Aus der Klinik für Neonatologie
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DISSERTATION

Analgesic effect of acetaminophen in neonates: Systematic Review

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Introduction

Despite the fact that many analgesics and sedatives are available, pain management in neonates is still a problem because many drugs have not been studied in neonates or show side effects that cannot be risked in infants at such an early stage of life. Paracetamol also known as acetaminophen is a widely used analgesic and antipyretic and is one of the medicines most frequently sold over the counter. It has been studied in adults and older children but a generalization about the effectiveness as an analgesic and antipyretic in neonates is not appropriate because a change in the pharmacokinetics of paracetamol in neonates, infants and children has been observed.[1] Acetaminophens effectiveness or lack thereof as an analgesic in neonates and small infants has been the topic of several studies over the past 20 years and has attracted even more discussion lately. Still there is no clear evidence concerning the effectiveness in neonates when applied in different ways. Therefore the AIM of this assignment was to search for trials that match that exact topic. In this context each trial was evaluated and the ones that entered a power analysis were selected. Based on this a statement about the actual state of research can be made.

Methods

This dissertation is a systematic review. Trials were found through searches in Medline, EMBASE, Cochrane Central and Cochrane Database. Matching trials were identified through inclusion and exclusion criteria. They were reviewed and evaluated based on the Critical Appraisal Skills Programme from Guyatt et al. and scored using the Jadad scale.

Results

After the study selection process of identification, screening, and eligibility, 14 trials that matched the topic were found. Out if the 14 trials 6 were excluded for different reasons so that in the end, 8 published trials could be included in the systematic review calculations. From the 8 studies included in the power analysis only Nursing Child Assessment Feeding Scale (NCAFS) from the trial by Macke et al. resulted in a statistical power of ≥ 80%.

Conclusion

The results of the power calculations indicate that the null hypothesis regarding the pain reduction effect of acetaminophen in neonates is true. In other words the alternative hypothesis could not be supported by the power calculations made. Therefore, based on the statistical power calculations it can be said that the pain reduction effect of orally and rectally administered acetaminophen in neonates in the dosages administered in the trials, if there is any effect at all, is extremely small.

Abstrakt

Einleitung

Auch bei der Vielzahl heute verfügbarer Analgetika und Sedativa stellt die Schmerzbehandlung von Neugeborenen immer noch ein Problem dar, weil viele Medikamente an Neonaten noch nicht getestet wurden oder Nebenwirkungen zeigen, die man nicht riskieren will. Paracetamol, im angloamerikanischen Raum auch bekannt als Acetaminophen, ist ein weit verbreitetes Analgetikum und Antipyretikum und eines der meist benutzten freiverkäuflichen Medikamente. Es ist an Erwachsenen und älteren Kindern getestet, jedoch ist eine Verallgemeinerung bezüglich des analgetischen und antipyretischen Effektes bei Neugeborenen nicht möglich, da in Studien eine veränderte Pharmakokinetik bei Neugeborenen, Kleinkindern und Kindern beobachtet wurde.[1] Ob Paracetamol schmerztherapeutisch wirkt bei Neonaten und Kleinkindern war in den vergangenen 20 Jahren Thema vieler Studien und ist in den letzten Jahren verstärkt Diskussionsthema. Es gibt weiterhin keine klare Evidenz bezüglich der Effektivität bei Neugeborenen, wenn Paracetamol unterschiedlich appliziert wird. Daher war die Zielsetzung dieser Arbeit Studien zu finden, die sich genau mit diesem Thema beschäftigen. In Rahmen der Arbeit wurden die Studien einzeln bewertet um die herauszufiltern, welche in eine Teststärkenberechnung eingeschlossen werden konnten. Auf dieser Basis sollte eine Aussage über den aktuellen Forschungsstand gemacht werden.

Methodik

Diese Dissertation ist eine systematische Übersichtsarbeit. Die Studien wurden in Medline, EMBASE, Cochrane Central und Cochrane Database gesucht. Die passenden Arbeiten wurden durch erstellte Ein- und Ausschlusskriterien identifiziert und dann anhand des Critical Appraisal Skills Programmes von Guyatt et al. überprüft und basierend der Jadad Skala bewertet.

Ergebnisse

Nach Identifikation, Überprüfung und Bewertung der Studien wurden 14 zum Thema passende Studien gefunden. Von den 14 identifizierten Studien wurden 6 Arbeiten aufgrund unterschiedlicher Gründe exkludiert. Somit konnten am Ende 8 Studien in die Berechnung der Teststärke und Effektgröße mit dem G Power Programm inkludiert

werden. Von den 8 berücksichtigten Studien hat keine eine Teststärke von ≥ 80% erreicht.

Schlussfolgerung

Die Ergebnisse der Teststärkenberechnung weisen darauf hin, dass die Nullhypothese bezüglich der schmerzlindernden Wirkung bei Neugeborenen stimmt. D.h. die Alternativhypothese konnte durch die Teststärkenberechnung nicht unterstützt werden. Daher kann basierend auf den Ergebnissen die Aussage getroffen werden, dass der schmerzreduzierende Effekt von rektal bzw. oral verabreichtem Paracetamol bei Neonaten, wenn es überhaupt irgendeinen Effekt gibt, extrem gering ist.

List of Abbreviations

Ac	Acetaminophen
ASA	Acetylsalicylic acid (Aspirin)
BSPN	Bernese Pain Scale for Newborns
CASP	Critical Appraisal Skills Program
CHIPPS	Children and Infants Postoperative Pain Score
EDIN	Échelle Douleur Inconfort Nouveau-Né (neonatal pain and discomfort scale)
IASP	International Association for the Study of Pain
LNPS	Leuven Neonatal Pain Score
NCAFS	Nursing Child Assessment Feeding Scale
NFCS	Neonatal Facial Coding System
NICU	Neonatal intensive care unit
NIPS	Neonatal Infant Pain Scale
PIPP	Premature Infant Pain Profile
Plc	Placebo
RCT	Randomised controlled trial
WBFPRS	Wong Baker Faces Pain Rating Scale

1 Introduction

1.1 Pain in neonates and infants

An infant is a child who is in the earliest stage of extra uterine life, a time extending from the first month after birth to approximately 12 months of age. The term “infants” derives from the Latin word of in-fans, meaning “unable to speak.” In the first 4 weeks of life an infant is called a newborn. Since there is no exact definition for infancy, sometimes children are considered infants up to 23 months of age.

Pain management for this group of patients was for decades insufficient, not to say non-existent. Continuous research has shown that even without getting a clear verbal feedback from infants and neonates about their pain condition, there is clear neurophysiologic and clinical evidence that neonates and infants are capable of mature pain perception, even at relatively immature gestational ages.[2] Pain causes behavioural, physiologic, and biochemical changes in infants and neonates. Several studies have reported that repetitive procedural pain leads to a dampened behavioural response to pain.[3-6] Dolorous procedures that neonates experience during their early days of life can have impacts on their developing systems, for example, on the nervous, endocrine, and cardiac systems.[7-10] The apprehension that pain can also cause long-term effects such as behavioural and emotional changes or even learning disabilities has been discussed.[11] Therefore, there is a need of pain management in this vulnerable group of patients. Infants and neonates admitted to intensive care unit or elsewhere in the hospital routinely undergo procedures that can cause acute pain because a lot of the treatments at the neonatal intensive care unit (NICU) require invasive procedures. It has been reported that critically ill neonates in the NICU undergo up to 14 painful procedures a day.[12] Such procedures as venipuncture, heel prick, lumbar puncture, intubation, and nasogastric or orogastric tube insertion are often performed in the first days of a neonate’s life possibly causing procedural pain that can lead to changes in pain perception in a later life decade. Through research we are continuously being made aware of these repetitive painful procedures in neonates but pain assessment and therefore pain treatment is still not performed routinely a lot of times.[13] Recent progress in the area of neonatology has led to more critically ill newborns being

admitted to the NICU and therefore the need for pain research and management in this group of patients has increased.

1.2 Pain assessment in infants and neonates

Paediatric pain management has been difficult to standardise because very young children cannot or do not verbalize their pain. This fact makes it challenging to measure pain in this group of patients. There are multiple ways of assessing pain in neonates and infants and different ways have been shown to be useful in objectifying their pain. For example, changes in physiological parameter like heart rate, blood pressure, and oxygen saturation, behavioural reactions like crying, and changes in facial expressions and limb movement. All these various different measuring and observing options have led to the introduction of numerous pain scales and pain assessment charts. Given the diversity of scales now available, it is difficult to compare them and therefore pain measurement in infants and especially neonates is even harder to standardise today. There is no doubt about the importance of evaluating pain in infants and neonates. This group depends on caregivers to assess and manage it. Treatment can only be provided when pain is evaluated and this should be done routinely when invasive procedures are being performed in order to provide timely treatment. During the past decade, a wealth of literature has been published regarding the validity of various pain scales based on demonstrating changes in pain scores during potentially painful procedures. There are multiple scales and pain scores available for different age groups and in order to compare studies on pain treatment in neonates and infants, it is necessary to have an overview of commonly used pain measurement scales. Therefore, in the following section some examples of commonly used pain measurement scales in neonates and infants are reviewed.

1.2.1 **P**remature **I**nfant **P**ain **P**rofile **(PIPP)**

The PIPP is a behavioural measure of pain for premature and term infants. It was developed at the Universities of Toronto and McGill in Canada. There are four scoring directions that have to be followed in order to use this scale. First, the gestational age has to be scored before examining the infant. Second, the behavioural state has to be scored before the potentially painful event by observing the infant for 15 seconds. Third, the baseline heart rate and oxygen saturation has to be recorded, and fourth, the infant has to be observed for 30 seconds immediately following the painful event while scoring

the physiologic and facial changes that can be observed during this time. The score has to be recorded immediately following the intervention.

Table 1.1: Premature Infant Pain Profile (PIPP) [14]

Indicators		Points
Gestational age	≥ 36 weeks	0
	32 weeks to 35 weeks 6 days	1
	28 weeks to 31 weeks 6 days	2
	< 28 weeks	3
Behavioural state	Active/awake eyes open facial movements	0
	Quiet/awake eyes open no facial movements	1
	Active/sleep eyes closed facial movements	2
	Quiet/sleep eyes closed no facial movements	3
Heart rate maximum	0-4 beats per minute increase	0
	5-14 beats per minute increase	1
	15-24 beats per minute increase	2
	≥ 25 beats per minute increase	3
Oxygen saturation minimum	0 to 2.4% decrease	0
	2.5 to 4.9% decrease	1
	5.0 to 7.4% decrease	2
	7.5% decrease or more	3
Brow bulge	None (≤ 9% of time)	0
	Minimum (10-39% of time)	1
	Moderate (40-69% of time)	2
	Maximum (≥ 70% of time)	3
Eye squeeze	None (≤ 9% of time)	0
	Minimum (10-39% of time)	1
	Moderate (40-69% of time)	2
	Maximum (≥ 70% of time)	3
nasolabial furrow	None (≤ 9% of time)	0
	Minimum (10-39% of time)	1
	Moderate (40-69% of time)	2
	Maximum (≥ 70% of time)	3

The PIPP ranges from 0 up to 3 points in each of the 7 given indicators. The scores obtained for the 7 indicators have to be summed up for a total pain score and can then be interpreted. The minimum score that can be given is 0 points, showing no pain behaviour, while the maximum score is 21 points indicating the greatest pain behaviour possible.

1.2.2 **N**eonatal **I**nfant **P**ain **S**cale **(NIPS)**

The NIPS is a behavioural assessment tool, which was developed at the Children's Hospital of Eastern Ontario. It was designed for pain measurement of preterm and full term neonates and can be used to monitor a neonate before, during, and after painful procedures such as venipuncture.

Table 1.2: Neonatal Infant Pain Scale (NIPS) [15]

Parameters	Findings	Points
Facial expression	Relaxed	0
	Grimace	1
Cry	No cry	0
	Whimper	1
	Vigorous crying	2
Breathing patterns	Relaxed	0
	Change in breathing	1
Arms	Restrained	0
	Relaxed	0
	Flexed	1
	Extended	1
Legs	Restrained	0
	Relaxed	0
	Flexed	1
	Extended	1
State of arousal	Sleeping	0
	Awake	0
	Fussy	1

The NIPPS scores 0, 1, or a maximum of 2 points in each of the 6 parameters given. The points obtained for each parameter have to be summed up and the total score can then be interpreted. The minimum score is 0 points, indicating no pain, and the maximum is 7 points, representing the highest score possible and therefore the most pain.

1.2.3 **C**hildren´s and **I**nfants´ **P**ostoperative **P**ain **S**core **(CHIPPS)**

Büttner and Finke developed the CHIPPS by comparing and summarizing studies of behavioural observational tools. The CHIPPS includes five behavioural items that were

found to be consistently indicative of pain in newborns, infants, and young children in a series of studies.

