Hormonal and metabolic stress responses after major surgery in children aged 0–3 years: a double-blind, randomized trial comparing the effects of continuous versus intermittent morphine†

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Children aged 0–3 yr were stratified for age and randomized to receive either continuous morphine (CM, 10 μg kg^{-1} h^{-1}) with three-hourly placebo boluses or intermittent morphine (IM, 30 μg kg^{-1} every 3 h) with a placebo infusion for postoperative analgesia. Plasma concentrations of epinephrine, norepinephrine, insulin, glucose and lactate were measured before and at the end of surgery and 6, 12 and 24 h after surgery. Pain was assessed with validated pain scales [the COMFORT scale and a visual analogue scale (VAS)] with the availability of additional morphine doses. Minor differences occurred between the randomized treatment groups, the oldest IM group (aged 1–3 yr) having a higher blood glucose concentration (P=0.003), mean arterial pressure (P=0.02) and COMFORT score (P=0.02) than the CM group. In the neonates, preoperative plasma concentrations of norepinephrine (P=0.01) and lactate (P<0.001) were significantly higher, while the postoperative plasma concentrations of epinephrine were significantly lower (P<0.001) and plasma concentrations of insulin significantly higher (P<0.005) than in the older age groups. Postoperative pain scores (P<0.003) and morphine consumption (P<0.001) were significantly lower in the neonates than in the older age groups. Our results show that continuous infusion of morphine does not provide any major advantages over intermittent morphine boluses for postoperative analgesia in neonates and infants.

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In adults, endocrine and metabolic responses to severe injury consist of a hypometabolic period, which lasts about 3 days, followed by a hypermetabolic period.[1 2] As a result of this homeostatic disturbance, cellular dehydration, capillary leakage and organ dysfunction may occur, leading to a prolonged convalescence period.[3] Although this endocrine-metabolic response can be modified by surgical anaesthesia, important reductions in stress responses depend on the analgesic method in adult patients[4 5 6] and in children.[7] Epidural anaesthesia was more effective in reducing surgical stress during low abdominal surgery than systemic opioids.[8] Diminished stress responses and improved postoperative outcomes were noted after high-dose opioids in neonates after cardiac surgery.[9 10] More recently, the use of i.v. opioids in non-surgical, mechanically ventilated neonates resulted in reduced physiological and behavioural measurements of pain and stress[11 12] and was associated with fewer periods of hypoxaemia[13] and

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improved neurological outcomes.[14] Because of the lack of randomized controlled trials in neonates and infants,[15] little is known about the alterations in hormonal-metabolic stress responses caused by postoperative analgesia or postnatal age in patients undergoing non-cardiac surgery.

This study was designed as a double-blind, randomized controlled trial to test the hypothesis that postoperative analgesia with continuous morphine infusion would provide improved analgesia with lower stress responses compared with intermittent doses. To obtain more information about physiological and behavioural responses after major surgery in young children, surgical stress was evaluated by measuring hormonal, metabolic and haemodynamic variables and postoperative pain was assessed by behavioural responses [COMFORT and a visual analogue scale (VAS)] and by the amount of morphine used. The ontogeny of these responses is unknown because of the paucity of data beyond the neonatal age group. Therefore, we randomized the patients into four developmentally relevant age groups.[16]

Methods

The study protocol was approved by the hospital medical ethics committee, and written consent was obtained from the parents. We included children aged 0–3 yr, admitted to the paediatric surgical intensive care unit (PICU) after non-cardiac thoracic and abdominal surgery. Patients were excluded if they had received analgesic or sedative drugs <6 h before surgery, if they were receiving neuromuscular blockade or if they suffered from hepatic, renal or neurological disorders or altered muscle tone. Patients were stratified by age into four groups [group I, 0–4 weeks (neonates); group II, 4 weeks to 6 months; group III, 6–12 months; group IV, 1–3 yr] and were assigned randomly to receive i.v. either continuous morphine (CM) or intermittent morphine (IM). The pharmacists prepared all study drugs, and the strata-specific schedules for randomization and the clinical staff were blinded to the study group allocation until data collection was complete.

Anaesthetic management was standardized. Anaesthesia was induced i.v. with thiopentone 3–5 mg kg^{-1} or by inhalation of halothane in oxygen. Fentanyl 5 μg kg^{-1} was given before orotracheal intubation, which was facilitated with atracurium 0.5–1 mg kg^{-1} or suxamethonium 2 mg kg^{-1}. Ventilation was controlled and anaesthesia was maintained with isoflurane 0.5 minimum alveolar concentration in 60% nitrous oxide in oxygen or air in oxygen. Perioperative fluids were standardized to maintain a glucose infusion rate between 4–6 mg kg^{-1} min^{-1}. Body temperature was kept within normal ranges. A peripheral artery was cannulated and the measured mean arterial blood pressure (MAP) and heart rate (HR) were used as preoperative baseline data. After the first arterial blood sample (baseline), patients received a second dose of fentanyl 5 μg kg^{-1} before surgical incision. Additional doses of fentanyl 2 μg kg^{-1} were administered when HR and/or MAP were 15% above baseline value. At the end of surgery, the neuromuscular block was antagonized and the tracheal tube was removed. Mechanical ventilation was continued in patients who required ventilatory assistance after surgery.

