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HANNU LINTULA

Acute Abdominal Pain in Children with Special Reference to Surgical Techniques and Effects of Opioid Analgesia on Diagnostic Accuracy

Doctoral dissertation

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ABSTRACT

The purpose of this study was firstly to construct and to validate a diagnostic score for acute appendicitis in children, secondly to evaluate the effect of opioid analgesics on pain relief and diagnostic accuracy in children with acute abdominal pain, and thirdly to compare the recovery and costs of laparoscopic appendicectomy with open appendicectomy in children with suspected appendicitis.

A total of 328 children were evaluated in three different studies. The Appendicitis Score was constructed from a prospectively collected sample and further validated in a separate, prospective cohort. Prospective, randomized, double-blind, and placebo-controlled study design was used to evaluate the effects of buccal oxycodone in children with acute abdominal pain. To compare laparoscopic appendicectomy with open appendicectomy a single-blinded, randomized, parallel group and prospective study design was used.

The stepwise multiple linear logistic regression analysis of 19 medical history and clinical attributes, and laboratory tests yielded a diagnostic score that comprised six medical history variables and three clinical finding variables. By application of the score, unnecessary appendicectomy rate would have been reduced from 27 % to 13 %.

Significant reduction in induced tenderness from 7 to 4.5 cm (P=0.05) on a 10-cm pain scale was attained at 30 min after oxycodone. The mean summed pain intensity difference was significantly greater in the oxycodone group, 22 ±18 cm, than in the placebo group, 9 ± 12 cm (mean difference 13 cm, with a 95 % confidence interval of 2-24 cm; P=0.04). The diagnostic accuracy increased from 72 % to 88% in the oxycodone group and remained at 84 % in the placebo group after the study drug administration.

Children who underwent laparoscopic appendicectomy had less pain and needed less analgesia after surgery than those who underwent open appendicectomy. After laparoscopic appendicectomy, children returned to school 1 day earlier (after 7 days) than those who had had open appendicectomy (8 days) (P= 0.09), and 4 days earlier to their sport activities (11 days vs 15 days; P= 0.01). A marginal difference of 53 euros in total procedure costs was found between the two techniques (total cost, 1023 euros in the laparoscopic appendicectomy group and 970 euros in the open appendicectomy group).

It is concluded that the use of a diagnostic score may facilitate the diagnosis of appendicitis to avoid unnecessary operations. Administration of buccal oxycodone (0.1 $mg \cdot kg^{-1}$) provided a significant pain relief to children with acute abdominal pain, without adversely altering the clinical signs or obscuring the surgical diagnosis. Laparoscopic appendicectomy is a feasible, safe and effective technique, and it has advantages compared with open appendicectomy.

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To Karin and Sofia

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Kuopio, February 2006

Hannu Lintula

ABBREVIATIONS

AA	acute appendicitis
ASA	The American Society of Anesthesiologist`s Physical Status Grading
℃	degrees of Celsius
CI	confidence interval
CO_2	carbon dioxide
CRP	serum C-reactive protein concentration
ED	emergency department
EUR	euros
FRC	functional residual capacity
H	hours
LA	laparoscopic appendicectomy
mmHg	millimetre of mercury
NA	non-surgical abdominal pain
NR	not reported
NSAP	non-specific abdominal pain
OA	open appendicectomy
P	probability value
PID	pain intensity difference
RLQ	right lower abdominal quadrant
SD	standard deviation
SPID	summed pain intensity difference
USA	United States of America
VAS	visual analogue scale
WBC	white blood cell count

LIST OF ORIGINAL PUBLICATIONS

This work is based on the following original articles referred to in the text by numerals I-V.

I. Lintula H, Kokki H, Vanamo K: Single-blind randomized clinical trial of laparoscopic versus open appendicectomy in children. Br J Surg 2001;88: 510-514.

II. Lintula H, Kokki H, Vanamo K, Antila P, Eskelinen M: Laparoscopy in children with complicated appendicitis. J Pediatr Surg 2002;37: 1317-1320.

III. Lintula H, Kokki H, Vanamo K, Valtonen H, Mattila M, Eskelinen M: The costs and effects of laparoscopic appendectomy in children. Arch Pediatr Adolesc Med 2004;158: 34-37.

IV. Lintula H, Pesonen E, Kokki H, Vanamo K, Eskelinen M: A diagnostic score for children with suspected appendicitis. Langenbecks Arch Surg 2005;390: 164-170.

V. Kokki H, Lintula H, Vanamo K, Heiskanen M, Eskelinen M: Oxycodone vs placebo in children with undifferentiated abdominal pain: a randomized, double-blind clinical trial of the effect of analgesia on diagnostic accuracy. Arch Pediatr Adolesc Med 2005;159: 320-325.

CONTENTS

1. INTRODUCTION

Acute abdominal pain unrelated to trauma is one of the most common conditions in children presenting to the hospital emergency department (ED). In the course of one year, four or five children out of 1000 develop acute abdominal pain that is severe enough to require hospital admission (Winsey and Jones 1967, Louhimo and Lindahl 2004). Acute appendicitis (AA) accounts for 24-51 % and self-limiting non-specific abdominal pain (NSAP) for 37-63 % of children with acute abdominal pain who are referred to the paediatric surgical ward (Winsey and Jones 1967, Dickson et al 1988, Williams et al 1998, Louhimo and Lindahl 2004). Because NSAP and several other conditions may mimic AA, the clinical examination should focus on differentiation of children with AA from those with non-surgical abdominal pain (NA).

AA is the most common surgical emergency in children (Blakely et a 1998). Over a 1-year period, two children in 1000 will undergo emergency appendicectomy (Winsey and Jones 1967). AA is one of the few surgical diagnoses that is made clinically, and appendicectomy remains a procedure that is performed without certainty of the definitive diagnosis. Despite recent increase of knowledge concerning acute AA, accurate diagnosis remains suboptimal. Delayed management of AA is associated with prolonged hospital stay, a delay in the return to normal life, and an increased rate of perforation (34 to 75 %), wound infection (0 to 11 %), pelvic abscess (2 to 5 %), and late intra-abdominal adhesions (Stone et al 1971, Graham et al 1980, Gilbert et al 1985, Curran and Muenchow 1993, Pearl et al 1995, Surana et al 1995). On the other hand, 3 –54 % of children undergo surgery unnecessarily, with a false preoperative diagnosis of AA (Pearl et al 1995, Surana et al 1995, Paajanen and Somppi 1996, Bachoo 2001).

Several methods have been suggested to increase the diagnostic accuracy and decrease the rate of unnecessary appendicectomy. Ultrasonography or computed tomography may be beneficial in equivocal cases of suspected AA although no study has reported them to be superior to clinical examination (Alford and McIlhenny 1992, Crady et al 1993, Ramachandran et al 1996, Roosevelt 1998, Stephen 2003, Martin 2004). Other imaging modalities have not become feasible means in discriminating those with or without AA (Hatch 1981, Rothrock et al 1992, Reynolds 1993).

Clinical and computer-aided scoring systems have shown both to increase the diagnostic accuracy and decrease the unnecessary appendicectomy rate in adults (Teicher et al 1983, Arnbjörnsson 1985, Alvarado 1986, Fenyö 1987, Lindberg and Fenyö 1988, de Dombal 1991, Christian and Christian 1992, Eskelinen et al 1992). However, diagnostic scores abstracted from adults` data have not found to be useful in children (Alvarado 1986, Bond et al 1990). Only one study has addressed the issue of a prognostic scoring system unique to children with suspected AA (Madan 2002).

Classical teaching in surgery has dictated that opioid analgesia should be withheld from patients with acute abdominal pain until a surgeon has established a definitive management plan. It has been claimed that analgesics would mask symptoms and physical signs, delay surgical diagnosis, and lead to increased morbidity (Silen 1979). Over the past few years, this traditional belief has been challenged, and some authors advocate rapid relief of abdominal pain (Cuschieri 1995, Tintinalli 2000). Recent clinical trials have supported the early administration of opioid analgesics in adults with acute abdominal pain (Zoltie and Cusp 1986, Attard et al 1992, Pace and Burke 1996, LoVecchio et al 1997, Vermeulen et al 1999, Mahadevan and Graff 2000, Thomas et al 2003). Until recently, only one clinical trial has addressed the issue of opioid analgesia for abdominal pain in children (Kim et al 2002).

Two different surgical procedures are currently used for appendicectomies: the open appendicectomy (OA) and laparoscopic appendicectomy (LA). Although LA has been practiced in children since the early 1990`s, OA is still the standard method employed. However, it is generally accepted that LA is feasible, safe and effective in children with acute simple AA, and in some centres one fifth of appendicectomies are performed laparoscopically (Kokoska 1999). The criticism directed at LA have focused on the increased technical difficulties compared with OA, a longer set-up time for the laparoscopic instrumentation, associated higher costs, and the fact that the LA has not produced a significant reduction in the duration of hospital stay or improvements in the patient recovery (Tate et 1993, Martin et al 1995, Mutter et al 1996, Heikkinen et al 1998, Little et al 2002). Moreover, some studies have shown a higher rate of intra-peritoneal abscess following LA compared with OA (Ortega et al 1995, Tang et al 1996)

The purpose of this study was to evaluate different aspects in children presenting to the paediatric surgery ward with acute abdominal pain: diagnostic score for children with suspected appendicitis, the effects of opioid analgesics on diagnostic accuracy and abdominal pain relief, and outcomes after LA and OA.

2. REVIEW OF THE LITERATURE

2.1. Acute abdominal pain

2.1.1. Definition

The term *acute abdomen* describes an emergency situation in which abdominal pain onsets suddenly and is sufficiently severe to require early decision-making and prompt treatment. Acute abdomen was defined in 1976 by the Research Committee of the World Organization of Gastroenterology (de Dombal 1979, de Dombal 1991): acute abdomen implies presentation of a patient to the hospital with a history of previously undiagnosed abdominal pain lasting less than one week. The definition excludes patients with abdominal trauma and strangulated groin or umbilical hernia.

2.1.2. Pathophysiology of abdominal pain

2.1.2.1. Visceral pain

Visceral pain occurs when noxious stimuli affect a viscus, such as the appendix. Visceral nociceptors are stimulated by an increased tension in the wall of hollow organs or by stretching of encapsulated organs. Ischemia, inflammation, and chemical irritation may also stimulate pain receptors (Boey 1991). Because visceral pain fibres are bilateral and unmyelinated and enter the spinal cord at multiple levels, visceral pain usually is dull, poorly localized, and felt in the midline (Cousins 1989, Irish et al 1998). Foregut pain (e.g. stomach) is epigastric in location, midgut pain (e.g. small intestine) is umbilical, and hindgut (e.g. large intestine) pain is felt in the hypogastrium (Irish et al 1998). Organs that are bilateral give rise to pain that is confined to the right or left flank (Cousins 1989).

2.1.2.2. Somatic pain

Somatic component of abdominal pain results from disruption, irritation, or inflammation of the abdominal wall, parietal peritoneum, root of the mesentery, or diaphragm. Somatic pain resulting from ischemia, inflammation, or stretching of the parietal peritoneum is transmitted through myelinated afferent fibres to specific dorsal root ganglia on the same side and at the same dermatomal level as the origin of the pain (Boey 1991). Somatic pain is sharp, intense, and localized, and movement or coughing can aggravate it (Boey 1991, Irish et al 1998).

2.1.2.3. Referred pain

Referred pain is felt in remote areas supplied by the same dermatome as the diseased organ. Referred pain develops as a result of the convergence of primary posterior root fibres on a few secondary fibres within the spinothalamic tract (Irish et al 1998). When afferent signals from viscera and somatic signals converge on the same neuron within a pathway, the resulting impulse received by the brain is interpreted as coming from the somatic distribution of the pain fibres (Boey 1991).

2.1.2.4. Pain characteristics

The pattern and nature of the abdominal pain can vary. It may be intermittent, colicky, or continuous (Spitz and Kimber 1997). The intermittent colic of bowel obstruction, intussusception or a ureteric stone correspond to peristaltic waves and eases or disappears between waves (Alford and McIlhenny 1992, Mason 1996). Acute appendicitis may begin with vague abdominal discomfort becoming continuously centred in the right lower abdominal quadrant. Radiation patterns are important clues. Biliary pain may radiate to the right scapular region. Ureteral colic may be

referred to the inguinal region (Boey 1991). Pelvic inflammation may result in painful micturition and lower abdominal discomfort (Spitz and Kimber 1997).

2.1.3. Aetiology of acute abdominal pain

2.1.3.1. Incidence

As with most paediatric emergencies, the causes of non-traumatic acute abdominal pain in children differ with the age group and can be divided into those that occur in neonates, infants and toddlers, and children aged 4 to 15 years. Inevitably, there is considerable overlap between these age groups as well as delay in presentation until adulthood in many of these conditions (Mason 1996).

Several causes of acute abdominal pain have been reported in children aged 4 to 15 years (Winsey and Jones 1967, Jones 1969, Hatch 1985, Dickson et al 1988, Neblett et al 1988, Buchert 1989, Alford and McIlhenny 1992, Velanovich et al 1992, Övrebo et al 1993, Driver and Youngson 1995, Mason 1996, Pollack 1996, Hotopf et al 1998, Williams et al 1998) (Table 1). NSAP is the most common cause of a child presenting to the paediatric surgical ward with acute abdominal pain (Barker et al 2002). NSAP has been found to be present in 37-63 % of cases (Winsey and Jones 1967, Jones 1969, Dickson et al 1988, Williams et al 1998). AA is the most common surgical condition accounting 24-51 % of children presenting with acute abdominal pain (Winsey and Jones 1967, Jones 1969, Dickson et al 1988, Williams et al 1998).

Conditions other than AA or NSAP account for 5-24 % of children presenting to the paediatric surgery ward with acute abdominal pain (Winsey and Jones 1967, Jones 1969, Övrebo et al 1993, Driver and Youngson 1995, Williams et al 1998). Surgical conditions other than AA have been

Table 1. Aetiology of acute abdominal pain in children.

DISEASE		*INCIDENCE(%)*
Acute appendicitis[1,2,3,4,5,6]		***24-51%***
Non-specific abdominal pain[1,2,3,4,5,6]		***37-63 %***
Surgical conditions other than AA[1,2,3,4,5,6]		***0-6 %***
1.Bowel obstruction[4,5]		*1-3 %*
2.Intussusception[1,3,4,5]		*1-2 %*
3.Trauma[1,5]		*2 %*
4.Meckel`s diverticulitis[1,7] 5.Gallstones[8,9] 6.Haematocolpos[5,8,9] 7.Volvulus[5,8,9] 8.Ovarian torsion[8,9] 9.Neoplasms/masses[3,5,8,9] 10.Primary peritonitis[8,9] 11.Renal stone[3,8,9] 12.Testicular torsion[8,9]		*< 1 %*
Medical conditions[1,2,3,4,5,6]		***5-21%***
1.Constipation[4,5,6]		*5-7 %*
2.Urinary tract infection[1,3,5,6]		*3-5 %*
3.Gastroenteritis/mesenteric lymphadenitis[1,2,5,6]		*1-4 %*
4.Pneumonia/tonsillitis[1,4,5]		*1-4 %*
5.Ovulatory pain[5]		*2 %*
6.Mesenteric torsion/cyst[10] 7.Pancreatitis[5,8,9] 8.Inflammatory bowel disease[8,9] 9.Henoch-Schönlein purpura[8,9] 10.Pelvic inflammatory disease[3,8,9] 11.Irritable bowel disease[8,9] 12.Haemolytic uremic syndrome[5,8,9] 13.Diabetes mellitus[1,8,9] 14.Ectopic pregnancy[8,9]	15.Ovarian cysts[2,8,9] 16.Endometriosis[8,9] 17.Dysmenorrhoea[5,8,9] 18.Epididymitis[8,9] 19.Varicella zooster[8,9] 20.Gastritis/ulcer[3,8,9] 21.Hepatitis[8,9] 22.Glomerulonephritis[8,9] 23.Abdominal migraine[5,8,9]	*< 1%*
Miscellaneous conditions 1.Child abuse[8,9] 2.Food poisoning[8,9] 3.Medication reaction[8,9] 4.Psychosomatic abdominal pain[11]		***< 1%***

[1]Winsey and Jones 1967; [2]Jones 1969, [3]Dickson et al 1988; [4]Övrebo et al 1993; [5]Driver and Youngson 1995; [6]Williams et al 1998; [7]Velanovich et al 1992; [8]Buchert 1989; [9]Mason 1996; [10]Hatch 1985; [11] Hotopf et al 1998.

reported to account for 0-6 % of those admitted to the paediatric surgery ward (Winsey and Jones 1967, Jones 1969, Övrebo et al 1993, Driver and Youngson 1995, Williams et al 1998).

2.1.3.2. Acute non-specific abdominal pain

NSAP refers to a short-lived acute abdominal pain for which no definite aetiology is ever established, which settles down spontaneously, and for which there is no useful surgical treatment (de Dombal et al 1972, de Dombal 1979). NSAP remains the most common alternative diagnosis to AA and the incidence of NSAP is increasing in both sexes (Driver and Youngson 1995). NSAP is a diagnosis of exclusion, and it identifies a non-specific syndrome that is self-limiting. On the other hand, some authors (Shepherd 1972) have suggested that NSAP may be a symptom of a group of cases with missed diagnosis, including those of AA.

NSAP represents a heterogenous group of conditions and is probably multifactorial in its aetiology (Williams et al 1999). Most of the children with NSAP never have any firm diagnosis made during their hospital attendance (de Dombal 1991). Some of the children in the NSAP group may have, in fact, mild appendicitis that resolves spontaneously (Jones 1969). There is some evidence that children with recurrent NSAP may develop later psychiatric disorders. Presentation of such symptoms may be associated with poor health and emotional disturbances in the parents. On the other hand, children are not prone to physical symptoms once psychiatric disorder is controlled for (Hotopf et al 1998).

Only few studies (Jones 1969, Barker et al 2002) have addressed the issue of the outcome of NSAP but they have shown that the vast majority of the children do not develop serious disease in the short-term follow-up. In one study (Jones 1969) 325 medical records were evaluated between 6 months and 2 years after discharge of such children and 6 % of them had required readmission, six

with AA, one with intussusception, one with urinary tract infection, one with torsion of the testicle, and nine with another self-limiting attack of acute abdominal pain.

In another study a total of 1238 children with NSAP were admitted to hospital, and 4 % of them were readmitted with further abdominal pain within a 30-day follow-up. In 40 % of children the diagnosis was changed on re-admission: 5 cases of AA, 4 of mesenteric adenitis, and 2 of gastro-oesophageal reflux. The remaining children were found to have a variety of other diagnoses including urinary tract infection, pelvi-ureteric junction obstruction, gastritis, gastroenteritis, viraemia, subacute intestinal obstruction, herpes zoster, and constipation (Barker et al 2002). Moreover, NSAP has been reported to be associated with lactose intolerance (Chaussain et al 1994), pinworm infestation (Mogensen et al 1985), pelvic inflammatory disease (Paterson-Brown et al 1989), ovulatory pain (O´Herlihy and Robinson 1980), neurogenic appendicopathy (a disease with the proliferation of neuroendocrine structures in the appendix) (Franke et al 2002), yersinia infection (Attwood et al 1987), abdominal wall pain (Gray et al 1988), and psychological and behavioural factors (Williams et al 1999).

Active observation has been shown to be reliable method of assessing NSAP, and discriminates between children requiring further investigation and those who have a self-limited disease (Jones 1969, Barker et al 2002). Screening methods such as a white blood count, C-reactive protein, urinalysis, and abdominal ultrasonography may be of help in obtaining a definite diagnosis in children with equivocal abdominal symptoms (Barker et al 2002).

2.1.3.3. Miscellaneous causes of acute abdominal pain

Gastroenteritis is one of the most common causes of acute abdominal pain accounting for 2-4 % of children presenting to the paediatric surgery unit (Driver and Youngson 1995, Williams et al 1998).

Symptoms of fever, vomiting, diarrhoea, and upper respiratory infection may occur simultaneously with onset of crampy, diffuse abdominal pain. The abdomen is soft and nondistended, and the abdominal palpation does not elicit localized tenderness. Bowel sounds are normal or hyperactive (Hatch 1985). Viruses such as rotavirus, adenovirus, and enterovirus are the most frequent causes of gastroenteris (Leung and Pai 1988, Mason 1996). The most common bacterial agents include Escherichia coli, Yersinia, Campylobacter, Salmonella and Shigella (Mason 1996, Sakellaris et al 2004). Recently, there have been deaths from haemolytic uremic syndrome in outbreaks of voluminous diarrhoea associated with a virulent Escherichia coli infection (Steward and Tina 1993).

Mesenteric lymphadenitis is a term used to describe clustering of inflamed lymph nodes in the mesenterium of the terminal ileum, and it should not be considered as a separate diagnosis but as a sequela of gastroenteritis (Folkman 1979, Arda et al 2001). Most cases of mesenteric lymphadenitis are short-lived, but stool cultures should be obtained in children with severe diarrhoea (Mason 1996, Arda et al 2001). Mesenteric lymphadenitis is usually caused by Yersinia enterocolitica, Yersinia pseudotuberculosa or Salmonella typhimurium (Arda et al 2001, Louhimo and Lindahl 2004).

Constipation accounts for 5-7 % of children presenting with acute abdominal pain (Övrebo et al 1993, Williams et al 1998). Acute constipation may be associated with a viral infection that causes diminished bowel motility and results in dietary changes (Mason 1996). Anal fissure may result in rectal pain and constipation (Sonmez et al 2002). Abdominal pain is often lateralized or diffuse, and it is accompanied by sensations of urgency and tenesmus. Hard stool on both abdominal and rectal examinations may be noted. Treatment includes enema and suppository only when clinically significant other conditions have been excluded (Moir 1996). Rectal biopsy may be indicated if Hirschprung`s disease is suspected (Mason 1996).

Intussusception occurs usually in infants between 4 and 10 months of age but in recent years the condition has become common in children over 2 years of age (Luks et al 1992). In older children, a pathologic leading edge (Meckel`s diverticulum, lymphoma, lymphadenopathy) is often found. Intussusception is commonly located at the ileo-caecal junction (Ong and Beasley 1990). The child presents with colicky abdominal pain, vomiting and bloody stools (Alford and McIlhenny 1992). The diagnosis of intussusception is pursued with ultrasonography or barium study (Davis et al 2003). The intussusception is primarily reduced with either barium, saline or air-contrast enema (Davis et al 2003). A comparative study of air, barium, and saline reduction showed that air had a higher reduction rate of 90 % compared with 70 % for barium and 67 % for saline, and fewer complications (Hadidi and El Shal 1999). Surgical reduction is mandatory in the case of incomplete reduction (Davis et al 2003).

*Meckel`s diverticulum* is found in 2 % of the population, and becomes symptomatic in 2 % of people in whom it occurs (Velanovich et al 1992). Complications are associated with the presence of gastric mucosa with haemorrhage and perforation (Matsagas et al 1995). Furthermore, Meckel`s diverticulitis may develop, with clinical signs typical of AA progressing to perforation and peritonitis (Velanovich et al 1992, Matsagas et al 1995). Other modes of presentation include intussusception in which the Meckel`s diverticulum is the lead point (Velanovich et al 1992). In addition, Meckel`s diverticulum may result in intestinal obstruction if bowel loops are herniated behind the Meckel`s diverticulum whose tip is attached to the mesentery. Intestinal loops may also twist around Meckel`s diverticulum when it is adhered to the umbilicus (Neblett et al 1988). Symptomatic Meckel`s diverticulum necessitates laparotomy and the excision of the diverticulum (Matsagas et al 1995).

Postoperative adhesive *bowel obstruction* is the most common cause of intestinal occlusion in children aged 4 to 15 years (Mason 1996). Adhesive bowel obstruction has been reported to account for 1-3 % of children presenting with acute abdominal pain (Övrebo et al 1993, Driver and Youngson 1995). In one study (Ritchey et al 1993) the incidence of obstruction after Wilms` tumour resection was 7 %. Janik and co-workers (1981) reported that 80 % of obstructions occur within two years and 95 % within 10 years after the primary operation. Appendicectomy and partial colectomy were the most common prior procedures, but the relative risk was highest for partial colectomy and lowest for appendicectomy. Surgical intervention is required if bowel obstruction does not resolve with fluid resuscitation and intestinal decompression or if localized tenderness is encountered (Janik et al 1981).

Gallstones in children are uncommon, but they can be present in those with haemolytic disease, a history of parental nutrition, and idiopathic disease (Mason 1996). However, disorders of the gallbladder represent the largest group of surgical diseases of the biliary tree in children (Neblett et al 1988). The mean age of presentation is 12 years (Mason 1996). Abdominal pain is often associated with nausea, vomiting, or anorexia in children with cholelithiasis (Neblett et al 1988). Children under 5 years of age may be unable to localize pain to the right upper quadrant, and they are also often asymptomatic. Cholecystitis or associated pancreatitis are uncommon in children (Mason 1996). Ultrasonography will allow accurate diagnosis of cholelithiasis and cholecystitis (Neblett et al 1988). Cholecyctectomy has been the procedure of choice for symptomatic gallstones in children, but also cholecystotomy have been suggested as an alternative approach (Ure et al 2001).

Urinary tract infections have been reported to account for 3-5 % of children with acute abdominal pain (Winsey and Jones 1967, Driver and Youngson 1995). Urinary frequency with dysuria and

increased pus cells suggest genitourinary infection, and flank pain is often associated with kidney infection. An accurate diagnosis is obtained by a urinalysis and culture (Mason 1996).

Right lower lobe *pneumonia* and *tonsillitis* can mimic appendicitis, and these conditions account for 1-4 % of children presenting with acute abdominal pain (Winsey and Jones 1967, Övrebo et al 1993, Driver and Youngson 1995). However, the character of the abdominal pain, even though localized in the right lower abdominal quadrant, is milder and more diffuse than that associated with AA. Moreover, a proper diagnosis can be achieved by the throat examination and the chest auscultation (Moir 1996).