Table 1.3: Children´s and Infants´ Postoperative Pain Score (CHIPPS) [16]

Item	Structure	Points
Crying	None	0
	Moaning	1
	Screaming	2
Facial expression	Relaxed/smiling	0
	Wry mouth	1
	Grimace (mouth and eyes)	2
Posture of trunk	Neutral	0
	Variable	1
	Rear up	2
Posture of leg	Neutral, released	0
	Kicking about	1
	Tightened	2
Motor restlessness	None	0
	Moderate	1
	Restless	2

The CHIPPS ranges from 0 to 2 points in each of the five given behavioural items. A maximum score of 10 points is a clear pain indicator while a minimum score of 0 represents a calm non-distressed newborn or infant.

1.2.4 **N**ursing **C**hild **A**ssessment **F**eeding **S**cale **(NCAFS)**

Doctor Barnard developed the NCAFS in the 1970s at the University of Washington´s School of Nursing. The scale is an observational method measuring the quality of the interaction between caregivers and infants during a feeding procedure. In order to rank the mother-infant feeding interaction, 76 behavioural items of both mother and infant are grouped into six subscales. Within those subscales, each of the behaviour items is scored to show either the presence or absence of pain. Four of these subscales refer to the caregiver and two to the infant. The four caregiver subscales include the sensitivity to cues, the response to the child's distress, the social-emotional growth fostering, and the cognitive growth fostering. The other two subscales refer to the child and include the clarity of cues and responsiveness to the caregiver. Within each subscale, the

scores can range from 0 points to the total number of items in each subscale. Zero indicates that none of the behaviours looked for were observed, while a high score shows that certain behaviour items were present in the interaction. The caregiver subscale scores add up to a maximum score of 50 and the child subscale scores combined can yield a total maximum score of 26.

Table 1.4: Nursing Child Assessment Feeding Scale (NCAFS) [17]

Caregiver subscales	**Points**
Sensitivity to cues	0-16
Response to the child's distress	0-11
Social-emotional growth-fostering	0-14
Cognitive growth fostering	0-9
Maximum points caregiver	50

Child subscales	**Points**
Clarity of cues	0-15
Responsiveness to caregiver	0-11
Maximum points child	26

Maximum points caregiver and child subscales combined	76

Points of the caregiver and child subscale have to be summed up at the end in order to score the maximum of 76 points that the NCAFS can possibly reach. A high score indicates the best possible responsiveness between the caregiver and the child while 0 points shows that there is no interaction.

1.2.5 **Postoperative Comfort Score**

This postoperative pain score evaluates ten criteria like sleep during preceding hour, facial expression of pain, consolability, sociability, sucking, spontaneous excitability, spontaneous motor activity, constant and excessive flexion of fingers, and toes and global evaluation of tone. The score was assessed and is now used in order to

demonstrate postoperative discomfort and pain in infants. Each rated criterion compromises defined behavioural descriptions and is scored with either 0,1, or 2 points.

Table 1.5: Postoperative Comfort Score [18]

Assessment		Points
Sleep during preceding hour	None	0
	Short naps: between 5 and 10 min	1
	Longer naps: ≥ 10 min	2
Facial expression of pain	Marked, constant	0
	Less marked, intermittent	1
	Calm, relaxed	2
Quality of cry	Screaming, painful, high pitched	0
	Modulated, i.e. can be distracted by normal sound	1
	No cry	2
Spontaneous motor activity	Thrashing around, incessant agitation	0
	Moderate agitation	1
	Normal	2
Spontaneous excitability responsiveness to ambient stimulation	Tremulous, clonic movement, spontaneous movement reflex	0
	Excessive reactivity (to any stimulation)	1
	Normal	2
Constant and excessive flexion of fingers and toes	Very pronounced, marked and constant	0
	Less marked, intermittent	1
	Absent	2
Sucking	Absent or disorganised suck	0
	Intermittent suck (3 or 4) and stops with crying	1
	Strong, rhythmic pacifying effect	2
Global evaluation of tone	Strong hypertonicity	0
	Moderate hypertonicity	1
	Normal for age	2
Consolability	None after 2 minutes	0
	Quiet after 1 minute of effort	1
	Calm before 1 minute of effort	2
Sociability, eye contact, and responsiveness to ambient stimulation	Absent	0
	Difficult to obtain	1
	Easy and prolonged	2

The score ranges from 0 to a maximum of 20 points. A high score is indicates a comfortable infant and the lower the score gets, the more uncomfortable the infant feels. Reaching a minimum score the infant is likely to be in severe pain, while a

maximum score in the postoperative phase shows no pain or more likely a sufficient pain treatment.

1.2.6 **W**ong **B**aker **F**aces **P**ain **R**ating **S**cale **(WBFPRS)**

Faces pain scales are common tools for self-report measurement of pain intensity in children.[19] One popular example is the WBFPRS that is made for children starting at the age of 3 years. They mostly cannot yet verbalise their pain but understand that they need to choose the face that best describes how they are feeling. The tool can be used in acute as well as procedural pain and is less abstract than numerical scales. Faces Scales are not commonly used in neonates, though there have been studies using modified Faces Scales to measure pain in neonates.[20]

Figure 1.1: Wong-Baker Faces Pain Rating Scale [21]

1.2.7 **N**eonatal **F**acial **C**oding **S**ystem **(NFCS)**

There are different anatomically based systems for assessing facial expressions in neonates and young infants. The NFCS was developed by Grunau and Craig and is an adaptation of the Facial Action Coding System (FACS) by Ekman and Friesen that describes discrete facial movements. The NFCS is designed especially for newborns and uses different facial activity in order to monitor their pain. It was developed specifically to code pain-related distress and includes facial expressions like brow lowering, eyes squeezed shut and mouth stretch.

Table 1.6: Neonatal Facial Coding System [22,23]

Facial action	Occurred	Did not occur
Brow lowering (lowering and drawing together of the brow can result in brow bulge)	1	0
Eyes squeezed shut	1	0
Deepening of the naso-labial furrow (fold)	1	0
Open lips (any separation of the lips is an occurrence)	1	0
Vertical mouth stretch	1	0
Horizontal mouth stretch	1	0
Taut tongue (cupping of the tongue)	1	0
Chin quiver (high frequency vibration of the chin and lower jaw)	1	0
Lip pursing (tightening the muscles around the lips to form an "oo")	1	0
In addition a tenth activity was monitored in preterm infants:		
Tongue protrusion (this is a "no pain" response in full term infants)	1	0

The Neonatal Facial Coding System comprises 10 facial actions, which can possibly occur in neonates when they are in pain. Each action can either be seen and is then scored with 1 point or not being seen and is hence scored with 0 points. Using this method, a maximum final score of 10 indicates that the neonate is in severe pain and a low count of 0 represents a relaxed neonate. A maximum score of 10 is only to be seen in premature neonates because the facial action “tongue protrusion” is just scored with 1 point in preterm neonates. Observing tongue protrusion in full term neonates is still coded with 0 points because this is a “no pain” response in them. Therefore in term neonates the highest score that can be observed is 9 points.

1.2.8 **COMFORT Behavior Scale**

The COMFORT Behavior Scale is based on the COMFORT Scale. Ambuel and colleagues originally designed the COMFORT scale in 1992 and it was back then designed to measure distress in ventilated children.[24] The COMFORT scale includes items like alertness, facial tension and muscle tone and is used to assess discomfort as well as changes in physiologic measurements, such as heart rate and blood pressure. Because the defined categories could also be considered as indicators of pain, it was later expanded to measure procedural and postoperative pain in infants.[25,26] The commonly used COMFORT Behavior Scale nowadays has been adjusted, for example, physiologic parameter have been excluded.

Table 1.7: Comfort Behavioral Scale [27]

Behavioral factors	Points
Alertness	
Deeply asleep (eyes closed, no response to changes in the environment)	1
Lightly asleep (eyes mostly closed, occasional responses)	2
Drowsy (child closes eyes frequently, less responsive to the environment)	3
Awake and alert (child responsive to the environment)	4
Awake and hyperalert (exaggerated responses to environmental stimuli)	5
Calmness–Agitation	
Calm (child appears serene and tranquil)	1
Slightly anxious (child shows slight anxiety)	2
Anxious (child appears agitated but remains in control)	3
Very anxious (child appears very agitated, just able to control	4
Panicky (child appears severely distressed, with loss of control)	5
Respiratory response (score only in mechanically ventilated children)	
No spontaneous respiration	1
Spontaneous and ventilator respiration	2
Restlessness or resistance to ventilator	3
Active breathing against ventilator or regular coughing	4
Fighting against ventilator	5
Crying (core only in children breathing spontaneously)	
Quiet breathing, no crying sounds	1
Occasional sobbing or moaning	2
Whining (monotone)	3
Crying	4
Screaming or shrieking	5
Physical movement	
No movement	1
Occasional (3 or fewer) slight movements	2
Frequent (more than 3) slight movements	3
Vigorous movements limited to extremities	4
Vigorous movements including torso and head	5
Muscle tone	
Muscles totally relaxed, no muscle tone	1
Reduced muscle tone, less resistance than normal	2
Normal muscle tone	3
Increased muscle tone and flexion of fingers and toes	4
Extreme muscle rigidity and flexion of fingers and toes	5
Facial tension	
Facial muscles totally relaxed	1
Normal facial tone	2
Tension evident in some facial muscles (not sustained)	3
Tension evident throughout facial muscles (sustained)	4
Facial muscles contorted and grimacing	5

The COMFORT Behavior Scale today compromises 6 categories each being scored with a minimum of 1 point, making 6 the lowest possible score. The highest score in each subscale is 5, which makes 30 the highest possible total count. A low score of 5 indicates no pain while a high count of 30 implies the greatest pain possible. The COMFORT Behavior Score can be used in combination with a Visual Analog Scale for pain (VAS for pain)[28] to set possible algorithms for post operative pain treatment.

1.3 Pain medications in Paediatrics

Pain is defined as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" by the International Association for the Study of Pain (IASP). The most commonly performed invasive procedures in neonates include heel lancing, venipuncture, intravenous or arterial cannulation, chest tube placement, tracheal intubation or suctioning, lumbar puncture, circumcision, and SC or IM injection.[29] Various drug classes for example opioid analgesics, sedative hypnotic drugs, injectable and topical local anaesthetics, nonsteroidal anti-inflammatory drugs and acetaminophen (paracetamol) are available for pain treatment. Non-steroidal anti-inflammatory drugs and acetaminophen are common analgesic drugs used in infants to reduce pain and fever. Even though a large number of analgesics and sedatives are currently available, most of them have not been studied sufficiently in neonates. The lack of data especially on pharmacodynamics of analgesics in neonates has created a perplexing situation in which there is a wide range of medications available for treating pain but pain management is still a problem in neonates and infants.

Opioids such as fentanyl and morphine are widely used in Paediatrics but neonates and infants have an increased risk of respiratory depression for example the in case of continuous morphine infusion because clearance is reduced. Besides that, morphine consumption has a large interindividual variability in infants, resulting in higher plasma concentrations than in older children given similar doses.[30,31] Another risk of continuous morphine consumption or even of the administration of high-dose opioids for a short period of time causes the neonatal abstinence syndrome (NAS). Different drugs can provoke this withdrawal syndrome. In the case of pain treatment, opioids can cause NAS either by prenatal consumption by the mother or postnatal use in neonates. Despite that, there is a danger of developing tolerance for certain opioids. This may

necessitate increased doses in order to maintain the same effect, which in turn may provoke reduced gastrointestinal motility and end up in severe complications like ileus. Apart from all the side effect risks, opioids are effective for the therapy of moderate to severe pain in patients of all ages including neonates. They seem to provide both analgesia and sedation and therefore opioids like morphine and fentanyl are popular in Paediatrics and often used in clinical settings.

NSAID and acetaminophen are extremely common in pain management in older children and adults. The treatment of neonates and small infants for pain control has been much discussed over the past years because of known potential side effects. NSAIDs have been used for many years to pharmacologically close the ductus arteriosus, and side effects like renal toxicity, gastrointestinal bleeding, and platelet dysfunction have been reported.[32,33] Based on this NSAID are not used frequently to provide neonatal analgesia.

Acetylsalicylic acid (ASA) is hardly used in the area of Paediatrics to avoid the risk of development of the Reye Syndrome. Reye syndrome is an extremely rare but serious illness that can affect the brain and liver, it occurs most commonly in children between the ages of 4 and 14 years recovering from a viral infection. Some studies have demonstrated an association between ASA taken for viral illnesses and the development of Reye's syndrome, whose incidence has dropped dramatically since the finding of a link between the illness and aspirin use in children.[34] Therefore ASA is less common in Paediatrics than acetaminophen.

1.3.1 **Acetaminophen in Paediatrics**

Paracetamol, also known as acetaminophen in North America, is chemically named N-acetyl-p-aminophenol. Acetaminophen as a drug agent was discovered about a century ago, but the exact mechanism was never finally determined and there still remain questions about the exact mechanism of action. It is a widely used over-the-counter analgesic and has replaced ASA as a widely used mild analgesic for children. Acetaminophen is known for its antipyretic and analgesic effect while being a poor antithrombotic and anti-inflammatory drug. Today we know that there is not only a COX inhibition mechanism[35] but acetaminophen also seems to influence the activity of endogenous cannabinoids and of serotonin and to effect the central nervous system.