Directly after surgery, all patients received an i.v. loading dose of morphine (100 μg kg^{-1}) followed by a morphine infusion of 10 μg kg^{-1} h^{-1} for children in the CM group, combined with three-hourly i.v. placebo (saline) boluses. Children in the IM group received a continuous placebo infusion (saline) combined with three-hourly i.v. doses of 30 μg kg^{-1}. The first intermittent bolus (morphine or placebo) was given 3 h after surgery. Additional analgesia was given by the nurse when there were signs of pain, indicated by a VAS score ⩾4. During the first hour after surgery, one-third of the loading dose of morphine could be repeated every 15 min, and thereafter morphine 5 μg kg^{-1} could be given every 10 min if required. No other analgesic or sedative drugs were used.

Arterial blood samples were taken after induction of anaesthesia, at the end of surgery and 6, 12 and 24 h after surgery to determine plasma concentrations of epinephrine, norepinephrine, insulin, glucose and lactate. From 24 to 36 h after surgery, urine was collected for determination of the 3-methyl histidine/creatinine molar ratio (3MH/CR), a measure of protein breakdown.

After surgery, the Surgical Stress Score (SSS)[17] was computed by the surgeon and anaesthetist. Nurses performed regular assessments before surgery (baseline) and every 3 h up to 36 h after surgery. Nursing interventions included pain assessment using a VAS and the COMFORT scale,[18] blood sampling (as indicated), giving the intermittent bolus (placebo or morphine), and then nursing as needed. Thus, hormonal and metabolic stress responses were measured as plasma concentrations at time points corresponding to trough plasma morphine concentrations in the IM group.

The SSS consists of seven items: amount of blood loss; site of surgery; amount of superficial trauma; extent of visceral trauma; duration of surgery; associated stress factors (hypothermia, localized or generalized infection and prematurity); and cardiac surgery.[17] The total scores in this study (excluding cardiac surgery and prematurity <35 weeks) ranged from 3 to 24, and were used to classify the degree of surgical stress.

The VAS, a horizontal continuous 10 cm line with the anchor points 'no pain' on the left and 'extreme pain' on the right, was used as an observational instrument. VAS scores <4 indicate absent or mild pain and scores ⩾4 indicate moderate to severe pain, as noted from previous studies in children.

The COMFORT scale[18 19] was originally developed and validated to assess distress in children ventilated mechanically (0–18 yr). This scale consists of six behavioural items (alertness, calmness, respiratory response, movement, muscle tone and facial expression) and two physiological

items (MAP and HR). For non-ventilated children, the respiratory response item was replaced by an assessment of crying, possible scores ranging from 1 (no crying) to 5 (screaming). Total score ranges from 8 to 40. We have recently validated the COMFORT scale as a measure of postoperative pain in this age group.[20]

Plasma concentrations of epinephrine and norepinephrine were measured by HPLC using fluorimetric detection.[21] Plasma concentrations of insulin were measured using the Insulin IRMA CT kit (Medgenix). Standardized automated laboratory analysers measured plasma concentrations of glucose, lactate, total bilirubin and plasma and urinary creatinine. The concentration of urinary 3-methylhistidine was measured by ion exchange chromatography on an amino acid analyser.

In previous studies, a SD of 0.6 nmol litre^{-1} was found for epinephrine and 1.4 nmol litre^{-1} for norepinephrine.[10] To detect differences between the group values for plasma epinephrine (0.24 nmol litre^{-1}) and norepinephrine (0.56 nmol litre^{-1}) with a power of 80% at a two-sided alpha error of 0.05 would require 100 patients in each group. Repeated measurements analysis of variance (RmANOVA)[22] was used to evaluate simultaneously the effects of treatment, age groups and time after surgery. Plasma concentrations before surgery and changes from baseline values directly after surgery were compared between age groups using one-way ANOVA. Comparison with baseline values within age groups was by the paired *t*-test. In these analyses, all hormonal and metabolic data had to be transformed logarithmically in order to obtain approximately normal distributions. The postoperative time points (directly after surgery and 6, 12 and 24 h after surgery) at which individual plasma concentrations were highest were compared between age groups using the Kruskal–Wallis/Mann–Whitney test. The same tests were used to compare morphine consumption between groups. Correlation coefficients given are Spearman's.

All enrolled patients were included in an intention-to-treat analysis. Nine patients dropped out during the study (five in CM, four in IM) because of the loss of arterial access (seven), the need for neuromuscular blockade (one) and one postoperative death 3 h after surgery.

Results

Table 1 shows the clinical and surgical characteristics of the enrolled patients according to their age categories and randomized treatment groups.