When dealing with teenage girls with acute abdominal pain, the following aspects should be taken into the consideration to differentiate tubo-ovarian pathology from acute appendicitis: a complete gynaecologic history, a pregnancy test, gynaecologic examination, and pelvic ultrasonography (Moir 1996, Mollitt and Dokler 1997). In one study (Driver and Youngson 1995) *ovulatory pain* accounted for 2 % of children with acute abdominal pain. A normal rupture of the graafian follicle may result in ovulatory pain in which the abdominal pain is abrupt occurring at the middle of the menstrual cycle. The pain is usually short lived localizing to one side of the lower abdominal quadrant. There is no abdominal guarding although the affected abdominal quadrant may be tender to palpation (Mollitt and Dokler 1997). *Pelvic inflammatory disease* is an acute infection that occurs secondary to infection of the upper female genital tract. Severe bilateral lower abdominal pain, tenderness with cervical and uterine movement, fever, and adnexal tenderness are usually associated with pelvic inflammatory disease. Ovarian abscesses are seen in 15-30 % of patients while inflammation of the capsule of the liver will complicate 15 % of cases. The differentiation of pelvic inflammatory disease from acute appendicitis may be difficult, and laparotomy or laparoscopy may be the only method of establishing the accurate diagnosis (Mollitt and Dokler 1997).

Ovarian cysts develop as a result of normal ovarian activity. Cysts may be associated with haemorrhage and acute abdominal pain on the affected side. Fever and gastrointestinal signs are rarely encountered, and leucocyte count is usually normal. Acute *ovarian torsion* is related to underlying ovarian pathology such as teratoma. Abdominal pain is often localized to the right lower abdominal quadrant making the differentiation of ovarian torsion from acute appendicitis difficult. Ovarian torsion presents with a mass on the affected side, but as ischemia of the ovary progress, pelvic peritonitis supervene. Other rare gynaecologic causes of acute abdominal pain in teen age girls include *endometriosis*, *ectopic pregnancy*, and *genital malformations* (Mollitt and Dokler 1997).

2.2. Acute appendicitis

2.2.1. History

> In every case the seat of greatest pain, determined by the pressure of one finger, has been exactly between an inch and a half and two inches from the anterior spinous process of the ileum on a straight line drawn from that process to the umbilicus (McBurney 1889).

In 1886, Reginald Fitz described first the perforating inflammation of the vermiform appendix. He named the condition "acute appendicitis", and stressed the importance of early detection and management of disease. In 1889, McBurney described the intra-abdominal abscess formation in the right lower quadrant, presented details on the selection of the site of surgical incision, and urged early laparotomy. McBurney (1889) also stated that "in the early stage, no accurate diagnosis can be made as to whether or not the appendix is perforated". This statement is still valid today.

2.2.2. Epidemiology

AA is the most common condition requiring emergency laparotomy in children. A total of 1065 children in Finland underwent appendicectomy for suspected AA in 2003 (National Research and Development Centre for Welfare and Health 2004). Every year approximately 60000 to 80000 appendicectomies are performed in the United States of America (USA) on children (Irish et al 1998). Appendicitis is more frequent in boys (55 % to 60 %) with a peak incidence in children between 10 and 12 years of age (Addiss et al 1990, Irish et al 1998). The incidence of AA is not constant in the world, and the disease is rarely encountered in African blacks consuming high-fibre diets (Irish et al 1998).

Appendicitis rates have significantly changed during the 20th century. The incidence of AA was 21/100000 in the 1910`s (Rendle Short 1920), peaking to 210/100000 in 1956-57 in England (McCahy 1994). Since 1950`s the incidence of appendicitis has been falling steadily in all age groups in western countries (Basoli et al 1993, Close et al 1995, Treutner and Schumpelick 1997, Kang et al 2003, Stringer and Pledger 2003). During the late 1900`s the incidence of appendicitis was 52/100000 in England (McCahy 1994), and 110/100000 in the USA (Addis et al 1990). However, the appendicitis rate in the USA has been reported to be 276/100000 in males aged 10-14 years (Addiss et al 1990).

During the last four decades, paediatric appendicitis rates in England and Wales have fallen from 309/100000 to 115/100000- a decrease of 63 % (Stringer and Pledger 2003). This reduction is noted in the six to ten year old age group, but also seen in children under five years of age (Driver and Youngson 1995). Between 1998 and 2003, the incidence of paediatric appendicitis in Finland fell from 183/100000 to 158/100000 (National Research and Development Centre for Welfare and Health 2004).

Several theories for the decrease in appendicitis have been suggested, including an increase in the dietary intake of vegetables and fibre (Arnbjörnsson et al 1982), and an increase in the use of antibiotics (Noer 1975), but no convincing explanation has yet been established. Recently, some authors (Heaton 1987, Morris et al 1987, Barker 1998) have argued that the decrease in appendicitis may have been associated with improved hygiene and reduced enteric infection rates.

2.2.3. Pathophysiology

AA results usually from luminal obstruction of the appendix. A faecalith, lymphoid hyperplasia, pinworm, ascaris lumbricoides, or carcinoid may obstruct the lumen (de Dombal 1991, Cloud 1993). Carcinoid is found in 0.25 % of patients who have their appendices removed (de Dombal 1991). Secretions from the mucosa accumulate within the lumen of the appendix resulting in acute distension of the appendix. Increased intraluminar pressure leads to arterial obstruction, ischemia, and destruction of the mucosa (Cloud 1993). Intestinal bacteria (Bacteroides fragilis, Escherichia coli, Streptococcus, Pseudomonas, Klebsiella, and Clostridium) invade the mucosa of the appendix and cause intramural infection (Stone 1976, Roberts 1988). Bacterial infection and arterial infarction may result in gangrene and rupture (Cloud 1993). A minority of inflamed appendices have no demonstrable luminal obstruction, and the pathogenesis of the inflammation remains unknown (Hatch 1981).

The histological criterion for AA is an inflammatory reaction with polymorphonuclear leucocytes in the mucous layer of the appendix and oedema (de Dombal 1979, de Dombal 1988). Focal appendicitis is a term applied to mild cases with limited areas of infection, and therefore the intra-operative findings of macroscopically normal appendices do not always exclude AA (Cloud 1993). In one study (Lau et al 1986) 19 % of grossly normal appendices were reported to be histologically inflamed, and vice versa microscopically normal appendices were found in 8 % of patients with

peroperatively diagnosed AA. The false-positive finding of acute appendicitis may result from other intra-abdominal infection or mechanical manipulation of the appendix (Bloch et al 1988, Sandermann et al 1989).

The following classification refers to the histological stages of acute appendicitis:

• In *simple or focal appendicitis*, the appendix appears normal or shows mild oedema with no serosal exudates evident. In *focal appendicitis*, obstruction of the lumen often is absent (Cloud 1993).

• In *suppurative appendicitis*, the lumen of the appendix is obstructed, and the appendix and mesoappendix are swollen. Intra-abdominal fluid is increased, and the appendix may be walled off by the adjacent structures (Cloud 1993).

• In *gangrenous appendicitis*, intramural venous and arterial thromboses ensue resulting in gangrene and microperforations in the appendiceal wall. Peritoneal fluid is increased and may be purulent (Cloud 1993).

• In *perforated appendicitis*, persisting tissue ischemia results in rupture along the antimesenteric border of the appendix. Perforation can cause localized or diffuse peritonitis (Cloud 1993).

• Palpable *appendiceal mass* develops as a result of appendicitis consisting of oedema, and an adherent omentum and intestinal segment. Appendiceal mass may contain free pus and this localized suppurative process is defined as an *appendiceal abscess* (Karaca et al 2001).

2.2.4. Diagnosis

2.2.4.1. Background

Acute appendicitis is one of the few surgical diagnoses that is made clinically, and appendicectomy remains an operation that is often performed without certainty of the diagnosis. Diagnostic imprecision is still reflected in the high appendiceal perforation rate (34 to 75 %) (Stone et al 1971, Graham et al 1980, Gilbert et al 1985), and in the unnecessary appendicectomy rate of 3-54 % (Neilson et al 1990, Close et al 1995, Pearl et al 1995, Paajanen and Somppi 1996, Bachoo et al 2001, Partrick et al 2003). Definite diagnosis is established in 50-70 % of patients at the time of initial evaluation (Balthazar et al 1991).

The child`s history and clinical examination findings are the most important means for the diagnosis of AA (Winsey and Jones 1967, Jones 1969, Graham et al 1980, Bower et al 1981). Furthermore, the examination of the children with acute abdominal pain is often focused to differentiate children with AA from those with abdominal conditions mimicking appendicitis (Winsey and Jones 1967). However, no symptom, sign or laboratory test is pathognomonic for the preoperative diagnosis of AA (Winsey and Jones 1967, Jones 1969, Graham et al 1980, Bower et al 1981).

To avoid the morbidity and postoperative complications of unnecessary appendicectomy, several methods have been introduced to improve diagnostic accuracy. Despite numerous reports documenting the diagnostic accuracy of different diagnostic modalities in paediatric AA, these techniques have remained adjuncts in surgical decision making (Ceres et al 1990, Owen et al 1992, Ramachandran et al 1996, Hahn et al 1998, Stephen et al 2003, Garcia Pena et al 2004). Only one study (Kaneko and Tsuda 2004) using ultrasonography has documented a sensitivity of 100% in diagnosing AA.

2.2.4.2. Valuable symptoms

The determination of the time of onset of symptoms is important for the early diagnosis of AA. Accurate information can be elicited in older children and adolescents but in younger children careful observation is important. The children under 5 years old cannot properly express themselves and this inability to verbally describe symptoms is reflected in high appendiceal perforation rate (70-75 %) (Stone et al 1971, Graham et al 1980, Gilbert et al 1985).

Abdominal pain is the predominant and presenting feature of AA. The patient senses poorly localized and dull visceral pain that is often referred to the periumbilical segment (T10 dermatome) (Boey 1991). This prodromal symptom is present in 70 % of children with AA (Winsey and Jones 1967, Jones 1969). Several hours after the onset of initial symptoms, the abdominal pain will eventually *shift to the right lower abdominal quadrant* (RLQ) (Boey 1991). In 27 % of children with AA pain starts in the RLQ (Winsey and Jones 1967).

Pain in the RLQ has been regarded as the most valuable symptom suggesting AA, and this symptom was found in 88-99 % of children of AA compared with 13 % of those with NSAP (Foster and Edwards 1957, Jones 1969, Harrison et al 1984). *Nausea* with or without *vomiting* may succeed abdominal pain in 36-95 % of cases with AA compared with 40-60 % of children with NSAP (Foster and Edwards 1957, Landsden 1963, Winsey and Jones 1967, Jones 1969, Stone et al 1971, Graham et al 1980, Bower et al 1981, Harrison et al 1984). *Abdominal pain* may get *worse on movement* supporting a diagnosis of AA, as this feature has been found in 60 % of children with AA and only in 6 % of those with NSAP (Winsey and Jones 1967).

2.2.4.3. Valuable physical examination findings

Careful observation of the behaviour of the child with suspected appendicitis is important. Limping and tender moving may refer to AA. Laying still with the legs drawn up towards the abdomen may be a sign of appendiceal perforation (Cloud 1993). The throat and the eardrums should be examined, and the chest auscultation performed in children with a prodromal upper respiratory infection (Winsey and Jones 1967).

Tenderness in the RLQ is the most sensitive examination finding in AA being noted in 93-100 % of children compared with 25-55 % of those with NSAP (Winsey and Jones 1967, Jones 1969, Bower et al 1981). Diffuse abdominal *tenderness* is associated with more advanced disease, and it is found in 15 % simple appendicitis, 39 % of gangrenous, and 83 % of perforated appendicitis (Stone et al 1971). In children under 6 years of age, diffuse abdominal *tenderness* is more common than localized tenderness (Graham et al 1980).

Voluntary guarding and *rebound tenderness* can be elicited in the RLQ or more diffusely as the inflammation process proceeds. *Voluntary guarding* (voluntary stiffening of the rectus muscles upon palpation) is a valuable sign in differentiating AA from NSAP although this sign does not seem to be accurate in the differential diagnosis between AA and acute mesenteric adenitis (Jones 1969, Janik and Firor 1979, Bower et al 1981). *Guarding* is noted in 80-91 % of children with AA, 50 % of acute mesenteric adenitis, and 8 % of NSAP. *Rebound tenderness* elicited with deep palpation followed by sudden release of the hand is found in 56-83 % of children with AA, 33 % of acute mesenteric adenitis and 1 % of NSAP (Jones 1969, Graham et al 1980, Bower et al 1981).

Rectal digital tenderness is noted in 44-68 % of children with AA compared with 11-12 % of those with NSAP (Foster and Edwards 1957, Jones 1969, Dickson and MacKinlay 1985). A low grade

fever (37.3 °C-38.9 °C) may be present in 36 % of children with AA (Winsey and Jones 1967). Body temperature may be elevated after appendiceal perforation although high fever (≥ 38.9 °C) is uncommon with AA (Winsey and Jones 1967).

2.2.4.4. Active observation

In the first hours of acute abdominal pain it can be difficult to distinguish those who have AA from those who have NA. Therefore, active observation has been suggested where the clinical diagnosis of AA has remained equivocal after the initial clinical assessment (Bachoo et al 2001). Active observation is a clinical practice, in which clinical examination is repeated every few hours until a definite diagnosis is established (Jones 1969). Furthermore, diagnostic accuracy and overall decision making may be improved when structured history and data collection sheets are used (Gunn 1976, Paterson-Brown et al 1989).

Several authors (Surana et al 1995, Bachoo et al 2001, Kirby and Sparnon 2001) have reported that active observation of children with suspected AA has not been associated with increased morbidity. In one study (Bachoo et al 2001) 72 % of children underwent appendicectomy on the day of admission, whilst in 28 % it was delayed for 1 to 6 days because the diagnosis of AA remained equivocal. The authors observed a positive predictive value for clinical assessment of 98 % and an unnecessary appendicectomy rate of 3 %. Surgical morbidity was recorded at 6 % with no correlation between post-appendicectomy morbidity and timing of surgical intervention evident. In another study (Kirby and Sparnon 2001) serial examination was associated with an overall diagnostic accuracy of 93 %, and an overall incidence of postoperative infective complications of 4 %.

2.2.4.5. Laboratory studies

The total white blood count (WBC) is the test most often obtained to diagnose AA. However, leucocytosis is a non-specific reaction resulting from emotional stress, acute or chronic inflammation, tumours, and haemorrhage (Hallan et al 1997). A low WBC threshold (>10.000 to 12.000 cells/mm^3) is 51 to 91 % sensitive for AA in children. However, the use of higher WBC threshold (>14.000 to 15.000 cells/mm^3) results in sensitivity of 41 to 68 % (Bower et al 1981, Williams et al 1998, Paajanen et al 1997). In one study (Doraiswamy 1978) leucocytosis (defined as a WBC count ≥ 15.000 cells/mm^3 in children < 10 years and > 13.000 cells/mm^3 in those ≥ 10 years) was reported to be 18 % sensitive for AA if symptoms had been present for less than 24 hours, whereas it was 90 % sensitive if symptoms had persisted more than 48 hours.

The WBC differential count has been suggested to be of value in diagnosing AA as neutrophilia is often associated with bacterial infections (Hallan et al 1997, Madan 2002). One study (Doraiswamy 1978) found that neutrophilia was more sensitive than leucocytosis (94 % vs 18 %) for diagnosing AA if symptoms had been present less than 24 hours. Either leucocytosis or neutrophilia is found in 90 to 96 % of children with AA, although the specificity of utilizing these measures in combination is unclear (Doraiswamy 1977, Doraiswamy 1978, Doraiswamy 1979, Bower et al 1981, Schwartz and Bulas 1997).

C-reactive protein (CRP) is an acute-phase reactant synthesized by the liver in response to bacterial infection. Serum level begins to rise within 6-12 hours of acute infection (Hallan et al 1997). CRP has been reported to be 43 to 92 % sensitive and 33 to 95 % specific for AA in children (Peltola et al 1986, Paajanen et 1997, Calvo et al 1998, Sanchez et al 1998). A meta-analysis that primarily evaluated adults concluded that the WBC was more accurate than CRP in diagnosing AA (Hallan and Åsberg 1997). However, some studies suggest that CRP may be more sensitive (>90 %) than

the WBC in detecting appendiceal perforation and abscess formation (Peltola et al 1986, Paajanen et al 1997, Sanchez et al 1998).

Children with suspected appendicitis require urinalysis to exclude a urinary tract infection or ureterolithiasis. Abnormal urine findings may result in misdiagnosis, however, as 7 to 25 % of children with AA have pyuria or haematuria (Blair and Gaisford 1969, Rothrock et al 1991, Green et al 1997).

Ectopic pregnancy must be considered for any sexually active adolescent female who presents with acute abdominal pain. Therefore, consideration of ectopic pregnancy necessitates obtaining the serum beta-human chorionic gonadotropin level (Mollitt and Dokler 1997).

2.2.4.6. Imaging studies

The use of imaging studies has increased markedly over the last few years and has resulted in an increase in the accuracy of the diagnosis of AA. On the other hand, diagnostic imaging modalities can increase the time to the diagnosis, the radiation exposure, the use of hospital resources, and the discomfort of the child (Garcia Pena et al 2004). Therefore, several authors (Douglas et al 2000, Garcia Pena et al 2004) have suggested imaging guidelines to reduce the number of unnecessary radiographic studies being performed for the diagnosis of acute appendicitis.

Ultrasonography using a high resolution linear transducer and graded abdominal compression has gained popularity in diagnosing AA in children (Ceres et al 1990, Crady et al 1993, Ramachandran et al 1996, Hahn et al 1998, Roosevelt and Reynold 1998, Emil et al 2001, Kaneko and Tsuda 2004). Three prospective studies using ultrasonography documented a sensitivity of 88-93 % and a specificity of 96-97 % in diagnosing AA (Ceres et al 1990, Ramachandran et al 1996, Hahn et al

1998), and the authors of these studies recommended the use of ultrasonography as an adjunct in equivocal cases. In one prospective study (Blab et al 2004) repeated sonographic examination resulted in a sensitivity of 97 % in the diagnosis of AA. In contrast, two studies have shown that there would be no role for ultrasonography where clinical evidence is convincing, given the known false negative rate of ultrasonography and the knowledge that the technique may delay surgical treatment (Roosevelt and Reynold 1998, Emil et al 2001). The main disadvantage is that ultrasonographic examination is operator dependent, and thus the technique requires considerable training and experience (Rosendahl et al 2004).

Kaneko and Tsuda (2004) have shown that the diagnosis and the treatment of AA can be based solely on ultrasonography findings. In their prospective consecutive study the ultrasonographic criterion for appendicitis was a diameter exceeding 6 mm while the severity of the disease was classified into four grades based on the appearance of the echogenic submucosal layer. Patients with grades I and II received antibiotic therapy, and those with grades III and IV underwent appendicectomy. An experienced sonographer diagnosed appendicitis in all children who underwent appendectomy. There was no unnecessary appendicectomy although diagnosis was delayed in one patient. Children in the conservative treatment group underwent antibiotic therapy without adverse events.

Computed tomography has been widely used in adults to diagnose appendicitis, with a reported accuracy higher than that of ultrasonography (Balthazar et al 1994). Rao and co-workers (1997) found that focused helical computed tomography with colon contrast had a sensitivity of 98 % and specificity of 98 % in diagnosing AA. In this technique radiation exposure is less than that of a standard obstruction series. Two retrospective studies of focused helical computed tomography in children have suggested sensitivity of 95-97 % in diagnosing appendicitis (Pena et al 1999, Stephen

et al 2003). Stephen and co-workers (2003) concluded that the use of computed tomography did not enhance the accuracy in diagnosing appendicitis when compared with patients diagnosed by clinical examination. On the other hand, some authors (McDonald et al 2001, Partrick et al 2003, Martin et al 2004) have reported that the increase in computed tomography use has not resulted in decreased rate of unnecessary appendicectomy or perforation. Disadvantages of this technique include potential for anaphylactoid reaction if intravenous contrast is used, and patient discomfort if rectal contrast is used (Sivit 2004). Moreover, it is known that the radiation effects in children can be many times that in adults because growing tissue can be more sensitive to radiation and children live long enough post-exposure to express tumours that would not have time to become clinically evident in adults. Recent reports have shown that computed tomography is related with the 1 in 1000 risk of malignancy developing in later life (Hall 2002).

There are few reports on the use of magnetic resonance imaging in the diagnosis of AA in children. This may be explained by the fact that the younger children need sedation. In one study (Hormann et al 1998), magnetic resonance imaging was able to identify all children who had ultrasonographic findings compatible with AA.

Plain abdominal X-ray has been reported to be normal in 73 %, misleading in 7 %, and diagnostic in only 7 % of children with confirmed appendicitis (Rothrock et al 1992). On the other hand, plain films may be useful children with clinically nonapparent appendiceal perforations. In one study (Johnson et al 1988) a retrospective analysis of plain films of children with perforated appendicitis resulted in sensitivity of 80 % and specificity of 94 % for detecting perforation. Acute small bowel obstruction was the most common sign of appendiceal perforation in that series. Therefore, abdominal plain films should be limited to selected patients with abdominal distension, abnormal bowel sounds and peritoneal signs (Rothrock et al 1992).

Previously barium enema has been used as an adjunct in making the accurate diagnosis of AA in children (Jona et al 1977). Incomplete filling of the appendix coupled with spasm in the caecum suggests appendicitis (Hatch et al 1981). In one study the use of barium enema resulted in diagnostic accuracy of 86 % in children with suspected appendicitis. However, false negative findings were detected in 5 % of children of whom two-thirds had early perforations at the time of their surgery. Hatch and co-workers (1981) concluded that a negative barium enema could not be relied upon to delay surgery in children with RLQ pain. Moreover, disadvantages of barium enema include radiation exposure and invasiveness. Barium enema has no role in the diagnosis of AA in the era of ultrasonography and computed tomography.

Several authors (Garcia Pena et al 2004, Kosloske et al 2004) have proposed selective imaging strategies for the diagnosis of appendicitis in children. In one retrospective study (Garcia Pena et al 2004) the authors compared three different imaging protocols and calculated the numbers of missed diagnoses of appendicitis, unnecessary appendicectomies, and ultrasonographies and computed tomography scans performed for each strategy. The authors found that these protocols may reduce the number of imaging studies while keeping the unnecessary appendicectomy and missed diagnosis of appendicitis rates stable. In another observational study (Kosloske et al 2004) a diagnostic strategy was based on the clinical acumen of a paediatric surgeon who used imaging only selectively. The authors reported low rates of unnecessary appendicectomy (5%) and perforation (17%) without the potential costs and radiation exposure of excess imaging.

2.2.4.7. Computer aided diagnosis

Computer programs for the diagnosis of AA have been developed since the 1970`s (de Dombal et al 1972). Bayes` theorem have been used to calculate the probability of the presence of AA given clinical features of patients with appendicitis (Gunn 1991). Physicians enter the clinical data,

collected on a structured data-sheet, into a computer-aided diagnosis program. Diagnostic probabilities are produced, using a previous clinical database for reference. Although initial results of the computer-aided diagnostic system resulted in overall diagnostic accuracy of 90 % (de Dombal et al 1972), other trials have been so far unable to reproduce this high figure (Adams et al 1986, Clifford et al 1986). This may result from the fact that the original report (de Dombal et al 1972) dealt with registrars, whereas also junior physicians were included in the later studies (Adams et al 1986).

2.2.4.8. Diagnostic scores

Several investigators have created diagnostic scoring systems in which a finite number of clinical variables is elicited from the patient and each is given a numerical value (Teicher et al 1983, Arnbjörnsson 1985, Alvarado 1986, Fenyö 1987, Lindberg and Fenyö 1988, deDombal 1991, Christian and Christian 1992, Eskelinen et al 1992, Izbicki et al 1992). The sum of these values have been used to predict the likelihood of AA. In contrast to computer-aided decision support, the score requires no special equipment, it is user-friendly, and it is comprehensible to the physician. Some of the scores have been validated clinically in a separate prospective study (Arnbjörnsson 1985, Fenyö 1987, Lindberg and Fenyö 1988, Christian and Christian 1992), but only few have been tested in different clinical environments (Bond et al 1990, Owen et al 1992, Fenyö et al 1997). Two scoring systems (Fenyö 1987, Christian and Christian 1992) have been tested repeatedly on prospective samples. No score has been evaluated in a prospective controlled trial.

All developers of the diagnostic scores have reported promising results in adults, and some have suggested a decrease of the unnecessary appendicectomy rate of up to 50 % (Arnbjörnsson 1985, Alvarado 1986, Christian and Christian 1992, Owen et al 1992). However, a retrospective evaluation of 10 different diagnostic scores on a multicentre database of patients with acute

abdominal pain resulted in poor performances for all of them. If the scoring system is tested in the different clinical environment, the results are known to be worse compared with testing in the same hospital in which the score is constructed (Ohmann et al 1995).

Diagnostic scores have been applied on children with varying success. In one prospective study the use of the Alvarado score (Alvarado 1986) decreased a false-positive appendicectomy rate of 44% to 14% (Owen et al 1992). Dado and co-workers (2000) tested retrospectively a modified Lindberg's score (Lindberg and Fenyö 1988) and showed that the scoring system could have reduced unnecessary surgery from 23% to 8%, and only 8% of children with appendicitis would have been discharged home. In contrast to these reports, some authors have claimed that the Alvarado score would not contain variables that would allow for separation of appendicitis from the other conditions mimicking it in children (Bond et al 1990, Macklin et al 1997).

One study has addressed the issue of a diagnostic score unique to children with suspected appendicitis. Madan (2002) evaluated prospectively 1170 children with acute abdominal pain suggestive of AA, and constructed a diagnostic scoring system comprising eight variables. These variables were cough/percussion/hopping tenderness in the RLQ, anorexia, pyrexia, nausea/emesis, tenderness in the RLQ, leucosytosis, polymorphonuclear neutrophilia, and relocation of pain. The predictive score was prospectively validated on 66 children resulting in a sensitivity of 100 %, a specificity of 87 %, a positive predictive value of 90 %, and a negative predictive value of 100 %. Madan did not report whether the predictions from the scoring system were actually used in clinical decision making.

2.2.4.9. Effects of analgesics on diagnostic accuracy

2.2.4.9.1. Background

"Morphine does little or nothing to stop serious intra-abdominal disease, but it puts an efficient screen in front of the symptoms. The fire burns, but it is not visible, and sometimes only when vitality is burnt out is the mistake realized. If morphine be administered, it is possible for a patient to die happy in the belief that he is on the road to recovery, and in some cases the medical attendant may for a time be induced to share the delusive hope." (Silen 1979)

Surgical tradition holds that opioid analgesia in the setting of an acute abdomen can change physical examination findings and should therefore be withheld until after a surgeon`s examination. The belief originated early in the 20$^{th}$ century and was emphasized by Cope (1921) in his influential book, *Early Diagnosis of the Acute Abdomen.* In the late 1970`s, Cope`s 15th revised edition cautioned against the use of opioid analgesics in patients with acute abdominal pain (Silen 1979). The concerns about masking pathology were based on contemporary use of intramuscular administration of up to 30 mg of morphine (Hughes 1979).

