Rectal acetaminophen does not reduce morphine consumption after major surgery in young infants

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Background. The safety and value of acetaminophen (paracetamol) in addition to continuous morphine infusion has never been studied in newborns and young infants. We investigated the addition of acetaminophen to evaluate whether it decreased morphine consumption in this age group after major thoracic (non-cardiac) or abdominal surgery.

Methods. A randomized controlled trial was performed in 71 patients given either acetaminophen 90–100 mg kg⁻¹ day⁻¹ or placebo rectally, in addition to a morphine loading dose of 100 µg kg⁻¹ and 5–10 µg kg⁻¹ h⁻¹ continuous infusion. Analgesic efficacy was assessed using Visual Analogue Scale (VAS) and COMFORT scores. Extra morphine was administered if VAS was ≥4.

Results. We analysed data of 54 patients, of whom 29 received acetaminophen and 25 received placebo. Median (25–75th percentile) age was 0 (0–2) months. Additional morphine bolus requirements and increases in continuous morphine infusion were similar in both groups (P=0.366 and P=0.06, respectively). There was no significant difference in total morphine consumption, respectively, 7.91 (6.59–14.02) and 7.19 (5.45–12.06) µg kg⁻¹ h⁻¹ for the acetaminophen and placebo group (P=0.60). COMFORT [median (25–75th percentile) acetaminophen 10 (9–12) and placebo 11 (9–13)] and VAS [median (25–75th percentile) acetaminophen 0.0 (0.0–0.2) and placebo 0.0 (0.0–0.3)] scores did not differ between acetaminophen and placebo group (P=0.06 and P=0.73, respectively).

Conclusions. Acetaminophen, as an adjuvant to continuous morphine infusion, does not have an additional analgesic effect and should not be considered as standard of care in young infants, 0–2 months of age, after major thoracic (non-cardiac) or abdominal surgery.


Keywords: anaesthesia, paediatric; analgesia, postoperative; analgesics, non-opioid, acetaminophen; analgesics opioid, morphine

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Continuous morphine infusion is considered as standard of care for postoperative analgesia after major surgical procedures in young infants.1 Neonates and infants have an increased risk of respiratory depression with continuous morphine infusion because clearance is reduced and has a large inter-individual variability, resulting in higher plasma concentrations than older children given similar doses.2 3 The additional use of acetaminophen (paracetamol) has become more and more popular, as it may be associated with reduced morphine use, reduction in stress responses, and a lower incidence of side effects.4 5 In adults, combinations of opioids with acetaminophen or
non-steroidal anti-inflammatory drugs (NSAIDs) have resulted in reduced morphine and fentanyl consumption and reduced postoperative pain.\textsuperscript{5–1 1} However, the combination of opioids with acetaminophen or NSAIDs did not change the incidence of morphine-related adverse effects (nausea, vomiting, pruritus, urinary retention, and apnoea) in the postoperative period in adults.\textsuperscript{5–1 1}

Morton\textsuperscript{12} has demonstrated reduced morphine requirements in postoperative children aged 3–15 given diclofenac 1 mg kg\textsuperscript{-1} 8 hourly, but no effect attributable to acetaminophen 15 mg kg\textsuperscript{-1} 6 hourly was shown. Nevertheless, NSAIDs have numerous contraindications and consequently cannot be used in >25% of postoperative patients.\textsuperscript{13}

The safety and value of acetaminophen in addition to continuous morphine infusion has never been studied in newborns and young infants. We conducted a randomized controlled trial in newborns and young infants to test the hypothesis that the addition of acetaminophen decreased morphine consumption in this age group after major thoracic (non-cardiac) or abdominal surgery.

The use of placebo in this study was justified by the fact that before the initiation of this study, standard treatment after abdominal or thoracic surgery in our Paediatric Surgical Intensive Care Unit (PSICU) was morphine administered by continuous infusion, as there were no data in the literature suggesting a morphine sparing effect of acetaminophen in children of this age. Furthermore, all children participating in this study were to have optimal analgesic treatment by the possibility of the administration of extra morphine boluses or increases in continuous morphine infusion when Visual Analogue Scale (VAS) scores indicated children were in pain (VAS $\geq 4$).