Acetaminophen overdosing can induce lethal liver damage, which limits its use in patients with liver or kidney diseases but acetaminophen tends to show a lack of toxicity in neonates even when administered in overdoses.[36] This may be due to reduced oxidative enzyme activity. Acetaminophen half-life varies according to age and neonates have the longest half-life, which diminishes with age. This results in higher plasma concentrations and lower plasma clearance in neonates.[37-39] In Paediatrics it is also often used as an antipyretic because its antipyretic effect has been studied.[40] There is a meta-analysis from 2007 that shows that acetaminophen is a pain reliever for children but whether it also reduces pain in neonates seems to be questionable.[41] The discussion concerning the postoperative treatment of pain in neonates with acetaminophen developed because published studies showed that acetaminophen given to infants and neonates does not show a significant effect in terms of immediate postoperative pain reduction.[42]

With reference to pain treatment with acetaminophen, rectal doses administered in RCT vary between single doses of 20 mg/kg up to 60 mg/kg and repeating doses of acetaminophen that add up from 45 mg/kg to 100 mg/kg per day.[42,43,44,45] The use of acetaminophen to reduce pain during and after circumcision and heel prick has been the topic of several trials, just as the additional use of acetaminophen to reduce morphine consumption and lower the incidence of side effects.[42,43,44] Even with access to all requisite data, there is still no clear consensus in view of controversial study results and case reports on whether acetaminophen significantly reduces pain in neonates.[43,46-48] Acetaminophen can be given orally, rectally and through the intravenous route. For a long time it was prescribed primarily for use by the enteral route. Lately there have been recommendations about the use of intravenous acetaminophen.[38,49,50] There is no doubt that acetaminophen can efficiently treat pain in children but there is a lack of knowledge on pharmacodynamics in full- and pre-term neonates. Despite this lack of knowledge, there are national surveys showing that numerous neonatal units routinely use acetaminophen as an analgesic.[51]

1.3.2 **Non-pharmacological pain treatment in neonates**

Over the past decade, not only pharmacological pain treatment in neonates but also non-pharmacological remedies such as oral glucose [52] or sucrose, which has become more popular, have been discussed. Skin-to-skin care which includes kangaroo care in

preterm, swaddling, sensorial saturation, and breast-feeding during minor painful stimuli [53] has become part of research studies. For potentially greater pain, repetitive painful procedures or long lasting pain in neonates, for example after surgery, pharmacological pain treatment is absolutely necessary.

1.4 AIM of this study

The aim of this study is a systematic review on the analgesic effect of acetaminophen in neonates. Acetaminophen can be administered orally, rectally, or intravenous as the study intervention. It can be given in order to reduce acute, procedural, or postoperative pain, or lower the consumption of other pain medications. The goal is to select the trials that match the inclusion criteria and to collect data from all included trials concerning a measurable effect in pain reduction through acetaminophen. The number of participants out of each trail needs to be combined in order to increase the number of participants in the study group and in this way to enhance the evidence concerning the analgesic effect of acetaminophen in this special group of patients. First of all a general overview of all selected trials that match the topic, whether they end up being excluded or included at the very end, will be given. The selected trials will be analysed according to the "Critical Appraisal Skills Programme" published by Guyatt et al.[54,55] Furthermore, the quality of the trials will be methodologically assessed based on the Jadad Scale [56] in order to only include comprehensive studies in the final analysing process. The role of acetaminophen as a pain management drug in neonates and small infants has been a topic of discussion over years now and availability of data about pharmacokinetics of acetaminophen has been increasing.[38,50,57] The popularity of acetaminophen as a potentially mild pain treatment drug has grown but the analgesic potency in neonates has not been finally established and therefore needs to be reviewed, improved and as a result of this assignment possibly advanced. Even knowing the risk of side effects of analgesics, it is necessary to treat neonates and infants´ pain for example in the NICU, in cases of circumcision, which is often practiced in North America, in screening tests like heel prick pain, in cases of postoperative pain after surgeries like fixing inguinal hernias, and after birth if the neonate was hurt or injured during the birth process. Therefore, the aim of this dissertation is to collect and combine all data that is available up to this point in order to give an overview and be able to make a statement concerning the pain reducing effect of acetaminophen in neonates and infants up to two months of age. At the end of this dissertation, after collecting all data, the goal is to

summarise and systematically analyse the data gained in order to be able either to optimise possible pain treatment with acetaminophen in neonates in the future or point out the specific need for further research if the available data is not sufficient to give clear guidelines.

2 Methods

A systematic review attempts to collate all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question.[58] It identifies and evaluates the effectiveness of interventions, with the aim of assessing the consistency and generalisability of research findings.[59] Within a systematic review the processes of identification and appraisal of the reviewed literature needs to be methodical and reproducible. The methodology used in this dissertation is based on a synthesis of techniques according to the "Critical Appraisal Skills Programme" published by Guyatt et al.[54] and the JADAD score.[56] A systematic review contains mathematically reanalysed data from primary studies and is the basis for a meta-analysis and later on for clinical guidelines. Therefore, a meta-analysis depends on an appropriate identification and selection of primary research done in a systematic review assignment. The development of a systematic review can be broken down into several steps, which include the setting of specific research questions, the identification of the data, possibly the appraisal, and based on that, the formulation of evidence statements. Organisations such as the Cochrane Collaboration have helped enormously to advance systematic review methodology.

2.1 Key questions and outcome measures

The first step in writing a systematic review is to divide the subject area into a number of key questions.[58] The selection of a set of questions with specified and clinically relevant outcomes is fundamental to the success of the review.[58]

In this review changes in pain and behavioural scores, which mostly consist of different indicators, will be looked at. The questions selected for this review are:

- Can acetaminophen demonstrably reduce pain in neonates in potentially painful procedures?
- Can acetaminophen reduce the consumption of other analgesics when administered simultaneously, beforehand or afterwards in neonates?
- Is there a difference in pain score reduction when acetaminophen is administered through different routes in neonates?

- Is there a preferable way of administering acetaminophen for certain procedures in neonates?
- Does a greater reduction of pain scores in neonates depend on the dosing of acetaminophen?

The outcome measure chosen to answer the key questions of this review was reduction of pain indicators based on pain scores or physiological parameter such as heart rate, blood pressure and respiratory rate. Pain evaluation based on pain scores is not a clear clinical parameter such as oxygen saturation and therefore relatively hard to measure in general and especially in neonates.

2.2 Inclusion and exclusion criteria

Inclusion criteria for this review were:

- Trials in which acetaminophen was administered to neonates
- Changes in pain behaviour, pain scores, or physiological changes were an outcome criterion or acetaminophen was administered to reduce the amount of other analgesics
- Included studies had to be randomised

Exclusion criteria for this review were:

- Trials that included age groups older than neonates and data of neonates were not presented separately or available upon request to the author
- Trials with acetaminophen use in neonates that did not focus on pain as an outcome criterion
- Case reports and small case series
- Study group treatment diverted in more than the administration of acetaminophen and placebo

2.3 Evidence Identification

2.3.1 **Literature research**

In the context of this dissertation, a literature search in MEDLINE Literature Database through PubMed (1966- August of 2013) and Excerpta Medica Database “EMBASE” (1974- August of 2013) was performed. Furthermore, research in the Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials

through “The Cochrane Library No. 7 of 12 July, 2013” (1993- August of 2013) was performed in August 2013. There were no restrictions on the language. The literature research was designed to focus on the best available evidence. Each database was reviewed separately one after another in order to maximise coverage but animal studies were not considered. The searches included the following term combinations:

- Acetaminophen AND analgesia AND infants
- Acetaminophen AND pain AND infants
- Acetaminophen AND neonates
- Pain treatment AND neonates AND acetaminophen
- Pain treatment AND infant AND acetaminophen
- Pain AND neonate AND acetaminophen

Acetaminophen with following limits: randomised controlled trial,
newborn: birth to 1 month, infant: 1 to 23 months

2.3.2 **Selection of search output**

The literature search outputs from all databases were then assessed for eligibility depending on the inclusion and exclusion criteria. The citation lists were initially reviewed for irrelevant material and titles that were not applicable to answering key questions were discarded. The abstracts of the remaining papers were read and trials that focused on pain reduction through acetaminophen in older children or even adults were discarded as well. When studies that included neonates were identified, the authors were contacted and asked whether data on neonatal age group was available and whether it could be provided for this systematic review. Trials that did not investigate the pain reducing effect of acetaminophen but, for example, examined the antipyretic aspect were excluded as well. The search was designed to identify and select RCTs that match the topic, discarding case reports and small case series. Knowing that computerized searches have limitations depending on databases and search strategies, I supplemented the selection process of the trials by manual cross-referencing. In summary articles were acquired on completion of a sifting process, which is diagrammatically shown in figure 2. The remaining trials were then appraised for being part of the power calculation analysis.

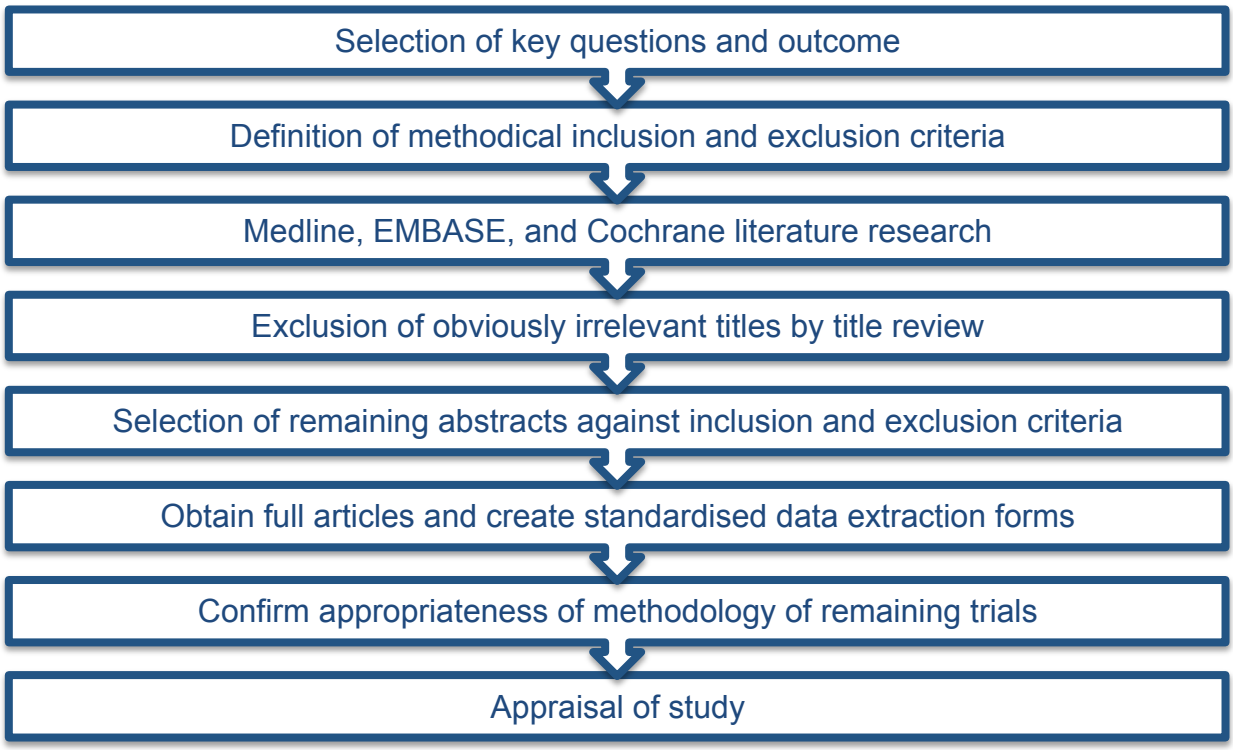


Figure 2.1: Trial Identification process

2.4 Data extraction form

A standardised form to assist and later, if necessary, review as part of the data extraction, was created for each trial obtained and confirmed.

Table 2.1: Sample of data extraction form

Author, year of publication	
Title	Full title of the paper
Journal	Name of the journal
Objectives	The study objective as stated by the authors
Study design	Type of trial
Pain measurement	How pain in the trial was assessed
Population	Age of the participants in the study
Intervention	Description of the intervention
Control	Description of the control group or alternative intervention
Outcome	Results of the intervention and how measured
Conclusion	Conclusion statement made by author
Comments	Details regarding the study outcome

First of all the author and the publishing year of each trial reviewed is listed, while the reference line includes the journal name, where the trial was published, and the title that was given by the author. The objective is presented as stated by the author. The study design was being identified in order to check the method that was chosen and document if the trial was randomised and placebo controlled or not. The population of the trial was closely looked at in order to ensure that only neonates were included in the review. Moreover, all articles were reviewed to establish the exact age of the participants. It was checked whether trials that also included older children had a separate appraisal for neonates and older infants. If so, the neonatal data was included. After that, the intervention performed in the trial was described in detail, i.e. it was documented whether acetaminophen was administered rectally or orally, in which dosage and how often during the observation period. The outcome measured as result of the intervention is also described. Since there are different measurement scales available to document pain in neonates and infants, the pain measurement that was used in each trial was documented and became part of the overview. All of those criteria were reviewed in the data extraction process to determine whether it would match the topic and criteria of the review being made. The last line of each form was reserved for documenting of comments or the effect regarding the study outcome that was observed and mentioned by the authors.

