al. untersuchte die Vorteile der Laser-Akupunktur als ergänzende Behandlungsoption bei Neugeborenen mit NAS. In dieser Diplomarbeit kontrollierten wir die weitere Entwicklung dieser Studienteilnehmer/innen.

Methoden: Das Entwicklungsergebnis von 28 Kindern (Akupunkturgruppe [AG]: n=14, Kontrollgruppe [CG]: n=14) wurde mit Hilfe einer retrospektiven Datenanalyse untersucht. Die Daten, welche aus einem Untersuchungszeitraum von 2009 – 2014 stammen, wurden überwiegend aus elektronischen Gesundheitsakten des Universitätsklinikums Graz erhoben. Zusätzlich wurden praktizierende Kinderärzte/innen mittels eines standardisierten Fragebogens befragt. Wir untersuchten die Entwicklung mit 12 und 24 Monaten und verglichen die Ergebnisse der AG und der CG.

Ergebnisse: Wir konnten die Entwicklungsdaten von 22 aus 28 Studienteilnehmern/innen (78.6%; AG: n=10, CG: n=12) erheben. Die beiden Gruppen unterschieden sich dabei in ihrem Entwicklungsergebnis mit 12- ($p = .594$) und 24 Monaten ($p = 1.000$) nicht signifikant.

Diskussion: Basierend auf diesen Erkenntnissen konnten wir keine signifikante Auswirkung der nicht-invasiven Laserakupunktur auf die Entwicklung unserer Studienteilnehmer/innen feststellen.

Contents

1. Introduction

1.1 Neonatal abstinence syndrome

1.1.1 Definition

Neonatal Abstinence Syndrome (NAS) is a drug withdrawal syndrome. It is caused by abrupt discontinuation of chronic foetal exposure to substances that were used or abused by the mother during pregnancy.(1) Kocherlakota (1) defined NAS as *"generalized multisystem disorder, which predominantly involves the central and autonomic nervous systems, as well as the gastrointestinal tract.*"(1) Even though NAS is rarely life-threatening, significant illness and prolonged hospital stays can be the result.(1)

1.1.2 Incidence

Today we know that maternal opioid abuse and the incidence of NAS have been increasing over the last ten years.(2) NAS involves all ethnicities and communities.(1) The increase in cases of NAS corresponds with the reported more liberal use of prescribed opioids for pain control in pregnant women.(3)

1.1.3 Pathophysiology

Sudden discontinuation of prolonged foetal opioid exposure leads to withdrawal symptoms of the neonate.(1) Opioids are easily conveyable across the placenta to the foetus, because they have several qualities like a low molecular weight, as well as their water – and fat solubility. The transmission of opioids across the placenta increases with the gestational age of the foetus. For this reason decreased incidence and less extensive severity of withdrawal is observed in preterm neonates.(4)

Opioid receptors play a huge role in the pathophysiology of opioid withdrawal. They occur in several systems of the human body, such as the central nervous system, the gastrointestinal- and reproductive tracts and in peripheral organs, e.g. lungs and liver.(5) *"A lack of opioids in a chronically stimulated state increases activity in the opioid receptors, leading to increased adenyl cyclase activity, and cellular ionic imbalance."(1)* As a result of the sudden lack of opioids; the locus coeruleus, which is one of the areas of the brain extremely sensitive to the opioid status, produces less norepinephrine.(6) This cascade is responsible for most signs and symptoms of NAS.(7) Norepinephrine is chemically released from the sympathetic nervous system in response to stress, what results in changes of our body functions.

Another example is the ventral tegmental area of the midbrain, which is a dopamine storage centre. Opioid withdrawal causes declined activity in the ventral tegmental area and consequently a lower dopamine release. The poor dopamine-levels provoke the expression of anxiety during opioid withdrawal.(8)

Furthermore the expression of many other neurotransmitters like serotonin, acetylcholine or cortico-tropine is affected by the sudden decrease of opioid-levels in the human body. The results are sleep disturbances, gastrointestinal dysfunction, hyperalgesia or affected gene expression.(1)

1.1.4 Symptoms

Typical signs and symptoms are associated with NAS, although the individual clinical manifestation can vary. It is not known by now, why this variation occurs, but it is supposed to be multifactorial.(3) NAS manifests itself mainly in the central-, in the autonomic- and in the gastrointestinal system.(9)

Table 1: Symptoms of NAS

"Central nervous system:
hyperirritability
hypertonia
high-pitched cries
tremors
increased reflexes (deep tendon reflexes, Moro reflex, rooting reflex)
ineffectual and uncoordinated sucking and swallowing reflexes
Autonomic nervous system:
sweating
frequent yawning and sneezing
rapid respiration
mottled skin
fever
Gastrointestinal system:
excessive sucking
poor feeding
regurgitation or vomiting
loose or watery stools"
(9,10)

The onset of these withdrawal symptoms is usually within 24 to 72 hours after birth, although sometimes symptoms are observed much earlier. Withdrawal symptoms can last up to five days.(9) Exposure to additional substances, such as selective serotonin-reuptake inhibitors (SSRIs), benzodiazepines, and nicotine, may also alter the onset of the syndrome, as well as the severity of symptoms.(11,12)

1.1.5 Differential diagnosis

If symptoms appear, diagnoses like infection, hypoglycaemia, hypocalcaemia, hyperthyroidism, intracranial haemorrhage, hypoxic-ischemic encephalopathy and hyper viscosity must be ruled out in the first line.(13,14)

1.1.6 Diagnostic:

If maternal characteristics are pointing to drug abuse in the course of pregnancy, a screening for intrauterine drug exposure is indicated.(14)

Table 2: Maternal characteristics pointing to drug abuse during pregnancy

"absent, late, or inadequate prenatal care
a previously documented or admitted history of drug abuse
a previous unexplained late foetal demise
precipitous labour
hypertensive episodes
severe mood swings
cerebrovascular accidents
myocardial infarction
repeated spontaneous abortions"

(14)

"Although NAS is a clinical diagnosis, toxicological confirmation is necessary to identify the exact type of substance that the mother was using or abusing and to confirm or rule out the use of other licit or illicit substances during pregnancy."(1)

There are different techniques to detect in utero drug exposure:(14)

Urine testing

Foetal urine is the most common matrix tested, because extraction is efficient and it is inexpensive.(1,15) Due to the short half-life of many substances, urine testing has some limitations and therefore the urine sample has to be collected as soon as practicable after birth.(1,14) Opioids can be detected up to 1 - 3 days after birth.(16) Urine testing is limited

by the not uncommon fact that mothers to stop taking drugs a short time before birth, which can lead to (false) negative test-results.(15)

Meconium testing

Meconium testing is more sensitive than urine-testing and specimen collection is easy, rapid and non-invasive. All the substances that the mother has consumed during pregnancy are directly detectable in the meconium. (1,14)

Further analytic possibilities are hair and umbilical cord tissue.(15)

Analysis is usually carried out by using the immunoassay technique, which can be done in hospital clinical laboratories. Miscellaneous drugs are differed by using specific lower cut-off concentrations for each drug.(1) The time of detection for each substance depends on the amount and duration of drug exposure, the dose and mode of maternal administration, the individual metabolism, the clearance of the drug in the mother and her foetus and the type of the detection method employed.(1,15)

1.1.7 Management

Clinical symptoms, as well as the maternal and collateral history are important guides for initial risk management. (13) (Taking a collateral history means to obtain the case history by interviewing relatives.) Different scoring systems are available to assess the degree of withdrawal and the parameters for treatment.(14)

The most frequently used assessment tool to quantify the severity of NAS and to guide treatment is the Finnegan Score.(17) The scale consists of 21 items, which are in connection with NAS.(14) Scoring is done after feeding in 2- 4 hour intervals. Pharmaceutical treatment is commenced if a threshold >8 is met on the Finnegan Scoring System, (see attachment). (13,17,18)

1.1.8 Therapy

Pharmacologic therapy

The optimal oral substitution therapy and treatment duration in new-borns suffering from NAS remains controversial.

