The impact of visceral osteopathic treatment on the meconium evacuation in very low birth weight infants

Master Thesis for obtaining the academic degree

„Master of Science“

in the study program Osteopathy

submitted by

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Vienna May 2014

STATUTORY DECLARATION

I, Nadja Haiden M.D. born the 7th.Oct 1968 in Linz hereby declare,

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Acknowledgements

The accomplishment of this Master thesis is a step forward to become an osteopath and therefore I would like to express my gratitude to all those who gave me the possibility to complete this thesis.

First of all I would like to show my deepest appreciation to my little patients and their parents who agreed to participate in this study and therefore enabled my work. Furthermore I'd like to thank all the doctors and nurses of the ward 9C for supporting me with patience. I am obliged to the Department of Pediatrics and Adolescents and Prof. M.D. Arnold Pollak and Prof. M.D. Angelika Berger for enabling and supporting this research project.

In particular I'd like to thank my research staff members Alexandra Kreissl and Birgit Pimpel, who assisted me in data collection and encouraged me within the project.

I like to thank my former osteopathic colleague Karin Sander for her support and advice. The time we have spent together in our osteopathic training weld us together and we still have a friendship. Furthermore I'd like to thank my osteopathic supervisor Uli Hämmerle who gave me the opportunity to work in her osteopathic practice and gave me an insight in pediatric osteopathy.

Finally I' d like to thank my family: My husband Claus, my boys Oscar and Vincent and my mother Gerda who believed in me, supported me and loved me. I hope this work helps understanding the mechanisms of osteopathic treatment and improves care of extremely immature infants.

Abstract English

OBJECTIVE: To determine whether the complementary approach of manipulative osteopathic treatment accelerates complete meconium excretion and improves feeding tolerance in very low birth weight infants.

METHODS: This study was a prospective, randomized, controlled trial in premature infants with a birth weight 1500 g and a gestational age 32 weeks who received a visceral osteopathic treatment algorithm 3 times during their first week of life or no treatment.

RESULTS: Passage of last meconium occurred after a median of 7.5 days (95% confidence interval: 6–9 days, n = 20) in the intervention group and after 6 days (95% confidence interval: 5-9 days, n = 21) in the control group (p = 0.11). However, osteopathic treatment was associated with a 12 day longer time to full enteral feedings (p = 0.02), and a longer hospital stay (44 days longer in the intervention group; n.s). Osteopathic treatment was tolerated well and no adverse events were observed.

CONCLUSIONS: Visceral osteopathic treatment oft the abdomen did not accelerate meconium excretion in VLBW-infants. However infants in the osteopathic group had a longer time to full enteral feedings and a longer hospital stay, represent adverse effects. Further investigations are needed with modified protocols focussed on cranial osteopathy in this vulnerable group of patients. Currently the application of visceral osteopathic techniques cannot be recommended in VLBW-infants without further clinical trials.

Keywords:

premature infant, visceral osteopathy, meconium passage, enteral feedings, hospital stay

Abstract German

ZIEL: Frühgeborene mit einem Geburtsgewicht unter 1500 haben aufgrund ihrer Unreife eine verzögerte Mekoniumausscheidung, die mit einem erschwerten enteralen Nahrungsaufbau und nachfolgenden Problemen assoziiert ist. Der alternativmedizinische Ansatz der viszeralen Osteopathie könnte die Mekoniumaussscheidung verkürzen und den Nahrungsaufbau beschleunigen,

METHODEN: Im Rahmen einer prospektiven, randomisierten , kontrollierten Studie wurden Frühgeborene mit einem Geburtsgewicht unter 1500 Gramm und einem Gestationsalter von unter 32 Schwangerschaftswochen 3 mal in der ersten Lebenswoche mit visceralen osteopathischen Techniken behandelt und mit einer Kontrollgruppe, die keine Behandlung erhielt, verglichen.

RESULTATE: Die Mekoniumpassage dauerte 7.5 Tage (95% Confidence Interval: 6–9 Tage, n =20) in der Interventionsgruppe und 6 Tage (95% Confidence Interval: 5-9 Tage, n = 21) in der Kontrollgruppe (p = 0.11). Die osteopathische Behandlung war mit einem um 12 Tage längeren Nahrungsaufbau (p = 0.02) und einem um 44 Tage längeren Krankenhausaufenthalt assoziiert. Die Behandlung selbst wurde von allen Patienten gut toleriert.

SCHLUSSFOLGERUNG: Die Behandlung mit viszeralen osteopathischen Techniken hatte keinen Einfluss auf die Mekoniumausscheidung bei Frühgeborenen unter 1500 Gramm Geburtsgewicht. Allerdings hatten die Kinder einen langsameren Nahrungsaufbau und einen längeren Spitalsaufenthalt als die Kinder in der Kontrollgruppe, was als negativer Effekt der Behandlung interpretiert werden muss. Weitere klinische Studien mit anderen osteopatischen therapeutischen Ansätzen sind unbedingt erforderlich, da die Anwendung von viszeralen osteopathischen Techniken in dieser Patientengruppe derzeit nicht empfohlen werden kann.

Schlagworte:

viszerale Osteopathie, Frühgeborenes, Mekoniumausscheidung, Nahrungsaufbau, Krankenhausaufenthalt

Table of Contents

1. Introduction

In neonatal intensive care medicine premature infants are an increasing population with special characteristics and distinct needs. Late premature infants are born between the 34th-37th week of gestation (Engle, Tomashek, Wallman, & Committee on Fetus and Newborn, 2007) and usually stay with their mothers in the nursery. Premature infants born below the 34th week of gestation are usually admitted to a neonatal intensive care unit (NICU). In 2011 in Austria 8.3% of the newborn infants were born prematurely. 72% of preterm infants were born between the 34th and 36th week of gestation, 23% between the 28th and 34th week and only 5%- representing the smallest ones- were born before the 28th week of gestation (Austria & Klimont, 2012). Survival and outcome depend on the level of immaturity of the preterm infant and on the access to health care utilities.

The reasons for preterm birth are manifold and underwent a change during the last decade. Preterm labour is thought to be a syndrome initiated by multiple mechanisms, including infection or inflammation, uteroplacental ischemia or haemorrhage, uterine over distension, stress, and other immunologically mediated processes (Goldenberg, Culhane, Iams, & Romero, 2008). The improving options in reproductive medicine also changed the outcome of the following pregnancies: since new techniques in reproductive medicine have been established many preterm infants are twins and triplets. Approximately 60% of multiple pregnancies are born prematurely (Austria & Klimont, 2012). Once the infant is born the immaturity of organs and immune system challenges the staff and parents. During the first days of life the physiologic adaption to extrauterine life requires respiration and nutrition. The establishment of proper gastrointestinal function and digestion is crucial because the physiologic immaturity of the intestinal motor mechanisms is associated feeding problems. In the premature infant meconium excretion is a prolonged process and often associated with problems like feeding intolerance, delayed introduction of enteral feedings, delayed gastrointestinal passage and- last but not least- meconium obstruction.

So far, osteopathic treatment is a rarely applied method to treat pathologic conditions in premature infants during their stay in the neonatal intensive care unit. This is astonishing because the treatment approach seems to be non-invasive and very safe, especially for newborns. Unfortunately, there is a lack of good research evidence to support many of the claims and assertions made by osteopathy.

Previously my studygroup and me performed two prospective trials focusing on the problem of delayed meconium evacuation in preterm with different therapeutic pharmacological approaches (Haiden et al., 2007; Haiden et al., 2012). None of the applied therapies appeared to be effective or had a beneficial effect- quite the contrary one agent (Gastrografin

(Haiden et al., 2012)) was supposed to have severe negative side effects. Therefore we were looking for an alternative, non-invasive, holistic solution for the problem of delayed meconium excretion. Osteopathic treatment with the emphasis on the relationship of the structural and functional integrity of the body and with its variety of therapeutic manual techniques seemed to be remedy. Treating the abdomen of premature infants with visceral osteopathic techniques might be more effective to mobilize meconium from small bowel and deep parts of the colon. Therefore we hypothesized that repeated visceral osteopathic treatment accelerates meconium evacuation in premature infants, and thereby enhances feeding tolerance in this population.

2. Theory

2.1. Definitions

2.1.1. Preterm infants

In the literature various definitions for prematurity and premature infants exist. The following gives an overview over most common phrases used in context with prematurity: The American Academy of Pediatrics (AAP) recommends the following standard terminology for description of the age of premature infants (American Academy of Pediatrics, 2004).

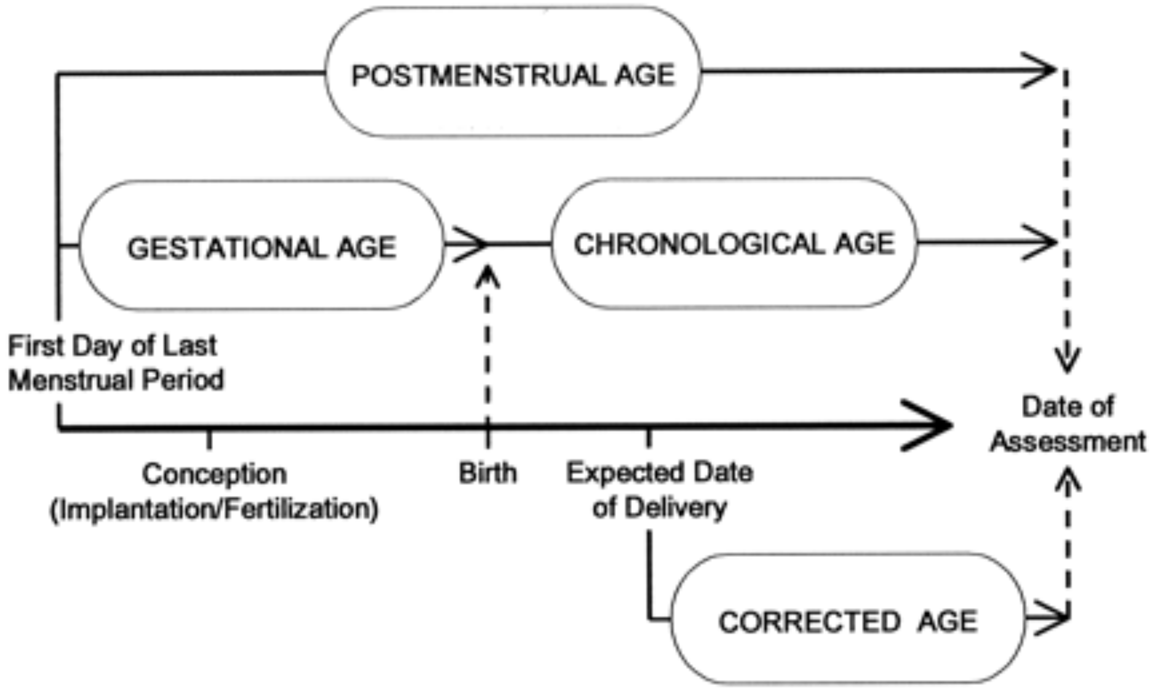

Figure 1: Terminology for description of the age of premature infants (American Academy of Pediatrics, 2004)

- Preterm infant: Infant born before the 37^{th} week of gestation (before 259 days of gestation).
- Late preterm infants: born between 34+0 and 36+6 week of gestation (Cow & Gate, 2010) (Raju, Higgins, Stark, & Leveno, 2006)
- Small for gestational age (SGA): Infant with a birthweight < the 10th percentile
- Large for gestational age (LGA): Infant with a birthweight > the 90th percentile
- Low birth weight infant (LBW): Infant with a birthweight below 2500 gram
- Very low birth weight infant (VLBW): Infant with a birthweight below 1500 gram
- Extremely low birth weight infant (ELBW): Infant with a birthweight below 1000 gram.

2.1.2. Meconium

The term meconium derives from the ancient Greek word "meconium-arion" which means "opium-like" referring to its tarry appearance or to Aristotle's belief that it induces sleep in the foetus. Meconium is the first stool of an infant. It is composed of material the foetus ingests during the time in utero, like intestinal epithelial cells, mucous glycoproteins, bile, liver and pancreatic enzymes, minerals, lipids, plasma proteins, amniotic fluid, swallowed vernix caseosa, lanugo and water. 80% of the dry weight of meconium consists of mucopolysaccharides. The concentration of liver and bile enzymes varies depending on the gestational age of the infant (Jiménez et al., 2008; Tsang, Uauy, Koletzko, & Zlotkin, 2005). Unlike later faeces, meconium is almost sterile (Jiménez et al., 2008), viscous, tenacious, inspissated and sticky like tar and has no odour. After the first few days of life it should be evacuated completely. Thereafter the stool turns into yellow corresponding to digested milk. Premature infants show a delayed meconium excretion compared to mature infants. 99.8% of the mature infants (n=500 (Sherry & Kramer, 1955)) excrete their first meconium within the first 48 hours of life while in preterm infants with a birthweight below 1500 g only 79.6% (n=171 (Jhaveri & Kumar, 1987)) do so. Furthermore preterm born infants show a wide variability concerning meconium excretion: the first meconium passage can vary between 1 hour and 27 days (median: 43 hours; n=47) (Meetze et al., 1993)

2. The gastrointestinal tract of preterm infants

2.2.1. Development:

Embryologic development (Peter & Michael, 1996)

During the embryonal development of the foetus several aspects of gastrointestinal maturation are important for the gastro intestinal tract (GIT) to become a correct working organ of digestion and absorption (Neu, 2007). The gastrointestinal tract receives tissue contributions from all three germ layers. The primitive gut first forms as a cavity lined by endoderm, which gives rise to the entire epithelial lining of the digestive tube. Most digestive glands, including liver, gallbladder and pancreas, arise as buds from the endodermal lining. Through lateral folding, the splanchnic mesoderm comes to lie adjacent to, and eventually to surround, the enddermal-lined gut tube, forming the connective tissue and muscular walls. These migrate from the neural tube and invade the mesodermal portion of the gut tube, where they form the neurons and glial cells intrinsic to the gastrointestinal tract. The foregut and hindgut are first identifiable as a blind endoderm-lined pouches surrounded by mesoderm. The midgut represents the region opening to the yolk sac and is the last region to be invested with mesoderm. The foregut undergoes differential growth and rotates so that the stomach assumes its adult shape and position. The liver, gallbladder and ventral pancreatic bud develop from an endodermal outgrowth appearing distal to the stomach, while the dorsal pancreatic bud arises from a different outgrowth. Rotation of the duodenum and migration of the ventral pancreatic bud result in juxtaposition, and ultimately fusion, of the pancreatic buds to form a single pancreas, as well as unification of the pancreatic and bile ducts. As the gut elongates, there is insufficient space to accommodate the midgut inside the peritoneal cavity, and the gut expands into extra embryonic coelom within the umbilical cord. During this herniation the gut rotates 90° about the axis of the superior mesenteric artery; an additional 180° counter clockwise rotation occurs upon the return of the midgut to the peritoneal cavity. The net result is to position the cecum in the right lower quadrant of the peritoneal cavity. The mesenteries fuse to the parietal peritoneum, fixing the ascending and descending colon in the place. The connection between the yolk sac and the gut is the vitelline duct, which can persist as an outpocketing of the ileum, also called Meckel diverticulum. The cloaca is divided by the urogenital sinus and eventually separates into the urinary bladder and rectum, which fuses with the overlying ectoderm to form the anus. At the site of the rectum is a depression in the ectoderm called the anal pit, this breaks down to permit continuity between the endodermal lining of the rectum and the endodermal lining of the anus (Peter & Michael, 1996)

Ontogenetic development

The ontogenetic timetable of development is shown in Figure 2 (Newell, 2000). Furthermore, the GIT is not only an absorptive and digestive organ, but also plays an important part in the immune system as one of the largest immune organs. The GIT is essential for endocrine and exocrine functions and has an own enteric nervous system, which controls its elementary motor and secretor functions.