A total of 204 patients were enrolled: 101 in the CM group and 103 in the IM group. The randomization schedule was stratified for age; other demographic and clinical variables were similar in the two randomized groups. Thirteen of the 35 neonates in the CM group (37%) were ventilated mechanically before surgery compared with six of the 33 in the IM group (18%). This difference was not significant.

For various reasons, 23 patients needed mechanical ventilation before surgery, seven of them for acute inflammatory surgical complications.

The median doses of fentanyl for age groups I, II, III and IV were 12, 12, 17 and 15 μg kg^{-1} respectively. Fentanyl doses did not differ significantly between the two treatment groups in any of the age groups (all $P>0.14$). The fentanyl dose correlated significantly with the duration of surgery ($r=0.43$, $P<0.001$). The age groups were similar with respect to SSS.

Hormonal and metabolic stress responses

Table 2 shows the median and interquartile range of the hormonal and metabolic variables before and after surgery (average of 6, 12 and 24 h after surgery) according to age and treatment.

Overall, no significant differences in plasma concentrations were found between the randomized treatment groups (all analyses $P\geqslant0.22$). For glucose, a significant interaction was found between the effects of treatment and age ($P=0.04$), indicating that the treatment difference was not the same in all age groups. Further analysis within each age group showed that blood glucose concentrations were lower in the CM group (16%, $P=0.003$) than in the IM group in the oldest age group (1–3 yr), although an opposite trend was noted among the neonates (CM>IM, $P=0.07$).

Figure 1 shows the geometric mean plasma concentrations with the SE for epinephrine, norepinephrine, insulin, glucose and lactate and the insulin/glucose ratio, for all patients, according to age, at the various time points (before and at the end of surgery and 6, 12 and 24 h after surgery).

Plasma concentrations of epinephrine before surgery were not significantly different between the age groups. The mean increase in plasma epinephrine concentration directly after surgery was significantly lower in the neonatal group than in the other age groups (1.6 *vs* 6–8 times baseline value, $P<0.001$), and no significant differences occurred between the older age groups. Mean values of the average postoperative plasma concentration of epinephrine (6, 12 and 24 h after surgery) were significantly lower in the neonatal group than in the older children (all $P<0.001$). RmANOVA showed that postoperative decreases in plasma epinephrine differed significantly between the age groups ($P<0.001$). In the neonates, the mean plasma concentration of epinephrine had returned to the baseline value 6 h after surgery and was below the baseline value at later time points ($P<0.05$). In the older age groups, mean values were still above baseline 24 h after surgery (all $P<0.001$). The highest plasma concentrations were mostly found directly after surgery in age groups I and III, and 6 h after surgery in age groups II and IV. Plasma epinephrine concentrations were not significantly different with respect to spontaneous or mechanical ventilation.

Plasma norepinephrine concentrations at baseline were significantly higher in the neonates than in age group II ($P=0.01$) and nearly so in comparison with age groups III

Table 1 Patient data [mean (range or SD)] and details of surgery. CM=continuous morphine; IM=intermittent morphine; *n*=number of patients. High abdominal surgery comprised diaphragmatic hernia/paresis, duodenal atresia, subtotal pancreatectomy, Nissen fundoplication, hepatic and choledochal surgery, (ad)renal surgery, stomic perforation. Superficial surgery comprised nephrectomy, ureter reimplantation, pyeloplasty, and operations for exstrophy of the bladder, sacroteratoma, yolk sac tumour, pull-through, incarcerated hernia. Acute gastrointestinal surgery comprised operations for atresia, malrotation, intussusception, necrotizing enterocolitis, meconium peritonitis and perforation, and ileus surgery

	Age group							
	I (0–4 weeks)		**II (4–26 weeks)**		**III (26–52 weeks)**		**IV (1–3 yr)**	
	CM (*n*=35)	**IM (*n*=33)**	**CM (*n*=34)**	**IM (*n*=33)**	**CM (*n*=16)**	**IM (*n*=15)**	**CM (*n*=18)**	**IM (*n*=22)**
Age (days)	8	3	97	101	267	254	632	639
(range)	(0–28)	(0–17)	(29–173)	(30–179)	(185–351)	(180–330)	(368–1070)	(393–1067)
Weight (kg)	3.1 (0.7)	2.9 (0.5)	4.9 (1.5)	4.6 (1.8)	6.9 (1.6)	7.3 (1.2)	11.1 (1.9)	11.1 (2.5)
Males/females (*n*)	21/14	19/14	21/13	22/11	9/7	9/6	9/9	10/12
Mechanical ventilation before surgery	13	6	4					
Total Surgical Stress Score	9.9 (2.8)	9.9 (2.9)	9.3 (3.3)	9.6 (2.5)	8.4 (3.1)	9.9 (2.7)	10.6 (2.9)	10.1 (3.7)
Generalized or localized infection	5	6		1			1	1
Surgical procedures								
Congenital diaphragmatic hernia	9	4			1	1		1
Tracheo-oesophageal atresia/TOF	6	9	1	1				
Bronchopulmonary (lobectomy, pneumectomy, cyst)		1	2	1			1	5
Cardiac (Blalock, vessel loop)			1	2				
Nissen fundoplication				2	2	2	2	4
Gastroschisis	1	1						
Acute gastrointestinal	15	15	11	5	5	2	3	2
Colonic pull-through					1			2
Closure of entero/colostoma			7	9	1	3	1	4
Rehbein's procedure	1		4	4	1	3		
Colon interposition							3	1
Urological (nephrectomy, pyeloplasty, reimplantation, bladder augmentation)		1	1	2			1	2
Miscellaneous (diaphragma paresis, tumour, teratoma, cyst, pancreatectomy, choledochal atresia)	1	2	7	7	5	3	2	7
Site of surgery								
Thoracic	5	8	6	4		2	5	1
Abdominal high/low	16/12	6/17	7/20	8/19	8/7	3/10	6/3	5/11
Thoracic combined with abdominal		2					3	2
Superficial			1	2	1		1	3