The most popular first-line medications are morphine and methadone. Both preparations are given orally. At the moment there is no evidence which agent is superior. Phenobarbital, clonidine, and clonazepam are administrated as second line agents for more severe withdrawal.(18)

Non-pharmacologic therapy

According to recent studies nonpharmacological adjunct interventions may be beneficial for infants diagnosed with NAS. Nonpharmacological treatment includes breastfeeding for eligible patients, shielding of noise and lights, swaddling, and rooming-in.(18) Sublett et al.(19) reported that tight swaddling and non-nutritive sucking, as well as the decrease of erratic, hypertonic and uncoordinated movements might reduce infant stress.

Breastfeeding

Several studies have shown that breastfeeding has various positive effects on the infant suffering from withdrawal. A decrease of the need for pharmacological treatment, reduced NAS-scores, and reduced length of hospital stays (LOS) are the results. It is also recommended for mothers who are on a methadone or buprenorphine maintenance therapy and who have currently not been using illicit drugs.(18)

Acupuncture

Occasionally there is literature showing an integrative use of acupuncture to the NAS.(20,21) Laser-acupuncture, a non-invasive acupuncture method, is another possibility of non-pharmacological treatment for infants suffering from withdrawal.(22)

1.1.9 Outcome

According to several reviews, which investigate the outcome of infants with NAS, reports on long term effects hardly exist.(23,24) Reasons therefore are methodological limitations in study design, like small sample-sizes, poorly defined comparison groups and difficulties in controlling for important environmental factors. Difficulties are also associated with the studied population, which means high drop-out rates and unstable lifestyle (what is characteristic for drug addicts). These issues make the long term outcome of in-utero-drug-exposed infants difficult to examine.(24)

Recent reports agree, that in-utero opioid-exposed infants have a higher risk for neurodevelopmental impairment, than non-drug-exposed, healthy children.(23,24)

Nevertheless environment seems to be a very important factor in modulating outcome and has to be taken into account.(24) Other studies, which compared in-utero-opioid-exposed children raised by their biological parents to infants growing up in adoptive homes, showed that the latter achieve higher psychometric scores.(25)

A case-control-study from Royal Prince Alfred Hospital in Sydney found, that in-utero-opioid-exposed infants remained shorter in height over an investigation period of three years. Cognitive function, social maturity and psychomotor development were also decreased in comparison with the healthy control group.(23)

1.2 Laser acupuncture for Neonatal Abstinence Syndrome: A randomized controlled trial

The study "Laser Acupuncture for Neonatal Abstinence Syndrome: A Randomized Controlled Trial" by Raith et al.,(22) which is a prospective, randomized, controlled, blinded, single-centre study and the groundwork of this diploma thesis, deals with the benefits of laser-acupuncture as a supplementary treatment option.

The study was conducted between March 2009 and November 2014 and included infants diagnosed with NAS after maternal opioid substitution therapy. The study population was randomly split in two groups (14 in each group). The patients of the acupuncture group (AG) were treated with pharmacologic therapy (opioid replacement therapy) and laser acupuncture. The control group received pharmacologic therapy alone.

The laser acupuncture therapy consists of five National Acupuncture Detoxification Association (NADA) ear points as well as four body points: Tai Chong (LR3), He Gu (LI4), Tai Xi (KI3) and Shenmen (HT7). LI4 is known as a painless acupuncture point, HT7 has a soothing and decelerating effect on the heart function, LR3 reduces pain and cramping. KI3 supports renal energy.

The acupuncture points were stimulated bilaterally in daily repeated sessions within a LABpen MED 10 ® (675nm/10mW). The primary endpoint was the duration of oral morphine therapy for NAS. Highest single Finnegan Score, time to highest single Finnegan Score, maximum amount of oral morphine solution, time to maximum amount of oral morphine solution and LOS were defined as secondary outcome measures.

Treating physicians and attending nursing staff were not informed (blinded) which group the respective new-born belonged to. The size of the disorder was calculated by applying a well-known scheme (Finnegan Score). Thereof the amount of morphine administration and ultimately the discharge date for the new-borns was derived from.

The study found that the duration of oral morphine therapy (28 vs 39 days, $p = .019$) and the LOS (35 days [interquartile range 25 to 47] vs 50 days [36 to 66], $p = .048$) were significantly reduced in the AG compared to the CG.

1.3 Research question / Aim

Aim of this diploma thesis was to evaluate the neurodevelopmental outcome of the infants included in the study by Raith et al.(22) and to compare the results of the AG with those of the CG.

2. Methods

2.1 Study design

This diploma thesis is based on a retrospective data analysis. The data, originated from an investigation period of 2009 - 2014, were gathered from electronic health records from the University Hospital of Graz, Department of Paediatrics and Adolescent Medicine, Division of Neonatology. In addition practising paediatricians were surveyed using a standardized questionnaire.

2.2 Patient collective

All new-born infants investigated in this diploma thesis have been included in the pilot study of Raith et al.(22)

2.3 Data acquisition

2.3.1 Sample size estimation

The initial case number of 28 patients in this diploma thesis corresponds to the number of investigated new-borns in the pilot study by Raith et al.(22)

2.3.2 Data acquisition

The collection of neurodevelopmental data was performed by utilising different sources. Firstly the hospitals database was searched for developmental check-ups, secondly an inquiry of practising paediatricians using a standardized questionnaire was conducted, and most recently the vaccination database of the "Scientific Academy for Preventive Medicine" (Styria, Austria; https://www.vorsorgemedizin.st) was used to assess the data of the medical examinations of the Mother-Child-Programme.

By examining medical reports, discharge summaries and doctors` notes using the hospital database, neurodevelopmental data were collected. In this context the focus was laid on the developmental check-ups at 12- and 24 months.

To acquire the missing developmental check-ups, practising paediatricians (who had been specified by the parents in the discharge letters) were contacted. In total 10 practising paediatricians of the asked test subjects (AG: n=7, CG: n=3) were contacted. First we sent a pre-information-email, in which the contents of the study was explained. Then the paediatricians received a letter with a standardized questionnaire (accompanied by the name

and birth date of the patient in question) and a self-addressed, stamped envelope. After a period of six weeks, paediatricians, who had not answered until then, were contacted again by email and phone-call.

By consulting the Scientific Academy for Preventive Medicine, a last effort was made to access the missing developmental check–ups. Using the vaccination – database after having obtained permission from the Land Steiermark practising paediatricians, who had carried out the vaccination on the subjects in request, were identified. These physicians (n=4, AG: n=2, CG: n=2) were also surveyed using the standardized questionnaire.

2.3.3 Target figures

2.3.3.1 Primary objectives

The primary objectives are represented by the results of the neurodevelopmental examination of the infants at 12- and 24 months. The screenings had been performed at the outpatient clinic for development, Division of Neonatology, Department of Paediatrics and Adolescent Medicine, University Hospital of Graz. The level of development had been objectified by using the Bayley Scales of Infant Development II, the Denver Developmental Screening Test, the Griffith Mental Development Scales and by directly observing the infant´s behaviour. Additionally a survey among the treating practising paediatricians was conducted, using a standardized questionnaire.