During the development of the GIT an enormous enlargement of tissue takes place. In the period of the last trimester of pregnancy the length of the intestine duplicates and especially the surface area expands through the growth of the villi and microvilli during this period (Neu, 2007).

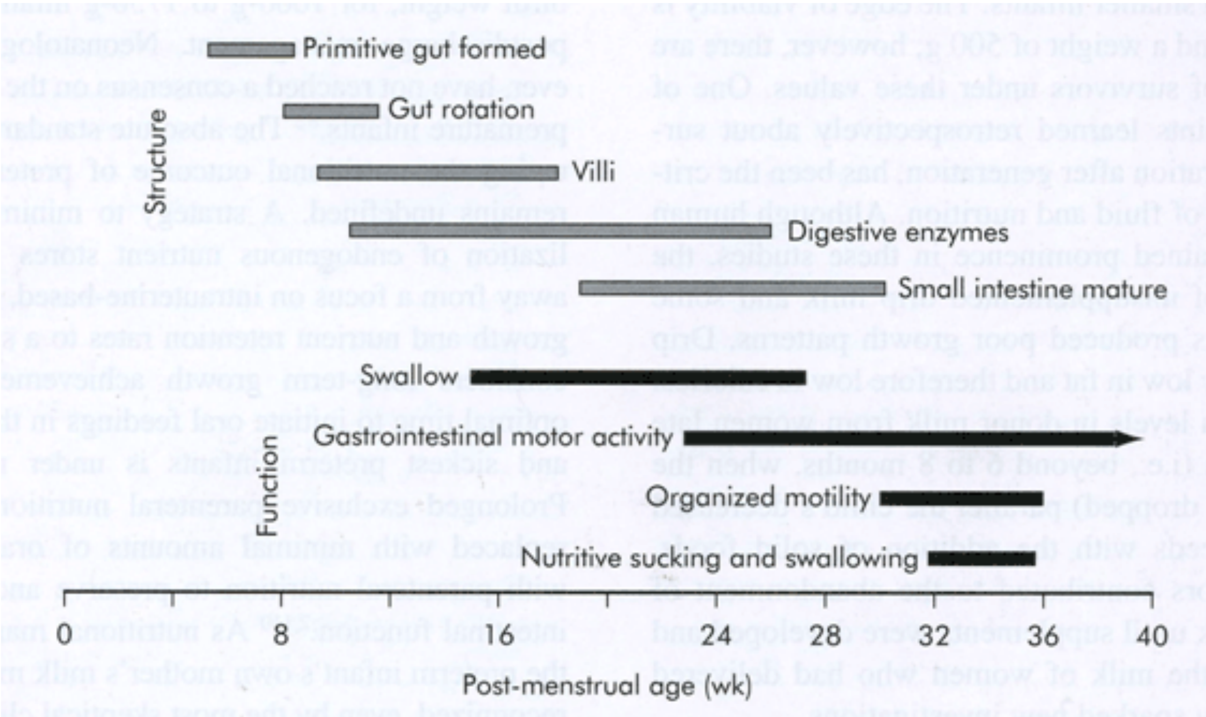

Figure 2: Ontogenetic timetable of function and structure of gastrointestinal development (Newell, 2000).

2.2.2. The premature GIT

Immaturity caused by preterm birth results in distinctive problems for the digestive system of preterm infants:

- Motility and gastric emptying are delayed (Newell, 2000)
- Sucking and swallowing coordination is not developed until the 32^{h} week of gestation (Newell, 2000)
- The oesophageal tone is lower in infants <30 weeks of gestation (Newell, Booth, Morgan, Durbin, & McNeish, 1989)
- Immature intrinsic activity of the enteric nervous system, causing that the motility of the small intestine is less organized than in term infant (Newell, 2000)
- Bacterial overgrowth caused by the delayed transit time of food develops (Gases which are the by-products of fermentation can cause distension of the abdomen). (Neu, 1989)
- Low hydrogen ion output in the stomach (Hyman et al., 1985)
- Low pancreatic proteolytic enzyme activity (Antonowicz & Lebenthal, 1977)

Coordinated sucking and swallowing can be expected from the 32th week of gestation on. As soon as an infant is able to drink a full meal from the breast or from the bottle the gastric tube is removed.

2.2.3. Nervous innervation of the GIT (Moeckel Eva, 2008)

The nervous plexuses influencing the function of the GIT are situated at different levels of the bowel wall - sub serous, myenteric, submucosal and mucosal. Essentially the parasympathetic plexuses of Auerbach and Meissner lie in the intestinal walls. The motor cells are connected with the central nervous system through connector neurons from the vagus, which is excitatory and so increases peristalsis and secretion of gastrin from the stomach. This is in turn produces acid and pepsin to digest proteins. The sympathetic plexuses on the other hand are inhibitory and come from the motor cells in the superior ganglion, receiving fibres from the greater splanchnic nerves in the T5-T9 thoracic segments. This same ganglion also supplies vasoconstrictor nerves to the vessels of the small intestine. The autonomic trunks through which visceromotor reflexes occur, lie on the anterior border of the psoas major, vertebral bodies and intervertebral discs; each trunk has four ganglia. The prevertebral plexuses are the coeliac, intermesenteric, superior hypogastric of which the coeliac or solar is the biggest. It lies behind the stomach, at the junction between Th12 and L1. The intestinal tract from the stomach to the rectum receives sympathetic information from T5-L3. The stomach itself receives from T5-T9, mainly T5-T 7, so a visceromotor reflex presents as spasm in upper portion of the left musculus rectus abdominalis. The small intestine receives from T5-T9 mainly T8-T9, whilst the colon receives from T10-L3. The colon receives supply from the both parasympathetic and sympathetic agents. The parasympathetic supply the ascending and descending colon from the vagal fibres from the solar plexus, whilst the sigmoid and rectum receive from the cord through the pelvic nerve and plexus haemorrhoidalis.

2.2.4. Meconium passage

Timing of the first and last meconium stool is critical for oral feeding tolerance and proper gastrointestinal function (Neu, 2007) The time until premature infants pass their first meconium ranges from 1 hour to 27 days (median: 43 hours) (Meetze et al., 1993; Wang & Huang, 1994) Obstruction of the gastrointestinal tract by tenacious, sticky meconium frequently leads to gastric residuals, a distended abdomen and delayed food passage (Figure 3). Recent data support the concept that complete rapid evacuation of meconium plays a key role in feeding tolerance (Mihatsch, Franz, Lindner, & Pohlandt, 2001) . If duration to full enteral feedings is extended, the probability to acquire infections due to intravenous access for parenteral nutrition increases and hospital stay of the infant prolongates.

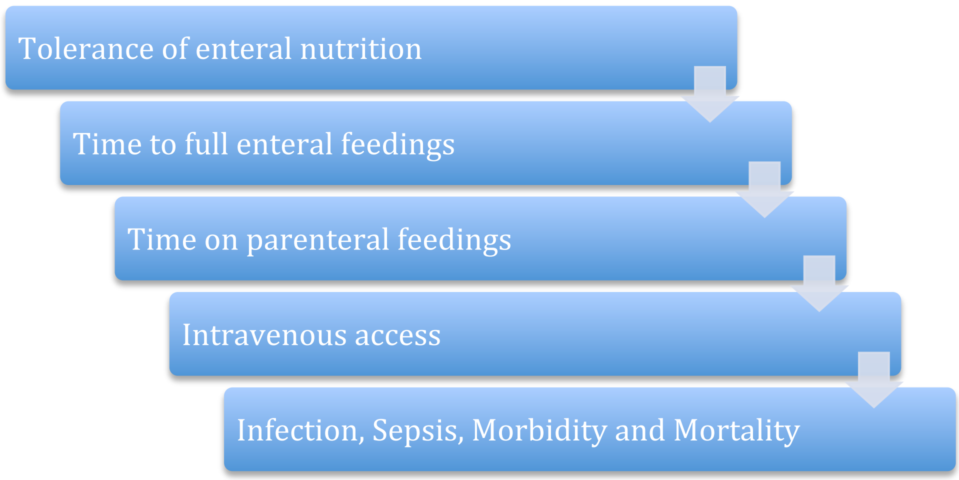

Figure 3: Cascade following delayed Meconium excretion

2.2.5. Trials on influencing meconium excretion

Functional bowel obstruction originates from highly viscous meconium of prematurity combined with poor motility of the premature gut and is associated with diverse problems in the infant's early life (Emil, Nguyen, Sills, & Padilla, 2004). The so called "meconium obstruction of prematurity" (Garza-Cox, Keeney, Angel, Thompson, & Swischuk, 2004) is a distinct clinical condition in VLBW infants with obstructive symptoms like abdominal distension occurring several days after having passed some initial meconium (Vinograd, Mogle, Peleg, Alpan, & Lernau, 1983). Passage of stools is typically infrequent and in small amounts and often requires rectal stimulation with a thermometer or glycerine suppository (Garza-Cox et al., 2004) . Treatment algorithms with different kinds of enemas have been established and are considered effective and safe therapeutic interventions to resolve obstructions (Emil et al., 2004). Significant advantages of any liquid used for enemas (e.g. glycerine or N-acetylcysteine) have not been reported so far and recommendations for the most effective substance to use do not exist. Data from a study including 21 preterm infants with the diagnosis "Meconium obstruction in the very low birth weight premature infant" showed that tenacious meconium is most frequently located in the distal ileum (Garza-Cox et al., 2004) In that study, various kinds of enemas were demonstrated to be effective and safe for promoting the evacuation of tenacious meconium plugs during or shortly after instillation. Resolution of obstruction with glycerine suppositories, saline, acetylcysteine or non-absorbable contrast media was conducted in 70% of symptomatic infants, thereby avoiding surgical removal of the plug.

To prevent meconium obstruction and improve feeding tolerance, premature infants may benefit from "prophylactic" administration of enemas. Recently, a prospective randomized trial was performed to determine whether repeated prophylactic applications of small volume glycerine enemas are effective in accelerating passage of meconium in VLBW infants (Haiden et al., 2007). The authors did not find a correlation between application of enemas and meconium evacuation. A reason for the ineffectiveness of glycerine enemas was supposed to be that the volume used was too small to mobilize tenacious meconium sufficiently from deep parts of the colon and small bowel (Colon ascendens, terminal Ileum). Another prophylactic approach to accelerate meconium excretion was to administer Gastrografin on the first day of life (Haiden et al., 2012). Gastrografin is a radiopaque contrast agent for the GIT, which can be applied orally or rectally. In neonatal intensive care, Gastrografin is used for the treatment of meconium ileus (Emil et al., 2004; O'Halloran, Gilbert, McKendrick, Carty, & Heaf, 1986). The results of the trial indicated that the osmotic contrast agent Gastrografin did not accelerate complete meconium excretion. However, the stool frequency was significantly higher during the first week of life indicating that gastrointestinal mobility was enhanced. Time to full enteral feedings and hospital stay in the NICU was significantly shorter in the Gastrografin group as compared to placebo. Although this is of clinical interest, the observed numerical increase in necrotizing enterocolitis (NEC) is a concern that strongly argues against prophylactic routine use of Gastrografin.

2.2.6. Enteral nutrition

As survival rates for preterm infants and all NICU patients improve, more attention is being focused on improving the quality of survival through optimal nutritional management (McLeod & Sherriff, 2007). Nutrition has profound effects on organ development, immune status, and gastrointestinal integrity. Although other factors may contribute, inadequate nutrition appears to be the predominant cause of growth failure. In infants with a birthweight below 1500g parenteral nutrition is started immediate after birth. In parallel, enteral nutrition is started as soon as possible, usually during the first 3 to 6 hours of life in terms of minimal enteral feedings (MEN). MEN are defined as 1ml human milk or pasteurized donor human milk every 2-4h (Tyson & Kennedy, 2005). MEN are not given for nutritional purposes but are used to prevent atrophy and to stimulate digestive enzymes and growth factors release.

For all infants including the preterm infants, human milk is the preferred nutrition (Tsang et al., 2005). Although the quantity of protein in human milk is smaller than in formula and therefore associated with poor weight gain (Simmer, 1997), the quality is unique and the health benefits derived from human milk are evident. Human milk contains substances which are essential for appropriate growth and proper neurodevelopmental outcome of newborn infants: Immune-related components such as IgA, leukocytes, oligosaccharides, lysozyme, lactoferrin, interferon-y, nucleotides, cytokines, and others. Several of these compounds offer passive protection in the gastrointestinal tract and to some extent in the upper respiratory tract, preventing adherence of pathogens to the mucosa and thereby protecting the breast-fed infant against invasive infections (Agostoni et al., 2009) These protective agents are especially important in the premature infant. Human milk especially supports the digestive tract of preterm infants as it contains at least 60 enzymes, including lipase, which have shown to enhance intestinal lipolysis and improve fat absorption. Human milk has a higher content and unique pattern of long chain polyunsaturated fatty acids (LCPUFA) and Gangliosides compared to formula milk. LCPUFAs are important for eicosanoid synthesis and cell membrane, cerebral and retinal function but there is disagreement on whether preterm infants are able to synthesize sufficient amounts of LCPUFA to satisfy the needs of their developing brain and retina (Tsang et al., 2005), (Kurlak & Stephenson, 1999). Gangliosides of human milk may also have a positive effect on neuronal development, somatic growth and development of intestinal immunity (Pan & Izumi, 2000). Beside the poor ability to absorb and digest nutrients, premature infants show immature motor mechanism in terms of slow gastric emptying. From the literature we know, that human milk feedings accelerate and promote gastric emptying. Prokinetic effects of human milk are linked to small amounts of the gut hormone motilin accelerating gastric emptying on the one hand and increasing frequency and variation of stool on the other hand (Liu et al., 2004). Preemies show high levels of the gut peptide somatostatin, which inhibits gut growth and motility. However, HM gavage might antagonize this inhibition by stimulation of gut hormones gastrin, cholecystokinin, enteroglucagon, motilin and neurotensin (Lucas, Bloom, & Aynsley-Green, 1986) (Lois, 2010) (Sann, Chayvialle, & Descos, 1982).

Several human milk compounds, e.g. sIgA, lactoferrin, lysozyme and cytokines have beneficial effects on protection against pathogens and facilitate the establishment of microbiota and thereby activate the mucosal immune system. This process is encouraged by the protective immune factors which coat the GI and even spread out in the upper respiratory tract by mucosa associated lymphoid tissue and prevents adherence of pathogens to the mucosa and though protecting the breast-fed infant against invasive infections (AAP Committee on Nutrition, 2009) (Goldman, 2000) (Lawrence & Pane, 2007). Preterm infants fed with their own mother’s milk have initial growth rates and accretion rates of nitrogen, fat, sodium, potassium and chloride, that approximately reach expected intrauterine rates but the concentration of nutrients progressively drops as time passes. Preterm milk collected after 30 days postpartum shows to little concentrations of protein, sodium, calcium, phosphorus and magnesium to meet the requirements of a growing preterm infant. Therefore human milk has to be enriched with “human milk fortifiers” containing bovine whey predominant protein, carbohydrate (mainly or exclusively glucose polymers or maltodextrin) and macronutrients like sodium, calcium, phosphorus and magnesium. Some of them also contain fat, lactose, micronutrients (zinc and copper) and vitamins. When added, human milk fortifiers provide about 2.5g/kg/d protein and 120 kcal/kg/d energy. For even more immature or smaller infants, the use of human milk fortifier is recommended, beginning from the time when they are able to tolerate 100ml/kg/d of milk. Last but not least human milk feeding is the one and only evidence based prophylaxis against NEC - a haemorrhagic inflammation of the gut affecting between 5-10% of preterm infants. Infants fed with human milk have a 6 fold lower risk to suffer from NEC than formula fed preterm infants (Lucas & Cole, 1990).

