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Acupuncture for postoperative morbidities in children, and placebo by proxy

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Fortis imaginatio generat casum

Michel de Montaigne (1533 – 1592)

Preface

Working as a nurse in the recovery room, I observed distressed patients suffering from nausea and vomiting. Later, as a nurse anaesthetist, I became engaged in the prophylaxis and treatment of this unwanted and unpleasant adverse event of surgery and anaesthesia. I performed a study for quality improvement at Lovisenberg Diakonale Sykehus in Oslo, and found that children admitted for adenoidectomy and/or tonsillectomy were most at risk for developing postoperative nausea and vomiting. Searching the literature for emetic prophylaxis, I came across a study on acupuncture for morning sickness in pregnancy conducted at NAFKAM (National Research Centre for Complementary and Alternative Medicine), UiT The Arctic University of Norway. Fortunately, director Vinjar Fønnebø and senior researcher Arne Norheim became interested in my idea of researching acupuncture in children and offered their expertise and cooperation. This became my way into research.

I am very grateful to my eminent supervisor Arne Johan Norheim, who repeatedly has assisted me in navigating my project through the uncharted waters of science of acupuncture. He has a formidable capacity to make me able to find directions and solutions. His vigour, enthusiasm, and good humour are catching and make most problems non-existent. I want to express special thanks to my co-supervisor Einar Borud for his valuable support and data analyses, and to Leiv Sandvik for contributing with his special competence in statistics. Thanks to all other co-authors and the members of NAFKAM research group, for their contributions. Further, I would like to convey my thanks to the staff at Lovisenberg Diakonale Sykehus, Nydalen Øre- Nese- Hals, Asker Øre- Nese- Halsklinikk AS, and Polikliniske Operasjoner AS for their goodwill and assistance in performing the interventions. I am also grateful to my friend Johnny for the graphic design of the PRECIS wheel and the OACIS wheel.

Last, but not least, very special thanks are granted my dearest family. Tone Maia has patiently listened to all my ideas and has skilfully contributed with her constructive critique, which has led to surprising recognitions and revelations. With his science skills, Ole has assisted me in looking at the work from different angles. Carl Joakim has enthusiastically done copy editing. Hercy and Dag Øyvind have, without complaints, patiently waited for me to allocate some time to visit them in their home in New York. I am coming! And my mum… She is my greatest admirer.

Content

Abstract

Acupuncture may be beneficial for the prevention of postoperative nausea and vomiting in children and is associated with minor adverse events. The two RCT's in this dissertation investigated the effects of acupuncture by means of a pragmatic randomised controlled trial design. This flexible design is well suited for investigation of complex and context-independent interventions such as acupuncture, and allows for investigating the system effects for the demonstration of whether a treatment works in real clinical settings.

Opponents of acupuncture contend that acupuncture is not effective beyond placebo. The power of placebo is affected by psychological factors, of which the most important is patient expectancy towards the treatment. Patient expectancy can be divided into two: the expected efficacy (i.e. treatment effect) and perceived treatment (i.e. participants' beliefs about group allocation). The present survey explored the *placebo effects by proxy* (e.g. parents, care-givers), which is a rather unexplored field.

The term acupuncture and the use of acupuncture in a clinical context involve huge diversities and heterogeneities, as does the reporting of acupuncture research including aims, methods, and endpoints. A narrative review of articles is a reasonable approach to summarise research on acupuncture and acupressure in ambulatory anaesthesia.

Objectives

The objectives in this thesis were to:

- Investigate the system effects of acupuncture during anaesthesia followed by postoperative acupressure for postoperative vomiting in children.
- Investigate the specific effects of acupuncture during anaesthesia for postoperative nausea and vomiting in children, with the intention to exclude possible placebo effects, in particular parental expectancy to perceived treatment by using a deceptive design.
- Explore whether parental anxiety to surgery and expectancy to perceived treatment influence on postoperative morbidities such as nausea and vomiting.
- Summarise research on acupuncture and acupressure in ambulatory anaesthesia.

Methods and design

A pragmatic, randomised, controlled trial design was used in the experimental studies (Paper I and II). The survey in Paper III reports on data based on a self-report, closed-ended questionnaire completed by parents of the children who participated in the RCT in Paper II.

Paper IV is a narrative literature review of relevant articles during the last 15 years on body needling acupuncture and acupressure in ambulatory anaesthesia.

Results

- Acupuncture during anaesthesia followed by acupressure after surgery showed to be effective for postoperative vomiting in children when using an open (non-blinded) study design. Children in the acustimulation group experienced less retching and vomiting than did children in the control group, 46.8% versus 66.2 % (p=0.015).
- Acupuncture during anaesthesia did not seem to be effective for postoperative nausea and vomiting in children when using a double-blinded, deceptive study design which controlled for expectancy to perceived treatment among parents (placebo by proxy). The overall vomiting in the acupuncture and usual care groups was 44.2 % and 47.9 %, respectively. Nausea was experienced by 31.7 % in the acupuncture group and by 32.6 % in the usual care group.
- A survey-based study did not detect any significant associations between parental expectancy in terms of treatment efficacy (placebo by proxy) and children experiencing vomiting and pain.
- In a review of relevant studies on acupuncture 16 studies were included. Nine studies found acupuncture effective on postoperative nausea/vomiting, pain, sore throat, and emergence agitation. Two studies found acupuncture partly effective. Further, acupuncture was shown to have similar effects as antiemetic medication.

Conclusions

- When investigating the system effect (Paper I), acupuncture during anaesthesia followed by postoperative acupressure seems to reduce vomiting in children after tonsillectomy and/or adenoidectomy.
- When investigating the specific effect with the intention to exclude placebo effects (Paper II), acupuncture during anaesthesia does not seem to reduce nausea and vomiting in children after tonsillectomy and/or adenoidectomy.

- The survey (Paper III), embedded in the Paper II study, on preoperative parental expectancy to treatment efficacy and anxiety was not able to detect any such placebo effect by proxy.
- The vomiting rates in the acupuncture groups in Paper I and II, and in the control group in Paper II were strikingly similar. All parents in these three groups were told that their child received acupuncture. There may have been a placebo effect that was not captured by our measure of parental *preoperative* expectancy.
- The explanations for the manifest discrepancy between the RCTs should be sought understood by the following factors:
    - Placebo effects not accounted for by parental expectancy or anxiety (as assessed preoperatively): Influences emerging into and throughout the postoperative period on/by parents and children.
    - Placebo effects conveyed by care-givers and assessor in the postoperative period.
    - Nocebo effects in the Paper I study conveyed by all involved persons (children, parents, care-giver, and assessor), knowing that the children were allocated to control group.
    - A specific effect of acupressure in the postoperative period, as opposed to only acupuncture during anaesthesia.
- The descriptive review (Paper IV) showed that acupuncture may alleviate postoperative morbidities, and it is reasonable to consider acupuncture as part of ambulatory anaesthesia. However, However, since conclusive evidence regarding acupuncture effect is lacking, there have to be a trade-off between these treatments and other strategies in the future.
- Studies investigating acupuncture treatment for children should manage a balance between an adequate acupuncture dose and technique, and a child-friendly approach.
- Interesting issues for the future may be research on different acupuncture techniques and characteristics – in addition to the essential question about specific effects versus placebo effects.

List of papers

The studies have led to the publication of four papers, which will be referred to by their Roman numerals.

Paper I Perioperative acupuncture and postoperative acupressure can prevent postoperative vomiting following paediatric tonsillectomy or adenoidectomy: a pragmatic, randomised, controlled trial[1]

Paper II Acupuncture versus usual care for postoperative nausea and vomiting in children after tonsillectomy/adenoidectomy: a pragmatic, multicentre, double-blinded, randomised trial[2]

Paper III The influence of parental anxiety to surgery and expectancy to acupuncture on postoperative morbidities in children[3]

Paper IV Acupuncture in ambulatory anaesthesia: A review[4]

Definitions of terms

- *Nausea* is an unpleasant subjective feeling associated with awareness of an urge to vomit. *Retching* is the attempt to vomit with spasmodic rhythmic contractions of respiratory muscles. *Vomiting* is an expulsion of gastric contents through the mouth.[5]
- *Acupuncture* is a method of inserting special needles into acupuncture points on the body to treat disease and alleviate pain according to the ancient theories of traditional Chinese medicine.[6] *Acupuncture* is also typically used as an umbrella term including several different techniques, and this term will accordingly be used in this dissertation.
- *Acupressure* is pinching or pressing at acupuncture points.[6]
- *Acupuncture points* or *acupoints* are certain defined areas/points on the body surface for diagnostic and therapeutic purposes.
- *Pericardium 6 (PC6), Stomac 36 (ST36), Large intestine 4* (*LI4),* and *Conception Vessel 13 (CV13)* are acupuncture points used for the treatment of different *syndromes,* including nausea and vomiting. In this thesis, the international nomenclature of acupuncture points is used throughout.

Abbreviations and acronyms

EA	ElectroAcupuncture
CAM	Complementary and Alternative Medicine
CTZ	Chemoreceptor Trigger Zone
fMRI	functional Magnetic Resonance Imaging
NAFKAM	NAsjonalt Forskningssenter innen Komplimentær og Alternativ Medisin
NTS	Nucleus Tractus Solitarius
POV	PostOperative Vomiting
PONV	PostOperative Nausea and Vomiting
POP	PostOperative Pain
RCT	Randomised Controlled Trial
STRICTA	STandards for Reporting Interventions of Controlled Trials of Acupuncture
TCM	Traditional Chinese Medicine
TEAS	Transcutaneous Electrical Acupoint Stimulation
$5\text{-}HT_3$	5-HydroxyTryptamin-3 receptor (serotonin receptor)

1 Introduction

A core function in nursing practice is to prevent and alleviate adverse events from treatments and procedures, including surgery and anaesthesia. Knowledge in treatment of adverse events and caring strategies is therefore of particular interest and value to nurses in order to select proper actions. Along with a growing awareness of quality in healthcare, a focus has emerged on postanaesthetic morbidities, which remain challenging in our daily practice of anaesthesia.

Nausea and vomiting after surgery and anaesthesia are inconvenient and undesirable physiological and psychological events. In addition to causing distress and discomfort for the patient, retching and vomiting can increase the risk of pain and bleeding, resulting in increased use of resources and prolonged stay in hospital. Antiemetic pharmacological drugs are only partly effective and involve several unwanted and unpleasant adverse events.[7]

Systematic reviews and meta-analyses indicate that acupuncture may be beneficial for the prevention of postoperative nausea and vomiting (PONV) in both adults and children, and is associated with minor adverse events.[8-13] Studies have also showed results in favour of acupuncture for postoperative pain (POP) after tonsillectomy in children and adults.[14,15] Acupuncture is a simple, easy-to-learn technique, and nurses can initiate and carry out the treatment on their own initiative without prescription of a physician. However, regarding the effect of acupuncture, the evidence base is sparse, and clinical studies show conflicting results.

The placebo concept is a single term to describe a set of disparate phenomena. Treatment, therapist and patient characteristics, including psychological factors, affect the power of placebo. Controlling for all these phenomena in a clinical trial is probably not possible, so it may be rational to control for one of the most important factors: patient expectancy. Colagiuri et al.[16] describe expectancy regarding treatment efficacy as *the expected efficacy*, i.e. to which degree a treatment is expected to work, and is one out of two forms of expectancies. A systematic review has shown a relationship between patients' expectancies toward acupuncture treatment and outcomes.[17] The second form of expectancy, related to RCTs, is *the perceived treatment*, constituting patients' beliefs about their group allocation, i.e. whether they have received active treatment or control treatment. The perceived treatment is a possible source for activating or deactivating expectancies regarding treatment effect, and may affect the outcome.

Studies have demonstrated that parents' previous experience with complementary and alternative medicine (CAM) contributes to a positive expectation toward these treatments for their children.[18,19] This concept, referred to as *placebo effects by proxy*, i.e. placebo effects

modulated by expectancies of family members or caregivers, is a rather unexplored field. A search in the literature identified some studies investigating placebo by proxy on behavioural changes in children.[20-22] The studies detected an association with expectancy by proxy and outcomes.

The design of a pragmatic randomised controlled trial (RCT) is more flexible relative to an explanatory design, and accommodates natural or normal conditions found in usual clinical practice. The pragmatic RCT design is particularly suitable for investigating complex and context-dependent treatments such as acupuncture. The design allows for investigating the system effect, i.e. the whole treatment package involving both specific effects and non-specific effects.[23]

2 Aims and objectives

The main aim of the research was to provide knowledge about acupuncture for postoperative nausea and vomiting in children and to contribute to a broader understanding of the concept and the contribution of placebo effect within acupuncture treatment.

The objectives were to:

- Investigate the system effects of acupuncture and acupressure as supplements to standard treatment for postoperative vomiting in children undergoing tonsillectomy and/or adenoidectomy.
- Investigate the specific effect of standardised acupuncture on nausea and vomiting in children after tonsillectomy with or without adenoidectomy, with the intention to exclude possible placebo effects, in particular parental expectancy by using a deceptive design.
- Explore whether there is an association between parental expectancy to acupuncture treatment and postoperative morbidities such as vomiting and pain.
- Appraise and summarise research on acupuncture and acupressure in ambulatory anaesthesia during the last 15 years.

Results

Acupuncture during anaesthesia followed by acupressure after surgery showed to be effective for postoperative vomiting in children when using an open (non-blinded) study

design. Children in the acustimulation group experienced less retching and vomiting than did children in the control group, 46.8% versus 66.2 % (p=0.015).

Acupuncture during anaesthesia did not seem to be effective for postoperative nausea and vomiting in children when using a double-blinded, deceptive study design which controlled for expectancy to perceived treatment among parents (placebo by proxy). The overall vomiting in the acupuncture and usual care groups was 44.2 % and 47.9 %, respectively. Nausea was experienced by 31.7 % in the acupuncture group and by 32.6 % in the usual care group.

A survey-based study did not detect any significant associations between parental expectancy in terms of treatment efficacy (placebo by proxy) and children experiencing vomiting and pain.

In a review of relevant studies on acupuncture 16 studies were included. Nine studies found acupuncture effective on postoperative nausea/vomiting, pain, sore throat, and emergence agitation. Two studies found acupuncture partly effective. Further, acupuncture was shown to have similar effects as antiemetic medication.

Conclusions

- When investigating the system effect (Paper I), acupuncture during anaesthesia followed by postoperative acupressure seems to reduce vomiting in children after tonsillectomy and/or adenoidectomy.
- When investigating the specific effect with the intention to exclude placebo effects (Paper II), acupuncture during anaesthesia does not seem to reduce nausea and vomiting in children after tonsillectomy and/or adenoidectomy.
- The survey (Paper III), embedded in the Paper II study, on preoperative parental expectancy to treatment efficacy and anxiety was not able to detect any such placebo effect by proxy.
- The vomiting rates in the acupuncture groups in Paper I and II, and in the control group in Paper II were strikingly similar. All parents in these three groups were told that their child received acupuncture. There may have been a placebo effect that was not captured by our measure of parental *preoperative* expectancy.
- The explanations for the manifest discrepancy between the RCTs should be sought understood by the following factors:

- Placebo effects not accounted for by parental expectancy or anxiety (as assessed preoperatively): Influences emerging into and throughout the postoperative period on/by parents and children.
- Placebo effects conveyed by care-givers and assessor in the postoperative period.
- Nocebo effects in the Paper I study conveyed by all involved persons (children, parents, care-giver, and assessor), knowing that the children were allocated to control group.
- A specific effect of acupressure in the postoperative period, as opposed to only acupuncture during anaesthesia.

- The descriptive review showed that acupuncture may alleviate postoperative morbidities, and it is reasonable to consider acupuncture as part of ambulatory anaesthesia. However, since conclusive evidence regarding acupuncture effect is lacking, there have to be a trade-off between these treatments and other strategies in the future.
- Studies investigating acupuncture treatment for children should manage a balance between an adequate acupuncture dose and technique, and a child-friendly approach.
- Interesting issues for the future may be research on different acupuncture techniques and characteristics – in addition to the essential question about specific effects versus placebo effects.

3 Background

3.1 Physiology of nausea and vomiting

The vomiting reflex involves detectors that identify the need to vomit, and a coordinating centre that organises the entire process. The need to vomit can be induced by ingestion of toxins or tissue damage, or by pharyngeal stimulation, ambulation, emotions, sights, smells, and thoughts. The main detectors are the gastrointestinal tract, the chemoreceptor trigger zone (CTZ), the labyrinthine apparatus of the ear processing ambulatory stimuli, and higher brain centres processing emotional stimuli. CTZ is located in area postrema on the floor of the IVth ventricle, which is outside the blood-brain barrier, and is therefore sensitive to agents circulating in the blood[24,25] such as anaesthetics, antiemetics and opioids.

