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Hesselgard, Karin

2005

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*Citation for published version (APA):*

Hesselgard, K. (2005). *Postoperative Intrathecal Pain Treatment in Children*. [Doctoral Thesis (compilation), Neurosurgery]. Department of Clinical Neuroscience, Lund University.

*Total number of authors:*

1

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# POSTOPERATIVE INTRATHECAL PAIN TREATMENT IN CHILDREN

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© Karin Hesselgard  
ISSN 1652-8220  
ISBN 91-85439-91-6  
Printed in Sweden 2005  
Media Tryck, Lund

To my son Christofer and to my life companion

*Når man føler hvor lidet man når med sin flid,  
er det nyttigt at mindes at, Ting Tar Tid  
(Piet Hein)*

ANNARS BLIR TIDEN SÅ LÅNG.....

(LB/EÖ/KH, 2005)



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# PUBLICATIONS

This thesis is based on studies reported in the following papers, which are referred to in the text by Roman numerals.

- I Hesselgard K, Reinstrup P, Strömblad L-G, Undén J, Romner B.  
Selective dorsal rhizotomy and postoperative pain management: A world-wide survey.  
Pediatric Neurosurgery 2005: Submitted for publication
- II Hesselgard K, Strömblad L-G, Reinstrup P.  
Morphine with or without a local anaesthetic for postoperative intrathecal pain treatment after selective dorsal rhizotomy in children.  
Paediatric Anaesthesia 2001; 11: 75-79
- III Hesselgard K, Strömblad L-G, Romner B, Reinstrup P.  
Postoperative continuous intrathecal pain treatment in children after selective dorsal rhizotomy with bupivacaine and two different morphine doses.  
Paediatric Anaesthesia 2005: Accepted for publication
- IV Hesselgard K, Larsson S, Romner B, Strömblad L-G, Reinstrup P.  
Validity and Reliability of the Behavioural Observational Pain Scale (BOPS): for postoperative pain measuring in children aged 1-7.  
Pediatric Critical Care Medicine 2005: Submitted for publication

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# ABBREVIATIONS

<b>BOPS</b>	Behavioural Observational Pain Scale
<b>CAS</b>	The Coloured Analogue Scale
<b>CHEOPS</b>	Children's Hospital of Eastern Ontario Pain Scale
<b>CSF</b>	Cerebrospinal fluids
<b>DCUC</b>	Day surgery Care Unit for Children
<b>ECG</b>	Electrocardiogram
<b>ED</b>	Epidural
<b>EMG</b>	Electromyogram
<b>FPS-R</b>	Face Pain Scale-Revised
<b>HR</b>	Heart rate
<b>IASP</b>	International Association for Study in Pain
<b>IT</b>	Intrathecal
<b>i.v.</b>	Intravenous
<b>IQR</b>	Interquartile range
<b><math>\kappa_w</math></b>	Weighted kappa
<b>MAP</b>	Mean arterial blood pressure
<b>NICU</b>	Neurosurgical Intensive Care Unit
<b>NPCU</b>	Neurosurgical Postoperative Care Unit
<b>PCA</b>	Patient controlled analgesia
<b>PMHPAT</b>	The Princess Margaret Hospital Pain Assessment Tool
<b>PONV</b>	Postoperative Nausea and Vomiting
<b>RR</b>	Respiratory rate
<b><math>r_s</math></b>	Spearman rank order correlations coefficient
<b>SD</b>	Standard deviation
<b>SDR</b>	Selective Dorsal Rhizotomy
<b>SaO<sub>2</sub></b>	Oxygen saturation
<b>TPPPS</b>	The Toddler Preschooler Postoperative Pain scale
<b>WMW</b>	Wilcoxon Mann-Whitney

# ABSTRACT

Selective dorsal rhizotomy (SDR) is an effective operation method that successfully decreases the degree of spasticity with long lasting beneficial effects for children with spastic diplegia. Children undergoing SDR are postoperatively in severe pain, a pain related to both the extensive surgical exposure with multilevel laminectomy and the nerve root manipulation. To achieve optimal pain relief, pain measurement is a necessity in pain treatment, but it can be difficult in pre-school children. The purpose of this thesis is to evaluate and improve pain treatment for children after major spinal surgery and to develop a pain measurement tool to evaluate postoperative pain in young children.

The number of SDR procedures is unknown. No comprehensive worldwide survey of different centers' postoperative pain management after SDR has been made. The aim of **study I** was to estimate the extent of SDR surgery, evaluate operation techniques and to clarify different centers pain management after SDR. A questionnaire comprising 8 questions was sent to 59 centers. 44 (75%) of the centers responded and 33 of these constitute the material of the present study.

We sought to develop an optimal intrathecal (IT) pain treatment regime. In a prospective study (**study II**), two different IT regimes of pain treatment, continuous infusion versus intermittent, was evaluated with respect to analgesia and side-effects. 12 children (age 3.1 - 6.3 year), 6 in each group, received either intermittent IT morphine,  $5 \mu\text{g kg}^{-1}$  four times a day or continuous infusion of a mixture of bupivacaine,  $40 \mu\text{g kg}^{-1}\text{h}^{-1}$  and morphine  $0.6 \mu\text{g kg}^{-1}\text{h}^{-1}$ . We found that intrathecal continuous infusion of bupivacaine and morphine was superior to intermittent morphine in the pain treatment after selective dorsal rhizotomy operations.

To define an optimal dose of continuous IT morphine and bupivacaine to treat severe pain after SDR, 26 children (2.7 - 7.4 years old) were included (**study III**). In this study we compared two different concentrations of morphine  $0.4 \mu\text{g kg}^{-1}\text{h}^{-1}$  and  $0.6 \mu\text{g kg}^{-1}\text{h}^{-1}$  in a fixed dose of bupivacaine  $40 \mu\text{g kg}^{-1}\text{h}^{-1}$  with regard to the analgesic effect and surveyed if they differed in side-effects. The Behavioural Observational Pain Scale (BOPS) was used to evaluate pain. Continue IT pain treatment with  $0.6 \mu\text{g kg}^{-1}\text{h}^{-1}$  morphine and  $40 \mu\text{g kg}^{-1}\text{h}^{-1}$  bupivacaine provides safe and satisfactory analgesia after major spinal operations. This is furthered strengthened by the fact that adverse side-effects did not differ between the groups and was therefore not a drawback of the high-dose group.

Effective pain management in infants and children starts with routine evaluation of pain and a clear documentation. This requires measurement of pain intensity and pain relief with reliable, valid and clinically sensitive assessment tools. Observation of behaviour can be an acceptable alternative when valid self-report is not possible. We evaluated the validity and reliability of BOPS, as a postoperative pain measurement scale for children aged 1 - 7 years (**study IV**). The scale assess three variables of pain behaviours; facial expression, verbalization and body position. With BOPS the nurses can evaluate and document pain with high reliability and validity and thereby improve the postoperative pain treatment in preschool children. The simple scoring system makes BOPS easy to incorporate in a postoperative unit.



# INTRODUCTION AND BACKGROUND

Postoperative pain in children has been under-treated compared to treatment of adults. It is not always obligatory that children receive adequate analgesia postoperatively. One of the reasons could be the difficulty in assessing pain especially in young children (Schechter, 1989, Karling et al., 2002), or that pre-school children may be unable to describe physical discomfort and pain intensity in the same way as adults, caused by general lack of verbal and cognitive skills (Merkel et al., 1997, Gauvain-Piquard et al., 1999; McGrath & Unruh, 2001). The standards for concluding that an infant is in pain are substantially more severe than those used for verbal adults (Anand & Craig, 1996). Another reason could be that pain treatment may not be given despite nursing notes, observation showing evidence of pain or physical discomfort and the existence of prescribed analgesics, depending on insufficient knowledge and fear of side-effects from medications (Jonston et al., 1992; Elander et al., 1993; Robertson J, 1993; Elander, 1995; Cummings et al., 1996; Rømsing et al., 1996,).

Today there is an increasing awareness among caregivers that pain in children should be prevented and treated but it is not yet optimal (van Dijk et al., 2000; Karling et al., 2002). The caregiver's attitude to pain registration and thereby pain management does still constitute an impediment to optimal treatment. Pain assessment ought to be incorporated into daily care as a routine as it would then increase the attention to children's pain (Jylli & Lundeberg, 2001). Studies made on children with postoperative pain prove that an optimal pain treatment includes both pain assessments with validated pain measurements and an adequate pain treatment (Berde, 1989; Cohen, 1993; Morton, 1997; Glass 1998, Karling et al., 2002). Hence, We have to increase our knowledge about how children express their pain and how we can treat children's pain in an optimal way. One of the problems is to treat pain after surgery.

## SELECTIVE DORSAL RHIZOTOMY

Spastic diplegia due to cerebral palsy (CP) is characterized by decreased range of motion and increased muscle tone resulting in impaired motor function. Selective dorsal rhizotomy (SDR) is an effective surgical method that successfully decreases the degree of spasticity with lasting beneficial effects for these children (Subramanian et al., 1998; Park, 2000; Kim et al., 2001; Mittal et al., 2002; Salame et al., 2003; Westbom et al., 2003). SDR substantially changes the muscle tonus and thereby reduces the spasticity in CP. There exists no other treatment today which affects severe spasticity as quickly and efficiently as SDR. Furthermore, this is the

only treatment that can permanently reduce CP spasticity (Park, 2000; Kim et al., 2001; Westbom et al., 2003).

## HISTORICAL DEVELOPMENT

Sherrington laid the groundwork in 1898 for our current understanding of mono-synaptic stretch reflex and the role of descending inhibitory tracts on the spinal cord. The discovery of the facilitator role of posterior spinal nerve roots in cats was the key to subsequent use of dorsal rhizotomy in spastic human being. He found that divisions of posterior spinal nerve roots could eliminate hypertonus (Sherrington, 1898). But, it is Foerster (1913) who should have the credit for the use of posterior rhizotomy in children with spastic diplegia. 88 patients with congenital spastic paraplegia underwent this surgery. He sectioned the entire dorsal spinal roots from L<sub>2</sub> to S<sub>1-2</sub>, sparing L<sub>4</sub> or L<sub>5</sub> in an attempt to preserve quadriceps tone for standing. He provided a description of improvement in these children's sitting and walking abilities. Unfortunately the procedure was only partially successful due to sensory side effects. However, his achievement is fundamental to the further development to present days SDR.

The next evolution was done by Fasano et al. in Italy. They developed the intraoperative electrical stimulation and created the term "Functional posterior rhizotomy". They noted that the reflex circuits within a rootlet not only had segmental effects. In patients with spasticity the stimulation of certain rootlets produced continued muscular contractions which sometimes triggered muscle activity outside the rootlets spinal segment. Fasano et al. saved the rootlets when inhibition was noted during high frequency stimulation and sectioned the rootlets which were considered abnormal (Fasano et al., 1978).

Some years later Peacock et al. modified this operation technique. They changed the site of the surgery from operating at the level of the conus medullaris to the cauda equina where each posterior nerve root could be identified. This was done to avoid bowel and bladder complications (Peacock & Arens, 1982). A change in the technique for intraoperative evaluation was developed in 1987. They performed simultaneous recording of electromyogram (EMG) activity from 10 muscle groups with supplement of visual observations and palpation (Peacock et al., 1990). This is the operation technique we use at our neurosurgical department in Lund.

There have been described some other operation technique after this. One is described by Park (1995). He preferred a two-level laminectomy which is carried out in several steps using ultrasound. He starts with a keyhole or a one-level laminectomy, at L<sub>1</sub> to expose the conus. Then the laminectomy is extended to a two-level laminectomy down to L<sub>2</sub>.

## PAIN TREATMENT AFTER SDR

An effective pain treatment is mandatory after SDR surgery. These patients have not only post-incisional pain from the lumbar laminotomy but in addition dysaesthesia of the lower extremities due to manipulation of the nerve rootlets (Peacock & Arens, 1982; Abbott, 1992; Lawhorn, 1994; Sparkes et al., 1989; Geiduschek et al., 1994; Dews et al., 1996; Malviya et al., 1999). The surgery is only a part of the spasticity treatment. To ensure maximum physical progress following SDR, intensive and consistent postoperative physical therapy is essential (Peacock et al., 1987; Abbott et al., 1989, Kim et al., 2001). Most children require physical therapy five times a week for the first 3-6 months (Kim et al., 2001). In order to facilitate the start of this treatment, it is vital that the children do not have any negative feelings with respect to the treating institution.

The first study dealing with postoperative pain treatment after SDR was published 1989. An epidural (ED) injection of morphine combined with bupivacaine or normal saline was given prior to the surgical closure resulting in a sufficient pain management (Sparkes et al., 1989). During the last two decades, various pain treatment strategies have been published for children undergoing SDR. Both ED (Lawhorn et al., 1994; Malviya et al., 1999) and IT opioids (Harris et al., 1991; Dews et al., 1996) have been reported to provide effective and safe pain therapy. Continuous i.v. morphine has been reported as an option (Geiduschek et al., 1994).

## INTRATHECAL PAIN MANAGEMENT

### HISTORIC PERSPECTIVE

IT pain treatment was devised more than 100 years ago. The method to relieve pain by subarachnoid medication is primarily attributed to Corning. In 1885 he injected cocaine IT in two patients, obtaining pain relief for few hours. He called this "local medication of the spinal cord" (Corning, 1885). In 1899 Tuffier administered cocaine subarachnoidally to relieve pain in a young man suffering a leg sarcoma. Tuffier found that the effect, although temporary, were successful (Tuffier, 1899). However, it was first in 1931 that neurolytic agent (alcohol) was injected intrathecally for relief of intractable pain (Dogliotti, 1931). The importance of the method was rapidly appreciated and an increasing number of reports of its use followed, although sometimes incidence of complications arises as a deterrent (Hay, 1962). Mahler suggested that phenol in glycerine was more easily manageable than alcohol and produced better pain relief (Maher, 1955). This management has since achieved widespread use (Bonica, 1958; Maher, 1960; Tank et al., 1963; McEwen et al., 1965).

It was not until 1979 that the first human administration of intrathecal morphine was reported by Wang. He reported the success of intrathecal morphine to relieve

unbearable malignant pain in 8 patients. He pointed out that intrathecally injected opioids are actually administered in close proximity to the opiate receptor site i.e. at the place of effectiveness (Wang et al. 1979). First five years later Jones et al. presented a study, which was undertaken to determine if IT morphine gave adequate and prolonged analgesia in children. They also tried to determine an appropriate dose and to assess complications.