**Methods**

Approval for the study was granted by the Medical Ethical Committee of the ErasmusMC Rotterdam and written informed consent was obtained from parents. Children were enrolled consecutively during the period from January 2001 to May 2002. Inclusion criteria were neonates and infants aged 0–1 yr, $\geq$36 weeks post-conceputational age, weight $\geq$1500 g, and abdominal, including urological or thoracic (non-cardiac) surgery. Exclusion criteria were current opioids, acetaminophen or other analgesics, sedative drugs or neuromuscular blocking agents $<12$ h before surgery, hepatic diseases interfering with drug metabolism, abnormal renal function (creatinine $>2$ s for age), neurological damage (post-hypoxic encephalopathy or major congenital anomalies of the central nervous system), and severe spasticity or hypotonia.

The study was discontinued if the parents withdrew informed consent, if the patient developed signs of hypersensitivity or an allergic reaction to either morphine or acetaminophen, or if the patients’ clinical condition deteriorated and re-operation was required.

Patients were studied for 48 h and were randomly assigned to receive rectal acetaminophen (30 mg kg\textsuperscript{-1} loading dose for children $<4$ kg and 40 mg kg\textsuperscript{-1} loading dose for children $\geq 4$ kg, followed by 20 mg kg\textsuperscript{-1} 6 hourly)\textsuperscript{14–1 6} in Group A or placebo as adjuvant to continuous morphine infusion in Group B.

Acetaminophen dose and the route of administration were based on international guidelines and on the results of previous studies\textsuperscript{14–1 6} showing that high acetaminophen doses (90–100 mg kg\textsuperscript{-1}) can be administered safely with a rectal loading dose (30–40 mg kg\textsuperscript{-1}) followed by regular maintenance doses (20 mg kg\textsuperscript{-1} 6 hourly or 30 mg kg\textsuperscript{-1} 8 hourly).

Anaesthesia was induced using i.v. thiopentone 3–5 mg kg\textsuperscript{-1} or by inhalation with sevoflurane in a nitrous oxide/oxygen mixture. Fentanyl 5 $\mu$g kg\textsuperscript{-1} was given through i.v. before tracheal intubation to all children. Tracheal intubation was facilitated with atracurium 0.5–1 mg kg\textsuperscript{-1} or suxamethonium 2 mg kg\textsuperscript{-1}. Artificial ventilation was continued and anaesthesia was maintained with oxygen/nitrous oxide or oxygen/air, isoflurane 0.5–1 mean alveolar concentration (MAC), and dose corrected for age.\textsuperscript{17 18} Monitoring consisted of ECG, non-invasive blood pressure (NIBP), oxyhaemoglobin saturation ($S_{pO_2}$), end-tidal carbon dioxide levels ($tCO_2$), and temperature. The NIBP and heart rate 10 min after tracheal intubation were used as peroperative baseline values, as described earlier.\textsuperscript{17 18} Before incision, a further dose of fentanyl 5 $\mu$g kg\textsuperscript{-1} was given. Extra doses of fentanyl (2 $\mu$g kg\textsuperscript{-1}) were given when the heart rates and/or the mean arterial blood pressure was 10% above the baseline values.

Peroperative fluids were given in a standardized way to maintain a glucose infusion rate between 4 and 6 mg kg\textsuperscript{-1} min\textsuperscript{-1}. Body temperature was kept within normal ranges. At the end of surgery, the neuromuscular block was antagonized and patients were extubated, unless the anaesthesiologist and surgeon decided to continue artificial ventilation.

The rectal loading dose (acetaminophen or placebo) was administered directly after induction of anaesthesia. At the end of surgery, all patients received an i.v loading dose of morphine HCl 100 $\mu$g kg\textsuperscript{-1}. After surgery, all children received a continuous morphine infusion, with a background of 5 $\mu$g kg\textsuperscript{-1} h\textsuperscript{-1} for children $<45$ weeks post-conceptional age and 10 $\mu$g kg\textsuperscript{-1} h\textsuperscript{-1} for children $\geq 45$ weeks post-conceptional age. The patients did not receive any additional regional anaesthesia.