and IV (both P=0.06). The increases in plasma norepinephrine concentrations (6, 12 and 24 h after surgery) compared with baseline values were significantly smaller in the neonates than in age groups II (P=0.004) and III (P=0.05). The mean average plasma concentration of norepinephrine (6, 12 and 24 h after surgery) showed no significant differences between age groups or assessment times. Only for the oldest age group was there a significant increase in plasma concentrations 6 h after surgery (P=0.03). No significant differences were found between age groups regarding the time at which individual patients reached the highest plasma concentration. In all age groups, plasma concentrations of norepinephrine were still significantly above baseline values 24 h after surgery (all P<0.001). Neonates who were ventilated mechanically showed significantly higher plasma concentrations of norepinephrine before operation compared with the non-ventilated neonates (P=0.02). This difference was not significant in the postoperative period. In patients of age group II (1–6 months) needing mechanical ventilation after surgery, there were significantly higher plasma concentrations of norepinephrine compared with the non-ventilated children of that age group (P=0.02).

Plasma insulin concentrations at baseline were not significantly different between the age groups; however, directly after surgery, plasma concentrations were significantly higher in the neonates than in age groups III (P=0.002) and IV (P<0.001). The average plasma concentration of insulin (6, 12 and 24 h after surgery) showed a significant correlation with age (r=–0.34, P<0.001).

Plasma glucose concentrations before surgery were not significantly different between the age groups and they were generally highest directly after surgery in all age groups. RmANOVA of glucose plasma concentrations 6, 12 and 24 h after surgery showed a significant decrease after surgery (P<0.001). At 24 h after surgery, mean plasma concentrations were not significantly different from baseline values in all age groups.

Table 2 Hormonal and metabolic variables before and after surgery (average of 6, 12 and 24 h after surgery) according to age and treatment. All values are median (interquartile range). CM=continuous morphine; IM=intermittent morphine; *n*=number of patients