2.2.7. NEC

NEC is one oft he most common gastrointestinal emergencies in preterm infants with a high mortality. While the pathogenesis is not fully understood yet infants present with clinical signs as feeding intolerance, abdominal distension or tenderness, occult or gross bloody stool, lethargy, apnoea, respiratory distress and sepsis (Lin & Stoll, 2006). Several risk factors have been identified and are listed in figure 4. Immature intestinal motility and digestion might predispose preterm infants to NEC. In addition to impaired intestinal motility, premature infants have not yet developed the ability to digest and absorb nutrients (Lebenthal & Lebenthal, 1999) and incompletely digested molecules could contribute to intestinal injury (Di Lorenzo, Bass, & Krantis, 1995). Thus, impaired digestion of nutrients, coupled with delayed transit time, could result in injury of intestines with immature host and barrier defences. Therefore it is essential to establish gastrointestinal passage as soon as possible to lower later risk of NEC and associated problems like surgery.

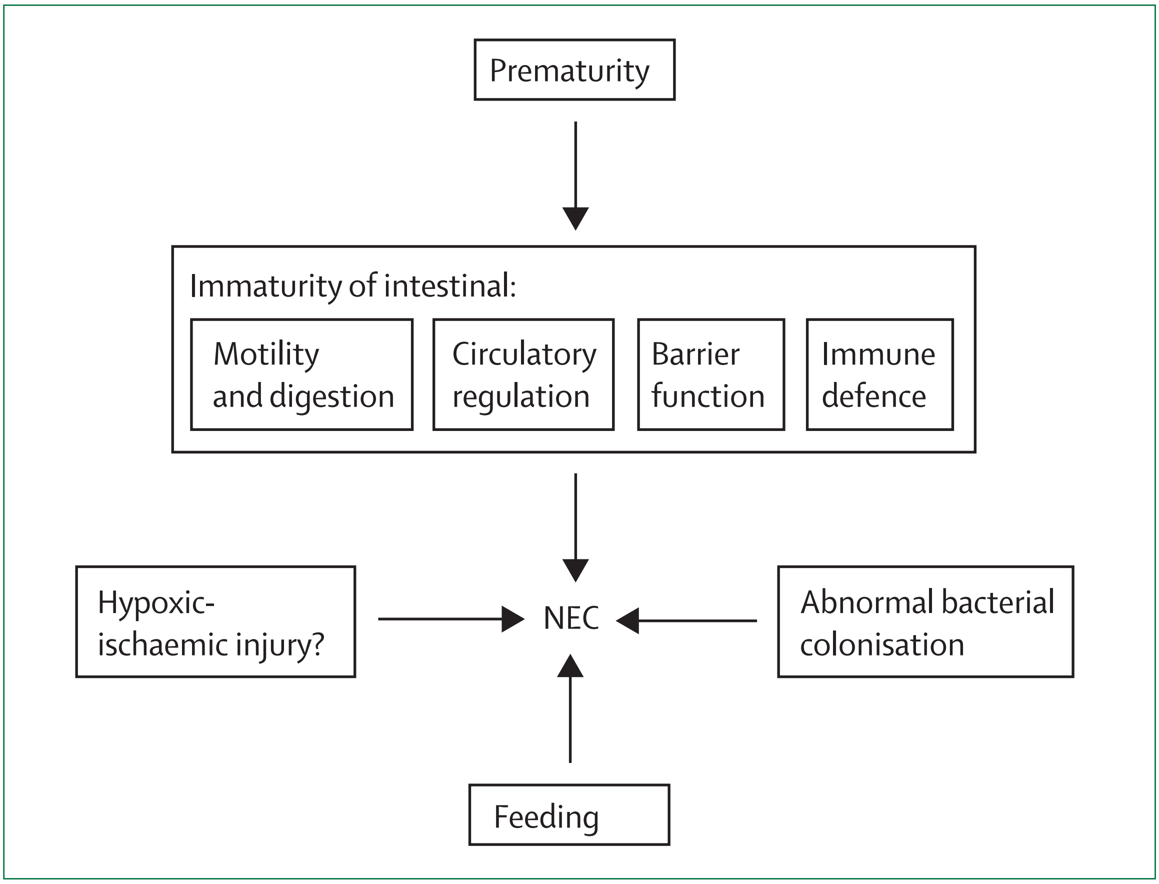

Figure 4: Risk factors for NEC

2.3. Principles of neonatal care today

Over the past 20 to 30 years, the incidence of preterm birth in most developed countries has been between 5-7% of live births. In incidence in Austria is higher at about 8.3 (Austria & Klimont, 2012). 77 % of all preterm births are due to infants born "late preterm". Twins and higher order multiples have elevated preterm rates compared to singletons. The risk of infant mortality declines dramatically with increasing gestational age. Only 70% of infants born before 28 weeks of gestation survive the first year, whereas survival rates increase up to 99% for infants born at 32 and more weeks of gestation (Austria & Klimont, 2012).

Mary Allen Avery- one of the most famous neonatologists in the world, explorer of the "surfactant", described the NICU as follows: " The neonatal intensive care unit of today is a bustling space station. The tiny baby in the incubator is dwarfed by technical equipment like a respirator, a multichannel monitor, intravenous pumps and transcutaneous oxygen module. The baby's chest is covered with electrodes, and tubes lead into and out of his or her body at several points. Eight to 12 electrical cords, 2 oxygen lines, and a suction catheter attach to the bedsides console. Alarms sound, knots of people move busily about, and large machines are pushed among the incubators" (Avery, 2005).

In this high tech environment premature infants are often attended according the Newborn Individualized Development Care and Assessment Program (NIDCAP) or similar programs. NIDCAP is an early intervention program, which includes systematic observations of the premature infant's behaviour (Institute). Each observation describes in detail the behaviour of the infant, strengths, difficulties, and a summary of the infant's medical history. Derived from this, recommendations are made to make care and environment more sensitive to the infant's tolerance. Guidance and support to understand the infant's signals and needs are given to the parents. NIDCAP emphasize the relationship between caregiver and the infant, between caregiver and infant's parents, as well as between themselves. The program is developmentally supportive. It helps us to adapt the care and environment to the maturity of the infant, and sees the infant as an active participant in his/her strivings to gain balance. The programme is family centred. The family is seen as the most important part in the care of the infant, and is given support in this role. Advances in medical and technical care of the premature infants have increased their possibility to survive and become healthy. These babies are cared for in the neonatal intensive care unit during a very sensitive time when brain develops more rapidly than in any other time during life. The interest in how environment affects the premature infant's development is increasing. Published research has shown that the NIDCAP model has positive effects for the development of the premature infant. The infants required fewer days on oxygen and ventilation; complications from brain and lung decreases, weight gain increases, and the infants establishes full nipple-feeding earlier. Hospital stay and hospital charges can be reduced. The mental and motor development increases and behavioural difficulties decrease. The interaction between child and parents is positively affected (Institute).The concept, which is also established at the Division of Neonatology of Medical University of Vienna, underlines an approach that focuses on minimizing noxious stimuli while individualizing infant care and stimulation based on observable physiologic response and behavioural cues (Sehgal & Stack, 2006).

2.3.1. The NIDCAP concept

<u>Encourage parental participation (family centred care): (Sehgal & Stack, 2006)</u>

Parents are taught appropriate touch to "tube in" with the baby and to provide or assist with infant's care. Family needs are considered when planning care and feed times. This advocates an individualized approach to family centred care with emphasis on promoting infant organization and enhancing optimal neuro-developmental outcomes. The goal is to support the family by helping them to develop such skills and techniques, thus including the family as apart of healthcare team.

Reduction of noise (Sehgal & Stack, 2006)

In utero infants are exposed to sound of 40-60 dB, yet in the NICU environment typically provides sound at 70-80 dB. These loud noises can lead to startles, apnoeas, bradycardias, colour changes, desaturations, and alterations in blood pressure and cerebral blood flow, which may lead to intraventricular haemorrhage. It's important to promptly attend to, rather anticipate, monitor alarms, open and close incubator doors gently, use blanket coverings over incubator to decrease noise level.

Reduction of light (Sehgal & Stack, 2006)

One of the most important stimuli is light, and bright light may come from phototherapy, procedure spotlights and so on. It has been suggested over-stimulation may interfere with the development oft he central visual system. The infants' overall socialization skills may be also affected. Bright lights increase the incidence of squinting and „shutting out" behaviours, whereas when exposed to reduced levels of lightning, infants seem to be more interested in and capable of engaging. Therefore lights in the units is dimmed, maintaining a safe level of accurate clinical observation as well as modifying lightning to simulate night-day patterns. Incubators are covered with blankets and adequate eye protection is provided during phototherapy or procedures like intravenous cannulation.

Tactile stimuli and pain management

Care- giving in the NICU can be intrusive and stress producing. It may also contribute to aversive behaviour and infants may associate all touch with pain, responding by squirming, crying and recoiling the arms and legs. Handling the infant gently, avoiding sudden changes in posture will help promote their tactile and vestibular development (Sehgal & Stack, 2006). Repeated pain exposures during critical windows of central nervous system development are associated with permanent changes in peripheral, spinal, and supraspinal pain processing, neuroendocrine function and neurologic development. These changes can be manifested by alterations in pain thresholds, stress responses, cognitive function, behavioural disorders, and long-term disabilities. Nonpharmacologic interventions (NPIs) are conducted for pain management. NPIs (e.g., oral sucrose, breastfeeding, non-nutritive sucking, facilitated tucking, kangaroo care, swaddling) effectively reduce pain for minor to moderately painful procedures. (Cignacco et al., 2012)

2.4. Osteopathy

Osteopathy is a philosophy and form of alternative healthcare that emphasizes the interrelationship between structure and function of the body, as well as the body's ability to heal itself. Osteopaths claim to facilitate the healing process, principally by the practice of manual and manipulative therapy ((ECOP) & (AACOM), 2011). Osteopathy has been considered a form of complementary medicine, emphasizing a holistic approach and the skilled use of a range of manual and physical treatment. Techniques and methods are non-invasive, and conducted by exclusively using the osteopaths hands as a diagnostic and treatment tool.

2.4.1. The tenets of Osteopathy

Every osteopathic treatment is based on the tenets of osteopathy: ((ECOP) & (AACOM), 2011)

The body is a unit; the person is a unit of body, mind, and spirit.

- The body is capable of self-regulation, self-healing, and health maintenance.
- Structure and function are reciprocally interrelated.
- Rational treatment is based upon an understanding of the basic principles of body unity, self-regulation, and the interrelationship of structure and function

2.4.2. Osteopathic manipulative treatment

The therapeutic application of manually guided forces by an osteopathic physician (U.S. usage) to improve physiologic function and/or support homeostasis that has been altered by somatic dysfunction. OMT (Osteopathic manipulative treatment) employs a variety of techniques including:((ECOP) & (AACOM), 2011)

2.4.2.1. Cranial osteopathy

Cranial osteopathy is a set of theory and techniques that have been developed from the observations of Dr. William Sutherland that the plates of the cranium permit microscopic movement or force dissipation and that there is a 'force' or rhythm that is operating in moving the plates of the skull (Osteohome, 2010). Cranial osteopathy is said to be based on a *primary respiratory mechanism*, a rhythm that can be felt with a very finely developed sense of touch. Some osteopaths believe that improving dysfunctional cranial rhythmic impulses enhances cerebral spinal fluid flow to peripheral nerves, thereby enhancing metabolic outflow and nutrition inflow. It has gained particular popularity in the treatment of babies and children (Osteohome, 2010).

2.4.2.2. Visceral osteopathy

Proponents of visceral osteopathy state that the visceral systems (the internal organs: digestive tract, respiratory system, etc.) rely on the interconnection synchronicity between the motion of all the organs and structures of the body, and that at optimal health this harmonious relationship remains stable despite the body's endless varieties of motion (askdefine.com, 2014). The idea is that both *somato-visceral* and *viscero-somatic* connections exist, and manipulation of the somatic system can affect the visceral system (and vice-versa). Practitioners contend that visceral osteopathy relieves imbalances and restrictions in the interconnections between the motion of all the organs and structures of the body—namely, nerves, blood vessels, and fascial compartments. During the 1940s, osteopaths like H V Hoover and M D Young built on the work of Andrew Taylor Still to create this method of assessment and manipulation. The efficacy and basis of this treatment remains controversial even within the osteopathic profession (askdefine.com, 2014).

The theory of visceral manipulation is distinguished by three movements of the internal organs (Eric, 2011): motricity, mobility and motility. Motricity refers to passive changes in the position of the organs that result from the arbitrary motor activity by the locomotor system. Mobility refers to the movement either between two organs or between an organ and the wall of the torso, diaphragm, or another structure in the musculoskeletal system. The engine for this movement can be motricity of different “automatisms”. Automatism refers to a movement that is performed involuntarily by striated or smooth muscles. Furthermore we can differentiate between automatisms that occur continuously and movements of the organs marked by periodicity (e.g. Diaphragmatic breathing, heart action, peristalsis of the visceral hollow organs in the GI tract.). Motility is defined as the intrinsic movement of the organs with slow frequency and small amplitude. It can be detected by the hand of a trained practitioner and is the kinetic expression of movements in the organ tissues. During embryonic development, the evolving organs carry out growth movements and position shifts that remain stored in each organ cell as a kind of memory. Motility is a rhythmic repetition of this embryonic migration to its place of origin and back to the final, postnatal position. Likewise it is impossible to rule out a connection to the craniosacral rhythm, in spite of the fact that motility shows a different frequency. An expiration phase- that is the movement toward the median line- should be distinguished from the inspiration phase-a movement in the opposite direction away from the midline (Eric, 2011). Changes in the axes of movement or amplitudes lead to deviation from the physiologic mobility and motility. Such changes lead to local pathologies first without and later with symptoms, recurring local pathologies and pathologies in visceral and parietal regions of the body that are linked via topographic, vascular, nervous or fascial osteopathic changes (Eric, 2011).

2.4.3. Osteopathic treatment of children

In the evaluation and treatment of children, the osteopathic physician must consider the medical, structural, social, psychological and spiritual needs of each young patient, as well as the child's age and developmental level. It is important to survey an accurate, detailed history, including birth trauma and associated physical, environmental, and emotional events that lead to trauma. The evaluation and treatment of a paediatric patient begins with the utmost respect and consideration oft he needs oft the child (Ward, 2003).

2.4.3.1. Osteopathic treatment in babies

Paediatric osteopathy and particular neonatal osteopathy is a specialist area requiring distinct knowledge on embryological and foetal development, birth and postnatal adaptation to extrauterine life, growth and neurologic development of an infant, emotional factors and family dynamics. Unsolved birth trauma can cause a sequence of various acute problems resulting in persisting disorders and diseases. Osteopathic treatment can help young babies to become more content and settled by handling structural imbalances in the whole body (Moeckel Eva, 2008). Therefore a detailed history of the course of pregnancy, including any trauma that the mother may have sustained during the pregnancy, should be obtained. Furthermore a detailed history of birth including gestational age, duration of labour, mode of delivery and use of anaesthesia should be surveyed. Any complications during delivery should be noted to assess the potential risk for somatic dysfunction (Ward, 2003).

2.4.3.2. Osteopathic treatment of gastrointestinal dysfunctions in babies and infants

The gastrointestinal system is one of the important systems in physiologic maintenance of health in children. It is fundamental for proper growth and development. Gastrointestinal complaints are among the most common reasons a child is seen by a paediatrician. A.T. Still and the early osteopathic physicians regarded the gastrointestinal system second only to the brain in its importance in well functioning of the body. In fact, it was often referred to as the second brain or abdominal brain. The enteric nervous system parallels the central nervous system in density and quantity of neurons. A.T. Still attributed many childhood diseases to dysfunction oft the system (Still, 1992; Ward, 2003).