The traditional teaching of withholding analgesia in patients with acute abdominal pain has been challenged recently. There exist several reasons for the changing attitudes. Several diagnostic methods have been developed to establish a definite diagnosis in patients with acute abdominal pain. The practice of administering high doses of opioids has been replaced by judicious modern-day titration of analgesia (McHale and LoVecchio 2001). In addition, several clinical trials have been published revealing a marked consistency in results (Zoltie and Cusp 1986, Attard et al 1992, Pace and Burke 1996, LoVecchio et al 1997, Vermeulen et al 1999, Mahadevan and Graff 2000, Thomas et al 2003). In no study there was an association between opioid analgesia and diagnostic

inaccuracy or clouding of the physical examination findings. Based on these initial reports, numerous surgical textbooks now advocate rapid relief of abdominal pain (Rosen 1992, Cuschieri 1995, Tintinalli 2000).

Publication of trials of analgesia for acute abdominal pain has not resulted in unanimous clinical practice. In 1996, a survey of 131 general surgeons in the USA revealed that 67% preferred that patients with acute abdomen should not be given pain medication until examined by a surgeon for fear that it may mask clinical symptoms and signs (Graber et al 1999). Another survey found that 76 % of USA emergency medicine respondents withheld opioid analgesia pending surgical assessment (Wolfe et al 2000). In contrast, a survey in 2002 showed that 98 % of respondents administered opioids before surgical consultation (Nissman et al 2003). However, only 15 % of them indicated it was their practice to inform the surgeon before administering analgesics.

Only few studies have addressed the issue of the analgesic use in children with acute abdominal pain. Green and co-workers (2004) reviewed medical records of 290 children presenting to a children`s hospital with acute abdominal pain, and the authors found that only 15 % of these children had received analgesics at the ED.

2.2.4.9.2. Double-blind placebo controlled trials

Several prospective randomized studies have addressed the issue of analgesia administration for adults with acute abdominal pain (Zoltie and Cusp 1986, Attard et al 1992, Pace and Burke 1996, LoVecchio et al 1997, Vermeulen et al 1999, Mahadevan and Graff 2000, Thomas et al 2003) (Table 2). In these studies, all patients were randomly assigned to receive either opioid analgesia or placebo, and visual analogue scales were used to evaluate abdominal pain before and after patients

received the study drug. All the studies compared the accuracy of the physician`s diagnosis and treatment in patients who did or did not receive narcotics.

Studies in adults have demonstrated that early administration of opioids provides pain relief to patients with acute abdominal pain, without adversely affecting diagnostic accuracy or delaying diagnosis (Zoltie and Cusp 1986, Attard et al 1992, Pace and Burke 1996, LoVecchio et al 1997, Vermeulen et al 1999, Mahadevan and Graff 2000, Thomas et al 2003). Zoltie and Cust (1986) noted a marked placebo effect such that buprenorphine resulted in pain relief in 37 % of those receiving 200 µg and 56 % of those receiving 400 µg compared with spontaneous pain relief in 48 % of patients receiving placebo. Abdominal pain disappeared in 19 % of the patients receiving no drug at all. However, LoVecchio and co-workers (1997) found no change in patients` rating of pain after administration of the placebo.

Physical examination changes after administering the study drug have been reported in several studies (Zoltie and Cusp 1986, Attard et al 1992, LoVecchio et al 1997, Mahadevan and Graff 2000, Thomas et al 2003). Some authors (Zoltie and Cusp 1986, Thomas et al 2003) did not find any differences between placebo and opioid groups with respect to alterations in clinical findings. However, in one study (Attard et al 1992) abdominal tenderness decreased in 70 % of patients receiving papaveretum compared with 16 % of those receiving the placebo.

In one study (LoVecchio et al 1997) a change in tenderness or localization (as defined by extent of tenderness decreasing from two or more quadrants to one, or negative rebound sign, or vice-versa) was encountered in 50 % of patients receiving morphine compared to 6 % of those receiving placebo. The authors even suggested that early analgesia may have allowed for a more exact examination through patient relaxation. Mahadevan and Graff (2000) addressed physical

examination findings in detail, and found that giving the tramadol resulted in more clinical signs better predictive of appendicitis retained on repeat examination when compared placebo.

Although most studies (Zoltie and Cusp 1986, LoVecchio et al 1997, Vermeulen et al 1999, Mahadevan and Graff 2000, Thomas et al 2003) have found no between-group difference with respect to accuracy of operative decision making, some authors (Attard et al 1992, Pace and Burke 1996) have suggested that administration of opioids could even facilitate diagnosis in patients with undifferentiated abdominal pain. Attard and co-workers (1992) noted that the surgeon`s decision of observation versus appendicectomy was incorrect in 18% of patients receiving placebo as compared to 2 % of those receiving papaveretum. In addition, 12 % of patients underwent unnecessary appendicectomy in the placebo group as compared with none in the papaveretum group. Furthermore, Pace and Burke (1996) found that the initial diagnosis was the same as the final diagnosis in 80 % of patients receiving morphine compared to 61 % of those receiving placebo.

Kim and co-workers (2002) have published a randomized clinical study of safety of opioid analgesics in children with acute abdominal pain (Table 2). They assessed the effects of intravenous morphine on the physical examination, diagnostic accuracy and adverse effects. Paediatric emergency physicians and surgeons independently indicated areas of tenderness to palpation and percussion before and after administration of either morphine or normal saline. Morphine administration was associated with a decrease in number of areas of tenderness as evaluated by paediatricians, but surgeons found no difference in the examination. All children in the morphine group undergoing laparotomy had persistent tenderness to palpation and percussion after analgesia. The authors concluded that intravenous morphine provided significant pain relief to children with acute abdominal pain without adversely affecting the examination. Furthermore, morphine administration did not adversely affect on the diagnostic accuracy.

Table 2. Double-blind randomized controlled trials evaluating the use of analgesics in acute abdominal pain.

Adults	**Type of acute abdominal pain**	**Number of patients**	**Type of study drug (number of patients)**	**Route of analgesia**	**Number of doses**	**Study period (minutes)**
Zoltie and Cusp 1986	Non-differentiated abdominal pain	288	1.Buprenorphine 200 µg (n=59) 2.Buprenorphine 400 µg (n=75) 3.Placebo (saline) (n=122) 4.No tablet (n=32)	Sublingual tablet	1 dose	60
Attard et al 1992	Non-differentiated abdominal pain	100	1.Papaveretum ad 20 mg (n=50) 2.Placebo (saline) (n=50)	Intra-muscular injection	Patient`s dose dependent on evaluation of pain occurring	60
Pace and Burke 1996	Non-differentiated abdominal pain	71	1.Morphine sulphate 0.1 $mg \cdot kg^{-1}$(n=35) 2.Placebo (saline) (n=36)	Intra-venous injection	First bolus, then repeat dose until pain was relieved	15
Lovecchio et al 1997	Non-differentiated abdominal pain	48	1.Morphine sulphate 10 mg (n=19) 2.Morphine sulphate 5 mg (n=13) 3.Placebo (saline) (n=16)	Intra-venous injection	1 dose	15
Vermeulen et al 1999	Suspected appendicitis	340	1.Morphine sulphate 0.1 $mg \cdot kg^{-1}$(n=175) 2.Placebo (saline) (n=165)	Intra-venous injection	1 dose	45
Mahadevan and Graff 2000	Suspected appendicitis	66	1.Tramadol 1 $mg \cdot kg^{-1}$ (n=33) 2.Placebo (saline) (n=33)	Intra-venous injection	1 dose	60
Thomas et al 2003	Non-differentiated abdominal pain	74	1.Morphine sulphate ad 15 mg (n=38) 2.Placebo (saline) (n=36)	Intra-venous injection	Doses and frequency of administration was left to the physician	60
Children						
Kim et al 2002	Non-differentiated abdominal pain	60	1.Morphine sulphate 0.1 $mg \cdot kg^{-1}$ (n=29) 2.Placebo (saline) (n=31)	Intra-venous injection	1 dose	30

2.2.5. Treatment

2.2.5.1. Background

The treatment of choice for appendicitis is early appendicectomy (Samelson and Reyes 1987, Stringel 1987, Neilson et al 1990). Minimal preoperative preparation is needed when the diagnosis is established early in the course of appendicitis. However, intensive resuscitation may be required in children with more advanced disease (Cloud 1993). Resection of a portion of the caecum and a tube caecostomy is occasionally mandatory in patients with severely inflamed appendices (Cloud 1993). When the appendix is perforated, copious peritoneal lavage with saline should be performed to rinse out the infectious debris (Samelson and Reyes 1987, Stringel 1987, Neilson et al 1990). Drains are not used except for well-localized abscess cavities in the abdomen (Cloud 1993). The surgical wounds should be closed primarily (Samelson and Reyes 1987, Stringel 1987, Neilson et al 1990).

Management of children with palpable abdominal mass has been controversial (Cloud 1993, Nitecki et al 1993, Karaca et al 2001). Some advocate immediate appendicectomy (Vakili 1976), others favour conservative treatment because manipulation of the appendix may lead to the dissemination of infections and fistulas (Cloud 1993, Karaca et al 2001). The management consists of antibiotics and active observation for signs of generalized peritonitis. If the mass enlarges on serial ultrasonography, the mass can be drained percutaneously (Cloud 1993, Karaca et al 2001), followed by interval appendicectomy in 4-6 weeks (Cloud 1993). However some authors (Nitecki et al 1993) have suggested that interval appendicectomy is unnecessary, because only 14 % of patients have recurrent symptoms, and recurrence of appendicitis within 2 years after initial diagnosis is uncommon.

Several reports have described the success of intra-venous antibiotics in treating all patients with AA (Bagi and Dueholm 1987, Eriksson and Granström 1995, Kogut et al 2001). In one prospective study (Eriksson and Granström 1995) of 20 patients with ultrasound-proven appendicitis, 95 % had resolution of symptoms with antibiotics alone, but 37 % of these patients had recurrent appendicitis within 14 months. Some authors (Bagi and Dueholm 1987, Kogut et al 2001) who have advocated conservative treatment for localized perforated appendicitis have reported a 9 % to 22 % failure rate for antibiotic therapy. On the other hand, spontaneously resolving appendicitis has recently been recognized and reported to account for 8 % of cases of AA (Cobben et al 2000).

Preoperative antibiotic therapy is recommended in all children with suspected appendicitis (Busuttil et al 1981, Winslow et al 1983, Samelson and Reyes 1987, Stringel 1987, Neilson et al 1990, Cloud 1993). It has been shown that a single prophylactic dose of metronidazole significantly decreases the rate of postoperative infectious complications in children with appendicitis (Söderquist-Elinder et al 1995). Broad spectrum antibiotics should be continued postoperatively in children with complicated appendicitis, but no consensus on duration of therapy exists; estimates range from 3 to 14 days (Neilson et al 1990, Cloud 1993, Curran and Muenchow 1993, Hoelzer et al 1999). However, some studies (Neilson et al 1990, Hoelzer et al 1999) have shown that the antibiotic treatment can be discontinued when the children are afebrile and without leucocytosis. In Finland, double antibiotic therapy (cefuroxime and metronidazole) has been widely used in the postoperative treatment of perforated appendicitis (Saario et al 1983).

2.2.5.2. Open appendicectomy

OA has been the "treatment of choice" for AA for nearly a century. OA is performed through a McBurney incision which is a standard muscle splitting approach with no restriction of incision size, caecal mobilization, or a small bowel delivery. The operative incision is often enlarged if the

inflamed appendix is located retrocaecally or subhepatically, or if it is attached to the floor of the pelvis. The appendiceal stump is usually secured and inverted with caecal sutures (Cloud 1993).

New open surgical techniques have been proposed to reduce morbidity related to the operative incision. Janik and Janik (2004) have described a mini-laparotomy technique in which the incision size is limited to a size large enough to accommodate the surgeon`s index finger. The abdominal wall is infiltrated with bupivacaine prior to the peritoneum is opened. Only the appendix and the part of the caecum is mobilized outside the peritoneal cavity. The authors reviewed retrospectively 100 consecutive children operated with a mini-invasive OA and 100 children treated with traditional open technique, and found that the mean hospital stay was significantly shorter in the mini-invasive OA group compared with traditional OA group (1.0 and 2.7 days, respectively). The authors concluded that the mini-laparotomy technique may be an advantageous alternative to laparoscopic or traditional appendicectomy in children with uncomplicated appendicitis.

2.2.5.3. Laparoscopic appendicectomy

2.2.5.3.1. Background

The size of the access wound has been shown to be a major determinant of perioperative morbidity. Moreover, the postoperative pain is influenced by the size of the surgical wound. Laparoscopic technique has been introduced to lessen the operative trauma. Therefore, LA is theoretically associated with earlier discharge and return to normal activities, and a decreased rate of postoperative pain, wound complications, scarring, and intra-abdominal adhesions. A great number of commonly performed surgical procedures that were once accomplished with an open operation are now approached with minimal invasive techniques (Blucher and Lobe 1994, Tan 1994, Lobe 1997).

Laparoscopy has been in use in adults since the turn of the 20th century (Schropp 1994). In 1930 Lamm made a significant advance by developing small flexible fibreglass bundles for the transmission of light (Gans 1983). Another advance was the development of the automatic insufflator in 1967 by Semm (Schaarschmidt et al 1996). In the 1960`s Hopkins developed the rod-lens optical system to give a larger viewing angle, more light transmission and good resolution. Miniaturization of the laparoscopic system became technically feasible and suitable for paediatric use (Gans 1983). The first significant use in children was not recorded until the early 1970`s when Gans and Berci (1971) reported their experience with modified cystoscopy equipment to perform evaluation of intra-abdominal lesions. In the 1980`s and 1990`s the laparoscopic system was further improved by the development of high-intensity cold-light, better videorecording, laparoscopes with a range of sizes from 2 to 10 mm, and variety of viewing angles (Hertzmann 1994, Lobe 1997).

The first successful LA in adults was performed by Semm in 1983. Since then many modifications have been reported (Leahy 1989, Götz et al 1990, Tate et al 1993), and by the late 1990`s LA had become an accepted technique for treating AA also in children. Large retrospective series of successful LAs in children have been published indicating that LA is a safe, effective, and feasible alternative to OA in paediatric patients (Valla et al 1991, Steyaert et al 1998, Canty et al 2000). Moreover, Newman and co-workers (2003) examined the current treatment patterns of children with AA in 30 paediatric hospitals in the USA, and they found that LA was performed in 31 % of children with AA.

2.2.5.3.2. Techniques of laparoscopic appendicectomy

Laparoscopic appendicectomy is performed in general anaesthesia with controlled ventilation (Sfez et al 1995). Ventilation with nitrous oxide should be avoided since this may distend bowel especially during prolonged procedures. There is an increased risk of perforation of the enlargened

bowel especially when the Veress needle is used (Neumann et al 1993). Nitrous oxide can pass into the abdominal cavity and cause combustion (Neumann et al 1993, Tobias et al 1995).

Risk of regurgitation of gastric contents may be related to emergency LA and therefore rapid induction of anaesthesia and tracheal intubation is required. In addition, a nasogastric tube is usually necessary to empty the stomach. It is important that the urinary bladder is empty before placing the umbilical trocar but catheterization is required only if the bladder is palpable (Najmaldin and Grousseau 1999).

To provide an adequate view, LA requires insufflation of the peritoneal cavity with a gas or abdominal refractors to lift the abdominal wall. Carbon dioxide (CO_2) has been preferred gas for pneumoperitoneum because it is non-combustible, inexpensive, highly soluble and least likely to produce embolism (Tobias 1998). However, CO_2 has physiological effects when absorbed. The qualities of other gases for insufflation have not been equally ideal. Since the solubility of helium, argon and nitrogen in blood is less than that of CO_2, the risk of intraoperative gas embolism is greater (Eisenhauer et al 1994, Junghans et al 1997). Air and oxygen are no longer used because they support combustion and increase the risk of gas embolization. Nitrous oxide has limited physiological effects after absorption, but it supports combustion as well (Tobias 1998). Abdominal wall suspension has not gained popularity among paediatric surgeons because CO_2 pneumoperitoneum is considered safe in children as well. Moreover, gasless technique requires specifically designed expensive devices (L, T or loop shaped) to create a working space (Najmaldin and Grousseau 1999).

Abdominal cavity can be approached and pneumoperitoneum created either by direct insertion of a Veress needle through the anterior abdominal wall (closed method) or by an open "cut down"

technique (Bridgewater and Mouton 1999, Najmaldin and Grousseau 1999). In the latter technique, the peritoneal cavity is opened under direct vision through the periumbilical incision, and the umbilical 10- or 12-mm trocar is attached to the abdominal wall by the purse-string suture. After the umbilical trocar is fixed, the abdominal cavity is insufflated with CO_2. The CO_2 pneumoperitoneum used should be limited to about 12 millimetres of mercury (mmHg) in children aged 4 to 15 years. The "cut down" technique is preferred since there is reduced risk of perforation of abdominal viscera or vessels, especially in small children where the liver is located partially below the rib cage and the urinary bladder is intra-abdominal (Najmaldin and Grousseau 1999).

The videoscope is placed through the umbilical trocar, and the abdominal cavity is explored. The two 5-mm working ports are inserted under direct vision. Three different techniques of LA have been described: the intracorporeal, "mixed", and extracorporeal LA. The intracorporeal appendicectomy with three trocars represents a true laparoscopic approach. The meso-appendix is cut, and the base of the appendix is ligated either with a pretied ligature (an endoloop) or intra- or extracorporeally tied knot. The appendiceal stump can be alternatively secured with an endoscopic stapler requiring a 12-mm trocar. The appendix is removed through the umbilical port. Three trocars are required also in the "mixed" technique in which the mesentery is cut intra-abdominally, while the stump of the appendix is ligated outside the abdominal cavity (Valla and Steyaert 1999). The extracorporeal technique is performed with one or two trocars (Valla and Steyaert 1999, Pappalepore and Tursini 2002). The appendix is grasped and pulled out with the mesentery through the umbilical port, and the appendicectomy is performed extracorporeally.

Several studies have been published comparing different LA techniques in children. Suttie and co-workers (2004) assessed retrospectively the outcome after intracorporeal and extracorporeal LA. The authors found that the operating time was significantly shorter in the extracorporeal LA group

compared with the intracorporeal LA group (51 vs 68 min; P=0.001). There were no differences in the hospital stay between the two study groups but extracorporeal technique was associated with slightly increased complication rate. Shalaby and co-workers (2001) conducted a randomized controlled trial, and evaluated the outcome of LA using three different techniques. The authors showed that children who underwent LA using an endoscopic stapler had shorter operating times, did not have complications, and had the shortest duration of hospital stay. On the other hand, higher operative costs were related to the use of the stapler. Endoloop LA techinique was the second most preferable approach, and the least preferred procedure was extracorporeal LA. The last technique was associated with high complication rate. The extracorporeal technique may be used in cases in simple appendicitis in which extensive mobilization of the caecum is not required (Shalaby et al 2001).

Laparoscopists and manufacturers have become increasingly interested in miniaturization of the laparoscopic instruments and camera lenses, and since 1994, a number of laparoscopic operations have been performed with needlescopic instruments (Cheah et al 1998, Gagner and Ruiz 1998). Gagner and Garcia-Ruiz (1998) defined the term needlescopic for an operation in which the instruments are smaller than 3 millimetres in diameter. In 2001, Huang and co-workers reported on the first prospective study of needlescopic procedures for acute appendicitis in adults. The authors compared OA, LA, and needlescopic LA, and found that needlescopic LA provided significant advantages over OA in terms of decreased postoperative pain and shorter hospitalization without significant increases in complication rate or operating time.

2.2.5.3.3. Physiological changes during laparoscopy

Laparoscopic technique exposes the child to physiological derangements which are not part of conventional open surgery. Although the operating time for LA is usually short significant

physiological changes may occur during the laparoscopic procedure. These changes may be related to an increased intra-abdominal pressure during pneumoperitoneum, or to the absorption of CO_2 from the abdominal cavity (Tobias et al 1995). Therefore special strategies are required of the anaesthetist to detect and treat any problems that occur in children.

Cardiovascular changes during laparoscopy may occur in the variables such as heart rate, blood pressure and peripheral perfusion (Johannsen 1989). These changes are related to the absorption of CO_2, Trendelenburg or reverse Trendelenburg position, and increased abdominal pressure during insufflation (Manner et al 1998). The absorption of CO_2 may lead to hypercapnia that may contribute to a small increase in heart rate and systolic blood pressure (Tobias et al 1996). However, there are no clinical data to support the role of hypercapnia in cardiovascular changes in children (Sfez 1999). Trendelenburg position further increases venous return, cardiac output, and arterial pressure (Sfez et al 1995, Wedgewood and Doyle 2001). Increased arterial pressure requires no specific therapy (Sfez et al 1995).

An intra-peritoneal pressure of less than 10 mmHg, may increase venous return, cardiac output, and mean arterial pressure by reducing blood volume from the splanchnic venous system (Versichelen et al 1984, Ekman and Abrahamsson 1988). However, an increase of the intra-peritoneal pressure of more than 10 mmHg may impede venous return, decrease cardiac output and increase afterload. If the intra-peritoneal pressure increases further to approximately 20 mmHg, the decreased cardiac output may result in a fall in mean arterial blood pressure. On the other hand, simultaneous release of catecholamines and vasopressin may result in enhanced systemic vascular resistance and pulmonary vascular resistance (Wedgewood and Doyle 2001). Therefore, the increase in peripheral arterial resistance may counterbalance a decrease in cardiac output and lead to normal blood

pressure. The simultaneous decrease in venous return together with elevated systemic vascular resistance can be of concern in children with limited cardiac reserve (Raux et al 1995, Sfez 1999).

The mechanical effects of gas insufflation may lead to impaired ventilatory function including increased airway pressure during Trendelenburg position, reduced functional residual capacity (FRC), and decreased lung compliance (Tobias et al 1995, Wedgewood and Doyle 2001). The reduced FRC can cause disturbances in ventilation-perfusion ratio. Ventilation of nondependent areas of lungs may result in intrapulmonary shunting and hypoxaemia (Manner et al 1998). On the other hand, insufflated CO_2 is absorbed through the peritoneum resulting in an elevation in total body CO_2 content. An enhanced CO_2 load can contribute to respiratory insufficiency, and respiratory acidosis (Tobias et al 1996, McHoney et al 2003). However, children adapt to the extra CO_2 load by increasing plasma and cellular buffering and by accelerating CO_2 transport and elimination (McHoney et al 2003). Therefore, the respiratory burden of hypercapnia is generally well tolerated in children (Wedgewood and Doyle 2001).

Pneumoperitoneum seldom has an adverse effect on postoperative respiratory function. On the contrary, ventilation is less impaired following laparoscopic surgery, and pulmonary function recovers sooner compared to open surgery (Wedgewood and Doyle 2001). The laparoscopic technique may even contribute to prevent early postoperative atelectasis related to decreased FRC (Sfez et al 1995, Sfez 1999).

Changes in body temperature, cerebral circulation, and renal function may occur during laparoscopy. Hypothermia is likely to occur during prolonged laparoscopic procedures or when cold saline solution is used for abdominal lavage (Sfez 1999). In general, laparoscopic technique is associated with reduced heat loss and less fluid loss compared with open technique (Wedgewood

and Doyle 2001). Enhanced intra-cranial pressure during laparoscopic procedures has been reported in patients with ventriculoperitoneal shunts (Uzzo et al 1997). On the other hand, pneumoperitoneum has been known to result in a rise in intra-cranial pressure in experimental studies (Josephs et al 1994, Wedgewood and Doyle 2001). In addition, hypercapnia increases cerebral blood flow, and consequently may also increase intra-cranial pressure. Therefore, caution is advised when laparoscopic technique is applied in children with an altered cerebral compliance (Wedgewood and Doyle 2001). Persistent renal insufficiency has not been reported after laparoscopy in healthy patients although during prolonged laparoscopic procedures enhanced intra-peritoneal pressure decreases glomerular filtration pressure and results in a time-limited renal dysfunction (Perez et al 2002).

2.2.5.3.4. Anaesthetic considerations

Changes of the ventilator settings are mandatory to compensate the restricted movement of the diaphragm, the reduction in lung volumes, and hypercapnia. Ventilation with large tidal volumes (12-15 $ml \cdot kg^{-1}$) prevents atelectasis and hypoxaemia and allows adequate alveolar ventilation and CO_2 elimination (Tobias et al 1995). The continuous monitoring of end-tidal CO_2 concentration allows adjustment of the minute ventilation to maintain normal concentration of oxygen and CO_2 (Tobias et al 1995).

After the laparoscopy, most of the intra-abdominal CO_2 should be removed, since the gas will irritate the diaphragm and may cause referred shoulder pain, nausea and vomiting (Tobias et al 1995). Lejus and co-workers (1996) reported that 35 % of children undergoing LA experienced shoulder pain compared with 10 % of those with OA. As the gas absorbs into circulation and is exhaled through lungs the pain will gradually disappear within 24-48 hours.

The port sites can be infiltrated with a local anaesthetic plus a vasoconstrictor to provide postoperative pain relief and to minimize bleeding (Blakely et al 1998). Intraoperative infiltration of a long-acting local anaesthetic may provide several hours of postoperative analgesia. This will need to be supplemented by non-opioid analgesics and a systemic opioid (Hay 1998).

Healthy children tolerate a brief (less than 15 minutes) laparoscopic procedure well, and no increase in minute ventilation is usually required (Tobias et al 1995, Tobias et al 1996). Increased ventilatory support may be required during prolonged laparoscopic procedures. The appendix is the best-suited intra-peritoneal organ for laparoscopic removal but the operating time depends on the surgeon`s experience. Steyaert and co-workers (1998) published a series of 1500 LAs in which the median time for LA was 23 min if the appendix was not complicated and 55 min if the appendix was perforated. The authors did not report any untoward anaesthetic events related to the use of pneumoperitoneum. Therefore, LA seems to be a safe alternative to OA in otherwise healthy children although more information of the physiological changes during the anaesthesia is required.