Since then there has been published many different IT pain treatment strategies for children during the last two decades. These studies of IT pain management report a single dose of morphine (Dalens & Tanguy, 1988; Tobias et al., 1990; Nichols et al, 1993; Arai et al., 1996; Goodarzi, 1998; Goodarzi & Narasimhan, 2001; Suominen et al., 2004) or a single dose of morphine with bupivacaine (Uguralp et al. 2002) given preoperatively. Other authors describe IT injection of morphine at the end of the operation followed by i.v. morphine (Harris et al., 1991; Kerchel et al., 1995; Dews et al., 1996; Gall et al., 2001) or a single IT injection of fentanyl followed by infusion of fentanyl i.v. (Pirat et al., 2002). The first description of continuous IT pain management postoperatively in children was a case report by Tobias (2000b). One patient received continuous fentanyl and the other bupivacaine plus sufentanil and in both cases an adequate pain relief was obtained. At our department we have used IT pain management since 1993, initially as intermittent morphine doses every 6<sup>th</sup> hour.

## SPINAL SPACE

Drugs injected into the ED space can block or modulate afferent impulses and cord processing of those impulses and most probably represents the same mechanism which operates when drugs are injected IT. There are some important differences between ED and IT spaces. The ED space is vascular and contains fat. A large proportion of drugs given epidurally are taken up by extradural fat and vascular absorption and lesser drugs are available for neuronal blocking (Bernards, 1998; McQuay & Moore, 1999). Moreover the ED tissues react to foreign bodies more than the IT space. IT catheters are much less prone to blockage compared to ED catheters which often become walled off by fibrous tissue within days to weeks (McQuay & Moore, 1999).

## LOCAL ANAESTHETIC

Local anaesthetic can be designated due to their chemical property; ester-anaesthetic and amid-anaesthetic. The ester drugs have short half-lives and they tend to hydrolyse spontaneously, especially on warming. The amides may be stored for longer periods without losing potency and are not heat sensitive unless mixed with glucose (Wildsmith & Kendeall, 2001; Lönnqvist, 2001). In children amid anaesthetic is mainly used, as prilocaine is not suitable due to the risk of methemoglobinemia. Postoperative analgesia is often the primary justification for

regional anaesthesia in children. Bupivacaine, with a slow onset and a long acting local anaesthetic, is the most commonly use local anaesthetic in this age group (Lönqvist, 2001; Gunter, 2002).

Studies have shown that the dura mater is permeable and ED and IT given local anaesthetics act at precisely the same sites. These sites are the spinal roots, mixed spinal nerves and the surface of the spinal cord to a depth of 1 mm or more. The depth depends on the lipid solubility of the anaesthetic. With both ED and IT injection the local anaesthetic drug enters the CSF and remains there until taken up by the lipids of the cord and spinal roots or until “washed out” by vascular uptake into the body vessels of the region. A hyperbaric drug diffuses across the dura with less ease than drugs of hypobaric weight (McQuay & Moore, 1999). When the specific gravity of solution being injecting is known, its distribution can be controlled, a hyperbaric solution descends in the subarachnoid space. Another important factor influencing the level of block is the drugs volume and concentration (Greene 1969).

The myelin sheath presents a significant barrier to drug diffusion. Small unmyelinated fibres such as C fibres are blocked more rapidly by most local anaesthetic drugs than large diameter fibres that are usually more myelinated. This difference in rate of blockage may be manipulated clinically with the aim of producing analgesia with relatively little motor blockade because skeletal muscle is innervated by large heavily myelinated fibres. Weak solutions as bupivacaine 0.125% are employed with the aim of producing analgesia with relative little motor blockade (Wildsmith & Kendeall, 2001).

#### ADVERSE EFFECTS OF LOCAL ANAESTHETICS

Local anaesthetic toxicity is extremely rare in infants and children, but, seizures, dysrhythmia, cardiovascular collapse, and transient neuropathic symptoms have been reported (Wildsmith & Kendeall, 2001; Gunter, 2002). However, serious side-effects as systemic toxicity arise by an inadvertent intravascular injection and it may also result from absolute over dosage (Lönqvist, 2001; Wildsmith & Kendeall, 2001). Local anaesthetics are bound to proteins in varying degrees (Mogensen, 1995; Wildsmith & Kendeall, 2001; Lönqvist, 2001; Gunter, 2002). Infants and children may be at increased risk from local anaesthetics compared with adults, as larger volumes of local anaesthetics are used in infants and children (Gunter, 2002). Metabolism and elimination of local anaesthetics can be delayed in children < 1 years of age, which also have decreased plasma concentrations of alpha (1)-acid glycoprotein, leading to increased concentrations of unbound bupivacaine (Lönqvist, 2001; Gunter, 2002). There is no specific antagonist to bupivacaine (McQuay & Moore, 1999).



Cardiovascular changes related to spinal anaesthesia are generally less frequent in children than adults. Minimal changes have been reported followed high thoracic spinal anaesthesia in infants. However, in patients over 5 years of age, the sympathetic block induced by spinal anaesthesia can result in hypotension and bradycardia (Tobias, 2000a; Lönnqvist 2001). Respiratory effects have generally only occurred with a high sensory and motor level above the Th<sub>1</sub> dermatome (Tobias, 2000a). Normal neurologic function should be demonstrated before use of ED or IT local anaesthetic in order to correctly distinguish and interpret complications. Postoperative weakness or neurologic changes should not be attribute to the ED or IT catheter but should immediately be evaluated because of a potential postoperative bleeding with spinal cord compromise (Lönnqvist, 2001; Tobias, 2004). Beside this, the greatest concern of neuraxial techniques after spinal surgery is the potential risk of infection related to the catheter. There are no reports of infection complications in children related to the regional anaesthetic technique but clinical experience has demonstrate the efficacy of tunnelled catheters in prolonged use (Tobias, 2004).

## OPIOIDS

There has been an increasing understanding of the mechanism of action of opioids in the last decades. There are three groups of endogenous opioids in the brain and spinal cord; endorphin, enkephalin, dynorphin. The preferential endogenous opioid bounded for each opioid receptor;  $\beta$ -endorphin bound to  $\mu$  ( $\mu$ ) receptor, encephalin to  $\delta$  ( $\delta$ ) and dynorphin to  $\kappa$  ( $\kappa$ ). Morphine acts mainly on the  $\mu$  receptor but also affects  $\delta$  and  $\kappa$  receptors. If morphine should achieve pain relief it is a necessity to have opioid receptors at the nerve tissues (Twycross, 1999). In recent years, there has been a great interest in the use of different opioids by ED or IT management of pain (Power & Smith, 2001). One explanation for the pharmacologic differences between opioids lies in the fact that opioids differ in their ability to reach opioid receptors. Especially for spinally administrated opioids, ED or IT, the net analgesic effect is a result of numerous process which must occur prior to activation of the opioid receptors (Bernards, 1998). After injection of opioid into the cerebrospinal fluid (CSF), the drug is taken up in the region of the substantia gelatinosa within the dorsal horn. It is thought that opioids act predominantly on the presynaptic receptors (McQuay & Moore, 1999; Power & Smith, 2001). How the opioids complete these steps is largely dependant on its physico-chemical properties (Bernards, 1998; McQuay & Moore, 1999). The uptake into the dorsal horn depends on how the drugs diffuse through the CSF and penetrate the spinal cord. The distribution of intrathecally administrated opioids between the CSF (water) and fat (nervous structures, membranes) phase is determined by the hydro-/lipophilicity and the magnitude of the ionized fraction. As has been shown for opioid diffusion through brain tissue, increasing lipid solubility actually decreases the ability of an opioid to diffuse into the spinal cord and increases the

likelihood that the drug will preferentially end up in the white matter instead of the grey matter (Bernards, 1998; McQuay & Moore, 1999; Power & Smith, 2001).

Furthermore, any opioid administered anywhere in the body will produce analgesia as the drug ultimately reaches the plasma and is redistributed to the brain's opioid receptors (Bernards, 1998; Twycross, 1999).

#### LIPID SOLUTION

Fentanyl, alfentanil and sufentanil are highly lipid-soluble drugs and they have a more rapid onset and a shorter duration of action with minimal residual CSF concentration (Bernards, 1998; McQuay & Moore, 1999; Power & Smith, 2001). Fentanyl was suggested as an ideal drug for spinal administration in the mid-eighties. Several investigators questioned the conventional wisdom with continuous fentanyl (+ local anaesthetic). They demonstrated that the infusion produced the same pain relief, side-effects, required the same fentanyl dose and produced the same fentanyl plasma concentrations irrespective of either i.v. or ED infusion. Continuous fentanyl infusion therefore appears to produce analgesia by systemic uptake and redistribution to the brain (Bernards, 1998; McQuay & Moore, 1999).

#### HYDROPHILIC SOLUTION

The most widely used opioid in pain management of acute postoperative pain in children is morphine (Lundberg & Lönnqvist, 2004). Morphine is a  $\mu$  agonist and a hydrophilic drug. Its slow onset of action after IT injection coincides with a late peak concentration in CSF. The highly water soluble drug with large ionized fraction will remain in CSF and ascend rostrally (Bernards, 1998; McQuay & Moore, 1999; Power & Smith, 2001). Morphine clearly produces analgesia by spinal mechanism if administered either ED or IT and it should probably be considered the "Golden Standard" for spinal administered opioids (Bernards, 1998).

The daily dose of morphine via epidural route is 1/10 of oral dose and the intrathecally dose is 1/10 of the epidural dose (Colett, 2001). The distribution of morphine might be considered similar throughout the neonatal period, infancy, childhood and adult life. It seems reasonable to consider that infants from two months of age have a half-life and a clearance rate of morphine similar to adults (Kart et al., 1997a). Usually body weight is used to calculate the morphine dose; other criteria as age, height and body surface area are also used. Morphine can be considered safe to use in infants and children (Kart et al., 1997b).

#### ADVERSE EFFECTS OF OPIOIDS

Adverse effects of morphine vary according to doses, whether the opioids are given ED or IT and whether usage is acute or chronic (Twycross, 1999). The

side's effects observed in infants and children are similar to those who are observed in adults (Kart et al., 1997b). Opioids are associated with many negative pharmacodynamics effects. All opioids cause nausea and vomiting as they stimulate the chemoreceptor trigger zone in the area postrema which is influenced by chemicals in both blood and CSF (Alexander, 2001). In the cardiovascular system most opioids cause bradycardia (Alexander, 2001) and hypotension (Twycross, 1999). The opioids' effect on gastrointestinal tract causing constipation and the effect on the urogenital tract is urinary retention. At the respiratory system, opioid depress ventilation by reducing the carbon dioxide sensitive and hypoxic drive and causing disorder in the rhythm of the ventilatory pattern. Opioids stimulate histamine release and pruritus (Twycross, 1999; Alexander, 2001). Particular pruritus, vomiting and nausea are frequent adverse effects associated with use of opioids in children. The adverse effects should be dealt with promptly (Lundeberg & Lönnqvist, 2001, Tobias 2004). Neuraxial opioids, particularly morphine, can result in rostral spread resulting in delayed respiratory depression (Tobias, 2004). Respirator depression may well occur if the underlying pain is suddenly relieved and the dose of morphine is not reduce (Twycross, 1999). Naloxone is a specific antagonist at all three opioid receptors (Twycross, 1999; Alexander, 2001).

#### COMBINATION OF LOCAL ANAESTHETICS AND OPIOIDS

The use of spinal combinations of local anaesthetic and opioids promises the greatest clinical benefit. At first it can produce satisfactory analgesia. Studies support what have been observed clinically, that small doses of local anaesthetic and opioid gives pain relief, doses which might be regarded as homeopathic for either drug independently. The mechanism of the synergism is unknown. It may be that the local anaesthetic, by reducing the afferent input, is moving the opioid dose-response to the right. (McQuay & Moore, 1999). Another benefit with a combination of a low dose local anaesthetic and morphine is to prevent development of tachyphylaxis (acute tolerance). Tachyphylaxis has been demonstrated with the use of all local anaesthetics and develops fastest with repeated administration of lidocaine (Mogensen, 1995; Choi et al 1997). The underlying mechanism to tachyphylaxis still remains unknown. It can depend on a decreased diffusion of the local anaesthetic from the epidural space to their binding sites at the sodium channel related to a decrease of pH, a perineural oedema, an increased protein binding or change in distribution of the local anaesthetic. It can also depend on increased clearance from the epidural space caused by increased blood flow, decreased protein binding or local metabolism (Mogensen, 1995). Lipfert et al. (1989) and Choi et al. (1997) found that tachyphylaxis due to local anaesthetics does not result from reduced drug effectiveness at the nerve itself. Accelerated clearance of local anaesthetics from the site of their action implies the possibility of local vasodilatation at the injected site.

Generally, lower doses of morphine should be used if bupivacaine is administered concurrently (Twycross, 1999). One has then to look at the risk:benefit ratio. It is not justifiable in itself to administer drugs ED or IT only to produce analgesia. Spinal route can only be rationalized if it results in equal or greater pain relief when the magnitudes of adverse effects are less than using the conventional route (Bernards, 1998; McQuay & Moore, 1999; Twycross, 1999).

## PAIN MEASUREMENT

Effective pain management in infants and children starts with routine evaluation of pain and a clear documentation. This requires measurement of pain intensity and pain relief with reliable, valid and clinically sensitive assessment tools (Johnston, 1998; Larsson, 1999; McGrath & Unruh, 1999; Merkel & Malvia 2000; American Academy, 2001). In a recent Swedish nationwide study, pain assessment was performed in only 43% of all postoperative units for children and pain measurements with a validated pain scale were less frequent (Karling et al., 2002). General pain assessment tools in children can be categorized as behavioural observation, self-report and physiologic instrument (McGrath & Unruh, 1999; Kain et al, 2002).

### DEFINITION OF PAIN

The definition of pain according to IASP (International Association for Study in Pain) is *“an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”* This is followed by *“Pain is always subjective. Each individual learns the application of the word through experiences related to injure in early life”*. (Merskey & Bogduk, 1994). Anand and Craig add that the definition of pain challenges our understanding of the matter because it *“does not apply to living organisms that are incapable of self-report. This includes newborn, preverbal children, mentally retard, comatose or verbally handicapped individuals. Because self-report may be absent or a faulty source of inference, nonverbal behavioural information is often needed and used for pain assessment”* (Anand & Craig, 1996a).

### PAIN MEASUREMENT

Assessment is a much broader concept which should encompass the measurement of the interplay of different factors on the total experience of pain. Measurement refers to the application of a metric scale to a specific aspect, usually intensity of pain. Measurement in this correlation is like using a scale to determine pain. (McGrath & Unruh, 1999).