Infant colic

Infantile colic is defined as episodes of crying for more than three hours a day for more than three days a week for three weeks in an otherwise healthy child between the ages of two weeks and four months (Kheir, 2012). The cause of the colic is generally unknown. Less than

5% of infants with excess crying have an underlying organic disease (Roberts, Ostapchuk, & O'Brien, 2004). Infantile colic is a common disorder in infants. Although it usually remits by six months of age, there is some evidence of longer-term sequelae for both children and parents. Manipulative therapies, such as chiropractic and osteopathy, have been suggested as interventions to reduce the severity of symptoms. Recently the Cochrane library published a meta analysis of 6 high quality studies, whereas five were suggestive of a beneficial effect and one found no evidence that manipulative therapies had any beneficial effect on the natural course of infantile colic. The studies included in this meta-analysis were generally small and methodologically prone to bias, which makes it impossible to arrive at a definitive conclusion about the effectiveness of manipulative therapies for infantile colic (Dobson et al., 2012). However infants with infant colic are often subsumed in the group of "crying disorders in infancy". Babies with excessive crying should not be viewed as a homogenous group (J. Miller & Newell, 2012). Excessive crying can also have its origin in irritable infant syndrome of musculoskeletal origin or inefficient feeding crying infants with disordered sleep. Treatment outcomes may be improved by targeting appropriate subgroups prior to treatment. Then manipulative osteopathic techniques can improve crying behaviour in infants with colic (J. E. Miller, Newell, & Bolton, 2012).

Gastroesophageal reflux disease

Gastroesophageal- reflux disease presents as frequent emesis shortly after feeding associated with failure to thrive, apnoea bradycardia and wheezing. These children may have a significant increase in their gag reflex. They often have a history of abnormal delivery events including vacuum extraction, augmentation with oxytocin, and prolonged labour. Somatic dysfunctions found include sphenobasilar lateral strain or torsion, antlanto-occiptial compression and sacral torsions. These infants may have compression of the fourth ventricle due to foramen magnum asymmetry. These somatic dysfunctions produce abnormal stimulation of the cranial nerves IX, X and XI. The increased vagal tone is responsible for bronchospasm, bradycardia and delayed gastric emptying. (Ward, 2003)

Constipation

Constipation in young children is a common complaint and responds readily to osteopathic manipulative treatment. Osteopathically the physician should be careful to examine for automatic imbalance and pay close attention to the atlanto- axial and atlanto-occipital joint as the vagus nerve involvement can contribute to autonomic imbalance. Both the pelvic and abdominal diaphragms should be examined and treated since ptosis of the viscera may be a problem. Treating the child with fascial release of the colon can be extremely helpful. (Ward, 2003) In children with cerebral palsy osteopathic treatment with fascial release, iliopsoas muscle release, sphincter release, and bowel mobilizations was successful to alleviate chronic constipation (Tarsuslu, Bol, Simşek, Toylan, & Cam, 2009).

2.4.4.Osteopathy in neonatal Intensive care medicine

Especially in children these techniques are well accepted because they are likely to cause no pain or other negative side effects. However, only little evidence- based data concerning safety and efficacy of osteopathic treatment in infants- especially in premature infants- are available so far. Therefore, we planned a study applying visceral osteopathic techniques in VLBW- infants with the aim to accelerate meconium evacuation and establish proper gastrointestinal function. Furthermore the safety and efficacy of the applied osteopathic techniques should be surveyed.

3. Hypothesis

The aim of this prospective randomized trial was to determine whether early visceral osteopathic treatment of bowel and colon has an influence on meconium evacuation in very low birth weight infants. We hypothesize that a standardized treatment algorithm of visceral osteopathic bowel techniques alters complete meconium evacuation in preterm infants.

4.Methods

4.1.Design

The study design was performed as a prospective randomized controlled trial at the Neonatal Intensive Care Unit, Department of Pediatrics, Medical University of Vienna/Austria. Infants with a birthweight <1500g and a GA <32 weeks were included, stratified according to their GA (< 28 vs. ≥ 28 weeks) and assigned randomly to the intervention or control group. The randomization list was created by www.randomization.com by a physician not otherwise involved in the trial conduct. Randomization was concealed by individually sealed opaque envelopes. The study was approved by the Ethics Committee of the Medical University of Vienna. Written informed consent was obtained from the parents after full explanation of the procedure. Infants were treated according the same standard care procedures for VLBW-infants used at our department.

4.2. Patients and Inclusion criteria

Premature infants with a birth weight ≤1500 g and a gestational age (GA) ≤32 weeks were eligible for inclusion in the study.

4.3. Exclusion criteria

Exclusion criteria were major congenital malformations and known gastrointestinal abnormalities.

4.4. Study site

The Division of Neonatology, Pediatric Intensive Care Medicine and Neuropediatrics, of the Department of Pediatrics, Medical University of Vienna is a tertiary care centre with approximately 2500 high risk deliveries per year. 450 patients per year are premature infants, 170 with a birthweight below 1500g. The department houses 4 wards with 2 NICUs (Level III), 2 IMC wards (Level II) and an outpatient clinic. The outpatient clinic offers a 6 year follow up program for former premature infants, including medical care, neurologic and neurodevelopmental follow up.

4.5. Study groups

After admission of the patient to NICU, the infant received primary care according to standard principles of neonatal intensive care (monitoring of oxygen saturation, heartrate, blood pressure, temperature, fluid intake and urine rate, intravenous access by peripheral or central venous line).

Intervention group

Infants in intervention group received osteopathic treatment within their first 48 hours of life according the following protocol:

Osteopathic Algorithm: All techniques were applied in the supine position:

1) Global listening (Picture 1) and local listening on the abdomen- any further treatment methods employed to improve mobility must be slow and gentle
2) Release lower ribs and thoracic diaphragm (Picture 2)
3) Pylorusrelaxation (Picture 3)
4) Release of the Duodenum and the C-Loop (Picture 4)
5) Small intestine diagnosis- Lifting the gut and bringing it to a stillpoint (Picture 5)
6) Root of mesentery diagnosis (and manipulation) (Picture 5)
7) Mobilisation of the ileocoecalic valve (Picture 6)
8) Mobilisation of colon ascendens (Picture 7), transversum (Picture 8), descendens (Picture 9)
9) Mobilisation of the Fasica of Toldt (Picture 7 and 9)
10) Root of sigmoid diagnosis and manipulation (Picture 10)
11) As the 10th cranial nerve influences the intestines' function by relaxing the sphincters and thus increases gut motility the parasypmathic nerval system was addressed with craniosacral therapy via the sacrum (Picture 11).

The following pictures show the treatment algorithm in a male patient with a gestational age 23+2 and a birthweight of 530 g on his second day of life. The patient is supported by facilitated tucking by a second person. He is in the incubator, breathing spontaneously and receives respiratory support by continuous positive airway pressure (CPAP; Infant flow)

Treatment algorithm:

Picture 1

Picture 2

Picture 3

Picture 4

Picture 5

Picture 6



Picture 7 Picture 8 Picture 9


Picture 10 Picture 11

The treatment algorithm was repeated three times during one treatment and on three days during the first week of life. The preterm infant was treated in the incubator, lying on his/her back. Heartrate, temperature, respiration rate and oxygen saturation of the infant were monitored during the whole procedure. Treatment was scheduled approximately one hour after feeding to avoid a hungry baby on the one hand and unpleasant pressure on the full stomach on the other hand. If a second person was available (nurse or doctor) all treatments were performed under facilitated tucking (see principles of neonatal care). To avoid irritation of the immature skin the abdomen of the infant was lubricated with an ointment. Each contact was performed with respect to the patient's inner tempo- pushy or fast movements were obviated. If the infant showed any signs of discomfort or cardiovascular instability the treatment was withheld until symptoms or condition disappeared.

Control group

The control group did not receive any intervention.

4.6. Definition of primary outcome

Primary outcome parameter was specified as complete meconium excretion. The time to complete meconium evacuation was defined as day of life on which the last meconium was passed. The nursing staff assessed the quality of stools as "meconium" (black, thick, sticky) or "non meconium" by appearance and documented data into the electronic patient documentation system. Documentation of stool consistency, colour and amount was continued until the end of the infants' stay at the NICU. The observation period ended when the infant was transferred or discharged.

4.7. Standardized feeding regimen

All preterm infants routinely received a gastric tube during the first hour of life. Within the first 12 hours of life minimal enteral nutrition was started, defined as 1ml of nutrition (preterm formula or breast milk) every 3 hours. The introduction of enteral feedings was achieved using colostrum of the premature infant's mother (Tsang et al., 2005). If no breast milk was available, undiluted hydrolysed preterm formula (Prematil HA®/Milupa, Puch, Hallein Austria) or Beba F®/Nestle Vevey, Switzerland) was used (Mihatsch, Högel, & Pohlandt, 2001). As soon as breast milk was available, nutrition was changed to breast milk. The daily amount of enteral nutrition was increased by 20ml/kg/d (McGuire & Bombell, 2008). Full enteral feedings were defined as 140ml/kg (Agostoni et al.). At an enteral intake of 100ml/kg, breast milk was supplemented with breast milk fortifier (BMF), e.g.: Aptamil FMS®/Milupa (Puch, Hallein Austria), FM 85®/Nestle (Vevey, Switzerland). If the concentration of the fortifier was increased, the volume of feedings remained the same for 2 days (Agostoni et al.).

4.8. Gastric residuals and feeding intolerance

The colour and amount of gastric residuals was assessed before each feeding by aspiration via a gastric tube. Colour and consistency of gastric residuals were assessed as clear (mucous), milk-coloured, clear green, green with flakes, blood-tinged or haemorrhagic. The sole presence of clinical conditions such as infection, hypotension or respiratory support and the subjective impressions of the attending nursing staff did not influence the feeding strategy. The following were considered as signs of feeding intolerance: (Meetze et al., 1993; Meetze et al., 1992): (i) increase in abdominal girth of >2 cm compare to the previous measurement; (ii) guaiac-positive stools; (iii) a single gastric residual greater than 3mL/kg body weight; (iv) grossly bloody stools; (v) emesis; (vi) ileus; (vii) bile-stained gastric residuals; (viii) radiologic evidence of necrotizing enterocolitis (NEC) (pneumatosis or portal venous gas). If signs of feeding intolerance occurred all stools were tested for presence of haemoglobin (Haemoccult®; Beckman-Coulter, Krefeld-Fischlen, Germany). Mild feeding intolerance was defined when one of the symptoms (i), (ii) or (iii) occurred and feeding was discontinued for six hours. Severe feeding intolerance was defined if one of these signs was accompanied by symptoms of illness such as sepsis, or if two signs occurred together, or if symptoms (iv) through (vii) occurred. Feeding was withheld according to the clinical condition of the infant. Furthermore feeding was withheld for six hours after extubation and during indomethacin therapy.

4.9. Data collection

Demographic data were recorded for all infants. Infants were monitored documenting clinical condition of the abdomen (size, tension, peristaltic, apparent standing intestinal loops), stooling pattern, ventilation and ventilator support (positive end expiratory pressure-PEEP) every hour, during the first 48 hours after osteopathic treatment. Blood pressure was monitored continuously by an arterial line during the first three days of life. Electrolytes and urinary output in ml/kg/h were monitored every 12 hours. During the further study period the following parameters were recorded daily: body weight, volume of enteral and parenteral fluids, volume and colour of gastric residuals before every meal, abdominal girth, presence of gross abdominal distension, presence of persistent visible loops without peristalsis, presence of abdominal tenderness, stool pattern, and respiratory support. Concomitant application of suppositories and enemas were recorded as well as laboratory parameters of infection (full blood count, CRP, interleukin-8, blood culture) and antibiotic therapy. NEC was defined according to the stages by Bell as proven NEC grade 2a (Bell, 1978)

Furthermore the following data were recorded:

<u>Obstetric history of the mother</u>

- Premature rupture of membranes
- Intractable contractions
- Gestosis
- Therapy with Antibiotics
- Treatment with corticosteroids for lung maturation of the infant
    - complete: 2 cycles of corticosteroids completed 24h before delivery

    - incomplete: 1 cycle or 2 cycles less than 24h before delivery
- Mode of delivery

<u>Before the first osteopathic treatment</u>

- Gestational age
- Birth weight
- Birth length
- Head circumference at birth
- APGAR
- Umbilical cord-PH
- Clinical condition of the abdomen (size, tension, peristaltic, apparent standing intestinal loops)
- Stooling pattern
- Ventilation and ventilator support (PEEP)

<u>For the whole duration of the study period, following data was recorded daily</u>

- Body weight
- Amount of parenteral fluids in ml/kg
- Enteral nutrition supply in ml/kg (Human milk or formula)
- Fortification of human milk
- Gastric residuals
- Stooling pattern
- Clinical condition of the abdomen (size, tension, peristaltic, apparent standing intestinal loops)
- Ventilation and ventilator support (PEEP and flow)
- Feeding intolerance
- Enemas
- Glycerine suppositories

4.10. Relevance for the patient

The potential benefit for the patient consisted in shortened meconium passage, improved feeding tolerance, shorter time of parenteral nutrition and intravenous access and therefore lower sepsis morbidity and shorted hospital stay.

4.11. Adverse events and withdrawal

Severe adverse events leading to withdrawal from the study:

- Ileus
- Volvulus
- NEC
- death

4.12. Statistics

4.12.1. Sample size

Based on studies investigating meconium passage in VLBW infants (Haiden, 2007), a sample size estimation (Stolley & Strom, 1986) indicated that a total of 40 infants would suffice to detect a 20% difference in the outcome between the groups with a power of 80% and a significance level of 0.05.

4.12.2. Primary outcome

- Time to complete Meconium evacuation in days.

4.12.3. Secondary outcome

- Introduction of enteral feeding in days
- Feeding volume on day 14^{th}
- Time to full enteral feeding in days
- Hospital stay

4.12.4. Randomisation

Based on the order in which they enter the study, infants are assigned a randomisation number. The randomization list was created by www.randomization.com by a physician not otherwise involved in the trial conduct. Randomization was concealed by individually sealed opaque envelopes. The details of the randomisation are known to the investigator and to the site staff. The infant received the treatment that corresponds with his/her randomisation number. The assigned randomisation number was documented in the CRF and in the infant file.

4.12.5. Statistical analysis

Data were checked for normal distribution visually by Histograms and with the Kolmogorov-Smirnow test. Given the non-normal distribution of the data, all comparisons were performed using non-parametric tests. The “Chi2- test” was used for dichotomous (demographic) variables. Data were checked for normal distribution visually by Histograms and with the Kolmogorov-Smirnow test. For all tests, a p-value < 0.05 was considered to indicate statistical significance. SPSS statistical software system® (SPSS Inc., Chicago, IL, version 10.0) was used for all calculations.

5. Results

5.1. Study population

During a fourteen moths study period from December 2010 to February 2012 193 infants were eligible for enrolment in the study. Infants were excluded for the following reasons: informed consent not obtained in time (n=139), parental refusal (n=8) and 5 infants died before randomization. Therefore the final cohort included 41 infants.

5.2. Obstetric History

The obstetric history oft the mother is given in Table 1. In one case in the control group parts of the obstetric history were not available.