Once receptors in the gastrointestinal tract have been stimulated, messages are relayed by means of the vagus nerve to the nucleus tractus solitarius (NTS), close to the CTZ. An agent can both stimulate the gut and cause messages to be relayed directly to NTS, or messages can pass from the gut by means of the CTZ to the NTS, or it can stimulate the CTZ directly. It is also possible for agents to act at all three sites. Once the stimulus has occurred, messages are passed on to the vomiting centre. The vomiting centre detects the need to vomit and coordinates the complex sequence of events that cause nausea and vomiting.[24]

Acetylcholine, histamine, dopamine, and serotonin are important neurotransmitters involved in the emetic reflex. Acetylcholine and histamine seem to be important in the vestibular pathway of motion sickness. Dopamine has direct actions on gastric motility. Serotonin appears in high concentrations in the gut mucosa.[24]

3.1.1 Antiemetic pharmacological drugs

The pharmacological drugs in current use are mostly directed towards the transmitters acetylcholine, histamine, dopamine, and serotonin. However, these drugs, and also other antiemetics, are only partially effective and entail several undesirable adverse events. A multimodal approach for antiemetic prophylaxis is therefore recommended.

Acetylcholine

Transdermal scopolamine (Scopoderm®), an anticholinergic agent typically used for motion sickness, is also found to be effective on PONV. Sedation, dry mouth, blurred vision, central cholinergic syndrome, and confusion are reported adverse events. However, the only adverse events found in a meta-analysis were visual disturbances.[26]

Histamine

Antihistamines (e.g. Phenergan®) are mostly also used for motion sickness. Due to adverse events as dry mouth and sedation, antihistamines are not preferred as an antiemetic for PONV.[27]

Dopamine

Metoclopramide (Afipran®) is mainly a dopamine receptor antagonist [by high doses also a serotonin receptor (5-HT_3) antagonist]. Adverse events are extrapyramidal symptoms, dystonia, restlessness, and dysphoria.

Droperidol

Droperidol (Dridol®), classified as a neuroleptic, is a dopamine receptor antagonist. Adverse events are hypotension, tachycardia, drowsiness, sedation, anxiety, hyperactivity, and extrapyramidal symptoms.[28]

Serotonin

Ondansetron (Zofran®) is a serotonin receptor (5-HT_3) antagonist and represent the *gold standard* in antiemetic treatment. It is more effective on vomiting than nausea. Adverse events are headache, constipation, and sedation.[29]

Other antiemetic drugs

The corticosteroid *dexamethasone* (Fortecortin®) is a commonly used antiemetic for PONV. The mechanism of action is still partly unknown, and adverse events are minimal when used as a single dose.[27]

Propofol is an anaesthetic drug used for induction and maintenance of anaesthesia, and sedation. Propofol has antiemetic properties as part of intravenous anaesthesia as well as in subhypnotic doses for sedation. There are several adverse events, including respiratory depression.[28,30]

Other therapies

Adequate *intravenous fluid* therapy has been shown to be effective in reducing PONV.[31,32] Limiting oral intake postoperatively and gastric decompression is no longer recommended for the reduction of PONV,[33,34] neither is supplemental oxygen.[7,35]

3.2 Risk factors for PONV in children

The aetiology of vomiting after tonsillectomy is unclear and probably multifactorial in origin.[36] Risk factors for PONV in children can be related to patient, surgery, and anaesthesia. Assessing risk factors, along with other considerations about patient condition, is important for making decisions about the need for prophylactic treatment of PONV. Patients' risk for PONV can be divided in low, medium and high[7] (Figure 1).

Patient related risk factors

Children are twice as likely as adults to develop PONV.[37] Children less than 3 years of age experience less PONV than do older children, and a history of PONV or a relative with a history of PONV also increases the risk. Obese patients have been considered more inclined to experience PONV, but previous evidence has been inconclusive, and new evidence is contradictive. Similarly, anxiety and fear were until recently held as risk factors for PONV, but this assumption has now been disproven.[7]

Surgery related risk factors

According to Eberhart's model on risk factors for PONV in children,[38] strabismus surgery is considered the main procedure associated with increased risk in infants. Studies have also shown that tonsillectomy is highly associated with PONV.[27,32] This is thought to be due to the irritant effect of blood on oesophageal chemoreceptors and direct stimulation of the trigeminal nerve.[39] The amount of blood entering the stomach during and after surgery also affects the occurrence of PONV.[36]

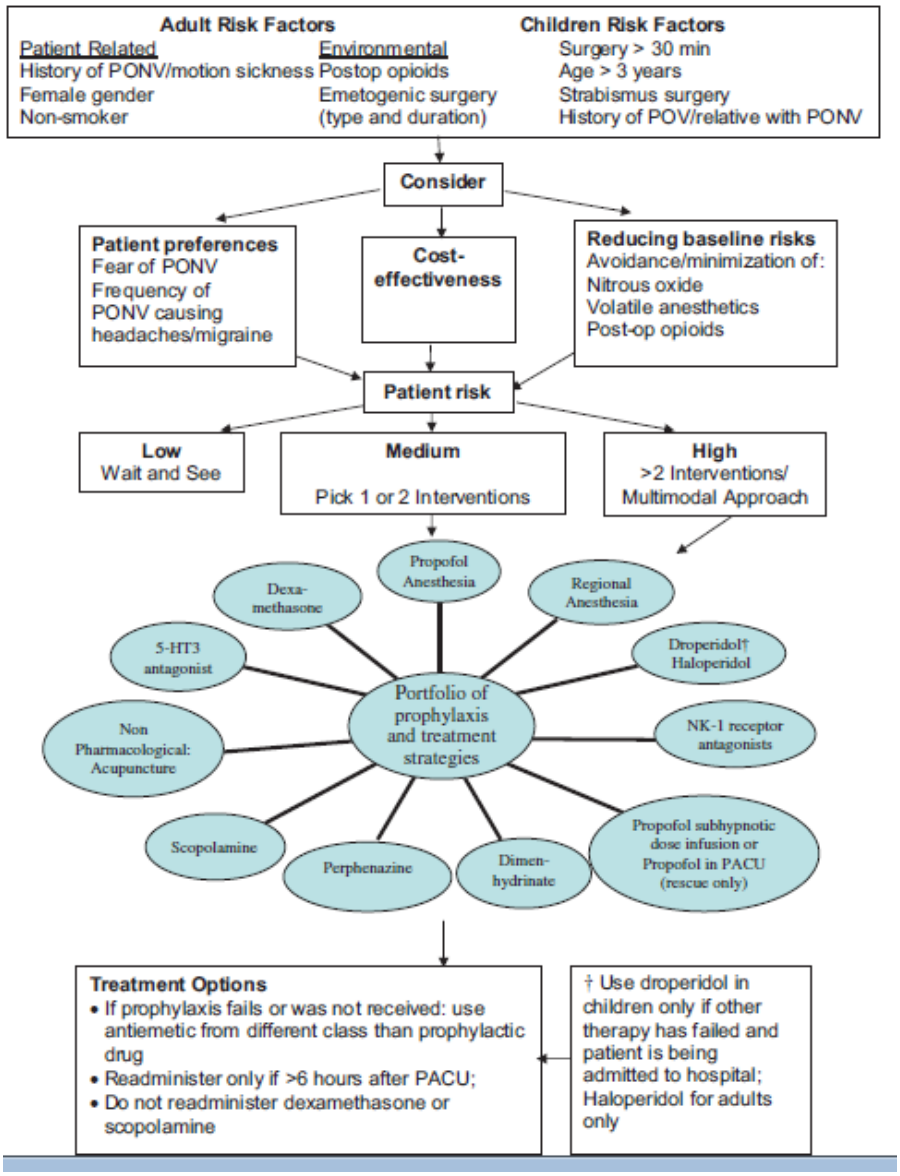
Anaesthesia related risk factors

Volatile anaesthetics, nitrous oxide, postoperative opioids, and duration of anaesthesia are some of the most reliable predictors of PONV.[40]

3.3 Guidelines for the management of postoperative nausea and vomiting

An update on guidelines for the management of PONV was published in 2014 by the Society for Ambulatory Anaesthesia.[7] A simplified risk score for children identifies four predictors: Surgery duration > 30 minutes, age ≥ 3 years, strabismus surgery, history of postoperative vomiting (POV), and PONV in relatives. The algorithm for management of PONV is displayed in Figure 1. Acupuncture is one of the remedies recommended by this scheme.

Figure 1 Algorithm for management of PONV. Published with permission from Tong J. Gan, corresponding author of the *Consensus Guidelines for the Management of Postoperative Nausea and Vomiting*[7]



3.4 The concepts placebo and placebo effect

The word *placebo* means "I shall please", and stems from the 13th century when mourning the dead. At the beginning of the 1800s, at the dawn of a scientific approach in medicine, placebo was described as "any medicine adapted more to please than to benefit the patient".[41] Until the beginning of the 1900s, doctors had few effective treatments to offer, and it might have been convenient to use placebo in order to please and reassure anxious patients, and maybe sometimes getting rid of the troublesome ones. In a seminal paper, Beecher[42] noted that "placebos can be a psychological tool for doctors at loss of adequate treatment of e.g. mental

illness or neurosis". Today, our values and respect for the individual have developed considerably, and our ethical view has put this point of view more or less to an end. However, a recent UK study demonstrated that doctors admit that they in certain situations turn to placebo treatment.[43]

The concept placebo has been exposed to various degrees of attention (or lack thereof) from medical and health care practitioners during the 20th century. First it was ignored, then regarded as a threat to objectivity and something that needed to be controlled for, and finally the interest emerged in exploring the phenomenon per se.[44] The use of placebo in research began in earnest during the 1950s for investigating medications in controlled studies. Placebo controlled studies are intended to rule out biases on the part of both patient and caregiver and thus determine the mechanisms and true efficacy of a drug. Placebo for this purpose can be defined as "an inactive material, often in the form of a capsule, pill or tablet, that is visually identical in appearance to a drug being tested in a clinical trial".[45] In the 1970s the exploration of the mechanisms of placebo gained popularity, as focus shifted from the concept of inert treatment (e.g. sugar pill) to psychosocial factors such as behaviours, conditioning, verbal suggestions, and expectancy.

A great amount of definitions have been launched, some contradictory, reflecting the complexity of the concept. The conceptualisation of placebo is thus troublesome. A simplistic definition is that "placebo is an inert substance or treatment".[46] This definition, however, implies an inherent contradiction: If something is inert, it cannot produce any (placebo) effect.[47] A more suitable definition, suggested by Stewart-Williams and Podd,[48] may be: "A placebo is a substance or procedure that has no inherent power to produce an effect that is sought or expected". According to the same authors, the definition of placebo effect is thus "a genuine psychological or physiological effect (…) which is attributable to receiving a substance or undergoing a procedure, but is not due to the inherent powers of that substance or procedure".

Benedetti explains the placebo effect as "a real, psychobiological phenomenon whereby the brain is actively involved and anticipates a clinical benefit".[49] Thus, the placebo effect does not imply other observed responses such as regression to the mean, natural course of the disease, symptom fluctuations, response bias with regard to patients reporting of subjective symptoms, or other concurrent treatments.[46,49] Benedetti et al. [49,50] point out that the term *placebo effect* should only be used when a placebo is administered. Placebo effects do in fact not require placebos, it may occur even when no placebo is given. In these cases, Benedetti suggests that *placebo-related effects* is an appropriate term. Kirsch[51] adds more to the discussion, as he

maintains that " the placebo effect is the difference between the *placebo response* and the changes that would be observed even without the administration of a placebo". Nonetheless, Kirsch agrees with Benedetti, and holds the view that "to assess the placebo effect, one has to subtract changes due to the natural history of the disorder and regression towards the mean".

The use of the terms *placebo effect* and *placebo response* is not straight forward. The literature uses the terms interchangeably, and this will also be the case in the present dissertation.

3.4.1 Placebo effects in therapeutic contexts

The placebo effect is attributable to the therapeutic context such as the treatment per se, individual patient and caregiver characteristics, the interaction or relationship between patient and caregiver, and the therapeutic setting. In a review, Finnis et al[46] have found reports of evidence for several placebo effects in different conditions and physiological systems, including:

- Pain and activation of endogenous opioids and dopamine.
- Parkinson's disease and activation of dopamine.
- Depression and changes of electrical and metabolic brain activity.
- Anxiety and serotonin.
- Cardiovascular system and β-adrenergic activity of the heart.
- Respiratory system and opioid receptors.
- Immune system and immune mediators.
- Endocrine system and hormones.
- Physical performance and endogenous opioids.
- Alzheimer's disease and prefrontal executive control.

In contrast, a much debated meta-analysis by Hrobjartsson et al.[52] questioned many placebo effects, except on subjective outcomes such as pain and nausea.[52] Kaptchuk[53] also has concluded that subjective outcomes are more influenced by placebo than objective outcomes.

3.4.2 Mechanisms of action

The concept of placebo effect contains several mechanisms of action. The two principal theories most accepted for explaining the psychological mediation are the two processes of expectation and classical conditioning.[49,54] These theories are not conflicting and should not be

pitted against each other. On the contrary, they represent explanations at different levels and may be regarded as complimentary. Expectancy can be formed through conditioning,[55] and in some instances conditioning can be mediated by expectancy.[48,56]

Benedetti [49] explains a conditioned stimulus to be "effective in inducing the reduction of a symptom if it is repeatedly associated with an unconditioned stimulus". Patients associate an effective treatment with the alleviation of e.g. a painful condition, and a subsequent "treatment" by an inert placebo can mediate this effect. The effective treatment is an unconditioned stimulus, and the placebo becomes a conditioned stimulus. Effects based on classical conditioning have been shown in several studies.[57-59]

The expectancy theory was investigated by Goldstein[60] more than 50 years ago. He postulated that patients' expectancy was an important determinant for patients' outcomes in psychotherapy treatment. Conditioning, verbal suggestions and behaviours influence patient expectancies, desires, and emotions. The strength of influence may vary depending on treatment contexts and settings, and thus produce varying degrees of placebo effects.[61] This is in keeping with a study by Colloca and Benedetti[62] where modulation of analgesic effects were found for both positive and negative experiences; large placebo effects occurred in the former case and small effects in the latter. The authors also contend that most medical treatments, whether effective or not, appear to be influenced by patient expectancy. Further, manipulated expectancy, i.e. manipulating the degree of expectation by positive verbal suggestions (along with treatment), produced larger outcome effects relative to no suggestions.[63]

Expectancy may also, not surprisingly, produce nocebo (from the Latin meaning I shall harm) effects; an open interruption of medication produced a greater worsening of symptoms compared to a hidden interruption.[50] Further, hidden administration of a drug resulted in reduced effect relative to open administration, presumably due to lack of patient expectancy.[64,65]

An emerging theory is that expectancy is produced by psychological and social stimuli resulting in activation of different neurotransmitters such as endorphin, dopamine, and cholecystokinin, and changes in certain areas of the brain; prefrontal cortex, anterior cingulate cortex, insula, and nucleus accumbens[64,66] The first article showing direct evidence for placebo activation of endogenous opioids was published only 10 years ago..[67]

Participating in a study may *per se* have a therapeutic effect on the participants, this is known as the Hawthorne effect.[68] The Hawthorne effect postulates that participation in a study implies attention and observation that may bring about a positive expectancy effect by itself.

3.4.3 Expected efficacy and perceived treatment

Expectancies may be divided into two types. Colagiuri et al.[16] describe the expectancies regarding treatment efficacy as *the expected efficacy*, i.e. to which degree a treatment is expected to work. The second type, relating to RCTs, is *perceived treatment*, constituting participants' beliefs about their group allocation, i.e. whether they have received active treatment or placebo.

