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Postoperative continuous intrathecal pain treatment in children after selective dorsal rhizotomy with bupivacaine and two different morphine doses

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Summary
Background: Children undergoing selective dorsal rhizotomy (SDR) are postoperatively in severe pain, a pain related to both the extensive surgical exposure with multilevel laminectomy and the nerve root manipulation. We sought to define an optimal dose of continuous intrathecal (IT) morphine and bupivacaine to treat this severe pain. The aim of this study was to compare two different concentrations of morphine in a fixed dose of bupivacaine with regard to the analgesic effect and survey if they differed in side effects.
Methods: 26 children, age 2.7 - 7.4 years undergoing SDR were included in this study. Postoperatively eleven children received a continuous infusion of morphine 0.4μg·kg^{-1}·h^{-1} and bupivacaine 40 μg·kg^{-1}·h^{-1} (low-dose group) and fifteen a continuous infusion of morphine 0.6 μg·kg^{-1}·h^{-1} and bupivacaine 40 μg·kg^{-1}·h^{-1} (high-dose group). The behavioural observational pain scale (BOPS) was used to evaluate pain.
Results: Better pain relief was obtained in the high-dose group seen in lower BOPS score compared with the low-dose group (P = 0.03, Fisher's permutation test and P = 0.06 Wilcoxon-Mann-Whitney (WMW) test). The low-dose group received seven times as much ketobemidone 0.43 ±0.54 mg/kh/48 h compared with 0.06 ±0.09 mg/kg/48 h in the high-dose group (P = 0.0005 Fisher's permutation test, P = 0.0017 WMW test). There was no statistical difference in pruritus and PONV between the groups. Respiratory and hemodynamic depression was not found.
Conclusion: This study shows that, when compared with low-dose, the higher dose of continuous IT morphine combined with bupivacaine, significantly reduce pain score and postoperative i.v analgesic requirements without increasing the adverse effects.

Keyword: Children, Intrathecal pain treatment, morphine, bupivacaine

Introduction
Serious lower extremity spasticity in children with cerebral palsy can cause significant disability, boundary activities of daily living and aggravate care. Selective dorsal rhizotomy (SDR) is a neurosurgical operation to reduce the spasticity. There are presently various operation techniques describing SDR (1 - 5). In 1978 Fasano et al. revised an old method. They developed a method to selectively divide the posterior spinal nerve rootlets based on an old technique that had previously been used nearly 100 years ago by Foerster (1). Ten years later Peacock et al. made a new modification of the surgical technique (4, 6) and this is the method used at our department since 1993. Postoperatively these children are in severe pain, a pain related to the extensive surgical exposure with multilevel laminectomy and the nerve root manipulation (2, 7 -11). During the last two decades there has been a devel-

Table 1. Demographical data in the two groups, data are presented as mean ± SD. There were no statistical differences between the groups.

	Low-dose group (n=11)	High-dose group (n=15)
Boys/girls (n)	6/5	9/6
Age (years)	4.8 ± 1.2	4.4 ± 1.1
Weight (kg)	15.9 ± 3.3	14.9 ± 1.50

n = number of children.

opment in intrathecal (IT) postoperative pain management for children. In 1984 Jones et al. (12) described IT morphine for postoperative pain relief in children with a single injection at the beginning of the surgery. This was followed by descriptions of IT pain management merely as a single dose of morphine (13 - 19) or morphine/bupivacaine (20) given preoperatively. Other authors describes IT injection of morphine at the end of the operation followed by intravenous (i.v) morphine (9, 21 - 24). The first description of continuous IT pain management postoperatively in children was a case report by Tobias describing two cases, where adequate postoperative or cancer pain relief was obtained (25). At our department we have used IT pain management since 1993, initially as intermittent morphine doses every 6^{th} hour. In order to improve the pain treatment for these patients we started with continuous infusion of morphine/bupivacaine (11). The amount of IT morphine seems to be related to the risk for developing pruritus, postoperative nausea and vomiting (PONV) and increases the risk for late respiratory depression making it desirable to use as small amounts of morphine as possible.

The aim of this study was to compare two continuous IT infusions with different amounts of morphine in fixed amounts of bupivacaine with regard to the analgesic effect and survey if they differed in side effects.

Patients and Methods

Patients

All children were premedicated with midazolam. General anaesthesia was induced with intravenous fentanyl and thiopental. Succinylcholine was given to facilitate tracheal intubation, followed by one dose of non-depolarizing muscle relaxant. Anaesthesia was maintained with isoflurane/N_2O/O_2/ and fentanyl. All children received a urinary bladder catheter.

A block laminotomy was performed from L_1 –L_5, the dura was opened and the cauda equina exposed. The posterior roots were identified and the level was confirmed by visible anatomical features and by using electrical stimulation. Each root was divided into rootlets and each rootlet was stimulated with microelectrodes and those rootlets associated with abnormal responses were cut.