Pain assessment was performed by Intensive Care Unit (ICU) nurses and investigators according to the algorithm (Fig. 1).\textsuperscript{18 1 9} using pain scores validated for this age group and these circumstances. Both nurses and investigators were trained to perform the COMFORT and VAS scores according to the guidelines of our hospital, as previously described by us.\textsuperscript{18 1 9} VAS (0–10) and COMFORT (0–30) scores were obtained every 2 h during the first 24 h after operation and every 3 h during the second 24 h after
surgery, as part of the routine nursing observations during handling of the child.\textsuperscript{20–23}

Continuous morphine infusion was routinely decreased in the second 24 h depending on the VAS score. When VAS≥4, extra amounts of morphine 5 νg kg\textsuperscript{-1} were administered until the child was in minimal pain, as indicated by a VAS score <4. Ten minutes after each extra dose of morphine, pain was re-assessed. When the child needed an extra morphine bolus ≥3 times h\textsuperscript{-1}, continuous morphine infusion was increased to 5 νg kg\textsuperscript{-1} h\textsuperscript{-1}, which could be increased if the child still needed extra doses of morphine >3 times h\textsuperscript{-1} (the maximum morphine background was 15 and 30 νg kg\textsuperscript{-1} h\textsuperscript{-1} for children <45 and ≥45 weeks post-conceptional age, respectively).

Distress other than that originating from pain was assessed by COMFORT scores ≥17 and VAS scores <4. Children then received midazolam for extra sedation (Fig. 1).

Blood samples (0.2 ml per sample) for acetaminophen plasma concentration analysis were obtained, respectively, before and 2 h after acetaminophen administration through the arterial catheter, which was inserted after induction, at 30 and 90 min, at the end of surgery, and 6, 8, 12, 14, 18, 20, 24, 26, 30, 32, 36, 38, 42, 44, 48 and 2, 12, 24, and 48 h after the arrival at the ICU. Blood samples (0.4 ml per sample) for morphine plasma concentration analysis were taken through the arterial catheter at 2, 12, 24, and 48 h after the arrival at the ICU, resulting in a total amount of 5.2 ml of blood obtained within 48 h for study purposes. The amount of blood collected for study purposes varied from 0.6 to 3.1 ml kg\textsuperscript{-1} body weight, respectively, 0.7–3.8% of the circulating blood volume, which is in accordance with the NIH/FDA guidelines indicating ~3% being acceptable.

The number of eligible patients was 110. The parents of 39 patients refused informed consent for varying reasons: too much extra handling of their child (n=30), dislike of clinical trials (n=6), no direct advantage to their child (n=2), and language difficulties (n=1). As a result, we included 71 patients in this study, of whom 17 were excluded from the analysis. Reasons for exclusion from data analysis were as follows: not receiving standard intervention as allocated (n=10), withdrawal of parental informed consent during the study (n=1), logistical problems (n=3), and cancelling or rescheduling of the procedure after inclusion (n=3). Twenty-nine of these 54 patients received acetaminophen and the rest received placebo as adjuvant to i.v. morphine.

Differences in morphine requirements and COMFORT and VAS scores were analysed using the summary measurement approach,\textsuperscript{24} that is, these variables were averaged for each patient. As these data were too skewed and could not be transformed to normality, an ordinal regression analysis was performed. Postoperative morphine requirement, in contrast, was analysed using the ordinal regression analysis, as this outcome variable was highly skewed and could not be transformed to normality. Ordinal regression analysis technique is generally used for categorical data and, therefore, is suitable for outcome data with a non-normal distribution. This technique does not evaluate relationships between the outcome variable and the independent variables, but rather computes cumulative probabilities for each category of the outcome variable. As the morphine requirements and COMFORT and VAS scores were measured on a ratio scale, these outcome variables were separated into four groups on the basis of the inter-quartile ranges. To obtain the optimal model, first, χ\textsuperscript{2} tests were used to select the negative log–log link function. Secondly, Pearson’s χ\textsuperscript{2} test statistics were used to assess whether the model predictions were consistent with the observed data. Thirdly, the test of parallel lines was performed to assess whether the ordinal regression model’s location parameters were equivalent across all levels of the dependent variable, that is, morphine requirements, COMFORT and VAS scores. Age of the infants was added as covariate in all three analyses and was entered as a dummy variable, that is <45 weeks post-conceptional age vs ≥45 weeks post-