Blinding and randomisation are integral components in traditional, explanatory RCTs, which are performed under strong control and optimised conditions. Blinding involves keeping the group to which the participants have been allocated hidden from those involved in the study. Due to the randomisation process, in which participants are arbitrarily assigned to treatment or control group, expectancies will be evenly distributed across groups. As a result, some participants in the treatment group may believe they are allocated to the treatment group and some believe they are in the control group. Others still may be unsure. Similarly, this will be the case for the participants in the control group. The intention of blinding is not to eradicate the expectancies, but to secure that they are evenly distributed between groups.[16]

However, blinding in RCTs is often found to be difficult,[69,70] and this may represent a threat to internal validity. Unsuccessful blinding may cause difficulties in determining whether an effect is caused by the treatment itself (specific effects), by both the treatment and participant expectancy (specific and unspecific effects), or participant expectancy alone (unspecific effects). In fact, better treatment effect tends to cause unsuccessful blinding, as the effect is more likely to be observed. The aim of levelling out patient expectancy in the research groups may thus be subverted. Consequently, *the perceived treatment* is a possible source for activating or deactivating expectancies about treatment effects, and consequently has effect upon the outcomes. If a participant presumes that the treatment under investigation is effective and finds out that she probably belongs to the treatment group, she will most likely expect and experience improvement. Alternatively, if the participant presumes that she most likely is allocated to the control group, positive expectancies will less likely appear; neither will any experience of improvement. In this sense, an unsuccessful blinding may introduce bias, instead of reducing bias. Several analyses of RCTs indicate a strong relationship between perceived treatment assignment to study groups and treatment outcomes.[71-75]

3.5 Acupuncture

Acupuncture is one among several constituents within traditional Chinese medicine (TCM) and has a prehistoric origin. According to TCM, the purpose of acupuncture is to re-establish the energy flow *de qi*, which has been blocked by the ailment or the disease.[76] The complementary and opposing elements of *yin* and *yang* restore the harmonious flow of *de qi* by means of thin needles placed at specific *acupuncture points* along *energy meridians* in the body. Pericardium 6 (PC6), Stomac 36 (ST36), Large intestine (LI4), and Conception Vessel 13 (CV13) are acupuncture points used for the treatment of different ailments, including nausea and vomiting. Acupuncture theory and philosophy, derived from Taoism, are interesting and intriguing, but difficult to integrate into western biomedical science.[76,77]

The acupuncture technique is primarily associated with the use of thin needles for penetration of the skin. Acupuncture related techniques include electroacupuncture (EA), transcutaneous electrical acupointstimulation (TEAS), acupressure, auricular- and hand acupuncture, and acupuncture injections (using e.g. herbal extracts, saline, liquid vitamins, sterile water). Acupuncture and some related techniques and their clinical features are listed and compared in Table 1 adapted from Lu and Rosenthal.[78]

Table 1 Acupuncture and related techniques: clinical features

Technique	Device/tools	Skin penetration	Stimulation intensity	Practice feature	Potential risks/ contraindications
Manual acupuncture	Fine metal needles with hand manipulation	Yes	Varies	General population, traditional style, most commonly used	Infections, bleedings
Electro-acupuncture	Fine metal needles or metal implants	Yes	Strong	General population, strong stimulation, long and lasting effect	Infections, bleeding, tissue/organ injury, cardiac arrhythmia
Ear acupuncture	Fine metal needles or metal implants	Yes	Medium	General population, quick and easy access, long-term stimulation	Infections, bleeding
Acupressure	Fingers or wristbands with pressure	No	Weak	Paediatric population, needle phobia	Bone metastases

Table 1 shows that Lu and Rosenthal contend that stimulation intensity (electricity, needle manipulation, etc.) differs between different acupuncture techniques. One may question whether the intensity increases the effect on outcomes, and, if so, electrical stimulation may be considered as a means to provide stronger treatment relative to manual stimulation. While electrical stimulation of the needle usually is continuous, manual stimulation is typically intermittent and often brief. One hypothesis is that even without any manual or electrical stimulation, the mere presence of the needle retained in the tissue may cause stimulation.[79] Modest evidence suggests that different manual manipulations (twirling-rotating and lifting-thrusting manipulations) and different electrical modalities (wave form, amplitude, wave width, frequency and duration) may exert different physiologic and therapeutic effects.[79,80] As to which techniques work better, the research is limited; the findings are inconclusive and difficult to interpret.[79] Nevertheless, a systematic review by Ezzo[11] found that PC6 stimulation was similarly effective for postoperative nausea and vomiting across different techniques of stimulation.

Traditional Chinese acupuncturists contend that needle insertion (depth, angle, direction) and manipulation, needling sensation and duration, and acupuncture point specificity influence on acupuncture effects.[81] A meta-analysis on pain by MacPherson et al.[82] contradict this and suggest two modifying characteristics of acupuncture only; more needles produce better pain outcomes, as do a higher number of acupuncture treatment sessions. Other characteristics investigated, but not found to be modifying, were acupuncture style (traditional Chinese style, western style, or a mixture), electrostimulation, duration of sessions, patient-practitioner interactions, and acupuncturist experience.

Ceccherelli et al. investigated in two studies outcomes from different number of needles on patients suffering from neck pain. Patients were treated with 5, 11, or 18 needles,[83] and 5 or 11 needles.[84] None of the studies detected any differences between groups. In contrast, Alizadeh et al.[85] found two acupuncture points to be more effective than one for alleviation of PONV after abdominal surgery. Obviously, the results are ambiguous, and it is difficult to draw any conclusions about whether the number of needles matter.

Acupuncture point specificity represents a formative theoretical basis for acupuncture theory, and is considered a key factor for successful acupuncture treatment. One review of studies on acupuncture points and sham points has supported the existence of acupuncture point specificity.[86] However, a systematic review on similar studies is contradicting this.[87]

In sum, it is debatable whether acupuncture characteristics play a crucial role in acupuncture treatment. There are clinical trials maintaining the notion that acupuncture techniques, number of needles, acupuncture point specificity, acupuncturist experience, duration of sessions, patient-practitioner interactions, and acupuncturist experience contribute to therapeutic effects. The evidence is, however, modest.

Since 1970, several studies have been conducted to establish evidence of acupuncture effect. However, sceptics contend that this evidence still fails to convince; it lacks rigor and presents controversies.[88] Moreover, there is a lack of a complete physiologic understanding of the mechanisms involved. Despite all this, acupuncture prevails as a significant technique in eastern medicine and has gained some credibility in the western world.[13,89-91]

3.5.1 Acupuncture effects and safety in children

Most acupuncture studies on effects and safety have been on adults. Acupuncture in children has received less attention. This may be due to the ethical issue concerning children's fear of needles and the potential difficulties regarding children's willingness to participate and cooperate. In spite of these challenges, some studies have been conducted. Jindal et al.[13] have reviewed research reporting on acupuncture effect and safety in children. The conditions reported on, were postoperative and chemotherapy induced nausea and vomiting, pain, asthma, allergic rhinitis, neurologic and gastrointestinal disorders.

Among these, the most extensive research focused on acupuncture for nausea and vomiting, and acupuncture seemed to be most effective in preventing PONV. The review also included nine studies addressing adverse events. The authors estimated the incidence of adverse events to be 1.55/100 treatments of acupuncture or sham acupuncture, and the most common was redness at the acupuncture site. There was only one serious adverse event among a total of 1865 children. The estimated risk of serious adverse events was 5.36/10 000 treatments. In conclusion, adverse events in children represent a minor problem, and serious adverse events are very rare.

From the first study in 1988 to date, acupuncture for PONV in children has been reported in 12 RCTs (excluding the present studies in this thesis). All studies used acupuncture point PC6, whereas two involved more than one point (LI4 and CV13 in addition to PC 6). Four studies dealt with tonsillectomy. Characteristics of the trials are displayed by publication order in Table 2 and Table 3. The tables also demonstrate the conflicting results.

Table 2 RCTs on acupuncture in children: tonsillectomy

1st author	Subjects	Arms		Blinding	Timing of intervention			Outcomes	Effect	Comments
		Intervention	Control		before	during	After			
		Duration				Anaesthesia				
Yentis [92]	n = 30 2 – 11 years	Acupuncture 5 min	Usual care	Double-blind		x		Vomiting	-	
Shenkman [93]	n = 100 2 – 12 years	Acupressure Acupuncture Duration until the next day	Sham	Children Parents? Caregivers? Data assessor	x	x	X	Retching Vomiting	- -	
Rusy [94]	n = 120 4 – 18 years	Electro acupuncture 20 min	Sham Usual care	Children Parents Caregivers Data collector			X	Nausea Vomiting	+ -	
Kabalak [95]	n = 90 4 – 12 years	Transcutaneous electrical acupuncture point stimulation 5 min + 5 min	Ondansetron No intervention	Children Parents Caregivers Data assessor	x		X	Vomiting Retching	+ +	TEAS similar effect as ondansetron

Table 3 RCTs on acupuncture in children: other surgical conditions

1st author	Subjects	Surgery	Arms		Blinding	Timing of intervention			Outcomes	Effect	Comments
			Intervention Duration	Control		Before anaesthesia	during anaesthesia	after anaesthesia			
Schlager[96]	n = 40 3 – 12 years	Strabismus	Laser acupoint stimulation 15 + 15 min	Placebo	Double-blind	X		x	Vomiting	+	
Lewis[97]	n = 66 3 – 12 years	Strabismus	Acupressure Duration not specified	Placebo	Double-blind	X	x	x		-	
Lin[98]	n = 60	Myringotomy	Acupuncture 10 min	Usual care	Children Parents Data-assessor		x		Pain Emergence agitation	+ +	
Yentis[99]	n = 45 2 – 11 years	Strabismus	Acupuncture 5 min	Droperidol Droperidol + acupuncture	Children Parents Caregivers Data assessor		x		Vomiting	+	Acupuncture similar effect as droperidol
Schwager[100]	n = 84 Age not specified	Circumcision Herniotomy Orchidopexy	Transcutaneous electrical acupoint stimulation PC6 + LI4 20 min	Placebo	Double-blind		x	x	Vomiting	-	
Somri[101]	n = 90 4 – 12 years	Dental	Acupuncture PC6 + CV 13 15 min	Ondansetron Placebo	Children Parents Caregivers Data assessor	X			Vomiting	+	Acupuncture similar effect as ondansetron
Wang[102]	n = 190 7 – 16 years	Outpatient surgical procedures	Acupoint injection	Droperidol + sham Sham point injection Sham	Double-blind		x		Nausea Vomiting	+ +	Acupoint injection similar effect as droperidol
Butkovic[103]	n = 120 6- 9 years	Circumcision Herniotomy Orchidopexy	Laser acupoint stimulation 60 sec	Metoclopramide Sham	Children Parents? Caregivers? Data assessor?	X			Nausea Vomiting	+ +	Acupoint stimulation similar effect as metoclopramide

3.5.2 Mechanisms of action

The mechanisms of action of acupuncture have been subjected to several investigations. Various possible explanations have emerged, and the mode of action is still not completely understood. Regarding the mechanisms of action of acupuncture for PONV, one must take into consideration the complexity of nausea and vomiting, involving multiple neurotransmitters and physiological processes.

There is evidence supporting neurotransmitters to be released by acupuncture. Pomeranz and Chiu[104] were probably the first scientists to discover that acupuncture stimulated secretion of endogenous opioids, or endorphins, in mice subjected to heat stimuli. Acupuncture reduced pain, but the effect was completely abolished after injection of naloxone. The authors concluded that acupuncture had triggered the release of endorphins. Release of endorphin by acupuncture has subsequently been confirmed by several studies.[105-108] These discoveries were of importance because they boosted the search for other pathways and neurotransmitters involved in acupuncture.[109]

The anticipations of other pathways and neurotransmitters involved have later been proven correct. Endorphins, encephalin, noradrenalin, and serotonin are known to be involved in the brain analgesia system and play a central role in pain modulation,[110,111] and subsequent research has revealed that acupuncture analgesia has been associated with an increased level of these transmitters.[112] Most studies on acupuncture and neurotransmitters have focused on chronic or acute pain, but a recent study has reported on TEAS for chemotherapy-induced nausea and vomiting; a favourable effect on vomiting by TEAS was accompanied by significantly reduced serum levels of circulating serotonin and dopamine.[113] The authors suggested that these transmitters were involved in the antiemetic mechanisms of electroacupuncture.

Studies on acupuncture effects on neural pathways have shown an excitatory response in the gastric vagal nerve and an inhibitory response in the gastric sympathetic nervous system.[114]

Tada et al.[115] have also suggested a nervous reflex system for acupuncture-induced gastric relaxation. Their study on rats indicated that different acupuncture points either inhibited or excited gastric motility. These pathways may be parts of acupuncture mechanisms involved in the alleviation of nausea and vomiting.

Another pathway of attention was investigated by means of functional magnetic resonance imaging (fMRI).[116] The study detected specific involvements of the hypothalamus and insula areas following acupuncture at PC6. These structures of the brain are involved in the autonomic

regulation of vestibular functions. Hypothalamus is also involved in the regulation of visceral functions, including vomiting.[117] The results indicated that stimulation at PC6 may exert modulatory effects in the processing of hypothalamus and vestibular functions, thereby alleviating vomiting and nausea.

However, it is important to note that surrogate outcomes including release of neurotransmitters and changes in the brain do not necessarily represent specific clinical effects of acupuncture. As MecGeeney points out, slapping you hard across the face can also result in such changes, as do placebos.[118]

Coincidentally (or maybe not) acupuncture actually seems to produce physiological changes partly similar to those observed during placebo treatment. Dhond et al.[119] concluded in their review *Do the neural correlates of acupuncture and placebo differ?* that current neuroimaging studies have validated that acupuncture modulates a widely distributed network of brain regions. These networks demonstrate remarkable overlap with those which are active during placebo analgesia.

3.6 Placebo in acupuncture

A systematic review by Colagiuri and Smith[17] demonstrated that five out of nine studies on placebo showed a significant association between patients' expectancies and acupuncture treatment outcomes, mostly for subjective symptoms such as pain. One of the studies in the review also investigated the relationship between patient anxiety and outcome, but no such relationship was found. Another study found that patient expectancy had a greater influence on outcome than did the acupuncture treatment itself.[120]

The concept *perceived treatment* (see chapter 3.5.3.) has also been explored in acupuncture studies; patients who believed they received acupuncture, experienced better pain relief compared to those who believed they received placebo.[71]

Evidence suggest that the more invasive placebo modalities, the greater placebo effects.[121] Famous examples from literature on powerful placebo effects include arthroscopic surgery for osteoarthritis of the knee,[122] and ligation of the internal mammary artery for angina.[123] By using sham surgery as control, the two studies indicated that true surgery may not be effective beyond placebo.

Even though acupuncture is far less invasive than most surgery, probably the needling procedure of acupuncture looks far more invasive to the patient than it actually is. Zheng et al.[124] regard placebo effects produced by acupuncture clinically relevant, and contend that potent placebo effects are due to the elaborate and invasive nature of acupuncture. Patients may develop greater expectations toward acupuncture because of the impressive treatment rituals.[125,126]

It has been demonstrated that acupuncture is associated with greater effects than pharmacological placebo treatments.[127] In a recent large meta-analysis,[82] MacPherson et al. concluded that the effects of acupuncture on pain were not modified by the number of needles when compared to sham acupuncture. However, when compared to non-acupuncture controls, the only difference between the groups appeared when more needles were used. These results indicate that sham acupuncture, perceived as invasive in line with true acupuncture, entails a powerful placebo effect.

3.7 Placebo by proxy

Placebo effect by proxy, or placebo by proxy, is a term used when a placebo effect is caused by other persons' positive expectancy rather than the patient's (e.g. parents, other family members, caregivers) Parents may respond emotionally when their child receive acupuncture treatment and interpret any sign as treatment response, no matter whether there is a physiological effect or other indications of improvement.[128] Similarly, parents may disregard symptoms or signs that do not fit into their comprehension or expectations, and vice versa. Attention may thus selectively be given to positive changes while observed negative changes are ignored or explained away. Moreover, being subjected to a study, parents may change their behaviour towards the child, e.g. pay more attention and care. They may also be more susceptive to the children's subtle improvements or changes.[129] These mechanisms may lead to misinterpretations of the evidence for treatment effect.

There is not much research available in this field. The phenomenon is underappreciated and rarely discussed, although Grelotti and Kaptchuk[128] contend that placebo *by proxy* probably occurs as frequently as other placebo effects and may have great implications.[128] A few studies have reported on the placebo effect by proxy in behavioural research. A correlation between parental mood and tantrum frequency in children has been demonstrated by Whalley and Hyland.[20] The authors concluded however, that they "cannot say whether tantrum reduction was due to objective changes in child behaviour, changes in parental perception, or both (…)".

Further, behavioural changes in children with development disability has been found to be due to placebo by proxy.[21] This finding has been supported by a subsequent review by Waschbusch et al.[22] So, emerging evidence shows that placebo by proxy plays a significant part in *subjective* treatment outcomes in children. However, placebo by proxy does not seem to be a significant component of *objective* measures such as frequency counts of children's behavior.[22]

3.8 Deception research

Deception research implies that the study participants are not completely informed about all aspects of the study. By avoiding confounding factors, more reliable data may be obtained, compared with a transparent study design.[130,131] Deception may involve participants not being clearly informed about their role in the study, or that aims and methods are not fully explained.[130] Such research may be ethically justifiable providing that deception is the only way to gain useful/unbiased knowledge. Furthermore, it should not influence on the decision to give consent and not imply any added risk for adverse events.[130,132] The missing transparency for the participants must be weighed against the benefits of the study. It is also important to assess any negative consequences for the reputation of the research project or the health institution.[133,134] The participants should give their consent to *authorised deception*;[135] which implies that they are aware that some aspects of their participation will not be disclosed until the completion of the study.