Bayley Scales of Infant Development II (BSID II): Memory skills, habituation, problem-solving skills, early number concepts, classification and categorization ability, vocalization and linguistic competencies, early social-communicative skills, motor skills (postural control and fine and gross motor coordination) / test form: step ladder / objective: developmental quotient (DQ)(26)

Denver Developmental Screening Test (DDST): social contact, fine motor adaption, speech and gross motor skills / test form: step ladder / objective: number of combinations of retardations. (27)

Griffith Mental Development Scales (GMDS): hearing, speaking, eyes, hands, behaviour (personal and social), motor skills, performances / test form: step ladder. / objective: area specific developmental age; total developmental age and – quotient(27)

The results of the developmental check-ups were gathered from electronic health records and from our questionnaires. We took over the diagnosis documented in the discharge letter

or questionnaire. The diagnosis of the developmental outcome was classified (as it has been done at the outpatient clinic for development in Graz) as follows:

- No developmental delay (NDD)
- Minor developmental delay (MIDD)
- Moderate developmental delay (MODD)
- Severe developmental delay (SDD)

2.3.3.2 Secondary objectives:

Secondary objectives included:

- sex (m = male / f =female)
- prematurity (gestational age [GA]; prematurity: ≤ 37+0 weeks of gestation)
- comorbidities during neonatal period
- lengths of hospital stay (LOS [days])
- need for pharmacologic therapy [therapy days]
- social environment (dismissal in home care [parents] or foster parents / crisis care space)

2.4 Statistics

Statistical data were compiled by using the study licence for IBM SPSS Statistics 23. Figures and tables were generated with Microsoft Exel and Adobe InDesign. In order to assess the statistical significance of differences in developmental outcome between the two groups, Fisher`s Exact Test was applied.

2.5 Ethical assessment

For the current study an application for ethical approval had been made to the Medical University of Graz. The application was independently audited by the Ethics Committee of the Medical University of Graz. The procession of the study was approved on January 13th 2016. (EK-Nr.: 28-225 ex 15/16)

2.6 Information privacy

Part of the data were extracted from medical records at the Department of Paediatrics and Adolescent Medicine, University Hospital of Graz. The rest of the data were acquired as part of a survey, using a standardized questionnaire. The questionnaires contained the name and

the birthdate of the patients of interest and were sent out by post. Replies (with completed questionnaires) were also received by letter.

All data employed were anonymized and saved on a computer with access restriction. Password security was applied to all files. Only authorized persons had access to the original and encoded data. Within this diploma thesis the privacy act 2000 was abided continually.

2.7 Benefit/risk evaluation

Our approach involved a strictly retrospective data analysis, and therefore did not present any risk for the patients. The study did not offer a direct benefit for the patients. This diploma thesis serves as groundwork for future studies.

3. Results

3.1 Data acquisition

3.1.1 Data acquisition: Hospital database

The medical records of 16 subjects (16 out of 28, 57.1%; AG: n=7, CG: n=9) contained the desired data of the developmental check-ups at 12 - and 24 months. Three patient files (3 out of 28, 10.7%; AG: n=2, CG: n=1) contained only data of the developmental check-ups at 12 months. Nine (9 out of 28, 32.1%; AG: n=5, CG: n=4) did neither contain data of check-ups at 12 months nor at 24 months (see Figure 1).

Although developmental check-ups at the outpatient clinic for development, (Division of Neonatology) are intended for in-utero-drug-exposed infants, not all of our patients underwent these examinations. Different reasons have been identified, which are discussed further in the next section and detailed in Figure 1).

Reasons for missing developmental check-ups (12 out of 28, 42.9%)

▪The hospital database research showed that there was no recommendation for a developmental check-up in the discharge letters of four patients.

▪Three families never visited the outpatient clinic for development for unknown reason.

▪Two families visited the outpatient clinic for development unregularly for the developmental check-up.

▪ Two of the families had moved to another region in Austria and, therefore, did not comply with recommended developmental check-ups.

▪In the case of one subject no further appointments were arranged because of good development.

3.1.2 Data acquisition: Survey

To acquire missing developmental check-ups we contacted practising paediatricians, who were generally announced by the parents upon dismissal of the infant. After having conducted the hospital database research, developmental data of 12 subjects (12 out of 28, 42.9%; AG: n=7, CG: n=5) were missing.

In two cases, the paediatrician who had carried out the recommended medical examinations of the Mother-Child-Programme could not be identified, because the two families had moved to another region and therefore was no indication in the discharge letter. Thus, ultimately ten

practising paediatricians received a pre-information via e-mail and were sent a questionnaire by mail.

The survey among paediatricians delivered neurodevelopmental data of one patient (AG: n=1, CG: n=0).

Reasons for missing developmental check-ups - survey (9 out of 10, 90%)

▪Unfortunately, five of the contacted practising paediatricians were not willing to participate in the study or did not respond to our invitation.

▪Two of the practising paediatricians had not been visited by the patients and could not provide data on them.

▪Two of the practising paediatricians had only seen the patients a few times, so that no developmental investigation was done.

3.1.3 Data acquisition: Vaccination database & second survey

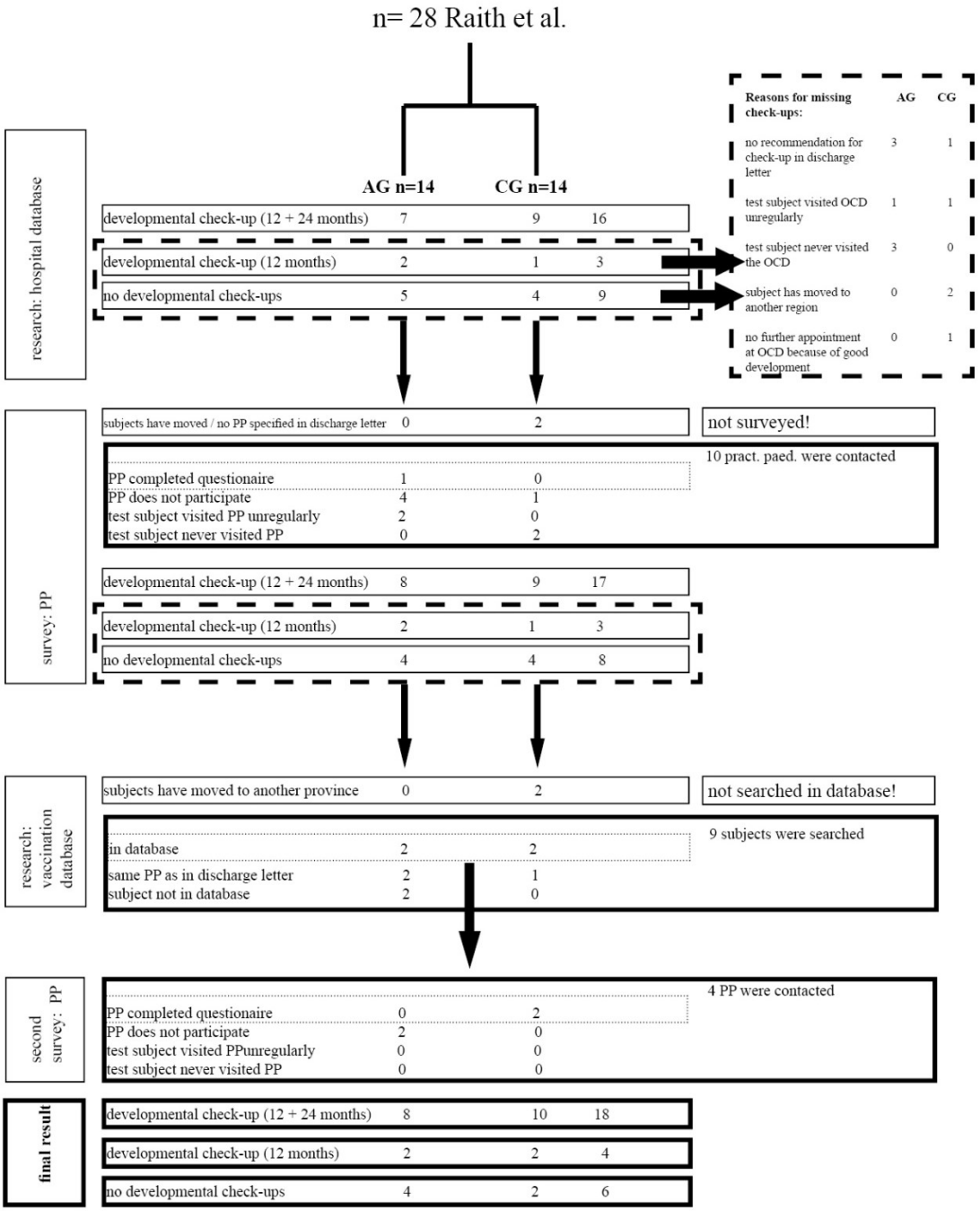
The previously conducted survey provided developmental data of one patient. Consequently, developmental data of 11 patients (11 out of 28, 39.3%; AG: n=6, CG: n=5) were missing at this point.