2.5 Appraisal of Evidence

After the selection of articles as potential sources of evidence, the methodological validity of each study was assessed one by one in order to decide which trial could be included and excluded based on validity.

2.5.1 **Critical Appraisal Skills Programme**

A systematic review depends critically on decisions relating to which studies are included and excluded, and on decisions relating to which data from these studies are presented and analysed. The trials were viewed according to the "Critical Appraisal Skills Programme" published by Guyatt et al.[54] Based on the users guide of that programme, questions 1.-9. were answered and all of the fully obtained trials were put in one table in order to have an overview in form of a chart. Questions were answered one by one by reviewing all trials closely.

Part A: Are the results of the trial valid?

1. Did the trial address a clearly focused issue?

Answering this question the issue was `focused` in terms of the population studied, the intervention given, and the outcomes considered.

2. Is the trial (RCT) an appropriate method to answer this issue?

Since trials are designed to test hypotheses, they are less efficient for investigating causes, generating new hypotheses or describing individual experience. The trial was judged to be an appropriate method if the researched question was addressed and if the study had an appropriate study design.

3. How were patients assigned to treatment groups?

Here the question was aimed at whether the allocation to intervention had been truly random or not.

4. Were participants, staff and study personnel "blind" to treatment?

It is not always possible to blind trials, but the question was, if every effort was made to ensure blinding. Efforts were made to rule out `observer bias` and 'Hawthorne effects`.

5. Were all of the participants who entered the trial properly accounted for at its conclusion?

This question was important because it is designed to identify bias caused by incomplete follow-up and inappropriate analysis. It was considered that all the participants needed to be analysed in the group they were assigned to.

***6.* Aside from the experimental intervention, were the groups treated in the same way?**

This question targeted on checking whether the groups were reviewed at the same time intervals and whether they received the same attention from researchers and health workers. This was important because any difference may introduce performance bias.

7. Did the study have enough participants to minimise the play of chance?

In this case the trials were checked for power calculation. This was done to estimate how many patients were needed to be reasonably sure of finding something important.

Part B: What are the results?

8. How are the results presented? What is the main result?

Here the purpose of the question was to find out if the results were presented as a proportion of people experiencing and outcome, for example a risk. They can also be presented as a measurement or a survival curve.

9. How precise are these results?

This question was aimed at whether the results are precise enough in order to make a decision on the treatment effect.

In part A, questions No. 1 and 2, as well as No. 5 to 7 were answered with Yes, 'not precise', or 'No', while question No. 3 was answered with either 'at random', 'systematic', 'other method', or 'not precise'. For question No. 4, the programme wants to sort out whether the trial was 'double blinded', 'single blinded', 'unblinded' or whether it is 'not precise'. In part B, (questions No. 8 and 9) of the programme, the author wants the researcher to further assess the results presented in the trial and investigate the mean of those results for patients and whether the results are precise enough to make a decision on further use with the treatment that was investigated.

2.5.2 JADAD Scale

The Jadad Scale [56], also named Jadad Assessment tool, Jadad scoring, or the Oxford quality scoring system is a scale which was developed through a standardised item reduction process in 1996 by Alejandro R. Jadad Bechara who is a Colombian physician and who at that time worked as a Research Fellow at the University of Oxford. The tool consists of a 3-item scale including randomisation, blinding, and description of withdrawals and dropouts. The total score is 5 and a score of 3 or more is an indicator of high quality. The reason why this tool was chosen is because it is not only easy to use but it contains many of the important elements that have empirically been shown to correlate with bias. Other than that, it has known reliability and external validity and it has been validated for evaluation of pain in drug trials.

The scoring of the JADAD scale comprimises the following questions:

Randomisation:

1a)	Was the study described as randomised (this includes the use of words such as randomly, random, and randomisation)?	+ 1
1b)	Was the method of randomisation described and appropriate to conceal allocation?	+ 1
1c)	If described and inappropriate, describe:	- 1

Blinding:

2a)	Was the study described as double blinded?	+ 1
2b)	Was the method of double blinding described and appropriate to maintain a double blinding?	+ 1
2c)	Was the method of blinding inappropriate?	- 1

Description of withdrawals and dropouts:

3)	Was there a description of withdrawals and dropouts?	+ 1

Each question gives a score of 1 point or 0 points. The authors cannot give an in between mark. This way questions 1a) and 1b) as well as 2a), 2b), and 3) require a scoring of either +1 or 0. If the question is answered with a 'Yes', the score is 1 point. If replied with 'No', the score is 0. To complete the scoring, the last two questions 1c) and 2c) were answered and only if confirmed with a 'Yes' reply one point was deducted.

2.6 G Power calculator

As the final step of this thesis, power analyses with the G*Power calculator version 3.1 were performed. This calculator is a statistical power analysis program. It can perform different statistical tests of the F, t, chi-square, and z test families. G*Power 3 provides an effect size calculator and offers different types of power analysis. Therefore it was used to identify the effect size and the sample size based on an 80% power for each trial that was included in the calculation process. The goal was to identify even the smallest pain reducing effect that could possibly be observed in the given data. Therefore, the data that presented the greatest changes in terms of pain scores or pain behaviour changes was used for the calculations.

3 Results

3.1 Study selection

The total number of search hits in Medline, EMBASE, Cochrane Central and Cochrane Database is shown in the following Table 3.1 with each term combination considered separately, there were 1650 hits that were reviewed by title.

Table 3.1: Number of hits from different search result term combinations

Term combinations	Medline	Embase	Cochrane Central	Cochrane Database	Hits in all databases
Acetaminophen AND analgesia AND infants	145	56	59	0	260
Acetaminophen AND pain AND infants	272	75	86	2	435
Acetaminophen AND neonates	345	78	6	2	431
Pain treatment AND neonates AND acetaminophen	95	2	2	2	101
Pain treatment AND infant AND acetaminophen	261	7	25	2	295
Pain AND neonate AND acetaminophen	100	20	6	2	128
Total hits in database	**1218**	**238**	**184**	**10**	**1650**

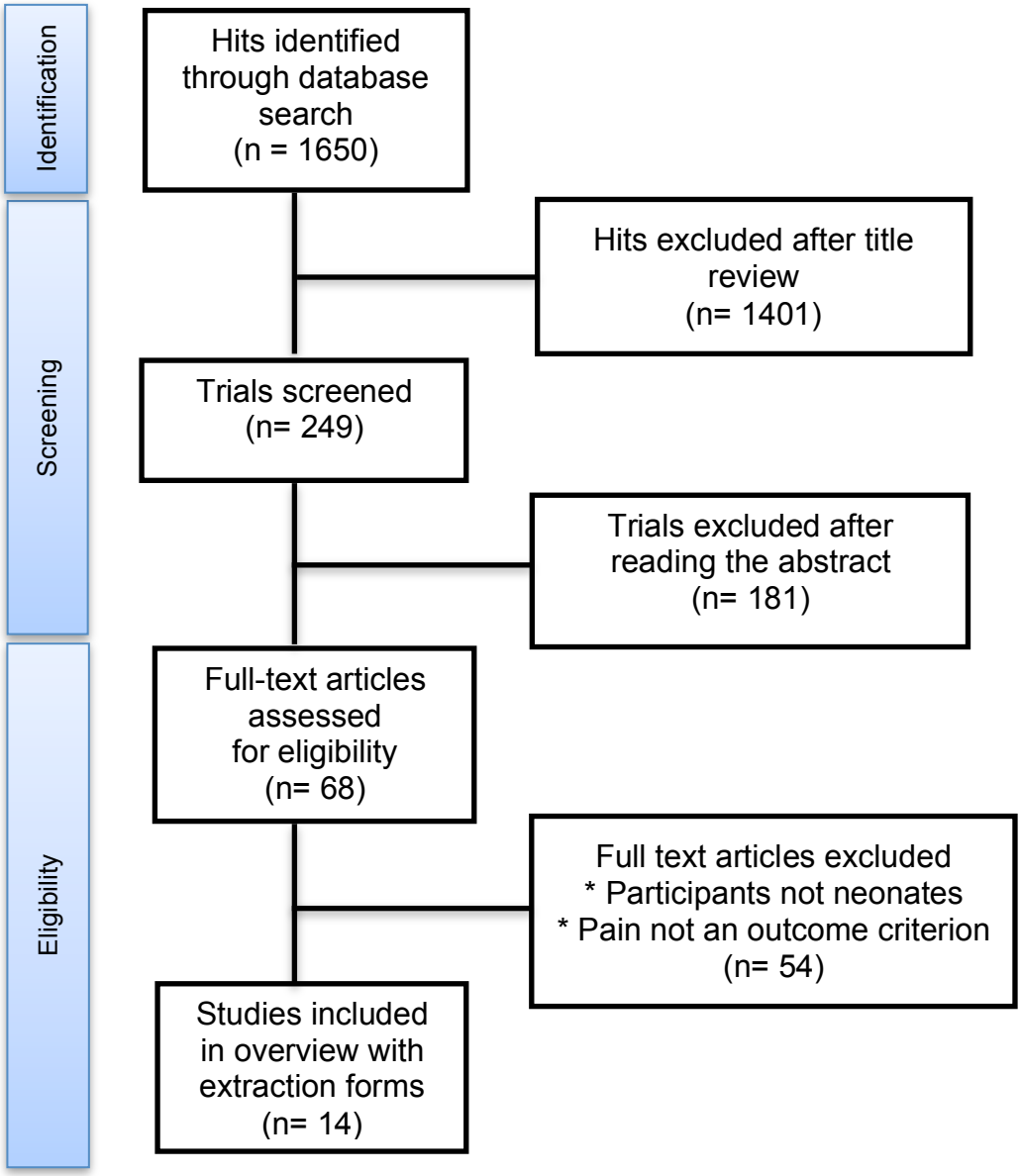
After the excluding of obviously irrelevant trials by title review and discarding papers that were found twice only 249 hits remained. Obviously irrelevant and therefore excluded in this early stage were, for example, trials that included only adults or older children. Papers that did not focus on pain treatment but, for example, on fever treatment with acetaminophen, or that did not use acetaminophen as an intervention drug, were excluded.

The 249 trials that remained were looked at closer by reading all of the abstracts. Within that step of the study selection process a further 181 papers could be excluded and 68 trials ended up being read completely including studying the exact data that was provided in each trial. At this stage trials like for example the study by Ipp et al.[60] from 1987 were excluded. This study team used acetaminophen as an intervention drug in young infants starting at 2 months, but here the study focused on reduction of fever incidence and local and systemic reactions and could therefore not be included. After discarding the studies that, after close investigation, only included older children and in which the effect of acetaminophen was aimed at its pharmacokinetics, not at pain as a main study focus, 14 trials matched. Those trials were chosen to answer the key questions and this way focus on the topic of the review and the specific age group of neonates. Authors of trials that seemed to include neonates in their calculations were contacted and asked whether the data on the neonatal age group could be provided and this way be included in the review calculations.

3.2 Overview of analysed trials

The following flow chart (Figure 3.1) was developed in order to give an overview of the study selection process. It shows the procedure on how the 14 studies were identified out of originally 1650 hits in all databases searched. Fourteen trials that remained after the study selection were identified as potentially examining the treatment of pain in neonates through administration of acetaminophen and this way entering the review calculations. The full texts of those trials were now studied closely in order to capture the exact study details and identify trials and data that focused on the special age group of neonates. Furthermore, the trials needed to be aimed at studying the reduction of acute or procedural pain or at lowering the amount of other analgesics through acetaminophen. To get an overview of those 14 trials, data extraction forms were produced step by step for each trial to give an overview of important study details.

Figure 3.1: Flow chart of the initial study selection process



3.2.1 **Study by Howard et al. 1994**

The paper by Howard et al.[42] studied the pain reduction effect in full-term neonates of 15 mg/kg rectally administered acetaminophen given every 6 hours starting 2 hours before circumcision until 24 hours post intervention. The procedure performed was neonatal Gomco circumcision in all participants. Pain was measured through intraoperative monitoring and assessing of the Postoperative Comfort Score. The study led to the conclusion that the dosage of acetaminophen given did not result in intraoperative or immediate postoperative pain reduction.

Table 3.2: Data extraction form from the study by Howard et al.[42]

Title	Acetaminophen Analgesia in Neonatal Circumcision: The Effect on Pain
Journal	Pediatrics
Objectives	Documenting changes in heart rate, crying rate, respiratory rate, comfort scale showing pain and stress
Study design	Prospective, randomised, double-blind, placebo- controlled, clinical trial
Pain measurement	Intraoperative monitoring of heart rate, respiratory rate, and crying time; after invasive procedure Postoperative Comfort Scores were measured
Population	23 healthy full term neonates
Control group	21 healthy full term neonates
Intervention	Starting 2 hours before Gomco circumcision neonates received either acetaminophen oral or placebo (15 mg/kg) every 6 hours for 24 hours
Outcome	No significant difference in changes of heart rate, crying rate, comfort scale, and respiratory rate between the groups
Conclusion	No intraoperative or immediate postoperative pain reduction in acetaminophen group
Comment by author	Starting at 360 minutes after circumcision comfort scores improved more in the acetaminophen group

3.2.2 **Study by Shah et al. 1998**

Shah et al.[44] assessed the potential of acetaminophen to decrease pain from heel prick. Pain was documented by videotaping neonates during the procedure and then evaluating the time spent crying and the facial expression during heel prick afterwards. In this trial acetaminophen was administered orally 60-90 minutes before the intervention in a dose of 20 mg/kg. The study group stated, that acetaminophen was ineffective for decreasing pain from heel prick in neonates. Furthermore no postoperative effect was noted.