2.2.5.3.5. Complications related to the laparoscopic technique

Several potential complications have been associated with the creation of pneumoperitoneum and the laparoscopic surgical technique (Nord 1992, Esposito et al 1997, Bax et al 1999) (Table 3). Complications are usually related to the surgeon`s experience, equipment malfunction, the type of the operation, anaesthetic complications, atypical presentation of the appendix or the intra-abdominal adhesions. As a surgeon becomes more experienced, the number of complications is likely to decrease. Furthermore, most of the complications of inadvertent perforation of organs and vessels can be avoided by using a cut down technique for the umbilical trocar (Hasson 1974, Nuzzo et al 1997). The open technique is usually recommended in children (Bax et al 1999).

Table 3. Potential complications related to the laparoscopic surgery.

Complications related to pneumoperitoneum	**Complications related to access and instrumentation**
□ *Consequences of an increased intra-abdominal pressure*	□ *Related to access*
•haemodynamic instability	•perforation of vessels and organs
•respiratory insufficiency	•neoplastic or infectious contamination
□ *Consequences of the use of gas*	•port site bleeding
•subcutaneous or scrotal emphysema	•port site herniation
•pneumothorax	□ *Related to instrumentation*
•pneumomediastinum	•inadvertent injury
•gas embolus	•tissue rupture and spillage during removal
•hypothermia	•dropped clips and staples
	•retained infectious material

Surgical complications related to the laparoscopic technique have been addressed in some retrospective studies. Esposito and co-workers (1997) reported a series of 490 procedures in 395 children. Eight (2 %) complications were registered including abdominal wall haematoma, perforation of the stomach, perforation of the ovary, pneumothorax, subcutaneous emphysema, and the laceration of the iliac vessels. Varlet and co-workers (1994) compared LA with OA, and reported a peroperative complication rate (bleeding vessel, intestinal perforation, ileo-caecal burn) of 4.6% in the LA group compared to 0.9 % in the OA group. However, the postoperative complication rate in the LA group was lower than in the OA group (2 % vs. 11 %).

A survey of 151 paediatric laparoscopists in the USA resulted in a sample of 5400 cases (Peters 1996). Complications were reported in 5.4 % of children but when preperitoneal insufflation or

subcutaneous emphysema were excluded the complication rate was 1.2 %. The injury to the bowel, bladder or great vessels were encountered in 0.4 % of cases necessitating surgical correction. The overall complication rate was inversely correlated with the laparoscopic experience of the surgeon. The complication rate when a closed technique was used to enter and fill the abdominal cavity was 7.8 % compared with 3.9 % when the first trocar was inserted under direct vision ("cut down technique").

2.2.5.3.6. Contraindications

The pneumoperitoneum required as part of the laparoscopic surgery may increase a complication risk in some children. Absolute contraindications to laparoscopy are similar to those in adults: haemodynamic instability, pulmonary distension, cardiac disease, uncorrected coagulopathy, and dense abdominal adhesions. Laparoscopy may be difficult in children who have had previous extensive abdominal surgery with possible diffuse adhesions. Therefore, previous laparotomy incisions may necessitate alterations of the usual trocar insertion sites, or may represent a contraindication to the laparoscopic procedure (Sfez 1999).

2.2.5.4. Laparoscopic versus open appendicectomy

2.2.5.4.1. Clinical randomized trials in adults

The advantages of laparoscopic appendicectomy have not found to be as obvious as for laparoscopic cholecystectomy, and therefore a number of clinical trials comparing LA with OA has been conducted. While some studies in adults showed LA to be superior to OA in terms of a faster and a less painful recovery, less postoperative complications, and better cosmesis (Attwood et al 1992, Cox et al 1996, Hansen et al 1996, Macarulla et al 1997, Karadayi et al 2003), other studies found no such advantages (Tate et al 1993, Martin et al 1995, Mutter et al 1996).

A meta-analysis of randomized controlled trials comparing LA with OA in adults have been published recently (Sauerland et al 2004). The Cochrane review was based on 45 studies, and the analysis showed that LA had diagnostic and therapeutic advantages as compared to OA. Wound infection was half as likely while intra-peritoneal abscesses were three times more frequent after LA. LA took 12 minutes longer to perform compared with OA (60 minutes vs 48 minutes) although the difference between the two techniques had become smaller during the more recent years. On the first postoperative day, the adult patients experienced less pain after LA compared with OA (pain score 4 cm versus 5 cm on a 10 cm visual analogue scale (VAS)). Hospital stay in the LA group was 1.1 days shorter compared with that in the OA group (3.6 vs 4.7 days), and the patients in the LA group returned 6 days earlier to their normal activities (15 days vs 21 days after LA compared with OA). The in-hospital costs of the LA were significantly higher than that of OA but the increased operative expenses related to the laparoscopic technique were offset by cost-savings from a societal perspective.

2.2.5.4.2. Clinical randomized trials in children

Four small-scale randomized controlled trials comparing LA with OA have been published in children (Lejus et al 1996, Yeung et al 1997, Lavonius et al 2001, Little et al 2002) (Table 4). All these series show that LA can be performed effectively and safely in comparison to the open technique, although there are some caveats. However, most of the authors concluded that LA offered no significant benefit over OA related to postoperative recovery since they did not find any differences between the two techniques in postoperative analgesia, resumption of oral intake, length of stay, return to normal activities, or complications (Lejus et al 1996, Lavonius et al 2001, Little et al 2002). In the series of Little and co-workers, median of the return to normal activity was 1 day in the LA group and 2 days in the OA group. In addition, longer operating times (Lejus et al 1996, Lavonius et al 2001, Little et al 2002), and increased cost (Little et al 2002) were related to LA.

Table 4. Summary of clinical randomized trials comparing laparoscopic (LA) with open appendicectomy (OA) in children with suspected appendicitis (AA).

Study	Total number of patients	Surgical technique LA/OA	Mean operating time (min) LA/OA	Number (%) of conversions to OA	Length of stay (days) LA/OA	Nonperforated: perforated AA[1] LA/OA	Minor complications LA/OA
Lejus et al (1996)	63	32/31	54/39	0	NR	29:3/27:4	NR
Yeung et al (1997)	181	91/90	60/60	11 (12 %)	NR	NR	0 / 11 %
Lavonius et al (2001)	43	23/20	42/34	1 (4%)	3/3	20:3/15:5	10 % / 0
Little et al (2002)	88	44/44	75/51	3 (7%)	3/2	34:10/33:11	5 % / 2 %

[1]Patients with a normal appendix included in the nonperforated AA group.

NR=not reported.

2.2.5.4.3. Non-randomized studies in children

Several non-randomized studies have been published comparing LA with OA in children (Varlet et al 1994, Hay 1998, Canty et al 2000, Meguerditchian et al 2002, McKinlay et al 2003, Ikeda et al 2004, Oka et al 2004, Wei et al 2004) (Table 5). In two studies the assignment to one of the two groups was based on the schedule of the attending surgeon on call (Hay 1998, Oka et al 2004).

In most of the studies (Varlet et al 1994, Hay 1998, Meguerditchian et al 2002, McKinlay et al 2003, Ikeda et al 2004, Wei et al 2004) the operating time has been reported to be longer in the LA group compared with that in the OA group. In one study (Canty et al 2000) there were no differences in operating times between the two groups, and in one study (Oka et al 2004) OA took 3 minutes longer to perform compared with LA. In most of the studies (Varlet et al 1994, Hay 1998, Meguerditchian et al 2002, Ikeda et al 2004, Wei et al 2004) the length of hospital stay has been found to be 1 to 3 days longer after OA compared with that after LA. However, in one study (McKinlay et al 2003) the hospital stay was similar between the two study groups.

Most of the authors (Canty et al 2000, Meguerditchian et al 2002, McKinlay et al 2003, Ikeda et al 2004, Oka et al 2004, Wei et al 2004) have reported similar complication rates between the the LA group and the OA group. However, Varlet and co-workers (1994) found that peroperative complications were more frequent in the LA group compared with those in the OA group (5 % vs 1 %; $P < 0.02$). On the other hand, the same authors reported a significantly lower postoperative complication rate after LA compared with that after OA (2 % vs 11 %; $P < 0.01$). Hay (1998) found that LA was superior to OA with regard to overall complication rate (5 % vs 13 %; $P < 0.01$), time to normal activities (7 days vs 12 days; $P < 0.01$), and the cosmetic appearance of the operative wounds.

Table 5. Summary of non-randomized studies comparing laparoscopic appendicectomy (LA) with open appendicectomy (OA) in children with suspected appendicitis (AA).

Study	Total number of patients	Surgical technique LA/OA	Mean operating time (min) LA/OA	Number (%) of conversions to OA	Length of stay (days) LA/OA	Nonperforated: perforated AA[2] LA/OA	Complications (%) LA/OA
Varlet et al (1994)	403	200/203	72/55	10 (5 %)	4/6	NR	7 % / 12 %
Hay (1998)	82	34/48	76/50	0	1/2	25:9/38:10	5 % / 13 %
Canty et al (2000)[1]	739	653/86	52/52	0	2/3	653:0/86:0	1 % / 1 %
Meguerditchian et al (2002)	388	126/262	46/41	3 (2 %)	2/3	113:13/223:39	10 % / 8 %
McKinlay et al (2003)	324	205/119	58/49	1 (0.5 %)	2/2	159:46/49:70	14 % / 20 %
Ikeda et al (2004)	100	53/47	88/59	NR	7/9	45:8/41:6	13 % / 13 %
Oka et al (2004)	517	141/376	47/50	NR	4/5	262:114/98:43	10 % / 11 %
Wei et al (2004)	100	84/17	57/49	1 (1 %)	2/5	72:12/11:6	14 % / 35 %

[1] Patients with perforated appendicitis excluded.

[2] Patients with a normal appendix included in the nonperforated AA group.

NR=not reported.

Wei and co-workers (2004) compared the outcomes between needlescopic LA and OA. The laparoscopic procedure was performed with one 10-mm umbilical port, and with two 2-mm working ports. A 2-mm laparoscope was used and inserted through the supra-pubic port. The length of hospital stay was significantly shorter in the needlescopic LA group compared with that in the OA group (2 days vs 5 days; $P< 0.01$). Moreover, the children in the needlescopic LA group required significantly less rescue analgesics compared with children in the OA group (0.5 vs 2 doses; $P< 0.01$).

2.2.5.4.4. Laparoscopy in children with complicated appendicitis

There still is controversy over the indications for LA in children with complicated (gangrenous or perforated) appendicitis. Some authors have reported a considerably high conversion rate after laparoscopic operation for an advanced appendicitis (Ure et al 1992).

Several non-randomized studies have been published comparing LA with OA in children with complicated appendicitis (Valla et al 1996, Horwitz 1997, Canty 2000, Paya 2000, Krisher et al 2001) (Table 6). Horwitz and co-workers (1997) found that 32 % of the children who had undergone LA developed postoperative intra-abdominal abscesses compared with 9 % of those who had undergone OA ($P=0.01$). The authors suggested that the laparoscopic technique should be avoided in children who have gangrenous or perforated appendicitis because of the increased risk for major postoperative complications. Krisher and co-workers (2001) found that the difference in the postoperative intra-abdominal abscess was statistically significant for perforated appendicitis (risk ratio, 5.6; 95 % confidence interval 2 to 16 for LA compared with OA). Most trocar site infections were encountered at the umbilical port.

Table 6. Summary of non-randomized studies comparing laparoscopic appendicectomy (LA) with open appendicectomy (OA) in children with complicated appendicitis (AA).

Study	Total number of patients	Surgical technique LA/OA	Mean operating time (min) LA/OA	Number (%) of conversions to OA	Length of stay (days) LA/OA	Gangrenous: perforated AA LA/OA	Complications (%) LA/OA
Valla et al (1996)	284	160/124	NR	11 (7 %)	7/11	0:160/0:124	15 % / 28 %
Horwitz et al (1997)	56	34/22	87/84	7 (20 %)	7/7	NR	44 % / 18 %
Canty et al (2000)	389	302/87	68/58	10 (3 %)	7/7	0;302/0:87	9 % / 8 %
Paya et al (2000)	75	10/65	79/53	0	6/8	0:10/0:65	10 % / 14 %
Krisher et al (2001)	234	50/184	NR	10 (20 %)	NR	21:29/43:141	14 % / 5 %

NR=not reported

On the contrary, several authors have reported LA being as safe and effective as OA also in children with complicated appendicitis. Paya and co-workers (2000) reported no postoperative abscesses in children who had undergone LA while 3 % of children in the OA group developed postoperative intra-abdominal abscesses. Canty and co-workers (2000) found that the length of stay, postoperative abscess rates and incidence of bowel obstruction did not differ between the LA group and the OA group. On the other hand, Valla and co-workers (1996) found that the complication rate was lower in the LA group compared with that in the OA group (15 % vs 28 %). Moreover, the hospital stay was also shorter in the LA group: 7 days versus 11 days.

2.2.5.4.5. Costs of laparoscopic appendicectomy

Laparoscopic surgery is generally more expensive to perform compared with conventional surgery (Hansen et al 1996, McCahill et al 1996, Williams et al 1996, Golub et al 1998). Cost surplus is related to the utilization of expensive instruments and materials, and the longer operating time required for laparoscopic procedures (Gilchrist et al 1992, Hansen et al 1996, McCahill et al 1996, Williams et al 1996, Golub et al 1998, Heikkinen et al 1998). The increased operative costs can be offset by a shorter hospital stay associated with laparoscopy (Botha et al 1995, Martin et al 1995). It is, however, difficult to claim cost savings in children who tend to have a short hospital stay and a fast recovery after conventional appendicectomy (Little et al 2002, Grewal et al 2004).

Only a few studies have evaluated costs between LA and OA in children. Luks and co-workers (1999) evaluated retrospectively the cost-effectiveness of LA compared with OA. The authors listed in detail all direct costs related to the hospital treatment to allow an economic analysis between the two techniques. LAs were performed with a standard set of reusable instruments and a limited number of disposable equipment. Excess operating costs per procedure were 442 United States dollars (358 euros) in LA but the increased operative expenses were offset by a shorter hospital

stay, resulting in an overall savings per laparoscopic procedure of 2370 United States dollars (1920 euros).

Little and co-workers (2002) compared prospectively LA and OA with respect to departmental costs. Laparoscopic procedures were performed with reusable instruments to save expense. The mesoappendix was divided between haemoclips, and the appendiceal stump was secured with endoloops. The authors found that LA was associated with 16 % increased surgical cost, 14 % increased anaesthesia cost, 16 % increased hospital cost, and 12 % increased total procedure cost. However, the increased total cost was related to the fact that the children in the LA group spent 3 days in the hospital, whereas those in the OA group spent 2 days.

Vernon and co-workers (2004) compared retrospectively the costs of LA with those of OA in children with non-complicated appendicitis. The authors listed in detail the costs of the entire hospital stay, including the preoperative costs. The authors found that the cost of LA for acute appendicitis was higher than for OA despite similar operating times and length of hospitalization. There were, however, no differences between the LA group and the OA group in costs for the hospital room, laboratory tests, and medications. On the other hand, operating room costs were almost double for the LA group compared with the OA group.

2.2.6. Complications/outcome

The incidence of postoperative complications is determined by the stage of AA. Therefore, complications are usually found in children with gangrenous or perforated appendicitis (Cloud 1993). Complications rates have previously varied from 25 to 45 % in large surveys of those children (Stone et al 1971, Samelson and Reyes 1987) but effective antibiotic therapy has brought a decrease in these rates (Cloud 1993).

Postoperative *infection* is the most common complication of AA. Fishman and co-workers (2000) reported a major infectious complication (intra-abdominal abscess, caecal fistula, phlegmon) rate of 7 %, and wound infection rate of 3 % in children with perforated appendicitis. In another study (Pearl et al 1995) major postoperative infections occurred in 1 % of children with uncomplicated appendicitis and in 7 % of those with perforated appendicitis, and wound infections in 2 % of children with simple appendicitis and in 7 % of those with perforated appendicitis. Neilson and co-workers (1990) used protocol of preoperative triple antibiotics (ampicillin, gentamycin, and clindamycin), and the authors reported an overall infectious complication rate of 3 % in children with complicated appendicitis. The authors found no postoperative infections in those with simple appendicitis or normal appendix. A wound infection requires the incision to be opened and drained (Pearl et al 1995, Fishman et al 2000), while an intra-abdominal abscess usually requires a percutaneous or transrectal drainage (Fishman et al 2000). A small abscess and a phlegmon may resolve on antibiotics (Curran and Muenchow 1993).

Paralytic ileus is associated with appendiceal perforation and peritonitis. Prolonged ileus longer than 7 days has been reported to occur in 3 to 7 % of children with complicated appendicitis (Curran and Muenchow 1993, Fishman et al 2000). *Bowel obstruction* is related to intra-abdominal abscess, phlegmon, or adhesions. Obstruction usually resolves with nasogastric suction and antibiotics if there is no abscess. Late bowel obstruction is related to intra-abdominal adhesions and necessitates often laparotomy (Cloud 1993). The incidence of small bowel obstruction has varied from 1 to 5 % of children with gangrenous or perforated appendicitis (Curran and Muenchow 1993, Fishman et al 2000). Other rare causes of complications of appendicitis include *appendiceal stump blowout* (Cloud 1993), *sterility* (Cloud 1993), *diarrhoea* (Fishman et al 2000), *pleural effusion* (Fishman et al 2000), *liver abscess* (Fishman et al 2000), *enterocutaneous fistula* (Pearl et al 1995), and *pylephlebitis* (Vanamo and Kiekara 2001).

2.2.7. Unnecessary appendicectomy

Unnecessary appendicectomy implies the removal of a histologically normal appendix in patients who have no other surgical disorder (Blind and Dahlgren 1986). Unnecessary appendicectomy is not in itself without serious consequence. Postoperative deaths after unnecessary appendicectomy in adults have been reported (Pieper et al 1982). The mortality rate has been calculated to be 0.1 % after the removal of a normal appendix (Velanovich and Satava 1992). Furthermore, postoperative bowel strangulations have been reported after unnecessary appendicectomy (Lau et al 1984). The incidence of postoperative complications has been reported to occur in 1-6 % of patients who have undergone unnecessary appendicectomy (Lau et al 1984, Blind and Dahlgren 1986, Bijnen et al 2003). In one study (Bijnen et al 2003) a re-operation was needed in 2 % of patients while the mean additional hospital costs of unnecessary appendicectomy were 2700 euros. On the other hand, unnecessary appendicectomy results in the missed chance to utilize the appendix for urethral reconstruction (Sheldon and Gilbert 1992).

3. AIMS OF THE STUDY

The aims of the present study were:

1. To construct and to validate a diagnostic score for acute appendicitis in children (publication IV).

2. To evaluate the effects of opioid analgesics on pain relief, physical examination findings, diagnostic accuracy, and clinical outcomes in children with undifferentiated abdominal pain (publication V).

3. To compare recovery and the costs of laparoscopic appendectomy with open appendectomy in children with suspected acute appendicitis (publications I-III).

4. PATIENTS

4.1. Patients

A total of 328 children, 167 girls and 161 boys, were studied between November 1997 and December 2003. The diagnostic criteria of acute undifferentiated abdominal pain and acute appendicitis were those set by the World Organization of Gastroenterology Research Committee (de Dombal 1979, de Dombal 1988).

Inclusion criteria for the diagnostic score for AA-study (**Study Group I**), the analgesics in acute abdominal pain-study (**Study Group II**), and the laparoscopic versus open appendicectomy-study (**Study Group III**) were:

1. Age between 4 and 15 years (**I-III**)
2. Suspected acute appendicitis (**III**)
3. Acute abdominal pain less than 7 days` duration (**I-II**)
4. American Society of Anesthesiologists (ASA) physical status I or II (**II, III**)
5. No known contraindications for laparoscopic appendicectomy (**III**)
6. Written informed consent given by the parents as well as children old enough to understand the planned (**I-III**)
7. Pain score of 5 cm or higher on a 10-cm long visual analogue scale (VAS) (**II**)

Exclusion criteria were:

1. Previous appendicectomy or other abdominal operations (**III**)
2. Abdominal trauma (**I-III**)
3. Obvious hernia (**I-III**)
4. Analgesia use prior emergency department arrival (**II**)

5. Known contraindication to oxycodone (**II, III**)
6. Hypotension (systolic blood pressure < 90 mm Hg) (**II**)
7. Allergy to ketoprofen or other non-steroidal anti-inflammatory drugs (**III**)
8. Asthma (**II, III**)
9. Kidney or liver dysfunction (**III**)
10. Haemorrhagic diathesis (**III**)
11. Neurological disease or developmental disability (**III**)
12. Patients with missing data on one or more of the variables (**I**)

4.2. Study Groups

Three studies were performed and the results were presented in five publications. Two hundred forty children were included in the **Study Group I** (Figure 1), 63 children were eligible to participate in the **Study Group II** (Figure 1), and 102 children were randomised to undergo either laparoscopic (n=48) or open appendicectomy (n=54) in the **Study Group III** (Figure 2). Fourteen children, 10 boys and 4 girls, participated in both the **Study Group I** and the **Study Group III**. All children in the **Study Group II** were included in the validation sample of the **Study Group I**. The patient characteristics are shown in Tables 7 and Table 8. In the **Study Group III** there were no differences between the LA group and OA group in terms of gender, ASA physical status, weight, height, and age.

Figure 1. Study Groups I and II.

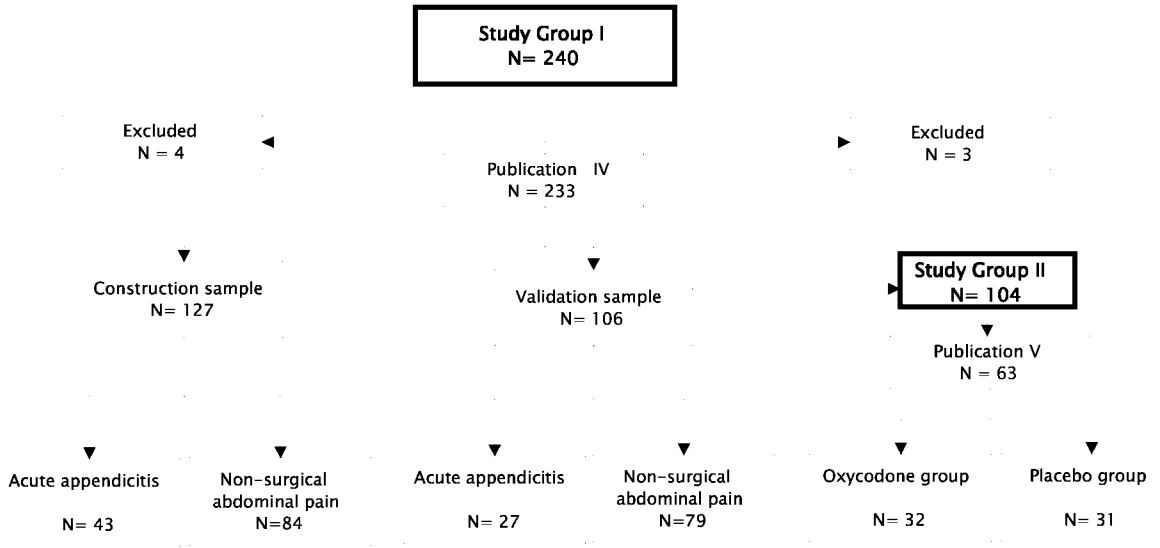


Figure 2. Study Group III. Laparoscopic (LA) vs. open appendicectomy (OA).

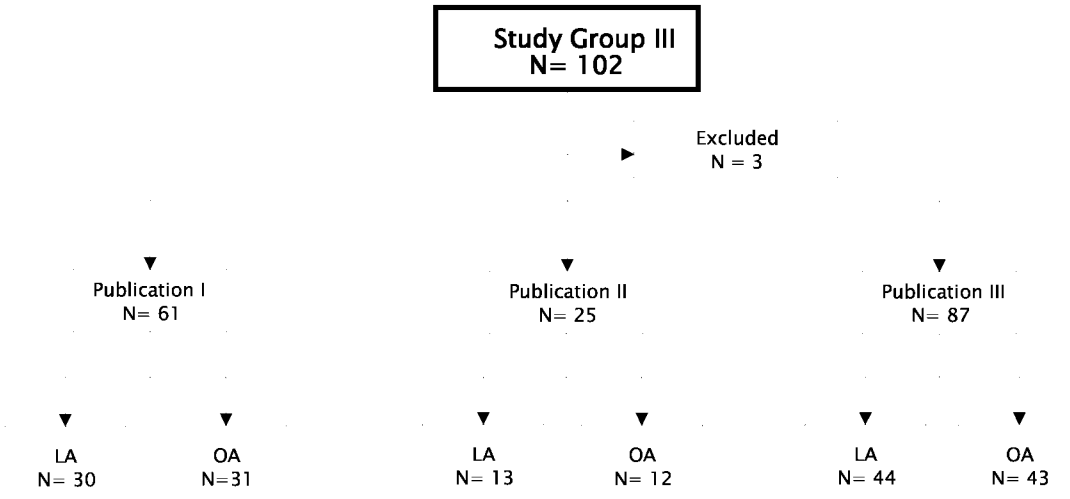


Table 7. Patient characteristics in the Study Groups I and II (N=240). Data represent number of cases of mean (±SD) with range.

	Acute appendicitis N=70	Non-surgical acute abdominal pain N=163	Other surgical disease N=7
Gender (male/female)	45/25	63/100	3/4
Age (years)	11 (±3)	9 (±3)	9 (±4)
Range	4-15	4-15	5-15
Height (cm)	149 (±15)	139 (±19)	137 (±11)
Range	100-180	90-170	120-145
Weight (kg)	43 (±15)	36 (±15)	29 (±10)
Range	11-75	10-67	15-35
Appendix			
-Normal	-	18*	-
-Simple appendicitis	59	-	-
-Gangrenous/perforated	11	-	-

*Children who were operated unnecessarily and had normal appendices removed, and who had no other surgical pathology were considered to have non-surgical acute abdominal pain.

Table 8. Patient characteristics in the Study Group III (N=99). Data represent number of cases of mean (±SD) with range.