We used the vaccination database of the "Scientific Academy for Preventive Medicine" to identify the practising paediatricians who were in charge of included infants. Two patients had to be excluded a priori, because the families had moved to another province and were thus not included in the Styrian database. Consequently, nine subjects were searched for in the database. Details of the vaccination database research are displayed in Figure 1.

With the help of the vaccination database, four practising paediatricians (AG: n=2, CG: n=2) could be identified, were contacted and sent a questionnaire. Two of them answered by returning a completed questionnaire.

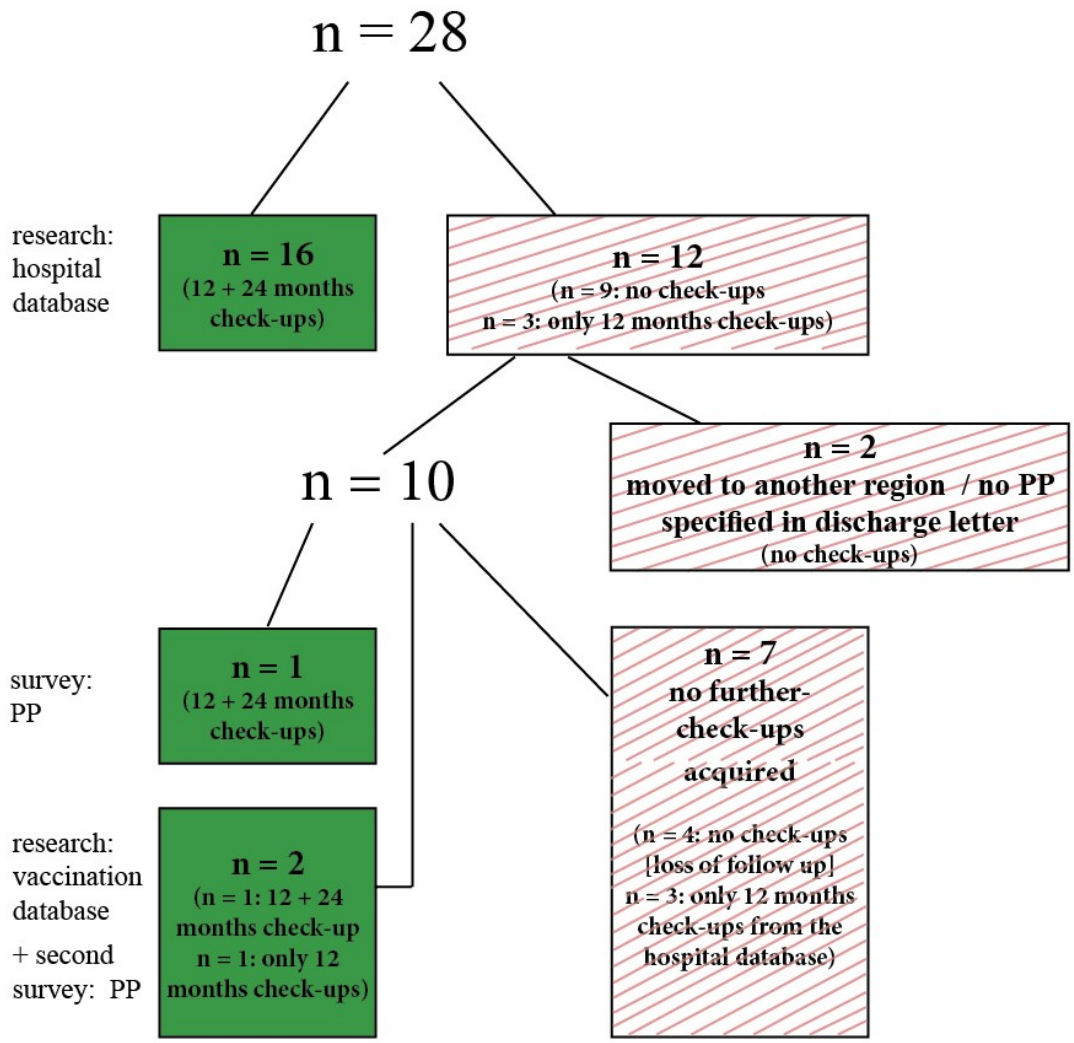
In conclusion, the survey among paediatricians, which was carried out with the help of the Styrian vaccination database, delivered neurodevelopmental data of two patients (AG: n=0, CG: n=2).

Figure 1: Data acquisition



PP or pract.paed. = practising paediatricians
OCD = outpatient clinic for development

Figure 2: Flow chart: data acquisition

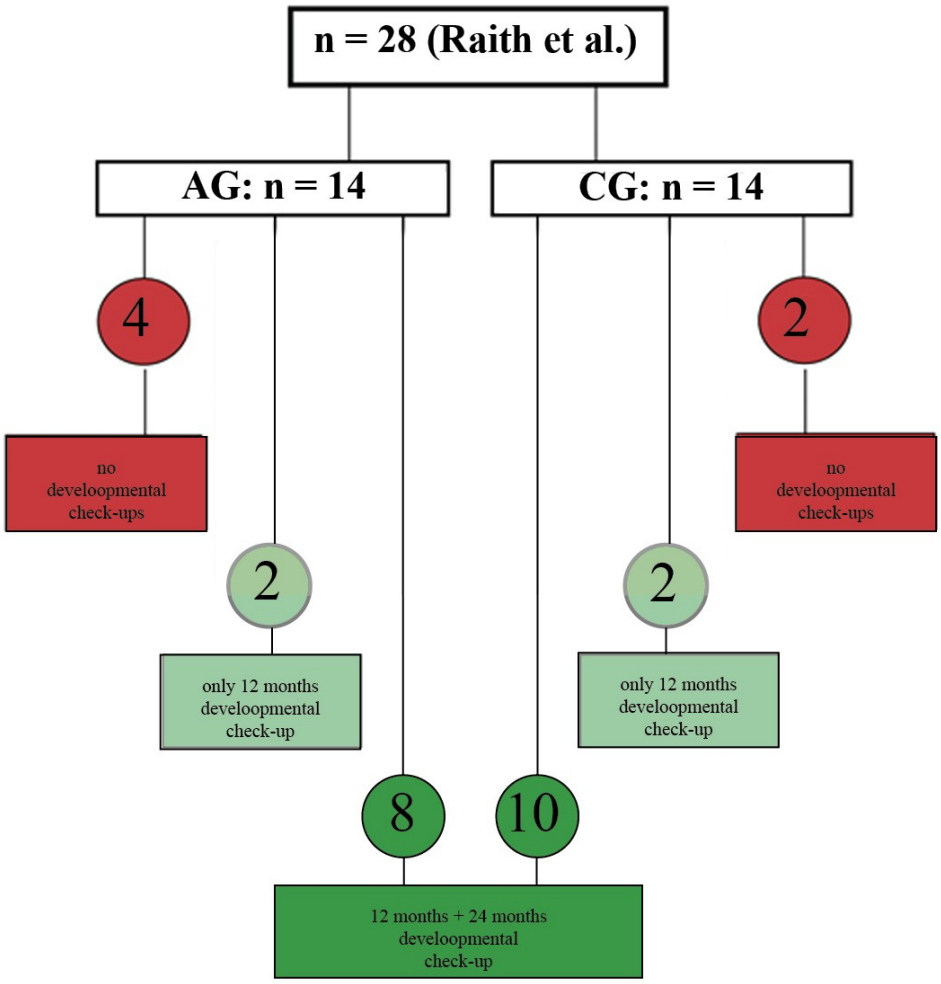


PP or pract.paed. = practising paediatricians
OCD = outpatient clinic for development