The use of deception may be considered unethical and not acceptable. However, a study found that participants in deception research versus non-deception research were more satisfied, and did not mind being deceived.[136] A study on healthy volunteers also showed that informing the study participants about the use of deception did not affect recruitment or retention, nor did the deception entail any significantly psychological harm to the participants.[135,136] It seemed like the study participants did not perceive deception as an unwanted or unacceptable method. Acknowledging the fact that it may be immoral not to investigate important topics and research questions, these arguments may contribute to justification and acceptance of deception in research.[136]

3.9 Pragmatic versus explanatory design

The traditional design of RCTs for effect studies in healthcare has been employed in large scale since the 1940s, and findings from RCTs are granted the highest status when information is ranked to guide evidence-based practice.[137] To ensure that effects can be attributed to the intervention and not to external or confounding factors (e.g. non-specific effects), studies should employ strong control under optimised experimental conditions.[138] This *explanatory* RCT design aims to study the component effect, i.e. the specific effect, or the pure *efficacy* of a treatment.

Three important properties are essential to secure internal validity: randomisation, placebo control, and blinding. Randomisation implies allocating patients by random to either treatment or placebo control group, thus evenly distributing different confounding characteristics of the participants between the groups. The use of placebo implies that participants allocated to the control group receive a presumably inert treatment, seemingly similar to the active treatment in the study group. The third property, blinding, is preferably used if possible, and is described as single, double, or triple, depending on whether the group allocation is concealed to one or more of those involved in the study. Blinding is considered an important strategy for minimising measurement and observer bias, and is in many cases desirable in all experimental trials, no matter design.[139] Due to the strong internal validity demanded in explanatory RCTs, the design fits well to answer the question: *Can this intervention work under ideal conditions?*

Another methodological design, which complements the explanatory RCT, is the *pragmatic* RCT. The pragmatic RCT is more flexible and accommodates natural or normal conditions found in usual clinical practice. Instead of placebo or sham control group, usual care is preferred as control, constituting a more natural setting, relevant to clinical practice. Further, the pragmatic approach does not necessarily imply blinding. Lack of blinding may on one hand reduce internal validity and be regarded as a weakness. On the other hand, an open study may contribute to a more natural way of conducting the intervention in accordance with real life.[140] No blinding may thus be a conscious choice by the investigator. Further, blinding is not always feasible in pragmatic trials, due to practical reasons. For example, it may be difficult to blind caregivers and patients to major surgery or nursing procedures. Nevertheless, blinding the outcome assessor to eliminate biased comparison of the outcomes is in most cases possible.[141]

A pragmatic RCT aims to attain strong external validity[142] and demonstrates that the results are of interest beyond the specific effects. Non-specific effects are considered “an outcome other

than predicted or caused by the treatment being employed".[143] The pragmatic design treats practical realities like ambiguity and complexity as parts of the results, and not as biases or casual noise. Thus, the pragmatic design allows for the possibility to investigate the system effect, or the whole treatment package, i.e. outcome measures including both specific effects produced by e.g. acupuncture needling, and associated non-specific effects produced by placebo. These effects include expectancy to treatment and interactions between caregiver and patient.[23,144] The outcome measures are referred to as the *effectiveness* of a treatment and are suitable to answer the question: *Can this intervention be useful in clinical practice?* Table 4 displays the different features of explanatory versus pragmatic trials.

Table 4 Features of explanatory and pragmatic RCTs

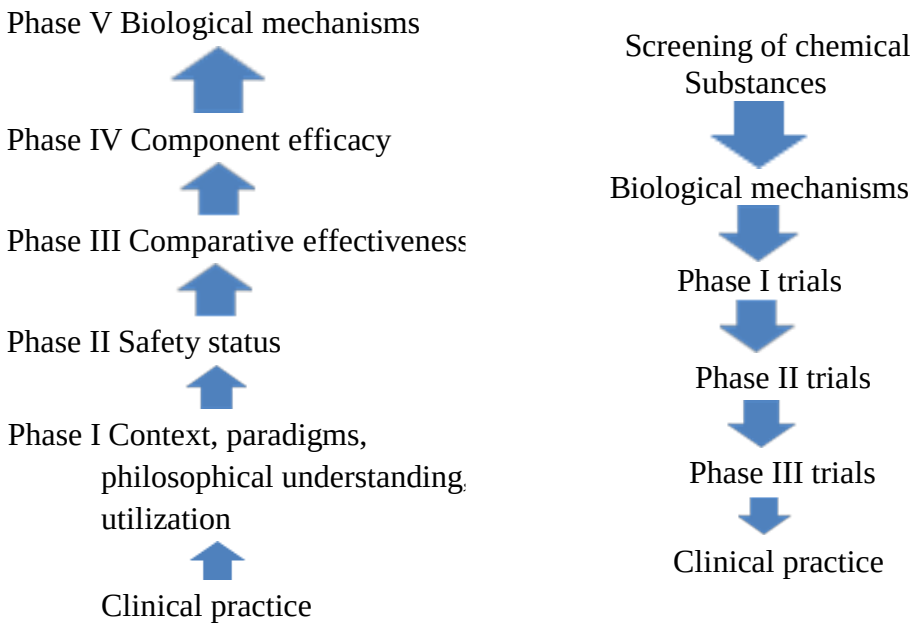
Explanatory RCTs	**Pragmatic RCTs**
Experimental setting	Routine care settings
Evaluate efficacy	Compare effectiveness
Placebo controlled	Not necessarily placebo controlled
Patients blinded to minimise bias	Patients unblinded to maximise synergy
Aim to equalise non-specific effects	Aim to optimise non-specific effects
Standardised treatment, simple interventions	Routine treatment, complex interventions
On-treatment-analysis	Intention-to-treat-analysis
Homogenous group of patients	Heterogeneous group of patients

The table is modified from Alford[139] and Macpherson[140]

Few studies are purely pragmatic or explanatory, and these pure designs may actually not be an optimal option. On the contrary, experimental studies are typically designed on a pragmatic – explanatory continuum.[145] To which degree a particular study displays varying levels of pragmatism depends on the purpose of the study and on the balance between internal and external validity.

NAFKAM [Nasjonalt Forskningssenter innen komplementær og alternativ medisin (National Research Centre in Complementary and Alternative Medicine)] at UiT the Arctic University of Norway proposes a five-phase research strategy for complementary and alternative medicine.[141] This strategy differs from the conventional drug trial strategy (Figure 2).

Figure 2 Research strategies in CAM trials and drug trials



Phases that contrast the proposed phased research strategy in CAM (left) with that conventionally used in drug trials (right). Figure reproduced with permission from Vinjar Fønnebø.

The rationale for investigating safety and effectiveness before efficacy of a treatment is stated by Fønnebø et al:[141]

> Unlike conventional medicine, CAM has no regulatory or financial gate-keeper controlling their therapeutic 'agents' before they are marketed. Treatments may thus be in widespread use before researchers know of their existence. In addition, the treatments are often provided as an integrated'whole system' of care, without careful consideration of the safety issue.

According to Fønnebø[140] it is thus important to provide secure evidence of safety and overall effectiveness of acupuncture in clinical practice before one start investigating presumed specific effects.

A pragmatic RCT is a feasible method of choice when it comes to phase III, comparative effectiveness, in the CAM research strategy. The flexibility of the pragmatic approach allows

the treatment to function as it is clinically practiced. Explanatory RCTs are well suited for phase IV, component efficacy. The specific effect is investigated per se, and little flexibility reduces the possibility of bias and confounders.

3.10 Surveys

Survey as a research method is non-experimental, obtaining "information about people's activities, beliefs, preferences and attitudes via direct questioning".[68] Study participants complete a self-report questionnaire, and they typically report on information about their attitudes and beliefs. Many different topics can be explored, and it is easy to obtain large sample sizes. However, the information obtained may be superficial compared to interviews, which goes deeper into participants' feelings and behavior.[68]

3.10.1 Validity and reliability

Testing validity and reliability is important for assessing the quality of a questionnaire. Validity is defined as "the conceptual adequacy of instruments that measure abstract human traits".[68] Validity is thus the degree of correspondence between the theoretically defined concept and the operational definition.[146] To be more precise, it is not the operational definition per se, it is also how successfully it is measured. Flaws during data collection reduce validity as it reduces the correspondence between the defined and operationalised construct.

Reliability is defined as "the degree of consistency or dependability with which an instrument measures an attribute".[68] Thus, reliability refers to the degree of accuracy with which the instrument measures the data, whether it actually measures what it is assigned to.

4 Paper I and II: Clinical trials on postoperative morbidities in children

- Paper I: Perioperative acupuncture and postoperative acupressure can prevent postoperative vomiting following paediatric tonsillectomy or adenoidectomy: a pragmatic randomised controlled trial[1]
    - Objective: To investigate the effectiveness of peroperative acupuncture and postoperative acupressure as supplements to standard treatment
- Paper II: Acupuncture versus usual care for postoperative nausea and vomiting in children after tonsillectomy/adenoidectomy: a pragmatic, multicentre, double-blinded, randomised trial[2]

- Objective: To investigate the effect of a standardised acupuncture on nausea and vomiting in children after tonsillectomy with or without adenoidectomy, with the intention to exclude possible placebo effects, in particular in parental expectancy by using a deceptive design

A presentation of Paper I and II in the same section is appropriate, as they are both clinical trials investigating the effect of acupuncture.

4.1 Material and methods Paper I and II

The material in Paper I and II are similar; children admitted for tonsillectomy and/or adenoidectomy to ambulatory departments were invited to participate in the studies. The inclusion criteria were children from 1 (12 kg) to 11 years of age and American Society of Anaesthesiologists physical status grade ≤ 2. The exclusion criteria were parents requiring interpreter, rash or local infection over the relevant acupuncture points, emesis or antiemetic treatment during the previous 24 hours, and gastrointestinal illness.

Further, some features of methods were similar in the two papers; usual care was used for control, the study period was 24 hours, and the analyses were performed in accordance with the intention-to-treat principle. However, since the objectives in Paper II involved ruling out placebo effects, different methods were chosen, as displayed in Table 5.

Table 5 The various methods in Paper I and II

	Paper I	**Paper II**
Study design	Pragmatic, open (unblinded) RCT	Pragmatic, multicentre, double-blinded RCT
Intervention	PC6 peroperative acupuncture and postoperative acupressure	PC6 peroperative acupuncture
Primary outcomes	Vomiting	Nausea, vomiting
Secondary outcomes	Overall experience of malaise, factors of predispositions to PONV	Overall experience of malaise, pain
Anaesthesia	Standardised regimen	Non-standardised regimen

Paper I should be classified as phase III, using research strategy of CAM as proposed by NAFKAM (Figure 2); the system effect of acupuncture and acupressure was investigated. Paper II should also be classified as phase III, but contain some phase IV characteristics; since parental expectancy, which is a part of the non-specific effects, was precluded in the two study groups, the whole treatment package was limited. Thus, Paper II tends towards a specific effect study. Nonetheless, a pragmatic RCT was an appropriate approach for the purpose of both Paper I and II; it allowed for the treatment to act as intended in clinical practice and to compare the treatment with usual care. When findings from a pragmatic study show that an intervention makes a significant difference compared to usual treatment, the study has demonstrated that the intervention may work in real clinical settings.

4.2 Procedures Paper I and II

The parents received beforehand an information letter about the study. On the surgery day, the parents were informed verbally by the principal investigator. The children were fasting, but they were allowed to drink clear fluids up to two hours before surgery. If eligible for the study and terms agreed on, the parents gave their written consent (appendix I and V), and completed forms containing baseline data (appendix II and VI).

The children were randomised to group allocation by the anaesthesiologist after induction of anaesthesia, thus concealing allocation until time of intervention. The anaesthesiologist performed PC6 needling acupuncture during anaesthesia (Paper I and II), and applied bilateral acupressure wristbands postoperatively (Paper I). The wristbands stayed on for 24 hours. There was no manipulation of the acupuncture needles after insertion. The needle retention mean time in Paper I and II was 17 and 18 minutes, respectively.

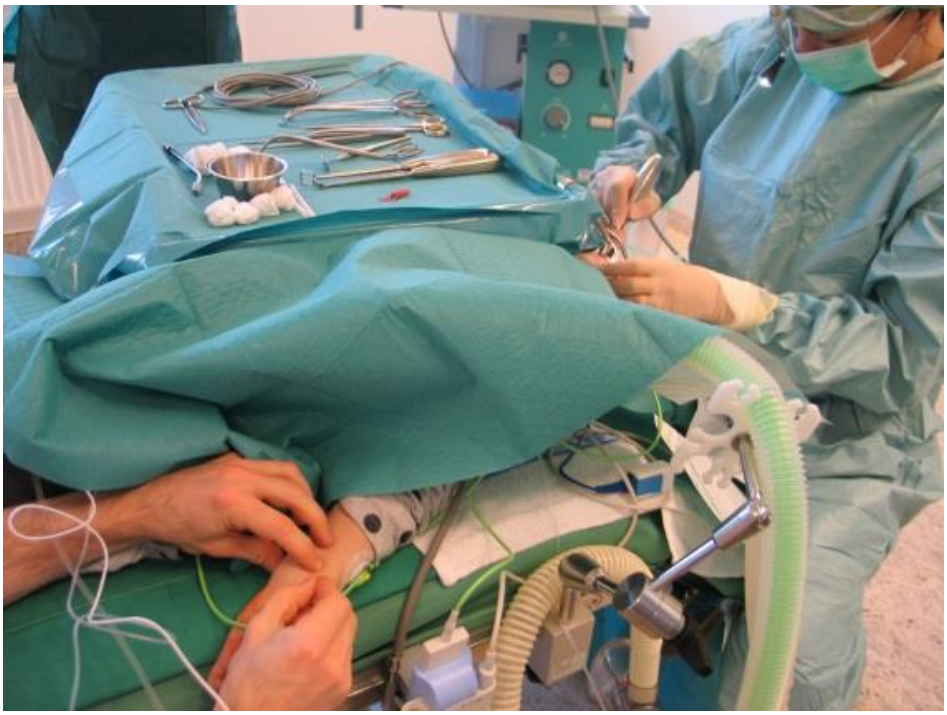
Paper II describes a double-blinded study. An adhesive tape covered the acupuncture points whether the child had received acupuncture or not. Thus, children, parents, and personnel in touch with parents and children postoperatively were blinded. Acupuncture during anaesthesia is illustrated in Figure 3.

4.3 Assessments and measurements Paper I and II

The parents were instructed about the position of the wristbands (appendix III) and how to assess and measure vomiting by using the designated forms (appendix IV and VIII). The parents also reported on their evaluation of the children's experience of overall malaise as none, minimal, moderate, great, or severe.

In Paper II, the parents were instructed to employ a behaviour tool, FLACC-N[147] to measure pain in children < 5 years of age[148] (appendix IX). In children >5 years of age, the parents used the Faces Pain Scale[149] (appendix X), and the BARF nausea scale[150] (appendix XI). The principal researcher collected the data by telephone 24 hours postoperatively.

Figure 3 Acupuncture peroperatively



4.4 Summary results Paper I

The study included 154 children admitted for tonsillectomy and/or adenoidectomy. A statistically significant lower proportion of children in the intervention group experienced vomiting compared to control; 46.8 % versus 66.2 % (p = 0,015). This difference was also expressed in the parents' overall subjective evaluations of their children's experience of discomfort; no discomfort was evaluated to 53.2 % in the acupuncture group versus 36.4 % in the control (p = 0.035).

4.5 Summary results Paper II

The study included 282 children admitted for tonsillectomy and/or adenoidectomy. This study did not demonstrate any significant differences in vomiting between intervention group and control; 44.2 % versus 47.9 % (p = 0.532). Likewise, the study showed no effect of acupuncture on nausea. Nausea was experienced by 31.7 % in the intervention group and by 32.6 % in the control (p = 0.928).

4.6 Discussion Paper I and II

Varying characteristics of the acupuncture treatment and methodological differences between the two studies may have produced the ambiguous results. The acupuncture complexity – customised versus standardised – should also be considered. These issues will be discussed in the next sections.