\textbf{Algorithm PSICU}

\begin{itemize}
  \item VAS ≥4, COMFORT behaviour ≥17: Investigate causes
  \item VAS ≥4, COMFORT behaviour <17: Investigate the causes
  \item VAS <4, COMFORT behaviour ≥17: No direct action repeat scores during regular care
  \item VAS <4, COMFORT behaviour <17: Hunger, positioning: non-pharmacological interventions
\end{itemize}

\textbf{After each bolus, VAS and COMFORT to be repeated}

\textbf{No improvement in scores consultation IC physician}

\textbf{PhD thesis (Bouwmeester et al., 2002)}

\textbf{Fig 1} Algorithm for receiving extra morphine or midazolam.
conceptional age, coded as 1 and 0, respectively. Loading
dose of morphine at the end of surgery and number of
postoperative rescue doses of morphine were added as
extra covariates to assess differences in morphine
requirements.

Logistic regression analysis was used to assess differ-
ences in number of children needing postoperative rescue
doses of morphine and increases in continuous morphine
infusion. Age was entered as covariate.

It was expected that 40% of the patients in the acetami-
nophen group would need extra morphine, compared
with 80% in the placebo group. For a power of 0.80 and
=0.05, at least 23 patients were required in each group.
Seventy patients were included to compensate for drop outs.

The randomization schedule for acetaminophen or
placebo, kept solely by the pharmacist to ensure blinding,
was made before the study by random permuted blocks of
placebo, kept solely by the pharmacist to ensure blinding,
Seventy patients were included to compensate for drop outs.

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placebo, kept solely by the pharmacist to ensure blinding,
Seventy patients were included to compensate for drop outs.

The study medication consisted of acetaminophen
suppositories (with acetaminophen and Witepsol H15,
synthetic saturated triglycerides with a chain length of
C12–C18, as base) or placebo suppositories, both manu-
ufactured in the hospital pharmacy. Patients, parents,
nurses, and investigators were blinded for the content of
the suppositories.12 The stability of these preparations was
tested by the laboratory of the Royal Dutch Association of
Pharmacists.

Acetaminophen plasma concentrations were measured
using fluorescence polarization immunoassay (Adx system,
Abbott Laboratories, North Chicago, IL, USA) (Erasmus
MC Rotterdam, The Netherlands). Detection limit of this
method is 1.0 mg litre \(^{-1}\). Precision was measured at acet-
aminophen concentrations of 15, 35, and 150 mg litre \(^{-1}\).
To determine coefficients of variation at these concen-
trations, 55 samples of each concentration were assayed
(coefficient of variation (CV)=(σ/mean); relative standard
deviation (RSD)=CV×100%), RSD was 7.22, 3.37, and
3.11% at 15, 35, and 150 mg litre \(^{-1}\), respectively. The
acetaminophen concentration range in which the accuracy
was determined is 10–150 mg litre \(^{-1}\).

The morphine, morphine-3-glucuronide, and
morphine-6-glucuronide assay stock solutions of morphine
(Lavoisier, France), morphine-d3, M3G, M3G-d3, M6G
(Sigma), and M6g-d3 (100 µg ml \(^{-1}\)) (Lipomed) were
prepared in deionized water and stored in 250 µl aliquots at
–20°C. Quality controls were stored at –20°C. Plasma
samples (200 µl) diluted in 200 µl of carbonate ammonium
10 mM (pH 9.3) and spiked with 75 µl of
appropriate dilutions, in water, of stock solutions of
internal standards (morphine-d3 at 37.5 mg ml \(^{-1}\) and
M3G-d3 and M6G-d3 at 18.75 mg ml \(^{-1}\)) were extracted
with solid-phase columns (BOND ELUT C18, 1 ml and
100 mg). The methanol phase was dried under nitrogen and
the residue was dissolved in 75 µl of mobile phase.