Reliability and validity are two important criteria for evaluating a quantitative instrument. In interrater reliability two trained observers are watching the event at the same time and independently assessing data according to the instrument instructions. The data can then be used to measure agreement between observers (Johnston, 1998; Polit & Beck, 2004). In pain measurements for children the focus has been on interrater reliability (Johnston, 1998; McGrath & Unruh, 1999). It is important as it provides dependable and trustworthy pain ratings regardless of the time of testing, the age or gender of the child and who administers the measure to the child (McGrath et al., 1996). Validity is the degree to which an instrument measures what it is supposed to measure (Johnston, 1998; McGrath & Unruh, 1999). The instrument must measure the child's pain so that change in pain ratings reflects meaningful differences in pain experience (McGrath et al., 1996). In concurrent validity a new scale and a standard measure is used at the same point in time to see if they correlate on the present criterion (pain) (Johnston, 1998; Polit & Beck, 2004). Construct validity has frequently been used in child pain measurement as it refers to any evidence that adds to the believability of the measures (McGrath & Unruh, 1999). In construct validity the instrument's ability to measure the concept of interest (pain) is tested by comparison with external variables related to the construct (Johnston, 1998; Polit & Beck, 2004). Systemic decreases in a pain measure after analgesic administration would suggest construct validity of the scale to measure pain (McGrath & Unruh, 1999).

The utility and versatility of a measure refers to its usefulness. One aspect of utility is the ease of use. A measure that requires a trained observer is less useful than a reliable and valid measure that can be carried out by anyone in a few seconds. Versatile measures have the advantage of being used in several different situations, e.g. across a wide age range or both in acute and chronic pain (McGrath & Unruh, 1999).

## BEHAVIOURAL MEASUREMENT

Preschool children or children who have cognitive and verbal deficits can be unable to describe their feeling of pain or physical discomfort (McGrath 1985; Stevens, 1998; McGrath, 1998; Guavain-Piquard et al., 1999; American Academic, 2001, McGrath & Unruh, 1999; Kain et al., 2002). Observations of behaviour are an acceptable alternative when valid self-report is not possible. This is a very useful measure and indicator of pain in children and is the primary way to assess pain in children when they are unable to provide a self assessment (Anand & Craig, 1996a; McGrath & Unruh, 1999). Even in neonatal units, intensive care and in the recovery room it is a valuable assessment tool (Guavain-Piquard et al., 1999). However, there is the ever-present challenge of distinguishing behaviour due to other forms of distress, such as hunger, anxiety or thirst, from behaviour due to pain (McGrath & Unruh, 1999). When children are recovering from anaesthesia and in the state of easy arousal it is difficult for them to self assess. It is important

that the person who measures the pain has knowledge of factors that can influence the scoring in a postoperative- or intensive care unit. Before the children are fully awake they can be restless and factors like excitement, agitation, or sedation can influence (Sutters et al., 1995; Bennie et al., 1998; Bolton et al., 2002).

Behavioural indicators such as facial expression, crying and body movements are used to estimate the presence pain and intensity in nonverbal or preverbal children (McGrath et al., 1985; McGrath, 1998, Stevens, 1998; McGrath & Unruh, 1999; Merkel & Malviya, 2000; Jylli, 2001). Previous studies have shown a strong correlation between these signs and pain (McGrath et al., 1985; Tarbell et al., 1992; Robertson, 1993; Merkel et al., 1997; Schade et al., 1996; Suraseranivongse et al., 2001).

There are many behavioural observational pain scales, for different kind of pain, which have been developed during the last two decade. The most widely used scale is the Childrens Hospital of Eastern Ontario Pain Scale (CHEOPS) for postoperative pain measurement in children age 1-7 year (McGrath et al., 1985). Other postoperative pain scales are; The Toddler Preschooler Postoperative Pain scale (TPPPS) for children age of 1-5 years (Tarbell et al., 1992), FLACC for children age of 2 month to 7 years (Merkel et al., 1997) and The Objective Pain scale (OPS) for children age of 8 month to 13 years (Norden et al., 1991). The COMFORT Scale was developed for pediatric intensive care patients age of 0-18 years (Ambuel et al., 1992) and for children with cancer pain the Douleur Échelle Gustav-Rossy (DEGR) was developed (Gauvain-Piquard et al., 1987, 1999). Some behavioural pain scales can be clinically difficult to use because of the complexity of the instrument (Tyler et al., 1993; Merkel et al., 1997; Voepel-Lewis et al., 2002) and there is a growing need for legal and simple pain evaluations instruments which can be incorporated into daily care (Larsson, 1999; Karling et al., 2002, Voepel-Lewis et al., 2002).

## SELF-REPORT OF PAIN

Self-report to estimate pain is the best way to assess pain and should be considered as “gold standard”. However, self-report can only be used in children old enough and cognitively competent to express and quantify pain (Johnston, 1998; McGrath & Unruh, 1999; American Academy, 2001). It is important to be sure that children are competent to provide information before their reports are accepted, especial in children between 3 - 7 years of age (American Academy, 2001). Also self-report measurement by verbal children can be hampered by several factors. Young children have relatively decreased cognitive ability to understand what is being asked of them in pain measurement and they may have difficult in articulating descriptions of their pain (McGrath & Unruh, 1999). The selection of self-report scales depends on the purpose, the category of pain and the age or stage of the child’s development (Champion et al., 1998).

In very young children (3-4 years) the self-report scale should be simple with a maximum of up to five options (Morton, 1997; Champion et al., 1998; Jylli, 2001). Hester's Poker-chip tool has been extensively tested and is validated for children as young as 4 years of age (Hester, 1979). Both sensory and motor responses are required in selecting the concept of "pieces" or "hurt". Therefore, the application of self-report scales is limited to children who can understand the objectives and descriptors of this technique (Kain et al., 2002).

Several facial scales have been developed. These scales include a series of faces, varying in emotional distress between "no pain" with a happy face and "worst pain" with a sad faces (Chambers & Craig, 1998, Champion et al., 1998, Jylli, 2001). Younger children may think that they have to choose the happiest face and do not relate the face to their own pain experience. Other select the extreme pain face rather than mid-range values (Morton, 1997; Chambers & Craig, 1998; Champion et al., 1998; Jylli, 2001). A well reputed face scale with no smiles or tears, the Face Pain Scale-Revised (FPS-R), has found to be useful in children over four years of age (Hicks et al., 2001).

Visual analogue scale can be used by children from five years of age. It has been discussed if the scale should be used horizontally or vertically (Champion et al., 1998; McGrath & Unruh, 1999). The Coloured Analogue Scale (CAS) is presented vertically, the colour being more intense at the worst pain, and it can be used for children 5-16 years (McGrath et al., 1996). The traditional Visual Analogue scale (VAS), a 10 cm length, is a horizontal scale with anchors indicating a continuum from no pain to worst pain at each end, the scale can be used in children from the age of six upwards (Jylli, 2001).

# AIMS

The overall aim of this thesis was to improve pain treatment for children after major spinal surgery.

The specific aims were as follows:

- I To worldwide estimate the extent of SDR surgery, evaluate operation techniques and to clarify different centers' pain management after SDR.
- II To compare intermittent IT morphine  $5 \mu\text{g}\cdot\text{kg}^{-1}$  four times a day with continuous infusion of a mixture of morphine  $0.6 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  and bupivacaine  $40 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  with regard to the analgesic effect and to examine if they differed in side-effects.
- III To compare two continuous IT infusions with different amount of morphine,  $0.4 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  and  $0.6 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  in fixed amount of bupivacaine  $40 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  with regard to the analgesic effect and examine if they differed in side-effects.
- IV To evaluate the validity and reliability of a behavioural observational pain scale, the BOPS, a simple pain evaluation instrument for postoperative pain in children aged 1-7 years.



# MATERIAL AND METHODS

This thesis is based on four publications (study **I-IV**). The designs of the studies included in this thesis are experimental (study **II, III**) and non experimental (study **I, IV**). The local Ethics Committee of Lund University Hospital approved the studies.

## SAMPLES AND SETTINGS

Participations were voluntary and confidentiality was guaranteed. All participants in **study II** and **IV** were given oral and written information about the study. The child was excluded if parent and child could not speak and read Swedish. In **study IV** children with known development delay and children who received pain relief with continuous infusion of analgesics were excluded. **Study III** was a retrospective investigation and participation was announced in the daily press.

### STUDY I

59 possibly centers worldwide believed to perform SDR was forwarded a questionnaire regarding operation techniques and pain treatment. 33 centers constitute the study material of the present study

### STUDY II

A prospective study was performed between January 1997 and September 1999. Twelve children aged range 3.1 - 6.3 year ( $4.41 \pm 0.97$ ) undergoing SDR were included. The children were postoperatively observed at the Neurosurgical Intensive Care Unit (NICU), Lund University Hospital, where the nurses were familiar with the use of IT pain management. The children was randomized to receive either injections of intermittent morphine ( $n = 6$ ) or infusion with continues morphine/bupivacaine IT ( $n = 6$ ) delivered by a Pharmacia Deltec® pump.

### STUDY III

A retrospective study with prospective collected data was performed between February 1998 to December 2003. Twenty-six children aged 2.7 - 7.4 year ( $4.5 \pm 1.1$ ) undergoing SDR were included. The children were postoperatively observed at NICU, Lund University Hospital where the nurses were familiar with the use of continuous IT opioid/bupivacaine infusion. Postoperatively 11 children were treated with IT infusion of morphine  $0.4 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  and bupivacaine  $40 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$

(low-dose group) and 15 with IT infusion of morphine  $0.6 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  and bupivacaine  $40 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  (high-dose group) delivered by a Pharmacia Deltec® pump.

## STUDY IV

A prospective study was performed between September 2003 and April 2004. Seventy-six children 1.1 - 7.7 years ( $4.5 \pm 1.8$ ), ASA I - II, were consecutively included in the study. The children were undergoing different elective surgery (Table 2) and were studied either in the Day surgery Care Unit for Children (DCUC) or the Neurosurgical Postoperative Care Unit (NPCU) at Lund University Hospital. The study was divided in three part; interrater reliability, concurrent validity and construct validity.

## MEASUREMENTS

### QUESTIONNAIRE

In **study I** a questionnaire based on 8 questions concerning SDR treatment was used. The questions posed regarded operation technique, frequency of SDR surgery, postoperative pain management; type of pain treatment, analgesics administered and, finally, duration and evaluation of pain treatment.

### BEHAVIOURAL OBSERVATIONAL PAIN SCALE (BOPS)

In **study II** and **III** the BOPS (Fig. 1) was selected for pain measurement as the staff at the NICU was familiar to use it. In 1996 at NICU, Lund University Hospital, Sweden, BOPS, was developed for nurses and physicians to identify, evaluate and document pain. It was important that the pain scale was simple, clear and easy to use for the caregivers. The scale was developed as a simplified hybrid between two well known behavioural pain scales, the Princess Margaret Hospital Pain Assessment Tool, PMHPAT, (Robertson, 1993) and the Children's Hospital of Eastern Ontario Pain Scale, CHEOPS (McGrath et al., 1985). The score in BOPS is derived by assessing three variables indicative for children in pain; facial expression, vocalization and body movements. Each of these variables was allocated in three grades 0, 1 or 2. The sum of these variables in BOPS will be between 0 and 6 points. After clinical experience and looking at how the score was constructed a decision was made that scores  $> 2$  point should lead to pain relief treatment if i.e. fear, discomfort or parent separation etc could be excluded as obvious reasons. In **study IV** the scale was reliability and validity tested. BOPS was used in Swedish language during the studies (Fig 2).

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BOPS (Behavioural Observation Pain Scale)

Score	Facial expression	Verbalization	Body position
<b>0</b>	Neutral/positive smiling, composed	Normal conversation laugh, crow	Inactive, laying relaxed with all extremities or sitting, walking
<b>1</b>	Negative facial expression and /or concerned	Completely quiet or sobbing and/or complaining but not because of pain	Restless movements, shifting fashion and/or touching wound or wound area
<b>2</b>	Negative facial expression grimace, distorted	Crying, screaming and/or complains about pain	Lying rigid and/or drawn up with arms and legs to the body

The score is composed of three variables which indicate pain in children. Each of these variables has three grades 0, 1 or 2. By scoring each variable and adding the scores, the sum of BOPS score will be between 0 and 6. Pain measurements performed every three hours. Analgesic effect is evaluated 15-20 minutes after intravenous administration or 30-45 minutes after oral / rectal administration. Score > 2 should lead to an analgesic consequence as other factors are not obviously apparent such as fear, discomfort, parent separation etc

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**Figure 1.** Behavioural Observational Pain Scale (BOPS) which includes the accompanying explanation text. Left column is the score. The next three columns facial expression, verbalization and body position are the items used for the pain evaluation.

BOPS (Behavioural Observation Pain Scale)

Poäng	Ansiktsuttryck	Verbalisering	Kroppsställning
0	Neutral/positiv mimik lugn, samlad	Normal konversation skrattar, jollarar	Inaktiv, ligger avslappnad med alla extremiteter eller sitter, går
1	Negativ mimik, spänt ansiktsuttryck	Helt tyst eller jämrar, snyftar och/eller klagar men ej över smärta	Rör sig oroligt, skiftande kroppsställning och/eller rör vid sårområdet
2	Negativ mimik, grimaserar, förvridet ansikte	Gråter högt och/eller anger smärta	Stel spänd ställning och/eller sammandragning av armar/ben mot kroppen

Skalan består av tre variabler som indikerar smärta hos barnet. Varje variabel har tre grader 0, 1 eller 2. Genom att poängvärdera varje variabel och lägga tillsammans poängen blir summan av alla tre variablerna mellan 0 - 6 poäng. Smärtskattning utförs var 3:e timme. Effekten av analgetika kontrolleras 15-20 min. efter intravenös administrering, 30-45 min efter per os/per rektum administrering. Poäng > 2 skall leda till smärstillande åtgärd om andra faktorer ej är alldeles uppenbara som t.ex. rädsla, olust, föräldraseparation etc.

(From: Modifierad av Gunnarsson, G. Hesselgard, K. Nellgård, B. Lund: Neurokirurgiska kliniken, 1996, (rev -00, -04 av Karin Hesselgard)

**Figure 2.** Behavioural Observational Pain Scale (BOPS), in Swedish, which includes the accompanying explanation text. Left column is the score. The next three columns facial expression, verbalization and body position are the items used for the pain evaluation.