4.6.1 Acupuncture timing

One issue much debated is whether the timing of acupuncture – before, during, or after emetic stimuli, including surgery and anaesthesia – is essential to outcomes.[92,93,151]

A long-lasting and not yet solved conundrum is whether the unconscious state of the brain during anaesthesia implies little or no response to acupuncture. Some researchers contend that using acupuncture for re-establishment of the energy flow in the body demands a nervous system unaffected by drugs. Another hypothesis put forward is that acupuncture is not effective beyond placebo and accordingly does not work during anaesthesia, because the patients are unconscious and not aware of the treatment.

Acupuncture during anaesthesia is of particular interest with regard to acupuncture needling in children, as they may be afraid of the procedure. One objective for care-givers is to reduce patients' anxiety and distress, and implementing another needling procedure may not be advisable. Performing acupuncture during anaesthesia is well tolerated, and is thus a means of limiting strains on both children and parents.

Table 2 and Table 3 show different timing of acupuncture treatment in children, pre-, per- and postoperatively; the results are ambiguous and inconclusive. However, 4 out of 12 studies applied acupuncture during anaesthesia, [92,98,99,102] and among them, three found acupuncture to be effective.[92,99,102] Acupuncture studies performed on adults are in line with these findings,[85,98,152] and support the notion that the brain actually is able to respond to acupuncture under the influence of anaesthesia. Based on this notion, the similar outcomes of nausea and vomiting in the Paper II study might be explained *not* by an ineffective acupuncture, but by the fact that all parents were told that the children received acupuncture, which in turn created a placebo effect in the postoperative period that levelled out potential differences (caused by a specific acupuncture effect) of the outcomes. Since peroperative acupuncture was followed by postoperative acupressure in the Paper I study, it is not relevant to draw any conclusions whatsoever on this matter.

4.6.2 Acupuncture techniques

The children in Paper I received acupuncture peroperatively followed by acupressure postoperatively. One may speculate whether the significant results in Paper I merely was caused by acupressure. The literature on effect of acupressure wristbands in children is sparse and lends little verification on this matter. One study, performed back in 1991, showed no effect of PC6 acupressure on postoperative nausea and vomiting after strabismus surgery.[97] A later study on strabismus surgery from 2000 used Korean hand-acupressure and showed that the incidence of vomiting in the acupressure group was significantly lower compared to the placebo group.[153] However, Korean hand acupressure in most respects differs from body acupressure, which makes this comparison somewhat like comparing apples with oranges.

A pioneer in acupuncture research, J.W. Dundee, performed a study on the antiemetic effect of acupuncture followed by acupressure.[154] His study suggested that acupressure prolonged the antiemetic effect of acupuncture. However, this study included cancer patients receiving chemotherapy, and the results cannot - without major reservations - be extrapolated to patients suffering from PONV.

4.6.3 Acupuncture performance

Another component considered important by the acupuncture community, is the needling sensation, or *de qi*, a phenomenon described by patients as a sensation of tingling, soreness, heaviness, or numbness at the stimulated acupuncture point. *De qi* is dependent on several factors related to the needling procedure such as needle stimulation and needle depth. Some acupuncture points are also more inclined to achieve *de qi* than do others.[155] In the present studies the dose of acupuncture might have been too small, as the acupuncture points were not further stimulated after insertion. The needle-depth of 7 mm was, however, satisfactory, according to clinical practice. The children's perception of *de qi* was precluded; it was impossible to assess whether *de qi* was obtained or not, as acupuncture was performed while the children were anaesthetised. However, literature indicates that assessing *de qi* is not necessarily important to obtain effects of acupuncture in children.[98,99,102]

The acupuncture needling experience of the acupuncturist has also been claimed to influence the provocation of *de qi*.[155] A post-hoc sub-analysis (Paper II), was not able to detect any differences in outcomes when acupuncture was performed by an anaesthesiologist who also was an experienced acupuncturist, compared to acupuncture performed by non-experienced.

4.6.4 Methodological differences

The flexibility, regarded a pinnacle in a pragmatic design, is prominent in both paper I and II. Similarly, both studies used usual care as comparison to acupuncture. The two studies are robust, characterised by large sample sizes and no loss of follow-up data. The two papers are similar in terms of baseline characteristics, settings, types of surgery and surgical procedures. However, the two studies had different objectives and approaches; in Paper I the whole system effect of acupuncture was investigated. In Paper II the specific effect was sought, by trying to exclude placebo effects, in particular placebo produced by parental expectancy. Hence, the Paper I study was open, in contrast to the Paper II study, which was double-blinded.

Singlecentre versus multicentre studies

Paper I is a singlecentre study, with obvious advantages regarding homogeneity in therapeutic procedures and data collection. However, according to the pragmatic RCT comprehension this may not be ideal; as the intentions are that the results should be applicable to more than one centre.

Paper II is a multicentre study. The ambiguity in methods appearing in multicentre studies is welcomed in a pragmatic design, as it strengthens the external validity, and the results can be generalised across settings in clinical practice.[156]

There are also ambiguities appearing within each centre. Care-givers, representing different personalities, experience, and knowledge influence differently on the experiment, settings and interaction between care-giver – patient.

A block-randomisation was used with the intention to control for this possible confounding variable in the studies.

Open versus blinded study

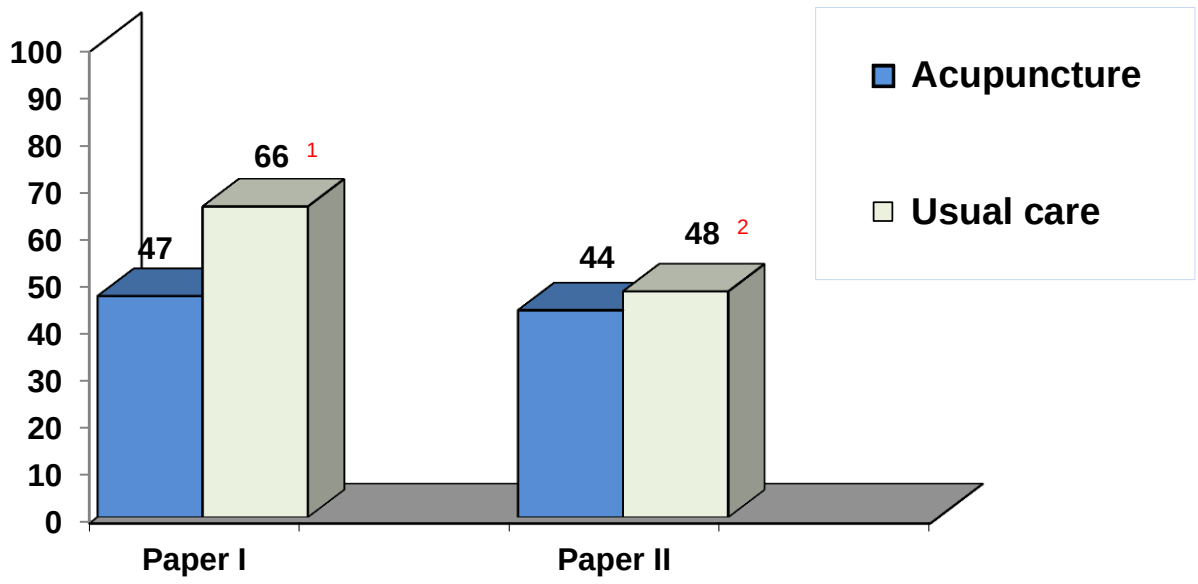
In the open Paper I study, the frequency of vomiting in the acupuncture group was 47 %, and 66 % in the control group. In the treatment group, the outcomes might have been positively influenced by expectancy to treatment, and the children might have benefitted from a positive attention entailed by the colourful wristbands. These factors may give rise to a placebo effect produced by both children and by proxies.

In the usual care group, the outcomes might have been negatively influenced by lack of expectancy. Some parents might also have been disappointed because their child did not receive acupuncture, resulting in change of attitudes and behaviour towards the child. This may give rise to a possible nocebo effect.

The Paper II study was double-blinded, and parental expectancy to perceived treatment was supposed to be levelled out between the groups by use of deception. The frequency of vomiting in the acupuncture group was 44 %, and 48 % in the control group. These similar rates of vomiting may be explained by the even distribution of expectancy to perceived treatment.

The vomiting rates in the acupuncture groups in Paper I and II, and in the usual care group in Paper II are strikingly similar (47 %, 44 %, and 48 %) (Figure 4). These three groups have one common characteristic; all parents *were told* that their child received acupuncture. A credible explanation may be that knowing or believing that the children received acupuncture lead to a positive parental expectancy to the acupuncture treatment, which in turn may have given rise to a placebo effect by proxy. One may question the comparison of results from the two studies with different design, but it is tempting to assume that the similarities between the vomiting rates indicate that a placebo and nocebo effect may be at play.

Figure 4 Vomiting in association with acupuncture and usual care in Paper I and II.
Numbers are in %



[1] The usual care bar in Paper I is significantly higher compared to the other three bars. One characteristic of this group was that parents and children knew that they had been allocated to the control group, possibly resulting in nocebo effects due to less expectancy.

[2] The usual care bar in Paper II is strikingly similar to the acupuncture bars in Paper I and Paper II. The three groups have one common characteristic: Parents were told that the children received acupuncture, and their expectancy to acupuncture might have produced similar placebo effects.

Types of anaesthesia and surgical techniques

In Paper I, volatiles were employed for induction of anaesthesia, and intravenous medication for maintenance. In Paper II, anaesthesia was given at the anaesthesiologist's discretion; either induction with volatiles and maintenance with intravenous anaesthesia, induction and maintenance with volatiles, or induction and maintenance with intravenous anaesthesia. Propofol has antiemetic properties, and it is well established that maintenance of anaesthesia with propofol is superior to volatile agents, including isoflurane and sevoflurane with or without nitrous oxide, in terms of reducing postoperative nausea and vomiting in adults and children.[157-161]

The surgical techniques were chosen at the surgeons' discretion, and included knife, loop, and scissors, with or without diathermy. The advantages of the different techniques are debated, and there is no consensus on which technique is considered superior. However, there may be more pain related to the use of diathermy relative to cold dissection.[162] In the present studies, no data on different surgical techniques were collected.

Again, block-randomisation was used to control for possible confounding variables, including type of anaesthesia and surgical technique.

Blood swallowed after surgery may stimulate the gastrointestinal tract and provoke the vomiting reflex. However, measuring the amount of swallowed blood is practically unfeasible.

4.6.5 Acupuncture complexity – customised versus standardised treatment

Traditional Chinese acupuncture is considered a complex intervention, and a customised treatment is a fundamental principle in TCM. This implies for instance that the same patient can be treated with different acupuncture techniques by different acupuncturists at different times. The treatment is based on individual syndromes; one single condition diagnosed in western biomedicine may in Traditional Chinese medicine be defined as several *syndroms*[163] implying stimulation of several acupuncture points, along with e.g. lifestyle recommendations. A common objection raised by traditional acupuncturists when referring to inadequacies of acupuncture studies, is that the acupuncture intervention was standardised. A standardised acupuncture protocol does not consider patient individuality, different *syndromes*, and delicate differences in acupuncture technique. Thus, a standardised procedure may be destined to failure.[141,164], According to these views, it may be considered inappropriate to design trials based on standardised interventions as was done in Paper I and II.

Access to the PC6 acupuncture points during ear, nose and throat surgery is easier than for other points, and the use of wristbands for acupressure is convenient. For feasibility reasons, which are emphasised in pragmatic studies, the PC6 points were chosen. The standardised acupuncture in the two studies did not demand any extra time or resources, and was easy to learn and perform by the existing personnel. An additional aspect is that a standardised intervention is more justifiable in terms of safety considerations, especially when the personnel performing the needling are not trained acupuncturists.

Based on the above considerations, one may question whether the standardised acupuncture methods were insufficient or too weak in the present studies, in terms of no individual treatment, acupuncture during anaesthesia, no manipulation of the needles after insertion, few acupuncture points, and relatively short needling retention time. However, the question whether an individualised acupuncture has better outcomes compared to standardised acupuncture is still not resolved.

As previously discussed in 8.6, it is uncertain whether different techniques and characteristics influence the effects of acupuncture, and a study on standardised versus individualised acupuncture did not detect any statistically significant difference.[163] A customised intervention makes it possible to take into consideration all individual aspects. However, to implement a new treatment in the busy daily routines of ambulatory anaesthesia, the treatment must be feasible and preferably not demand any extra resources. Introducing a customised acupuncture may be too challenging in a busy clinical setting, as it demands more resources including educated personnel and time. So, there remains a challenge to manage this trade-off between a customised and a standardised intervention.

4.7 Alternatives to controlling for participant expectancy

An unsuccessful blinding may give rise to an uneven distribution regarding perceived treatment, which could contribute to any observed differences between treatment and control group. Recognising that perfect blinding in RCTs is hard to achieve, and that expected efficacy and perceived treatment may influence treatment outcomes, some alternatives to the RCT design have been suggested. This includes the balanced placebo design, the cross-over design, the open versus hidden design, and the active placebo design.[16,165] These designs are not all suitable for every kind of treatment modalities. The balanced placebo design represents an alternative to the design used in Paper II. In this setting half of the participants *are told* that

they are receiving the treatment of investigation and the other half are told that they are receiving control treatment (or placebo). However, in both groups, only half of the participants in each group actually receive the treatment or control (Table 6).[165]

Table 6 The balanced placebo design

Participants told they receive	**Participants receive**	
	Treatment	***Control***
Treatment	Treatment with expectancy A	Treatment without expectancy B
Control	Placebo with expectancy C	Placebo without expectancy D

The design permits several different assessments of treatment and control (or placebo) effects. Comparing the groups A and C is similar to the method used in Paper II, and might have given corresponding results. Another way to level out participant expectancy could be to compare B and D. As in Paper II, the balanced placebo design implies deception and is accordingly subjected to guidelines for deception in research.[166]

A drawback of the design is that it may be difficult to convince sceptic participants about the rationale for explicit information on group allocation beforehand. It may be necessary to have a "cover story" at hand to explain why that kind of information is given.[165] Furthermore, in order to attain statistical power, a much higher number of participants would be needed, compared with a conventional RCT.

4.8 Ethics

Burdening participants with inquiries about baseline characteristics, registration of postoperative morbidities, and questionnaires was one among several ethical problems raised in the present RCTs. However, parents usually have a positive opinion of paediatric clinical research. Most parents believe that participating in a study accrues benefits to the child, both through getting access to an additional treatment that may be effective, and because the

attention entailed by participation is per se considered a positive experience. Further, most participants find satisfaction in contributing to science and to knowledge benefitting children in the future.[167,168]

In many cases admission to hospital for surgery involves unpleasant feelings like distress, anxiety and fear in parent and child. We found that adding further distress by acupuncture needling was not desirable. Acupuncture needling while the child was anaesthetised was thus a solution beneficial to all parties in the present RCTs.

A thorough deliberation within the research group concluded that the benefits from a deception study (Paper II) outweighed the objections; the aim and objectives of the study justified the design. The evidence of the effect of acupuncture is inconclusive, and all children received prophylactic antiemetics. The probability that parents would think that the children in the control group were exposed to inadequate treatment was very small. Accordingly, there were little indications that parents would not want their child to participate if the study design were explained beforehand.

5 Paper III: Survey

- Paper III: Placebo by proxy – The influence of parental anxiety and expectancy on postoperative morbidities in children[3]
    - Objective: To investigate whether parental anxiety to surgery and expectancy to acupuncture treatment influence on postoperative morbidities such as nausea and vomiting in children.

5.1 Material and methods Paper III

The study reports on data based on a self-report closed-ended questionnaire (appendix VII), completed by one of the parents of the children participating in the Paper II study. To avoid selection bias due to possible inadvertent preferences of the researcher, we assigned mother to be first choice, father second, for participation. The questionnaire had a 9-point rating scale. The answer options *yes/no* and *don't know* were employed when appropriate. The questions reflected preoperative parental expectancy to acupuncture, their anxiety to the impending surgery, and their previous experience of acupuncture. The questionnaire is displayed in Appendix VII.

5.2 Procedures Paper III

Parents who had given consent for their children to participate in the RCT completed the questionnaire under guidance from the principal investigator while the children underwent surgery.

We performed a pilot study to assure that the parents perceived the questions straightforward and easy to comprehend, and that the timeframe available for the completion of the questionnaire was sufficient. No need of changes of the protocol was detected in the pilot.

5.3 Results Paper III

Parental preoperative anxiety to surgery and expectancy to acupuncture treatment did not influence on postoperative morbidities such as nausea and vomiting. However, a type II error cannot be ruled out, as a post-hoc power calculation yielded a value of 0.82, assuming a 40 % prevalence of vomiting/pain in the 1st quartile of anxiety or expectancy, and 65 % in the 4th.