	Age group															
	I (neonates, 0–4 weeks)				**II (4 weeks to 6 months)**				**III (6 months to 1 yr)**				**IV (1–3 yr)**			
	CM	***n***	**IM**	***n***	**CM**	***n***	**IM**	***n***	**CM**	***n***	**IM**	***n***	**CM**	***n***	**IM**	***n***
Epinephrine (nmol litre^{-1})																
Before surgery	0.1 (0.03–0.36)	34	0.11 (0.04–0.33)	32	0.07 (0.02–0.2)	29	0.10 (0.05–0.22)	32	0.11 (0.05–0.34)	16	0.16 (0.08–0.37)	15	0.19 (0.04–0.29)	18	0.10 (0.05–0.65)	21
After surgery	0.14 (0.05–0.28)	33	0.06 (0.03–0.29)	30	0.56 (0.31–0.97)	27	0.57 (0.36–0.97)	26	1.02 (0.6–1.81)	15	1.05 (0.67–1.67)	14	1.42 (0.94–2.02)	15	1.93 (1.43–2.55)	17
Norepinephrine (nmol litre^{-1})																
Before surgery	1.6 (.98–3.2)	34	1.6 (0.9–2.6)	32	1.1 (0.6-.9)	29	0.9 (0.6–1.8)	32	1.0 (0.6–1.9)	16	1.0 (0.7–1.8)	15	0.8 (0.5–1.5)	18	1.0 (0.4–2.3)	21
After surgery	2.6 (1.8–4.2)	33	2.1 (1.3–3.2)	30	2.7 (2.0–3.7)	27	2.6 (2.0–4.4)	26	2.6 (1.7–2.9)	15	2.6 (1.7–3.1)	14	2.4 (1.5–2.9)	15	2.3 (1.8–3.6)	17
Insulin (mU litre^{-1})																
Before surgery	5.0 (5.0–8.0)	31	5.0 (5.0–7.5)	29	5.0 (5.0–8.0)	31	5.0 (5.0–5.8)	32	5.0 (5.0–5.0)	16	5.0 (5.0–9.0)	15	5.0 (5.0–7.0)	18	5.0 (5.0–6.0)	22
After surgery	13.8 (9.4–17.1)	32	12.0 (8.5–19.6)	28	11.0 (8.7–14.3)	27	8.3 (6.0–12.2)	25	7.0 (5.7–11.3)	15	9.7 (7.5–12.6)	14	6.7 (5.3–10.0)	15	10.0 (6.8–12.8)	17
Glucose (mmol litre^{-1})																
Before surgery	5.5 (3.9–7.1)	35	5.7 (3 9–7.1)	32	5.8 (4.5–6.8)	31	5.6 (4.5–6.3)	32	4.5 (4.1–5.8)	16	5.6 (4.6–6.2)	15	4.5 (3.9–5.5)	18	4.9 (3.7–6.0)	22
After surgery	5.8 (5 2–6.7)	34	5.1 (4.5–6.7)	31	6.3 (5.1–6.5)	27	5.6 (5.1 –7.0)	25	5.8 (5.5–6.3)	15	6.3 (5.7–6.6)	14	5.9 (4.4–6.3)	15	6.7 (5.8–7.1)	18
Lactate (mmol litre^{-1})																
Before surgery	1.9 (1.3–2.7)	35	2.1 (1.3–2.8)	31	1.2 (1.0–1.4)	29	1.1 (0.8–1.3)	32	1.2 (0.9–1.5)	16	1.0 (0.9–1.5)	15	1.2 (0.8–1.5)	17	1.1 (0.8–1.3)	22
After surgery	1.5 (1.2–1.8)	32	1.5 (1.2–2.2)	29	1.2 (0.8–1.4)	25	1.0 (0.8–1.3)	24	0.9 (0.8–1.0)	15	0.8 (0.8–1.0)	14	0.9 (0.8–1.0)	15	0.9 (0.7–1.0)	17
Insulin/glucose ratio (U mol^{-1})																
Before surgery	1.1 (0.8–2.5)	31	1.1 (0.8–1.6)	28	1.1 (0.9–1.5)	31	1.0 (0.9–1.4)	32	1.2 (1.1–1.3)	16	1.1 (0.9–1.3)	15	1.2 (1.1–1.3)	18	1.1 (0.9–1.5)	22
After surgery	2.2 (1.8–3.0)	34	2.3 (1.7–3.1)	33	1.9 (1.6–2.5)	29	1.6 (1.1–2.0)	30	1.2 (1.0–2.1)	15	1.5 (1.3–2.1)	15	1.4 (1.1–1.7)	18	1.4 (1.0–1.9)	21