#### CHILDREN'S HOSPITAL OF EASTERN ONTARIO PAIN SCALE

In **study IV** CHEOPS was used as a "gold standard or standard measure" for testing the concurrent validity to BOPS. The CHEOPS (Fig 3) was developed in 1985 by McGrath et al.. It is an observation scale for measuring postoperative pain in children aged 1-7 year. The scale includes six categories of pain behaviour; cry, facial, verbal, torso, touch and legs. Each category has three or four grades. CHEOPS has a minimum possible score of 4 points (no pain) to a maximum of 13 points (the worst pain). The scale has been tested both for its reliability and valid-

ity. In order to use the CHEOPS in Sweden the scale was first translated to Swedish (Fig.4)

### Behavioral Definition and Scoring of CHEOPS

Item	Behavior	Score	Definition
Cry	No cry	1	Child is not crying
	Moaning	2	Child is moaning or quietly vocalizing, silent cry
	Crying	2	Child is crying but the cry is gentle or whimpering
	Scream	3	Child is in a full-lunged cry; sobbing: may be scored with complaint or without complaint
Facial	Composed	1	Neutral facial expression
	Grimace	2	Score only if definite negative facial expression
	Smiling	0	Score only if definite positive facial expression
Child verbal	None	1	Child is not talking
	Other complaints	1	Child complains but not about pain, e.g., "I want to see my mommy", or "I am thirsty."
	Pain complaints	2	Child complains about pain
	Both complaints	2	Child complains about pain and about other things, e.g., "It hurts", "I want mommy"
	Positive	0	Child makes any positive statement or talks about other things without complaint
Torso	Neutral	1	Body (not limbs) is at rest; torso inactive
	Shifting	2	Body is in motion in a shifting or serpentine fashion
	Tense	2	Body is arched or rigid
	Shivering	2	Body is shuddering or shaking involuntarily
	Upright	2	Child is in vertical or upright position
	Restrained	2	Body is restrained
Touch	Not touching	1	Child is not touching or grabbing at wound
	Reach	2	Child is reaching for but not touching wound
	Touch	2	Child is gently touching wound or wound area
	Grab	2	Child is grabbing vigorously at wound
	Restrained	2	Child's arms are restrained
Legs	Neutral	1	Legs may be in any position but are relaxed; includes gentle swimming or serpentine like movements
	Squirming/kicking	2	Definitive uneasy or restless movements in the legs and/or striking out with foot or feet
	Drawn up/tensed	2	Legs tensed and/or pulled up tightly to body and kept there
	Standing	2	Standing, crouching, or kneeling
	Restrained	2	Child's legs are being held down

From: Mc Grath, et al. (1985). Advance in pain research and therapy. In: HL Fields, R. Dubner, F. Cervero (eds.), *The CHEOPS: a behavioral scale for rating postoperative pain in children* (pp 392-402). New York: Raven Press.

**Figure 3.** CHEOPS (The Children's Hospital of Eastern Ontario Pain Scale)

## CHEOPS (The Children's Hospital of Eastern Ontario Pain Scale)

Kriterier	Beteende	Poäng	Definition
Gråt	Inget gråt	1	Barnet gråter inte
	Jämmer	2	Barnet jämrar sig eller ljuder ett tyst gråt
	Gråter	2	Barnet gråter, men gråten är mild eller gnyr
	Skriker	3	Barnet gråter högt, snyftningar, kan noteras med klagomål eller utan klagomål
Ansikte	Samlad	1	Neutralt ansiktsuttryck
	Grimaserar	2	Poängsätts endast vid avgjort negativt ansiktsuttryck
	Ler	0	Poängsätts endast vid avgjort positivt ansiktsuttryck
Verbal	Ingen	1	Barnet pratar inte
	Andra klagomål	1	Barnet klagar men inte över smärta, ex "jag vill se mamma", "jag är törstig"
	Klagar över smärta	2	Barnet klagar över smärta
	Både klagomål	2	Barnet klagar både över smärta och annat, ex "det gör ont", "jag vill mamma ska komma"
	Positiv	0	Barnet gör positiva uttalande eller pratar om andra saker utan att klaga
Bål	Neutral	1	Kroppen (inte extremiteter) vilar; bålen är inaktiv
	Skiftande	2	Kroppen är i rörelse, på skiftande eller ålande vis
	Spänd	2	Kroppen är stel eller ligger som en båge
	Skakar	2	Kroppen darrar eller ryser ofrivilligt
	Upprätt	2	Barnet är i en vertikal eller upprätt ställning
	Behärskad	2	Inskränkta rörelser med kroppen
Beröring	Rör ej	1	Barnet rör ej eller griper ej tag om såret
	Sträcker ut	2	Barnet sträcker ut för att ta på såret men berör det ej
	Berör	2	Barnet tar försiktigt på såret eller sårområdet
	Griper tag	2	Barnet griper kraftfullt tag om såret
	Behärskad	2	Barnets armar är återhållsamma
Ben	Neutrala	1	Benen är i vilken position som helst fast avslappnade, ink. simmande el. ålande rörelser
	Vridande/sparkande	2	Definitiv orolig eller rastlösa rörelser i benen och/eller slående med foten eller fötterna
	Uppdragna/spända	2	Benen är spända och/eller tätt uppdagna mot kroppen och hålls kvar där
	Stillastående	2	Stillastående, hukande eller knäande
	Behärskad	2	Barnets ben hålls nere

**Figure 4.** CHEOPS in Swedish. The scale was first translated to Swedish by a general medical doctor and back again to English by an anaesthesiologist, both were fluent in both languages as they worked in Sweden and had English as their mother tongue.

# PROCEDURE

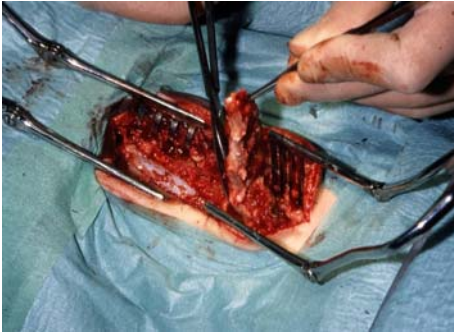
## STUDY I

To identify centers worldwide performing SDR-surgery we used the internet search motor PubMed, the National Library of medicine and The Cochrane Collaboration. The keywords were; *selective dorsal rhizotomy*, *SDR* and *rhizotomy* and within PubMed we used the limits; *child 0-18 years* and *humans*. A total of 183 abstracts were retrieved, three of these were in Russian. In total we found 59 potential centers. A questionnaire with 8 questions was sent by mail and/or e-mail to these selected centers. 28 (47%) of the centers responded initially. After a reminder, 16 (27%) more centers answered, giving a total of 44 centers. 11 centers do not perform SDR surgery at present. The remaining 33 centers constitute the study material of the present study

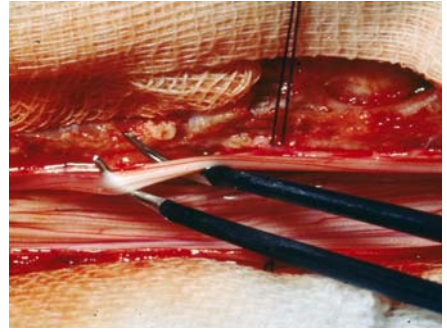
## STUDY II AND STUDY III

All children were premedicated with midazolam. General anesthesia was induced with intravenous fentanyl and thiopental. Succinylcholine was given to facilitate tracheal intubation, followed by one dose of non-depolarizing muscle relaxants. Anesthesia was maintained with isoflurane/N<sub>2</sub>O/O<sub>2</sub>/ and fentanyl. All children received a urinary bladder catheter. A block laminotomy was performed from L<sub>1</sub>–L<sub>5</sub> (Fig 5), the dura was opened and the cauda equina exposed (Fig 6). The posterior roots were identified and the level was confirmed by visible anatomical features and by using electrical stimulation (Fig. 7). Each root was divided into rootlets and each rootlet was stimulated with microelectrodes and those rootlets associated with pathological responses (Fig. 7a) were cut (Fig. 8). In order to administer the postoperative pain management a thin 19-gauge catheter was placed IT with the tip at the L<sub>2</sub>–L<sub>3</sub> level (Fig. 9). This was done at the end of the operation just before closing the dura. Immediately before the awakening procedure all children received a bolus dose of morphine 5 µg·kg<sup>-1</sup> in this catheter and rectal paracetamol 20 mg·kg<sup>-1</sup>.

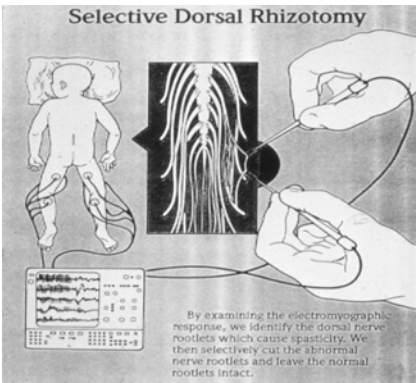
In **study II**, postoperatively, six children were treated with 5 µg·kg<sup>-1</sup> of morphine every 6 h IT and the other six with an IT continuous infusion of bupivacaine, 40 µg·kg<sup>-1</sup>·h<sup>-1</sup>, and morphine, 0.6 µg·kg<sup>-1</sup>·h<sup>-1</sup> delivered by a Pharmacia Deltec® pump. Both regimes were phased out 64 hours after the end of operation. IT morphine administration in the morphine group was reduced to three times a day and the amount in the bupivacaine/morphine by 30%. 24 hours later a further reduction was made. The morphine group was reduced to two times a day and the bupivacaine/morphine group was reduced to 50 % of the original amount. Both regimes ended the following morning with removal of the IT catheter. All children received rectal paracetamol 20 mg·kg<sup>-1</sup> every 6<sup>th</sup> hours, and cefuroxim (Lifurox®, Lilly Sweden) in the standard amount.



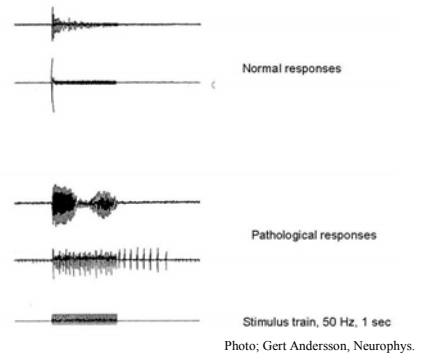
**Figure 5.** A block laminotomy is performed from L<sub>1</sub>–L<sub>5</sub>



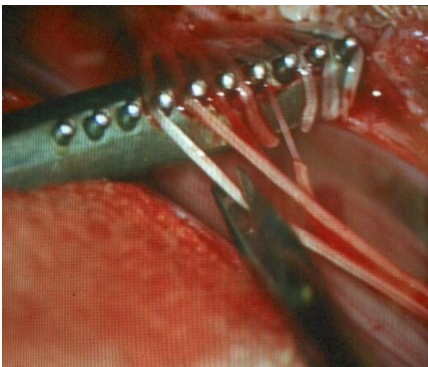
**Figure 6.** The dura is opened and the cauda equina is exposed



**Figure 7.** The posterior roots were identified and the level was confirmed by visible anatomical features and by using electrical stimulation



**Figure 7a.** Normal and pathological responses due to stimulation



**Figure 8.** The nerve roots associated with pathological responses is cut



**Figure 9.** A thin 19-gauge catheter is placed IT with the tip at the L<sub>2</sub>–L<sub>3</sub> level



In **study III**, postoperatively 11 children were treated with IT infusion of morphine  $0.4\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  and bupivacaine  $40\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  (low-dose group) and 15 with IT infusion of morphine  $0.6\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  and bupivacaine  $40\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  (high-dose group) delivered by a Pharmacia Deltec® pump. The concentration of the infusion was morphine 10  $\mu\text{g}/\text{ml}$  and bupivacaine 1000  $\mu\text{g}/\text{ml}$  or morphine 15  $\mu\text{g}/\text{ml}$  and bupivacaine 1000  $\mu\text{g}/\text{ml}$  respectively. On the 3<sup>rd</sup> postoperative day the dose was reduced with 30%, on the 4<sup>th</sup> day with 50% and on the 5<sup>th</sup> postoperative day the intrathecal catheter was removed. All children received rectal paracetamol 20  $\text{mg}\cdot\text{kg}^{-1}$  every 6<sup>th</sup> hours, and cefuroxim (Lifurox®, Lilly Sweden) in the standard amount.

In **study II** and **III** every third hour the children were pain scored by the use of the Behavioural Observational Pain Scale, BOPS, (Fig 1). All children were monitored postoperatively by intra-arterial blood pressure, continuous electrocardiogram (ECG), pulsoximetry and respiratory rate (RR) (Hewlett Packard Merlin 68S, Böblingen, Germany). These values were noted every 15 minutes for the first 2 hours, every 30 minutes the next 2 hours succeeded by hourly registration the following 44 hours and then every third hour until they left NICU.

#### Adverse effects

In **study II** and **III** a respiratory rate of  $< 12\text{ breaths min}^{-1}$  and/or oxygen saturation ( $\text{SaO}_2$ )  $< 93$  was considered to be respiratory depression. Mean arterial blood pressure (MAP)  $< 50\text{ mm Hg}$  in 2-3 years old,  $< 55\text{ mm Hg}$  in 3-4 years old and  $< 60\text{ mm Hg}$  in 4-7 years old was noted as hemodynamic instability. Heart rate (HR)  $100-160\text{ beat min}^{-1}$  (2-3 year old child),  $65-145\text{ min}^{-1}$  (3-4 years old) and  $70-132\text{ min}^{-1}$  (4-7 years old) was considered as normal.

Every third hour postoperative nausea and vomiting (PONV) and pruritus was assessed. A two-point scale was used to record PONV; not present or nausea/vomiting. PONV was treated with metoclopramide and/or ondansetron. A two-point scale (present or not present) was used to record pruritus. Pruritus was treated with clemastine and/or ondansetron.

We were unable to evaluate the incidence of urinary retention since all patients had a urinary bladder catheter.

#### Drug consumption

In **study II** and **III** additional i.v. pain management ketobemidone  $0.05\text{ mg}\cdot\text{kg}^{-1}$  was given if BOPS score was  $> 2$  provided other factors were not quite obvious as fear, parent separation, agitation etc. The effect of the additional analgesic if any was scored 15-20 minutes after the i.v. administering. Total supplementary i.v. consumption of ketobemidone was registered.

## STUDY IV

In order for the evaluation to commence several criteria were first met; children had to be awake/easily arousable after anaesthesia, had to be to the postoperative wards and finally there had to be clinical assumption that the child was in pain. The nurses were generally knowledgeable in the use of behavioural observation pain scales, but received organised education in the use of the two implicated pain scales BOPS and CHEOPS. Furthermore the nurses involved were individually instructed in the use of the CHEOPS and the BOPS immediately preceding their first usage of the scales. This training included discussion of the elements, definition of behaviour and the scoring system. The study consisted of three parts in order to assess the interrater reliability, concurrent validity and construct validity for the BOPS.