5.4 Discussion Paper III

5.4.1 Reporting bias

Reporting bias is an umbrella term consisting of several biases that are challenging problems in the design and administration of questionnaires. Reporting biases are outlined and discussed in the following section.

Selection bias occurs if those who are invited to participate are not representative of the whole, relevant population.[169] A low refusal rate for study participation is therefore favorable.[68] A non-response bias may also be a problem in questionnaires, especially if the characteristics of those who do not respond differ from those who do. All parents who had given consent to participation in the Paper II study completed the questionnaire.

Questionnaire biases can produce inaccurate or incorrect results due to unintentional communication problems between researcher and participants.[170] We used a face-to-face survey; the parents completed the questionnaires under guidance from the principal researcher. This should enhance data quality, as misapprehensions could be clarified. “Faking good”, also known as social desirability, may produce response bias;[170] participants may alter their responses in the direction that they perceive to be desired by the investigator. Moreover, participants want to do well, and may be inclined to give socially desirable responses that do not reflect how they actually feel or believe.

A so called "forced choice" is another source to create response bias, i.e. questions that provide too few options can force participants to choose imprecisely among limited alternatives. Example: *Have any friends or family members ever received acupuncture?* The response options in the present survey were *Yes/No/Don't know*. If the *don't know* category were absent, it might have produced a bias because participants who didn't know were forced to select an answer that did not correspond to their experience. On the other hand researchers are often reluctant to give the *don't know* option, because it may reduce the effective sample size and representativeness of the data. However, this issue is probably more relevant when the questionnaire is intended to reveal opinions, which was not the case in the present questionnaire.

An even or an odd number of categories in a scale may produce different results. Example: *How logical does acupuncture treatment seem to you?*

Not at all logical 1 – 2 – 3 – 4 – 5 Very logical
Not at all logical 1 – 2 – 3 – 4 Very logical

The first scale, with an odd number of categories, tends to result in neutral answers (participants checking the 3 on the scale). The second scale, with an even number of categories, tends to force participants to take a stand. The two approaches produce different results, but there is no general consensus as to which one is better. Further, participants usually avoid extremes of scales, and tend to try to be in the middle. This is referred to as the *central tendency bias*.[170]

Finally, it is important to be aware of participants' different reasons to complete a questionnaire. It can be due to interest, boredom, a desire to help others (particularly true in health-related studies). They may feel a pressure, or a wish to please the researcher. [171]

5.4.2 Placebo by proxy

Understanding the extent to which parental expectancy to acupuncture has an impact on treatment outcomes may provide important knowledge about the placebo response, including specific and unspecific effects of acupuncture treatment in children. Paper III is, to my knowledge, the first paper publishing results of placebo by proxy on acupuncture in children.

The outcomes were subjective measurements of pain and nausea, and objective measurements of the frequency of vomiting. We presumed that parents having high expectancy about the effect of acupuncture would be positive and provide a supportive and less stressful environment, resulting in children experiencing less pain and vomiting. Surprisingly, we found

no placebo effects by proxy. Since parents in both groups thought that their child received acupuncture, the perceived treatment was the same. This indicates that there was placebo effect, and not a specific effect involved in both groups – a different placebo effect than the one associated with the preoperative expectancy that we have accounted for.

The concept *placebo by proxy* is only part of the total placebo/nocebo picture, and may be modulated significantly by a potentially strong postoperative influence. The assessed preoperative expectancy would be suspected to change by time, emerging into and through the postoperative period. These supposedly changing attitudes at critical moments during the postoperative period are not accounted for by the survey.

Another possible explanation to the non-significant result might be small variations between the quartiles of which parental expectancy was measured. However, when comparing first and fourth quartile, the mean scores of the scale from 0 to 9 were 4.0 and 7.8, respectively. Since this obviously is a significant difference, the result cannot be explained by a small variation.

5.4.3 Manipulated versus assessed expectancy

Colagiuri and Smith[17] found fewer studies demonstrating relationship between expectancy and outcomes when expectancy was assessed (without manipulation) relative to when expectancy was manipulated (produced by verbal suggestions). The strength of assessed expectancy is that the researcher can directly evaluate the effect on outcomes; but assessed expectancy is equivocal and arbitrary in nature and may be a weaker source. A manipulated expectancy, albeit reliant on the ability to influence expectancy, may be superior in determining an expectancy effect.

In the present study, the investigator emphasised on a neutral approach, in order not to manipulate parents' comprehensions or opinions about acupuncture. It was attempted to give all parents and children the same neutral information about acupuncture and the study. One may question whether it might have been possible to detect any association between a manipulated expectancy and treatment outcomes, since manipulated expectancy is a stronger source than the assessed one.

6 Paper IV: Review

- Paper IV: Acupuncture in ambulatory anaesthesia: A review[4]
    - Objective: To apprise and provide a summary of relevant literature evidence of acupuncture in ambulatory anaesthesia during the last 15 years

This article was initiated by a personal invitation from the journal *Ambulatory Anesthesia*[172] to contribute with a narrative review of acupuncture in ambulatory anaesthesia.

Writing this paper was a trade-off between doing a scientific full-scale systematic review versus responding to this specific and personal invitation, and the subsequent instructions from the journal. The scope for this article was to provide an overview of the results from RCTs on acupuncture and acupressure for postoperative morbidities in ambulatory anaesthesia over the last 15 years. The review is also picturing and comparing different acupuncture-like treatment modalities. This was regarded a fruitful approach to obtain a knowledge base relevant to the core aspects of this thesis.

According to the articles included in paper IV, *acupuncture in ambulatory anaesthesia*, is not a well-defined and agreed on topic. Writing the review uncovered a huge diversity of acupuncture modalities used in clinical contexts. There is a large heterogeneity of the term *acupuncture*, as a large number of treatment modalities presented as being acupuncture, are quite different from the definition of acupuncture as "inserting needles into well-defined acupuncture points".

The selection of different acupuncture points also differs greatly, and there is a myriad of treatment options like depth of needle insertion, frequency and number of treatments, degree of stimulation and timing. And finally – the methodology in the published papers located under the search words *acupuncture in ambulatory anaesthesia* varies greatly, regarding different aims, research methods, and endpoints.

The variation and heterogeneity cause difficulties in credible appraisals and interpretations of the results. To scrutinise acupuncture in ambulatory anaesthesia in a systematic review may be challenging. Therefore, a narrative review became a more reasonable approach, considering the available papers, and the purpose and aim of this thesis.

6.1 Material and methods Paper IV

Articles were identified through computerised literature searches. Medline, PubMed and Embase were searched for publications from 1st of January 2000 up to 1st of February 2015, with the search terms *acupuncture* or *acupuncture therapy* in combination with *ambulatory anaesthesia*/ambulatory *surgery*/*day surgery/postoperative*. Filters were English language, human, and clinical trial. Corresponding searches were performed using the terms *acupressure* or *wristbands.*

The intervention in the studies included whole body needling acupuncture or acupressure for alleviation of postoperative morbidities on patients who had undergone surgery in general or regional anaesthesia in an ambulatory setting. To secure quality, only peer-reviewed RCTs were included. In the wake of the development of standards for reporting scientific studies, including the CONSORT (Consolidated Standards of Reporting Trials) Statement[173] and STRICTA,[174] the quality of research articles have developed through the years. The anaesthesiological and surgical techniques have also evolved rapidly. We therefore decided to include articles published after the year 2000.

Skin-penetrating body acupuncture may differ from other acupuncture related techniques in terms of acupuncture relevance. Some acupuncture related techniques have quite different therapeutic approaches in terms of point selection, point specificity, skin penetration, theoretical foundation, stimulation intensity, and accuracy. Skin-penetrating body acupuncture may be regarded as *optimal acupuncture stimulation*, compared with other acupuncture related techniques, even though these techniques are featured as acupuncture.

6.2 Summary results Paper IV

Sixteen studies were included, eight on acupuncture and eight on acupressure. Five studies included children. Twelve studies reported on PONV and three reported on POP as primary endpoint. The studies encompassed a range of surgical procedures. Volatiles or intravenous agents were used for maintenance of anaesthesia.

Nine studies out of 16 found acupuncture/acupressure effective for primary endpoints including PONV, POP, sore throat, and emergence agitation.[1,15,98,101,152,175-178] One study found acupressure effective for vomiting, but not nausea,[179] and one study found acupuncture partly effective for pain.[180] Among the studies demonstrating the benefit of acupuncture, four studies found that acupuncture and antiemetics had similar effects.[101,175,177,178]

6.3 Discussion Paper IV

Despite inconsistency of evidence and lack of complete physiologic understanding, acupuncture is a significant therapeutic technique in eastern medicine and is gaining credibility in the western world as well. The results from the studies in the present review, albeit ambiguous, support the notion that acupuncture and acupressure may be beneficial adjuncts to antiemetics for PONV. Research supporting effects of acupuncture/acupressure for PONV are presented in several reviews and meta-analyses, including a Cochrane Systematic review,[11] and a Cochrane metaanalysis.[9] Meta-analyses are often fronted as scientific evidence at the highest level that can measure quality and validity in RCTs.[181] The Cochrane Collaboration[182] states that the *Cochrane Database of Systematic Reviews* "is the gold standard in evidence-based medicine and provides access to the most objective information on the latest in medical treatment". It is therefore reasonable to consider acupuncture for PONV as part of ambulatory anaesthesia. On the other hand, it is debateable whether acupuncture for other postoperative morbidities can be regarded evidence-based.

Acupuncture is gaining some acceptance in Norway. The national guidelines recommends acupuncture for hyperemesis gravidarum[183] and acknowledges acupuncture as evidence-based treatment for chemotherapy-induced emesis and PONV.[184] Accordingly, St. Olav Hospital in Trondheim, Norway, has integrated acupuncture as supplemental treatment for chemotherapy-induced emesis.[185]

6.4 Reporting bias

A review has limitations due to potential risks of reporting biases, which may be defined as an artefact of the selection and reporting process that may distort the results and undermine internal validity.[68] There are several types of reporting bias related to the present review that need to be addressed.

Collecting information from primary sources, i.e. from articles prepared by the original authors, is essential.[68] Reviews then, are secondary sources and should be avoided, as they may have flaws in terms of inaccuracies and lack of details. Further, they are seldom completely objective. This is referred to as publication bias. In the present trial, we collected information from primary sources, i.e. RCTs.

Duplicate publications bias entails several issues; apart from giving unfair credits to authors and waste resources, it may bias results of reviews.[186] Some duplicate publications fail to cross-reference each other, so it may be difficult to determine whether two papers are duplicate

publications of one study.[187] In this review process, we did detect duplicate publication; one study was published under different titles in two different journals and years, and no cross-references were stated.[178,188]

Location bias refers to where the article is published. It has been suggested that journals ranked with low impact factors tend to publish articles of lower quality and with more insecure results than do journals with high impact factor. This has been found to be the case in a study comparing CAM-journals and main-stream medical journals.[189] The majority of the articles in the present review were published in mainstream journals, predominantly specialised in anaesthesiology. Nonetheless, we cannot disregard the possibility of location biases.

Language bias refers to restricting literature search to English or other languages. This may cause bias against the representativeness of articles. The extent of language bias may have diminished because of the shift towards publication of studies in English over the years.[187] One cannot disregard that searching English language articles only, will entail the risk of missing useful information from articles written in other languages.

Outcome reporting bias implies selective reporting of some outcomes but not others, depending on the nature and direction of the results. An example of reporting bias in research is a study on antipsychotics sponsored by pharmaceutical companies,[190] in which it was found relationship between the sponsor of the trial and the drug favoured in the study's outcome.

Reporting only positive results is another outcome reporting bias; authors tend to refrain from submitting articles with negative results, peer-reviewers tend to reject reviewing, editors tend not to publish, and readers tend to ignore negative results. Assessing unpublished studies, if possible, is an attempt to remedy this bias. In the present review, only published studies were included.

Publication bias is also a problem in terms of adverse events. However, acupuncture adverse events are minimal and well known in the acupuncture society. Nevertheless, the possibility of reporting bias cannot be disregarded in the present review.

6.5 Possible confounding variables

A literature search on *bias* and *confounders* suggests that the distinction between the two terms is not clear from a statistical and methodological point of view. A stringent definition of a confounding variable is "a variable, other than the independent variable that you're interested

in, that may affect the dependent variable".[191] Confounding variables can lead to erroneous results about the relationship between the independent and dependent variables.

RCTs are designed to control confounding variables by randomisation and blinding. The purpose is to keep confounding variables similar or at the same level, in this case for all the participating individuals. All studies in the present review performed a randomisation procedure for group allocation. However, randomisation and blinding cannot be perfect in all aspects. Due to the fact that blinding the acupuncturist is difficult, quite a few of the studies reported that at least the patients and the data assessors were blinded. Thus, the unblinded acupuncturist may have influenced the outcome by conscious or unconscious attitudes towards the patients and other persons involved in the study. Moreover, one of the studies was open,[2] meaning that all persons involved knew about the patients' group allocation.

None of the studies used statistical techniques to control for confounders. Even not stated, one may presume that imperfect randomisation and blinding have occurred. Further, there are always confounding variables that are difficult to identify, and some cannot even be controlled, e.g. inherent properties of participants that are not registered as baseline characteristics. The possibility of confounding variables must be taken into consideration when judging the results.

7 Clinical implications: Future acupuncture treatment

The awareness and interest of CAM is increasing among patients and health caregivers in Europe and worldwide.[89-91] This trend has also been seen in Norway.[192] In a study performed in 2008 on *Use of complementary and alternative medicine at Norwegian and Danish hospitals*,[193] the authors concluded that "The extent of CAM being offered has increased substantially in Norway during the first decade of the 21st century. This might indicate a shift in attitude regarding CAM within the conventional health care system". However, a more recent survey has indicated that CAM use in Norway in 2014 has declined since 2012.[194] Nevertheless, one third of the responders in the latter survey had received CAM in 2014, and CAM is at present a significant part of the medical healthcare.[194] In the Paper II study, sixty-four percent of the parents reported that they had previously received acupuncture.

A report from 2008[18] showed that during the last decades, the use of CAM among children has been increasing in the U.S. Furthermore, CAM as supplement to conventional medicine seems to be appreciated by American parents.[19] Nurses are more positive to CAM than are physicians, and general practitioners are more positive than are hospital physicians. Surgeons are the most

sceptical of them all. Acupuncture is recognised as an additional medical qualification in several European countries, including Austria, Bulgaria, Czech Republic, France, Germany, Greece, Hungary, Italy, Portugal, Slovenia, Spain, and Switzerland. In Latvia acupuncture is recognised as a medical specialty.[195] In Norway it is allowed for everyone, with or without a medical authorisation, to perform acupuncture for therapeutic purposes, with some exceptions.[196]

In May 2014, the Health Assembly approved WHO's traditional medicine strategy 2014–2023. They stated that:

> Traditional medicine covers a wide variety of therapies and practices which varies from country to country and region to region. The strategy aims to build the knowledge base for national policies and strengthen quality assurance, safety, proper use, and effectiveness of traditional and complementary medicine through regulation. It also aims to promote universal health coverage by integrating traditional and complementary medicine services into health care service delivery and home care.[197]

Acupuncture treatment has been offered at a small scale to patients in Norwegian hospitals for decades. Different fields of medicine in which acupuncture is implemented are represented, e.g. maternity wards, palliative care, departments of emergency medicine, oncology and pain therapy, and surgical and anaesthetic departments.[193]

There are several barriers to a successful application of evidence based acupuncture to clinical practice. The process of integrating acupuncture treatment along with usual care rests on the caregivers' commitments and dedication to the process. The decision to introduce a novel treatment depends on a consensus in the department. Further, the integration must not only be supported, but also followed up, by the head management personnel. It is often a tremendous challenge to attain all care givers' loyalty towards translating a novel procedure into practice, especially over time. Therefore, a committed stakeholder is essential to maintain interest and engagement among the staff.

Recently, we published an article on a pilot study[198] and on a subsequent main study (Paper I).[1] The daily routines in ambulatory wards do not lend much time or resources to extra chores, but as expected, the pilot study demonstrated that the acupuncture treatment did not demand any of the kind. Further, the main study showed that acupuncture may be an appropriate adjunct to usual care for the alleviation of postoperative nausea and vomiting in children. One may speculate why acupuncture has not yet been integrated as part of usual care at the research site.

A predominant reason is that system effects including the whole treatment package, rather than the specific effects, is disregarded as evidence. Further, many medical scholars consider acupuncture unscientific[199] and pay little attention to it whatsoever.