	Laparoscopic appendicectomy group N=48	Open appendicectomy group* N=51
Gender (male/female)	28/20	31/20
Age (years)	11 (±3)	12 (±3)
Range	4-15	4-15
Height (cm)	147 (±18)	150 (±16)
Range	125-180	120-180
Weight (kg)	42 (±15)	45 (±14)
Range	15-55	21-62
Body temperature (°C)	36.9 (±5)	37.3 (±5)
Range	36.0-39.2	36.0-39.0
C-reactive protein ($mg \cdot l^{-1}$)	47 (±44)	47 (±52)
Range	5-145	5-188
Appendix		
-Normal	10	12
-Simple appendicitis	25	27
-Gangrenous	2	7
-Perforated	9	4
-Mass	2	1
Other pathologies		
1.Perforation of Meckel`s diverticulum	1	-
2.Omental necrosis	1	-
3.Ovarian cyst rupture	1	-

* Excluded: 3 children

4.2.1. Study Group I

The study was conducted in two phases. During the first phase, a total of 258 children with acute abdominal pain were admitted to the ED between December 1999 and November 2000. Abdominal pain resolved spontaneously in 127 children (49 %), and they were discharged. One hundred thirty-one children (51 %) were taken to the paediatric surgical ward as inpatients. During the second phase between December 2001 and December 2003, a total of 257 children were admitted to the paediatric surgery ward, and 109 of them (42 %) were included in the study. Children with surgical conditions other than AA were excluded from the construction and validation samples.

Publication IV:

The history variables and clinical findings of each child presenting with acute abdominal pain to the paediatric surgery ward were recorded. The diagnostic score for AA score was constructed and further validated in a separate cohort.

1. In the first phase, 35 items of clinical data in 127 consecutive patients were prospectively recorded (construction sample)
2. In the second phase, the performance of the score was prospectively evaluated on 106 non-consecutive children (validation sample)

4.2.2. Study Group II

A total of 250 children were taken to the paediatric surgery ward between December 2001 and November 2003. A total of 104 children with acute abdominal pain were assessed for eligibility, but 41 were excluded; 10 refused to participate and 31 did not meet inclusion criteria (pain score lower than 5 cm on a 10 cm VAS).

Publication V:

The outcome of 63 children who were randomly allocated to receive buccally either

1. 0.1 $mg \cdot kg^{-1}$ of oxycodone hydrochloride (Oxanest 10 $mg \cdot ml^{-1}$ solution for injection, Leiras Oy, Turku, Finland) (n=32)

2. a same volume of 0.9 % sodium chloride (n=31)

were presented in the publication 5.

4.2.3. Study Group III

A total of 105 children underwent emergency appendicectomy at Kuopio University Hospital between November 1997 and April 2000. Eighty nine (85 %) children were enrolled in the present study. Thirteen children were studied in the North Karelian Central Hospital, and they were included in the publication 2. Three children who underwent OA were excluded. One child with complicated appendicitis was withdrawn because a possible allergic reaction developed toward ketoprofen the first day after the operation. One child was lost to follow-up. One child with Still`s syndrome developed postoperative respiratory insufficiency, and he was transferred to the Intensive Care Unit. He was discharged 4 weeks after the operation.

Publication I:

The outcome of 61 children with simple appendicitis or normal appendix were presented in the publication I.

1. Laparoscopic appendicectomy (n=30)

2. Open appendicectomy (n=31)

Publication II:

The outcome of 25 children with operative findings of periappendicular abscess and patients with a histologically confirmed gangrenous or ruptured appendix were presented in the publication II.

1. Laparoscopic appendicectomy (n=13)
2. Open appendicectomy (n=12)

Publication III:

The outcome and costs of appendicectomy in 87 children were presented in the publication III. Cost surplus of the laparoscopic appendicectomy and recovery after surgery were compared with those of open appendicectomy.

1. Laparoscopic group (n=44)
2. Open group (n=43)

5. METHODS

5.1. Aetiology, symptoms and signs of acute abdominal pain

5.1.1. Study design

A total of 35 items of clinical data were recorded in 131 consecutive children with acute abdominal pain and the appendicitis score was constructed. The cut-off points were determined for the presence and absence of appendicitis as final diagnosis. The performance of the score was prospectively evaluated on 106 children, and the results of the scoring system was compared with the operative and histological findings and clinical outcome.

5.1.2. Collection of clinical data

The total population of the Northern Savo Hospital District was 250000 inhabitants (31.12.2000), of whom 37340 (15 %) were 4-15 years old (National Research and Development Centre for Welfare and Health, 2004). Consecutive children admitted to the paediatric surgical ward were included in the first phase of the study. Each patient could enter the study only once with the same diagnosis.

The attending surgeon examined the patients, and established the initial diagnoses of the children. Furthermore, he recorded altogether 35 history variables, clinical examination findings and laboratory tests using a predefined structured data sheet based on the modified abdominal pain chart of the World Society of Gastroenterology (de Dombal 1979) (Appendix 1).

Most of the variables were self-explanatory but some needed to be defined:

- *Relocation of pain* was determined as pain starting in the epigastrium, centrally, or in the whole abdomen, shifting eventually to the RLQ (de Dombal 1991).

• *Rigidity* was defined as involuntary reflex spasm of the abdominal muscles in the RLQ. It cannot be overcome by tact and reassurance. The patient cannot voluntarily relax the abdominal muscles (de Dombal 1991).

• *Guarding* was defined as voluntary contraction of the abdominal muscles in the RLQ. Guarding can be partially or completely overcome by tact and persuasion. The child holds the abdominal muscles contracted because he/she fears that further examination is likely to be painful (de Dombal 1991).

• *Rebound tenderness* was elicited in the RLQ when a hand depressing the abdomen was suddenly withdrawn (de Dombal 1991).

• *Percussion tenderness* was defined as pain in the RLQ when percussion was performed gently by a finger (Mahadevan and Graff 2000).

• *Rovsing`s sign* was defined as pain in the RLQ when palpatory pressure was exerted in the left lower quadrant (Smith 1965).

• *Psoas sign* was elicited when the right thigh was lifted against clinician`s hand resulting in right lower quadrant pain (Smith 1965).

• *Bowel sounds* were defined as normal if they were not high pitched or tinkling, and if they were continuously heard for three minutes (de Dombal 1991).

The final diagnoses of acute appendicitis, ruptured mesenterial cyst and omental necrosis were based on histological examination of the specimen (de Dombal 1979). The children who were operated unnecessarily and had normal appendices removed in fact had NSAP as their true diagnosis. In addition, the criteria for having NSAP was based either on normal abdominal ultrasound or computed tomography findings or clinical changes in those whose symptoms resolved without operation. Bacteriuria revealed urinary tract infection. Constipation was diagnosed by rectal examination and plain abdominal film. The diagnosis of short lived ovulatory pain was based on

pertinent gynaecologic history and palpable tenderness on the affected side. An ovarian cyst was diagnosed by ultrasound. Ureterolithiasis was diagnosed by computed tomography. An intra-abdominal tumour was detected by abdominal ultrasound and computed tomography. Acute pancreatitis was diagnosed by abdominal computed tomography. Children with NA were followed by telephone call at 4 weeks, and by then the definitive diagnosis was established in each child.

5.1.3. Appendicitis Score

5.1.3.1. Construction

The frequency distribution of the 35 variables were determined in the group of children with and those without verified AA. Children with other surgical entities were excluded. All children with non-surgical acute abdominal pain were included in the NA group. To facilitate data analysis, and for ease of comparison between the two groups, the multinomial and continuous variables were changed to dichotomous variables. A p-value ≤ 0.05 was considered statistically significant. Those variables with statistically significant weights were regarded as the best predictors of acute appendicitis, and they were included in the backward stepwise binary logistic regression analysis (the Statistical Package for the Social Sciences for Windows 10.0, SPSS Inc., USA). The package was utilized to predict the presence or absence of appendicitis. A mathematic model assigning regression coefficients to each variable was constructed. The coefficients of the model were rounded to the nearest integer resulting in an Appendicitis Score. By choosing the two cut-off points in the score, the children could be divided into the three groups: low probability – amenable to discharge; intermediate probability of appendicitis – necessitating further observation; and high probability of appendicitis – justifying emergency laparotomy.

5.1.3.2. Validation

The test sample was collected in a prospective, separate study. The attending surgeon examined the children and recorded the data with variables of the score onto forms at the time of admission of the child (initial score) and at 60 min after the first examination (end score). The attending surgeon was not asked to express any probabilities but only to record the clinical data and state what he considered the most likely diagnosis (AA versus NA). The decision to operate was based on overall clinical suspicion and not the clinical score. The definitive diagnosis of children with NA was available at the time of the follow-up call at 4 weeks.

The Appendicitis Score was further validated in the test sample. The validation was performed to assess whether the Appendicitis Score would have been able to improve differentiation of AA from NA compared to that of clinical judgement alone. The children who had a surgical condition other than appendicitis were excluded. The results of the scoring system were compared with the final diagnoses of the children of the validation sample. The criteria for rates of unnecessary appendicectomy, potential perforation, missed perforation, and missed appendicitis were determined:

- *Unnecessary appendicectomy rate* was determined as proportion of patients who did not have AA as their final diagnosis but who were assigned to the AA group and operated on for suspected appendicitis..
- *Potential perforation rate* was defined as proportion of patients with AA not assigned to the AA group.
- *Missed perforation rate* was defined as proportion of patients with perforated AA not assigned to the AA group.
- *Missed appendicitis rate* was determined as proportion of patients with AA assigned to discharge.

5.2. Opioid analgesics in acute abdominal pain

5.2.1. Study design

A double blind, randomised, parallel group and prospective study design was used to evaluate the effects of buccal oxycodone on pain relief, physical examination findings, diagnostic accuracy, and final clinical outcomes in children with acute abdominal pain. The children were randomly allocated to either the oxycodone group or the saline group. A sealed envelope method was used for blinding. A research nurse not involved in the treatment of the child prepared the drug solution with identical appearance. A blinded study protocol was followed: children, parents, research nurses and physicians remained unaware of the exact study drug.

The blinding was tested in 20 cases, and the surgeon was able to correctly identify the type of study drug in 6 of 12 children (50 %) in the oxycodone group and in 6 of 8 children (75 %) in the placebo group. The surgeon gave a wrong guess for 6 children in the oxycodone group and 2 children in the placebo group.

5.2.2. Pain management

Children were eligible to participate in the trial, if they presented to the ED with acute abdominal pain and had pain score of 5 cm or higher on a 10 cm VAS. Children were randomised into two study groups by a computer generated allocation sequence. A research nurse prepared the study solution with an identical appearance and taste to the saline solution. The children in the oxycodone group received 0.1 $mg \cdot kg^{-1}$ of oxycodone hydrochloride buccally and in the placebo group a same volume of 0.9 % sodium chloride. If the pain score was persistently $\geq$ 5 cm on a 10-cm VAS the

study medication was repeated one or two times. No other analgesics were allowed during the 3.5 hours (h) trial period.

5.2.3. Evaluation of pain

The children were instructed to use VAS. The children expressed induced tenderness while the research nurse exerted a light pressure in the abdomen in an identical fashion. The research nurse recorded pain scores at baseline and at 0.5, 1, 1.5, 2, 2.5, 3 and 3.5 h after the first dose of study drug (Appendix 2).

A total of 3 surgeons participated in the trial, and they investigated the patients before administration of study medication. The surgeon indicated a provisional diagnosis, a differential diagnosis, a provisional disposition, and whether abdominal guarding was present or absent (Appendix 2). The surgeon focused to differentiate surgical disease from self-limited non-surgical abdominal pain (NA).The same surgeon re-examined the child at one hour after the first dose of study drug. If the diagnosis and final disposition were not definitively established at one hour, the patient was re-evaluated at 3.5, 6, and 9 h. Children with NA were followed until abdominal pain resolved spontaneously. Surgical disease was confirmed either by histological examination or operative findings.

The main outcome measurements were the maximal pain intensity difference (PID) and the summed pain intensity differences (SPID) (McQuay and Moore 1998), the presence of abdominal guarding before and after medication, and the diagnostic accuracy between the oxycodone and placebo groups.

5.3. Laparoscopic versus open appendicectomy

5.3.1. Study design

To compare laparoscopic appendicectomy with open appendicectomy a single-blinded, randomised, parallel group and prospective study design was used. The children were assigned to undergo either a laparoscopic (LA group) or an open procedure (OA group). Randomisation was performed with consecutively numbered sealed envelopes containing a random number.

Children, parents, research nurses and surgeons, except the principal investigator, were blinded with respect to whether the patient was operated on via a laparoscopic or open technique, and remained unaware of the exact procedure until a control visit scheduled 7 days after the operation. After surgery each child had a similar wound dressing (see the publication I).

At discharge 14 of 36 children (39 %), 10 of 30 parents (33 %), and 11 of 34 nurses (32 %) were able to guess correctly the type of operation performed, with a similar distribution between the LA group and the OA group. Five children (14 %), seven parents (24 %) and nine (27 %) nurses gave a wrong guess, and 17 children (47 %), 13 parents (43 %) and 14 nurses (41 %) were not able to give any answer.

At one week control visit 17 of 34 children (50 %), 17 of 34 parents (50%) and 15 of 34 nurses (44 %) were able to guess correctly the type of operation performed, with a similar distribution between the two study groups. Seven children (21 %), seven parents (21 %) and twelve nurses (35 %) gave a wrong guess, and ten children (29 %), ten parents (29 %) and seven nurses (21 %) were not able to give any answer.

No other analgesic treatment was permitted during the study. The research nurse recorded postoperative pain score, vital signs and all adverse effects.

Laparoscopic procedures were performed by one paediatric surgeon in the Kuopio University Hospital and 3 general surgeons in the North Karelian Central Hospital. Children in the OA group were operated on by 13 surgeons in the Kuopio University Hospital, and 6 surgeons in the North Karelian Central Hospital.

5.3.2. Pre- and intraoperative care

Children were allowed neither solid food nor clear liquids after the decision to operate. An intravenous infusion was started at the ED. Children were premedicated with diazepam orally.

All appendicectomies were performed in general anaesthesia. An infusion consisting of saline 0.9 % was administered at $10ml \cdot kg^{-1} \cdot h^{-1}$. Fentanyl $2\mu g \cdot kg^{-1}$ was given intravenously and anaesthesia induced with thiopenthal; neuromuscular block was achieved with cis-atracurium. Anaesthesia was maintained with sevoflurane in oxygen 35 % in air with intermittent positive pressure ventilation. All patients had a nasogastric tube during the procedure. Metronidazole hydrochloride 7 $mg \cdot kg^{-1}$ was given intravenously at induction as antibiotic prophylaxis.

Intraoperative monitoring consisted of continuous electrocardiogram, respiratory frequency, haemoglobin oxygen saturation as measured by pulse oximeter and end-tidal carbon dioxide concentration using a nasal adapter. Operating time, anaesthesia time, nurses´ time, and all adverse events were recorded for each child (Appendix 3).

On completion of the operation each patient was administered ketoprofen 1 $mg \cdot kg^{-1}$ as an intravenous bolus followed by 4 $mg \cdot kg^{-1}$ over 24 h for background anaesthesia. The use of postoperative antibiotics depended on the severity of the disease. After surgery each child with complicated appendicitis was given cefuroxime sodium, 80 $mg \cdot kg^{-1} \cdot 24\ h^{-1}$ and metronidazole hydrochloride, 20 $mg \cdot kg^{-1} \cdot 24\ h^{-1}$ intravenously until they tolerated a normal oral diet. Oral antibiotics were continued for 10 days after the operation. Nasogastric tube was left in place in children with generalized peritonitis until bowel function returned.

5.3.3. Postoperative care

After the operation, children were transferred to the post-anaesthesia care unit and then to the paediatric ward for continuous monitoring of vital signs, pain, and complications (Appendix 4).

Postoperative pain was assessed using a 10-cm long and 2-cm in height rectangle VAS (Tigerstedt and Tammisto 1988). In the visual analogue, left end represents "no pain", and the right end "worst imaginable pain". After 24 h, pain management was continued with ketoprofen tablets (5 $mg \cdot kg^{-1}$ over 24 h).

If the child was in pain (pain score of 3 cm or more at rest, or 5 cm or more on coughing) oxycodone hydrochloride 0.05 $mg \cdot kg^{-1}$ intravenously or 0.1 $mg \cdot kg^{-1}$ transmucosally was given for rescue analgesia. Oxycodone was repeated at 15-min intervals until the child was comfortable. The number of doses was recorded. No other analgesics was allowed during the trial. All adverse events were recorded for each child.

5.3.4. Operative techniques

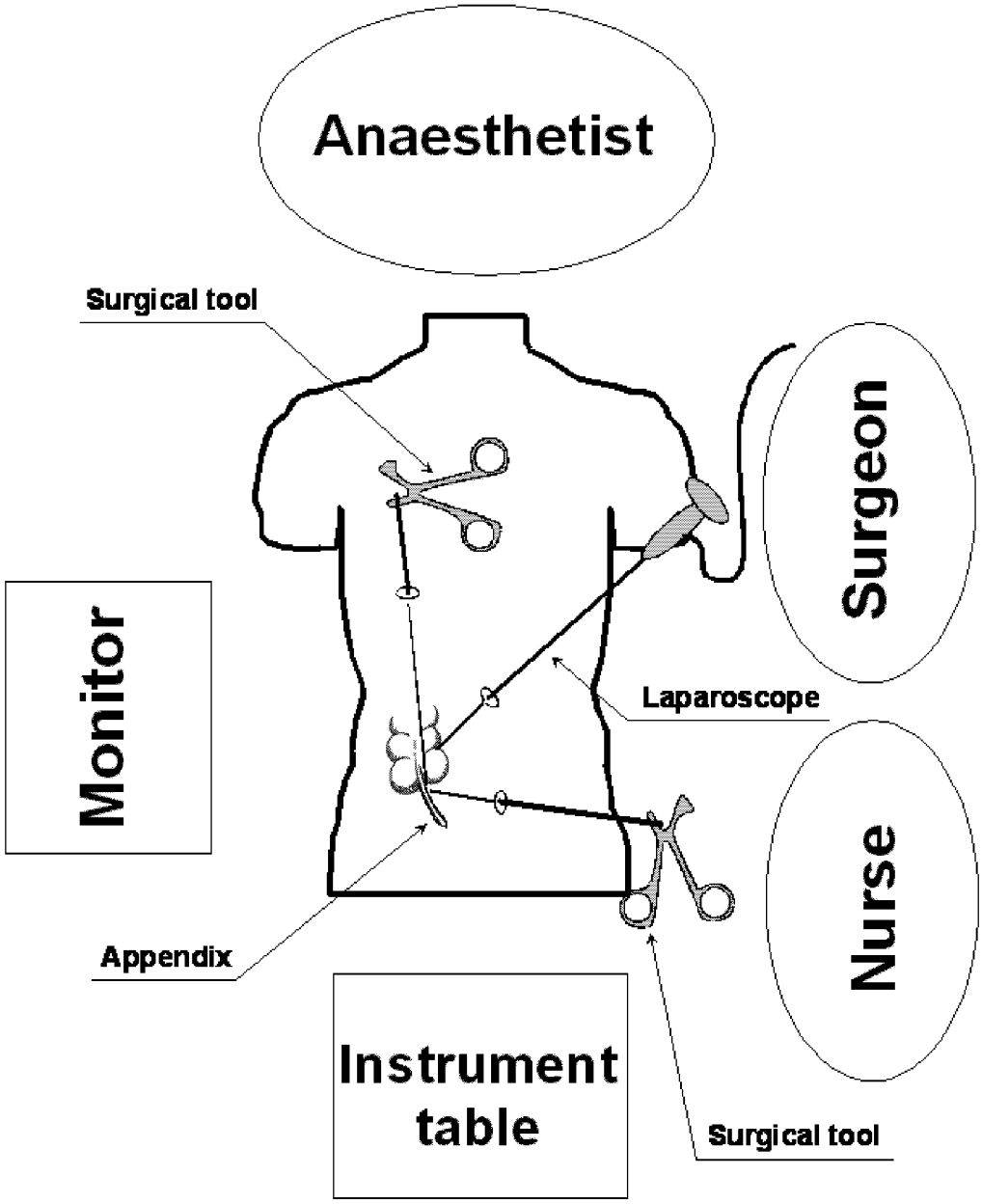
5.3.4.1. Laparoscopic appendicectomy

Laparoscopic appendicectomies were performed in a standardized manner. The patient was placed in the supine position with both arms positioned along the sides. The surgeon stood on the patient`s left side, with the assistant who operates the camera on the patient`s right side. The monitor was placed at the foot of the operating table allowing both the surgeon and the assistant to view the procedure at all times (Figure 3).

The abdomen was prepared and draped in a sterile fashion in order to expose the entire abdomen. The laparoscopic procedure was performed with reusable instruments using two 5-mm working ports and one 5- or 10-mm sheath for camera. The first port was inserted supraumbilically using an open technique, and a pneumoperitoneum was established with the pressure maintained below 12 mm Hg. A 5-mm 30 degree angled telescope was inserted through the umbilical port, and a complete diagnostic laparoscopy was performed. The working ports were placed under direct vision in the right upper quadrant, and the left lower quadrant.

The appendix was exposed and its base on the caecum was identified by using an atraumatic retracting forceps. In patients with retrocaecal or severely inflamed appendix, the caecum was mobilized completely by dissecting the lateral reflection of the peritoneum around the ascending colon and the terminal ileum with laparoscopic scissors. The tip of the appendix was grasped and retracted anteriorly toward the anterior abdominal wall. If the appendix was attached to the floor of the pelvis, laparoscopic appendicectomy was performed in a retrograde fashion by beginning the dissection from the base of the appendix. The mesoappendix was divided with a cauterising hook (Figure 4).

Figure 3. Laparoscopic appendicectomy. Position of the patient, crew, equipment and trocars.



The base of the appendix was cleared circumferentially of adipose and connective tissue and its stump was secured with two 2-0 polydioxanone sutures (EndoLoop; Ethicon; Sommerville, USA) (Figure 5). The stump was neither inverted or cauterised. The proximal opening of the appendix was closed with the forceps, and the appendix was removed through the umbilical port. A specimen retrieval bag (Endocatch; US Surgical Corp, Norwalk, USA) was utilized for removal of perforated appendix.

In children with peritonitis, the operative field was irrigated and aspirated dry. No drains were left in the abdominal cavity. Haemostasis was confirmed, and the caecum was inspected to ensure definitive closure of the appendiceal stump. The trocars were removed under direct vision, the absence of bleeding from the trocar sites were confirmed, and the abdominal cavity was decompressed. The fascial defect in the umbilicus was closed with 2-0 absorbable sutures. The skin incisions were reapproximated with one or two 4-0 absorbable sutures.

Figure 4. Dissection of the mesoappendix.

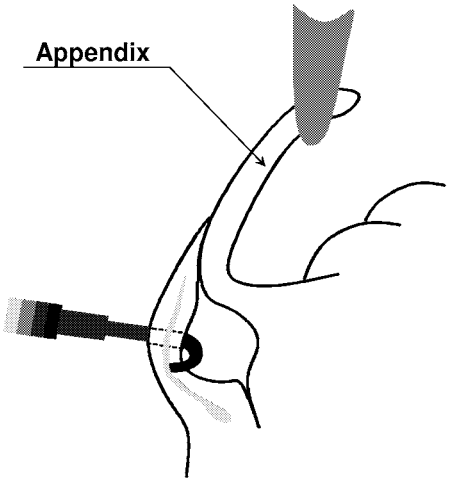
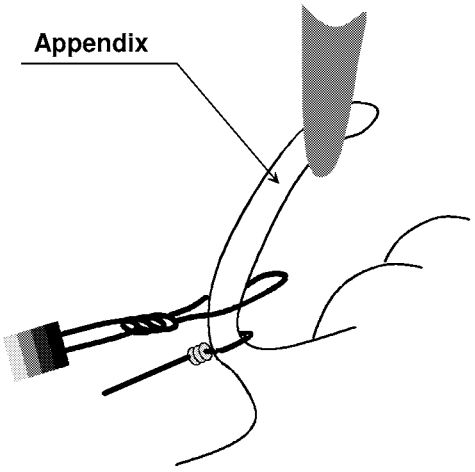


Figure 5. Ligation of the base of the appendix



5.3.4.2. Open appendicectomy

Open appendicectomy was performed through a McBurney incision (McBurney 1889). The patient was placed in the supine position, and the abdomen was prepared and draped in a sterile fashion as to expose the RLQ.

The skin incision was made in an oblique direction, passing a line drawn between the umbilicus and the anterior superior iliac spine at a point about 2 to 3 cm from the iliac spine. This McBurney`s point is one third of the way from the iliac anterior spine to the umbilicus. The external oblique aponeurosis was incised in the direction of the fibres of the muscle and its tendon. The fibres of the internal oblique and transversalis muscles were separated at a right angle to the incision on the external oblique aponeurosis. The parietal peritoneum was lifted up, and it was opened in a transverse fashion. If larger vision was required, the lateral edge of the rectus sheath was incised and the rectus abdominis muscle was retracted medially.

The appendix was identified by following the caecal taeniae distally. The peritoneal fluid was collected for bacteriologic analysis. The appendix was delivered into the surgical incision. In patients with retrocaecal appendix, the caecum was mobilized by cutting the lateral reflection of the peritoneum around the terminal ileum and up the ascending colon.

The mesoappendix was divided between clamps and ligated with 2-0 absorbable sutures. The base of the appendix was crushed and secured with 2-0 absorbable sutures. The appendix was divided by running a scalpel along the underside of the forceps. The stump was not routinely invaginated into the caecum. If invagination was done, a 2-0 absorbable purse-string suture was placed in the caecum, and the appendiceal stump was invaginated as the suture was tied. In children with

peritonitis, the abdominal cavity was thoroughly irrigated and aspirated dry. The operative field was checked for haemostasis.

The peritoneum was closed with a continuous 3-0 absorbable suture. The transversalis and internal oblique muscles were reapproximated with 3-0 absorbable ligatures. The external oblique aponeurosis was closed with interrupted 2-0 absorbable sutures, and the skin was reapproximated with interrupted 4-0 non-absorbable sutures.

5.3.5. Discharge

Hospital stay was defined as the time from patients` arrival in the ED to their discharge. The children were discharged when they could tolerate a normal oral diet, had no nausea or vomiting, were able to walk unaided, had been apyrexial for 12 h (temperature lower than 37.5°C), had no difficulty in passing urine, and had no pain or mild pain (VAS score < 3 cm). At discharge, parents were instructed in the post-operative care of their children, and given telephone numbers to take contact in case of problems at home. Verbal information was reinforced with written instruction.

5.3.6. Follow-up

Follow-up of the children at home was recorded by means of a diary for the first 7 days. The diary was returned, the wound dressings were removed and the blinding was opened at the control visit 7 days after the surgery. Children who were competent filled in the diary by themselves and parents checked that the information was appropriate.