3.2 Data acquisition: Final results

Ultimately we were able to acquire full developmental data of 18 subjects (18 out of 28, 64,3%, AG: n=8, CG: n=10). In four cases only data of the 12 months check-up (4 out of 28, 14,3%, AG: n=2, CG: n=2) could be collected. In six cases (6 out of 28, 21,4%, AG: n=4, CG: n=2) we could not acquire the data of any developmental check-ups. (See Figure 1)

Figure 3: Results: data acquistion



3.3 Neurodevelopmental outcome results:

By applying the Fisher`s-Exact Test we compared the categories NDD and MIDD as results of the developmental check-ups at 12 months and the categories NDD, MIDD and SDD as results of the developmental check-ups at 24 months. The results of the developmental check-ups showed that AG and CG did not differ in their developmental outcome. This was consistent for 12 months (p = .594) and 24 months (p = 1.000) of follow up.

3.3.1 Neurodevelopmental outcome with 12 months (n= 22, AG: 10, CG: 12)

AG (n=10): The neurodevelopmental examination at 12 months revealed nine patients with NDD and one with MIDD.

CG (n=12): Nine patients showed NDD and three presented with MIDD.

3.3.2 Neurodevelopmental outcome with 24 months (n= 18, AG: 8, CG: 10)

AG (n=8): Five patients had NDD and three revealed MIDD.

CG (n=10): Six patients presented with NDD, three with MIDD and one with SDD.

Figure 4: developmental outcome at 12 months

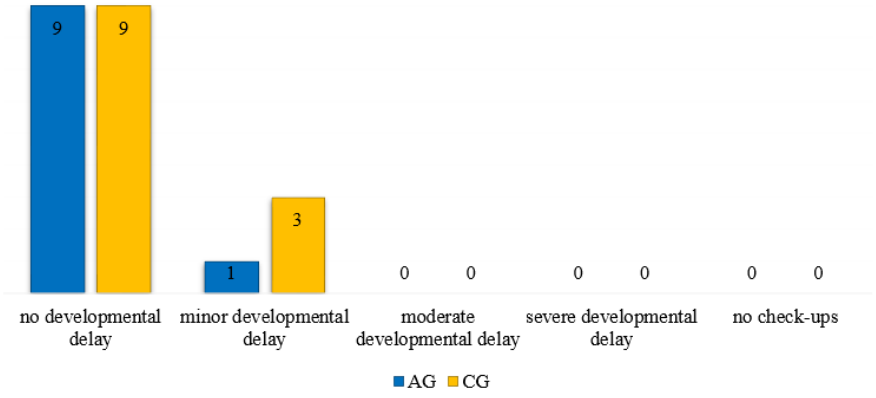
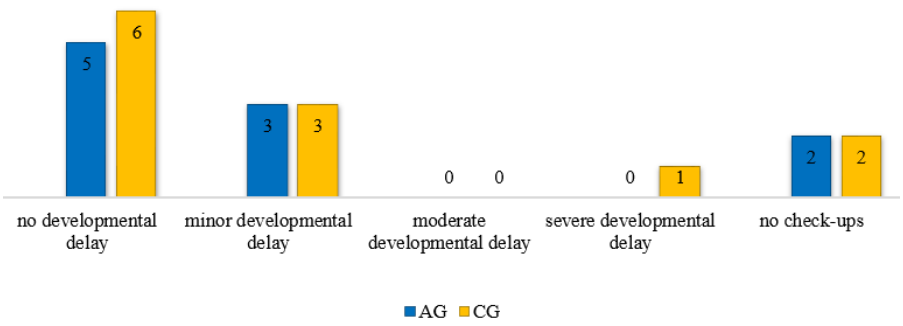


Figure 5: developmental outcome at 24 months



Abrreviations:
NDD = no developmental delay
MIDD = minor developmental delay
MODD = moderate developmental delay
SDD = severe developmental delay

3.4 Neurodevelopmental outcome results in relation to secondary objectives

Table 3: Developmental outcome and secondary objectives - AG

AG	Pat.n° 1	Pat.n° 2	Pat.n° 3	Pat.n° 4	Pat.n° 5	Pat.n° 6	Pat.n° 7	Pat.n° 8	Pat.n° 9	Pat.n° 10
developmentl outcome with 12 months	MIDD	NDD	NDD	NDD	NDD	NDD	NDD	NDD	NDD	NDD
developmentl outcome with 24 months	MIDD	NDD	no check-ups	MIDD	NDD	NDD	MIDD	NDD	no check-ups	NDD
sex	m	f	f	m	m	f	m	f	f	m
gestational age (GA)	38+0	36+3	39+6	39+2	40+0	40+1	37+5	40+2	39+3	32+1
comorbidities (during neonatal period)	nc.	nc.	nc.	nc.	nc.	nc.	nc.	micro-cephaly	nc.	nc.
Length of stationary stay (LOS) [days]	35	30	47	35	30	35	22	60	38	49
need for drug therapy [days]	27	23	40	28	30	29	15	40	22	33
Social environment	bp	bp	bp	r	bp	bp	bp	ccs, r	bp	ccs

Abrreviations: NDD = no developmental delay, MIDD = minor developmental delay, MODD = moderate developmental delay, SDD = severe developmental delay, m = male, f = female, nc = no comorbidities, fp = foster parents, bp = biological parents, ccs = crisis care space, a = adoption, r = relatives

Table 4: developmental outcome and secondary objectives - CG

CG	Pat.n° 11	Pat.n° 12	Pat.n° 13	Pat.n° 14	Pat.n° 15	Pat.n° 16	Pat.n° 17	Pat.n° 18	Pat.n° 119	Pat.n° 20	Pat.n° 21	Pat.n° 22
developmental outcome with 12 months	NDD	NDD	NDD	NDD	NDD	NDD	MIDD	MIDD	NDD	NDD	NDD	MIDD
developmental outcome with 24 months	NDD	no check-ups	no check-ups	NDD	NDD	NDD	MIDD	NDD	MIDD	SDD	NDD	MIDD
sex	f	f	f	f	f	f	m	f	f	f	f	m
gestational age (GA)	35+6	35+2	35+1	37+0	36+0	39+6	37+6	38+5	39+0	37+1	40+0	39+2
comorbidities (during neonatal period)	convulsions	micro-chephalie, convulsions	micro-chephalie, convulsions	micro-chephalie	nc.	nc.	nc.	nc.	nc.	nc.	malformation	nc.
Length of stationary stay (LOS) [days]	36	36	36	36	55	46	15	53	63	61	38	35
need for drug therapy [days]	30	32	32	30	40	41,5	9	49	57	48	35	32
Social environment	fp	fp	bp	bp	fp	fp, ccs	bp	ccs, a	bp	r	bp	fp

A =Abrreviations: NDD = no developmental delay, MIDD = minor developmental delay, MODD = moderate developmental delay, SDD = severe developmental delay, m = male, f = female, nc = no comorbidities, fp = foster parents, bp = biological parents, ccs = crisis care space, a = adoption, r = relatives

4. Discussion

The aim of the present diploma thesis was to investigate the neurodevelopmental outcome of the 28 infants from the study of Raith et al.(22) and to compare the results between the AG and the CG. Our analysis showed that the two groups did not significantly differ in their developmental outcome at 12 and 24 months. As a result of this findings, we can conclude that non-invasive laser acupuncture had no significant effect on the developmental outcome of our subjects.