Streitberger and Kranke maintained in a very aptly commentary[88] that there are several reasons for why acupuncture for postoperative nausea and vomiting has failed to enjoy the same popularity as pharmacological treatment: "1) Many anaesthesiologists are unfamiliar with acupuncture compared to the ease of an intravenous push, 2) Clear recommendations as to when and how to stimulate at PC6, and for how long, have yet to emerge, 3) Drugs are easier to administer (anaesthesiologists like the intravenous route because they have visual evidence that the drug has been given, and the effect is immediate), 4) The evidence for acupuncture point stimulation still fails to convince".

Acupuncture studies on adults are more extensive and also more conclusive than studies on children. However, findings in studies on adults cannot be extrapolated outright to children. Just as when treated with drug therapy, children may respond differently to acupuncture treatment. The literature indicates some evidence of effect of acupuncture even though the total evidence of effect for PONV in children is weak. Nevertheless, it is not appropriate to dismiss the use of combined treatment of acupuncture and antiemetic drugs, as one should not exclude the notion of synergy. The nature of neurophysiology of nausea and vomiting is complex, involving several transmitter substances and brain structures. A strategy of combining different antiemetics to address different causal pathways has therefore been recommended, and acupuncture is, in fact, one of the remedies listed.[7]

According to the pioneer of evidence based medicine, David L. Sackett,[200] evidence based medicine is "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients". Further, "The aim of evidence based health care is to provide the means by which current best evidence from research can be integrated to clinical practice". Up to date, the current best evidence of acupuncture may be regarded inconsistent; there is still controversy about the effect of acupuncture for PONV.[201] The results of the present thesis are in keeping with this view.

Even though the evidence of acupuncture effect might become more consistent and convincing over the next years, it will probably take several years before patients will be offered acupuncture treatment on a regular basis in Norwegian hospitals. Not surprisingly, it takes on average 17 years to implement research evidence into practice.[202] So the situation described is

not exclusive for acupuncture. Nevertheless, in the future, if a consistent body of knowledge emerges, acupuncturists might be incorporated as staff members and provide acupuncture to patients as supplement to conventional medicine.

8 Future research

Studies investigating acupuncture treatment for children in ambulatory anaesthesia should balance adequate dose and techniques for a child-friendly acupuncture treatment. In order to attain an optimal acupuncture effect, some issues are recommended: additional use of points in other parts of the body, e.g. ST36 (near the knee) and/or LI4 (at the dorsal aspect of the hand), and acupuncture stimulation after needling insertion.

Mitigating *de chi*, which is suggested from the acupuncture society to be a modifying factor, may be an option when performing acupuncture in children when awake. For the purpose of a child friendly approach, acupuncture should be performed during anaesthesia when appropriate.

Acupressure in terms of wristbands in addition to peroperative acupuncture is very well suited for the whole perianaesthetic period.

9 Conclusions

This thesis is based on acupuncture studies for alleviation of postoperative nausea and vomiting in children after adenoidectomy and/or tonsillectomy. In the two present RCTs using different design and methods, 436 children were included. Further, the concept placebo by proxy was investigated by means of a survey with 282 participating parents. Last, a review of 16 studies on acupuncture in ambulatory anaesthesia over the past 15 years has been provided.

The RCTs showed different results.

- When investigating the system effect as a whole treatment package using an open, pragmatic RCT (Paper I), acupuncture during anaesthesia followed by postoperative acupressure seems to reduce vomiting in children after tonsillectomy and/or adenoidectomy.
- When investigating the specific effect using a double-blinded, pragmatic, deceptive RCT with the intention to exclude placebo effects, in particular parental expectancy to perceived treatment (Paper II), acupuncture during anaesthesia does not seem to reduce nausea and vomiting in children after tonsillectomy and/or adenoidectomy.

- The survey (Paper III), embedded in the double-blinded study (Paper II), on preoperative parental expectancy to treatment efficacy and anxiety was not able to detect any such placebo effect by proxy.
- The vomiting rates in Paper I and II and in the control group in Paper II were strikingly similar in the acupuncture groups. It should be emphasised that these three groups had one common characteristic; all parents were told that their child received acupuncture. There may have been a placebo effect that was not captured by our measure of parental *preoperative* expectancy.
- The explanations for the manifest discrepancy between the RCTs – presuming that the results of Paper III are valid – should be sought understood by the following factors:
    - Placebo effects not accounted for by parental expectancy or anxiety (as assessed preoperatively): Influences emerging into and throughout the postoperative period on/by parents and children.
    - Placebo effects conveyed by care-givers and assessor in the postoperative period.
    - Nocebo effects (negative or indifferent influence) in the Paper I study, conveyed by all involved persons (children, parents, care-giver, and assessor) knowing that the children were allocated to control group.
    - A specific effect of acupressure in the postoperative period, as opposed to only acupuncture during anaesthesia.

    An explanation to the discrepancy is not straight forward, and probably there is a combination of several factors involved.

- The descriptive review (Paper IV) showed that acupuncture may alleviate postoperative morbidities in ambulatory settings. Some studies also found that the effect of acupuncture is similar to that of antiemetic drugs. These results are in line with a Cochrane meta-analysis. It is therefore reasonable to consider acupuncture as part of ambulatory anaesthesia. However, since conclusive evidence of acupuncture specific effects is lacking, there have to be a trade-off between these treatments and other strategies (such as antiemetics), where both ethical and economic considerations have to be assessed in the future.

- Based on the experience from the RCTs in this thesis, investigation on acupuncture treatment for children should manage a balance between an adequate acupuncture dose and technique, and a child-friendly approach.

- Interesting issues for future investigations may be use of several stimulation points, stimulation of the acupuncture points by the needles, and a combination of acupuncture and acupressure – in addition to the essential question about specific effects versus placebo effects.

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Appendix I

Paper I: Information and informed consent

Lovisenberg Diakonale Sykehus
Pionér i kompetanse og omsorg

Appendix I

Forespørsel og samtykkeerklæring om deltakelse i forskningsprosjektet *"Akupunktur og akupressur mot kvalme og oppkast etter operasjon"*

Bakgrunn
Dette er en forespørsel til deg, som forelder/foresatt, og barnet om å delta i et forskningsprosjekt for å se om akupunktur og akupressur kan forebygge kvalme og oppkast hos barn etter operasjon. Barn som får fjernet falske mandler (polypper) og/eller mandler (adenotomi/tonsillektomi), er dessverre spesielt utsatt for ubehag i form av kvalme og oppkast. Vitenskapelige studier viser at akupunktur og akupressur kan forebygge dette.

Lovisenberg Diakonale Sykehus er oppdragsgiver for prosjektet. Sykehuset samarbeider med Nasjonalt Forskningssenter for Komplementær og Alternativ Medisin ved Universitetet i Tromsø (NAFKAM). Prosjektleder er lege og spesialist i allmennmedisin/dr. philos. Arne Johan Norheim, som også er seniorforsker ved NAFKAM.

Forskningsprosjektet blir finansiert av Lovisenberg Diakonale Sykehus og er godkjent av Datatilsynet og Regional komité for medisinsk og helsefaglig forskningsetikk, Nord-Norge.

Hva innebærer forskningsprosjektet?
Dersom du vil at barnet ditt skal være med i forskningsprosjektet, ber vi deg skrive under to eksemplarer av *samtykkeerklæringen* nederst på dette dokumentet. Du må også fylle ut vedlagte dokument "*skjema for pasientopplysninger*". Begge dokumentene skal leveres til anestesilegen på operasjonsdagen. Ett eksemplar av samtykkeerklæringen beholder du selv.

Når barnet blir utskrevet fra postoperativ avdeling ber vi deg å notere om barnet har hatt kvalme eller kastet opp inntil 24 timer etter operasjonen. (Dette innebærer ikke at du må overvåke barnet kontinuerlig i 24 timer men bare føre på skjema de tilfellene du registrerer av kvalme/oppkast.) Du vil bli oppringt en av de nærmeste dagene etter operasjonen av en prosjektmedarbeider, som vil notere dine registreringer. Samtalen vil ta noen få minutter.

Sykepleieren som er ansvarlig for barnet på postoperativ avdeling vil også registrere kvalme og oppkast på det samme skjemaet. Registreringene vil bli lagret sammen med "Skjema for pasientopplysninger", "Forespørsel og samtykkeerklæring om deltakelse i forskningsprosjektet" og en kopi av anestesijournalen. For ordens skyld vil vi opplyse om at pasientskadeerstatning gjelder alle pasienter, og selvsagt er også barna som deltar i studien forsikret gjennom denne ordningen.

For at forskningsprosjektet skal bli gjennomført etter vitenskapelige prinsipper vil 168 barn bli fordelt i to grupper:

- Gruppe 1: Etter at barnet har sovnet av narkosen, stikkes en tynn nål i hver underarm (akupunktur). Nålene er tynne og fjernes før barnet våkner. Barnet får også et armbånd på hver arm, som trykker på ett bestemt akupunkturpunkt (akupressur). Det er ideelt om armbåndet får sitte på i 24 timer etter operasjonen, men dersom barnet ikke vil ha det på, kan det fjernes.
- Gruppe 2: Vanlig behandling, det vil si ingen akupunktur/akupressurbehandling. Barn som får vanlig behandling utgjør en svært viktig og verdifull kontrollgruppe.

Appendix I

Mulige fordeler og ulemper

Behandlingen, som vil bli utført av en anestesilege, vil normalt ikke medføre noe ubehag for barnet, men mindre punktblødninger og små blåmerker ved stikkstedet kan en sjelden gang forekomme. Barn som får akupunktur/akupressur kan ha fordeler av behandlingen, og erfaringer fra forskningsprosjektet vil senere kunne hjelpe andre i samme situasjon.

Hva skjer med informasjonen om barnet?

All registrert informasjon om barnet skal bare brukes slik som beskrevet i bakgrunnen for forskningsprosjektet. Alle data (pasientopplysninger, anestesijournal og registreringer om kvalme/oppkast) vil bli behandlet strengt fortrolig og uten navn og fødselsnummer eller direkte gjenkjennende opplysninger. En kode knytter barnet til opplysningene gjennom en navneliste, og det er kun autorisert personell knyttet til forskningsprosjektet som har adgang til. Det vil ikke være mulig å identifisere barnet i resultatene av forskningsprosjektet når disse publiseres.

Du har rett til å få innsyn i opplysninger som er registrert på barnet ditt. Du har videre rett til å få korrigert eventuelle feil. Dersom du trekker barnet fra forskningsprosjektet, kan du kreve å få slettet opplysningene som angår forskningsprosjektet.

Opplysningene blir senest slettet i februar 2009. Resultatene av forskningsprosjektet vil være klare i begynnelsen av mars 2009. Dersom du er interessert i å vite resultatene, kan du kontakte oss (Anestesisykepleier Ingrid Liodden, tlf. 23 22 61 86 eller anestesilege Michael Howley, tlf. 23 22 64 29). Resultatene vil bli publisert i norske og internasjonale medisinske tidsskrifter og vil også inngå i en masteroppgave i sykepleievitenskap ved Universitetet i Oslo.

Frivillig deltakelse

Det er frivillig å delta i forskningsprosjektet. Dersom du ikke ønsker å la barnet delta, trenger du ikke å oppgi noen grunn, og det får ingen konsekvenser for den videre behandlingen barnet får ved sykehuset.

Du kan når som helst trekke tilbake ditt samtykke uten å begrunne dette nærmere, og uten at det påvirker barnets øvrige behandling på sykehuset. Dersom du ønsker å trekke barnet fra forskningsprosjektet, kan du kontakte anestesilege Michael Howley, tlf 23 22 64 29.

Samtykkeerklæring

Jeg har lest informasjonen om prosjektet og fått muntlig informasjon og samtykker i å delta	Jeg bekrefter å ha gitt informasjon om forskningsprosjektet
----------	----------
(Signert av forelder/foresatt, dato)	(Signert av anestesilege, dato)

Samtykkeerklæringen fylles ut i 2 eksemplarer, hvorav det ene eksemplaret beholdes av barnets foreldre/foresatte, det andre leveres til anestesilegen operasjonsdagen.

Appendix II

Paper I: Children data form

Appendix II

Pasientopplysninger til undersøkelsen
"Akupunktur og akupressur mot kvalme etter operasjon"

Under finner du spørsmål som du som forelder/foresatt bes besvare. Besvarelsen tas med til sykehuset operasjonsdagen. Dersom noe er uklart med spørsmålene, kan du få avklart dette med anestesilegen når du kommer.

Barnets navn:

Fødselsnummer:

	Sett et kryss i ruten under det svaret som passer		
	Ja	**Nei**	**Vet ikke**
1. Har barnet opplevd reisesyke?			
2. Har barnet vært operert tidligere?			
3. Hvis ja på spørsmål 2, opplevde barnet kvalme/oppkast etter operasjon?			
4. Har noen av barnets biologiske foreldre vært operert tidligere?			
5. Hvis ja på spørsmål 4, opplevde noen av barnets biologiske foreldre kvalme/oppkast etter operasjon?			
6. Har barnet hatt kvalme/oppkast siste 24 timer før operasjon?			
7. Har barnet fått noen medisiner siste 24 timer før operasjon?			
8. Har barnet mage-tarmsykdom?			

Hvis du har spørsmål om undersøkelsen, kan du kontakte medisinskfaglig ansvarlig for studien: Overlege Michael Howley, anestesiavdelingen, tlf.: 23 22 64 29.

Med vennlig hilsen anestesiavdelingen

Appendix III

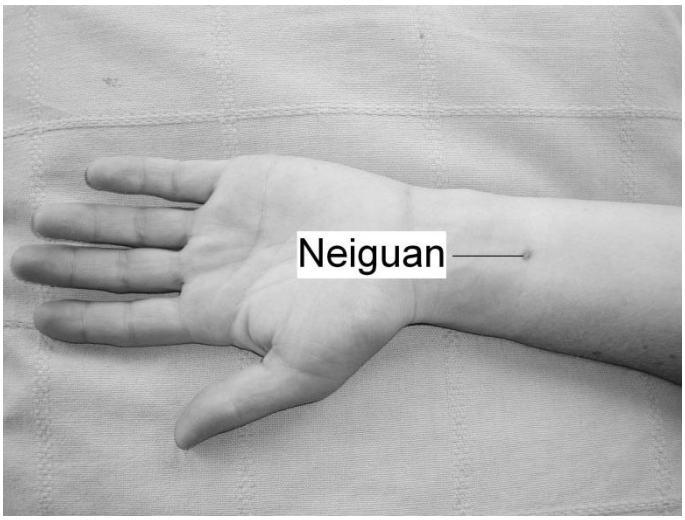
Paper I: Position of acupressure wristbands

Appendix III

Akupunktur/akupressur og postoperativ kvalme hos barn som har gjennomgått adenotomi og/eller tonsillektomi

Hvordan skal akupressur-armbåndet sitte på?

Informasjon fra sykepleiere til foreldre



Armbåndet har en plastknapp som stikker litt ut på innsiden.
Plastknappen skal plasseres over det lille, røde punktet (neiguan på kinesisk), som har oppstått etter akupunktur-nålestikket, på innsiden av armen.

Appendix IV

Paper I Data collection form

Lovisenberg Diakonale Sykehus

Pionér i kompetanse og omsorg

ID-lapp

Appendix IV

Registreringsskjemaet benyttes først av sykepleier på postoperativ avdeling, deretter av foreldre/foresatte

Foreldres/foresatte tlf. mobil: ..... tlf. hjem.....

Hvis barnet opplever **brekninger (B) eller oppkast (O)**, ber vi om at du noterer dette med en **B** eller **O** på linjen for det aktuelle tidspunktet, der **0 time** markerer når operasjonen er avsluttet, og **24 timer** er siste registreringstidspunkt. Flere tilfeller av brekning/oppkast i løpet av to minutter regnes som ett tilfelle.

Operasjon slutt kl...	**kl...**	**kl...**	**kl...**	**l...**	**kl...**	**kl...**
0 time	**1 time etter operasjon**	**2 timer**	**3 timer**	**4 timer**	**5 timer**	**6 timer**

kl	**kl**	**kl**	**kl**	**kl**	**kl**	**kl...**	**kl...**	**kl...**	**kl...**	**kl...**	**kl...**	**kl...**	**kl...**	**kl...**	**kl...**	**kl...**	**kl...**
7 timer	**8 timer**	**9 timer**	**10 timer**	**11 timer**	**12 timer**	**13 t**	**14 t**	**15 t**	**16 t**	**17 t**	**18 t**	**19 t**	**20 t**	**21 t**	**22 t**	**23 t**	**24 t**

Utskrevet fra postop. (fylles ut av sykepleier) kl.: ..... **Sykepleier tar kopi av registreringsskjemaet når barnet blir utskrevet fra postoperativ avdeling og legger kopi til mappen "Case Report form". Originalen overlates til foreldre/foresatte som fortsetter registreringen inntil 24 timer etter operasjonen**	**Sign. sykepleier:**

- For barn over 5 år: Har barnet opplevd kvalme? **Ja** □ **Nei** □ Hvis ja, hvor mange timer varte kvalmen etter operasjonen? ..... timer
- Har barnet hatt ubehag av akupunktur-nålestikkene? **Ja** □ **Nei** □ Hvis ja, på hvilken måte? Beskriv kort :.....