### Interrater reliability

Interrater reliability of BOPS was tested in twenty five children. Three observations at 10 minute intervals were completed. At each observation two different nurses, independently of each other observed the child at the same time, and made a BOPS evaluation. A total of twenty-four different nurses made the ratings in this part. The nurses did not share or discuss observations or ratings.

### Concurrent validity

In the second part of the study, we used CHEOPS as a “gold standard or standard measure” for testing the concurrent validity to BOPS. 26 children were observed for 30 minutes postoperatively with both the BOPS and the CHEOPS, for three consecutive 10 minute intervals. CHEOPS scores were done by the investigator while BOPS scores were simultaneously performed independently by another nurse. Each observer was blinded to each others observations.

### Construct validity

In the third part, 25 children were observed before and after analgesic administration. The decision to administer further postoperative analgesic intravenously, morphine 0,05 - 0,1 mg·kg<sup>-1</sup> or ketobemidone 0,05 mg·kg<sup>-1</sup> was based on the departments routine pain management. The nurses were instructed to make their own decision when to give pain treatment and estimate BOPS score immediately before they administer analgesics and at 15, 30 and 60 minutes after intravenous medication. The nurses were not blinded to the pain relief medication.

# STATISTICAL ANALYSIS

## STUDY I

The data were entered onto an Excel spreadsheet and analyzed with Kruskal-Wallis Test. The statistic program used was GraphPad InStat, Version 3 (GraphPad, Software, San Diego, CA, USA).

## STUDY II

Data was analyzed by a two-way ANOVA with post hoc t-test and Bonferoni correction. The difference in pain score, BOPS was analyzed with Wilcoxon Mann-Whitney (WMW). All values are given as mean with standard deviation (SD). The statistic program used was GraphPad InStat (GraphPad, San Diego, CA, Software, USA). P values less than 0.05 were considered statistically significant.

## STUDY III

The binary variable gender was analyzed by means of Fisher's exact test. All other variables were analyzed by means of the WMW rank sum test, first in the usual way relying on large sample properties of the test, then, in case of small P values, also using exact inference. In some cases also Fisher's permutation test was used. The computations were performed in the programs Stata 7.0 (2000, CYTEL software Corporation, Cambridge, MA) and StatXact 4.0 (Stata statistical Software: Release 7.0. College Station, TX, Stata Corporation 2001). P values less than 0.05 were considered statistically significant. All data except for BOPS, pruritus and PONV are given as mean with SD. Average frequency of symptoms (pruritus and PONV) that are noted each third hour during the 48 hours is given in % of the group.

## STUDY IV

Weighted kappa ( $\kappa_w$ ) evaluation was used to determine interrater reliability with the software program Analyse-it + Clinical Laboratory 1.71. The correlation between BOPS and CHEOPS was analyzed with Spearman rank order correlations coefficient ( $r_s$ ). A cross tabulation between BOPS and CHEOPS was used to confirm agreement between the scales, after BOPS was divided in three categories; no pain (scored 0-2 point), moderate pain (3-4 point) and severe pain (5-6 point). Differences in CHEOPS scores between BOPS categories were analysed using Kruskal-Wallis test. Values for CHEOPS are given as median and interquartile range (IQR). To compare pain scores obtained before and after analgesia, Friedman test was used.  $P < 0.05$  was considered as significant. Wilcoxon Signed Ranks test with Bonferoni correction was used to compare the effect of analgesic between two intervals of time  $P < 0.01$  was considered as significant. Values are given as median and IQR. To analyze the validity we used the software SPSS 11.5 for Windows.

# RESULTS

## STUDY I

Of the 59 possibly centers 44 (75%) responded, 11 of this centers didn't perform SDR any more. The remaining 33 centers constitute the study material of the present study (Table 1).

**Table 1.** Possibly centers that perform SDR and frequency of sent and returned questionnaires.

		Complete answer	Don't perform any more	Don't answered	Read e-mail / don't answer ordinary mail
Centers	(59)	33	11	11	4
Australia	(1)	1			
Asian	(10)	5	1	3	1
Europe	(11)	5	4	1	1
Canada	(4)	3		1	
USA	(29)	18	6	3	2
Mexico	(1)			1	
South America	(1)			1	
South Africa	(1)			1	
The Middle east	(1)	1			

## SDR SURGERY

20 (61%) centers use Peacock and eight (24%) use Park operation technique. Three (9%) centers do not specify which operation technique they use. 13 centers perform 1-5 SDR's per year, seven centers perform 6-10 per year, four centers 11-15 per year, seven centers 16-20 per year and one center performs > 25 SDR's per year (150-170 per year). From this information, the total number of SDR's performed is estimated to lie between 459 and 507 per year.

## PAIN MANAGEMENT

No correlation was found between the operation technique and pain treatment.

### Intravenous pain treatment

Continuous intravenous (i.v.) infusion of opioids is used in nearly half of the centers, 16 centers (48%) (Fig. 10). These centers administer either morphine or fentanyl. In addition to continuous i.v. morphine, one center also uses ketamine. One center use continuous i.v. infusion of Ketorolac with Tramadol. Nine of the centers administer continuous i.v. infusion in combination with either bolus or intermittent i.v. injection. Oral medication is given when necessary. Only one center treats older children with patient controlled analgesia (PCA) (Fig. 10). Pain treatment with i.v. intermittent injection of morphine is applied by four (12%) centers. Bolus doses of intravenous treatment with opioids or NSAID is always combined with other pain treatment regime.

### Epidural pain treatment

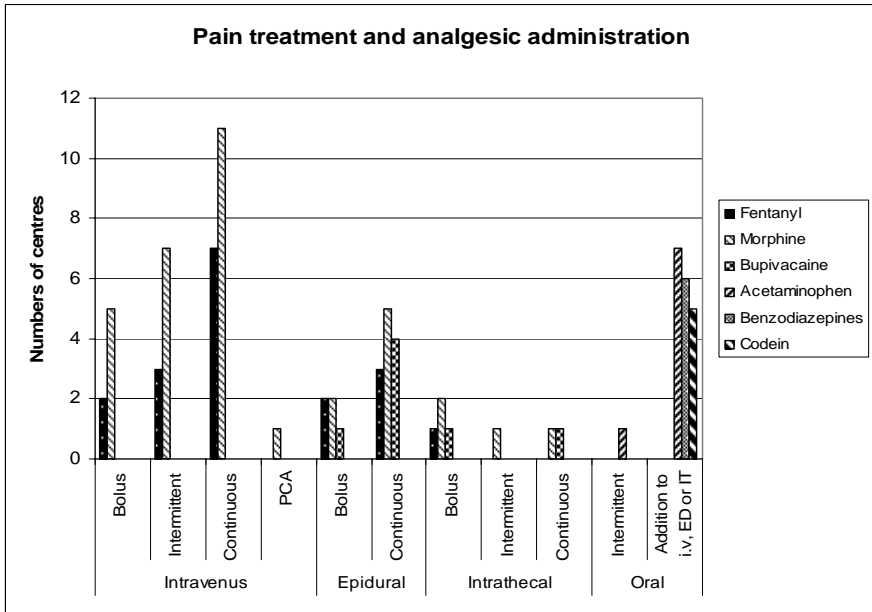
Seven (21%) centers use epidural pain treatment. 6 of these use epidural (ED) continuous infusion, three of these use morphine or butorphenol, two of these centers use fentanyl and one use either morphine or fentanyl. Three centers add bupivacaine to the ED infusion (Fig. 10). Two centers give bolus ED injection when pain treatment is insufficient and two centers administer morphine i.v. One of the centers gives a bolus dose of morphine ED.

### Intrathecal pain treatment

Six (18%) centers use intrathecal (IT) pain treatment. Two of these centers administer IT as a bolus dose, two with morphine, one with bupivacaine and one with fentanyl and lidocaine (Fig. 9). One center administers intermittent morphine, one center combines morphine with bupivacaine as a continuous infusion, with the use of ketobemidone i.v. for treatment of breakthrough pain.

### Oral medication

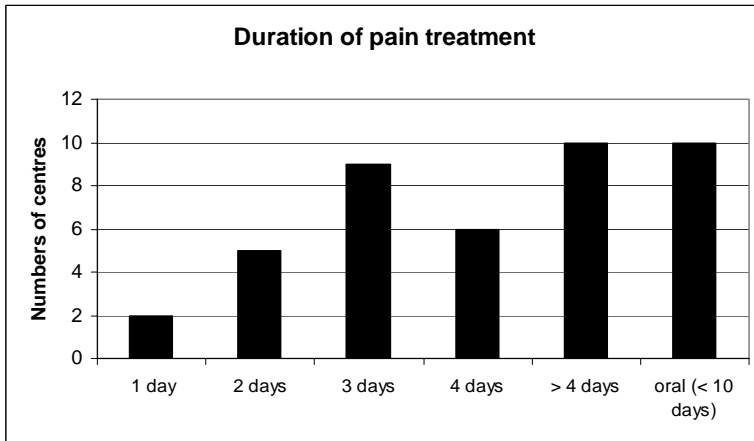
Two centers use solely oral medication. One of the centers gives acetaminophen, the medication at the other center is unknown. In combination with i.v., ED or IT pain treatment acetaminophen with or without codeine is used in 10 (30%) centers (Fig. 10). Amitriptyline is used by two centers in addition to continuous i.v. morphine; one of these centers initiates the treatment two days before surgery. Six (20%) centers use benzodiazepines for treatment of muscle spasm.



**Figure 10.** Pain treatment and analgesic administration at the centers. Some centers use more than one analgesic administration. The bars presented the number of centers using the treatment describing below with the drugs representing by the bar code.

### Duration of pain treatment

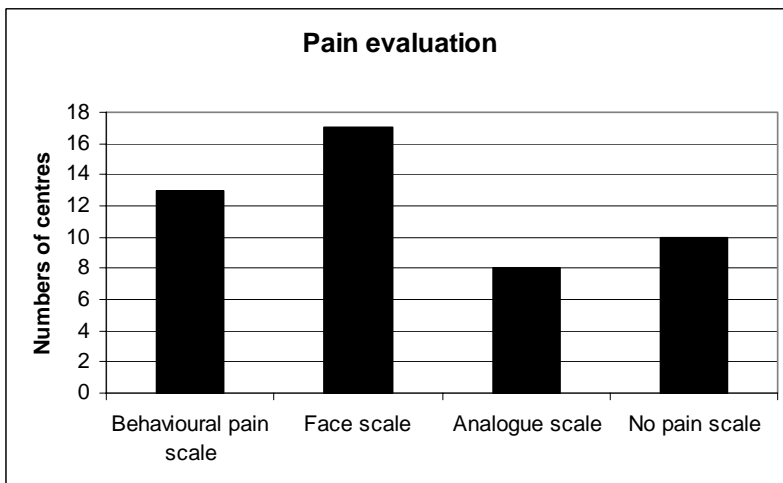
No correlation was found between the operation technique and the duration of the given pain relief. The duration of pain relief with i.v., ED or IT approaches range from 24 hours up to 7 days. Two (6%) centers administer pain relief for 24 hours. A pain treatment duration of 2 days is used by five (15%) centers, 3 days by nine (27%) centers, 4 days by six (18%) centers while 10 (30%) centers continuing pain treatment for more than 4 days (1 center did not reply). After the i.v., ED or IT regimes were discontinued, 10 centers treated pain up to 10 postoperative days by use of oral medication (Fig. 11).



**Figure 11.** The duration of pain treatment at the different centers. The bars represent the numbers of centers and duration of pain treatment, the period stated below.

### Pain evaluation

To evaluate pain relief, 23 (70%) centers used some form of pain scale with 14 (42%) of these using more than one scale. Behavioural pain scale is used in 13 (39%), face scale in 17 (51%) and analogue pain scale in 8 (24%) centers (Fig. 12). One center used all pain scales. Six (18%) centers used a behavioural pain scale as well as a face scale and five (15%) centers used either face scale or an analogue scale. 10 (30%) centers do not use any type of pain assessment scale.

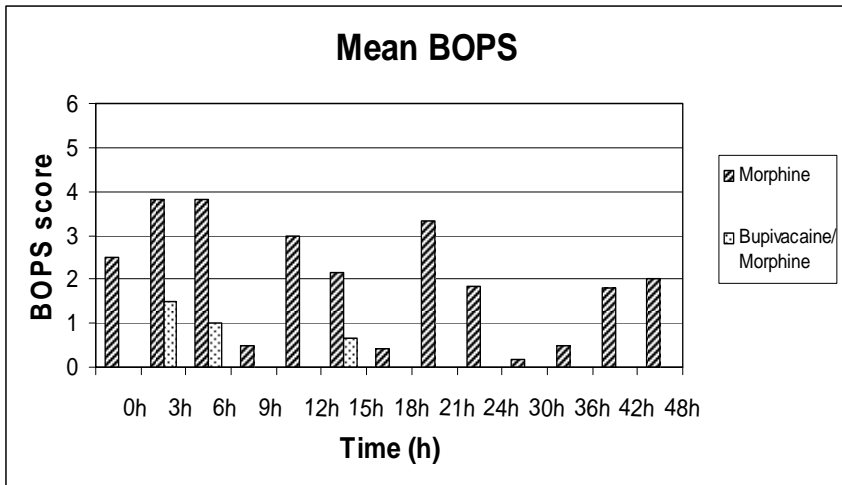


**Figure 12.** The use of pain assessment tools used by the different centers. The bars represent the numbers of centers using the specific method.

## STUDY II

### PAIN

The groups did not differ in age, gender or weight. Both regimes provided analgesia. Better pain relief was obtained in children receiving bupivacaine/morphine compared to morphine seen in a lower pain score (BOPS)  $P < 0.0001$  (morphine group:  $2.0 \pm 2.4$  – bupivacaine/morphine group  $0.2 \pm 1.1$ ) (Fig. 13). Furthermore, the morphine group received four times as much ketobemidone ( $0.09 \pm 0.16 \text{ mg kg}^{-1} \cdot 48 \text{ h}^{-1}$ ) as the bupivacaine/morphine group, ( $0.02 \pm 0.04 \text{ mg kg}^{-1} \cdot 48 \text{ h}^{-1}$ ) even though the difference was not significant. Three children in the morphine group had to be given midazolam during the first 48 hours for lower extremity muscle spasm, none in the bupivacaine/morphine group.



**Figure 13.** Mean BOPS every third hour for the morphine and bupivacaine/morphine group. During these 48 hours there was a significant difference between the groups ( $p < 0.0001$ ).