Table 3.3: Data extraction form from the study by Shah et al.[44]

Title	Randomised controlled trial of paracetamol for heel prick pain in neonates
Journal	Archives of Disease in Childhood - Fetal and Neonatal Edition
Objectives	Decreasing pain from heel prick
Study design	Prospective, randomised, double blind, placebo-controlled trial
Pain measurement	Cry time and facial actions were observed from videotapes that were taken during heel prick procedure
Population	38 neonates in group 1
Control group	37 neonates in group 2
Intervention	Oral paracetamol cherry elixir or an equal volume placebo given 60-90 minutes before heel prick (20 mg/kg)
Outcome	No analgesic effect could be demonstrated
Conclusion	Paracetamol is ineffective for decreasing pain from heel prick in neonates
Comment	No postoperative effect measured

3.2.3 **Study by Korpela et al. 1999**

The paper by Korpela et al.[61] tested the sparing effect of morphine in paediatric day surgeries by giving 20, 40, or 60 mg/kg rectal acetaminophen after general anaesthesia was induced. The procedures performed were different types of paediatric day surgeries such as herniorrhaphy, orchidopexy, hydrocoelectomy, adenoidectomy, or excision of subcutaneous tumour. The study presented a morphine-sparing effect in the study groups that received either 40 mg/kg or 60 mg/kg acetaminophen, but the trial did not include neonates and could therefore not be included. The age group studied were children starting at the age of one year.

Table 3.4: Data extraction form from the study by Korpela et al.[61]

Title	Morphine-sparing Effect of Acetaminophen in Paediatric Day-case Surgery
Journal	Anesthesiology
Objectives	Morphine-sparing effect of acetaminophen
Study design	Randomised, double blind, placebo-controlled study
Pain measurement	Postoperative pain measurement every 10 min after arrival at the post anaesthesia care unit using a 0-100 visual analog scale
Population	42 boys and 78 girls from 1-7 years of age randomised in 3 groups (20, 40, or 60 mg/kg of rectal acetaminophen)
Control group	30 children aged 1-7 years
Intervention	Administration of a single dose of 0, 20, 40, or 60 mg/kg of rectal acetaminophen after general anaesthesia with sevoflurane
Outcome	Lower post anaesthesia care unit pain scores in the 40 mg/kg and 60 mg/kg groups; dose related reduction of morphine
Conclusion	Single dose of 40 or 60 mg/kg of rectal acetaminophen has a clear morphine-sparing effect
Comment	Incidence of pain reduction

3.2.4 **Study by Taddio et al. 2000**

The trial by Taddio et al.[62] was performed in order to measure the efficiency of a combination of interventions on the pain response of infants undergoing circumcision. One group in this trial received combined analgesia including 40 mg of oral acetaminophen 45 minutes before the circumcision appointment while the other group was treated with topical anaesthesia. Pain was rated by evaluation of facial activity scores of videotapes that were taken during the procedure. Within the study by Taddio et al.[62], the two groups were treated with different circumcision techniques and therefore the actual potential of acetaminophen itself is hard to evaluate. The trial showed that the group that was treated with the Mogen clamp technique and combined

analgesia including acetaminophen showed a less pronounced pain response. This intervention group received a dorsal penile block as well, so the pain reduction effect of acetaminophen itself remains unclear in this trial.

Table 3.5: Data extraction form from the study by Taddio et al.[62]

Title	Combined Analgesia and Local Anaesthesia to Minimize Pain During Circumcision
Journal	Archives of Pediatrics and Adolescent Medicine
Objective	Pain reduction during circumcision
Study design	Cohort study
Pain measurement	Videotaping during circumcision; then evaluation of facial activity scores (NFCS)
Population	57 infants (group 1)
Control group	29 infants in (group 2)
Intervention	Group 1 circumcised using Mogen clamp and combined analgesics (lidocaine dorsal penile nerve block, lidocaine-prilocaine, acetaminophen [0.5 mL of 80-mg/ml acetaminophen administered orally 45 minutes before the clinic appointment by parents], and sugar-coated gauze dipped in grape juice); group 2 circumcised using the Gomco clamp and lidocaine-prilocaine
Outcome	Group 1 with Mogen clamp and combined analgesic had less pain than group 2 with Gomco clamp and lidocaine-prilocaine
Conclusion	Mogen clamp and combined analgesia is safe and minimizes pain from circumcision
Comment	Less pain with penile block which was part of combined analgesia in group 1

3.2.5 **Study by Macke et al. 2001**

Macke et al.[63] focused on the effect on newborn behaviours and mother-infant feeding interaction after circumcision when 10 mg/kg acetaminophen was administered one hour before the procedure. During circumcision the monitoring of heart rate and crying documented neonatal pain distress. There was no significant difference noted between the study and the control group regarding pain distress, but based on the NCAFS the neonates that received acetaminophen demonstrated a smaller decrease in cue clarity and responsiveness.

Table 3.6: Data extraction form from the study by Macke et al.[63]

Title	Analgesia for Circumcision: Effects on Newborn Behavior and Mother/Infant Interaction
Journal	Journal of Obstetric, Gynecologic, & Neonatal Nursing
Objectives	Reduction of pain distress; decrease of behavioural changes during mother-infant feeding interaction after circumcision
Study design	Randomised, double blind, placebo-controlled trial
Pain measurement	Observation of newborn behaviours during feeding interaction; pain distress assessment during and after circumcision
Population	29 full term newborns; uncomplicated pregnancies; vaginal deliveries
Control group	31 full term newborns; uncomplicated pregnancies; vaginal deliveries
Intervention	Administration of 10 mg/kg acetaminophen 1 hour before circumcision
Outcome	Increase in heart rate and crying rate in both groups, no significant differences between groups
Conclusion	No effect in controlling pain during intraoperative period
Comment	Positive effect on post circumcision mother-infant feeding interactions

3.2.6 **Study by Van Lingen et al. 2001**

A rectal dose of 20 mg/kg acetaminophen was used in the study by Van Lingen et al.[20] in neonates within an hour after delivery by vacuum extraction. Neonatal pain was rated with a modified faces scale. Acetaminophen was administered again at 6, 12, and 18 hours after delivery and pain was assessed an hour after administration. The authors stated that acetaminophen, given as a rectal dose after vacuum extraction, does not make a significant difference between study and placebo group when comparing objective pain scores.

Table 3.7: Data extraction form from the study by Van Lingen et al.[20]

Title	Effects of rectally administered paracetamol of infants delivered by vacuum extraction
Journal	European Journal of OBSTETRICS &GYNECOLOGY and Reproductive Biology
Objectives	Documenting changes in pain scores and clinical conditions
Study design	Prospective, randomised, double-blind, placebo-controlled study
Pain measurement	Modified facies scale
Population	61 newborns delivered by vacuum extraction
Control group	61 newborns delivered by vacuum extraction
Intervention	Single rectal dose of 20 mg/kg acetaminophen within 1h after delivery and at 6, 12, and 18 hours after first dosage
Outcome	Improvement of clinical conditions, but no changes in objective pain scores
Conclusion	Acetaminophen given after vacuum extraction does not show improvement in pain scores
Comment	Improvement of clinical condition after first dose of ac noticed by nurses

3.2.7 **Study by Bremerich et al. 2001**

Another trial by Bremerich et al.[45] used 10, 20, or 40 mg/kg of rectally administered acetaminophen in order to possibly reduce postoperative opioid requirements after cleft palate repair. Postoperative pain was measured with the CHIPPS. The data collected, as stated by the author, did not show significant changes in terms of postoperative opioid requirements between the acetaminophen and the placebo group. To conclude, rectal acetaminophen up to 40 mg/kg did not result in an opioid-sparing effect in infants after cleft palate repair in the study by Bremerich et al.

Table 3.8: Data extraction form from the study by Bremerich et al.[45]

Title	Prophylactically-Administered Rectal Acetaminophen Does Not Reduce Postoperative Opioid Requirements in Infants and Children Undergoing Elective Cleft Palate Repair
Journal	Anesthesia and Analgesia
Objectives	Postoperative opioid reduction
Study design	Double blind, prospective, randomised study
Pain measurement	Standard monitoring; *CHIPPS*
Population	60 infants randomised in 3 groups (10, 20, or 40 mg/kg) starting at the age of 3 months
Control group	20 infants
Intervention	After anaesthesia single rectal dose of acetaminophen (10, 20, or 40 mg/kg) or placebo
Outcome	No reduction in postoperative opioid dose for pain management
Conclusion	Rectally administered acetaminophen doses up to 40 mg/kg do not help to reduce postoperative opioid doses
Comments	None

3.2.8 **Study by Malnory et al. 2003**

The following table shows data extracted from the trial by Malnory et al.[64] studying behavioural and physiological responses to circumcision in newborns. In this study a single oral solution of 40 mg acetaminophen preoperatively was given. It remains unclear how long before surgery the acetaminophen solution was given. Monitoring the NIPS score did pain assessment. This non-randomised, non-blinded study resulted in getting lower postoperative NIPS scores in the analgesic group, which could be due to the lack of blinding. On the other hand, the NIPS scores did not differ in the pre- and intraoperative phase of the procedure.

Table 3.9: Data extraction form from the study by Malnory et al.[64]

Title	Newborn Behavioural and Physiological Responses to Circumcision
Journal	The American Journal of Maternal/Child Nursing
Objectives	Changes in newborns' behavioural response during circumcision
Study design	Non-randomised study
Pain measurement	(pre-, intra-, postoperatively)
Population	26 male newborns
Control group	27 male newborns
Intervention	Single dose of 40 mg acetaminophen oral solution preoperatively
Outcome	No remarkable differences in NIPS scores in either group during the preoperative or intraoperative time period
Conclusion	Preoperative use of acetaminophen could be helpful in reducing pain after circumcision
Comments	Lower NIPS score 15 minutes after circumcision

3.2.9 **Study by Van der Marel et al. 2007**

The next data extraction form shows the key data of a trial by Van der Marel [43] and colleagues. The study was designed in order to measure morphine consumption after major surgery when rectal acetaminophen was administered in doses of 30-40 mg/kg after the induction of anaesthesia followed by maintenance doses of 20 mg kg 6 hourly or 30 mg kg 8 hourly. In this case pain was evaluated using COMFORT and VAS scores. The study group came to the conclusion that there was no additional effect of the administered acetaminophen in terms of lowering the need of morphine for postoperative analgesia.

Table 3.10: Data extraction form from the study by Van der Marel et al.[43]

Title	Rectal acetaminophen does not reduce morphine consumption after major surgery in young infants
Journal	British Journal of Anaesthesia
Objectives	Reduction of morphine consumption during postoperative period
Study design	Randomised, placebo-controlled trial
Pain measurement	COMFORT and VAS scores
Population	29 infants (0-10 month of age)
Control group	25 infants (0-9 month of age)
Intervention	Total amount of 90-100 mg/kg acetaminophen rectally or placebo
Outcome	No difference in total morphine consumption between groups
Conclusion	No additional analgesic effect of rectally given acetaminophen
Comment	None

3.2.10 **Study by Bonetto et al. 2008**

The following table shows the key data of a study by Bonetto et al.[65] who tested Emla creme, oral glucose, and 20 mg/kg acetaminophen in neonates in order to reduce pain from heel prick. Fifty-seven neonates were divided into 3 groups and each group of neonates received either Emla cream, glucose orally, or 60 minutes before intervention acetaminophen. NIPS and PIPP scores rated pain in neonates. The study results led to the conclusion that there was no pain relieving effect of acetaminophen based on the reduction of the objective pain scores used.

Table 3.11: Data extraction form from the study by Bonetto et al.[65]

Title	Pain prevention in term neonates: randomised trial for three methods
Journal	Archivos argentinos de pediatria
Objectives	Reduction of pain caused by heel prick in newborns
Study design	Prospective, randomised, double- blind, placebo- controlled study
Pain measurement	Pain was measured by two independent observers, using two scales (NIPS and PIPP)
Population	57 healthy newborns at term randomised in 3 groups
Control group	19 healthy newborns at term
Intervention	Glucose orally, EMLA cream on the heel, or 20 mg/kg acetaminophen orally 60 minutes before intervention
Outcome	No significant differences in PIPP score between groups, NIPS score favours glucose
Conclusion	Administration of paracetamol or EMLA did not reduce pain caused by heel prick
Comment	Pain reduction in oral glucose group

3.2.11 **Study by Badiee et al. 2009**

The data extraction form made for the study by Badiee et al.[66] gives an overview of the trial which was designed to study pain relief from heel prick in premature infants. In this case, the study group chose to orally administer 40 mg/kg acetaminophen 90 minutes before the intervention was performed. Pain was in this case evaluated by documenting PIPP, duration of crying, decreases in SpO_2, and increases in heart rate. The analysis of the trial did not show a statistical difference in any of the monitored measured parameters. Therefore, the authors came to the conclusion that 40 mg/kg single dose acetaminophen given orally is ineffective to decrease pain from heel prick in premature infants.

