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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.

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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.[5–11] 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.[5–11]

Morton[12] has demonstrated reduced morphine requirements in postoperative children aged 3–15 given diclofenac 1 mg kg^{-1} 8 hourly, but no effect attributable to acetaminophen 15 mg kg^{-1} 6 hourly was shown. Nevertheless, NSAIDs have numerous contraindications and consequently cannot be used in >25% of postoperative patients.[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 ≥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, ≥36 weeks post-conceptional age, weight ≥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 SD 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^{-1} loading dose for children <4 kg and 40 mg kg^{-1} loading dose for children ≥4 kg, followed by 20 mg kg^{-1} 6 hourly)[14–16] 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,[14–16] showing that high acetaminophen doses (90–100 mg kg^{-1}) can be administered safely with a rectal loading dose (30–40 mg kg^{-1}) followed by regular maintenance doses (20 mg kg^{-1} 6 hourly or 30 mg kg^{-1} 8 hourly).

Anaesthesia was induced using i.v. thiopentone 3–5 mg kg^{-1} or by inhalation with sevoflurane in a nitrous oxide/oxygen mixture. Fentanyl 5 μg kg^{-1} was given through i.v. before tracheal intubation to all children. Tracheal intubation was facilitated with atracurium 0.5–1 mg kg^{-1} or suxamethonium 2 mg kg^{-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.[17 18] Monitoring consisted of ECG, non-invasive blood pressure (NIBP), oxyhaemoglobin saturation (Sp_{O_2}), end-tidal carbon dioxide levels (E'_{CO_2}), and temperature. The NIBP and heart rate 10 min after tracheal intubation were used as peroperative baseline values, as described earlier.[17 18] Before incision, a further dose of fentanyl 5 μg kg^{-1} was given. Extra doses of fentanyl (2 μg kg^{-1}) were given when the heart rate 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^{-1} min^{-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 μg kg^{-1}. After surgery, all children received a continuous morphine infusion, with a background of 5 μg kg^{-1} h^{-1} for children <45 weeks post-conceptional age and 10 μg kg^{-1} h^{-1} for children ≥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),[18 19] 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.[18 19] 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