In order to administrate the postoperative pain management a thin 19-gauge catheter was placed IT with the tip at the L_{2-} L_3 level. 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 in this catheter and rectal paracetamol 20 mg/kg. Postoperatively 11 children were treated with IT infusion of morphine $0.4 \mu g \cdot kg^{-1} \cdot h^{-1}$ and bupivacaine $40 \mu g \cdot kg^{-1} \cdot h^{-1}$ (low-dose group) and 15 with IT infusion of morphine $0.6 \mu g \cdot kg^{-1} \cdot h^{-1}$ and bupivacaine $40 \mu g \cdot kg^{-1} \cdot h^{-1}$ (high-dose group) delivered by a Pharmacia Deltec® pump. The concentration of the infusion was mor-

phine 10 µg/ml and bupivacaine 1000 µg/ml or morphine 15 µg/ml and bupivacaine 1000 µg/ml respectively. On the 3rd postoperative day the dose was reduced with 30%, on the 4th day with 50% and on the 5th postoperative day the intrathecal catheter was removed. All children received rectal paracetamol 20 mg/kg/6 h, and cefuroxim (Lifurox®, Lilly Sweden) in the standard amount.

Pain

The children were postoperatively observed at the Neurosurgical Intensive Care Unite (NICU) where the nurses were familiar with the use of continuous IT opioid/bupivacaine infusion. Every third hour the children were pain scored by the use of the Behavioural Observational Pain Scale, BOPS, (Fig. 1) the first 48 hours of their stay. Additional i.v pain management ketobemidone 0.05 mg/kg 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.

Adverse effects

All children were monitored postoperatively by intra-arterial blood pressure, continuous ECG, pulsoximetry and respiratory rate (Hewlett Packard Merlin 68S, Böblingen, Germany). These values were noted every 15 minutes for the first 2 hours, every 30 minutes the following 2 hours, by hourly registration the following 44 hours with a total registration of 48 hours postoperatively. A respiratory rate (RR) of < 12 breaths min^{-1} and/or oxygen saturation (SaO_2) < 93 was considered as respiratory depression. Mean arterial blood pressure (MAP) < 50 mm Hg in 2-3 years old, < 55 mm Hg in 3-4 years old and < 60 mmHg in 4-7 years old was noted as hemodynamic instability. Heart rate (HR) 100 -160 beat min^{-1} (2-3 year old child), 65-145 min^{-1} (3-4 years old) and 70-130 min^{-1} (4-7 years old) was considered as normal.

Every third hour 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.

Statistical analysis

The binary variable gender was analyzed by means of Fisher's exact test. All other variables were analyzed by means of the Wilcoxon- Mann-Whitney (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 standard deviation (SD). Average frequency of symptoms (pruritus and PONV) that are noted each third hour during the 48 hours is given in % of the group.

BOPS (Behavioural Observation Pain Scale)

Score	Facial expression	Verbalization	Body position
0	Neutral/positive smiling, composed	Normal conversation laugh, crow	Inactive, laying relaxed with all extremities or sitting, walking
1	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
2	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.

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.

Results

Baseline data is given in Table 1. There were no statistically significant differences between the groups with respect to age, gender or weight.

Pain

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 2 and 3) (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 ± 8.69 mg /48h versus 0.90 ± 1.39 mg /48h in the high-dose group (P = 0.0016, WMW test). Shown in mg/kg/48h the low-dose group received 0.43 ±0.55 compared to 0.06 ±0.09 in the high-dose group (P = 0.0017 WMW test and P = 0.0005 Fisher's permutation test).