Table 3.12: Data extraction form from the study by Badiee et al.[66]

Title	Effects of high dose orally administered paracetamol for heel prick pain in premature infants
Journal	Saudi medical journal
Objectives	Pain relief from heel prick
Study design	Prospective, randomised, double-blind, placebo-controlled study
Pain measurement	PIPP, duration of crying, decreases of SpO_2, increases of heart rate
Population	36 newborns
Control group	36 newborns
Intervention	40 mg/kg orally administered acetaminophen 90 minutes before heel prick
Outcome	No statistical difference in PIPP, duration of crying, decreases of SpO_2, increases of heart rate between groups
Conclusion	No adequate analgesia for heel prick through single dose oral acetaminophen (40 mg/kg)
Comments	None

3.2.12 **Study by Allegaert et al. 2013**

Allegaert et al.[67] examined for the acetaminophen concentration-effect relation in neonates. The paper was based on data collection from another so called PARANEO study and included 19 term or preterm neonates who received 20 mg/kg intravenous acetaminophen as a loading dose followed by 5-10 mg/kg acetaminophen intravenous administration every 6 hours. Pain was measured through the Leuven Neonatal Pain Score. The authors' described lower pain scores within 30 minutes of administration and concluded intravenous acetaminophen to be effective for moderate pain.

Table 3.13: Data extraction form from the study by Allegaert et al.[67]

Title	The paracetamol concentration-effect relation in neonates
Journal	Pediatric Anesthesia
Objectives	Documentation of pharmacokinetics and pharmacodynamics of intravenous paracetamol in neonates for mild to moderate pain of different origins
Study design	Data collection from prospective open label PARANEO study
Pain measurement	Pain scores (Leuven Neonatal Pain Score)
Population	19 term or preterm neonates (data extraction from PARANEO study)
Control group	None
Intervention	Intravenous paracetamol loading dose of 20 mg/kg followed by postmenstrual age-dependent maintenance dose of 5-10 mg/kg every 6h
Outcome	Lower pain scores within 30 min after administration, with a slight increase in pain scores from 5 to 6 h
Conclusion	Intravenous paracetamol is effective for moderate pain
Comments	Paracetamol effect compartment concentration in neonates similar to that of children

3.2.13 **Study by Tinner et al. 2013**

Tinner et al.[46] performed a multicentre study in neonates in order to measure the pain relieving effect of rectally given acetaminophen. All neonates were born by assisted vaginal delivery and acetaminophen was administered 2 and 8 hours after birth. Acetaminophen was given in a dose of 60, 80, or 100 mg per dose depending on the infant's birth weight. Pain was then assessed through the neonatal pain and discomfort scale (EDIN) and Bernese Pain Scale for Newborns (BSPN) at 2, 4, 8, 12, and 24 hours after delivery and before and after a heel prick, which was done 2-3 days after birth. The authors concluded that rectal acetaminophen given to newborns after assisted vaginal delivery does not show an effect in reducing pain scores within 24 hours after delivery. However, study data showed higher pain scores in the acetaminophen group following the heel prick procedure 2-3 days after delivery.

Table 3.14: Data extraction form from the study by Tinner et al.[46]

Title	Rectal paracetamol in newborn infants after assisted vaginal delivery may increase pain response
Journal	The Journal of Pediatrics
Objectives	Assess efficacy of paracetamol (acetaminophen) for neonatal pain relief
Study design	Randomised, double-blind placebo-controlled multicenter trial
Pain measurement	Neonatal pain and discomfort scale (EDIN) and Bernese Pain Scale for Newborns (BSPN)
Population	71 term and near-term neonates delivered by vacuum extraction
Control group	69 term and near-term neonates delivered by vacuum extraction
Intervention	Rectal acetaminophen (60/80/100 mg per dose in infants <3000 g/ 3000-4000 g/ >4000 g birth weight) or placebo at 2 and 8 hours after assisted delivery, then pain assessment after heel prick 2-3 days later
Outcome	Increased BPSN score after heel pricks in paracetamol group
Conclusion	Paracetamol given to newborns soon after birth may aggravate a subsequent stress response
Comments	Administration of paracetamol after assisted delivery was associated with an increased response to heel prick performed 2-3 days later

3.2.14 **Study by Ceelie et al. 2013**

The trial by Ceelie and colleagues [47], the last trial reviewed, tested intravenous acetaminophen in neonates and infants up to one year of age undergoing major non-cardiac surgery. The study was designed to check postoperative morphine requirements and the cumulative morphine dose after surgery. Morphine was administered as an analgesic 30 minutes before the end of surgery and then the two

groups received either continuous morphine or intermittent intravenous paracetamol up to 48 hours post surgery. Intravenous acetaminophen (30 mg/kg per day) was given in 4 doses and pain was assessed by NRS-11 and COMFORT-B scale. Morphine as a rescue medication was the same for both groups depending on pain scores, which were not significantly different in the two groups. Ceelie et al. was able to show a significantly lower cumulative morphine dose when acetaminophen was given as an analgesic to neonates and infants up to one year after major noncardiac surgery.

Table 3.15: Data extraction form from the study by Ceelie et al.[47]

Title	Effect of intravenous paracetamol on postoperative morphine requirements in neonates and infants undergoing major noncardiac surgery: a randomized controlled trial
Journal	The Journal of the American Medical Association
Objectives	Reduction of morphine requirements through intravenous acetaminophen after major surgery
Study design	Randomised, double-blind study
Pain measurement	Numeric Rating Scale-11 (NRS-11) and COMFORT-Behavior Scale (COMFORT-B)
Population	17 neonates 10 days or younger of age
Control group	18 neonates 10 days or younger of age
Intervention	Intravenous paracetamol (30 mg/kg per day) in 4 doses or continuous morphine infusion of 2.5 g/kg per hour as primary analgesic
Outcome	Cumulative morphine dose in paracetamol group, pain scores
Conclusion	When paracetamol is administered as primary analgesic after major surgery significantly less morphine is required, no significant difference in pain scores
Comments	Intravenous paracetamol may be an interesting alternative as primary analgesic in neonates

To sum up, after studying the 14 trials intensively and extracting data based on a standardised form, only 11 trials remained for further methodology assessment. The paper by Van der Marel et al.[43] had to be excluded from this review because the trial did not only include neonates in the study groups. The trial included infants up to 9 months of age, and data on the neonatal age group could not be separated from that on older children. The author herself and the hospital research department were contacted in order to possibly obtain data extracted from the neonatal age group, but this data could not be provided. The study by Bremerich et al.[45] was reviewed closely and it was found that the data included different age groups so that the data comprised older and younger infants in the study results. After contacting the author, data on infants up to one year old were provided separately for every participant. The youngest infants included were 3 months of age and therefore the data did not match the inclusion

criteria. The trial by Korpela et al.[61] was excluded after further investigation because Korpela et al. did not include infants younger than 1 year of age. After excluding those 3 papers, 11 trials remained which were then judged based on the methodology assessment.

3.3 Assessment of methodology

Further appraisal of the 11 remaining trials was now based on the JADAD scale (see 2.5.2) and the Critical Appraisal Skills Programme (see 2.5.1). The assessment was made at the end after excluding another 3 studies that did not match the inclusion criteria concerning methodology assessment.

3.3.1 **JADAD scale appraisal**

The Jadad scale appraisal was done separately for all trials and each question was answered one by one after reviewing the trial closely. Each question was scored at the score that is listed in the table. At the end, a total Jadad score is given for every trial. An overview is given in the following table, showing the combined total score for all trials.

Table 3.16: JADAD score overview from the 11 trials that underwent an the assessment of methodology

	Howard et al. 1994 [42]	Shah et al. 1998 [44]	Taddio et al. 2000 [62]	Macke et al. 2001 [63]	Van Lingen et al. 2001 [20]	Malnory et al. 2003 [64]	Bonetto et al. 2008 [65]	Badiee et al. 2009 [66]	Allegaert et al. 2013 [67]	Tinner et al. 2013 [46]	Ceelie et al. 2013 [47]
Are the results of this trial valid?											
Was the study described as randomised?	+1	+1	0	+1	+1	0	+1	+1	0	+1	+1
Was the method of randomisation appropriate to conceal allocation?	+1	+1	n.a.	+1	+1	n.a.	+1	+1	n.a.	+1	+1
Was the study described as double blinded?	+1	+1	0	+1	+1	+0	+1	+1	0	+1	+1
Was the method of double blinding appropriate to maintain a double blinding?	+1	+1	n.a.	+1	+1	+1	+1	+1	n.a.	+1	+1
Was there a description of withdrawals and dropouts?	0	+1	+1	+1	+1	0	0	0	+1	+1	+1
Total Jadad Score	**4**	**5**	**1**	**5**	**5**	**1**	**4**	**4**	**1**	**5**	**5**
n.a. = not answered											

Using the Jadad score assessment, the studies by Howard et al.,[42] Bonetto et al.,[65] and Baddie et al.[66] were given a score of 4 points and the trials by Shah et al.,[44] Macke et al.,[63] Van Lingen et al., Tinner et al.,[46] and Ceelie et al.[47] a score of 5 points. The studies by Malnory et al.[64] and Taddio et al.[62] were excluded with a Jadad score of 0 and 1 points, respectivly after assessment as only studies with a score of 3 or more were included in the systematic review. By focusing on blinding and randomisation, the Jadad scale of those trials only resulted in low scores, which disqualified the trials from being considered for the systematic review calculations. Furthermore, Taddio et al.[62] and Malnory et al.[64] were still reviewed based on questions of the Critical Appraisal Skills Programme. In the study by Taddio et al.[62] the intervention and the control groups were treated differently in more than the administered acetaminophen intervention and

therefore the paper had to be excluded. The trial was focused on minimising pain during circumcision and both groups were circumcised but with different techniques and therefore a possible difference in pain response might not only be based on the acetaminophen administration. The paper “The paracetamol concentration-effect relation in neonates“ by Allegaert et al.[67] was reviewed and given a low Jadad score. The data for the study by Allegaert et al.[67] was extracted from the PARANEO study [38], whose data had in turn, been pooled from three other published trials. The data for the publication was extracted from the PARANEO study and the primary outcome focused on pharmacokinetics of intravenous acetaminophen in neonates. The study was therefore not blinded and patients were not randomised into groups, which resulted in a low Jadad score as well. Therefore, the trial could not be included in the final calculation process.

3.3.2 **Critical Appraisal Skills Programme**

Table 3.17 shows the evaluation according to the questions by Guyatt et al. Each question was answered one by one for every trial in the context of methodology assessment and the answers are presented in the following synoptical table.

The screening of all the trials based on the questions by Guyatt et al. led to the conclusion that all trials addressed a clearly focused issue and used an appropriate method to answer the issue addressed. Out of 11 trials, 3 showed a lack of randomisation. Nor were those 3 trials by Taddio et al.,[62] Malnory et al.,[64] and Allegaert et al.[67] blinded. The 8 remaining trials were all blinded and randomised. Except for the participants from the trial by Van Lingen et al.,[68] all participants of the other studies who were considered in the trials were properly accounted for at its conclusion.