Det er ideelt om armbåndene får sitte på i 24 timer etter operasjonen, men dersom barnet ikke vil ha det på, kan det fjernes. Uansett er det viktig å notere tidspunktet:

- Armbåndene ble **fjernet kl .....**
- Har barnet hatt ubehag av armbåndet**? Ja** □ **Nei** □ Hvis ja, på hvilken måte? Beskriv kort: .....
- Vi ber deg sette ett kryss i en av boksene under som passer best med hensyn til hvordan du totalt sett synes barnets kvalme/oppkastplager har vært i løpet av de første 24 timene etter operasjonen.
  Ingen plager □ **Lite plager** □ **Moderate plager** □ **Mye plager** □ **Svært mye plager** □

Du vil bli oppringt en av de nærmeste dagene av en prosjektmedarbeider, som vil be deg svare på disse spørsmålene. Vi takker for at du vil delta i studien.
Med vennlig hilsen anestesiavdelingen

Appendix V

Paper II: Information and informed consent

Appendix V

Invitasjon til barn og foreldre om deltakelse i forskningsprosjektet «*Akupunktur mot oppkast og smerte etter operasjon*» i forbindelse med øre-nese- halsoperasjon

Bakgrunn
Barn som får fjernet mandler eller falske mandler (tonsillektomi/adenotomi), kan oppleve kvalme, oppkast og smerter etterpå. Resultater fra vitenskapelige studier tyder på at akupunktur kan forebygge disse plagene. Du og ditt barn inviteres nå til å være med i et forskningsprosjekt for å undersøke effekten av akupunktur gitt under narkose.

Forskningsprosjektet er et samarbeid mellom Asker, Diploma A/S og Nydalen øre-nese- halsklinikker og Nasjonalt Forskningssenter for Komplementær og Alternativ Medisin ved Universitetet i Tromsø (NAFKAM). Prosjektet er godkjent av Regional komité for medisinsk og helsefaglig forskningsetikk, Nord-Norge. Prosjektleder er akupunktør og spesialist i allmennmedisin/dr. philos. Arne Johan Norheim, som også er seniorforsker ved NAFKAM.

Hva innebærer forskningsprosjektet?
Prosjektet vil bli gjennomført etter vitenskapelige prinsipper, og 280 barn vil bli inkludert i studien. Opplysninger om deler av metoden i studien vil først bli avdekket når forskningsprosjektet er avsluttet.

Akupunkturbehandlingen vil bli utført av anestesilegen etter at barnet har fått narkose og sover. Det blir da satt en tynn nål i underarmene. Nålene fjernes igjen før barnet våkner, og et lite plaster vil bli satt over stikkstedet. Barnet vil således ikke merke akupunkturbehandlingen.

Anestesisykepleier/forskningsstipendiat Ingrid Liodden vil registrere oppkast, smerte og andre plager hos barnet etter operasjonen. Registreringene vil bli lagret sammen med skjema for pasientopplysninger, samtykkeerklæring om deltakelse i forskningsprosjektet og kopi av anestesi-journalen.

For ordens skyld vil vi opplyse om at pasientskadeerstatning gjelder alle pasienter, og selvsagt er også barna som deltar i studien forsikret gjennom denne ordningen.

Mens barnet ditt blir operert, vil vi be deg fylle ut et spørreskjema om hvilke holdninger og forventninger du har til at barnet ditt får akupunkturbehandling. Utfyllingen vil ta omtrent fem minutter.

Når barnet blir utskrevet etter operasjonen, ber vi deg frem til neste dag registrere om barnet har vært kvalm, kastet opp eller hatt smerter. Du vil bli oppringt en av de nærmeste dagene etter operasjonen av forskningsstipendiat Ingrid Liodden, som vil notere dine registreringer.

Mulige fordeler og ulemper
Akupunkturbehandlingen vil normalt ikke medføre noe ubehag for barnet, men en sjelden gang kan mindre punktblødninger og små blåmerker ved stikkstedet forekomme. Barn som får akupunktur kan ha

fordeler av behandlingen, og erfaringer fra forskningsprosjektet vil senere kunne hjelpe andre i samme situasjon.

Hva skjer med informasjonen om barnet?
All registrert informasjon om barnet skal bare brukes slik som beskrevet i bakgrunnen for forskningsprosjektet. Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller direkte gjenkjennende opplysninger. En kode knytter barnet til opplysningene gjennom en navneliste. Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten. Det vil ikke være mulig å identifisere deg eller barnet i resultatene av forskningsprosjektet når disse publiseres.

Du har rett til å få innsyn i opplysninger som er registrert på barnet ditt. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker barnet fra studien, kan du kreve å få slettet innsamlede opplysninger. Opplysningene blir senest slettet desember 2013. Resultatene av forskningsprosjektet vil være klare høsten 2013. Dersom du er interessert i å vite resultatene, kan du kontakte Ingrid Liodden på tlf 92 444 033. Resultatene vil bli publisert i internasjonale medisinske tidsskrifter og også inngå i et doktorgradsarbeid ved Universitetet i Tromsø.

Frivillig deltakelse
Det er frivillig å delta i forskningsprosjektet. Dersom du ikke ønsker å la barnet delta, trenger du ikke å oppgi noen grunn, og det får ingen konsekvenser for deg eller barnet.

Dersom du vil at barnet ditt skal være med i forskningsprosjektet, ber vi deg skrive under på *samtykkeerklæringen* nederst på dette dokumentet. Om du nå sier ja, kan du senere trekke tilbake ditt samtykke uten at det medfører ulempe for deg eller barnet. Dersom du senere ønsker å få slettet dine/barnets opplysninger eller trekke barnet ditt fra undersøkelsen, eller har spørsmål til studien, kan du kontakte Ingrid Liodden, tlf. 92 444 033.

Samtykkeerklæring for deltakelse i forskningsprosjektet
Jeg/vi har fått informasjon om prosjektet og samtykker til deltagelse.

Barnets navn: Dato:

_____ _____

1)_____2)_____
Signert av en forelder, eventuelt begge foreldre

Jeg bekrefter å ha gitt informasjon om studien.

_____
Signert av forskningsstipendiat/anestesisykepleier Ingrid Liodden

Appendix VI

Paper II: Children and parents data form

Informasjon om barn og foreldre

Navn:

Gutt ☐ Jente ☐ Telefon:

Alder:

	Behov for tolk
	Utslett/infeksjon i akupunkturområdet
	Kvalme siste 24 timer
	Mage- tarmsykdom
	Medikamentbruk siste 24 timer:
	Ønsker ikke å delta
	Har ikke fått informasjon
	Strøket av programmet
	Annen årsak til ikke å delta i studien:

	Ja	**Nei**	**Vet ikke**
9. Har barnet opplevd reisesyke?			
10. Har barnet vært operert tidligere?			
11. Hvis ja på spørsmål 2, opplevde barnet kvalme/oppkast etter operasjon?			
12. Har noen av barnets biologiske foreldre vært operert tidligere?			
13. Hvis ja på spørsmål 4, opplevde noen av barnets biologiske foreldre kvalme/oppkast etter operasjon?			

Om barnets mor

Alder:_____ år Fødeland: _____

Sett kryss

Høyeste fullførte utdanning: Grunnskole..... ☐

Videregående..... ☐

Har hun helsefaglig utdanning? Høyskole/universitet..... ☐

Nei☐ Ja☐

Om barnets far Alder:_____ år Fødeland: _____

Sett kryss

Høyeste fullførte utdanning: Grunnskole..... ☐

Videregående..... ☐

Har han helsefaglig utdanning? Høyskole/universitet..... ☐

Nei☐ Ja☐

Appendix VII

Paper II: Questionnaire

Appendix VII

Spørreskjema

Hvor fornuftig/meningsfull synes du akupunkturbehandlingen dere har blitt tilbudt virker?

Helt ufornuftig 0------1--------2--------3--------4--------5-------6--------7--------8--------9 Svært fornuftig

Hvor sikker er du på at behandlingen vil redusere barnets kvalme- og oppkastplager?
Overhodet ikke sikker 0--------1---------2---------3--------4--------5---------6--------7--------8--------9 Helt sikker

Hvor sikker er du på at du ville anbefale denne behandlingen til andre som har lignende plager?

Ville ikke anbefale 0------1------2------3-------4-------5------6------7------8-------9 Helt sikker på å anbefale

Hvor effektiv tror du denne behandlingen vil være for andre plager?
Ingen effekt 0------1-------2-------3-------4-------5-------6------7------8-------9 Fjerner plagene fullstendig

Har du noen gang fått akupunktur? Ja □ Nei □

Hvis ja, var behandlingen nyttig for deg?
Overhodet ikke nyttig 0------1-------2-------3------4------5------6-----7-----8------9 Veldig nyttig

Har du barn som har fått akupunktur tidligere? Ja □ Nei □

Hvis ja, var behandlingen nyttig for barnet ditt?
Overhodet ikke nyttig 0------1-------2-------3------4------5------6-----7-----8------9 Veldig nyttig

Har noen av dine venner eller familiemedlemmer (ektefelle, søsken) fått akupunktur?
Ja □ Nei □ Vet ikke □

Hvis ja, var behandlingen nyttig for dem?
Overhodet ikke nyttig 0-----1------2-------3------4------5------6-----7-----8------9 Veldig nyttig

Vet ikke □

Hvor engstelig er du i forbindelse med at barnet skal gjennomgå denne operasjonen?

Overhodet ikke engstelig 0-----1-----2-----3-----4-----5-----6-----7------8-----9 Veldig engstelig

Appendix VIII

Paper II: Data collection form

nafkam Nasjonalt forskningssenter innen komplementær og alternativ medisin

Appendix VIII

Registreringsskjema for oppkast og brekninger

Hvis barnet kaster opp, ber vi om at du markerer med en O på linjen på det aktuelle tidspunktet. Hvis barnet har brekninger, ber vi deg om at du markerer med en B på linjen på det aktuelle tidspunktet. *Flere tilfeller av oppkast eller brekninger i løpet av to minutter regnes som ett tilfelle.*

Operasjon slutt kl	1 time etter operasjon	2 timer	3 timer	4 timer	5 timer	6 timer	7 timer	8 timer	9 timer
	kl	kl	kl	kl	kl	kl	kl	kl	kl

10 t	11 t	12 t	13 t	14 t	15 t	16 t	17 t	18 t	19 t	20 t	21 t	22 t	23 t	24 t
kl	kl	kl	kl	kl	kl	kl	kl	kl	kl	kl	kl	kl	kl	kl

- Vi ber deg sette ett kryss i en av boksene under som passer best med hensyn til hvordan du totalt sett synes barnets plager har vært i løpet av de første 24 timene etter operasjonen.

  Ingen plager □ Lite plager □ Moderate plager □ Mye plager □ Svært mye plager □

- Har barnet fått kvalmestillende medisin i løpet av 24 timer etter operasjon? Nei □ Ja □

- Har barnet fått smertestillende medisin i løpet av 24 timer etter operasjon? Nei □ Ja □

Bivirkninger

- Har det oppstått blødning/blåmerke etter akupunktur-nålestikkene? Ja □ Nei □
- Har barnet hatt ubehag av akupunktur-nålestikkene? Ja □ Nei □ Hvis ja, på hvilken måte? Beskriv kort:

Du vil bli oppringt en av de nærmeste dagene av anestesisykepleier, som vil be deg svare på disse spørsmålene. Vi takker for at du vil delta i studien.
Med vennlig hilsen anestesisykepleier Ingrid Liodden

Appendix IX

Paper II: FLACC behavioral tool for pain score

Appendix IX

FLACC Smertevurderingsskjema Barn 1 til 5 år

Kategori	0 poeng	1 poeng	2 poeng	Poeng	Poeng	Poeng
Ansikt	Ingen spesielle uttrykk	Av og til grimaser eller rynker i pannen, tilbaketrukket, uinteressert	Hyppig til konstant rynke i pannen, stram kjeve, skjelvende hake			
Ben	Normal stilling eller avslappet	Urolige, rastløse, anspente	Sparker eller trekkerbena opp			
Aktivitet	Ligger rolig, normal stilling, beveger seg lett	Vrir seg, flytter seg frem og tilbake, anspent	Bøyd i kroppen, stiv eller rykninger			
Gråt	Ingen gråt (våken eller sovende)	Stønner eller klynker, klager av og til	Gråter uavbrutt, skriker eller hulker, klager ofte			
Trøst-barhet	Tilfreds, avslappet	Lar seg trøste av berøring, klemming eller ved å bli snakket med, kan avledes	Vanskelig å trøste eller roe			
			Totalt:			

Merkel, S., Voepel-Lewxis, Tl, Shayevitz, J., & Maviya, S. (1997). FLACC: En atferdskala for å score postoperative smerter hos små barn. Pediatric Nursing 23(3), 293-297.

Appendix X

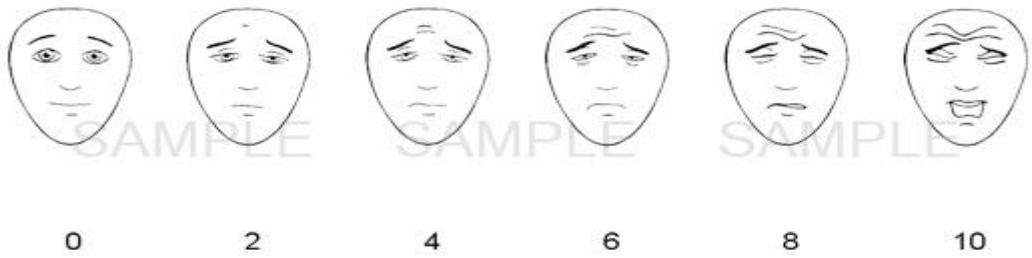
Paper II: The Faces Pain Scale

Smerteskala – barn over 5 år

I følgende instruksjon, si ”vondt” eller ”smerte”, ut fra hva som virker riktig for det enkelte barnet.

«Disse ansiktene viser hvor vondt noe kan gjøre. Dette ansiktet (pek på ansiktet lengst til venstre) viser ingen smerte. Ansiktene viser mer og mer smerte (pek på hvert og ett fra venstre mot høyre) helt til dette (pek på ansiktet lengst til høyre) – det viser veldig mye smerte. Pek på det ansiktet som viser hvor vondt du har (akkurat nå).»

Poengsett det valgte ansiktet 0, 2, 4, 6, 8 eller 10, telt fra venstre til høyre, slik at ’0’ = ’ingen smerte’ og ’10’ = ’veldig mye smerte’. Ikke bruk ord som ’glad’ og ’trist’. Denne skalaen har til hensikt å måle hvordan barn føler seg, ikke hvordan deres ansikt ser ut.



Translation credit: Kari Sorensen and Lise Tuset Gustad

Smerteregistrering	1. gang	2. gang	3. gang
Poeng			

Appendix XI

Paper II: Barf Nausea Scale

Kvalmeskala – barn over 5 år

FIGURE 2
BARF Nausea scale.

Har du kastet opp eller følt at du skulle kaste opp noen gang? Hvordan kjentes det i magen din da? Vi kaller den følelsen av å være syk i magen for kvalme.
Dette ansiktet (pek på ansiktet lengst til venstre) viser ingen kvalme. Ansiktene viser mer og mere kvalme (pek på hvert og ett fra venstre mot høyre) helt til dette (pek på ansiktet lengst til høyre) – det viser veldig mye kvalme. Pek på det ansiktet som viser hvor kvalm du er (akkurat nå).
Poengsett det valgte ansiktet 0, 2, 4, 6, 8 eller 10, telt fra venstre til høyre, slik at ’0’ = ’ingen kvalme’ og ’10’ = ’veldig mye kvalme’. Ikke bruk ord som ’glad’ og ’trist’. Denne skalaen har til hensikt å måle hvordan barn føler seg, ikke hvordan deres ansikt ser ut.

Kvalmeregistrering	**1. gang**	**2. gang**	**3. gang**
Poeng			