Table 1: Obstetric history of the mothers (Chi2 test)

	Controlgroup (N=21)	**Interventiongroup (N=20)**	**p-value**
	N (%)	N (%)	
Delivery by C- Section	19 (90.5)	16 (80)	0.34
Vaginal delivery	2 (9,5)	4 (20)	0.34
Intractable contractions	7 (35)	12 (60)	0.11
Gestosis	7 (35)	5 (25)	0.49
Premature rupture of membranes	5 (25)	8 (40)	0.31
Mother received antibiotics	12 (60)	15 (75)	0.3
Lung maturation completed	14 (70)	12 (60)	0.51

Lung maturation incomplete	6 (30)	8 (40)	0.5

5.3. Baseline characteristics and outcome data

Baseline characteristics between study groups were balanced and are summarized in Table 2. No differences between the groups were observed. Birthweight and GA of the patients was very low reflecting the focus of our centre. Primarily the Division of Neonatology of the Medical University of Vienna is specialized on infants with a birthweight below 1000g and a gestational age of less than 28 weeks. Given that 40% of our patients are infants from multiple pregnancy we included 2 pair of twins in the intervention group and 1 pair in the control group. Furthermore quintuplets were included in the control group.

Table 2: Demographic characteristics of the study population (Mann- Whitney- U test)

	Controlgroup (N=21) Median (Range)	**Interventiongroup (N=20)** Median (Range)	**p-value**
Birthweight (grams)	765 (503-1150)	730 (380-1400)	0.76
Length at birth (cm)	35.5 (30.5- 40)	33 (27.5-40)	0.25
Head circumference at birth (cm)	24.5 (21-27)	23 (20-28.5)	0.66
Gestational age at birth (days)	193 (167-204)	182 (163-218)	0.74
Gestational age at birth (weeks)	28+2 (23+6-30+0)	26+1 (23+2-31+1)	0.74

There were no significant differences in baseline characteristics between groups ($p>0.05$).

Outcome data on relevant neonatal morbidities were also distributed equally and are given in Table 3. These data indicate that visceral osteopathic treatment had no negative effect on the outcome of our patients. Especially the incidence of NEC remained stable in the intervention group and showed no difference to controls.

Table 3: Morbidity and mortality of the study population (chi2- test)

	Controlgroup (N=21) N (%)	**Interventiongroup (N=20)** N (%)	**p-value**
Male sex	6 (28.6)	6 (30)	0.92
Deceased	0 (0)	1 (5)	0.29
NEC	1 (4.8)	2 (10)	0.52
NEC surgery	0 (0)	2 (10)	0.14
IVH I+II	5 (23)	5 (25)	0.93
IVH III+IV	1 (4.8)	1 (5)	0.97
PDA	14 (66.7)	15 (75)	0,56

(NEC=Necrotizing enterocolitis, IVH= intraventricular haemorrhage, PDA=persisting ductus arteriosus) There were no significant differences in outcome data between groups ($p>0.05$)

5.4. Primary and secondary outcome

Meconium evacuation

Clinical characteristics including feeding and stooling variables of study patients are given in Table 4. In the intervention group the primary endpoint meconium evacuation lasted median 7.5 days (95% CI: 6.4-9.4 days) and 6 days (95% CI 5.2-9.1 days; n.s.) in the control group. A post-hoc subgroup analysis showed no difference in meconium evacuation between infants with a birthweight below 1000g and between 1001-1500g.

Time to full enteral feedings was nearby 2-fold longer in the intervention group (median 40 days, 95% CI: 30.4-50.6 days) than in the control group (median 28 days, 95% CI: 20.6- 31 days; p=0.02), which was significant. This was associated with a 44 days longer stay in the NICU in the intervention group than in the control group (Table 4). In both groups enteral nutrition started on the second day of life (=median; 95% CI controls: 1.6-2.5; 95%CI: 1.2-2.8 n.s.). 50% of the infants in the Intervention and 71% in the control group received primarily mother's own breastmilk as source of enteral nutrition.

All infants in the study received respiratory support by continuous positive airway pressure (C-PAP). Infants were on C-PAP for 19,5 days (=median, 95%CI: 16.1-32.3) in the intervention group and for 32 days (=median, 95% CI: 19.8-51.1) in the control group, respectively. 13 infants in the intervention and 7 infants in control group needed mechanical ventilation. Mean days on respirator were 3,5 days (=mean, range: 0-15 days; median=0 days; 95% CI: 0.84-6.16) in the control group and 12,4 days (=mean, range: 0-75 days; median 5 days; 95%CI: 3.74-21.12) in the intervention group (p=0.09). Overall infants in the intervention group needed twice as long respiratory support and were 4-times longer on ventilator than in the control group. Although this achieved no statistical significance there was a trend that infants in the intervention group were the sicker ones.

Table 4: Primary and secondary outcome
Clinical characteristics of the study population including feeding and stooling pattern (Mann-Whitney-U test)

	Controlgroup (N=21) Median (Range)	**Interventiongroup (N=20)** Median (Range)	**p-value**
First meconium (days)	2 (1-7)	2 (1-5)	0.16

Last meconium (days)	6 (2-21)	7.5 (3-18)	0.11
Feeding amount on 14th day of life (ml/kg)	84 (11-158)	99 (4-133)	0.74
Full enteral feedings (day of life)	28 (11-52)	40 (14-99)	0.02
Duration of stay in the NICU (days)	66 (13-139)	100 (13-229)	0.14
Weight at discharge home (gram)	2920 (2060-5428)	3255 (1948-6225)	0.58

Suppositories and enemas

As suppositories or enemas might have an impact on meconium evacuation we analysed the frequency how often these therapies were administered. No differences were observed between groups in terms of receiving glycerine suppositories or enemas until complete meconium excretion was achieved (Table 5).

Table 5. Enemas or suppositories applied in the study (chi2test)

	Controlgroup (N=21) N (%)	**Interventiongroup (N=20)** N (%)	**p-value**
Glycerine suppository once until complete meconium evacuation	4 (19)	7 (35)	0.24
Glycerine suppositories multiple until complete meconium evacuation	13 (61.9)	11 (55)	0.74
Enema once until complete meconium evacuation	5 (23.8)	2 (10)	0.28
Enema multiple until complete meconium	17	18	0.07

evacuation	(80)	(90)

5.5.Tolerance of the osteopathic procedure

In general the procedure was tolerated very well. All infants were monitored during the treatment and no one showed signs of cardiorespiratory instability, apnoea or pain. Only 1 infant (4.8%) reacted with agitation and showed signs of discomfort- after a short break of 5 minutes the patient calmed down and the treatment was continued without further problems.

6. Discussion

This prospective, randomized, controlled trial examined the effect of visceral osteopathic treatment on meconium evacuation in VLBW-infants. Osteopathic treatment was well tolerated without any impact on respiratory or cardiovascular system. However, the results indicate that visceral osteopathic treatment did not accelerate complete meconium excretion. Time to full enteral feedings was significantly longer in the osteopathic group as compared to controls, which must be interpreted as long-term negative side effect in context with visceral osteopathic treatment.

Obstetric history of the mothers

Most of the infants in the present study were born via caesarean section. This reflects the current practice of our obstetric department although data on best practice for the delivery mode of preterm infants are still inconclusive (Alfirevic, Milan, & Livio, 2012). A slight imbalance in obstetric history of the mothers occurred in the cause for premature delivery between our study groups. More mothers in the control group suffered from Gestosis, fewer mothers had a premature rupture of membranes when compared to the intervention group. However the outcome of the infants was balanced- therefore we found no evidence that the origin for premature delivery had any impact on study outcome.

Patients on the border of viability

In the present study visceral osteopathic treatment was applied in preterm infants with a median birthweight between 700-800g and a gestational age about 28 weeks. Our smallest patient had a birthweight of 422g and a gestational age of 23+2. This definitely represents the minimum weight and age of viability. Infants with extremely low birth weight are more susceptible to all of the possible complications associated with premature birth, both in the immediate neonatal period and after discharge from the nursery. Do these babies have any chance to survive with a proper neurodevelopmental outcome? Every day inside the mother's womb increases the chance of survival for a micropreemie, and every week is a major significance continuing to push that percentage higher. Recently our team published data on survival and neurodevelopmental outcome in our hospital (Klebermass-Schrehof et al., 2013). Infants born between the 23+0 and 25+6 week of gestation survived in 68.1%, Infants born between the 26+0-27+6 survived in 84.8%, respectively. 9.4 % of the survivors suffered from a major cerebral lesion (intraventricular haemorrhage and periventricular leukomalacia), which is associated with a poor neurodevelopmental outcome like cerebral palsy or major loss in vision or hearing. Therefore the majority of these small micropreemies survived their stay in the NICU with almost no or only mild impairment. To the best of our knowledge no one has published data on osteopathic treatment such tiny micropreemies previously.

Osteopathy in the NICU

In general complementary methods are very well tolerated by NICU staff and parents. Both groups feel comfortable that „something pleasant“ is done to the baby. Almost all other procedures in daily care (except kangarooing) are disturbing the baby or are painful. Osteopathic treatment is noticed to be „natural, painfree and cures imbalances“. Especially craniosacral osteopathy is very well accepted after prolonged labour, vacuum extraction of forceps delivery (Moeckel Eva, 2008). After such a stressful birth event infants are often irritable or difficult to calm. In addition, excessive wakefulness at night or reluctance to fall asleep, spitting up or vomiting can have their origins in structural disturbances. Cranial osteopathy for the newborn is a safe, gentle, non-invasive form of manipulative treatment. Babies often fall asleep during treatment or fall into a deep, restful sleep thereafter. Sometimes babies fuss or squirm during the treatment, actions that can help release the troubled areas. Osteopathic treatment does not alter the underlying birth injury factors, but it can be very effective in enhancing the child's functional capabilities as well as improving general health and quality of life for the child and family. Therefore a lot of parents in the NICU asked for extra visits and consultations even after the study was finished. However also osteopathic treatment has an impact on the organism and it is important to prove efficacy of the therapies. To date, osteopathic research primarily focused on the reliability of palpation, with only a few good-quality studies focused on the effectiveness of osteopathic manipulative medicine (Jäkel & von Hauenschild, 2011). In a prospective study Pizzolorusso found osteopathic manipulative treatment effective to improve gastrointestinal function and reduce the hospital stay of preterm infants (Pizzolorusso et al., 2011). From the infant 's 14th day of life the author’s applied osteopathic techniques during their hospital stay like indirect myofascial, sutural spread, balanced ligamentous tension according to Sutherland and others. Gastrointestinal symptoms like vomiting, regurgitation and reflux could be reduced in 55% per subject. A significantly higher rate of premature infants of 75% receiving osteopathic treatment could be discharged before 28 days regardless of gender, gestational age birthweight and feeding at admission. (Pizzolorusso et al., 2011) Recently the Italian group around Cerritelli started a prospective multicentre trial on the effectiveness of osteopathic manipulative treatment in neonatal intensive care units (Cerritelli, Pizzolorusso, Renzetti, et al., 2013). The study is currently ongoing and focuses on the impact of osteopathic manipulative treatment on the length of hospital stay of preterm infants. Furthermore the study investigates feeding and stooling pattern of preterm infants and explores weightgain, time to full enteral feedings and abdominal symptoms- very similar to the approach in the present study. The results will hopefully help to understand the effects of osteopathic manipulative techniques in preterm infants more distinctly.

Delayed meconium excretion – the somatic dysfunction

The Osteopathic Terminology defines somatic dysfunction as "impaired or altered function of related components of the somatic (body frame work) system: skeletal, arthrodial, and myofascial structures, and related vascular, lymphatic and neuronal elements. The diagnosis of the somatic dysfunction is supported by visible and palpable findings of tissue texture changes, asymmetry of structure, restriction of motion and tenderness to palpation. The somatic dysfunction consists of neuronal, vascular and connective tissue adaptions.(Ward, 2003) The activity and condition of body tissues (the soma) are partly influenced via excitation and inhibition of nerves that emerge from the central nervous system. In the present study delayed meconium excretion of the preterm infant was defined as the somatic dysfunction to be treated. In this context the special background of this somatic dysfunction had to be considered. In this special group of patients proper function of the organ has never been established and the somatic dysfunction is determined by the immaturity of the intestinal motor mechanisms and associated feeding problems (Newell, 2000). Timing of the first and last meconium stool is critical for oral feeding tolerance and proper gastrointestinal function (Meetze et al., 1993). Almost all term infants pass their first meconium within 48 h of life (Kramer & Kakuma, 2004; Sherry & Kramer, 1955). In contrast, many premature infants pass their first meconium only after considerable delay up to 27 d (median, 43 h) (Meetze et al., 1993; Wang & Huang, 1994). Obstruction of the gastrointestinal tract by tenacious meconium frequently leads to gastric residuals, a distended abdomen, and delayed food passage. In the literature the relation between meconium evacuation and feeding tolerance in premature infants is discussed controversially. While some authors showed a link between feeding tolerance and meconium passage (Mihatsch, Franz, et al., 2001), others could not prove a causality (Meetze et al., 1992). However the establishment of proper gastrointestinal function is characterized by feeding tolerance and a normal, regular stool pattern. The so called "meconium obstruction of prematurity" (Garza-Cox et al., 2004; Siddiqui MMF, 2012) is a distinct clinical condition in VLBW infants with obstructive symptoms like abdominal distension occurring several days after having passed some initial meconium (Morgan, Young, & McGuire). This meconium obstruction should be avoided by all means but so far it remains unclear, if meconium passage can be influenced prophylactically e.g. by enemas. No pharmacological treatment or treatment with suppositories and enemas seemed to be safe and effective to solve the problem so far.

The osteopathic approach

Frustrated by the contemporary medical management of delayed meconium evacuation in preterm infants we intended to perform a study with non-invasive manual medicine, also designated as complementary and alternative medicine. The goal was to improve the physiological function and restore homeostasis of the premature gut. The somatic dysfunction was defined as delayed meconium evacuation caused by immaturity and inadequate uncoordinated motility of the gut. In visceral osteopathy disturbed mobility is usually defined as an organ completely or partly loses its ability to move caused by adhesions, fixations, viscerospasms or ptosis (Eric, 2011) A disturbed motility reduces the amplitude and the range of motion of the organ itself in either one or both directions (Eric, 2011). The focus of the present study was to address to motion restrictions and tissue texture abnormalities, which are an expression of homeostatic disturbances. Osteopathic treatment was intended to have an impact on improvement of organ function and neuroflexive factors influencing circulation. Gentle application of visceral and craniosacral osteopathic techniques on the infant's abdomen should activate and support the body's self-regulation. We hypothesized that in a preterm infant proper mobility and motility of the gut has never been established due to the sudden interruption of physiologic development caused by preterm birth. The self-regulation and self-healing capability should be supported by visceral osteopathic techniques and initialize the motor mechanisms of the gut to establish proper mobility and motility. The visceral osteopathic treatment algorithm should also address to the vagal nerve, increase the range of motion of the several segments of the gut and release facial tensions.

Gastric motility is strongly influenced by the vagal nerve. It was shown previously that in preterm infants moderate pressure massage stimulates the vagal nerve leading to increased gastric motility (Field, Diego, & Hernandez-Reif, 2011; Field, Diego, Hernandez-Reif, Deeds, & Figuereido, 2006). This turned into greater weightgain and increased the release of insulin and IGF-1 (insulin growth factor) (Field et al., 2011). Field et al reported a greater weight gain of 21-47% in preterm infants treated with moderate pressure massage. The change in insulin and IGF-1 suggested two parallel pathways via which massage therapy leads to increased weight gain: 1) insulin release via the celiac branch of the vagus and 2) increased gastric activity via the gastric branch of the vagus. (Field et al., 2011). The pressure on the abdomen given in visceral osteopathic treatment is comparable with moderate pressure massage described by Field. Therefore the intention to stimulate gastric and bowel motility by moderate pressure manipulative techniques seemed also to be a favourable method to enhance meconium evacuation.