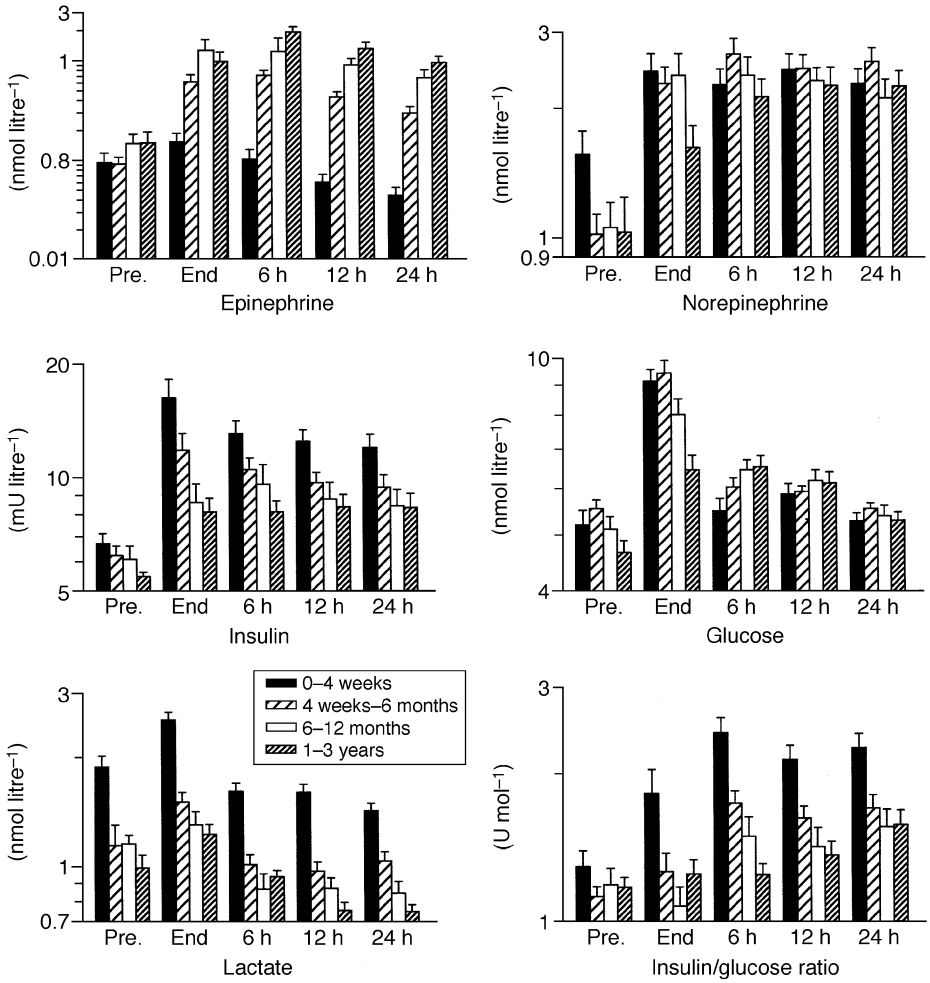

Fig 1 Plasma concentrations of epinephrine (nmol litre^{-1}), norepinephrine (nmol litre^{-1}), insulin (mU litre^{-1}), glucose (mmol litre^{-1}) and lactate (mmol litre^{-1}) and the insulin/glucose ratio (U mol^{-1}). The figure concentrates on the effects of age when the two treatment groups are combined. Data are geometric means with SE before surgery (Pre.), at the end of surgery (End) and 6, 12 and 24 h after surgery. Note the logarithmic scale of the vertical axes.

The insulin/glucose ratio was not significantly different before operation, but showed significant differences after surgery between the age groups in their patterns of postoperative changes. There was a significant correlation (r=–0.45, P<0.001) between age and insulin/glucose ratio 6, 12, and 24 h after surgery. At 24 h after surgery, the mean insulin/glucose ratio was still above baseline for all age groups.

The mean plasma concentration of lactate at baseline was significantly higher in the neonates than in the other age groups (all P<0.001). Highest concentrations were found directly after surgery, with no significant difference in the change from baseline values between the age groups. In the neonatal group there was a significant decrease from 6 to 24 h after surgery (P=0.02). A similar effect was found in age group IV (P<0.001), but there were no significant postoperative differences for age groups II and III. Mean plasma concentrations of lactate were significantly below baseline values 24 h after surgery (all P<0.001). There was no significant difference in the urinary 3MH/Cr ratio (from 12 to 36 h after surgery) between the randomized treatment groups or the age groups.

Plasma concentrations of epinephrine (P=0.01) and norepinephrine (P=0.003) were significantly higher after upper abdominal surgery than after thoracic or superficial surgery. A repeated analysis that excluded the eight patients with 'superficial' surgery (Table 1) gave results similar to those in Table 3. In 14 patients (11 of them neonates), hormonal and metabolic stress responses may have been influenced by acute, inflammatory surgical complications. A repeated analysis that excluded the 14 patients with 'localized or generalized infection' again gave results similar to those in Table 3.

Significantly higher plasma concentrations of norepinephrine occurred after blood transfusion in neonates compared with neonates without transfusion at 6 (P=0.01), 12 (P=0.07) and 24 h (P=0.03) after surgery. These differences were not found in the other age groups.

Table 3 Comparison between continuous morphine (CM) and intermittent morphine (IM) by RmANOVA, while controlling for age group (I, II, III and IV), sampling time (6, 12 and 24 h after surgery) and preoperative (baseline) plasma concentration. Data are the ratio of geometric means (CM/IM). *Significant differences between the age groups: I, 1.12 (P=0.07); II, 0.99 (P=0.75); III, 0.96 (P=0.57); IV, 0.84 (P=0.003)

Variable	Ratio (CM/IM)	95% CL	*P*
Epinephrine	1.08	0.81–1.44	0.59
Norepinephrine	1.05	0.91–1.20	0.51
Insulin	0.92	0.81–1.05	0.22
Glucose	0.98*	0.95–1.04	0.52
Insulin/glucose ratio	0.97	0.86–1.08	0.55
Lactate	0.98	0.90–1.07	0.67

RmANOVA showed that postoperative increases in MAP (3–36 h after surgery) from baseline values depended on age. Significantly greater increases in the IM group compared with the CM group were found in age group III [12.0 (SD 5.8) mm Hg, P=0.04] and within age group IV [10.6 (4.4) mm Hg, P=0.02], but no significant differences were found in the other age groups.

In the neonates, mean HR at baseline was significantly higher in the CM than in the IM group (P=0.03). Increases in HR at the end of surgery or postoperatively were not significantly different between the two treatment groups. However, the change from baseline HR increased significantly with age (P=0.002), with maximum values recorded 6 h after surgery for all age groups.

Pain assessment

Postoperative pain scores, morphine consumption during the first 24 h after surgery and the number of patients needing postoperative mechanical ventilation during >36 h after surgery are shown in Table 4.

Mean VAS scores (3–36 h after surgery) were significantly different between the age groups but not between the CM and IM groups. VAS scores generally declined with time after surgery. More than 24 h after surgery, the mean VAS was still significantly higher in age group II than in each of the other age groups (all P<0.04).