According to several studies, in utero drug exposed infants are more likely to have neurodevelopmental problems during childhood than healthy children.(23) A recent study demonstrated that NAS correlates with a higher risk of health, social and psychological issues, even as teenagers.(28) It remains unclear whether in utero drug exposure during precarious phases of foetal development or rather the social situation (due to a family background involving drug abuse issues) is responsible for the poor developmental outcome of infants with NAS.(29) It is known that opioids have long lasting morphological effects on the developing infant brain, but it remains uncertain if these opioid-induced changes influence neurological outcome.(29) By investigating the high school performance of 2234 children diagnosed with NAS in comparison with a healthy population, it could be shown that children with NAS performed much poorer in high school.(29) Landi et al.(30) investigated neural circuits associated with parenting and were able to demonstrate that these circuits are disrupted in substance-using mothers. Thus, Landi and colleagues concluded as follows: "*These findings suggest, that infant stimuli may be less salient for drug-using mothers."(30)* With this in mind, it seems likely, that it is more difficult for drug-using mothers to forge a bonding with their infant, which may have a significant impact on the child´s development. To sum it up, as the above mentioned examples clearly show, there may be various factors influencing the outcome of children with NAS. Further studies are needed to learn more about the possible causes for the poorer developmental outcome in infants with in utero drug exposure.

Although we put in huge efforts to gather the desired data comprehensively, we experienced a relevant loss of follow up in our study cohort. Review of our hospital database did not yield full developmental data (i.e. developmental check-ups at 12 months and 24 months) of 12 (out of 28) infants:

I) In four cases discharge letters did not contain recommendations for a developmental check-up.

II) Five families did not comply with recommended appointments at the outpatient clinic for development for unknown reasons or only made visits unregularly. One possible explanation may be a lack of information about the importance of regular developmental check-ups.

III) Two families had moved to another province and, therefore, did not visit the outpatient clinic as recommended. It is unclear whether developmental examinations were made at other paediatric institutions.

IV) In the case of one patient no further appointments were necessary due to initially satisfying neurological development.

To acquire missing developmental check-ups, we contacted those practising paediatricians who had been named by the parents in the discharge letters. A total of ten paediatricians were contacted, however the survey delivered little results. Only one paediatrician sent back a completed questionnaire, with five paediatricians being unwilling to participate in the study and two acknowledging that they had never seen the respective patients. In two cases patients of interest only visited the paediatrician unregularly, rendering a statement in regard to their developmental outcome at 12 and 24 months impossible. Possible explanations for these unregular medical consultations are that the families had changed to another paediatrician or were not willing to undergo developmental check-ups.

In order to gather the developmental data of the still missing eleven patients, we used the vaccination database of the "Scientific Academy for Preventive Medicine" for identification of responsible paediatricians. Overall, our search revealed four paediatricians, who were contacted by mail. Two of them sent back a completed questionnaire, whereas the other two did not want or were unable to take part in the survey.

Despite the fact that some discharge letters did not contain recommendations for developmental check-ups and a significant number of paediatricians did not participate in our survey due to several reasons, we were able to show that families with in utero drug exposed infants do consult practising paediatricians relatively unregularly for developmental check-ups. A recent study investigated the latest documented consultation at the University Hospital of Graz among a cohort of 61 patients diagnosed with NAS. Over the observation period, 39.7% of the cohort had their latest consultation at the Department for Paediatric Surgery, 30.2% at the general paediatric outpatient clinic and only 10.9% at the outpatient

clinic for development, Division of Neonatology.(31) These data show that although a distinct number of children do not adhere to arranged developmental check-ups, they regularly visit outpatient clinics – either for paediatric surgery or general paediatrics – at our paediatric centre. This finding raises the question of reasons behind the non-compliance regarding appointments for development examinations. The authors of the present study concluded that children with conspicuous development, who do not present to the agreed developmental check-ups, may be reached via other paediatric outpatient clinics. They suggest for instance to stress the need for regular developmental check-ups of infants with NAS in case of consultations at paediatric surgery or general paediatric outpatient clinics.(31)

Another possible explanation for families of in utero drug exposed infants not attending developmental check-ups involves negative experiences during former hospital stays in terms of stigmatization because of their addiction. In a study by Atwood et al. (28) families with newborns suffering from NAS were interviewed to learn about their experiences during hospitalization. The impact of hospital environment and transfers between units turned out to be important issues, as continuity of care, 'rooming in' concepts and minimizing transfers may improve parents' experiences. Furthermore, the quality of interactions with staff (supportive versus judgmental) constituted an additional challenge during hospitalization.

It is commonly known that mental health problems, poverty, violence and homelessness are issues with high prevalence among drug users. In many cases drug addicts have been traumatized and therefore require a differentiated approach in terms of support in hospitals. A recent study highlighted the topic of "trauma-informed care": *"The concept of trauma-informed practice has emerged in the fields of mental health, addiction, and child psychology as an approach to care that is effective in addressing these complex challenges."(*29) The trauma-informed approach is about the four "R's": 'realizing' the prevalence of trauma, 'recognizing' how trauma affects all individuals involved with the organization, 'responding' by putting this knowledge into practice, and finally 'resisting' re-traumatization.(29)

These two publications (28,29) clearly show how complex the situation may be for parents of newborns with NAS. This complex situation presumably has an influence on the

continued care of these children, highlighting the importance of improved long term, family-centered care of newborns with NAS.

4.1 Limitations

As one of the limitations of this study the small sample size has to be mentioned. Due to this limitation, we were not able to show a difference in developmental outcome between the two groups. Another limitation are the different assessment methods used to categorize the developmental outcome. For example, at the outpatient clinic for development different tests such as the Bayley Scales of Infant Development (see "Methods") as well as subjective evaluation by the examining paediatricians were used to quantify the developmental outcome. In regard to the survey of practising paediatricians, we did not evaluate which tool(-s) had been applied to assess infants' developmental outcome. Therefore, inconsistency among applied methods cannot be ruled out and may have led to deviant results in terms of the developmental outcome of included infants in our study.

4.2 Conclusion

The neurodevelopmental data collected in the course of the present diploma thesis did not show a significant difference between AG and CG, which may at least in part be explained by the small sample size. What has been shown is the fact that it is challenging to locate families with substance use issues. Our findings suggest that part of these families are trying to avoid developmental check-ups or do not see value in attending regular examinations. The available data also adress the difficulties of regular developmental screening at the outpatient clinic for development or within the framework of the medical examinations of the Mother-Child-Programme.

However, frequent developmental check-ups are indeed very important for infants with NAS especially during the first years of life, as developmental delays, behavioural disorders or other anomalies can be recognized much earlier and appropriate support therapies can be initiated. So how to achieve that more parents of in utero drug exposed infants make regular use of developmental check-ups? One approach may be improved cooperation and communication between different clinical departments and medical professions dealing with paediatric patients. Highlighting the importance of developmental check-ups during initial

hospitalization could also help to motivate parents. Another measure could be to render the hospital stay a (more) positive experience for parents and their newborns, which may include the need for more profound staff education and training. Introducing the concept of "trauma-informed care" could also prove to be beneficial.