Adaptation of visceral osteopathic techniques for the premature infant

Visceral Manipulation is based on the specific placement of soft manual forces to encourage the normal mobility, tone and motion of the viscera and their connective tissues. These gentle manipulations can potentially improve the functioning of individual organs, the systems the organs function within, and the structural integrity of the entire body (Field et al., 2006). Before starting the study visceral osteopathic treatment had to be adapted to the body size of preterm infants. Usually these visceral techniques are applied in adults or children. Due to the small size of a premature infant- sometimes not more than a handful of life- the different anatomic structures are located close together and the abdomen has a maximum size of tennis ball. This small area was the field of working and the hand of adult was much too large to execute "classical" osteopathic treatment. So the working mode had to be adapted in motion, pressure and range for the tiny baby. Transferring distinct osteopathic procedures from generous powerful movements to a gentle, precise treatment algorithm was a challenge for the practitioner. Methods of Barral and Finet/Williame were combined and are described in the following section. In general Jean Pierre Barral views the organs from a mechanical perspective: organs from visceral joints with another organ or a part of the locomotion system e.g. the diaphragm. Similar to the parts of a joint, the organs are tested for their ability to move and directly treated to increase mobility (Eric, 2011). He intended a concept of visceral motility that follows a more energetic approach. Georges Finet and Christian Williame studied movements of abdominal organs in relation to diaphragmatic breathing with ultrasound. They discovered organ movements that follow certain rules and defined directions and extents, which largely concur with Barral's results. In addition they developed a treatment method to influence disturbed organ movements. In contrast to Barral, who palpates the organs and moves them directly in his mobilizing techniques, Finet and Williame utilize the anterior parietal peritoneum in their therapy. The peritoneum is seen as a fascia and connects all abdominal organs with each other (Eric, 2011) Ultimately, both treatment concepts succeed in restoring the physiologic mobility of an organ, with the only difference being that Finet and Williame do so a little less invasively (Eric, 2011) Therefore a combination of both methods seemed to be the perfect approach to treat the abdomen of preterm infants.

In detail the treatment algorithm was based and adapted from the following visceral osteopathic techniques:

Reflexpoint treatment according to Barral (Eric, 2011)

Reflexpoints are anatomic structures in the gastrointestinal tract that function as sphincters (e.g. Pylorus). The sphincter can be treated with friction in a clockwise direction, vibration, inhibition or rebound. Treatment is continued until relaxation occurs or the sensitivity of the point is noticeably reduced.

Inhibitions according to Barral (Eric, 2011)

Inhibitions are constant applications of pressure on a structure. Reflexogenically, they cause detonification and pain reduction at the treated point- an inhibition is sustained for 30 seconds to 2 minutes.

Treatment of mobility according to Barral (Eric, 2011)

Mobility is improved by manually supporting an organ directly or indirectly in its physiologic movements in three dimensions. In direct treatment the practitioner places his hand directly on the organ to mobilize the structure. At indirect treatment the organ is mobilized by levers. Both techniques can be combined.

Fascial treatment according to Finet and Williame (Eric, 2011)

The diaphragm is the engine of fascial movement in the abdominal organs. Migration of the organs caudally during inhalation also includes a fascial movement caudally in the abdomen. In addition to this caudal movement, the individual organ fascia carries out concomitant rotations. For the purpose of treatment, the respiratory movement is used as the mobilizing element. Normalization aims restoring the physiologic fascial dynamic if the organ by mobilizing the superficial abdominal fascia. In this way the organ has its specific direction for mobilization.

In particular the treatment algorithm was designed with respect to anatomic and functional considerations of the preterm baby and adapted to the following: (Eric, 2011)

1) Global and local listening on the abdomen:
   Procedure (Eric, 2011):
   A global listening according to Barral can be performed in a standing position, a seated position or in supine position by a “leg or armpull”. The practitioner looks for fascial tensions, imbalances and a possible dysfunctional side. It is followed by a local listening with a hand placed flat on the patient’s abdomen, noting the movement of the fascia. The practitioner should follow the movement to find a diagnostic zone.
   Adaptation:
   The infant was always positioned in the supine position. Turning and rolling the baby during osteopathic treatment would be exhausting for the infant. Usually a device for respiratory support (CPAP-Infant flow) was fixed on the infant’s head with a cap. This disturbed access to the infant’s head and impeded direct contact. Safety tests like

Soto Hall or rebound tests were too invasive and therefore had to be omitted. The focus was on the fascial tension of the abdomen- the practitioner was looking for dysfunction with two or three fingers on the abdominal fascia moving the fascia toward the place of greatest tension.

2) Release lower ribs and thoracic diaphragm:

The diaphragm is the propelling force for the movement of the colic flexures and treatment of the diaphragm has also an impact on circulatory -(Eric, 2011)- therefore we included this technique in the treatment algorithm. Furthermore the respiratory movement of the 12^{th} rib is essential for the rhythmic flow of lymph in the thoracic duct where it enters the thorax under the median accurate ligament. Thoracic respiration is responsible for 50% of the lymph movement in the thorax, and diaphragmatic movements especially are essential for enabling the lacunae on the undersurface of the diaphragm to absorb the abdominal fluid, the gut being the largest lymphoid organ in the body (Moeckel Eva, 2008).

Procedure (Eric, 2011)

The patient is in supine position. The practitioner spreads out with both hands on the right and left side, grasping the patient's lower ribs. The practitioner applies mobilizing pressure to the thorax in translation, altering rhythmically to the left and to the right.

Adaptation

The technique was performed using two fingers grasping the lower rib cage instead of the two hands.

3) Pylorusrelaxation

Procedure (Eric, 2011)

To find the pylorus, the practitioner looks for its approximate projection on the stomach wall. For this purpose, move from the navel about five fingerwidths cranially. From there place your fingers slightly to the right, next to the median line. At this point, slowly slide posteriorly into the abdomen. Once you have advanced deeply enough to palpation, you will find a supple, roughly hazelnut-sized solidification with 0.5-1cm of its palpation point. You can now carry out small circulations vibrations or inhibitions on this point until the tonus and sensitivity are clearly reduced.

Adaptation

The technique was applied with one finger of the practitioner moving one fingerwidhts cranially from the navel. Only slight pressure was applied allowing the structures to relax.

4) Release of the Duodenum and the C-Loop

Procedure according to Barral (Eric, 2011)

The duodenum has 4 parts, which can be treated separately in an adult. (superior part, descending part, horizontal part, ascending part):

The superior part is usually treated in the sitting position with the left hand on the right costal arch, medial to the Murphy point and the right hand placed next to the left hand. The patient is brought into a kyphotic posture by gliding medially to the gallbladder in a posterior-cranial-lateral direction toward the superior part of the duodenum. Palpate as far as possible in this direction and then make contact with the liver. By lifting the liver cranially, also mobilize the superior part cranially with a pull on the hepatoduodenal ligament. In a second step drop the liver and mobilize the superior part caudally. The descending and horizontal part is usually treated in the side position with the hands of the osteopath medial to the ascending colon and lateral to the loops of the small intestine. Palpate into the depth of the abdomen posteromedially. The loops of the small intestine are in your palms. The fingertips reach the descending part laterally and stretch it simultaneously medially and craniocaudally. This has also an effect on the horizontal part. Hold this position until you notice relaxation in the tissue.

Procedure according to Finet and Williame (Eric, 2011)

During inhalation, both hands simultaneously pull caudally and medially, and rotate clockwise. During exhalation maintain the position reached.

Adaptation

In the present study infants were always treated in the supine position. Both techniques described above were combined together. The fascial structures of the duodenum were mobilized with the index finger along the anatomical structure with a slight pull in the of direction functional movement from oral to aboral. The pull was intensified during inspiration and maintained during expiration.

Small intestine diagnosis- Lifting the gut and bringing it to a stillpoint

Procedure (Eric, 2011)

General relief technique of the peritoneum and intestinal loops in the supine position according to Barral. With a pinch grip, grasp the entire abdominal wall, including the peritoneum, and carefully stretch all structures anteriorly. In this way a pulling sensation may arise all the way to the spinal column. Hold this pull. This technique is very effective for adhesions/fixations but must be applied with caution because it can be very painful. If you apply the grip slightly further posteriorly into the abdomen, you capture part of the small intestinal loops as well. The anterior pull can thus also include the root of mesentery.

Adaptation

The technique was applied with a two finger (thumb and index finger) pinch grip grasping the whole small intestine. The technique was combined with the root of mesentery diagnosis. Small clockwise movements were applied and synchronized with in and exhalation until tissue relaxed. Finally the gut was lifted and brought to stillpoint.

5) Root of mesentery diagnosis (and manipulation)

   Procedure and Adaptation: please see above

6) Mobilisation of the ileocoecal valve

   Procedure (Eric, 2011)

   To find the ileocoecal valve, you have to look for its approximate projection onto the abdominal wall. For this purpose, draw a line from the right anterosuperior iliac spine to the navel and divide it into thirds. At the transition from the lateral to the middle third, place your fingers on the abdominal wall. Now slide slowly posteriorly to the abdomen. You should proceed slowly in order to give the superficial located structures time to move out of the way and allow fascial relaxation. Once you have advanced deeply enough in this palpation, you will find a supple, roughly hazelnut-sized solidification within 0.5-1 cm of this palpation point. You can now apply small circulations, vibrations or inhibitions until the tonicity or sensitivity is clearly reduced.

   Adaptation

   The technique was applied with the index fingers of both hands. A line was drawn from the right anterosuperior iliac spine to the navel and divided into two halves. Both fingers slided slowly posteriorly to the abdomen- the finger closer to the midline fixed the ileocoecal valve and the finger of the other hand slightly pulled to lateral in direction of the anterosuperior spine. Small vibrations or inhibitions were applied until the tissues relaxed.

7) Mobilisation of colon ascendens, transversum, descendens with treatment of the Toldt fascia

   Procedure (Eric, 2011)

   The several parts of the colon are usually treated together (Finet and Williame)

Cecum and ascending colon

Place the right hand on the cecum with the fingertips pointing in a medial- cranial direction toward the navel. The left hand grasps the flank as close as possible to the costal arch, the fingertips lie posterior. The ascending colon lies in your hand. During inhalation pull with both hands caudally. The right hand rotates with the fingertips outward, while at the same time the left hand exerts pressure medially. During exhalation, maintain the position reached. Repeat this procedure until you have reached the end of the fascial movement. During the next exhalation release the pull.

To treat the ascending colon, right colic flexure and right part of the transverse the left hand grasps the flank as close to the costal arch as possible, the fingertips lie posterior. The left hand grasps the flank as close to the costal arch as possible; the fingertips posterior. The ascending colon is in the hand of the practitioner with the fingertips touching below the right costal arch. The fingers point toward the right shoulder. During inhalation, both hands simultaneously pull caudally and rotate clockwise. In this way, the right colic flexure is pulled caudal-left direction. During exhalation, maintain the position reached. For the descending colon the same technique was applied form the other side of the body.

The Toldt fasciae (Barral) of the ascending and descending colon are usually treated in lateral position. Sink the fingers of both hands deeply into the abdomen on the posterior side of the colon between the colon and the lateral abdominal wall. Mobilize the fascia with constant pressure vibrations, rebounds of frictions.

Adaptation

This technique was mostly difficult to adapt. The abdominal surface of a preterm infant is too small to use a second hand for mobilization of the fasciae. Therefore the individual parts of treatment were all taken together in a fluently applied deep pull, starting caudally in the ascending area, rotating clockwise to the transversum area and going down caudally to the Colon descendens. Finally the Toldt fascia was mobilized with a pinch grip of the thumb, which was positioned on the ascending/descending colon and the index finger, which was positioned posterior. The fascia was mobilized with rebounds and frictions.

8) Root of sigmoid diagnosis and manipulation (Ward, 2003)

Procedure

The root of sigmoid is a thickening of the peritoneum, extending from the sigmoid to the area of the bifurcation of the iliac vessels. The mechanical tension extends further to the area of duodeno-jejunal junction. The patient is treated in supine position.

Grasp the sigmoid with a pinch grip and move the mesocolon superior-lateral and inferior-medial checking for tension. Engage the tension and let the tissue come back, noting the speed the tissue responds. Continue this rhythm until the tissue releases and there is no more tension.

Adaptation

The technique was applied with one or two fingers (thumb and index finger) pinch grip grasping the mesocolon. Small clockwise movements were applied until tissue relaxed.

9) As the 10th cranial nerve influences the intestines' function by relaxing the sphincters and thus increases gut motility, treatment of the parasympatic nerval system should be always in involved.

   Procedure:

   The vagus nerve was treated by craniosacral therapy via the sacrum. The hand of the osteopath was put under the sacrum of the infant and cranial treatment was given as long as the infant's body reached a stillpoint.

Failure of visceral osteopathic techniques to accelerate meconium evacuation

In the present study visceral osteopathic techniques were applied to accelerate meconium evacuation in preterm infants. Although the intention of the study was well defined and the selected techniques were convenient to serve the purpose, the study failed in success. Meconium excretion lasted 7.5 days after visceral osteopathic treatment and 6 days without. Time to full enteral feedings was nearby 2-fold longer in the intervention group than in the control group, which was significant. This was associated with a 44 days longer stay in the NICU as compared to controls. Furthermore infants in the intervention group needed twice as long respiratory support and were 4-times longer on ventilator than in the control group. Although baseline and outcome data were well balanced between groups, these data indicate, that infants in the intervention group were the sicker ones. However the results of secondary outcome must be interpreted as negative side effects and it is likely that they are associated with osteopathic treatment.

In the present study the osteopathic approach failed to accelerate meconium evacuation in preterm infants. Before, several studies focussing on acceleration of meconium evacuation by pharmacological treatment or mechanical treatment by enemas also showed inconclusive results. (Haiden et al., 2007; Haiden et al., 2012). Osteopathic treatment belongs to the complementary and alternative medicines. Parents and nurses very well accept it. The holistic approach referring to physical, cognitive and spiritual aspects of the individual could be perfectly included in the NIDCAP concept.

To date various osteopathic techniques have been applied in children to treat somatic dysfunction: cranial osteopathy, balanced ligamentous tension (BLT) or muscle energy techniques. Only little literature on visceral techniques is available so far. Especially the very tiny body and the small surface of the abdomen was a challenge for the therapist. Furthermore the synchronization of techniques from Finet and Williame with rhythm of breathing was very difficult. Preterm infants have a breathing frequency of 40-70 breaths per minute depending on the gestational age of the infant. Therefore it is conceivable that the techniques were not applied properly and not as effective as supposed. In addition preterm infants are very susceptible to touch. Although the infants in our study showed no signs of discomfort during osteopathic treatment it is conceivable that the algorithm was too rude and therefore failed to be effective.