### ADVERSE EFFECT

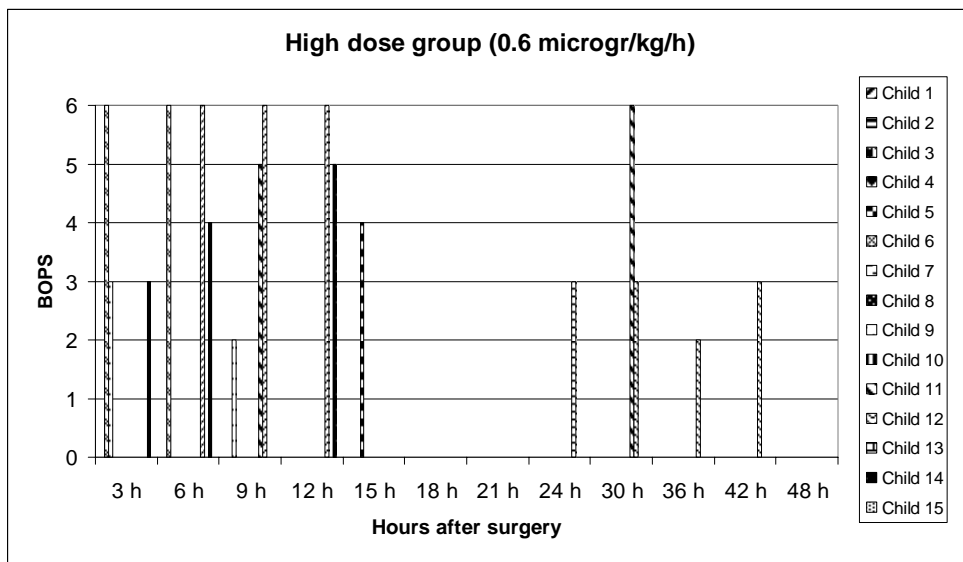
There were no statistically significant differences in hemodynamic or respiratory signs between the groups when compared hour by hour. In the first 48 hours the morphine group had a MAP  $65 \pm 10$ , HR  $117 \pm 18$ , RR  $20 \pm 4$  and  $\text{SaO}_2$   $98 \pm 2$ , and in bupivacaine/morphine group MAP  $67 \pm 12$ , HR  $117 \pm 20$ , RR  $23 \pm 3$  and  $\text{SaO}_2$   $97 \pm 2$ . The IT morphine gave rise to pruritus, five in the morphine group and two in the bupivacaine/ morphine group (ns). Nausea and vomiting did not differ between the groups. Urinary retention could not be assessed because all children had a urinary catheter. No wounds became infected.



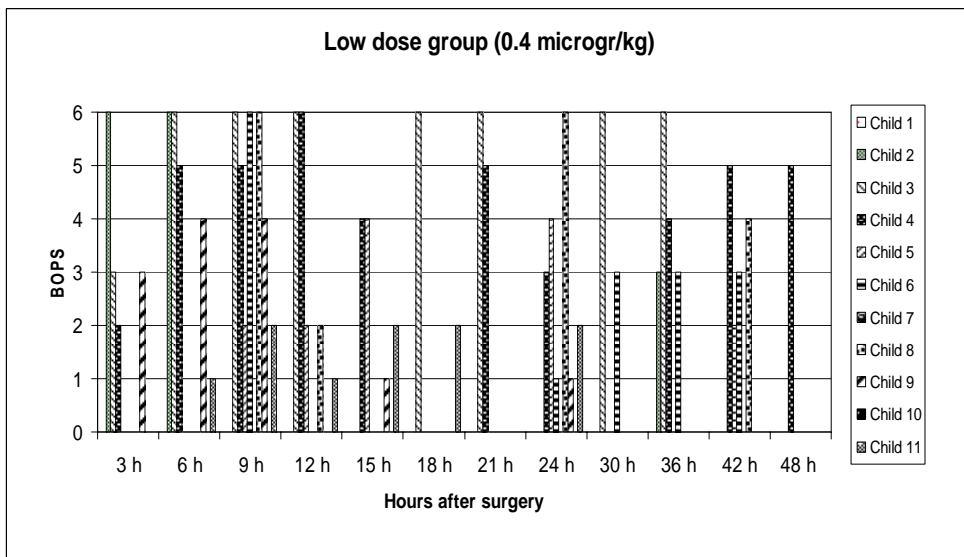
# STUDY III

## PAIN

There were no statistically significant differences between the groups with respect to age, gender or weight. Both regimes provided analgesia. For each child, the frequency of BOPS values above 2 was calculated. Lower such frequencies were seen in the high-dose group compared to the low-dose group (Fig. 14 and 15) ( $P = 0.027$ , Fisher's permutation test and  $P = 0.060$ , WMW test). In the low-dose group seven of 11 children (64%) had at least one episode with pain score  $> 2$  points during the first postoperative 48 h compared with six of 15 children (40%) in the high-dose group. In addition, the low-dose group received seven times as much intravenous ketobemidone as the high-dose group. In the low-dose group, the children received  $6.74 \pm 8.69 \text{ mg} \cdot 48 \text{ h}^{-1}$  versus  $0.90 \pm 1.39 \text{ mg} \cdot 48 \text{ h}^{-1}$  in the high-dose group ( $P = 0.0016$ , WMW test). Shown in  $\text{mg} \cdot \text{kg}^{-1} \cdot 48 \text{ h}^{-1}$  the low-dose group received  $0.43 \pm 0.55$  compared to  $0.06 \pm 0.09$  in the high-dose group ( $P = 0.0017$  WMW test and  $P = 0.0005$  Fisher's permutation test).



**Figure 14.** Postoperative BOPS score after intrathecal pain treatment with bupivacaine  $40 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  and morphine  $0.6 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  (high-dose) during the first 48 hours. The horizontal axis represent BOPS score 0 - 6 points and the vertical axis represent hours after surgery. Each column symbolizes one child.



**Figure 15.** Postoperative BOPS score after intrathecal pain treatment with bupivacaine  $40 \mu\text{g kg}^{-1} \text{h}^{-1}$  and morphine  $0.4 \mu\text{g kg}^{-1} \text{h}^{-1}$  (low-dose) during the first 48 hours. The horizontal axis represent BOPS score 0 - 6 points and the vertical axis represent hours after surgery. Each column symbolizes one child.

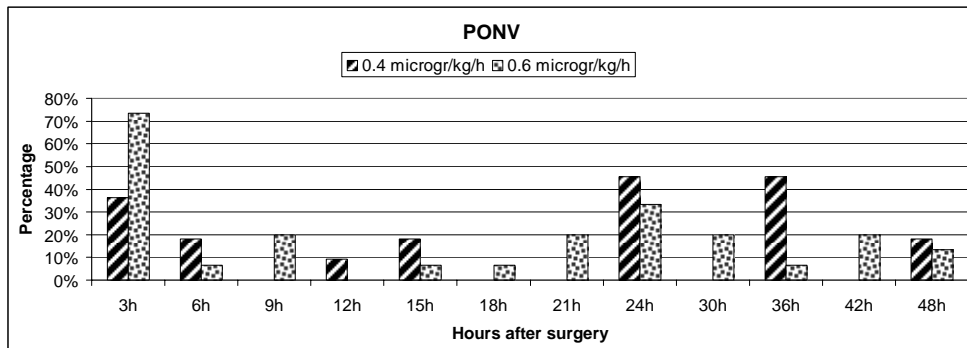
#### ADVERSE EFFECT

All children were respiratory and hemodynamic stable and there were no statistical significances in hemodynamic or respiratory parameters between the groups.

Pruritus occurred in both groups. In the low-dose group seven children (64%) suffered from pruritus with an average frequency of 24% during the 48 hours compared with nine children (60%) with an average frequency of 14% in the high-dose group ( $P > 0.05$ ). Pruritus was treated with clemastine  $0.3 \text{ mg} \times 3$  and/or ondansetron  $2 - 4 \text{ mg} \times 2$ . In both groups three children received clemastine. All children in the low-dose group received ondansetron and 11 (73%) children in the high-dose group.

PONV did not differ between the groups. During the first 48 postoperative hours there were eight children (73%) with an average frequency of 14% in the low-dose group who suffered from PONV and 13 children (87%) with an average frequency of 13% in the high-dose group ( $P > 0.05$ ). Three hours after surgery PONV reached its maximum in the high-dose group 11 (73%) of the children while the maximum was seen in the low-dose group after 24 h with 5 (45%) of the children (Fig 16). PONV was treated with metoclopramide  $0,2 \text{ mg/kg} \times 3$  and/or ondansetron  $2 - 4 \text{ mg} \times 2$ . In the low-dose group the children received  $7.09 \pm 5.00 \text{ mg}$

ondansetron /child and in the high-dose group  $7.73 \pm 4.19$  mg ondansetron /child during the first 48 postoperative hours.



**Fig 16.** Figure. 4 Showing the percentage of postoperative nausea and vomiting (PONV) in the low-dose ( $0.4 \mu\text{g kg}^{-1}\text{h}^{-1}$ ) and high-dose ( $0.6 \mu\text{g kg}^{-1}\text{h}^{-1}$ ) group at different times after operation.

## STUDY IV

There were no statistically significant differences between the groups with respect to age and gender (Table 2).

**Table 2.** Patients characteristics and type of surgery for the three different parts, n = number of participants. The figures in bracket are the percent of total in each group. Age is given as mean  $\pm$  SD.

	Interrater reliability Part I n = 25	Concurrent validity Part II n = 26	Construct validity Part III n = 25
Male	15 (60)	18 (69)	17 (68)
Female	10 (40)	8 (30)	8 (32)
Age (yr) m (SD)	$4.5 \pm 2.0$	$4.5 \pm 1.7$	$4.0 \pm 1.6$
Type of surgery (%)			
Abdomen	3 (12)	1 (4)	4 (16)
Ear, nose or throat	10 (40)	24 (92)	11 (44)
Groin, genitals	1 (5)	0 (0)	5 (19)
Neurosurgery	11 (44)	1 (4)	5 (19)

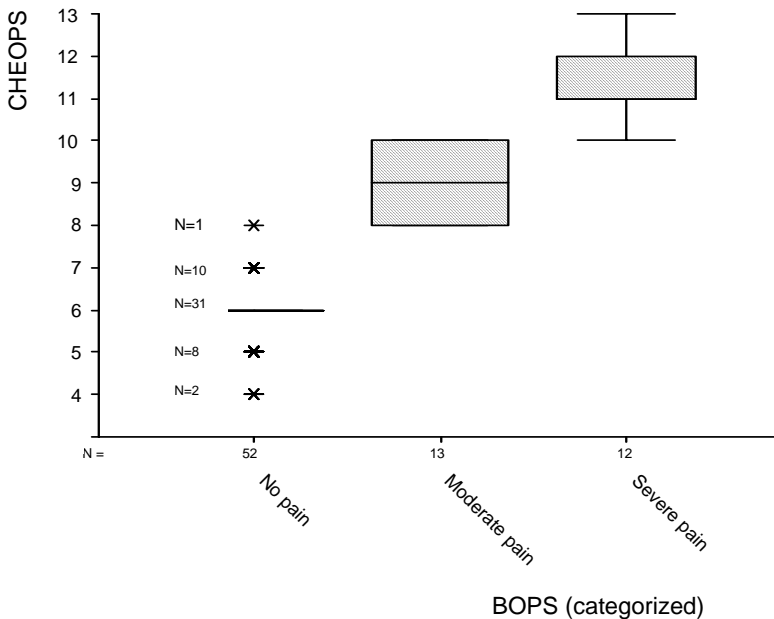
## INTERRATER RELIABILITY

In interrater reliability 150 observations were made by twenty-four nurses. The interrater reliabilities of the observers were good. There was a high agreement between the different nurses BOPS scores.  $\kappa_w$  values for facial expression was

0.86 (90%), verbalization 0.92 (93%), body position 0.95 (97%) and the totally BOPS score was  $\kappa_w$  0.93 (89%).

### CONCURRENT VALIDITY

Of 78 possible evaluations, 77 were performed in the concurrent validity. One scoring was not possible as the child had left the ward earlier than expected. BOPS and CHEOPS scores had positive correlation indicating that both tools described similar behaviours. The correlation between the two scales BOPS and CHEOPS were statistically significant,  $r_s = 0.871$ , ( $P < 0.001$ ). In the cross tabulation BOPS was divided into three categories. In the no pain group the median score for CHEOPS was 6 (IQR = 0), moderate pain 9 (2) and in the severe pain group 11 (1) ( $P < 0.001$ , Kruskal-Wallis test). A high agreement (96.1%) was found comparing BOPS categories with the CHEOPS 4-13 points score (Fig. 17).



**Figure 17.** Box and whisker plot where the horizontal axis represents BOPS categorized in no pain (0-2 p), moderate pain (3-4 p) and severe pain (5-6 p). The vertical axis represents CHEOPS scores 4 - 13 points. In BOPS no pain group, at the four point level in CHEOPS there were two registrations, eight registration at five point level, thirty-one registrations at six point level, ten registrations were made at seven point level and at the eight point level there was one observation.

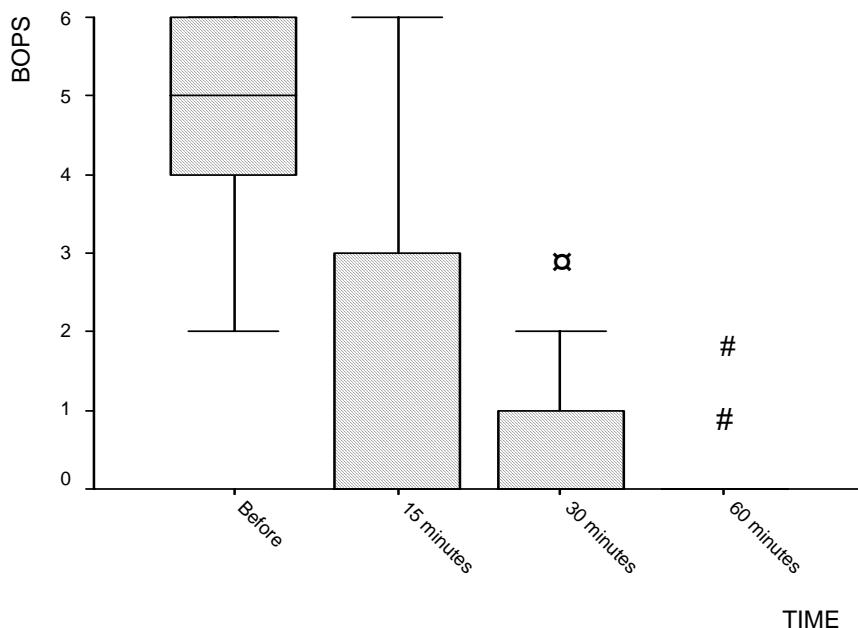
### CONSTRUCT VALIDITY

There were 100 pain treatment occasions. Table 3 shows when the nurses decided to give pain relief. 98% of the nurses decided to give pain relief when BOPS was  $> 2$  points.