In essence, this diploma thesis could point out that there are deficiencies in the process of caring out regular developmental check-ups for the vulnerable group of infants with NAS. Several measures have been proposed to counter this relevant issue. This study shall serve as an encouragement for paediatric hospitals and health care institutions to establish practice guidelines in order to ensure the optimal care for infants with NAS and their parents.

5. Bibliography

(1) Kocherlakota P. Neonatal abstinence syndrome. Pediatrics 2014 Aug;134(2):e547-61.

(2) Tolia VN, Patrick SW, Bennett MM, Murthy K, Sousa J, Smith PB, et al. Increasing incidence of the neonatal abstinence syndrome in US neonatal ICUs. N Engl J Med 2015;372(22):2118-2126.

(3) McQueen K, Murphy-Oikonen J. Neonatal Abstinence Syndrome. N Engl J Med 2016;375(25):2468-2479.

(4) Nanovskaya TN, Nekhayeva IA, Hankins GD, Ahmed MS. Transfer of methadone across the dually perfused preterm human placental lobule. Obstet Gynecol 2008;198(1):126. e1-126. e4.

(5) Feng Y, He X, Yang Y, Chao D, H Lazarus L, Xia Y. Current research on opioid receptor function. Curr Drug Targets 2012;13(2):230-246.

(6) Scavone J, Sterling R, Van Bockstaele E. Cannabinoid and opioid interactions: implications for opiate dependence and withdrawal. Neuroscience 2013;248:637-654.

(7) Little PJ, Price RR, Hinton RK, Kuhn CM. Role of noradrenergic hyperactivity in neonatal opiate abstinence. Drug Alcohol Depend 1996;41(1):47-54.

(8) Radke AK, Rothwell PE, Gewirtz JC. An anatomical basis for opponent process mechanisms of opiate withdrawal. J Neurosci 2011 May 18;31(20):7533-7539.

(9) Logan BA, Brown MS, Hayes MJ. Neonatal abstinence syndrome: treatment and pediatric outcomes. Clin Obstet Gynecol 2013 Mar;56(1):186-192.

(10) Finnegan LP, Hagan T, Kaltenbach KA. Scientific foundation of clinical practice: opiate use in pregnant women. Bull N Y Acad Med 1991 May-Jun;67(3):223-239.

(11) Patrick SW, Dudley J, Martin PR, Harrell FE, Warren MD, Hartmann KE, et al. Prescription opioid epidemic and infant outcomes. Pediatrics 2015 May;135(5):842-850.

(12) Kaltenbach K, Jones HE. Neonatal Abstinence Syndrome: Presentation and Treatment Considerations. J Addict Med 2016 Jul-Aug;10(4):217-223.

(13) Kelly L, Madden S, Dooley J, Antone I. The occasional management of narcotic exposure in neonates. Canadian Journal of Rural Medicine 2011;16(3):98.

(14) Hudak ML, Tan RC, COMMITTEE ON DRUGS, COMMITTEE ON FETUS AND NEWBORN, American Academy of Pediatrics. Neonatal drug withdrawal. Pediatrics 2012 Feb;129(2):e540-60.

(15) Chan D, Klein J, Koren G. New methods for neonatal drug screening. NeoReviews 2003;4(9):e236-e244.

(16) Reinarz S, Ecord J. Drug-of-abuse testing in the neonate. Neonatal Network 1999;18(8):55-61.
(17) Finnegan LP, Connaughton JF,Jr, Kron RE, Emich JP. Neonatal abstinence syndrome: assessment and management. Addict Dis 1975;2(1-2):141-158.
(18) Bagley SM, Wachman EM, Holland E, Brogly SB. Review of the assessment and management of neonatal abstinence syndrome. Addiction science & clinical practice 2014;9(1):1.
(19) Sublett J. Neonatal abstinence syndrome: therapeutic interventions. MCN Am J Matern Child Nurs 2013 Mar;38(2):102-7; quiz 107-9.
(20) Janssen PA, Demorest LC, Kelly A, Thiessen P, Abrahams R. Auricular acupuncture for chemically dependent pregnant women: a randomized controlled trial of the NADA protocol. Substance abuse treatment, prevention, and policy 2012;7(1):48.
(21) Filippelli AC, White LF, Spellman LW, Broderick M, Highfield ES, Sommers E, et al. Non-insertive acupuncture and neonatal abstinence syndrome: a case series from an inner-city safety net hospital. Global Advances in Health and Medicine 2012;1(4):48-52.
(22) Raith W, Schmolzer GM, Resch B, Reiterer F, Avian A, Koestenberger M, et al. Laser Acupuncture for Neonatal Abstinence Syndrome: A Randomized Controlled Trial. Pediatrics 2015 Nov;136(5):876-884.
(23) Hunt RW, Tzioumi D, Collins E, Jeffery HE. Adverse neurodevelopmental outcome of infants exposed to opiate in-utero. Early Hum Dev 2008;84(1):29-35.
(24) Bandstra ES, Morrow CE, Mansoor E, Accornero VH. Prenatal drug exposure: infant and toddler outcomes. Journal of Addictive Diseases 2010;29(2):245-258.
(25) Ornoy A, Segal J, Bar-Hamburger R, Greenbaum C. Developmental outcome of school-age children born to mothers with heroin dependency: importance of environmental factors. Developmental Medicine & Child Neurology 2001;43(10):668-675.
(26) Baumann T. Atlas der Entwicklungsdiagnostik. 3rd ed.: Stuttgart ; New York, NY : Thieme; 2002.
(27) Petermann F, Macha T. Strategien in der testgestützten allgemeinen Entwicklungsdiagnostik. Monatsschrift Kinderheilkunde 2003;151(1):6-13.
(28) Uebel H, Wright IM, Burns L, Hilder L, Bajuk B, Breen C, et al. Reasons for Rehospitalization in Children Who Had Neonatal Abstinence Syndrome. Pediatrics 2015 Oct;136(4):e811-20.

(29) Oei JL, Melhuish E, Uebel H, Azzam N, Breen C, Burns L, et al. Neonatal Abstinence Syndrome and High School Performance. Pediatrics 2017 Feb;139(2):10.1542/peds.2016-2651. Epub 2017 Jan 16.
(30) Landi N, Montoya J, Kober H, Rutherford H, Mencl E, Worhunsky P, et al. Maternal neural responses to infant cries and faces: relationships with substance use. Frontiers in psychiatry 2011;2:32.
(31) Kopf N, Langzeitverlauf von Neugeborenen mit Neonatalem Entzugssyndrom (NAS) unter spezieller Berücksichtigung entwicklungsneurologischer und sozialmedizinischer Aspekte. Graz: Graz Medical University; 2016. pp. 138; 2016.