However only a few high-quality randomized controlled trials focussing on the therapeutic effectiveness of osteopathic treatment in premature infants and neonates are published and most of them failed to prove efficacy:

A previously published review evaluated osteopathic manipulative therapies (OMT) in paediatric conditions and identified only 1 study in preterm infants (Posadzki, Lee, & Ernst, 2013). Cerritelli et al (Cerritelli, Pizzolorusso, Ciardelli, et al., 2013) tested the effects of OMT on the length of hospital stay and daily weight gain in 101 premature infants. In this study, 47 infants received OMT +usual care (no details provided), and 54 received usual care only. The authors reported significant improvements in length of hospital stay ($p = 0.03$, no CIs) and daily weight gain ($p = 0.03$, no CIs) in the OMT group compared with controls and concluded that OMT plays an important role in the management of hospitalized preterm infants. Furthermore 4 studies in neonates were identified (Posadzki et al., 2013): Hayden and Mullinger (Hayden & Mullinger, 2006) aimed to investigate the effect of cranial OMT on the pattern of increased crying, irritability, and disturbed sleep associated with infantile colic. Of the 28 infants in this study, 14 received 4 sessions of cranial OMT over 4 weeks, and 14 received no treatment. These authors reported significant improvements in crying (mean difference = 1.0 (Newell), $p<0.02$) and time spent sleeping (mean difference = 1.17 [95% CI: 0.29 to 2.27], $p<0.05$) in the treatment group and concluded that cranial OMT can benefit infants with colic. (JP, I, & JV, 2009) aimed to evaluate the efficacy of cranial osteopathy in 30 children with congenital nasolacrimal duct obstruction 15 infants received 1 session of cranial osteopathy, and 15 received 1 sham treatment (light touch only). The authors reported significant post treatment improvements ($p<0.05$, no CIs) and no between groups differences at 14 weeks follow-up ($p >0.05$, no CIs) in the fluorescein disappearance test and the modified Jones test in the OMT group compared with controls and concluded that cranial OMT is an effective short-term therapy Philippi et al (Philippi et al., 2006) aimed to assess the therapeutic efficacy of OMT in 32 infants with postural asymmetry (PA), 16 of whom received 4 sessions of OMT over 1 month and 16 of whom had sham therapy (light touch only). The authors reported significant reductions in postural asymmetry in the OMT group compared with the sham group (p =0.001 [95% CI: 2.0 to 7.3]) and concluded that OMT in the first months after birth reduces the degree of asymmetry in infants with postural asymmetry. Vandenplas et al (Vandenplas et al., 2008) aimed to test whether OMT could reduce the incidence of obstructive sleep apnoea. Of the 34 infants in this study, 15 received 2 sessions of OMT, and 13 received 2 sessions of gentle mobilizations over a period of 2 weeks. These authors reported no significant intergroup difference in the decline in the number of obstructive apnoea (p =0 .43, no CIs); and significant (within group) decrease in the number of apnoea in the OMT group (p=0 .01, no CIs) and concluded that OMT may have a positive influence on the incidence of apnoeas during sleep in infants with a previous history of obstructive apnoea, as measured by polysomnography.

The authors of the review mainly criticized low methodical quality and paucity of the analysed osteopathic studies. More than half of the studies (9 of 17 randomized controlled trials) did not report on any statistical calculations for effect size. Five of 17 trials had a high risk of bias with regard to adequate sequence generation. Nine of 17 trials had a high risk of bias with regard to allocation concealment. Twelve of 17 trials had a high risk of bias with regard to patient blinding and nine to assessor blinding. Six trials had a high risk of bias with regard to addressing of incomplete data and selective outcome reporting and 4 trials failed to provide any details about the OMT, making them impossible to be replicated. So overall the quality of the reported randomized controlled trials was poor and no trial was free of major methodical limitations. The aim of this article was to summarize and critically evaluate the evidence for or against the effectiveness of OMT in paediatric conditions. Seventeen trials were found; 7 of them favoured OMT, whereas the remaining 7 revealed no effect, and 3 did not report between group comparisons. In general, small and biased randomized controlled trials favoured OMT, whereas the largest and most methodologically sound studies failed to reveal effectiveness (Posadzki et al., 2013). The evidence from randomized controlled trials of OMT for treating paediatric conditions is thus limited, weak, and contradictory.

Further investigations are needed with modified protocols focussing on cranial osteopathy to treat delayed meconium evacuation in this vulnerable group of patients. Currently the application of visceral osteopathic techniques cannot be recommended in VLBW-infants without further clinical trials.

Strengths and limitations

This was the first prospective randomized controlled study on visceral osteopathic techniques applied in premature infants. This study contributes knowledge to the interactions between somatic and visceral structures in infants - a field of interest, which is very under researched so far. The study provides a sampled size calculation and primary and secondary outcome was clearly defined. Applied visceral osteopathic techniques and their adaptation were described in detail, guaranteeing reproducibility by every osteopath. Furthermore the study achieved all requirements of a prospective randomized controlled trial.

One limitation was that in 139 cases informed consent could not be achieved in time: Osteopathic treatment had to be applied during the first 48h hour of life- therefore informed consent had to be obtained during this time span. Due to limited manpower this was very difficult to conduct, especially on weekends and holidays. The present study was an academic study, not an investigator driven one - therefore financial resources to enhance manpower were limited. This leaded to a high number of parents who were not asked to participate.

Secondly, parents had to be contacted twice: The guidelines of good clinical practice (GCP) postulate, that there has to be a timespan between information of the parents/patients and signing the informed consent- ideally ”over the night”- so the parents should have the opportunity to consider participation in the study. We always encouraged the parents to take their time afterwards asked again for informed consent. Therefore it happened, that informed consent was signed after the first 48 hours of the infant’s life and the infant had to be excluded.

A further limitation was that all treatments were performed by one and the same osteopath, which might cause bias. Although the osteopath was very experienced in neonatology one may speculate that the therapist was still too inexperienced to apply osteopathic techniques properly. This might also have influenced the outcome the study.

7. Conclusion

The question of the present study was generated out of a relevant clinical problem in neonatal intensive care medicine. So far osteopathic medicine has already started to explore the field of neonatal intensive care. However also alternative therapies like osteopathy have to proof its efficacy and effectiveness. In the present study we aimed to investigate the effect of visceral osteopathic treatment on meconium evacuation in VLBW-infants. Osteopathic treatment was well tolerated without any impact on respiratory or cardiovascular system. However, the results indicate that visceral osteopathic treatment did not accelerate complete meconium excretion. Time to full enteral feedings was significantly longer in the osteopathic group as compared to controls, which must be interpreted as long-term negative side effect in context with visceral osteopathic treatment. The study failed to confirm any benefit form visceral osteopathic treatment for the premature patients. Further investigations are needed with modified protocols focussed on cranial osteopathy in this vulnerable group of patients. Currently the application of visceral osteopathic techniques cannot be recommended in VLBW-infants without further clinical trials.

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9. List of Tables

10. List of Figures and Pictures

11. Abbreviations

NICU	neonatal intensive care unit
AAP	American acedemy of pediatrics
SGA	small for gestational age
LGA	large for gestational age
LBW	low birth weight
VLBW	very low birth weight
ELBW	extreme low birth weight
GIT	gastro intestinal tract
NEC	necrotizing enterocolitis
MEN	minimal enteral feedings
LCPUFA	long chain polyunsaturated fatty acids
NIDCAP	Newborn Individualized Development Care and Assessment Program
NPI	Nonpharmacological interventions
GA	Gestational age
CPAP	continuous positive airway pressure
BMF	breast milk fortifier
PEEP	positive end expiratory pressure
IVH	intraventricular haemorrhage
PDA	persisting ductus arteriosus
IGF	insulin-like growth factor
BLT	balanced ligamentous tensions
OMT	osteopathic manipulative therapies
SAS	SAS software

12. Attachments

12.1. Checklist

Studienbeginn			**Handzeichen**
☐	Einverständnis		
☐	Randomisierung/ID		
☐	Stammdatenblatt		
Studienintervention			
☐	1.Behandlung NW:	Datum/Uhrzeit	
☐	2.Behandlung NW:	Datum/Uhrzeit	
☐	3.Behandlung NW	Datum/Uhrzeit	
wöchentlich			
☐	Datenblatt		
Studienende			
☐	Datenblätter/Befunde komplett		
☐	Arztbrief		
☐	Dateneingabe Computer		

12.2. Source data

STAMMDATENBLATT- OSTEOSTUDIE

NAME: …………………………………….. GEB.DATUM …………………………

STUDIEN-ID: …………………………………….. GEB.UHRZEIT …………………………

GRUPPE: ☐ Kontrolle ☐ Intervention

Geschlecht: ☐männlich ☐ weiblich

Geburtsgewicht: ………………………..g

Geburtslänge: ………………………..cm

Geburtskopfumfang: ………………………..cm

Gestationsalter: ………………………..SSW

SGA : ☐ nein ☐ ja

APGAR: ……../………/……..

Nabelschnur-PH: arteriell:………. venös:…………

PDA: ☐nein ☐ja Kur (von –bis):………………………..

Chir.Verschluss:……………………..

IVH: ☐nein ☐ja Grad:…………………………………..

NEC: ☐nein ☐ja Grad:……………………..(Bell-stage)

Chir.Intervention:……………………

BPD: ☐nein ☐ja BPD-Kuren:...................... ………..

OPERATIONEN: ☐nein ☐ja Welche:………………………………

BEATMUNGSTAGE: Konventionell.....................

HFOV:................................

N-CPAP.............................

Aufenthaltsdauer /Transfer: ……………..……………….d

12.3. Documentation

Lebenswoche:………………. GEWICHT:…………….g LÄNGE:………….cm

KOPFUMFANG:……………cm

DATUM/ **LEBENSTAG**							
Gewicht							
Parenterale Flüssigkeitszufuhr in ml							
Enterale Nahrungszufuhr in ml (MM oder Formula)							
Magenreste (Menge pro Tag und Aussehen)							
Abdomen (path Aussehen oder Größe)							
Nahrungsintoleranz (Mild/schwer/Pause)							
Stuhl (Art, Menge, Farbe, Konsistenz, Uhrzeit)							
C-PAP(flow/Peep)							
Vent (konv/ HFOV)							
Spülungen (Glycerin 5ml/kg)							
Hohe Einläufe (Acetylcystein)							
Opiate (ja/nein)							

12.4. Patient Information

Patienteninformation und Einwilligungserklärung zur Teilnahme an der klinischen Studie

Einfluss viszeraler osteopathischer Behandlungen auf die Mekoniumentleerung bei sehr kleinen Frühgeborenen

Sehr geehrte Mutter, sehr geehrter Vater!

Wir laden Sie und Ihr Kind ein an der oben genannten klinischen alternativmedizinischen Studie teilzunehmen. Die Aufklärung darüber erfolgt in einem ausführlichen ärztlichen Gespräch.

Die Teilnahme an dieser klinischen Prüfung erfolgt freiwillig. Sie können jederzeit ohne Angabe von Gründen aus der Studie ausscheiden. Die Ablehnung der Teilnahme oder ein vorzeitiges Ausscheiden aus dieser Studie hat keine nachteiligen Folgen für die medizinische Betreuung Ihres Kindes.

Klinische Studien sind notwendig, um verlässliche neue medizinische Forschungsergebnisse zu gewinnen. Unverzichtbare Voraussetzung für die Durchführung einer klinischen Studie ist jedoch, dass Sie Ihr Einverständnis zur Teilnahme an dieser klinischen Studie schriftlich erklären. Bitte lesen Sie den folgenden Text als Ergänzung zum Informationsgespräch mit Ihrem Arzt sorgfältig durch und zögern Sie nicht Fragen zu stellen.

Bitte unterschreiben Sie die Einwilligungserklärung nur

- wenn Sie Art und Ablauf der klinischen Studie vollständig verstanden haben,
- wenn Sie bereit sind, der Teilnahme zuzustimmen und
- wenn Sie sich über Ihre Rechte als Teilnehmer an dieser klinischen Studie im Klaren sind.

Zu dieser klinischen Studie, sowie zur Patienteninformation und Einwilligungserklärung wurde von der zuständigen Ethikkommission eine befürwortende Stellungnahme abgegeben.

1. Was ist der Zweck der klinischen Studie?

Frühgeborene haben aufgrund der Unreife ihres Magen-Darmtraktes eine deutlich verzögerte Mekoniumausscheidung (= Kindspech= erste schwarze Stühle des Neu- und Frühgeborenen) im Vergleich zum reifen Neugeborenen. Die Mekoniumausscheidung spielt aber beim Nahrungsaufbau mit Muttermilch oder Flaschennahrung eine entscheidende Rolle: Die Verlegung von tieferen Darmabschnitten durch klebriges, zähes Mekonium führt häufig zum Rückstau zugeführter Nahrung im Magen, einem aufgeblähten Bauch und einer verlängerten Nahrungspassage. Der Nahrungsaufbau wird dadurch verzögert. Dadurch steigt die Infektionsgefahr, weil das Baby länger durch die Vene ernährt werden muss und dadurch venöse Zugänge (Venflons, Katheter) benötigt, die eine Eintrittspforte für Keime sein können. Das Baby ist länger „krank“ und der stationäre Aufenthalt des Kindes verlängert sich.

Die Osteopathie ist eine alternativmedizinische ganzheitliche Behandlungsmethode, die mit weitgehend manuellen (=mit den Händen durchführte) Methoden versucht, Beschwerden und Störungen zu behandeln und Gesundheit wiederherzustellen. In der Osteopathie gibt es den Bereich der „visceralen Osteopathie“. Dieser Teil der Osteopathie beschäftigt sich mit der Funktionsverbesserung von inneren Organen (z.B. Magen, Darm, Leber) im Sinne der Verbesserung von Mobilität (Beweglichkeit) und Motilität (Bewegung) sowie der Behandlung funktioneller Störungen (z.B. Verstopfung) beschäftigt. Die Anwendung dieser Methoden ist weitgehend schmerzfrei und zum gegenwärtigen Standpunkt der Wissenschaft auch frei von Nebenwirkungen.

Ziel der vorliegenden Studie ist es, den Einfluss visceraler osteopatischer Techniken auf die Mekoniumentleerung Frühgeborener zu untersuchen. Mit einem genau festgelegten Ablauf von Berührungen und Bewegungen des Arztes auf dem Brustkorb, der Bauchdecke und dem Kreuzbein des Kindes versucht der Arzt, den Darm des Babies anzuregen und eine normale Stuhlpassage in Gang zu setzten.

Der Zweck dieser klinischen Prüfung ist es zu untersuchen, ob osteopathische Techniken die Mekoniumentleerung beim Frühgeborenen beschleunigen und in weiterer Folge zu einem rascheren Nahrungsaufbau führen.

2. Wie läuft die klinische Studie ab?

Diese klinische Studie wird an der Neonatologie der Universitätsklinik für Kinder- und Jugendheilkunde der Medizinischen Universität Wien durchgeführt, und es werden insgesamt ungefähr 40 Personen daran teilnehmen.

Die Teilnahme Ihres Kindes an dieser klinischen Studie wird voraussichtlich 1 Woche dauern.

Folgende Maßnahmen werden ausschließlich aus Studiengründen durchgeführt:

Während dieser klinischen Studie werden in der ersten Lebenswoche 3 osteopathische Behandlungen an Ihrem Kind durchgeführt. Einmal in den ersten 48 Lebensstunden und danach noch 2 Mal bis zum 8. Lebenstag. Danach sollte das Mekonium ausgeschieden sein. Danach sind keine weiteren Besuche oder Kontrolluntersuchungen nötig- es werden lediglich noch Daten Ihres Kindes aufgezeichnet (Gewicht, Nahrungsmenge usw.)

3. Worin liegt der Nutzen einer Teilnahme an der Klinischen Studie?

Es ist möglich, dass Ihr Baby durch die Teilnahme an dieser klinischen Studie keinen direkten Nutzen für seine Gesundheit zieht. Es ist aber auch möglich, dass durch die osteopathische Behandlung die Magendarmpassage beschleunigt und Entleerung des ersten Stuhls gefördert wird. Dadurch kann ihr Baby möglicherweise rascher mit Muttermilch oder einer Frühgeborenennahrung ernährt werden. Eine Ernährung durch die Vene ist für einen kürzeren Zeitraum nötig.

4. Gibt es Risiken, Beschwerden und Begleiterscheinungen?

Zum gegenwärtigen Zeitpunkt sind keine Risiken oder Nebenwirkungen von viszeralen osteopathischen Behandlungen bekannt.

5. Zusätzliche Einnahme von Arzneimitteln?

Es müssen keine zusätzlichen Arzneimittel eingenommen werden.

6. Hat die Teilnahme an der klinischen Studie sonstige Auswirkungen auf die Lebensführung und welche Verpflichtungen ergeben sich daraus?

Die Teilnahme an der Studie hat keinerlei Auswirkungen auf die Behandlung Ihres Kindes-es ergeben sich aus einer Teilnahme auch keinerlei Verpflichtungen für Sie oder Ihr Baby.