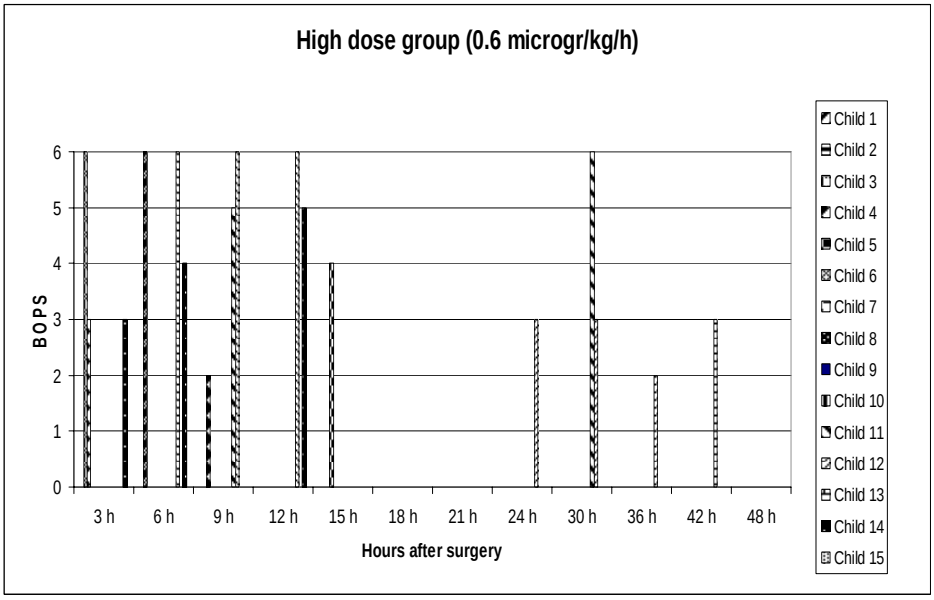

Figure 2. Postoperative BOPS score after intrathecal pain treatment with bupivacaine 40 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and morphine 0.6 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (high-dose) during the first 48 hours. The horizontal axis represent BOPS score 0 - 6 points and the vertical axis represent hours after surgery. Each bar symbolizes one child.

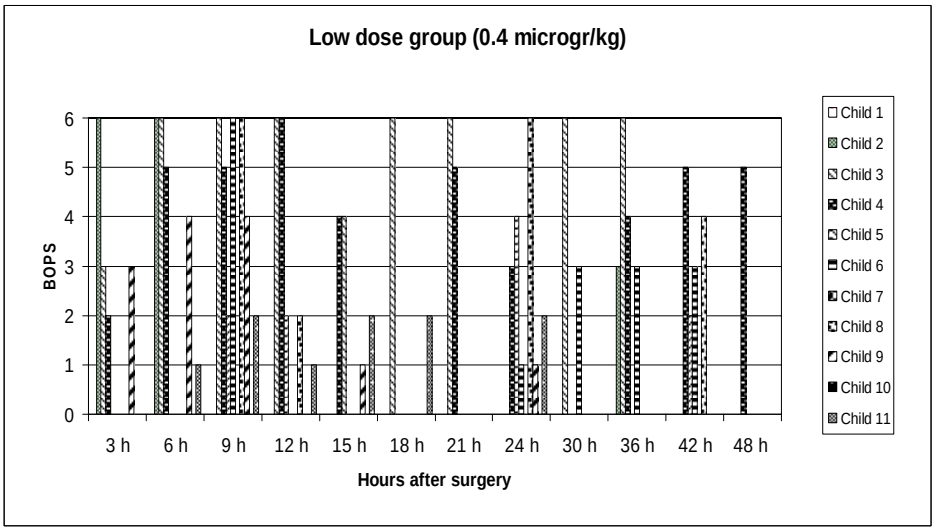

Figure 3. Postoperative BOPS score after intrathecal pain treatment with bupivacaine 40 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and morphine 0.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (low-dose) during the first 48 hours. The horizontal axis represent BOPS score 0 - 6 points and the vertical axis represent hours after surgery. Each bar symbolizes one child.

Table 2. Physiological data during the first 48 postoperative hours, data are presented as mean ± SD. PONV and pruritus in the two groups are presented in absolute values and in average frequencies (number of positive registration/48h) in percents. There were no statistical differences between the groups.

	Low-dose group (n=11)	High-dose group (n=15)
Heart rate (beats/min)	114 ± 9	116 ± 10
Mean arterial blood pres (mmHg)	73 ± 6	67 ± 6
Respiratory rate / min	22 ± 3	22 ± 2
Oxygen saturation ($SaO_{2)}$	97 ± 1	97 ± 1
Children with pruritus	7	9
Average frequency of pruritus	24%	14%
Children with PONV	8	13
Average frequency of PONV	14%	13%

n = number of children

Adverse effects

Physiological effects during follow-up are given in Table 2. All children were respiratory and hemodynamic stable and there were no statistical significances in hemodynamic or respiratory parameters between the groups. All children received antibiotic prophylaxis and no wound became infected.

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 mg x 3 and/or ondansetron 2 – 4 mg x 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. 4). PONV was treated with metoclopramide 0,2 mg/kg x 3 and/or ondansetron 2 – 4 mg x 2. In the low-dose group the children received 7.09 ± 5.00 mg ondansetron /child and in the high-dose group 7.73 ± 4.19 mg ondansetron /child during the first 48 postoperative hours.

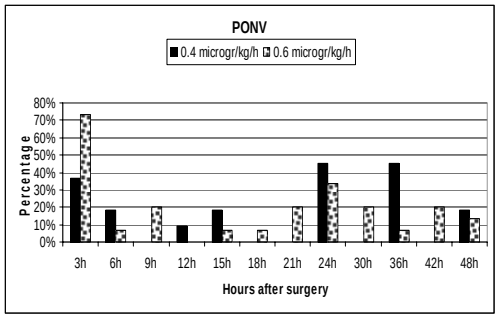

Figure. 4 Showing the percentage of postoperative nausea and vomiting (PONV) in the low-dose (0.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and high-dose (0.6 $\mu g \cdot kg^{-1} \cdot h^{-1}$) group at different times after operation.