**Table 3.** Distribution of the nurses pain treatment, n = 100, listed in occasions. All children with moderate and severe pain received pain treatment except for the four with moderate pain who received pain treatment 15 min. previously.

BOPS Score	Occasions	No Pain relief	Pain relief
No pain (0-2 p)	65	64 (98%)	1 (2%)
Moderate pain (3-4 p)	14	4 (29%)	10 (71%)
Severe pain (5-6 p)	21	0 (0%)	21 (100%)

BOPS score was higher, median (IQR), 5 (2), than BOPS scored 15 min after analgesic administration where it was 0 (3.5) and 30 min later 0 (1) followed by 0 (0) after 60 min,  $p < 0.001$  Friedman’s test. The differences between the time intervals (Wilcoxon Signed Ranks test) were significant ( $P < 0.01$ ) between before analgesia and 15 min, 30 min and 60 min after as well as between 15 min and 60 min. There were no significant difference between 15 min and 30 min after analgesic ( $P < 0.31$ ) and between 30 min and 60 min after analgesic ( $P < 0.26$ ) (Fig. 18).



**Figure 18.** Box and whisker plot showing change in BOPS score in response to analgesic administration. The vertical axis represents BOPS score. The horizontal axis represents time. Scores were estimated prior to the administration of analgesic (Before) and 15, 30 and 60 minute after analgesic administration. □ represents two outliers at 30 min. # represents one outlier with one point and one with two points at 60 min.

# DISCUSSION

## SELECTIVE DORSAL RHIZOTOMY

General aspects of SDR operations and postoperative pain management in children suffering from spasticity who are operated with SDR have been evaluated. The results are naturally not conclusive, mainly due to the fact that it is logistically difficult to find all the worldwide centers performing SDR surgery. The response to our questionnaire of 75% allows for further inaccuracies. Various countries have not responded, possibly because they simply do not perform these techniques. In Northern Europe, for example, Sweden is the only country utilising SDR for CP spasticity; Denmark, Island, Finland and Norway do not perform this procedure.

In 1978, Fasano et al revised the old method introduced by Foerster in 1908 and some years later Peacock et al did a further modification of Fasanos surgical technique. Peacock et al. altered the surge location from the level of conus to the cauda equina where each posterior nerve root could be identified. Thereby, bowel and bladder complications could be avoided (Peacock and Arens, 1982). In 1987, a new improvement in operative technique was made by simultaneous recording of EMG activity from 10 muscle groups, supplemented with visual observation and palpation (Peacock et al., 1990). Park preferred a two-level laminectomy to expose the conus. The smaller laminectomies should theoretically reduce the risk of subsequent development of spondylolisthesis, increased lumbar lordosis or scoliosis. To localize the conus, laminectomy is carried out in several steps using ultrasound examination (Park, 1995). Worldwide, it seems that the two most common operation techniques used are described by Peacock et al. (1982, 1990) and by Park (Park, 1995) even though three centers did not specify which surgical technique was used.

The actual number of children who are recipients for this type of surgery is difficult to estimate. In our study (**study I**) we found a number between 459 - 507 performed per year by the 33 centers. Van de Wiele et al. treated 105 children with spasticity with SDR between 1986 - 1991 (Van de Wiele et al., 1996). Park (Park, 2000) operated 681 patients between 1989 - 1999 with spastic diplegia and quadriplegia. In another study 154 patients underwent SDR during 30 years in Israel (Salem et al., 2003). Kim et al. (2001) report their experience of 198 patients with spastic cerebral palsy treated with SDR during 1990 - 1999 in Korea. This study shows considerable variation in the amount of operations performed at each center. The majority of centers perform 1-5 operations per year in contrast to one cen-

ter which performs as many as 150 -170 per year, using the operation technique described by Park.

## PAIN MANAGEMENT AFTER SDR

The postoperative pain treatment is a small but vital part of these children's overall treatment. Our experience is that postoperative pain treatment in these children can be demanding. Postoperatively these children are in severe pain; a pain related to the extensive surgical exposure with multilevel laminectomy and the nerve root manipulation (Peacock et al., 1982; Abbott, 1992; Lawhorn, 1994; Sparkes et al., 1989; Geiduschek et al., 1994; Dews et al., 1996; Malviya et al., 1999). During the 1980's, it is most probable that these children were treated with conventional i.v. and/or oral medication. First in 1989 a study with pain treatment after SDR was published (Sparkes et al., 1989). Since then many different pain treatment regimes have been presented (Harris et al., 1991; Lawhorn et al., 1994; Dews et al., 1996; Malviya et al.; 1999).

**Study I** shows that the majority of centers, 23 (70%), use some form of continuous pain treatment strategy given either i.v., ED or IT. Most commonly, continuous i.v. infusion of opioids are used, even though one center uses continuous ketorolac infusion i.v. These treatments are complemented with bolus, intermittent i.v. injections or oral medication. Even continuous ED and IT infusion do often require complementary i.v. injection or oral medication due to breakthrough pain. Generally the centers use combinations of different drugs or techniques but four centers treated the postoperative pain only with i.v. intermittent injection of morphine. Two centers use exclusively oral medication. Both these centers use the surgical technique described by Park. One of the centers treated postoperative pain for 3-4 days and the other center for up to 5 days. One could therefore speculate that postoperative pain was less of a problem after an operation where the Park technique was used. This could, however, not be verified. Two centers (one from the oral regime and one from intermittent i.v. regime) do not utilize any type of pain assessment tool which could be the reason for the simple pain treatment regime. We expected that the vast majority of centers would use some sort of pain assessment tool. However, we found that only 23 (70%) use some form of pain scale, i.e. 1/3 of the centers do not assess pain. Of the centers that do assess pain, 14 (42%) use more than one kind of pain assessment scale.

## INTRATHECAL PAIN MANAGEMENT

### PAIN TREATMENT

According to our knowledge, continuous IT infusion of bupivacaine/morphine for postoperative pain management has not been described before in children after SDR. The amount of continuous bupivacaine/morphine used in our first study

(**study II**) was a result of pilot investigations with titration, increasing the amount of a morphine/bupivacaine mixture with morphine 15 µg/ml and bupivacaine 1000 µg/ml until the children were totally pain free. Single injections of IT morphine given pre- or peroperatively has earlier been found to be effective in treating the postoperative pain in children after spinal surgery (Dalens & Tanguy, 1988; Harris et al., 1994; Dews et al., 1996; Kerchel et al., 1995; Goodarzi, 1998; Goodarzi & Narasimhan, 2001; Gall et al., 2001). Even after other surgical procedures, single injections of IT morphine have been found to have a satisfactory pain relief in children. However, the effect was of limited duration (Jones et al., 1984; Tobias et al., 1990; Krechel et al., 1995; Tobias, 2000b; Uguralp et al., 2002; Suominen et al., 2004) and during our 12 years of experience with pain treatment of these children, we have found that continuous IT pain management with bupivacaine and morphine is superior to intermittent IT morphine treatments for children after major spinal surgery (**study II**). The pain relief was excellent in this study, but it was desirable to reduce the administered amount of IT morphine in order to try to reduce side effects such as pruritus and PONV. In **study III**, we examined IT bupivacaine with two different concentrations of morphine and found pain relief during the postoperative period, especially in the high-dose group. The better pain relief was seen with a lower BOPS score in the high-dose group compared with low-dose. This observation was further strengthened when examining the difference in ketobemidone consumption ( $\text{mg}\cdot\text{kg}^{-1}\cdot 48\text{h}^{-1}$ ) in order to keep the BOPS score below 2 points (Fig.14 and 15). In children only few publications describe the use of continuous IT opioids with or without local anaesthetics (Tobias, 2000b; Galloway et al, 2000). Tobias (2000b) reports two successful cases, one case with continuous IT fentanyl for 72 hours postoperatively and a second case with sufentanil infused IT in combination with bupivacaine to treat cancer pain. Also, Galloway (2000) used continuous IT morphine to treat cancer pain. In both publications the pain relief was satisfactory, supporting the concept.

IT infusion of local anaesthetic is an alternative. Not only will it give a good pain relief, but it could also relieve the postoperative muscle spasm of the SDR patient. None of the children in the bupivacaine/morphine group complained about muscle spasm compared with 3 children in the morphine group (**study II**). The reason for this could be the addition of bupivacaine IT which causes some degree of muscle relaxation (motor blockade) (Bösenberg, 1998). Further studies to evaluate this effect are needed. Tachypylaxis can be a problem if local anaesthetic is used alone and the increased amount of local anaesthetic needed to block the nerves makes it difficult to administer the correct quantity while controlling the effect (Mogensen et al., 1989). An extensive blocking effect of the local anaesthetic might mask devastating bleeding complications around the spinal cord. The regimens with a combination of local anaesthetic and low-dose of morphine have previously been found to prevent tachypylaxis of the local anaesthetics and make the administration of local anaesthetics more predictable (Scott et al., 1989). Another reason to use morphine is because hydrophilic opioids are associated with good analgesia,



not only limited to the segment where it is injected. IT injected morphine has a slow rostral diffusion as well as a slow penetration of morphine into the surrounding nervous tissue giving rise to pain relief as well as adverse effects (Nordberg et al., 1984; Jacobson et al., 1988; Goodarzi, 1999).

## ADVERSE EFFECTS

The half-life of morphine in cerebrospinal fluid (CSF) is similar to plasma (Nordberg et al., 1984). A long duration of IT morphine can only be due to a relatively high concentration locally at the injection site. In SDR children such a local effect on the medulla pain receptors is desirable, making morphine the best option (Bernards, 1998). However, with increased doses a rostral spread of IT morphine can be a potential risk for respiratory depression and circulatory collapse, resulting in a desire to reduce the injected amount and/or disperse it over time. Another reason for reducing IT morphine are the side-effects such as pruritus, nausea and vomiting.

The mean arterial blood pressure tended to be lower in the high-dose group (**study III**) even though the differences were not statistically significant. Goodarzi & Narasimhan (2001) hypothesized that the effect of a small dose IT opioid could be predominantly mediated via spinal cord opioid  $\mu$  receptors. This direct effect could be the reason for the blood pressure reduction effect by a sympatholytic effect, or more plausible, by the direct pain reducing effect.

Postoperatively all children in **study II** and **III** were breathing at normal rate and had normal SaO<sub>2</sub> with no differences between the groups. We did not observe any respiratory depression after continuous infusion of 14  $\mu\text{g} \cdot \text{kg}^{-1} \cdot 24 \text{ h}^{-1}$  in the high-dose group (0.6  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ). Respiratory depression has been described after single injections of 20  $\mu\text{g}/\text{kg}$  (Jones et al, 1984; Nichols et al, 1993; Goodarzi, 1998) even though other authors have used this dose without mentioning this complication (Tobias et al., 1990; Dews et al. 1996).

Pruritus is a general problem following spinal opioid administration (Jacobson et al., 1988; Harris et al, 1991; Arai et al., 1996; Dews et al., 1996; Weber et al., 1998; Borgeat & Stirnemann, 1999; Gall et al., 2001). In **study II**, incidence of pruritus was greater in the intermittent morphine group (83%) compared to the bupivacaine/morphine group (33%) and the amount of IT morphine was also 39% higher in the intermittent group. This finding supported the concept of reducing the amount of IT morphine. In **study III** 64% of the children in the low-dose group and 60% in the high-dose group were recorded to have pruritus at sometime during the first 48 postoperative hours, with average frequency of 24% in the low-dose group compared with only 14% in the high-dose group. This result was the opposite of what was expected. A considerably higher amount of i.v. ketobemidone was given to the children in the low-dose group. This observation is the only

obvious reason that the low-dose group had more pruritus. In fact, i.v. opioids have been found to give rise to pruritus. In a recent study in children, i.v. ketobemidone administered alone gave itching in 56% (Jylli et al. 2004). The general incidence of pruritus found in this study was low compared with other studies (Sparkes et al., 1988; Dews et al., 1995; Goodarzi, 1999) and one reason could be our use of ondansetron to treat PONV. Former studies have implicated that ondansetron is effective in treating spinally administered morphine induced pruritus (Arai et al., 1996; Borgeat & Stirnemann, 1999; Yeh et al., 2000). All children in the low-dose group and 73% of the children in the high-dose group received ondansetron.

The incidence of PONV can depend on the study design, the type of operation performed, the anaesthetic procedure and the pain treatment regime. The incidence of PONV varies from 10% to 77% in different studies; Krechel et al. (1995) found that PONV occurred both when morphine was given IT and i.v. as PCA. The incidence of PONV in the IT morphine group was 31% compared with 22% in the PCA group. PONV was also present after ED administration of opioids and Goodarzi (1999) reported an incidence of 10% in the hydromorphone group, 20% in the group who received fentanyl and 25% in the morphine group. In a study comparing continuous ED morphine and intermittent i.v. bolus doses of morphine the incidence of PONV was high in both groups (Malviya et al., 1999). The evening after surgery, incidence was 77% in the ED group and 64% in the i.v. group. In contrast, Weber et al. (1998) stated that intrathecal addition of morphine does not cause PONV. Furthermore, Jacobson et al. (1988) found that nausea and vomiting even occurred in the group who did not receive morphine IT and this was further strengthened by Gall et al. (2001) and Suominen et al. (2004). There was only one patient of 15 who experienced nausea after IT morphine injection in the Nordberg et al. study (1984) and none suffered from PONV in the Pirat et al. study (2002). During the first 48 postoperative hours in **study III** the incidence of PONV did not differ between the groups. In the low-dose group PONV was found with an average frequency of 14% and 13% in the high-dose group. The maximum percentage of the children's suffering PONV was 73% three hours after surgery in the high-dose group compared to 36% in the low-dose group. PONV in the immediate postoperative period can be due to either the general anaesthesia/operation and/or elected by the IT morphine. The reason for this difference is not clear.