7. Was ist zu tun beim Auftreten von Symptomen, Begleiterscheinungen und/oder Verletzungen?

Ihr Kind wird während der osteopathischen Behandlung intensivmedizinisch überwacht, das bedeutet, dass Atmung, Kreislauf und Körpertemperatur zu jedem Zeitpunkt aufgezeichnet werden. Sollten im Verlauf der klinischen Studie irgendwelche Symptome, Begleiterscheinungen oder Verletzungen auftreten, können diese aufgrund der Überwachung sofort registriert werden. Gegebenfalls wird die Behandlung unterbrochen oder abgebrochen.

8. Wann wird die klinische Studie vorzeitig beendet?

Sie können jederzeit auch ohne Angabe von Gründen, Ihre Teilnahmebereitschaft widerrufen und aus der klinischen Prüfung ausscheiden ohne dass dadurch irgendwelche Nachteile für die weitere medizinische Betreuung Ihres Kindes entstehen.

Ihr Prüfarzt wird Sie über alle neuen Erkenntnisse, die in Bezug auf diese klinische Prüfung bekannt werden, und für Sie wesentlich werden könnten, umgehend informieren. Auf dieser Basis können Sie dann Ihre Entscheidung zur weiteren Teilnahme an dieser klinischen Prüfung neu überdenken.

Es ist aber auch möglich, dass Ihr Prüfarzt entscheidet, Ihre Teilnahme an der klinischen Prüfung vorzeitig zu beenden, ohne vorher Ihr Einverständnis einzuholen. Die Gründe hierfür können sein:

a) Sie können den Erfordernissen der Klinischen Prüfung nicht entsprechen;

b) Ihr behandelnder Arzt hat den Eindruck, dass eine weitere Teilnahme an der klinischen Prüfung nicht in Ihrem Interesse ist.

9. In welcher Weise werden die im Rahmen dieser klinischen Studie gesammelten Daten verwendet?

Sofern gesetzlich nicht etwas anderes vorgesehen ist, haben nur die Prüfer und deren Mitarbeiter Zugang zu den vertraulichen Daten, in denen Sie namentlich genannt werden. Diese Personen unterliegen der Schweigepflicht.

Die Weitergabe der Daten erfolgt ausschließlich zu statistischen Zwecken und Sie werden ausnahmslos darin nicht namentlich genannt. Auch in etwaigen Veröffentlichungen der Daten dieser klinischen Studie werden Sie nicht namentlich genannt.

10. Entstehen für die Teilnehmer Kosten? Gibt es einen Kostenersatz oder eine Vergütung?

Durch Ihre Teilnahme an dieser klinischen Studie entstehen für Sie keine zusätzlichen Kosten.

11. Möglichkeit zur Diskussion weiterer Fragen

Für weitere Fragen im Zusammenhang mit dieser klinischen Studie stehen Ihnen Ihr Prüfarzt und seine Mitarbeiter gern zur Verfügung. Auch Fragen, die Ihre Rechte als Patient und Teilnehmer an dieser klinischen Studie betreffen, werden Ihnen gerne beantwortet.

Name der Kontaktperson: Doz. Dr. Nadja Haiden

Ständig erreichbar unter: +43 676 4155511

12. Sollten andere behandelnde Ärzte von der Teilnahme an der klinischen Studie informiert werden?

Alle behandelnden Ärzte des neonatologischen Teams sind von der klinischen Studie informiert.

13. Einwilligungserklärung

(Die Einwilligungserklärung muss INTEGRALER Bestandteil des Dokumentes sein!)

Name des Patienten in Druckbuchstaben: ....

Geb.Datum: .... Code: ....

Ich erkläre mich bereit, an der klinischen Studie „Einfluss viszeraler osteopathischer Behandlungen auf die Mekoniumentleerung bei sehr kleinen Frühgeborenen“ teilzunehmen.

Ich bin von Frau Doz. Dr. Haiden ausführlich und verständlich über die osteopathischen Behandlungen, mögliche Belastungen und Risiken, sowie über Wesen, Bedeutung und Tragweite der klinischen Studie, sich für mich daraus ergebenden Anforderungen aufgeklärt worden. Ich habe darüber hinaus den Text dieser Patientenaufklärung und Einwilligungserklärung, die insgesamt 6 Seiten umfasst gelesen. Aufgetretene Fragen wurden mir vom Prüfarzt verständlich und genügend beantwortet. Ich hatte ausreichend Zeit, mich zu entscheiden. Ich habe zur Zeit keine weiteren Fragen mehr.

Ich werde den ärztlichen Anordnungen, die für die Durchführung der klinischen Prüfung erforderlich sind, Folge leisten, behalte mir jedoch das Recht vor, die freiwillige Mitwirkung meines Kindes jederzeit zu beenden, ohne dass meinem Kind daraus Nachteile für die weitere medizinische Betreuung entstehen.

Ich bin zugleich damit einverstanden, dass meine im Rahmen dieser klinischen Studie ermittelten Daten aufgezeichnet werden. Um die Richtigkeit der Datenaufzeichnung zu überprüfen, dürfen Beauftragte des Auftraggebers und der zuständigen Behörden beim Prüfarzt Einblick in meine personenbezogenen Krankheitsdaten nehmen.

Beim Umgang mit den Daten werden die Bestimmungen des Datenschutzgesetzes beachtet.

Eine Kopie dieser Patienteninformation und Einwilligungserklärung habe ich erhalten. Das Original verbleibt beim Prüfarzt.

....

(Datum und Unterschrift des Patienten)

....

(Datum, Name und Unterschrift des verantwortlichen Arztes)

(Der Patient erhält eine unterschriebene Kopie der Patienteninformation und Einwilligungserklärung, das Original verbleibt im Studienordner des Prüfarzte

13. Data

ID	Gruppe	Geburts-datum	Gestations-tag	Sex	Geburtsmodus	unhemmbare Wehen	Gestose	Blasensprung	mütterl. AB
1	1	21.12.10	204	2	1	1	0	1	1
2	0	28.12.10	190	2	1	0	0	0	0
3	0	20.01.11	169	2	1	1	0	0	1
4	0	13.02.11	167	1	1	1	0	1	1
5	1	13.02.11	185	2	1	0	1	0	0
6	0	18.02.11	201	2	1	0	0	0	1
7	0	18.02.11	201	2	1	0	0	0	1
8	0	08.01.11	169	2	1	1	0	1	1
9	1	02.03.11	205	2	2	1	0	0	1
10	0	16.03.11	175	1	1	0	0	1	1
11	0	18.03.11	204	2	1	0	1	0	0
12	0	18.03.11	204	2	1	0	1	0	0
13	0	18.03.11	204	2	1	0	1	0	0
14	0	18.03.11	204	2	1	0	1	0	0
15	0	18.03.11	204	2	1	0	1	0	0
16	0	27.03.11	196	1	1	0	0	0	0
20	1	26.04.11	218	2	1	1	0	1	1
21	1	26.04.11	218	2	1	1	0	1	1
22	0	03.05.11	176	1	1	0	0	1	1
23	1	07.06.11	167	2	1	1	0	0	1
24	1	07.06.11	167	1	1	1	0	0	1
25	0	14.07.11	190	1	1	0	1	0	1
26	1	24.07.11	178	2	1	0	1	0	0
27	0	02.08.11	168	1	2	1	0	0	1
28	0	17.08.11	184	2	1	0	0	1	1
29	1	16.09.11	171	1	1	0	0	1	1
30	1	16.09.11	174	2	2	1	0	0	1
31	1	21.09.11	187	2	2	1	0	0	0
32	1	27.09.11	171	2	1	1	0	1	1
35	1	13.10.11	177	1	1	1	0	1	1
36	1	12.10.11	205	2	2	1	0	0	1
37	0	08.10.11	203	2	1	1	0	0	1
38	0	21.10.11	200	2	1	1	0	0	1
39	0	23.10.11	175	2	1	1	1	0	0
40	1	30.11.11	180	1	1	0	0	1	1
41	1	29.11.11	182	2	1	0	0	1	1
42	1	27.12.11	163	1	1	1	0	0	1
43	1	24.12.11	175	2	1	0	1	0	1
44	1	24.02.12	202	2	1	0	1	0	0
45	1	15.02.12	195	1	1	0	1	0	0
46	1	23.02.12	202	2					

ID	Lungenreifung	Geburts-gewicht	Geburts-länge	Geburts-KU	Apgar 1	Apgar 2	Apgar 3	NS-PH	Aufenthalt AKH Intensiv: E9C+10C
1	3	1376	40	27,5	6	8	9	7,3	21
2	1	790	35	24,5	7	8	9	7,34	32
3	1	605	32,5	21	7	8	8	7,41	40
4	3	503	32	21	6	8	9	7,27	80
5	1	460	28,5	22	4	7	8	7,09	89
6	1	1065	38	26	7	8	9	7,32	15
7	1	1140	40	26,5	8	8	8	7,32	15
8	1	630	32	22	5	7	8	7,31	40
9	1	1241	38,5	26,3	7	7	9	7,3	7
10	1	570	30,5	22,5	8	8	8	n.b.	80
11	1	1125	40	26,5	7	9	9	7,33	8
12	1	960	38	25,5	7	8	9	7,31	22
13	1	1130	38	27	8	8	9	7,28	22
14	1	1130	36	26,5	7	8	9	7,35	7
15	1	1130	36	26	8	9	9	7,21	6
16	1	986	37	24,5	8	9	9	7,36	13
20	3	1176	38	27,5	8	9	9	7,31	13
21	3	1400	40	28,5	8	9	9	7,33	13
22	3	690	33	22,5	7	9	9	7,31	56
23	3	616	32,5	23	8	9	9	7,35	58
24	3	722	34	24	8	9	9	7,33	87
25	3	603	38	23,4	8	9	9	7,12	64
26	1	422	27,5	20	8	9	9	7,38	137
27	1	650	33,5	22	6	8	9	7,38	58
28	3	642	31	23	5	7	8	7,25	34
29	1	593	31	21	6	8	9	7,11	61
30	1	605	29	21,5	7	9	9	7,34	229
31	3	730	34	24,5	5	7	8	7,38	71
32	1	603	33	21	8	8	9	n.b.	53
35	1	800	34	24	8	8	9	7,45	49
36	1	1320	40	27,5	8	9	9	7,35	19
37	3	1020	36,5	26	8	9	9	7,34	18
38	3	740	33,5	24,5	7	8	9	7,35	22
39	1	530	30,5	21,5	8	9	9	7,3	55
40	1	800	31	22,5	8	9	9	7,38	25
41	1	806	34	22,5	8	9	9	7,41	38
42	3	530	31	22,5	5	7	8	7,22	86
43	3	380	29	20,5	7	9	9	7,29	67
44	1	800	36	26	8	8	9	7,33	43
45	1	665	32	23	7	8	9	7,27	52
46		861	32	25,5	8	9	9	7,22	12

ID	AKH gesamt: E9+10+12+15	Transfer gesamt	Tod	Enteral ab LT.	Enteral 14 LT.	Voll enteral LT.	Enteral was	1. Mekonium
1	52	1	0	1		20	1	1
2	79	2	0	2	96	16	1	2
3	99	1	0	2	69	32	1	1
4	118	2	0	2		37	1	2
5	130	2	0	2		32	1	3
6	15	1	0	2	151	14	1	1
7	15	1	0	2	145	11	1	2
8	117	2	0	2	71	28	2	1
9	22	3	0	1		16	2	2
10	139	2	0	2	56	34	2	2
11	29	2	0	2	19	28	2	2
12	32	2	0	1	120	17	2	2
13	28	2	0	2	126	15	2	2
14	29	2	0	1	122	17	2	1
15	28	2	0	1	128	15	2	1
16	13	1	0	2			1	2
20	13	1	0	1	123	14	1	1
21	13	1	0	1	101		1	2
22	120	2	0	2	73	35	1	1
23	120	2	0	2	133	21	1	2
24	111	2	0	2	83	44	1	4
25	112	2	0	2	11	52	2	1
26	158	5	1	2	44	99	1	2
27	95	2	0	2	54	40	1	2
28	85	2	0	1	71	24	1	1
29	100	2	0	1	118	34	1	1
30	229	3	0	2	45		1	1
31	100	2	0	2	106	64	1	1
32	112	5	0	1		50	2	
35	69	1	0	1	114	51	2	2
36	57	3	0	9	128	40	2	4
37	55	2	0	6	158	14	1	7
38	54	3	0	2	95	28	1	2
39	77	3	0	3	66	43	2	3
40	99	1	0	2	113	30	1	1
41	37	2	0	2		34	1	2
42	149	4	0	2	93	68	1	3
43	140	4	0	2	41	44	2	5
44	50	2	0	2	4	44	2	3
45	115	1	0	2	46	47	1	4
46	56	1	0	2	97	17	1	4

ID	Mekonium bis	Anzahl der Behandlungen	Nebenwirkungen	Glycerinsupp	Spülungen	PDA	IVH	C-PAP	Beatmet	NEC
1	8	3	0	1	2	1	0	5	0	0
2	10	0		2	2	1	2	32	10	0
3	4	0		1	1	1	0	36	1	0
4	21	0		2	2	1	2	46	14	0
5	18	3	0	2	2	1	0	47	22	0
6	4	0		0	1	1	0	10	0	0
7	6	0		2	2	1	0	7	0	0
8	6	0		2	2	1	2	36	0	0
9	5	2	0	0	1	0	0	5	0	0
10	13	0		1	2	1	3	19	15	0
11	6	0		2	2	1	1	14	0	0
12	6	0		2	2	0	0	20	0	0
13	4	0		2	2	0	0	18	0	0
14	4	0		2	1	0	0	6	0	0
15	4	0		1	1	0	0	4	0	0
16	7	0		1	2	1	0	12	0	0
20	7	3	0	1	2	0	0	3	0	0
21	9	3	0	2	2	0	0	6	0	0
22	4	0		2	2	0	2	42	12	0
23	6	3	0	2	2	1	0	15	2	0
24	9	3	1	2	2	1	2	48	31	0
25	7	0		2	2	1	0	48	13	0
26	6	3	0	1	2	1	2	34	10	0
27	5	0		2	2	1	0	57	5	0
28	8	0		2	2	1	0	25	0	0
29	7	3	0	2	2	0	0	26	9	0
30	9	3	0	1	2	1	0	150	75	0
31	5	3	0	1	2	1	3	60	4	0
32		3	0	2	2	1	2	57	5	0
35	3	3	0	0	0	1	0	21	16	1
36	7	3	0	0	1	1	0	4	6	1
37	7	0		2	2	0	0	5	0	0
38	5	0		0	0	1	0	2	0	0
39	12	0		0	1	1	0	46	0	1
40	8	3	0	2	2	1	0	40	0	0
41	9	3	0	2	2	1	0	32	0	0
42	7	3	0	2	2	1	2	21	42	0
43	9	3	0	1	2	1	0	34	34	0
44	9	3	0	2	2	0	1	41	0	0
45	12	3	0	2	2	1	0	87	5	0
46	5	3	0	1	2		0	8	0	0

ID	Nec-stadium	NEC-LT	Transfergewicht	Entlassungsgewicht	Gewicht bei Tod
1				2630	
2				2100	
3				2646	
4				2060	
5				2556	
6			1210		
7			1260		
8				3374	
9			1365		
10				3944	
11			1670		
12			1650		
13			1618		
14			1624		
15			1734		
16			1156		
20			1438		
21			1542		
22				3193	
23				3255	
24				3490	
25				3511	
26					2451
27				5428	
28				2216	
29				4082	
30			5606	6225	
31				2520	
32				3694	
35	3	17		3054	
36	3	13		2550	
37				2374	
38			1574		
39	2	29	2224		
40				3310	
41				2996	
42				3696	
43				3660	
44				2076	
45				3500	
46				1948	