A Perkin Elmer series 200 pump (Perkin Elmer,
Norwalk, CT, USA) equipped with a vacuum membrane
degasser delivered the mobile phase at a flow rate of
200 µl min \(^{-1}\) into a phenyl 5-µm particle size stability
column (CIL Cluzeau, St Foy La Grande, France). The
mobile phase consisted of a mixture of acetonitrile and
10 mM ammonium formate pH 3.0 with formic acid (8/92,
v/v) and was splitted with a ratio of 1/5 at the entrance of
the mass spectrometer. A Perkin Elmer series 200 auto
sampler with a 2 µl loop was used. Mass spectrometric
parameters (declustering potential, focusing potential, and
entrance potential) were adjusted to obtain the maximum
signal for these MHT \(^+\) ions. Data were acquired in the posi-
tive ion mode with an ionspray probe voltage of 5000 V
and in single ion monitoring at m/z 286.3 and 289.4 for
morphine and morphine-d3, respectively, and at m/z 462.3
for M3G and M6G and m/z 465.4 for M3G-d3 and
M6G-d3.

Under the chromatographic conditions described, the
retention times were 10.41 and 10.33 min for morphine and
morphine-d3, 5.0 and 4.92 min for M3G and M3G-d3, and
9.28 and 9.20 min for M6G and M6G-d3, respectively. The
intra-assay variabilities (n=4) were <10% for all the con-
centrations tested (2.5–250 ng ml \(^{-1}\) for M3G and M6G and
5–500 ng ml \(^{-1}\) for morphine) and for quality controls. The
coefficient of variation for inter-assay (n=7) was <10% for
calibration standards and quality controls.

Results

Median (25–75th percentile) age and weight of patients
receiving acetaminophen (16 boys and 13 girls) and
placebo (13 boys and 12 girls) as adjuvant to i.v morphine
were, respectively, 0 (0–1) months, 3.1 (2.6–3.6) kg and
0 (0–2.5) months, 3.1 (3.8–5.2) kg. The pre- and per-
operative details of the acetaminophen and placebo
and the group of patients excluded from analysis
are shown in Table 1. The most frequent abdominal,
urological, and thoracic surgical procedures were closure of
diaphragmatic hernia, intestinal atresia, nephrectomy,
and oesophageal atresia repair.

Ordinal regression analysis, using the complementary
logit link function, showed no significant differences
between the acetaminophen and placebo groups in median
(2–75th percentile) total morphine consumption, 7.91
(6.59–14.02) and 7.19 (5.45–12.06) µg kg \(^{-1}\) h \(^{-1}\), respect-
ively (P=0.60). Age was not related to total morphine
consumption (P=0.38). Logistic regression showed no
difference between the groups with respect to additional
morphine boluses [median (25–75th percentile) acetami-
nophen 0 (0–1) and placebo 0 (0–3) (P=0.36)], increases in
continuous morphine infusion [median (25–75th percentile)
acetaminophen 0 (0–0) and placebo 0 (0–1) (P=0.06)], and
decreases in continuous morphine infusion [median (25–75th percentile) acetaminophen 0 (0–0) and
placebo 0 (0–1) (P=0.51)].

Infants <45 weeks post-conceptional age needed
significantly fewer additional morphine boluses when
compared with infants ≥45 weeks (1 out of 30 patients vs 10 out of 24 patients; \( P < 0.01 \)); pseudo \( R^2 \) (Nagelkerke) was 0.44. The number of children needing an increase in continuous morphine infusion was significantly lower in infants <45 weeks when compared with infants ≥45 weeks (3 out of 30 patients vs 16 out of 24 patients; \( P < 0.01 \)); pseudo \( R^2 \) (Nagelkerke) was 0.43. There was no significant difference in continuous morphine infusion decreases in the second 24 h after operation (18 out of 30 patients vs 10 out of 24 patients; \( P = 0.69 \)); pseudo \( R^2 \) (Nagelkerke) was 0.06.