The mean VAS scores were significantly lower in the neonates (1.3) than in the three older age groups (2.4, 2.1 and 1.8 respectively) (all P<0.003) and in group IV compared with group II (P<0.001). VAS scores of $\geqslant$4 occurred less frequently in neonates than in the older age groups (P<0.002) and in group IV compared with age group II (P=0.004). The occurrence of VAS $\geqslant$4 was correlated significantly with plasma concentrations of norepinephrine, but only in age groups III and IV at 6 h after surgery (both P<0.05).

The mean COMFORT score (3–36 h after surgery) was significantly different between CM and IM only in age group IV (18.8 and 20.8 respectively, P=0.02). Overall, the mean COMFORT score was significantly (P<0.001) lower in the neonates (17.4) than in the older age groups (21.4, 20.6 and 19.8 respectively). Generally, the plasma concentrations of epinephrine and norepinephrine were weakly correlated with COMFORT scores at the various time points.

Morphine consumption (excluding the loading dose) during the first 24 h after surgery was significantly different between the age groups, but not between the CM and IM groups. Morphine consumption during the first 24 h after surgery was significantly lower in the neonatal group than in age groups II, III and IV (all P<0.001), and significantly higher in group II than in group IV (P=0.035).

Discussion

We present the first randomized, placebo-controlled trial that includes a double-blind assessment of the clinical and physiological effects of continuous *vs* intermittent morphine for postoperative analgesia in neonates and older infants. In addition, we report important differences between the different age groups that will allow deeper understanding of the ontogeny of hormonal-metabolic stress responses in early life. Although the post-neonatal period is associated with major changes in the regulation of the hypothalamic-pituitary-adrenal axis and the hypothalamic sympathetic outflows (via the posterior hypothalamic nuclei and locus coeruleus), the effect of these developmental events on the neuroendocrine responses to surgical stress remains unclear.

On the basis of these data, we can reject our primary hypothesis that continuous infusions of morphine postoperatively produce improved postoperative analgesia and lower hormonal-metabolic responses. Although supplementary doses of morphine were used to treat clinical signs of distress after surgery, standard criteria were used for these treatments in the CM and IM groups. Clinical bias was eliminated by a double-blind study design and total morphine consumption was similar in the two randomized groups. The additional morphine doses were considered to be necessary for the patient's comfort and for ethical reasons. In infants aged 1–3 yr, greater degrees of stress were noted in the IM group than in the CM group, as noted by significant increases in postoperative hyperglycaemia, mean arterial pressure and clinical assessment by the COMFORT score. Because these measurements were performed at the time of trough morphine concentrations for the IM group, these differences may have been caused by the relatively great plasma clearance of morphine in this age group.[23–25] Thus, it is likely that the longer duration of opioid effect after intermittent morphine boluses in the younger age groups resulted in clinical and physiological effects that were similar to those of a continuous infusion.

Similar clinical trials in adult patients have reported conflicting results, suggesting superior[26], equivocal[27] or inferior[28] clinical effects of continuous i.v. infusions *vs* intermittent doses of morphine for postoperative analgesia. To our knowledge, a similar clinical trial has not been reported in paediatric patients, although several studies

Table 4 Postoperative pain scores [mean (SD)], morphine consumption in the first 24 h after surgery (excluding loading dose) [median (interquartile range)], and number of patients ventilated mechanically >36 h after surgery. The range of the visual analogue scale (VAS) is 1–10 and that of the COMFORT score is 3–24. *Average of values 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33 and 36 h after surgery. CM=continuous morphine; IM=intermittent morphine; *n*=number of patients. Data are mean (SD)

	Age group													
	I (neonates, 0–4 weeks)				II (4 weeks to 6 months)				III (6 months to 1 yr)				IV (1–3 yr)			
	CM	*n*	IM	*n*	CM	*n*	IM	*n*	CM	*n*	IM	*n*	CM	*n*	IM	*n*
VAS score*	1.3 (0.8)	34	1.3 (0.5)	32	2.6 (0.8)	28	2.3 (0.9)	29	2.0 (0.8)	15	2.1 (0.8)	14	1.5 (1.2)	16	2.1 (1.2)	20
COMFORT score*	17.4 (2.9)	31	17.3 (2.3)	28	21.8 (2.0)	26	21.0 (3.1)	27	20.2 (3.1)	15	21.2 (3.1)	12	18.7 (3.1)	15	21.0 (2.6)	17
Morphine (μg kg^{-1} h^{-1})	10.0 (10.0–11.3)	34	10.0 (10.0–10.5)	33	12.3 (11.2–17.8)	29	11.6 (10.2–14.8)	30	11.7 (10.4–14.9)	15	12.1 (10.2–15.2)	15	10.9 (10.2–11.5)	17	11.0 (10.0–15.4)	21
Mechanical ventilation >36 h after surgery		26		15		4		7		0		1		2		2

comparing i.v. with epidural morphine analgesia have been reported.[29]

These data indicate that the pattern of surgical stress responses differs between neonates (postnatal age 0–4 weeks) and older age groups. Robust developmental differences were found for the postoperative changes in hormonal-metabolic variables (plasma epinephrine, norepinephrine, insulin and lactate), cardiovascular responses (MAP and HR), behavioural variables used for pain assessment (VAS and COMFORT scores), and postoperative morphine consumption.