The diary consisted of structured questions (Appendix 5). The following details were sought: wound pain, need for analgesics, fever, nausea/vomiting/diarrhoea, and ability to tolerate normal

diet at home. Special attention was paid to the intensity and duration of pain, concurrent symptoms, and medication or other treatment needed. Pain was evaluated using a four-point verbal rating scale (0=no pain; 3=severe pain) (Guignard et al 2000). The time to return to school was recorded as well as the need to consult with a physician or the hospital.

Following indicators of recovery were recorded at the time of the control visit: body temperature, the condition of the operative incision(s), the intensity of wound pain, and the CRP. The research nurse measured the length of the operative wound(s) in each patient. Bacterial culture of the operative incision(s) was taken in children with suspected wound infections. Radiological investigations were performed in patients with suspected intra-abdominal abscesses.

All children were contacted by a follow-up call 4 weeks after discharge (Appendix 5). The presence of nausea/diarrhoea and pain, and the need for analgesics were recorded. The time to return to sport and other normal activities were recorded as well as the need to take contact with a physician or the hospital. The patients and their parents were asked to evaluate the cosmetic appearance of the operative wound.

Operations were regarded as necessary (therapeutic) if pathology was found, the pathology was considered to be the cause for the child`s pain, and surgery was the appropriate management for the patient`s pain. All other operations were classified as unnecessary (non-therapeutic). For the purpose of the study, appendicitis was classified as either simple or complicated based on the operative and histological findings. Gangrenous appendicitis was categorized as complicated appendicitis.

All complications and other adverse events were recorded. Complications were classified as either major or minor. Major complications included intra-abdominal abscesses, enterocutaneous fistulas, paralytic ileus and bowel obstruction. Minor complications included wound infections, suture granulomas, allergic reactions towards antibiotics, and outpatient evaluations of complaints of emesis, fever, pain, and diarrhoea. Intra-abdominal infection was defined as clinical symptoms plus laboratory findings of inflammation plus a positive ultrasound examination. Wound infection was defined as local signs of inflammation plus positive bacterial culture.

5.3.7. Evaluation of costs

The direct costs related to the hospital care were calculated. The costs were evaluated from the perspective of the health care payer. The most important cost items (operation room times, bed-day costs, and costs of reoperation and readmission) were calculated for each patient. The fixed costs were calculated as the mean per patient. Data were collected prospectively (Appendix 3-5). Costs common to both LA and OA were not determined.

Laparoscopic appendicectomies were performed with the same standard set of reusable instruments. For items of laparoscopic hardware and reusable instruments (Karl Storz Endoscopy, Tuttlingen, Germany), an estimate of their life span was obtained as well as an approximation of the number of times used. An annual equivalent cost was estimated and divided by the annual use to get a cost per patient. The annual use of equipment was obtained from a hospital database. The amortization of reusable instruments was estimated at 150 cases. The monitor, camera, and light source were used in 130 laparoscopies, thoracoscopies, and arthroscopies per year. The 5-mm Hopkins rod-lens telescope and insufflator were used in 60 laparoscopies per year. The hardware was expected to be used for 6 years. The annual use of carbon dioxide was evaluated to estimate a cost per patient. Valuation was carried out at year 2000 prices.

The consumption of analgesics and antibiotics was recorded for each child, and the costs were calculated by the hospital pharmacy prices for 2000. The same standardized antibiotics and analgesics were used. The cost of inhalation anaesthetics was calculated from the formula presented by Dion (1992). The cost of hospitalisation was calculated by multiplying the inpatient day price by the total inpatient length of stay.

Fixed basic salary was paid for operation room staff during regular working hours. Employees assigned to on-call duty were paid additional compensation for being placed on an on-call duty roster. During night hours, one nursing team was in reserve to be called for urgent operations if several patients needed to be operated on at the same time.

Only the differences between the two techniques were considered, ie, the additional costs of laparoscopic equipment, complications, and length of stay. The costs for operating room consumables, overhead property, administration, salaries of ancillary staff, anaesthetic equipment, equipment maintenance, sterilization of the instruments, antibiotics, nonopioid analgesics, and anaesthetics (except sevoflurane) were considered to be the same between LA and OA. Prices and wages were counted as euros.

5.4. Sample size and statistical methods

In the **Study Group II**, to detect a two-fold difference in SPID between the two groups at 5 % significance and 80 % power level, a total of 21 children per group was required. In the **Study Group III**, to obtain a 35 per cent reduction in the need for rescue analgesia at 5 % significance and 80 % power level, a minimum of 30 children per group would be needed.

The statistical analysis was done using the SPSS for Windows program package. Statistical methods are described in the original publications I-V. Statistical analyses were performed using chi-square test and Fisher`s exact test for categorical variables. Student`s t test and Mann-Whitney test was used for continuous variables. Association between independent variables was tested by Pearson`s correlation coefficient or logistic/linear regression analysis. A backward stepwise binary logistic regression analysis was used to construct a diagnostic score for children with suspected appendicitis. Results are presented as mean and standard deviation (±SD), range, number of patients (%), and the difference in proportions with 95 % confidence interval (95 % CI) as appropriate. A p-value (P) of < 0.05 was considered statistically significant.

5.5. Ethical aspects

The studies were approved by the Research Ethics Committee of University of Kuopio and Kuopio University Hospital (10.06.1997 and 05.08.1999) and were conducted in accordance with the ethical principles for medical research involving human subjects presented in the Declaration of Helsinki (World Medical Organization 1996). Parents and children old enough gave written informed consent, and children old enough gave their assent.

6. RESULTS AND DISCUSSION

6.1. Aetiology, symptoms and signs of acute abdominal pain

6.1.1. Aetiology of acute abdominal pain

A total of 55 children underwent either laparotomy (n=45) or laparoscopy (n=10). The diagnosis of acute appendicitis was established in 43 children (33 %) while other surgical diseases were found in 4 children (3 %). Unnecessary appendicectomy was performed in 8 children of 55 (15 %). A definite diagnosis was established in 60 children while NSAP remained as the final diagnosis in 71 children (Table 9).

6.1.2. Symptoms and signs differentiating AA from NA

The prevalences of the history, clinical, and history variables were obtained from 84 children with NA and 43 children with AA (Table 10). Four children had other surgical conditions and were excluded from the final analysis: a 7-year old boy had a ruptured mesenterial cyst, an 8-year old girl omental necrosis, and two 13-year old girls had bowel obstruction.

The multinomial and continuous variables were changed to dichotomous variables. Nineteen of the 35 variables analysed were shown to have prognostic significance in differentiating between AA and NA (Table 11). Variables common to both boys and girls were listed. The menstrual period had begun in 8 of 16 (50 %) in the AA group compared with 9 of 39 (19 %) in the NA group (P=0.02). Testicular tenderness experienced one 10-year old boy in the NA group.

Many symptoms, signs, and laboratory tests were typical for both AA and NA. The most valuable symptoms in diagnosing acute appendicitis were pain in the RLQ, relocation of the pain, pain intensified by movement, coughing, respiration or food, and pain relieved by lying still, vomiting or food. Pain in the RLQ was found in 82 % of children with AA and only in 44 % of those with NA (Table 11). Pain was intensified by movement or other aggravating factors in 95 % of patients with AA compared with 60 % of children with NA. Pain was alleviated by lying still, vomiting or food in 95 % of children with AA compared with 61 % of those with NA (Table 11). The most important clinical signs in the diagnosis of AA were rebound tenderness, guarding, rigidity, positive percussion sign, and Rovsing`s sign. Moreover, enhanced CRP concentration suggested acute appendicitis.

Table 9. The distribution of diseases. Data are number of patients (%).

	Study group N=131	Male N=63	Female N=68
Non-specific abdominal pain	71 (54 %)	31 (50 %)	40 (60 %)
Acute appendicitis	43 (33 %)	27 (43 %)	16 (24 %)
Bowel obstruction	2 (1 %)	0	2 (3 %)
Urinary tract infection	2 (1 %)	0	2 (3 %)
Constipation	2 (1 %)	2 (3 %)	0
Ovulatory pain	2 (1 %)	0	2 (3 %)
Mesenterial cyst	1 (1 %)	1 (2 %)	0
Omental necrosis	1 (1 %)	0	1 (1 %)
Ovarian cyst	1 (1 %)	0	1 (1 %)
Nephroblastoma	1 (1 %)	0	1 (1 %)
Acute pancreatitis	1 (1 %)	0	1 (1 %)
Urinary retention	1 (1 %)	1 (2 %)	0
Varicella zooster	1 (1 %)	0	1 (1 %)
Aseptic arthritis of the right hip joint	1 (1 %)	0	1 (1 %)

Table 10. Prevalence of multinomial and continuous variables in the acute appendicitis- group and in the non-surgical abdominal pain- group. Data are represented as number (%) of cases with range.

Multinomial variables	Acute appendicitis (n=43)	Non-surgical abdominal pain (n=84)	P-value
Location of initial pain			0.23
Right upper quadrant	0	0	
Right lower quadrant	12 (27 %)	22 (25 %)	
Right side	0	0	
Upper lower quadrant	0	0	
Left lower quadrant	1 (2 %)	5 (6 %)	
Left side	0	0	
Upper abdomen	6 (14 %)	2 (1 %)	
Lower abdomen	2 (5 %)	12 (14 %)	
Middle abdomen	9 (21 %)	14 (17 %)	
Upper and middle abdomen	2 (5 %)	3 (4 %)	
Right lower quadrant and middle abdomen	2 (5 %)	3 (4 %)	
Left lower quadrant and middle abdomen	0	3 (4 %)	
Lower and middle abdomen	2 (5 %)	3 (4 %)	
Right flank	0	3 (4 %)	
Left flank	0	0	
Whole abdomen	7 (16 %)	14 (17 %)	
Location of pain at ED			0.04
Right upper quadrant	0	1 (1 %)	
Right lower quadrant	35 (82 %)	37 (44 %)	
Right side	0	0	
Upper left quadrant	0	0	
Left lower quadrant	0	2 (2 %)	
Left side	0	0	
Upper abdomen	0	3 (4 %)	
Lower abdomen	4 (9 %)	14 (17 %)	
Middle abdomen	0	3 (4 %)	
Upper and middle abdomen	0	4 (5 %)	
Right lower quadrant and middle abdomen	0	2 (2 %)	
Whole abdomen and both flanks	0	2 (2 %)	
Lower and middle abdomen	2 (5 %)	3 (4 %)	
Right flank	0	0	
Right flank and right upper quadrant	0	1 (1 %)	
Left flank	0	0	
Whole abdomen	1 (2 %)	12 (14 %)	
Right upper and lower quadrants, middle abdomen	1 (2 %)	0	

Multinomial variables	Acute appendicitis (n=43)	Non-surgical abdominal pain (n=84)	P-value
Duration of pain			0.07
<12 hours	8 (19 %)	30 (36 %)	
12-24 hours	11(25 %)	15 (18 %)	
24-48 hours	15 (35 %)	16 (19 %)	
>48 hours	9 (21 %)	23 (27 %)	
Intensity of pain at ED			0.01
Weak	0	0	
Moderate	27(63 %)	70 (83 %)	
Severe	16 (37 %)	14 (17 %)	
Progression of pain			0.02
Weaker	8 (19 %)	30 (36 %)	
Same	15 (35 %)	34 (40 %)	
Worse	20 (46 %)	20 (24 %)	
Factors aggravating pain			0.001
Movement	3 (7 %)	21 (25 %)	
Coughing	2 (5 %)	0	
Respiration	0	0	
Food	0	3 (4 %)	
Movement/coughing*	24 (55 %)	17 (20 %)	
Movement/coughing/respiration*	6 (14 %)	2 (2 %)	
Movement/respiration*	0	3 (4 %)	
Coughing/respiration*	4 (9 %)	4 (5 %)	
Movement/coughing/respiration/food*	2 (5 %)	0	
No aggravating factors	2 (5 %)	34 (40 %)	
Factors relieving pain			0.001
Lying still	38 (88 %)	47 (56 %)	
Vomiting	1 (2 %)	3 (4 %)	
Food	0	1 (1 %)	
Lying still/vomiting*	2 (5 %)	0	
No relieving factors	2 (5 %)	33 (39 %)	
Bowel habit			0.22
Constipation	1 (2 %)	6 (7 %)	
Diarrhoea	7 (17 %)	8 (9 %)	
Blood	0	0	
Mucus	0	4 (5 %)	
Normal	35 (81 %)	66 (79 %)	

Multinomial variables	Acute appendicitis (n=43)	Non-surgical abdominal pain (n=84)	P-value
Micturition			1.00
Frequent	3 (7 %)	7 (8 %)	
Pain	0	0	
Haematuria	0	0	
Normal	40 (93 %)	77 (92 %)	
Inspection			1.00
Scars	0	0	
Movement	1 (2 %)	1 (1 %)	
Normal	42 (98 %)	83 (99 %)	
Bowel sounds			0.001
Absent	7 (16 %)	0	
High pitched	1 (2 %)	0	
Tinkling	1 (2 %)	2 (2 %)	
Normal	34 (80 %)	82 (98 %)	
Rectal digital tenderness			0.06
Left sided	0	1 (1 %)	
Right sided	8 (19 %)	3 (3 %)	
Middle, right and left sided	6 (14 %)	8 (9 %)	
Mass	0	0	
Normal	29 (67 %)	69 (83 %)	
No rectal examination	0	3 (4 %)	
Urine sample			1.00
Infection	0	6 (7 %)	
Haematuria	0	0	
Normal	43 (100 %)	78 (93 %)	
Continuous variables			
Body temperature (°C)	37.5	37.1	0.04
Range	36.6 - 40.0	36.0 – 40.0	
C-reactive protein ($mg \cdot l^{-1}$)	58	22	0.001
Range	5 - 336	5 - 185	
Leucocyte count ($E^{9} \cdot l^{-1}$)	13.0	10.1	0.001
Range	5.0 – 23.0	5.0 – 21.0	

Table 11. Variables with prognostic significance in differentiating between appendicitis and non-surgical abdominal pain. Data are represented as number (%) of cases.

Variables	Acute appendicitis (n=43)	Non-surgical abdominal pain (n=84)	P-Value
Age*:			
>11y	25 (58 %)	32 (38 %)	0.04
<11y	18 (42 %)	52 (62 %)	
Gender:			
male	27 (63 %)	36 (43 %)	0.04
female	16 (37 %)	48 (57 %)	
Location of pain at emergency department:			
right lower abdominal quadrant	35 (82 %)	37 (44 %)	0.001
other quadrants/flanks	8(18 %)	47 (56 %)	
Intensity of pain**:			
severe	16 (37 %)	14 (17 %)	0.02
weak or moderate	27 (63 %)	70 (83 %)	
Progression of pain**:			
worse	20 (46 %)	20 (24 %)	0.02
same or weaker	23 (54 %)	64 (76 %)	
Relocation of pain:			
yes	26 (61 %)	20 (24 %)	0.001
no	17 (39 %)	64 (76 %)	
Vomiting:			
yes	21 (49 %)	21 (25 %)	0.01
no	22 (51 %)	63 (75 %)	
Anorexia:			
yes	33 (77 %)	46 (55 %)	0.02
no	10 (23 %)	38 (45 %)	
Aggravating factors** :			
movement,coughing,respiration and/or food	41 (95 %)	50 (60 %)	0.001
no aggravating factors	2 (5 %)	34 (40 %)	
Relieving factors**:			
lying still and/or vomiting	41 (95 %)	51 (61 %)	0.001
no relieving factors	2 (5 %)	33 (39 %)	
Rebound tenderness:			
yes	42 (98 %)	32 (38 %)	0.001
no	1 (2 %)	52 (62 %)	
Guarding:			
yes	36 (84 %)	16(19 %)	0.001
no	7 (16 %)	68 (81 %)	
Rigidity:			
yes	13 (30 %)	4 (5 %)	0.001
no	30 (70 %)	80 (95 %)	
Percussion test:			
yes	43 (100 %)	33 (39 %)	0.001
no	0	51 (61 %)	

Variables	Acute appendicitis (n=43)	Non-surgical abdominal pain (n=84)	P-Value
Rovsing`s sign:			
yes	32 (74 %)	14 (17 %)	0.001
no	11 (26 %)	70 (83 %)	
Bowel sounds**:			
absent or high pitched tinkling	9 (20 %)	2 (2 %)	0.001
normal	34 (80 %)	82 (98 %)	
Rectal digital tenderness**:			
right sided, left sided or mass	14 (33 %)	12 (16 %)	0.02
no	29 (67 %)	69 (84 %)	
Body temperature*:			
≥37.5 °C	28 (65 %)	37 (44 %)	0.04
<37.5 °C	15 (35 %)	47 (56 %)	
CRP*:			
≥5 $mg \cdot l^{-1}$	30 (70 %)	28 (33 %)	0.001
<5 $mg \cdot l^{-1}$	13 (30 %)	56 (67 %)	

* Continuous variables were changed to dichotomous variables.

** Multinomial variables were changed to dichotomous variables.

6.1.3. Construction of the Appendicitis Score

Nineteen statistically significant variables were included in the stepwise binary logistic regression analysis that was performed to construct a prognostic model for the diagnosis of AA. The coefficients of the variables of the logistic regression analysis were used to derive a model with 9 variables for predicting appendicitis. The nine variables were *gender, intensity of pain, relocation of pain, vomiting, fever, pain in the RLQ, guarding, bowel sounds, and rebound tenderness.* According to the model, the probability of acute appendicitis (p(AA)) for an individual child can be calculated as: 1/(1+exp(-z), in which z = gender (male 1.6, female 0) + intensity of pain (severe 2.4, mild or moderate 0) + relocation of pain (yes 3.6, no 0) + pain in the RLQ (yes 3.9 no 0) + vomiting (yes 1.8, no 0) + fever (yes 3.0, no 0) + guarding (yes 3.5, no 0) + abnormal bowel sounds (yes 4.1, no 0) + rebound tenderness (yes 6.6, no 0) – 17.7 (constant). The coefficients of the model were rounded to the nearest integer resulting in an Appendicitis Score (Table 12).

Table 12. Appendicitis Score. The numbers are presented as points. RLQ=right lower quadrant.

Gender	Male	2	Female	0
Intensity of pain	Severe	2	Mild/Moderate	0
Relocation of pain	Yes	4	No	0
Vomiting	Yes	2	No	0
Pain in the RLQ	Yes	4	No	0
Fever	≥ 37.5°C	3	< 37.5°C	0
Guarding	Yes	4	No	0
Bowel sounds	Absent, tinkling, high-pitched	4	Normal	0
Rebound tenderness	Yes	7	No	0
TOTAL SCORE				

The Appendicitis Score had a minimum of 0 points and a maximum of 32 points. The cut-off level for AA was ≥ 21, corresponding to an appendicitis probability of 100 %, and the cut-off level for NA was ≤ 15, at which the probability of appendicitis was zero. In the construction sample (n=127), each child with AA had a score > 15, and each child with NA had a score < 21. Observation would have been recommended in children with the Appendicitis Score between 15 and 21.

6.1.4. Validation of the Appendicitis Score

The test sample consisted of 109 children (Table 13). Forty children were operated on for suspected appendicitis. In three of 13 patients with a normal appendix other peroperative findings at the ileo-caecal junction justified the laparotomy (a 5-year old with Burkitt's lymphoma and bowel obstruction, a 6-year boy with a perforation of distal ileum, and a 12-year old girl with a previously undiagnosed Crohn's disease and bowel occlusion). When these cases were excluded, the unnecessary appendicectomy rate was 27 %. One child was initially misdiagnosed as having NA, but she was operated on for a perforated appendix with localized peritonitis at 14 hours. For 78 children with NA, abdominal pain resolved spontaneously before a definitive diagnosis was provided.

Table 13. The distribution of diseases in children with acute abdominal pain in the test sample. Data are number of patients (%).

Disease	Test sample: N=109	Male: N=48	Female: N=61
NSAP	77 (70 %)	27 (56 %)	50 (83 %)
Acute appendicitis	27 (25 %)	18 (38 %)	9 (15 %)
Bowel obstruction	1 (1 %)	0	1 (1 %)
Perforation of ileum	1 (1 %)	1 (2 %)	0
Burkitt`s lymphoma	1 (1 %)	1 (2 %)	0
Ovarian cyst	1 (1 %)	0	1 (1 %)
Gastroenteritis	1 (1 %)	1 (2 %)	0

The Appendicitis Score was validated in 106 children presenting at the ED either with AA or NA. The three children with other surgical conditions were excluded from the validation analysis. All children with non-surgical diagnosis were included in the NA group.

The classification according to the Appendicitis Score was compared to the final diagnoses of the children. The initial score would have suggested discharge in four children (15 %) with AA and emergency appendicectomy in four children (13 %) with NA. Twenty-four children, seven with AA and 17 with NA, would have been observed. Therefore, the initial score would have resulted in the unnecessary appendicectomy rate of 13 %, the potential perforation rate of 26 %, the missed perforation rate of 4 % and missed appendicitis rate of 15 %.

By repeated application of the Appendicitis Score (end score), three children (11 %) with AA would have been discharged, and four children (13 %) with NA would have been operated on. Twenty-

three children, six with AA and 17 with NA, would have been observed. The end score would have resulted in the unnecessary appendicectomy rate of 13 %, the potential perforation rate of 22 %, the missed perforation rate of 4 %, and the missed appendicitis rate of 11 %.

Unnecessary appendicectomy rate would have been reduced from 27 % (n=10) to 13 % (n=4). In contrast, the Appendicitis Score would have suggested discharge in three children (11 %) with AA; all of them had typical tenderness in the RLQ, and therefore none of them were discharged before the definitive management.

6.1.5. Discussion

6.1.5.1. Study design

The diagnostic score was constructed with respect to differentiate between AA and non-surgical acute abdominal pain because those conditions account for over 90 % of children who are referred to the hospital (Winsey and Jones 1967, Jones 1969, Driver and Youngson 1995, Williams et al 1998). In agreement with other reports (Alvarado 1986, Fenyö 1987, Madan 2002), two basic phases were required to construct and validate the score. In the first phase, the physicians recorded the symptoms and signs on structured record sheets. A logistic regression was applied to create the Appendicitis Score. A logistic regression analysis was used instead of discrimination analysis, since basic assumption in discriminant analysis is that both groups are equal in size. In the second phase, the performance of the Appendicitis Score was evaluated on the validation sample. In the validation sample, the nine variables of the Appendicitis Score were prospectively recorded in each child without actually using the predictions from the score in clinical decision making.

A total of 63 patients in the Study Group II were also included in the validation sample of the Study Group I. It remains open to speculation whether administration of oxycodone would have affected the interpretation of the results of the Study Group I. After the administration of oxycodone, six children altered their abdominal guarding: guarding was normalized in three children and became positive in three children. By repeated application of the Appendicitis Score, the unnecessary appendicectomy rate would have been reduced from 23 % to 13 % in children who received oxycodone, and from 28 % to 13 % in those who received placebo.

6.1.5.2. Aetiology of acute abdominal pain

Acute appendicitis (AA) and non-surgical abdominal pain (NA) accounted for 97 % of children with acute abdominal pain who were referred to the paediatric ward. The overall incidence of these two conditions was similar with that reported in other studies in children (Winsey and Jones 1966, Dickson et al 1988, Övrebo et al 1993, Driver and Youngson 1995, Williams et al 1998). The incidence of AA was 33 %, which is similar with the incidences (24-51 %) found in other studies (Winsey and Jones 1967, Dickson et al 1988, Övrebo et al 1993, Williams et al 1998). The incidence of surgical conditions other than AA has been reported to vary from 0 to 6 % (Winsey and Jones 1966, Dickson et al 1988, Övrebo et al 1993, Driver and Youngson 1995, Williams et al 1998). In some studies (Winsey and Jones 1967, Dickson et al 1988, Driver and Youngson 1995), higher incidence of surgical conditions other than AA was related to the fact that also infants and toddlers, and children with acute abdominal trauma were included in the analyses. In the present series, 1 of 2 children with surgical disease other than AA had in fact condition mimicking AA. Similarly, Madan (2002) has published a large prospective series of 1170 children, aged 4-15 years, and found that the only surgical condition except AA was Meckel`s diverticulitis.

Driver and Youngson (1995) evaluated the change in incidence of appendicitis in the years 1967 and 1992 in a single European paediatric unit, and their analysis revealed that the incidence of AA among children presenting with acute abdominal pain to the hospital had fallen by one third from 36 to 24 %. However, the same authors reported an increase in NSAP from 38 to 52 % over the period of study. On the other hand, an overall decline in the incidence of AA has been reported in western countries between the 1930s and the early 1990s (Kang et al 2003, Stringer and Pledger 2003). Several explanations for the reduced incidence of appendicitis has been suggested including an increased dietary intake of vegetables and fibre, and an increased use of antibiotics (Driver and Youngson 1995).

The NSAP pain is the most common cause of acute abdominal pain in children presenting to the hospital. In the present study, the incidence of NSAP (54 %) was in the range of previous studies (Winsey and Jones 1966, Dickson et al 1988, Övrebo et al 1993, Driver and Youngson 1995, Williams et al 1996). Dickson and co-workers (1988) have reported the incidence of 63 % in children with whom no follow-up was attempted after hospital discharge. In contrast, 10 different medical diagnoses were confirmed in the present study during the 4-week follow-up period. Therefore, the incidence of NSAP in children with acute abdominal pain seems to be lower in those series in which the patients are more carefully investigated and followed up.

The NSAP is not diagnosis in a strict sense but a diagnostic category. However, it is a useful category because it enables the physician to compare and contrast children with NSAP against those with AA. In one study in adults, a firm diagnosis was established in 37 % of patients with NSAP in the short-term follow-up. However, none of the established diagnoses were based on firm histology, and none of them required emergency surgery (de Dombal 1991). On the other hand, psychosomatic abdominal pain is a clinical entity that must be considered after organic causes have

been ruled out. School problems or emotional disturbances may cause older children to complain of abdominal pain and loss of appetite (Hotopf et al 1998).