## PAIN MEASUREMENT

When caregivers estimate pain as well as the effect of pain treatment the usage of any kind of scale is important (Tyler et al., 1993; Schade et al., 1996; Johnston, 1998). Guidelines from the American Academy of Pediatrics (2001) recommend that effective pain management in infants and children should be monitored routinely and documented clearly in a visible place. This requires measurement of

pain intensity and pain relief with reliable, valid and clinically sensitive assessment tools. Many Swedish hospitals use different behavioural scales which are modifications after translations from other languages but none of them have been validated or reliability tested (Jylli, 2001). Some behavioural observation scales have been reported to be difficult to use. They are lengthy and lack the attributes necessary for easy implementation into clinical practice (Tyler et al., 1993; Merkel et al., 1997; Voepel-Lewis et al., 2002). There is a growing need for approved and simple pain evaluations instruments which can be incorporated into daily care (Larsson, 1999; van Dijk et al., 2000). With regard to this, we have created a behavioural observational pain scale, the BOPS (Fig.1) which is simple and easy to use in a busy clinical care unit. In order to use such an instrument, its reliability and validity has to be proven.

### INTERRATER RELIABILITY

BOPS rating as a showed had a superior interrater reliability with a kappa value of 0.93. Other pain scales do not have the same high interrater reliability. The kappa values for the TPPPS with 7 individual behaviours items were from 0.53 to 0.78 (Tarbell et al., 1992), the 5 items in FLACC pain assessment tool were from 0.52 to 0.82 (Merkel et al., 1997) and in the COMFORT scale the 9 items including the three physiologic parameters were from 0.54 to 0.93 (van Dijk et al., 2000). BOPS is a simple hybrid derived from two other behavioural pain scales. If the simplification had made the BOPS a more inaccurate instrument one would expect a lower kappa value. A small amount of investigators could be one reason for the better interrater reliability. 41 persons were involved in the evaluation of the COMFORT scale (van Dijk et al., 2000) contra 24 in this, however, only 2 observers performed the TPPPS (Tarbell et al., 1992) while the numbers of investigators involved in the FLACC study are not clearly mentioned (Merkel et al., 1997). Therefore, the fact that only three behaviours were evaluated, that BOPS has a smaller sum score, and the reality that a simple scale is easier to understand and use could be the reason for this better interrater reliability. Looking at the three items in the scale one surprising fact was that the best reliability was found in the body position.

### CONCURRENT VALIDITY

Because CHEOPS is so well reputed and has been used in many studies (Sutter et al., 1995; Bennie et al., 1998; Bolton et al., 2002; Tyler et al., 1993; Rose et al., 1999; Bridget et al., 2000; McCarty et al., 2000; de Negri et al., 2001; Özbek et al., 2002; Suraseranivongse et al., 2003; Tay et al., 2002) we chose it as our “gold standard” for testing the concurrent validity. CHEOPS was one of the first behaviour observational pain scales and has been found to be very good for postoperative pain measurement (McGrath et al., 1985; Suraseranivongse et al., 2001; McCarty et al., 2000). BOPS and CHEOPS had a high correlation indicating that

BOPS could discriminate pain of different intensity to the same extent. When we compared BOPS, divided into no pain, moderate pain and severe pain, with CHEOPS the agreement between the scales was 96% (Fig. 17).

In planning this study we assumed that children between 5 and 7 years old could self-report their pain as an extra control to BOPS and CHEOPS using CAS (McGrath et al., 1996). However, most of the children were unable to do so when they were in the state of easy arousal after anaesthetics when these tests were performed. Such findings have been published before and the noted reasons were factors like excitement, agitation, pain and/or sedation (Sutter et al., 1995; Bennie et al., 1998; Bolton et al., 2002).

### CONSTRUCT VALIDITY

If the pain scale measures pain it should score lower after administration of analgesic (McGrath & Unruh, 1999). By selecting times when the clinical presumption was that the child was in pain, the nurses could evaluate the response to analgesics. Similar approaches have used in other comparable studies in validating pain measures (McGrath et al., 1985; Tyler et al., 1993; Suraseranivongse et al., 2001). BOPS was sensitive and the score decreased after pain relief was given. A significant decrease in BOPS was found already 15 minutes after analgesia administration. The children received their analgesic intravenously being the most probably reason for the fast BOPS response. An effect of the analgesic was found in all children with a BOPS score above 2 which strengthens our normal recommendation to treat pain when BOPS is  $> 2$  points (Table 3). Unfortunately an univocally cut-off point, to give pain treatment is not described for our “gold standard” CHEOPS. A CHEOPS score around 7 points releases pain treatment in most studies (Suraseranivongse et al., 2001; McCarty et al., 2000; Özbek et al., 2002; Suraseranivongse et al., 2003; Tay et al., 2002), even though other wait until 9 points (Bolton et al., 2002; Bridge et al., 2000; de Nigri et al., 2001) or even until the score is  $\geq 10$  (Bennie et al., 1998). Our study showed that a CHEOPS score between 4 – 7 points was equal to BOPS 0 - 2 points supporting that a BOPS score  $> 2$  should lead to pain treatment.

There are factors that can influence the nurses scoring in a postoperative- or intensive care unit. Just before the children recovered from anaesthesia they are commonly restless during a period of time before they are fully awake (Sutter et al., 1995; Bolton et al., 2002; Suraseranivongse et al., 2001; Bridge et al., 2000). Even hunger, fear and anxiety as well as parental separation can enhance pain scoring in all observational pain scales (Merkel & Malviya, 2000; Bennie et al., 1998; Jylli, 2001; Bridge et al., 2000). In this study, nurses were instructed to exclude such reasons for high BOPS scores and try to correct the problem that influenced the measuring. However, the study was hampered by the fact that the nurses performing the BOPS assessment were the same nurses giving the analgesic.

## CONCLUSION

The most common operation techniques worldwide is described by Peacocks et al. (1982, 1990) and Park (1995).

The majority of the centers performing SDR have a satisfactory pain management strategy. These centers use continuous infusion of opioids, given i.v., ED or IT, and incorporate the use of some sort of pain assessment tool to evaluate pain and guide the pain treatment.

IT pain treatment with morphine and bupivacaine provides safe and good analgesia after major spinal operations. Continuous infusion of IT morphine/bupivacaine is superior to intermittent morphine, even though the amount of morphine was higher in the intermittent group.

The present data recommend that a morphine dose of  $0.6 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  may be a better option than  $0.4 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  in combination with  $40 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  of bupivacaine seen in better pain relief. This is furthered strengthened by the fact that the adverse effect did not differ between the groups and was therefore not a drawback of the high-dose group.

With BOPS the nurses are able to evaluate and document pain with a reliable and valid assessment tool and thereby improve pain treatment in preschool children. BOPS was found to be simple, clear and easy to use for the caregivers. The simple scoring system could make BOPS easy to incorporate in a busy postoperative unit.

## SUMMARY IN SWEDISH

Selektiv dorsal rhizotomi (SDR) är en effektiv operationsmetod som framgångsrikt minskar graden av spasticitet med bestående positiva effekter för barn med spastisk diplegia. Barn som genomgår SDR har svåra smärtor postoperativt, smärtan är relaterad till både den stora kirurgin med blocklaminotomin och nervrots manipulation. För att kunna ge en optimal smärtlindring är smärtskattning en nödvändighet i smärtbehandlingen, smärtskattningen kan vara svår att bedöma hos små barn. Avsikten med denna avhandling är att evaluera och förbättra smärtbehandlingen till barn som genomgår stor ryggekirurgi samt att utveckla ett smärtskattningsinstrument för att evaluera postoperativ smärta hos förskolebarn.

Antalet centra som utför SDR är okänt. Ingen omfattande världsomspännande studie av olika centras postoperative smärtbehandling efter SDR har gjorts. Syftet med **studie I** var att uppskatta omfattningen av SDR kirurgin, evaluera vilken operations metod som används och kartlägga smärtbehandlingen efter SDR. Ett frågeformulär bestående av 8 frågor sändes ut till 59 tänkbara centra. 44 (75%) svarade. 33 centra utgör studiematerialet, 11 centra utför inte längre SDR kirurgi. De mest använda operationsteknikerna är Peacock et al. (1982, 1990) och Park (1995). Majoriteten av centrarna (70%) har en tillfredställande smärtbehandlings regim. Dessa centra använder kontinuerlig infusion av opioider given intravenöst, ED eller IT och de utvärderar smärtlindringen med någon form av smärtskattningsinstrument.

Vi eftersträvade att utveckla en optimal IT smärtlindringmetod. I en prospektiv studie (**studie II**) användes två olika IT smärtlindrings regimer, kontinuerlig infusion kontra intermittent injektion för att evaluera smärtlindringen och eventuella sidoeffekter. 12 barn (3.1 - 6.3 år), 6 barn i varje grupp, fick antingen intermittent IT morfin,  $5 \mu\text{g}\cdot\text{kg}^{-1}$  fyra gånger per dag eller en kontinuerlig infusion av en blandning med bupivacaine,  $40 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  och morfin  $0.6 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ . IT kontinuerlig infusion med bupivacaine och morfin var överlägsen jämfört med intermittent morfin som smärtlindring efter SDR kirurgi.

För att definiera en optimal dos (**studie III**) med kontinuerlig IT morfin och bupivacaine som behandling för svåra smärtor efter SDR, inkluderades 26 (2.7-7.4 år) barn i studien. I denna studie jämförde vi två olika koncentrationer av morfin  $0.4 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  och  $0.6 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  med en fixerad dos av bupivacaine  $40 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  med avseende till den analgetiska effekten och undersöka om det fanns någon skillnad i sidoeffekter. BOPS användes för att värdera smärtan. Kontinuerlig IT smärtlindring med  $0.6 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  morfin och  $40\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  bupivacaine utgör en säker och tillfredställande smärtlindring efter stora spinala operationer. Detta styrks ytterligare genom det faktum att sidoeffekterna inte skiljer sig mellan grupperna.

För att kunna ge en effektiv smärtbehandling till barn ska det finnas rutiner och tydlig dokumentation för att evaluera smärta. Detta kräver mätning av smärtintensitet och smärtlindringen med reliabla, valida och kliniska känsliga mätverktyg. Observationer av barnets smärtbeteende är ett acceptabelt alternativ då själv skattning inte är möjlig. I **studie IV** evaluerade vi reliabiliteten och validiteten av BOPS som en postoperativ smärtskattningsskala för barn 1-7 år. Skalan bedömer tre smärtbeteendevariabler; ansiktsuttryck, verbalisering och kroppsställning. Med BOPS kan sjuksköterskan evaluera och dokumentera smärtan med hög reliabilitet och validitet och därmed förbättra den postoperativa smärtbehandlingen till förskolebarn. Det enkla bedömningssystemet gör att BOPS är lätt att införa på en postoperativ avdelning.

# ACKNOWLEDGEMENTS

I want to express my sincere and deep thanks to everyone that have helped me during this journey. This work would not have been possibly without the enthusiasm and support from my family, co-workers, colleagues and my friends. Especially I want to thank:

*Peter Reinstrup*, associated professor in Neuroanaesthesia, my tutor, supervisor, co-author and dearest friend. For introducing me into Intrathecal pain treatment and in a professional way has guided me along the path from novice to researcher you have generously shared your knowledge. Especially I want to thank you for your support and all the discussions that gave me courage to continue with my researches and for all fun we have had together during this time.

*Bertil Romner*, associated professor in Neurosurgery, my co-supervisor and co-author, for your enthusiasm and support when I mistrust and for constructive criticism. Especially I want to thank you for the intention of always trying to be my main tutor. Do not stop running!

*Lars-Göran Strömblad*, Senior consultant in Neurosurgery, my co-supervisor and co-author, for your generosity in sharing clinical experience and for constructive criticism. Your interest for our small patients is admirable.

*Leif G Salford*, Professor in Neurosurgery, for a never ending enthusiasm and full support to this dissertation. Without you I have had to write all this by hand with a pencil.

*Lisbeth Rosengren* and *Ann Boklund*, my colleagues and dear friends. Two fantastic colleagues with great humor and many laughs. To both of you, without your support and understanding this would have been difficult to accomplish, especially thanks for all Tuesdays.

*Lizzian Brost*, colleague and dear friend, for your god advice in moments with disbelief and mistrust and for your enthusiasm. You deserve a widespread recognition for the wonderful person you are.

*Eva Öfverström*, colleagues and dear friend, for your never failing enthusiasm to support me and for your invaluable friendship. You are always there when I need you, with great sense of wonderful humor.



My lovely *Staff* at Neurosurgery Intensive Care Unit, for what you are, your friendship, positive attitudes and all your support. I also wish to thank for the help with collecting some of the data.

*Gunnar Gunnarsson*, computer genius and dear friend, for all your help when I needed it, you are always there. A big thanks to you for help with creating the BOPS, without BOPS this couldn't be done.

*Sylvia Larsson*, RN PhD and co-author, for valuable comments.

*Bengt Nellgård*, MD PhD, for you help with creating the BOPS.

*Johan Undén*, MD, co-author, and *Harald Bettger*, MD, for your help with translating the pain scales, and *Johan*, I especially want to thank you for linguistic revision.

*Bodil Eriksson* and *Ida Abbas*, for excellent secretarial assistance.

*Gunilla Moullin*, for superb help with creating the questionnaire and finding all sorts of references.

*Jan Lanke*, professor, and *Per Nyberg*, university lecturer, both in Statistics, for help with statistical evaluations, sharing your knowledge and valuable discussions.

*Mads Werner*, associated professor in Anaesthesia, and *Lena Westbom*, associated professor in Pediatric for valuable comments.

The *staff* of the Day surgery Care Unit for Children, BUS, for your assistance with collecting the data.

*Hans Säveland*, associated professor in Neurosurgery, and *All other colleagues* and *staff* at the Department of Neurosurgery for supporting me. I also want to especially thank the girls in *Qultur Klubben* (Q-club) – you are a source of mental power.

*Catarina Carlson*, my fellow student in Pediatric, who inspired me into the field of children's pain.

To all participating *patients* and *centers* and to all of you who not have been mentioning, but not forgotten – THANKS!

Last but not least, a big thought should be given to all my *Close Friends* for your encouragement and supports.

To my *family*, Granny *Olga*, *Misen*, *Benny*, and *Uffe*, for always believing in me and thanks to my “new” *family*, for your supports and especially for all Sundays.

My mother *Elisabeth* and father *Olle* for your love and excellent support and advice. I could not have had better parents.

But most of all I would thank *Christofer*, my dearest son for being the one you are. I thank you for your patience and to endure with a mother who always is working. You are a fantastic graffiti painter, thanks for “Betty BOPS”.

And finally, my dearest *friend and life companion*, you are a god listener and thanks for your exceedingly patience and understanding, friendship and love, without you, this book would never have been written.

## GRANTS

This work was supported by grants from Södra Sveriges Sjuksköterske Hem, SSSH, and Einar Björkelunds fond.

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