Discussion

Pain

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 (9, 13, 17, 18, 21 - 23). 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 (12, 13, 19, 20, 22, 25) 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 (11). Tachyphylaxis can be a problem if local anaesthetics are used alone. The regimes with a combination of local anaesthetic and a low-dose of morphine have earlier been found to prevent such a development (27, 28). Another reason to use the rather hydrophilic morphine is because hydrophilic opioids are associated with good analgesia, not only limited to the segment were it is injected. IT injected morphine has a slow rostral diffusion as well as a slow penetration of the morphine into the surrounding nervous tissue giving rise to pain relief as well as adverse effects (29,30, 31).

In children only a few publications describe the use of continuous IT opioids with or without local anesthetics. Tobias (25) reports two successful cases, one with continuous IT fentanyl for 72 hours postoperatively and in the second case sufentanil was infused IT in combination with bupivacaine to treat cancer pain. Also, Galloway (32) used continuous IT morphine to treat cancer pain. In both these case stories the pain relief was satisfactory supporting the concept. Continuous infusion of IT morphine and bupivacaine for postoperative pain treatment was described in 2001 (11). 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 due to the treatment. In present study, looking at IT bupivacaine with two different concentration of morphine, we found pain relief during the postoperative period, especially in the high-dose group. The better pain relief was seen in 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 mg/kg/48h in order to keep the BOPS score below 2 points (fig.2 and 3).

Adverse effect

The mean arterial blood pressure tended to be lower in the high-dose group even though the differences were not statistical significant. A direct effect on the spinal cord opioid μ receptor with a sympatholytic effect could be the reason for the blood pressure reducing effect, or more plausible by the direct pain reducing effect (18).

Postoperatively all patients in both groups were breathing at normal rates and had normal SaO_2 with no differences between the groups. We did not observe any respiratory depression after continuous infusion of 14 μg/kg/24h in the high-dose group. Respiratory depression has been described after single injections of 20 μg/kg (12, 14, 17) even though other authors have used this dose without mentioning this complication (9, 13).

Pruritus is a general problem following spinal opioid administration (9, 16, 21, 23, 26, 30, 33). 64% of the children in the low-dose group and 60% in the high-dose group were recorded to have pruritus one or another time during the first 48 postoperative hours with an average frequency of 24% in the low-dose group compared with only 14% in the high-dose group. This findings was opposite of what was expected. A considerably higher amount of i.v ketobemidone was given to the children in the low-dose group being the only obvious reason that the low-dose group had more pruritus. In fact opioids i.v has been found to give rise to pruritus. In a recent study in chil-

dren i.v ketobemidone administrated alone gave itching in 56% (34). The general incidence of pruritus found in this study was low compared with other studies (7, 9, 31) and one reason could be our use of ondansetron to treat PONV. Former studies have implicated that ondansetron is effective in treating spinal morphine induced pruritus (16, 26, 35) and all children in the low-dose group and 73% of the children in the high-dose group received ondansetron.

The incidence of PONV varies from 10% to 77% in different studies and it can depend on the study design, the type of operations performed, the anaesthetic procedure and pain treatment regime. Krechel et al. (22) found that PONV occurred both when morphine was given IT and i.v as patient-controlled analgesia (PCA). The incidence of PONV in the IT morphine group was 31% compared with 22% in the PCA group. PONV was also present after epidural (ED) administration of opioids (31). In a study comparing continuous ED morphine and intermittent i.v. bolus doses of morphine the incidence of PONV was high in both groups with an incidence of 77% and 64% respectively (10). During the first 48 postoperative hours in this study 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 percentages of the childrens suffering PONV were 73% three hours after surgery in the high-dose group compared to 36% in the low-dose group (Fig. 4). The reason for this difference is not clear.

One concern of neuraxial techniques after spinal surgery is the potential risk of infection related to the catheter. Prophylactic cefuroxime was used to all patients in this study as well as during the last 12 years and no wound has never been infected. In fact no reports of infections complications in children related to the regional anaesthetic technique can be found (36).

In conclusion, continue IT pain treatment with morphine and bupivacaine provides safe and superior analgesia after major spinal operations. The present data recommend that a morphine dose of 0.6 $\mu g \cdot kg^{-1} \cdot h^{-1}$ may be a better option than 0.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$ in combination with 40 µg/kg/h of bupivacaine seen in better pain relief. This is further strengthened by the fact that adverse effects did not differ between the groups and was therefore not a drawback in the high-dose group.

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