In agreement with the results in the present study (Driver and Youngson 1995), the average age of the children with AA has been reported to be between 10 and 12 years of age (Folkman 1979, Driver and Youngson 1995, Kokoska et al 1999, Madan 2002). Acute appendicitis is rare in younger age groups, but its incidence increases progressively throughout childhood (Alford and McIlhenny 1992, Williams and Kapila 1994). In contrast to some reports (Madan 2002), the results in the present study revealed that the children with NSAP were significantly younger than those with AA. This may result from the fact that the threshold to observe small children in the hospital was lower compared with that in adolescents. In the present study, boys were found more likely to have AA than girls. Supporting the reports of previous studies (O´Shea et al 1988, Williams et al 1998, Kokoska et al 1999, Madan 2002) sex ratio (male to female) of children with AA was 1.7:1 (27/16).

6.1.5.3. Symptoms and signs typical of AA

The prevalence of the most important history and clinical variables obtained from the local paediatric population with AA were quite similar to that reported previously (Jones 1969, Stone et al 1971, Graham et al 1980, Bower et al 1981, Harrison et al 1984). According to the literature the most valuable symptoms and signs in diagnosing appendicitis are pain in the RLQ, relocation of the pain, vomiting, guarding, rigidity, rebound tenderness, nausea, pain intensified by movement, and rectal tenderness (Jones 1969, Stone et al 1971, Graham et al 1980, Bower et al 1981, Harrison et al 1984, Dickson and MacKinlay 1985).

Pain in the RLQ has been regarded as the most valuable symptom suggesting AA (Jones 1969, Harrison et al 1984, Williams et al 1998). In the present study, 82 % of children with AA had pain in the RLQ compared with 44 % of those with NA (Table 11). Moreover, 9 % of children with AA had pain in both lower abdominal quadrants, 5 % in the middle and lower abdomen, 2 % in the whole abdomen, and 2 % in the right upper quadrant and the middle and lower abdomen (Table 10).

Percussion tenderness was found in all children of AA. However, the percussion test was not pathognomonic of AA since percussion tenderness was detected also in 39 % of children with NA (Table 11). The sign of percussion tenderness is closely related to the rebound test that was positive in 98 % of children of AA compared with 38 % of those of NA (Table 11). In the present study, the prevalence of the rebound tenderness in children with AA was slightly higher compared with that reported in previous studies (Jones 1969, Graham et al 1980, Bower et al 1981). Madan (2002) has not recommended rebound test to be elicited in children because it results in undue pain, and finally may lead to loss of cooperation.

In this study, voluntary guarding and rigidity were found to be useful signs in differentiating AA from NA. In agreement with previous reports (Jones 1969, Graham et al 1980, Bower et al 1981), guarding was present in 84 % of children with AA and in 19 % of those with NA. Furthermore, the prevalence of rigidity was 30 % of those with AA and 5 % of those with NA (Table 11).

In the present study, pain was intensified by some aggravating factors (movement, coughing, respiration, or food) in 95 % of children of AA compared with 60 % of those with NA (Table 11). The prevalence of this symptom has been reported to be previously 41-75 % in children with AA and 16 -25 % of those with NA (Jones 1969, Williams et al 1998). In one study relocation of pain was found in 64% of patients with AA compared with 14% of those with NA (Harrison et al 1984).

In the present study, the prevalences were similar since the pain was relocated in 61 % of children of AA and in 24 % of those with NA (Table 11).

Vomiting was previously noted in 68-95% of cases with AA compared with 60% of children without AA (Stone et al 1971, Graham et al 1980, Bower et al 1981). In contrast, only 49 % of children of AA and 25 % of those with NA experienced vomiting in this study (Table 11).

In the present work, rectal digital tenderness was found in 33 % of children with AA and in 13 % of those with NA while in one previous study the sign was positive in 53 % of those with AA and in 12 % with NA (Dickson and MacKinlay 1985). However, Dickson and MacKinlay noted that many children experienced severe discomfort and in only 2 of 103 examinations of AA did the rectal findings change treatment. Therefore they concluded that rectal examination is unpleasant for children, and that the diagnosis of AA may be made in over 90 % of cases without rectal examination.

In the present study, the clinical finding of abnormal bowel sounds was of value in differentiating AA from NA. The prevalence of the abnormal bowel sounds was 20 % in children with AA, and all of them had complicated appendicitis. On the other hand, Williams and co-authors (1998) have reported the bowel sounds to be normal in 95 % of children with NA compared with 90 % of those with AA. It may be difficult to interpret correctly the bowel sounds, and therefore de Dombal (1991) has suggested only two categories to differentiate normal from abnormal bowel sounds: continuously heard or absent bowel sounds. Moreover, he has stressed a careful listening of the bowel sounds for at least three minutes.

Because the clinical diagnosis of AA is difficult, it is necessary to predefine accurately the symptoms and the signs to elicit a complete history, and to conduct a comprehensive physical examination. It is probably easier to take a history, but clinical experience is needed to evaluate signs. Therefore, all surgeons participating in the study were briefed on the abdominal examination techniques.

The decision to operate is not based on a single symptom or sign, but on a combination of findings. Since many symptoms and signs seem to be typical for both AA and NA, the simple count of typical variables predicting appendicitis does not yield an accurate means of differentiating between the two groups. Thus a more appropriate approach would be to weight the symptoms, signs and laboratory test results and then combine the result into a diagnostic score, which would predict the probability of the child having AA.

6.1.5.4. Appendicitis Score

In the present study, the stepwise multiple linear logistic regression analysis of 19 medical history and clinical attributes, and laboratory tests yielded a diagnostic score comprising six medical history and three clinical finding variables. In contrast to other scores (Teicher et al 1983, Arnbjörnsson 1985, Alvarado 1986, Fenyö 1987, Lindberg and Fenyö 1988, de Dombal 1991, Christian and Christian 1992, Eskelinen et al 1992, Madan 2002), no laboratory test was included in the Appendicitis Score. The scoring system was calibrated on the same patient group that it was devised from, and the cut-off levels for recommendation of surgery, observation, and discharge were defined. Thereafter, the Appendicitis Score was validated on the separate test sample. By applicating the Appendicitis Score two times at one hour interval, unnecessary appendicectomy rate would have been reduced from 27 to 13 %.

A total of five variables have been found to be used in most of the diagnostic scores investigated: duration of pain, pain in the RLQ, tenderness in the RLQ, rebound tenderness, and WBC (Arnbjörnsson 1985, Alvarado 1986, Fenyö 1987, Lindberg and Fenyö 1988, Eskelinen et al 1992, Madan 2002). Three of the variables were included in the Appendicitis Score: pain in the RLQ, guarding in the RLQ (corresponding tenderness), and rebound tenderness. On the other hand, five common variables were found between the Appendicitis Score and the Alvarado score (1986) which has been proposed as a standard for all diagnostic scores: relocation of pain, vomiting, fever, guarding (tenderness in the Alvarado score), and rebound tenderness. In addition to the Appendicitis Score, gender has been included in the Teicher (1983), Arnbjörnsson (1985), Lindberg (1988), and Izbicki (1990) scores. Intensity of pain has been included in the Fenyö score. The sign of bowel sounds has not been incorporated in any diagnostic score.

Initial assessment studies have reported an excellence performance for some of the diagnostic scores (Alvarado 1986, Lindberg and Fenyö 1988, Christian and Christian 1990). However, the ability of the scoring systems to fulfill standardized performance criteria has varied. An overall unnecessary appendicectomy rate of less than 15 %, a potential perforation rate of less 35 %, an initial missed perforation rate of less than 15 %, and a missed appendicitis rate of less than 5 % have been suggested in adults in the recent literature (Hoffmann and Rasmussen 1989, Ohman et al 1995). Ohmann and co-workers (1995) measured the performance of ten scoring systems, and found that only the Alvarado score (1986) fulfilled all four criteria.

The performance of a prognostic score is usually evaluated by a receiver-operating characteristic curve, combining sensitivity (the percentage of patients with a score above the cut-off point in the AA group) and specificity (the percentage of patients with a score below the cut-off point in the NA group) for several cut-off points (Ohman et al 1995). Receiver-operating characteristic curve is used

to determine acceptable cut-off points to differentiate children with AA from those with NA. In the present study, logistic regression analysis was applied to the construction sample resulting in the model with two ideal cut-off points: cut-off level ≤ 15 for patients with NA and cut-off level ≥ 21 for those with AA.

In the construction sample, no child with AA had a score of 15 or less, and no child with NA had a score of 21 or more. However, it is well documented that the testing of a score on the same database may underestimate the error rates (Alvarado 1986, Eskelinen et al 1992). On the other hand, the findings of the present study may partially be explained by the fact that the score was abstracted from the more selected sample of suspected appendicitis and not from that with acute abdominal pain. Therefore, the outcomes of the construction sample were of limited value for assessing the usefulness of the Appendicitis Score.

The Appendicitis Score was prospectively validated on the separate sample. If the Appendicitis Score would have applicated two times at one hour interval, management errors would have occurred in three (11 %) children with the final diagnosis of simple AA, and unnecessary appendicectomy in four (13 %) with the final diagnosis of NA. In addition to the unnecessary appendicectomy rate, rates of potential perforation (22%) and missed perforation (4%) were well with the range of those performance criteria for the diagnostic scores suggested by Hoffmann and Rasmussen (1989) and Ohmann and co-workers (1995). One child with an end score of 15 had tenderness in the RLQ, and positive rebound and guarding signs. She had three physical findings typical of acute appendicitis, but in the absence of other signs, the end score remained at 15. Two children, with an end score of 7, had fewer symptoms and signs than other children with AA, and they were initially diagnosed as having NA. Each of them had tenderness in the RLQ at the ED, but guarding and rebound tenderness did not develop until 4-5 h after admission. On the other hand, the

end score would have allocated 6 children with the final diagnoses of AA to observation. Only one of them had perforated appendicitis. She had no abdominal tenderness at the time of ED examination but she developed later on the ward persistent tenderness locating at the RLQ.

Rates of missed appendicitis and unnecessary appendicectomy were well in the range of previous studies in children. Owen and co-workers (1992) found that the use of Alvarado score (1986) decreased unnecessary appendicectomy rate by a factor of 3, from 44 to 14 %. Similarly, Dado and co-workers (Dado et al 2000) have reported that a modified Lindberg`s score (Lindberg and Fenyö 1988) would have reduced the unnecessary appendicectomy rate to one third from 23 to 8 %. On the other hand, the application of Lindberg`s score would have resulted in the missed appendicitis rate of 8 %.

Madan score (Madan 2002) was validated in a separate test sample resulting in a sensitivity of 100 %, and specificity of 87 %. These results, however, seemed to be optimistically biased because all children with AA had a score of ≥ 8, and all children with NA, except four patients, had a score of ≤ 5. Madan had not defined the cut-off levels for observation, and there were no cases with Madan score between 5 and 8. In addition, children with surgical conditions other than AA were in the NA group. If these children would have been excluded, the Madan score would have yielded a specificity of 93 %.

The decision to operate or discharge the patient cannot be based solely on the Appendicitis Score but also on repeated structured clinical examination. Since the nine variables in the Appendicitis Score do overlap with non-surgical conditions, the score does not give 100% reliability. It is known that the diagnosis of appendicitis may not become clear in a minority of patients until some hours, or even days, after the onset of symptoms, and delay often ensues before an accurate diagnosis is

established (de Dombal 1991). Therefore, repeated application of the score should be integrated into the diagnostic process, in which children with uncertain diagnosis should be re-evaluated, for example, at 3 h intervals. Because children dislike repeated blood samples the diagnostic score unique to children should comprise only history and clinical variables.

The Appendicitis Score can be used as a diagnostic aid, but it cannot supplant careful clinical judgement. It may well be that for one cut-off point certain criteria are fulfilled but for others they are not. Therefore, the results of the scoring system depend on the selection of the cut-off point. Since the use of the Appendicitis Score, combined with repeated clinical examination, would have resulted in reduced rate of unnecessary appendicectomy, the cut-off level ($\geq$ 21) for recommendation of appendicectomy can be considered acceptable. Since the presence of abdominal pain in the RLQ, rebound or guarding are indicative of appendicitis, the children with these findings should be observed in the paediatric surgical ward even if the score is $\leq$ 15.

6.2. Analgesics in children with acute abdominal pain

6.2.1. Analgesic effect

Both oxycodone and normal saline had a significant analgesic efficacy. The mean (±SD) SPID was significantly larger in the oxycodone group, 22 (±18) cm, than in the placebo group 9 (±12) cm (mean difference 13 cm, 95 % CI 2 to 24 cm, *P*=0.04). The mean maximal PID was 3.7 (±2.8) cm in the oxycodone group and 2.7 (±2.6) cm in the placebo group (mean difference 1.0 cm, 95 % CI – 0.4 to 2.4 cm, *P*=0.14). A total of 67 study drug doses (mean 2.1 (±0.9) doses) was administered in the oxycodone group and 74 doses (mean 2.4 (±0.8) doses) in the placebo group.

6.2.2. Analgesia and diagnostic accuracy

In the oxycodone group diagnostic accuracy was improved from 72% to 88% (P=0.12) after the administration of study medication while in the placebo group the accuracy of diagnosis remained at 84% pre- and post-dose. Pre-dose abdominal guarding was present in 16 of 32 in the oxycodone group and in 13 of 31 in the placebo group. After administration of study medication seven had guarding altered, guarding was normalized in three and became positive in three in the oxycodone group compared with one normalized guarding in the placebo group (P=0.05). Children with post-dose guarding underwent appendicectomy for acute appendicitis. Pre- and post-dose guarding was absent in three children (in one in the oxycodone group and in two in the placebo group) with acute appendicitis.

Seventeen of 32 in the oxycodone group and 14 of 31 in the placebo group underwent exploratory laparotomy. In all children, except one in the placebo group, the decision to operate was made at 1

hour after triage. Two, one in the placebo group and one in the oxycodone group, with localized abscesses were operated on at 20 and 24 hours after triage. In clinical examination both had mild abdominal tenderness and a correct surgical diagnosis was established already in the ED. However, clinical findings were atypical and a confirmatory computer tomography was performed before surgery. Delay in operation had no clinical consequence for these two patients because none of them had generalized peritonitis at the time of surgery. A 15-year old girl in the placebo group had no abdominal tenderness at the time of pre- or post-dose clinical examination, and she was taken to the paediatric ward for follow-up. On the ward she developed an intensive abdominal pain with persistent abdominal tenderness, and was operated on for perforated appendicitis with localized peritonitis at 14 hours after triage.

Twelve in the oxycodone group and nine in the placebo group had histologically confirmed appendicitis. The appendix was abscessed in one and perforated in two in the placebo group. Two had another surgical disease; one in the oxycodone group had a perforation of distal ileum and an abscess caused by a plastic splinter, and one in the placebo group had a previously undiagnosed Crohn's disease with partial bowel obstruction in the terminal ileum. Four of 17 (23%) underwent unnecessary laparotomy in the oxycodone group compared with four of 14 (28%) in the placebo group. For 14 children in the oxycodone group and 17 in the saline group, symptoms resolved before a definitive diagnosis occurred. One in the oxycodone group had a small ovarian cyst confirmed by ultrasonography.

One child experienced headache and another developed urticaria after receiving oxycodone. No sedation, hypoxia, or hypotension was observed.

There were three readmissions in the placebo group and one in the oxycodone group. In the placebo group one 11-year old girl experienced abdominal pain three weeks after discharge, and she underwent exploratory laparotomy with normal findings. Abdominal pain resolved spontaneously in other three. All children were asymptomatic at 4 weeks from final discharge.

6.2.3. Discussion

6.2.3.1. Study sample

The small sample size may be considered a limitation of this study because evaluating the adverse events of patients, for example, requires more subjects for a definitive conclusion on adverse events occurring with a frequency of < 5 %. In addition, a total of 750 children in both arms would have been required to determine whether the use of opioids would have altered the outcome compared to placebo (Lee et al 2000). This would have implied either a multicentre study or a study conducted over many years.

6.2.3.2. Study design

A randomized double-blind clinical trial is considered the most reliable method in the testing of efficacy of analgesics in patients with acute abdominal pain. To minimize bias, patients and investigators should be blinded to the identity of the assigned intervention group (Zoltie and Cust 1986, Attard et al 1992, Pace and Burke 1996, LoVecchio et al 1997, Vermeulen et al 1999, Mahadevan and Graff 2000, Kim et al 2002).

The present study was randomized and each patient had an equal chance of being allocated to the oxycodone or placebo group. The patients were, however, no consecutive because only three surgeons were involved in the study. Because analgesic effect was a primary endpoint, the potential lack of blinding must be considered. Due to changes in patient comfort level, it becomes difficult to

conduct a truly blinded trial (Nissman et al 2003). Moreover, the ability of enrolled children to identify their treatment group was not assessed in the present study. A significant difference in the surgeons` abilities to discern group allocation was not noted but the surgeons correctly identified placebo recipients 75 % of time.

One of the limitation of the study was that the same surgeon performed the pre- and post-study medication examinations for each child. The previous assessment may have biased the post-study medication diagnosis. Another limitation was that all children were admitted to the paediatric ward for observation and thus the results obtained should not necessarily be generalized to outpatients. The third limitation may have been a selection bias, as the study was not consecutive, and the all potentially eligible children were not included.

6.2.3.3. Effects of opioid analgesia on diagnostic accuracy

Even though the placebo effect was significant, buccal oxycodone provided significantly better analgesia than buccal saline. Oxycodone did not adversely influence the clinical examination or the appropriateness of the decision to operate. Slight relief on pain to gentle pressure actually improved the diagnostic accuracy in oxycodone treated children. Moreover, no serious adverse effects or any major untoward outcomes occurred in associating with the opioid administration, e.g. the only misdiagnosed case was in the placebo-group.

The results of the present study are consistent with several recent prospective randomized studies addressing the effects of opioid analgesia on definitive diagnosis and treatment in patients with acute abdominal pain which have failed to give any evidence that opioid analgesia prior to definitive diagnosis would be harmful (Zoltie and Cusp 1986, Attard et al 1992, Pace and Burke 1996, LoVecchio et al 1997, Vermeulen et al 1999, Mahadevan and Graff 2000, Kim et al 2002,

Thomas et al 2003). These studies have demonstrated that a judicious administration of opioids can effectively reduce pain to a greater degree than it does the localization of tenderness, and thus may even improve the diagnostic accuracy.

Clinical signs are critical for the diagnostic process in children with abdominal pain but very few studies have attempted to evaluate which and how much clinical signs change with the administration of opioids. In four previous studies in adults the investigators concluded that the administration of opioids to the patients with abdominal pain resulted in some clinical finding changes (Zoltie and Cust 1986, Attard et al 1992, LoVecchio et al 1997, Mahadevan and Graff 2000) whereas in one study reported no changes in peritoneal tenderness (Pace and Burke 1996). No standard exists in the literature concerning what constitutes a significant clinical examination change in the setting of acute abdomen. Although the decision to operate the patient is not based on the single sign but a combination of findings, the presence or absence of guarding was used as the single most important examination finding because guarding is found in 80-91% of children with AA (Jones 1969, Janik and Firor 1979, Bower et al 1981). In the present study preoperative guarding was absent in three children with AA. After oxycodone administration, three children with final diagnosis of appendicitis developed peritoneal tenderness, and guarding disappeared in three with self-limited abdominal pain. Oxycodone at 0.1 $mg \cdot kg^{-1}$ did not mask or hide clinical examination evidence of peritoneal irritation. Thus the examination changes represented improvement of the examination findings. The precise mechanism for the change in abdominal tenderness is unknown. Decrease in abdominal tenderness may be more related to spontaneous resolution of symptoms in children with self-limited abdominal pain.

Divergent results have been reported in recent literature concerning the effects of opioids on diagnostic accuracy. Some authors suggest that early pain relief would actually facilitate a definitive

diagnosis (Attard et al 1992, Pace and Burke 1996) while others conclude that opioid analgesia is not associated with harmful effects on diagnostic accuracy (Zolty and Cust 1986, Kim et al 2002). In the present study there were relationships between the use of oxycodone and an altered diagnosis or treatment. In five children the provisional diagnosis of NA changed to the correct diagnosis of AA after administration of oxycodone; post-dose guarding developed in three while peritoneal tenderness was present already in two with the initial diagnosis of NA. The diagnostic sensitivity, the ability to diagnose a surgical disease, was increased after administration of oxycodone although no changes were noted in diagnostic specificity, the ability to diagnose a non-surgical disease.

In contrast to the results in the present study, Kim and colleagues reported higher specificity in the in the morphine group suggesting that morphine might help in finding those children with non-surgical condition (Kim et al 2002). Although morphine might facilitate diagnosis of non-surgical disease, Kim and colleagues (2002) noted that their sample size was insufficient to address the question of diagnostic accuracy, which is consistent with the results in the present.

Appendicitis is the most common indication for emergency laparotomies in children, which meant that in this study the clinical examination was focused especially on children with suspected appendicitis or those with conditions mimicking appendicitis. Most children presenting to the hospital with acute abdominal pain have either AA or NA (Dickson et al 1988), and surgical conditions other than appendicitis are rare in children aged 4-15 years. In the present study all patients except three had either AA or NA. In some patients the diagnosis of appendicitis may become clear only after some hours observation, as occurred in the present study in one child with a perforated appendicitis and local peritonitis. She had no abdominal tenderness in pre- and post-dose clinical examinations, and that may have been the time of perforation prior to the onset of pain of peritonitis. The child was initially misdiagnosed as having NA, but at 14 hours after triage she was

operated on for appendiceal perforation. This patient had fewer symptoms and signs of appendicitis than children whose diagnosis was made initially at the ED. Physician errors occur on the patient with atypical presentation of the appendix, and errors and delays in surgery will correlate with adverse effects. On the other hand, delay often ensues before an accurate diagnosis is established. Eight unnecessary laparotomies were performed on non-appendicitis patients with clinical findings similar to those of patients with histologically confirmed appendicitis.

6.3. Laparoscopic versus open appendicectomy

6.3.1. Surgery

No LA was converted to open procedure. The mean (±SD) operative time was 44 (±26) min in the LA group compared with 31 (±13) min in the OA group (mean difference 13 min, 95 % CI 5 to 21 min, P=0.001). The mean anaesthesia time was 62 (±25) min in the LA group and 51 (±14) min in the OA group (mean difference 11 min, 95 % CI 2 to 19 min, P=0.02). The total procedure time was similarly significantly longer in the LA group compared with that in the OA group (94 (±36) min versus 63 (±16) min (mean difference 31 min, 95 % CI 20 to 43 min, P=0.001). There was no significant difference between the LA and OA group in the total post-anaesthesia care unit time: mean 245 (±142) min in the LA group vs 231 (±123) min in the OA group (mean difference 14 min, 95 % CI –40 to 69 min, P=0.61).

6.3.2. Postoperative pain

The children in the LA group required less rescue analgesics compared with children in the OA group. In the LA group 44 of the 48 children received rescue analgesics compared with 50 of the 51 children in the OA group. A total of 24 children (50 %) in the LA group received three or more doses of oxycodone, compared with 43 (84 %) in the OA group (P=0.001). A total of 3.9 (±2.5) doses of rescue analgesics per patient were required in the LA group compared with 5.0 (±3) doses in the OA group (mean difference 1.1 doses, 95 % CI 0.2 to 2.0 doses, P=0.01).

No child in the OA group experienced shoulder pain compared with eight children in the LA group (P=0.002). In these eight children the shoulder pain lasted for a mean of 14 (±9) (range 2 to 29) hours.

6.3.3. Outcome

6.3.3.1. Recovery and adverse effects at hospital

Children tolerated normal diet in the LA group at 13 (±17) hours and in the OA group at 15 (±16) hours after the operation (mean difference 2 hours, 95 % CI –0.8 to 6.0 hours, P= 0.73). Children had normal walk in the LA group at 20 (±19) hours and in the OA group at 24 (±18) hours after the surgery (mean difference 3 hours, 95 % CI –0.1 to 4.0 hours, P=0.39).

No patient vomited in the post-anaesthesia care unit but one child in each group experienced nausea. On the ward nine children in the LA group and four in the OA group vomited (P=0.51). One child in the LA group had urinary retention requiring bladder catheterisation.

6.3.3.2. Discharge

The mean length of hospital stay was 2.7 (±1.8) days in the LA group compared with 2.9 (±1.1) days in the OA group (mean difference 0.2 days, 95 % CI –0.8 to 0.4 days, P=0.22). Hospitalization of 2 days or more was required for 36 children (75 %) in the LA group, compared with 49 children (96 %) in the OA group (P= 0.01). No child in the OA group required hospital stay of 7 days or more, compared with two children with complicated appendicitis in the LA group.

6.3.3.3. Recovery at home

One child in each group had no pain at home. Twenty one children in the LA group and 23 children in the OA group experienced moderate or severe pain at home. However, the children in the LA group had pain for a significantly shorter duration compared with those in the OA group (Table 14). Moreover, children in the LA group received fewer analgesic doses compared with children in the

OA group (3 (±3) vs 6 (±7) doses) although the difference was not statistically significant. Children in the LA group had significantly less pain at a control visit scheduled for 7 days after operation. The children in the LA group returned earlier to normal daily activities compared with children in the OA group.

There was no mortality, and all children healed eventually. There were two major complications in children with periappendicular masses in the LA group. One child was discharged 4 day after LA but she was readmitted 1 day later because of vomiting and diarrhoea. The abscess resolved with antibiotic treatment in 14 days. In another child, the perforated appendix was attached to the floor of the pelvis, and the tip of the appendix remained in situ after LA. One month after LA he developed an enterocutaneous fistula which was excised by open laparotomy. Five children in the OA group had wound infections, which were cured by local debridement.

Two children in the LA group and one child in the OA group were readmitted to the hospital. Three children in the LA group and 2 children in the OA group were once readmitted to the emergency department. One child in the OA group was twice readmitted to the emergency department. Postoperative abdominal ultrasonography was performed in 3 children in the LA group and in 1 child in the OA group.

Table 14. Recovery at home after laparoscopic (LA) and open appendicectomy (OA). Values are mean (±SD) (range).

	LA group N=48	OA group N=51	Mean difference*	P-value
Duration of post-operative pain (days)	3.0 (±2)	4.0 (±3)	1.0 (0.1 to 2.0)	0.03
Range	0-8	0-13		
Number of ketoprofen doses	3.0 (±3)	6.0 (±7)	3.0 (-0.5 to 3.8)	0.15
Range	0-16	0-30		
Return to school (days)	7.0 (±3)	8.0 (±3)	1.0 (-0.6 to 2.3)	0.09
Range	2-13	2-14		
Return to normal sport activities (days)	11.0 (±6)	15.0 (±6)	4.0 (1.8 to 6.8)	0.005
Range	2-30	6-45		
Return to sport at school (days)	15 (±5)	18 (±6)	3.0 (0.5 to 6.0)	0.02
Range	7-28	9-30		
Pain at 1 week**	0.1 (±1)	1.0 (±2)	0.9 (0.3 to 1.3)	0.002
Range	0-3	0-8		

* Values in parenthesis are 95 per cent confidence intervals.