Table 3.17: Evaluation based on the Critical Appraisal Skills Program of the 11 trials that underwent assessment of methodology

	Howard et al. 1994 [42]	Shah et al.1998 [44]	Taddio et al. 2000 [62]	Macke et al. 2001 [63]	Van Lingen et al. 2001 [20]	Malnory et al. 2003 [64]	Bonetto et al. 2008 [65]	Badiee et al. 2009 [66]	Allegaert et al. 2013 [67]	Tinner et al. 2013 [46]	Ceelie et al. 2013 [47]
Are the results of this trial valid?											
a. Did the trial address a clearly focused issue?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
b. Is the trial (RCT) an appropriate method to answer this issue?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
c. How were patients assigned to treatment groups?	R	R	NR	R	R	NR	R	R	NR	R	R
d. Were participants, staff and study personnel “blind” to treatment?	DB	DB	UB	DB	DB	UB	DB	DB	UB	DB	DB
e. Were all of the participants who entered the trial properly accounted for at its conclusion?	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
f. Aside from the experiment intervention were the groups treated in the same way?	Y	Y	N	Y	Y	Y	Y	Y	n.d.	Y	Y
g. Did the study have enough participants to minimize the play of chance?	Y	Y	Y	n.d.	n.d.	N	n.d.	Y	n.d.	Y	Y
What are the results?											
h. How are the results presented?	M	M	M	M	M/O	M	M	M	M	M	M
i. How precise are these results?	p	p	p	p	p	n.p.	p	p	n.d.	p	p
R= randomised; NR= not randomised; DB= double blinded; UB= unblinded; Y= yes; N= no; p= precise; n.p.= not precise; n.d.= not determined; O= outcome; M= measurement											

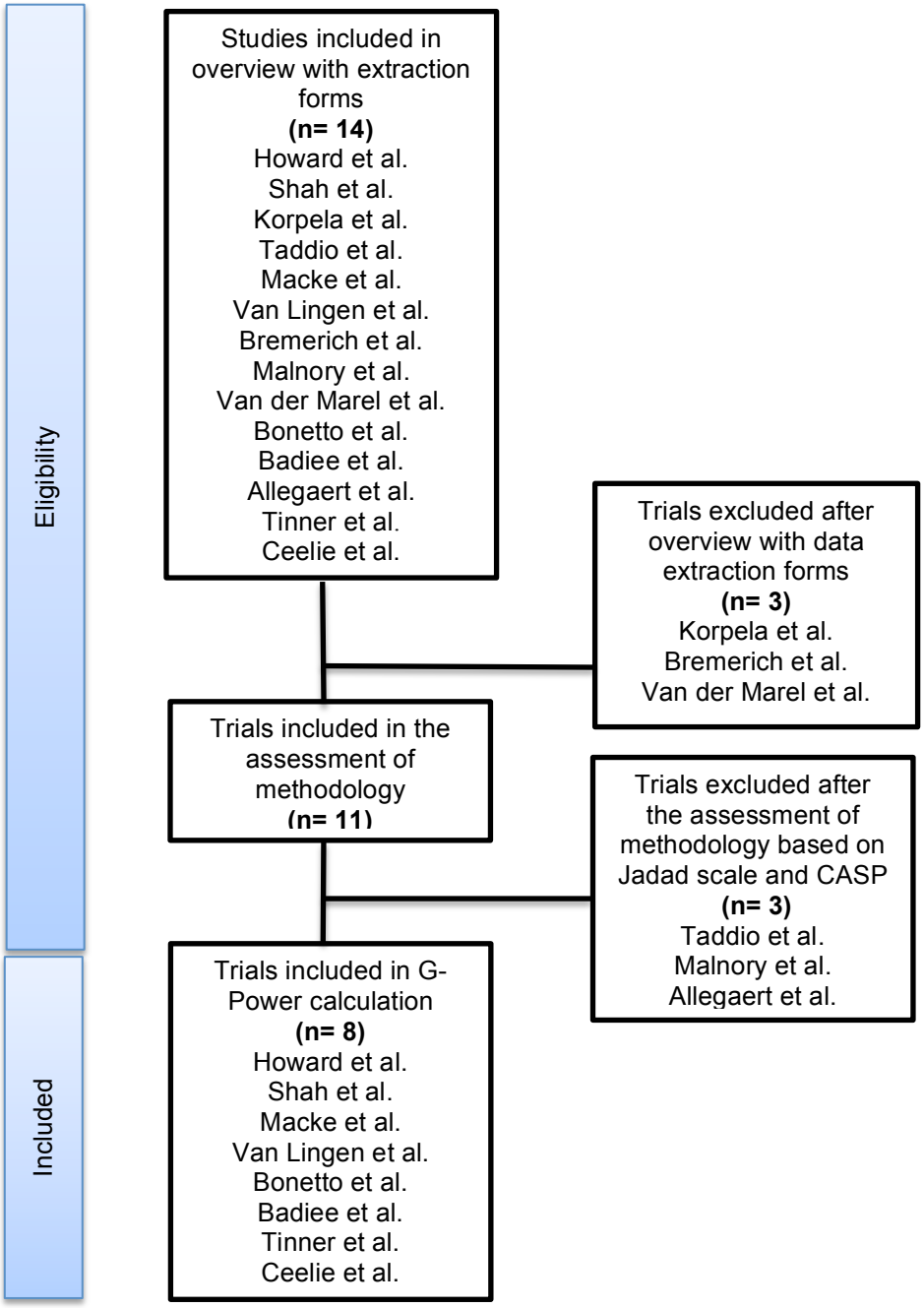
In question f. from the Critical Appraisal Skills Programme, the focus is on whether the study and the control group of a trial are treated in the same way, apart from the intervention. In the case of the trials examined this means whether the administration of acetaminophen is the only difference being made between the groups. Of the 11 trials looked at, only in one trial, the study and the control groups were treated differently when putting the focus on acetaminophen. In the study by Taddio et al. both study groups were circumcised and during circumcision treated with analgesics.[62] The study

intervention used different circumcision techniques and therefore different analgesics, which were used in conjunction with these techniques. This way it is hard to state that the groups were really given the same treatment when looking at the acetaminophen effect. One group used combined analgesics, which included a lidocaine dorsal penile nerve block, lidocaine-prilocaine, acetaminophen, and sugar-coated gauze dipped in grape juice, while the other group included infants who were circumcised using a different clamp technique and lidocaine-prilocaine only. In the trial by Ceelie, question f. was not determined because there was no control group at all to compare whether control and study group were given the same treatment. Another objective was to see whether the trials had enough patients to minimise the play of chance. Of the 11 trials, 6 described that a calculation was made beforehand in order to identify the sample size needed to show a difference between the placebo and the acetaminophen group concerning the pain reduction effect of acetaminophen. This is based on the assumption that there is a certain percentage of pain reduction in the paracetamol group with a specific power and a specific p-value. Macke et al.[63], Van Lingen et al.[20], Bonetto et al.[65] and Allegaert et al.[67] did not specifically mention a sample size calculation and therefore it was not determined whether those studies had enough participants to minimise the play of chance. The last two questions from the CASP highlighted the results of the reviewed trials and the way the results were presented within a study. In the case of the 11 trials reviewed all results were given as a measurement, while the study by Van Lingen also presented their results as an outcome. The results of the study by Malnory et al.[64] were rated as not being precise because of the lack of randomisation, the study not being blinded, and the small sample size of the trial, which did not have enough statistical power to test for significant differences in the first place. Other than that the trial by Allegaert et al. was ranked as being “not determined” concerning the precision because the trial consisted of data collection from other trials and power calculation was not done for that specific outcome.

3.4 Overview of study selection process

The following flow chart shows the progress of the study selection process starting with 14 trials that were also part of a data extraction form and the assessing of methodology.

Figure 3.2: Flow chart of the continuous study selection process



A total of 6 trials were excluded from originally 14 trials. Therefore, at the end only 8 trials remained and were included in the G Power calculation and are mentioned by name in this flow chart.

3.5 G Power Calculation

The following table gives an overview of important study details of each of the 8 trials that were taken into account in the G Power calculation process. It lists the name of the author and the year the trial was published. Furthermore, it shows the number of participants of the acetaminophen and the control groups of each trial that entered the power calculation. In the last column the main and the secondary outcome criteria are given.

Table 3.18: Overview of the study details of the 8 trials that were considered in the G Power calculation process

	Number of participants		**Main outcome criteria**	**Secondary outcome criteria**
	Ac group	Control group		
Howard et al. 1994 [42]	23	21	• Heart rate • Respiratory rate • Crying time • Postoperative Comfort Score	• Intraoperative changes • Postoperative pain after circumcision
Shah et al. 1998 [44]	32	33	• Facial action (%) • Cry duration (%)	• Changes through ac administration
Macke et al. 2001 [63]	29	31	• Behaviours during feeding interaction and pain distress during and after circumcision	• Differences in heart rate • Cry percentage • NCAFS
Van Lingen et al. 2001 [20]	61	61	• Modified facies scale	• Changes in clinical symptoms
Bonetto et al. 2008 [65]	19	19	• NIPPS • PIPP	• Pain reduction through ac
Badiee et al. 2009 [66]	36	36	• Duration of crying • PIPP • Increase in heart rate • Decrease in SpO_2	• Pain relief
Tinner et al. 2013 [46]	71	69	• BPNS • EDIN • Crying after heel prick	• Ac efficacy for neonatal pain
Ceelie et al. 2013 [47]	17	18	• Cumulative morphine dose	• Pain scores and morphine-related adverse effect
	288	288		

The 8 trials were published between 1994 and 2013. The total number of participants of the 8 trials considered was 288 neonates for each group, the acetaminophen and the control group.

Power calculations were then performed with data from the 8 trials in order to get sample size estimations and statistical power calculations for each individual study. The power analysis calculates the probability that the trial will reject the null hypothesis if the alternative hypothesis is true. This means it shows the probability that the trial detects a pain reduction effect of acetaminophen if there is one. Therefore, as stated earlier, the data from all trials, which represented the greatest change in terms of pain scores or pain behaviour, was included in the power calculation. This way any effect that acetaminophen could possibly have caused concerning changes in pain scores and physiological parameters was identified.

The results of the power calculations for each of the 8 remaining trials are presented in Table 3.19. It shows exactly which data from each trial was used to calculate the power for each individual score. The table also shows which intervention was performed in the trial. Furthermore, the sample size was calculated to give the reader an idea of how big an appropriate sample size would have needed to be in order to end up having an 80% power for this particular score in the setting of that specific trial. In order to have a valid power calculation, each score given was considered separately. Another value given in the table is the effect size, which is a generic term for the estimated treatment effect for a study. It is a dimensionless measure of effect that is commonly used when different scales are employed. In this systematic review different ways of measuring pain were used. The outcome is usually defined as the difference in means between the intervention and control groups divided by the standard deviation of the control or both groups.

Table 3.19: Results of the power calculations of the 8 considered trials

Authors and year of publication	Intervention performed in the trial	Scores considered	Scores of ac group M±SD or Median (IQR) or Frequency	Scores of control group M±SD or Median (IQR) or Frequency	Effect size	Power	Required sample size per group for 0.8 power
Howard et al. 1994 [42]	Heel prick	Heart rate (beats/min)	149.4±19.6 (n= 23)	140±22.1 (n= 21)	0.45	0.307	79
		Respiratory rate (breaths/min)	59.9±13.3 (n= 23)	67.8±19.3 (n= 21)	0.476	0.338	71
		Crying time (% time)	0.16±0.2 (n= 23)	0.35±0.29 (n= 21)	0.762	0.694	29
		Postoperative Comfort score	17.1±1.6 (n= 23)	16.3±2.3 (n= 21)	0.403	0.09	98
Shah et al. 1998 [44]	Heel prick	Facial action (%)	227.6±44.7 (n= 32)	203.6±79.2 (n= 33)	0.387	0.336	106
		Cry (%)	51.4±27.1 (n= 32)	44.3±30.5 (n= 33)	0.246	0.164	261
Macke et al. 2001 [63]	Circumcision	Heart rate (beats/min)	166.1±12.1 (n=29)	164±12.4 (n= 31)	0.171	0.099	539
		Cry percentage	70.4±16.3 (n= 29)	69.1±16.3 (n= 31)	0.079	0.06	2522
		NCAFS [1] (points)	59.9±6.28 (n= 29)	53.5±9.70 (n= 31)	0.783	0.846	27
	Diaper change postoperative	Heart rate (beats/min)	127.6±13.3 (n=29)	131.4±10.8 (n= 31)	0.313	0.218	162
		Cry percentage	31.8±33.8 (n= 29)	44.7±33.6 (n= 31)	0.382	0.306	109
Van Lingen et al. 2001 [20]	Vacuum extraction	Frequency of pain on handling	8 (n= 61)	11 (n= 61)	0.127	0.291	483
Bonetto et al. 2008 [65]	Heel prick	NIPS [2]	4.74±1.4 (n= 19)	3.89±1.7 (n= 19)	0.545	0.373	54
		PIPP [3]	9.53±2.3 (n= 19)	8.05±2.7 (n= 19)	0.59	0.424	47
Badiee et al. 2009 [66]	Heel prick	PIPP [3]	11.1±3.8 (n= 36)	9.7 ±4.2 (n= 36)	0.349	0.309	130
		Increase in heart rate (beats/ min)	15.9±15.8 (n= 36)	14.0±12.8 (n= 36)	0.132	0.085	902
Tinner et al. 2013 [46]	Heel prick	BPSN [4]	5 (3-8)	3 (2-7)	[5] ---	[5] ---	[5] ---
		Crying after heel prick (sec)	19 (0-72)	0 (0-31)	[5] ---	[5] ---	[5] ---
Ceelie et al. 2013 [47]	Major non cardiac surgery	Cumulative morphine dose (µg/kg)	121 (99-264)	357 (220-605)	[5] ---	[5] ---	[5] ---

1) Nursing Child Assessment Feeding Scale 2) Neonatal Infant Pain Scale 3) Premature Infant Pain Profile 4) Bernese Pain Scale for Neonates

5) Power calculation not possible because only median (IQR) was given in the study

The study by Macke et al.[63] noticed a significant difference between the groups concerning the NCAFS. This score, which was evaluated and documented by nurses, shows a better feeding interaction in between the infant and the mother in the acetaminophen group. The statistical power calculation for the NCAFS reached a power of 84% for this individual score. The sample size calculated in the power analysis in order to determine the difference in between the groups in this specific case was 27 participants per group. The chosen group size was 29 and 31 per group and a difference in between the groups was measured. Within the same trial none of the other parameters such as cry percentage and heart rate showed a significant difference in between groups. None of the other scores assessed besides the NCAFS showed a power of 80%.