COMFORT and VAS scores of the patients receiving vecuronium (\( n = 4 \)) were excluded from our final analysis, as COMFORT and VAS scores are not valid when used in paralysed patients. There were no significant differences between patients receiving acetaminophen (\( n = 29 \)) and placebo (\( n = 25 \)) as adjuvant to i.v. morphine with respect to COMFORT scores [median (25–75th percentile) acetaminophen 10 (9–12) and placebo 11 (9–13) \( (P = 0.06) \)] and VAS scores [acetaminophen 0.0 (0.0–0.2) and placebo 0.0 (0.0–0.3) \( (P = 0.73) \)]; pseudo \( R^2 \) (Nagelkerke) was 0.29 and 0.20, respectively.

VAS scores were low and showed a decline after the first 4 h of operation (Fig. 2a). In the acetaminophen group, the lowest and highest median (25–75th percentile) VAS scores in the first 4 h after operation were, respectively, 0.0 (0.0–0.3) and 0.2 (0.0–0.5). After the first 4 h, the lowest and highest median (25–75th percentile) VAS scores were respectively, 0.0 (0.0–0.1) and 0.1 (0.0–0.4). In the placebo group, the lowest and highest median (25–75th percentile) VAS scores in the first 4 h after operation were, respectively, 0.2 (0.0–1.2) and 0.3 (0.0–2.2). After the first 4 h, the lowest and highest median (25–75th percentile) VAS scores were 0.0 (0.0–0.0) and 0.2 (0.0–1.0), respectively. VAS scores ranged from 0.0 to 6.6.

Although individual COMFORT scores exceeded 17, median COMFORT scores were low (Fig. 2n). In the acetaminophen group, the lowest and highest median (25–75th percentile) COMFORT scores were, respectively, 9.0 (8.0–11.0) and 12.0 (9.0–13.0). In the placebo group, the lowest and highest median (25–75th percentile) COMFORT scores were, respectively, 10.0 (9.0–12.0) and 12.0 (10.0–16.0). COMFORT scores ranged from 6 to 26.

Acetaminophen plasma concentrations increased during the first hours after operation and then reached a steady-state concentration, but individual acetaminophen concentrations varied widely (0.8–59.9 mg litre\(^{-1}\)) (Fig. 3). Individual morphine, M3G, and M6G plasma concentrations varied widely, ranging from <5.0 to 40.0 mg litre\(^{-1}\), <2.5 to 51.0 mg litre\(^{-1}\), and <2.5 to 194.0 mg litre\(^{-1}\) (Table 2).

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**Table 1 Patient characteristics**

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<th>Excluded for analysis (( n = 17 ))</th>
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<tr>
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<td>Placebo (( n = 25 ))</td>
<td>Acetaminophen (( n = 29 ))</td>
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<tr>
<td>Age (months)*</td>
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<td></td>
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<td>0–10</td>
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<td>1.7–9.2</td>
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<tr>
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<tr>
<td>Female</td>
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<tr>
<td>Baseline heart rate (beats min(^{-1}))*</td>
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<td>Baseline mean arterial pressure (mm Hg)*</td>
<td>51 (49–64)</td>
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<td>38–81</td>
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<tr>
<td>Urological</td>
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<td>Peroperative blood loss (ml)*</td>
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<td></td>
<td>85–365</td>
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<tr>
<td>Peroperative fentanyl dosing (mg kg(^{-1}))*</td>
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<td>12 (11–14)</td>
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<td></td>
<td>10–18</td>
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<tr>
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<td>Patients artificially ventilated after operation</td>
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<td>26</td>
</tr>
<tr>
<td>Mean duration of artificial ventilation after operation (h)*</td>
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*Median (25–75th percentile); range.