6. Attachment

Figure 6: Modified Finnegan Neonatal Abstinence Score Sheet

NEONATAL ABSTINENCE SCORING SYSTEM

Modified Finnegan Neonatal Abstinence Score Sheet[1]

System	Signs and Symptoms	Score	AM						PM						Comments
Central Nervous System Disturbances	Excessive high-pitched (or other) cry < 5 mins	2													
	Continuous high-pitched (or other) cry > 5 mins	3													
	Sleeps < 1 hour after feeding	3													
	Sleeps < 2 hours after feeding	2													
	Sleeps < 3 hours after feeding	1													
	Hyperactive Moro reflex	2													
	Markedly hyperactive Moro reflex	3													
	Mild tremors when disturbed	1													
	Moderate-severe tremors when disturbed	2													
	Mild tremors when undisturbed	3													
	Moderate-severe tremors when undisturbed	4													
	Increased muscle tone	1													
	Excoriation (chin, knees, elbow, toes, nose)	1													
	Myoclonic jerks (twitching/jerking of limbs)	3													
	Generalised convulsions	5													
Metabolic/ Vasomotor/ Respiratory Disturbances	Sweating	1													
	Hyperthermia 37.2-38.3C	1													
	Hyperthermia > 38.4C	2													
	Frequent yawning (> 3-4 times/ scoring interval)	1													
	Mottling	1													
	Nasal stuffiness	1													
	Sneezing (> 3-4 times/scoring interval)	1													
	Nasal flaring	2													
	Respiratory rate > 60/min	1													
	Respiratory rate > 60/min with retractions	2													
Gastrointestinal Disturbances	Excessive sucking	1													
	Poor feeding (infrequent/uncoordinated suck)	2													
	Regurgitation (≥ 2 times during/post feeding)	2													
	Projectile vomiting	3													
	Loose stools (curds/seedy appearance)	2													
	Watery stools (water ring on nappy around stool)	3													
	Total Score														
	Date/Time														
	Initials of Scorer														

1. Finnegan LP. Neonatal abstinence syndrome: assessment and pharmacotherapy. In: Nelson N, editor. Current therapy in neonatal-perinatal medicine. 2 ed. Ontario: BC Decker; 1990.

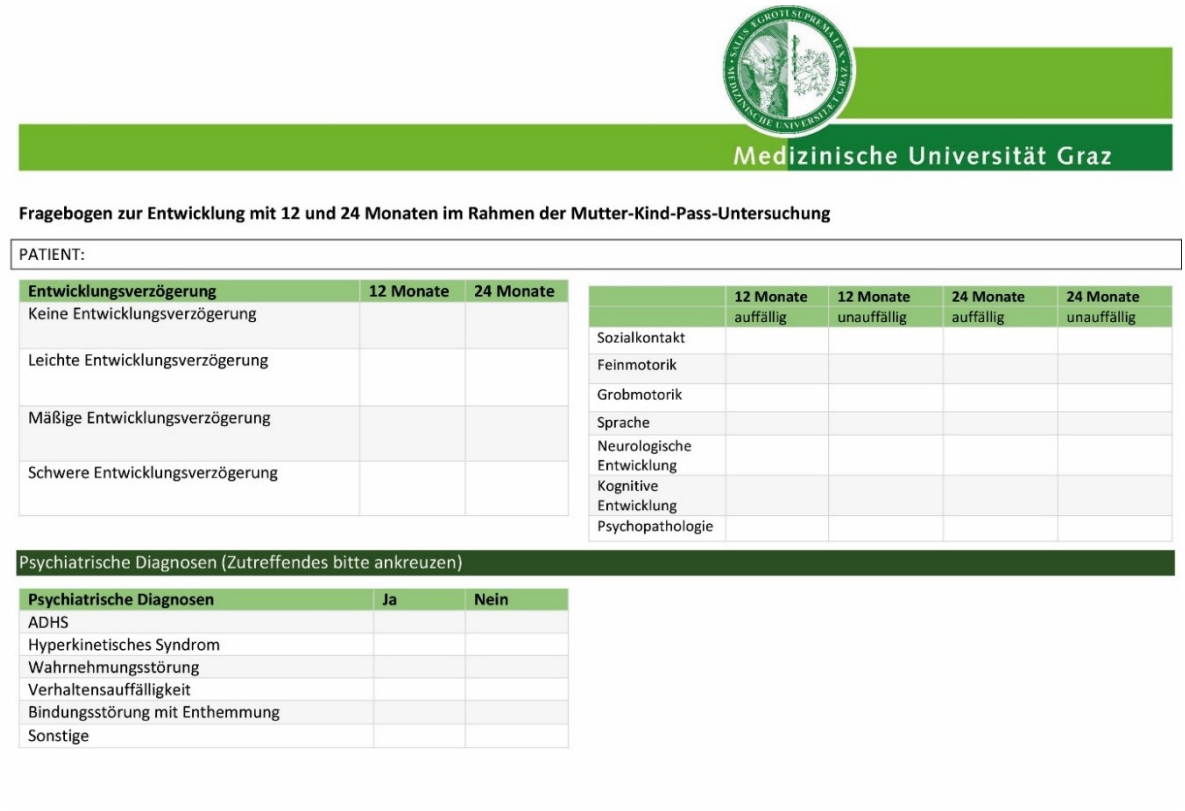
Figure 7: Finnegan Score Sheet (german version)

SCORE ZUR ERFASSUNG/GRADUIERUNG VON ENTZUGSSYMPTOMEN BEI NEUGEBORENEN

ENTZUGSSYMPTOME – SCORE (FINNEGAN)

	Datum:															
	Uhrzeit:															
Symptome	**Punkte**															
schreit schrill	2															
weint, schreit kontinuierlich	3															
schläft < 1 Std. nach Mahlzeit	3															
< 2 Std. nach Mahlzeit	2															
< 3 Std. nach Mahlzeit	1															
Schreckreaktionen spontan, gehäuft	2															
Schreckreaktionen hyperaktiv	3															
Tremor bei Manipulation, gering	1															
Tremor bei Manipulation, heftig	2															
Spontantremor, gering	3															
Spontantremor, heftig	4															
Muskeltonus gesteigert	2															
Myklonismen	3															
Krampfanfall	5															
Schwitzen	1															
Temp.: 37,5° - 38,5°	1															
Temp.: > 38,5°	2															
gähnt häufig	1															
Cutis marmorata	1															
Schniefen	1															
Niesen	1															
Nasenflügeln	2															
Tachypnoe (> 60/Min.)	1															
Dyspnoe (Einziehungen)	2															
Saugen gesteigert	1															
Trinkschwäche	2															
Spucken/Reflux	2															
Erbrechen im Guss	3															
Stühle auffallend weich	2															
Stühle auffallend wässrig	3															
Gesamt-Score:																
Morphin - Lsg. 0,04 % - ml/p.os																
Phenobarbital - Plv. – mg/p.os																

Figure 8: Questionnaire



Medizinische Universität Graz

Fragebogen zur Entwicklung mit 12 und 24 Monaten im Rahmen der Mutter-Kind-Pass-Untersuchung

PATIENT:

Entwicklungsverzögerung	12 Monate	24 Monate
Keine Entwicklungsverzögerung		
Leichte Entwicklungsverzögerung		
Mäßige Entwicklungsverzögerung		
Schwere Entwicklungsverzögerung		

	12 Monate auffällig	12 Monate unauffällig	24 Monate auffällig	24 Monate unauffällig
Sozialkontakt				
Feinmotorik				
Grobmotorik				
Sprache				
Neurologische Entwicklung				
Kognitive Entwicklung				
Psychopathologie				

Psychiatrische Diagnosen (Zutreffendes bitte ankreuzen)

Psychiatrische Diagnosen	Ja	Nein
ADHS		
Hyperkinetisches Syndrom		
Wahrnehmungsstörung		
Verhaltensauffälligkeit		
Bindungsstörung mit Enthemmung		
Sonstige		

Soziale Aspekte (Zutreffendes bitte ankreuzen)

Obsorgeberechtigte:	
Leibliche Eltern bzw. Elternteil	
Großeltern bzw. Großelternteil	
Pflegeeltern	
Sonstige Personen, welche die Obsorge haben	

Betreuerwechsel (z.B. Wechsel von leiblichen Eltern zu Pflegeeltern oder Großeltern)	
1 mal	
2 mal	
3 mal	
Kein Betreuerwechsel	

	12 Monate	24 Monate
Sonstige Anmerkungen zu Auffälligkeiten in sozialem Umfeld (z.B. Kindergarten, Familie)		

Allgemeines

Diagnosen	

Figure 9: Denver Developmental Screening Test