**Visual analogue scale (cm).

6.3.3.4. Cosmetic appearance of the operative wound

The research nurse measured the length of the operative wounds in each child. The operative wounds were significantly shorter in the LA group compared with those in the OA group: 3.4 (±0.8) cm (range 1.5 to 6.0 cm) versus 6.3 (±3.0) cm (range 3.0 to 11 cm) (mean difference 2.9 cm, 95 % CI 0.4 to 7.0 cm, P=0.001).

The cosmetic appearance of the operative wounds was subjectively evaluated by children and their parents at 1 month after the operation (Appendix 5). A total of 41 children (93 %) in the LA group regarded the cosmetic result as fine compared with 39 of 51 children (81 %) in the OA group (P=0.27). All 48 parents of the children in the LA group considered the appearance of the operative wounds to be fine compared with 42 of 51 parents (82 %) of children in the OA group (P=0.01).

6.3.3.5. Costs

Excess operating and complication costs per procedure were 96 euros in LA. The increased operative expenses were offset by a shorter hospital stay, resulting in a marginal difference of 53 (95 % CI; -83 to 247 euros) euros in itemized total costs between the two procedures (total cost, 1023 (±585) euros in the LA group and 970 (±402) euros in the OA group). Assuming that operating room scheduling would have been tight and that operating room time costs would have been calculated, the difference in total costs between the two groups would have been 255 (95 % CI; -146 to 1243 euros) euros (total cost, 1690 (±51) euros in the LA group and 1435 (±40) euros in the OA group). The operating room time was 89 (±35) minutes in the LA group and 62 (±17) minutes in the OA group (mean difference 27 minutes, 95 % CI 15 to 39 minutes, P=0.001), and the operating room time costs were 7.5 euros per one minute.

6.3.4. Discussion

6.3.4.1. Study sample

The sample size in this study can be considered small (n=99), and, therefore, the power to identify differences between the study groups was limited. In a small paediatric surgery centre with a catchment area of 38 000 children, it was not possible to recruit high number of children in reasonable time. To detect a smaller difference between LA and OA in children with complicated appendicitis, a sample size of $\geq$ 300 patients would have been required per group, or if a perforation rate of 30 % would have been assumed, a series of 2000 patients with simple or complicated appendicitis would have been required.

When the present study was started in 1997, the laparoscopic experience was scarce and the mini-invasive equipment unsuitable for children in Finnish paediatric surgical centres, and therefore it was not possible to conduct a large multicentre study. On the other hand, the multicentre study-design would have probably created enough bias to preclude the identification of minor differences.

6.3.4.2. Study design

There is unanimous agreement that a randomized controlled trial remains the best method to assess objectively a new treatment such as LA. However, flaws in the design of randomized controlled trials will result in difficulties in interpretation of their relevance to daily practice. Therefore, a well conducted randomized clinical trial should provide a stated aim, an adequate control group, an account of randomization technique, demonstration of baseline equivalence, definition of the study endpoints, a description of the operations, and adequate postoperative follow-up (Slim et al 1997). Moreover, some authors have indicated that the effect of blinding is of critical importance in the

analysis of laparoscopic techniques in the comparison to open techniques (Majeed 1996, McCall et al 1997).

OA has been the gold standard of management of AA against which all mini-invasive techniques should be compared. Several authors initiated randomized controlled trials in the early 1990`s to compare LA with OA in adults (Attwood et al 1992, Tate et al 1993, Martin et al 1995). When the present study was started there was only one report of randomised clinical trial comparing LA with OA in children (Lejus 1996). In addition few non-randomized studies had been published (Valla et al 1991, Gilchrist et al 1992, Varlet al 1994, Valla et al 1996).

Cochrane review (Sauerland et al 2004) of LA versus OA for suspected appendicitis revealed that only 4 (Ortega et al 1995, Lejus et al 1996, Huang et al 2001, Ignacio et al 2004) of 45 trials had taken measures to blind patients (and parents) and investigators against treatment received. In these trials the blinding ended at the time of discharge. In the present study children, parents, research nurses and surgeons, except the principal investigator, were blinded, and remained blinded until a control visit scheduled for 7 days after surgery. If the clinical trial is not blinded it may be possible that patients who are allocated to the LA group and the investigators have high expectations, since LA is the more modern surgical technique. The results of the non-blinded trials may be influenced by such bias (Majeed 1996, McCall et al 1997). In this study the effect of blinding was of critical importance in lessening positive expectations related to LA.

The clinical results were reported in three related publications. Although there were significant overlap between the patients in those three series they were not identical. Data for publications I and III were gathered solely from Kuopio University Hospital. Data for the publication II were obtained from two centres. The focus of the publication I was the postoperative pain differential

between LA and OA in children with simple appendicitis or normal appendix. In the publication II the clinical outcomes between the two groups of children with complicated appendicitis were reported. In the publication III the focus was on the cost differential between LA and OA from a health care payer perspective.

Findings in this study may not be generalizable because all the laparoscopic procedures in the Kuopio University Hospital were performed by a single surgeon. On the other hand, LA involves some critical problems that may affect the success of the procedure. First, extensive training and experience is required, and second, it is very difficult to treat laparoscopically children with complicated appendicitis. Although only one surgeon performed LA exclusively, bias could have been introduced in the form of surgeon variance, differences in treatment protocol, and differences in experience of laparoscopic technique. In contrast to LA, OA is not highly operator dependant, and all of the surgeons would appear capable and experienced.

Patients in the present study were not consecutive because of difficulties in providing laparoscopic expertise throughout the 24 hours. During the trial period in Kuopio University Hospital, a total of 105 children were operated upon for suspected appendicitis, and 87 of them (83 %) were enrolled and randomized. At least 4-5 experienced laparoscopists would have been required to conduct a consecutive series (Macarulla et al 1997, Kald et al 1999). Another alternative would have been a quasi-randomised trial in which assignments of patients to LA and OA would have been based on the schedule of the attending surgeon on call (Hay 1998, Oka et al 2004). In fact, no prospective consecutive series of LA versus OA has been published in children to date but some consecutive studies have been reported in adults (Frazee et al 1994, Macarulla et al 1997, Kald et al 1999).

6.3.4.3. Surgery

The operating time was 13 minutes longer in the LA group compared with OA group while there were 11 minutes difference in the anaesthesia time between the two groups. The preoperative installation of the video-laparoscopic equipment took up to 18 minutes, thus increasing the total procedure time in the LA group. There was no need for conversion from LA to OA.

The Cochrane review revealed strong heterogeneity in operating times among the 45 studies in adults and 4 studies in children (Sauerland 2004). The mean operating time of trials included in the Cochrane review was significantly longer in the LA group, 58 (range 23 to 102) minutes, compared with the OA group, 46 (range 23 to 87) minutes (Sauerland et al 2004). In children, the operating time was similarly longer in the LA group compared with that in the OA group (58 vs 46 min). This wide diversity may be explained by the fact that patients with complicated appendicitis were excluded in some studies (Heikkinen et al 1998, Huang et al 2001, Lavonius et al 2001). According to Sauerland and co-workers (2004) the difference in operating time between LA and OA has become even smaller during the most recent years.

The main disadvantage of the laparoscopic technique is the increase in operating time. Increased experience with this technique may reduce the duration of surgery to that of the conventional technique (Attwood et al 1992, Pier et al 1993). However, there is a prolonged surgical learning curve before LA can be fairly compared with OA. One systematic review showed that there were improvements in operating time, conversion rate, complication rate, and length of hospital stay for different laparoscopic procedures between the initial and late experience (Dagash et al 2003). Proficiency is attained when the learning curve reaches its plateau, and further improvement in outcome is not detectable. However, there is no agreement on the number of procedures a laparoscopist must perform becoming proficient in laparoscopic surgery (Dagash et al 2003). In the

present study the principal laparoscopist had an experience of more than 30 LAs before the onset of the trial, and no improvement in the operating times was detected during the course of the trial.

Increased surgeon experience decreases the total procedure time but the presence of dedicated operating room system may be as important. Kenyon and co-workers (1997) showed that the procedure time could be reduced by 30 minutes per case, and conversion rates are significantly lower when a designated nursing team helped perform various laparoscopic procedures. Only few studies have addressed the issue of counting the time necessary for setting up the laparoscopic equipment for LA. In one study (Heikkinen et al 1998) the installation of the laparoscopic system resulted in 7 minutes increase in the total procedure time. However, in the present study it took 18 minutes per case to set up the laparoendoscopic equipment. This may have related to the fact that most appendicectomies were performed as urgent cases during on-call duty, and thus the level of the laparoscopic experience of the nursing team may have varied.

In the present study there were no conversions from LA to OA. In the Cochrane review (Sauerland et al 2004) the conversion rates varied from 0 to 26 % in adult and paediatric studies. Oka and co-workers (2004) published a non-randomized study including 141 LAs of which none was converted to OA. Canty and co-workers (2000) reviewed retrospectively 1128 children of whom 955 underwent LA. Only 1 % of the LAs were converted to OAs, all in cases of appendiceal perforation. According to the retrospective analysis of 1500 paediatric LAs, conversions from LA to OA (conversion rate of 3 %) occurred mostly in patients with complicated appendicitis (Steyaert et al 1998). Some authors (Horwitz et al 1997, Blakely et al 1998) have even suggested that LA should be avoided in patients with known perforated appendicitis because of the technical difficulties related to the manipulation of inflamed tissue. Therefore, conversion to open procedure is advised, especially when secure dissection of the appendix can not be carried out.

6.3.4.4. Postoperative pain and recovery

In the present study the recovery after LA was significantly improved compared with that following OA. Children who underwent LA had less pain and needed less analgesia after surgery than those who underwent OA. After LA, children returned to school 1 day earlier (after 7 days) than those who had had OA (8 days), and 4 days earlier to their sport activities (11 days vs 15 days after LA compared with OA). On the other hand, the length of hospital stay was not significantly different between the two techniques.

Three smaller scale randomized clinical trials have evaluated the postoperative pain and recovery in children (Lejus et al 1996, Lavonius et al 2001, Little et al 2002). Blinded study design was used in one study (Lejus et al 1996) in which the authors found no difference in postoperative pain and analgesics use between the LA and the OA groups. In one study (Little et al 2002) the hospital stay was shorter in the OA group compared with LA group (4 vs 3.5 days) while in another study (Lavonius et al 2001) there were no difference in hospitalization between the two groups. In contrast to the present study, Little and co-workers (2002) and Lavonius and co-workers (2001) applied no standard discharge criteria for the patients. Moreover, Little and co-workers (2002) found that the children in the OA group returned one day earlier (after 1 day) to their normal activity compared with those in the LA group (2 days). However, resumption of normal activity was not defined in the trial conducted by Little and co-workers (2002). On the other hand, in one non-randomized study Hay (1998) found recovery to be superior after LA.

Infiltration of the operative wound with a long-acting local anaesthetic such as bupivacaine can provide effective analgesia for 1.5 to 6 hours (Charlton 1997). Wound infiltration with bupivacaine has been shown to reduce both postoperative analgesic requirements (Wright 1993) and length of hospitalization (Foulds and Beasley 2000) in children undergoing appendicectomy. Morton and

O`Brien (1999) described a trial in which all children had wound infiltration with bupivacaine at the end of the skin closure. Despite additional postoperative analgesia with opioids, a significant proportion of children still experienced severe pain. In the present trial a local anaesthetic was not used because the duration of pain relief was known to be limited.

In the present study there were no significant difference in hospitalization between the two study groups. However, the hospital stay was 0.7 days shorter in the LA group (1.9 days) compared with OA group (2.6 days) in children with uncomplicated appendicitis or normal appendix. In contrast, the hospitalization was 1 day longer in the LA group (5 days) compared with OA group (4 days) in children with complicated appendicitis. This may be explained by the fact that hospitalization of 6 days or longer was required for one child in the OA group, and for 4 children in the LA group. All these children had complicated appendicitis. On the other and, the overall sample size of the present study was too small to detect a significant difference in hospital stay between the two groups.

6.3.4.5. Outcome

There was no mortality, and all children healed eventually. There were two major complications in children with periappendicular masses in the LA group. On the other hand, 5 children in the OA group had superficial wound infections, which were treated by local debridement. Postoperative imaging studies were performed in three patients in the LA group and in one patient in the OA group.

The Cochrane review (Sauerland et al 2004) in adults reported wound infection rate of 3.9 % in patients who had undergone LA compared with 7.7 % in those who had undergone OA, and intra-abdominal abscess rate of 1.9 % in patients who had undergone LA compared with 0.6 % in those who had undergone OA. Yeung and co-workers (1997) reported wound infection rate of 10 % in

children who underwent OA, and no postoperative infectious complications in those who underwent LA. In the present series, there were no wound infections in the LA group but the incidence of wound infection was 10 % in the OA group. On he other hand, there were no major complications in the OA group but the incidence of intra-abdominal abscess was 4 % in the LA group. The high incidence of intra-abdominal abscess may be related to the fact that children with periappendicular masses were also included in the present trial. Some authors have even considered OA preferable in patients with appendiceal masses, because the dissection of the inflamed mass without manual palpation may lead to bleeding and visceral injuries (Valla et al 1996).

There may be several reasons for the increased incidence of postoperative intra-abdominal abscess related to the laparoscopic procedure in children with complicated appendicitis. The infectious material may be spread throughout the peritoneal cavity during pneumoperitoneum (Blakely et al 1998). Furthermore, the risk of intra-abdominal contamination may be enhanced in the laparoscopic technique in which dissection and division of the appendix take place inside the abdominal cavity. Manipulation of gangrenous tissue may be difficult with the laparoscopic equipment because there is no sensation at the tip of the instruments. Therefore, intraoperative complications related to LA may occur frequently in patients with appendiceal masses. One of the most important factors of the LA is to avoid intra-peritoneal abscess by proper irrigation and drainage and postoperative ultrasound controls (Valla et al 1996, Canty et al 2000, Paya et al 2000).

Morbidity rates have varied from 10% to 45% in large surveys of children with perforating peritonitis, thus the complication rate in the present study was in the range of previous studies (Stone et al 1971, Samelson and Reyes 1987, Pearl et al 1995). Both major complications occurred in patients with periappendicular abscesses in the LA group. One patient initially had an intrapelvic abscess surrounded by adhesive bowel loops, and the perforated appendix was attached to the floor

of the pelvis. A 2-cm-long remnant of the appendix was left in place after the laparoscopic operation resulting later in a enterocutaneous fistula. It remains open to speculation whether conversion from laparoscopic to an open procedure would have allowed the laparoscopist to notice the remaining appendiceal tip and avoid the re-operation one month later. Another child with diarrhoea and vomiting was unable to take antibiotics by mouth, and later had a pelvic abscess. She was treated first by intravenous and then by oral antibiotics for two weeks with eventual cure. There were no major complication in the OA group, but this may result from the fact that there were fewer children with perforated or abscessed appendices in this group.

7. SUMMARY AND CONCLUSIONS

1. The Appendicitis Score was constructed from a prospectively collected sample and further validated in a separate, prospective cohort. By application of the score, unnecessary appendicectomy rate would have been reduced from 27 % to 13 %. The use of the Appendicitis Score may facilitate the clinical diagnosis of acute appendicitis to avoid unnecessary operations.

2. Significant reduction in abdominal pain was attained after oxycodone 0.1 $mg \cdot kg^{-1}$. The diagnostic accuracy improved with oxycodone analgesic care of children with severe abdominal pain. Early administration of opioid analgesics provides a significant pain relief to children with acute abdominal pain, without adversely changing the clinical examination findings or obscuring the surgical diagnosis.

3. Laparoscopic appendicectomy was marginally more expensive, but it was associated with less postoperative pain and earlier return to normal daily activities than open appendicectomy. Laparoscopic appendicectomy is a feasible, safe, and effective alternative to open appendicectomy in children with suspected appendicitis

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9. APPENDIX

Appendix 1: Clinical and laboratory variables gathered at the emergency department (ED).

History variables (19)	*Category*	***Clinical signs (13)***	*Category*
Age	years	**Inspection**	normal/scars/movement
Gender	male/female	**Abdominal distension**	yes/no
Location of initial pain	right upper/right lower/right side/upper left/lower left/left side/upper/lower/middle abdominal quadrant/right flank/left flank	**Rebound**	yes/no
Location of pain at ED	(same as above)	**Guarding**	yes/no
Duration of pain	<6h/6-12h/12-24h/24-48h/>48h (h=hours)	**Rigidity**	yes/no
Relocation of pain	yes/no	**Psoas sign**	yes/no
Intensity of pain at ED	weak/moderate/severe	**Percussion test**	yes/no
Progression of pain	same/worse/weaker	**Rovsing`s sign**	yes/no
Type of pain	steady/intermittent	**Bowel sounds**	normal/absent/high pitched tinkling
Factors aggravating pain	movement/coughing/respiration/food/ no aggravating factors	**Rectal digital tenderness**	none/left sided/right sided/mass
Factors relieving pain	lying still/vomiting/food/ no relieving factors	**Tumour**	yes/no
Nausea	yes/no	**Testicular tenderness**	yes/no
Anorexia	yes/no	**Body temperature at ED**	degrees of Celsius (°C)
Vomiting	yes/no	**-**	-
Bowel habit	normal/constipation/diarrhoea/ blood/mucus	**-**	-
Micturition	normal/frequent/pain/haematuria	***Laboratory tests (3)***	*Category*
Cough	yes/no	**C-reactive protein**	$mg \cdot l^{-1}$
Cold	yes/no	**Leucocyte count**	$E^{9} \cdot l^{-1}$
Beginning of menstrual period	yes/no	**Urine sample**	Normal/infection/ haematuria

Appendix 2: Follow-up data sheath used in the Study Group II.

MEDICAL HISTORY AND CLINICAL FINDINGS

Right lower quadrant pain	Yes/No
Rebound tenderness	Yes/No
Abnormal bowel sounds	Yes/No
Guarding	Yes/No
Migration of pain	Yes/No
Vomiting	Yes/No
Fever ≥ 37.5 °C	Yes/No

PAIN SCORES* (scores from 1 to 10)

Baseline	___
At 0.5 hours after the first dose	___
At 1 hour after the first dose	___
At 1.5 hours after the first dose	___
At 2 hours after the first dose	___
At 2.5 hours after the first dose	___
At 3 hours after the first dose	___
At 3.5 hours after the first dose	___

SURGICAL ASSESSMENT

ASSESSMENT BEFORE THE STUDY DRUG ADMINISTRATION

Primary diagnosis: appendicitis/NSAP**/other disease

Differential diagnosis: appendicitis/NSAP**/other disease

Abdominal guarding: yes/no

Provisional disposition: observation/operation

ASSESSMENT AT 1 HOUR AFTER THE FIRST STUDY DRUG ADMINISTRATION

Primary diagnosis: appendicitis/NSAP**/other disease

Differential diagnosis: appendicitis/NSAP**/other disease

Abdominal guarding: yes/no

Provisional disposition: observation/operation

ASSESSMENT AT 3 HOURS AFTER THE FIRST STUDY DRUG ADMINISTRATION

Primary diagnosis: appendicitis/NSAP**/other disease

Differential diagnosis: appendicitis/NSAP**/other disease

Abdominal guarding: yes/no

Provisional disposition: observation/operation

ASSESSMENT AT 6 HOURS AFTER THE FIRST STUDY DRUG ADMINISTRATION

Primary diagnosis: appendicitis/NSAP**/other disease

Differential diagnosis: appendicitis/NSAP**/other disease

Abdominal guarding: yes/no

Provisional disposition: observation/operation

ADVERSE EFFECTS

1 no 2 yes, specify_____

* Visual analogue scale (left end, no pain; right end, worst imaginable pain)

**NSAP=non-specific abdominal pain

Appendix 3: Follow-up data form used at the operation theatre.

THE OPERATING TIME (MIN)___ THE NURSES` TIME (MIN)___

THE ANAESTHESIA TIME (MIN)___

DISPOSABLE ITEMS USED AT SURGERY

_____

_____

_____

THE MACROSCOPIC APPEARANCE OF THE APPENDIX

normal/inflamed/perforated/abscessed

THE LOCALIZATION OF THE APPENDIX

normal/retrocaecal/subhepatic/pelvic/left-sided

BLADDER CATHETERIZATION

1 no 2 yes

THE OPERATIVE BLEEDING (ML)___

THE INTRAOPERATIVE COMPLICATIONS

1 no 2 yes, specify_____

THE ANAESTHETIC COMPLICATIONS

1 no 2 yes, specify_____

Appendix 4: Follow-up data form used in the post-anaesthesia care unit (PACU) and in the paediatric ward.

TIME IN PACU (MIN)___	LENGTH OF HOSPITAL STAY (D)___
POSTOPERATIVE PAIN*	
Pain scores 1 hour after surgery: at rest___	on cough___
Pain scores 2 hours after surgery: at rest___	on cough___
Pain scores 3 hours after surgery: at rest___	on cough___
Pain scores 4 hours after surgery: at rest___	on cough___
Pain scores 6 hours after surgery: at rest___	on cough___
Pain scores 12 hours after surgery: at rest___	on cough___
Pain scores 18 hours after surgery: at rest___	on cough___
Pain scores 24 hours after surgery: at rest___	on cough___
Pain scores 30 hours after surgery: at rest___	on cough___
Pain scores 36 hours after surgery: at rest___	on cough___
NUMBER OF OXYCODONE DOSES___	TOTAL OXYCODONE DOSE (MG)___
NUMBER OF KETOPROFEN DOSES___	TOTAL KETOPROFEN DOSE (MG)___
NAUSEA	VOMITING
1 no 2 yes___ times	1 no 2 yes___ times
SHOULDER PAIN	URINARY RETENTION
1 no 2 yes___ hours	1 no 2 yes
NORMAL DIET**___ hours	NORMAL WALK**___ hours

POSTOPERATIVE BODY TEMPERATURE (°C)	POSTOPERATIVE C-REACTIVE PROTEIN CONCENTRATION
1. postoperative day___(°C)	1. postoperative day___$mg \cdot l^{-1}$
2. postoperative day___(°C)	2. postoperative day___ $mg \cdot l^{-1}$
3. postoperative day___(°C)	3. postoperative day___ $mg \cdot l^{-1}$
POSTOPERATIVE INVESTIGATIONS	POSTOPERATIVE COMPLICATIONS
1 no 2 yes, specify_____	1 no 2 yes, specify_____

*Pain was determined by a visual analogue scale (VAS): 0, no pain; 10, worst possible pain.

**Determined by hours after the arrival in the paediatric ward.

Appendix 5: Follow-up questionnaire used after discharge.

DID YOUR CHILD HAVE PAIN AT THE SITE OF SURGERY?

1 no

2 mild pain___ days

3 moderate pain___ days

4 severe pain___ days

DID YOUR CHILD HAVE FEVER AT HOME?

1 no

2 fever (37.0-37.9 °C)___ days

3 fever (≥ 38 °C)___ days

DID YOUR CHILD HAVE OTHER SYMPTOMS?

1 no 2 nausea__ days 3 vomiting__days

4 diarrhoea___ days

DID YOUR CHILD NEED KETOPROFEN TABLETS?

1 no 2 yes___ tablets

WHEN DID YOUR CHILD RETURN TO NORMAL ACTIVITIES AFTER THE SURGERY?

Drink	immediately	after___ days
Eat	immediately	after___ days
Play	immediately	after___ days
Sleep	immediately	after___ days
Sport	immediately	after___ days
Went to school	immediately	after___ days

AFTER DISCHARGE DID YOU NEED TO CONTACT:

the hospital	1 no	2 call	3 visit
physician	1 no	2 call	3 visit

THE COSMETIC APPEARANCE OF THE SURGICAL WOUNDS (at 1 month after surgery)

fine/satisfactory/unsatisfactory

10. ORIGINAL PUBLICATIONS I-V

Kuopio University Publications D. Medical Sciences

D 355. Kukkonen, Jarmo. Terveydenhuollon vaikuttavuuden arviointi rutiinisti kerätyn tiedon pohjalta.
2005. 252 p. Acad. Diss.

D 356. Papp, Anthony. Experimental thermal injury: new methods in assessing tissue damage.
2005. 78 p. Acad. Diss.

D 357. Berg, Marja. CT angiography in the assessment of atherosclerotic carotid and renal arteries.
2005. 143 p. Acad. Diss.

D 358. Miettinen, Timo. Whiplash injuries in Finland: incidence, prognosis and predictive factors for the long-term outcome.
2005. 86 p. Acad. Diss.

D 359. Kotaniemi-Syrjänen, Anne. Wheezing requiring hospitalisation in infancy - outcome at early school age: viral aetiology of wheeze and predictive factors for outcome.
2005. 97 p. Acad. Diss.

D 360. Huopio, Jukka. Predicting fractures in middle-aged women.
2005. 86 p. Acad. Diss.

D 361. Gül, Mustafa. Cytotoxic and antifungal acetophenone-derived Mannich bases: effects on redox thiols and heat shock proteins.
2005. 68 p. Acad. Diss.

D 362. Virtanen, Jyrki. Homocysteine, folate and cardiovascular diseases.
2005. 65 p. Acad. Diss.

D 363. Tuomainen, Petri. Physical exercise in clinically healthy men and in patients with angiographically documented coronary artery disease with special referense to cardiac autonomic control and warm-up phenomenon.
2005. 125 p. Acad. Diss.

D 364. Lindgren, Annamarja. Cancer incidence in hypertensive patients.
2005. 94 p. Acad. Diss.

D 365. Töyry, Saara. Burnout and self-reported health among Finnish physicians.
2005. 102 p. Acad. Diss.

D 366. Haapalahti, Mila. Nutrition, gastrointestinal food hypersensitivity and functional gastrointestinal disorders in schoolchildren and adolescents.
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D 367. Lindi, Virpi. Role of the Human PPAR-γ2 Gene on Obesity, Insulin Resistance and Type 2 Diabetes.
2005. 102 p. Acad. Diss.

D 368. Penttilä, Karri. Evaluation of different biochemical methods to detect myocardial injury.
2005. 99 p. Acad. Diss.

D 369. Sipola, Petri. Magnetic resonance imaging in hypertrophic cardiomyopathy.
2005. 160 p. Acad. Diss.