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van der Marel et al.
Despite concerns about the adverse effects, such as respiratory depression, morphine is the standard analgesic after major surgical procedures in young infants. Combined analgesic regimens, leading to adequate analgesia with lower doses of opioids and reduced side effects, have been proposed. Our study assessed the potential morphine-sparing effect of acetaminophen in infants (0–2 months) after major thoracic or abdominal surgery. There was no significant benefit from acetaminophen over placebo as an adjuvant to i.v. morphine as assessed by additional morphine boluses, incidence of increase in continuous morphine infusion, or incidence of continuous morphine infusion decrease in the second 24 h after operation. There was no significant difference in total morphine consumption between acetaminophen and placebo group.

All patients received comparable doses of fentanyl during operation and all patients received a loading dose of morphine at the end of surgery, followed by continuous morphine infusion. The additional analgesic effect of acetaminophen was expected in the postoperative period when

Fig 2 (a) VAS scores: I, acetaminophen group and II, placebo group. (b) COMFORT scores: I, acetaminophen group and II, placebo group.
acetaminophen reached its maximum analgesic effect 2 h after administration. We therefore, expected that analgesia would be balanced at the end of surgery in both groups and that any possible additional analgesic effect of acetaminophen would show in the amount of extra morphine boluses or in the increases in continuous morphine infusion or in the second 24 h when continuous morphine infusion was decreased based on the VAS scores. Finding no difference in total morphine consumption between both groups supports the presence of balanced analgesia at the end of surgery.

The result that VAS scores were not significantly different between both groups supports the absence of a morphine sparing effect of acetaminophen. These findings are in line with the results of Morton, showing no morphine sparing effect of acetaminophen in children 3–15 yr of age after appendectomy. In contrast, studies in adults have reported a decrease in postoperative morphine consumption when morphine was combined with acetaminophen.

Patients ≥45 weeks post-conceptional age (n=24) received a loading dose of 100 µg kg⁻¹ followed by continuous morphine infusion of 10 µg kg⁻¹ h⁻¹, based on a study showing that morphine infusion at a dose of 10.9–12.3 µg kg⁻¹ h⁻¹ provided adequate analgesia in children 0–3 yr of age after major abdominal surgery. On the basis of the previous studies advising a continuous morphine infusion of 7 µg kg⁻¹ h⁻¹ and indicating that neonates had lower morphine requirements, children <45 weeks (n=30) received a loading dose of 100 µg kg⁻¹, followed by a continuous infusion of 5 µg kg⁻¹ h⁻¹. These patients had a lower incidence of additional morphine requirements and need for increases in continuous morphine infusion was lower, regardless of acetaminophen or placebo group. This is consistent with previous results, indicating that neonates had lower morphine requirements. On the basis of our results, 5 µg kg⁻¹ h⁻¹ continuous morphine infusion was sufficient for children <45 weeks post-conceptional age. Although there was no relation between age and total morphine consumption, we did show that children ≥45 weeks post-conceptional age had a higher incidence of additional morphine boluses and increases in continuous morphine infusion.

Most of the children included in this study had adequate analgesia, which makes it difficult to assess a dose–effect relationship for morphine, which is even harder taking into account the large inter-individual variability in acetaminophen plasma concentrations. Individual acetaminophen plasma concentrations showed wide variability (range 0.8–59.9 mg litre⁻¹), despite dosing equivalence. This is well recognized by others and is attributable, in part, to absorption variability, size effects, and genetic polymorphisms interfering with acetaminophen metabolism, such as from CYP2E1 and CYP3A4.

Acetaminophen, as an adjuvant to continuous morphine infusion, does not have an additional analgesic effect and should not be considered as standard of care in young infants, 0–2 months of age (39–48 weeks post-conceptional age), after major thoracic or abdominal surgery.

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### References
Rectal acetaminophen adjuvant to i.v. morphine

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22 van Dijk, de Boer JB, Koot HM, Tibboel D, Passchier J. Duivenvoorde HJ. The reliability and validity of the COMFORT scale as a postoperative pain instrument in 0 to 3-year-old infants. Pain 2000; 84: 367–77


30 Anderson BJ. Comparing the efficacy of paracetamol and NSAIDs in children. Paediatr Anaesth 2004; 14: 201–17