All the other trials would have needed a greater number of participants to measure a possible difference in between the groups. For example, the study by Howard et al.[42] would have needed 79 participants per group in order to reach a statistical power of 80% and this way prove a possible difference in changes of heart rate in between the placebo and the acetaminophen group. With the actual sample sizes of the two groups of 23 and 21 participants, respectively, the power was only 33% when looking for example at the differences in changes of the respiratory rate in between the two groups. In contrast to that, the same study reached a higher power of 69% when looking at the differences in between the acetaminophen and the control groups based on the crying time. For the studies by Ceelie et al.[47] and Tinner et al.[46] a power calculation was not performed. Those study groups presented a median (IQR) in the result parts of their studies and with only those values given, a power calculation could not be carried out. Therefore a statement about the statistical power analysis of those studies could not be made.

The trials by Baddie et al.[66] and Bonetto et al.[65] both performed heel prick as the study intervention and used the PIPP score to measure pain. Neither of them noticed a difference in between the groups and hence no pain reducing effect could be shown.

The trial by Shah et al.[44] documented neonatal facial action and cry percentage in neonates after heel prick. Neither one of those scores reached a power of 80% in the

power analysis performed post hoc. Group sizes would have needed to be more than three times the chosen group size in order to reach a statistical power of 80%.

In the study by Van Lingen et al.[68] no M or SD for a pain score or pain parameter was given. Therefore, the power analysis had to be performed with the frequency of the clinical symptom “pain on handling” that was documented. With a group size of 61 participants per group a power of only 29% was calculated. In order to reach a power of 80% in this trial a group size of 483 would have been needed.

Apart from the trial by Macke et al.[63], none of the trials that the power calculation was performed for showed a statistical power of 80% for any of the pain scores or pain parameters. This means that, based on the power calculation performed post hoc, the trials were underpowered.

4 Discussion

4.1 Aim and results of literature research

It was shown in the present study that 14 trials were found through an identification and screening process that matched the topic of pain reduction effect of acetaminophen in neonates. The challenge was to decide which trials should be included in or excluded from the power calculation process for reasons of quality. Suitable is the use of a scoring system giving a certain number of points for special criteria. A high quality score is usually a sign of high methodical quality of a trial. In this systematic review the Jadad Scale [56] was used as a scoring system. Another quality check that was additionally used in this assignment was the “Critical Appraisal Skills Programme" published by Guyatt and colleagues.[54,55] This combined quality assessment resulted in the exclusion of 6 out of 14 trials for different reasons like for example not being blinded or randomised properly, or including older patients while neonatal data was not available separately.

Doing a systematic review on the topic of the analgesic effect of acetaminophen in neonates turned out having to deal with trials using totally different pain measurement scores. The 8 remaining trials were therefore evaluated by doing a G Power calculation for each pain score or physiological pain parameter. Using post hoc analysis, the statistical power for each individual score of the 8 trials was calculated. Furthermore, in another step the required sample size per group was calculated. This is the sample size that would have been needed to identify, with a probability of 80%, an effect, if any, on the intervention being performed in the setting of each particular trial. This calculation was done based on the results of the different scores used in the trials.

None of the 8 trials that were taken into account except the trial by Macke et al.[63] reached a power of 80% in any of the scores used. In order to measure a pain reduction effect of acetaminophen and this way reject the null hypothesis with a probability of 80% if the alternative hypothesis is true, all of the trials would have needed greater sample sizes. The null hypothesis declares that acetaminophen does not show a pain reducing effect in neonates. The sample sizes calculated in order to achieve a power of 80% are mostly triple the amount of the sample size chosen in the

trials. None of the 8 trials identified a pain reduction effect in terms of significant differences in pain scores and pain parameters in between the acetaminophen and the control groups. The fact that out of 16 power calculations performed, only 2 scores showed a power higher than 42% indicatives that the null hypothesis is true, meaning the alternative hypothesis could not be supported by the power calculations performed. This in agreement with the conclusions stated by most of the authors. A pain reduction effect of acetaminophen in neonates based on changes in pain scores and physiological pain parameters could not be identified, and in the power calculation, none of the trials except the NCAFS in the study by Macke et al.[63] reached a power of 80% for any of the scores with the sample sizes used in each group.

Based on the statistical power calculations it can be said that the pain reducing effect, if any, of orally and rectally administered acetaminophen in neonates in the dosages administered in the trials is extremely small, if there is any effect at all. Therefore, the chances of measuring an effect with the group sizes chosen in the trials are extremely low. To put this in a clinical prospective, the NNT (number needed to treat) in an everyday clinical setting would probably be really high when acetaminophen is used orally or rectally in neonates. With this said, the results of the power calculation performed in this work are in concord with all of the trials that failed to identify an analgesic effect of acetaminophen. In multiple studies dosages up to 40 mg/kg were being used in order to reduce acute pain and failed to show a significant pain reducing effect.[42,44,66,68] Therefore, the results of the power calculations of this systematic review are in line with the position of the IASP, which states, that available data on the pain reduction effect of acetaminophen in neonates is generally negative except for marginal effects after circumcision. This effect was also observed in the trial by Howard et al. from 1994. In this trial only the 6-hour postoperative comfort score showed a significantly better score in the acetaminophen group. On the other hand, at no other point in time was any significant pain reduction effect in the intraoperative or immediate postoperative period observed.[42]

4.2 Clinical studies on pain in neonates

The World Health Organization constitution defines health as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity. Pain is one of the major symptoms of disease and therefore the IASP is bringing together professionals from all over the world in order to advance research on pain and push the study of pain relief forward. Even today, clinical studies on pain in non-verbal infants and especially neonates and preterm neonates pose a challenge for researches. There are multiple factors that have to be taken into account when doing pain assessment in this special group of patients. On the one hand, different pain scales are evaluated for different age groups, since for example, preterm neonates might not be able to express their pain like full term neonates and therefore, physiological and behavioural changes might have to be taken into account in order to assess pain. But it is not just gestational age that makes clinical studies of pain in newborns difficult. The behavioural state and the type of pain an infant is experiencing can also change the outcome of pain studies. Therefore, it has to be taken into account whether acute or chronic pain is being assessed. In most cases neonatal pain scales are developed for assessing acute pain, but there are also scales like the EDIN scale [69] used in the trial by Tinner et al.[46] from 2013 that evaluate prolonged pain. One should also bear in mind that pain assessment in clinical studies on neonates depends on the caregiver who is either a professional or sometimes even a parent and therefore results are based on education, training, and experience of the one that assesses the score. All of these variables make pain studies tremendously challenging and the setting of trials that lead to a clear statement hard. To sum up, those might be some of the reasons for the lack of studies on pain in neonates. The method of doing a post hoc power calculation was used to make a statement about the power of the studies that are available on the topic up to this point. The problem being faced is not just the lack of available data on neonates but also the fact that a lot of studies include neonates but the data on that age group is not available separately. When neonates are put in one study group along with older infants, the risk of reporting a false pain reducing effect for neonates is high. Often there is a lack of data on the neonatal age group in trials. From studies that include several different age groups and only very few neonates, a general statement is hard to make.[70] Another conclusion of this systematic review is that there is a need of a uniform reporting system of outcome in order to make findings from

different studies comparable. This way it would be much easier to pool data for meta-analysis. Furthermore, neonatal data needs to be available separately to be able to make a statement about this unique group of patients. Their data on pain studies should not be put in one group along with older infants since based on research studies of the past decade, newborn infants seem to be more sensitive to pain experience than older infants and children.[71]

4.3 Influence of administration route, age, and dosing

Neonates and infants have historically been treated with anaesthetics and analgesics based on extrapolations from studies performed in adults and older children. Over the past 25 years, clinical research on pharmacology and clinical outcomes in neonates and infants has been growing. Different results seem to depend on the administration route, the age and weight of patient, the point in time of administration, and the intervention or procedure used. Children and especially infants at an early stage of life show great individual variability concerning drug metabolism based on organ systems that are still developing and therefore results from studies in adults cannot be extrapolated to this group of patients.[72] It has also been shown that infants´ and neonates´ pharmacokinetics of acetaminophen is different from that of adults.[1] The first year of a child's life is a period of rapid growth and development. The enzyme processes responsible for drug clearance are developing, and body composition is changing to reach adult level. Acetaminophen clearance increases from birth in term neonates with a maturation half-life of 3.25 months to reach rates similar to adults by the age of 12 years.[1] There has been a great deal of discussion in recent years whether to use acetaminophen as an analgesic in neonates because numerous of trials have been showing that acetaminophen does not have a pain reducing effect in neonates and infants when administered in certain doses.[42,43,65] There seems to be a discrepancy between the clinical use and the actual data-based results of acetaminophen in neonates and young infants. The results of RCT studies concerning the effectiveness of acetaminophen as an analgesic in neonates and infants have been inconsistent. This may be caused by inefficient absorption or variability in plasma concentrations so that a therapeutic blood level may have never been reached in a lot of cases when acetaminophen seemed to be ineffective.[42-44] The considerable paracetamol clearance variability within the neonatal age range has been the topic of several trials not just as single dosages administered but also as repeated doses.[73,74] Most of the overall

variability in paediatric clearance is predictable from covariate information such as weight and age, but there are still unexplained covariates that are involved, which have to be considered.[75] On the other hand there has been a case report, which showed that intravenous paracetamol has been successfully used for neonatal analgesia and two European Centers have published dosing guidelines in neonates.[48,76,77] In 2002 Anderson and colleagues published a recommendation concerning loading doses of acetaminophen in premature infants and neonates that were clearly higher than the ones used in most trials up to that point.[37] Van der Marel et al. used higher doses of acetaminophen in their trials but Bonetto and colleagues still used 20 mg/kg as the intervention dose trying to decrease pain caused by heel prick in neonates.[43,65]

The results of this systematic review and power calculations show that with the exception of the NCAFS in the trial by Macke et al.[63] none of the studies considered in the final power calculation of this systematic review showed a clear pain reduction effect from acetaminophen when it was administered rectally or orally. The study by Tinner et al. even reported that rectally administered acetaminophen after assisted vaginal delivery may increase pain response later on.[46]

As described by Van Lingen et al. several years ago, rectally administered acetaminophen shows a high variation in plasma levels when administered in multiple doses and therefore does not always lead to therapeutic levels.[78] Therefore, it is hard to predict the effect of acetaminophen when administered rectally or orally. Furthermore, two studies stated the lack of an opioid-sparring effect of acetaminophen in small infants.[43,45] In both of these studies acetaminophen was administered rectally. Another trial by Lin et al. reported low plasma levels of acetaminophen after 20 mg/kg administered rectally.[79] These high variations after rectal and oral administration of acetaminophen seem to be in contrast to the more constant bioavailability of paracetamol when given as an intravenous drug.[80] The recently published trial by Ceelie et al.[47] reports a lower cumulative morphine dose with the postoperative use of intermittent intravenous acetaminophen compared with continuous morphine after major noncardiac surgery in neonates and infants. Apart from the trial by Ceelie et al., none of the study groups used intravenous acetaminophen trying to detect a pain reduction effect. The lack of intravenous use of acetaminophen might be explained by the fact that out of 8 trials that ended up being included in the power calculation, in 5

studies heel prick was the intervention being performed. In this case, the administration of intravenous acetaminophen is relatively invasive compared to the intervention being performed. The intravenous formulation of acetaminophen is propacetamol, which is the prodrug of acetaminophen. It was shown in older children that propacetamol administered intravenously has a 100% bioavailability.[81] The data available on neonates concerning the pain reduction effect is insufficient. The recommendations given are mainly based on pharmacokinetic studies.[38] There is still a lack of trials on the pharmacodynamics of acetaminophen in neonates as shown in this systematic review. The issue with the intravenous use of acetaminophen seems to be at what point in time to use it so it is effective, on the one hand, and still safe to use on the other. Having the pharmacokinetic data available is an important part, but there is a need of validated pharmacodynamics and therefore the analgesic potential of intravenous acetaminophen needs to be studied in further research, especially in neonates, because there is a potential of having a „new“ intravenous drug available that might cause fewer adverse effects than the routinely used opioids that are common in the NICU. The need for further research because of a lack of available pharmacodynamic data dovetails with statements by other authors. Van der Anker et al. declared that dosing guidelines are still insufficient, especially in preterm neonates.[82] On top of that, the recently published article by Cuzzolin et al. states that there is a discrepancy between the clinical use and the actual recommendations concerning use of acetaminophen.[83] Therefore, it has to be said that even if further research would result in acetaminophen not being used on its own, acetaminophen might be a helpful supplement to pain therapy with opioids in order to reduce the total amount of opioid use and this way reduce side effects.

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6 Appendix

6.1 Statement/ Erklärung an Eides statt

Eidesstattliche Versicherung

„Ich, Claudia Kühnel, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: “Analgesic effect of acetaminophen in neonates: Systematic Review” selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung (siehe „Uniform Requirements for Manuscripts (URM)“ des ICMJE -*www.**icmje**.org*) kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) entsprechen den URM (s.o) und werden von mir verantwortet.
Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Betreuer/in, angegeben sind. Sämtliche Publikationen, die aus dieser Dissertation hervorgegangen sind und bei denen ich Autor bin, entsprechen den URM (s.o) und werden von mir verantwortet.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum Unterschrift

6.2 Curriculum vitae

"Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht."

Appendix

"Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht."

6.3 Acknowledgement

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