Compared with previous data,[30] the magnitude of postoperative epinephrine responses was reduced in these neonates because of the effective anaesthetic and analgesic regimens used in the present study, although the brief duration of this response was similar to those in previous data.[30] Neonates with complex congenital heart defects were able to mount greater epinephrine responses,[10] suggesting that neonates are capable of increasing their production of epinephrine depending on the level of surgical stress. Decreased plasma concentrations of epinephrine at the end of surgery and decreased postoperative VAS and COMFORT scores in the neonates compared with older infants suggest that the doses used for fentanyl anaesthesia during surgery and postoperative morphine analgesia were inadequate for the older infants.[31] This is further corroborated by the greater amounts of additional postoperative morphine required by the older infants than by the neonates.

These findings can be explained by developmental differences in pharmacokinetic and pharmacodynamic factors between neonates and older infants. In studies comparing the effect of i.v. opioids (fentanyl at a mean dose of 1.3 μg kg^{-1} and morphine to a maximum of 0.2 mg kg^{-1}) with spinal and extradural analgesia during major surgery in infants (0–4 yr), all methods gave adequate postoperative analgesia, but more effective suppression of epinephrine and norepinephrine was found in the spinal and extradural groups.[8] In the present study, the mean plasma concentrations of epinephrine and norepinephrine were similar to those of the spinal and extradural groups, suggesting that the fentanyl doses were adequate even for high abdominal and thoracic surgery. Most full-term infants older than 4 weeks did not require mechanical ventilation, because they had opioid-induced ventilatory depression.

In contrast with the neonates, the older age groups had plasma concentrations of epinephrine that remained increased during the first 24 h after surgery, which might have been a result of additional stress factors operative in older infants, such as their emotional reactions to a strange environment, hunger, and separation anxiety. Alternatively, greater catecholamine responses may have resulted from direct or reflex stimulation of the efferent nerves supplying the adrenal glands during upper abdominal surgery.[32]

The significantly higher plasma concentrations of norepinephrine at baseline in the ventilated than in the non-ventilated neonates might be explained by the withdrawal of

sedative and analgesic drugs before surgery (according to the study protocol) in a limited number of patients.

Preoperative neonatal plasma concentrations of lactate were comparable with those in previous studies.[10] Baseline values in the present study were not quite comparable with published results,[8 10] because the first blood sampling in the present study occurred after the administration of fentanyl anaesthesia, whereas in the other studies baseline samples were drawn before analgesia.

Neonates had lower pain scores and needed less morphine than older children, probably because of the increased morphine metabolism more than 4 weeks after birth, resulting from closure of the ductus venosus and maturation of hepatic enzymes.[33 34] We found no consistent correlation of physiological signals of acute pain (plasma concentrations of epinephrine and norepinephrine) with behavioural pain scores (VAS and COMFORT scale).

The results of the present study allow us to draw important clinical and physiological conclusions. We can resolve the clinical controversy regarding continuous *vs* intermittent morphine analgesia. We have shown that neonates and infants up to 1 yr of age can be given intermittent morphine doses, thereby avoiding excessive fluid intake and the need for infusion equipment. Older infants (1–3 yr) may require either a continuous infusion or more frequent dosing (every 1–2 h) or judicious increases in the intermittent doses used for postoperative morphine analgesia.

In addition, we have documented significant differences in hormonal and metabolic stress responses, physiological variables, behavioural responses and morphine consumption between neonates and older infants. These differences may result from the developmental changes in opioid pharmacology that occur in early infancy. Either neonates are unable to mount robust behavioural responses to postoperative pain or they may need less morphine for satisfactory behavioural pain scores. It is also evident that neonates need analgesia and/or sedation during mechanical ventilation in order to control catecholamine responses. In the different age groups between 4 weeks and 3 yr, we found similar patterns of hormonal-metabolic responses, behavioural responses and postoperative morphine consumption (although minor differences were found between infants aged 1–6 months and 1–3 yr).

We speculate that combined therapy with different classes of analgesic and sedative drugs will provide more effective control of physiological and behavioural responses, especially in children 1–3 yr of age, who may have a high level of anxiety in the PICU. Further studies are needed to establish the efficacy and safety of such combinations. We strongly support the recent editorial calling for more randomized clinical trials to investigate analgesic regimens in young children, due to the absence of validated clinical protocols for infants undergoing surgery.[15] Not only will these studies provide a scientific framework for the postoperative management of neonates and young infants, but they may also provide clues about the development of pain and stress-responsive systems in the developing brain.

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