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Oral clonidine *vs* midazolam in the prevention of sevoflurane-induced agitation in children. A prospective, randomized, controlled trial†

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Background. This randomized, double-blind study tested the hypothesis that, in comparison with midazolam, premedication with oral clonidine reduces the incidence of emergence agitation in preschool children anaesthetized with sevoflurane.

Methods. Sixty-eight ASA I–II children undergoing circumcision were randomized into three groups to receive different oral premedication given 30 min before anaesthesia: midazolam 0.5 mg kg^{-1}, clonidine 2 μg kg^{-1}, and clonidine 4 μg kg^{-1}. Sevoflurane anaesthesia was administered via a facemask (O_2/N_2O: 40/60). Analgesia was with penile block (bupivacaine 0.5% 0.3 ml kg^{-1}) and rectal paracetamol (30 mg kg^{-1}). During the first postoperative hour, children were evaluated using a modified 'objective pain scale'.

Results. Only the 4 μg kg^{-1} dose of clonidine was associated with a significant reduction in emergence agitation. Fewer children in the clonidine 4 μg kg^{-1} group displayed agitation (25%) than in the midazolam group (60%) ($P = 0.025$). Incidence of hypotension and bradycardia, time to first micturition and first drink did not differ among groups.

Conclusions. In comparison with midazolam, clonidine 4 μg kg^{-1} reduced sevoflurane-induced emergence agitation without increasing postoperative side-effects.

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Emergence agitation is a common postoperative problem in children who have received sevoflurane anaesthesia.[1] This agitation is characterized by a change in perception of the environment with signs of disorientation, hypersensitivity to stimuli, and hyperactive motor behaviour.[1] Although it is usually of short duration, it may require pharmacological intervention, resulting in a prolonged post-anaesthesia care unit stay. Its aetiology remains unclear. Pain appears to be a promoting factor since administration of analgesic agents reduces its incidence.[2 3] However, post-anaesthesia agitation can also appear after sevoflurane anaesthesia without surgery.[4] Gender, age, type of surgery, and preoperative anxiety equally seem to be promoting factors.[1 5]

Clonidine provides both sedation and analgesia in children.[6 7] In addition, i.v. clonidine administered after induction of anaesthesia has been shown to reduce the incidence of early post-anaesthetic agitation associated with sevoflurane.[8–12] However, the effect of oral premedication with clonidine on post-anaesthetic agitation has not been fully evaluated. The hypothesis tested in the present study was that oral premedication with clonidine is effective in reducing early postoperative agitation after sevoflurane anaesthesia, provided that adequate postoperative analgesia has been achieved.

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Methods

After approval of the Hospital's Ethics Committee and parental written informed consent, 68 children, ASA status I or II, aged between 1 and 6 yr, and undergoing circumcision, were included in this double-blind, prospective, randomized study. Exclusion criteria included a family history of malignant hyperthermia, mental retardation, and any neurological disease potentially associated with symptoms of agitation.

Children were randomized into three groups. Each group received different premedication given orally 30 min before induction of anaesthesia: midazolam 0.5 mg kg^{-1} with a maximum dose of 15 mg, clonidine 2 μg kg^{-1}, and clonidine 4 μg kg^{-1}. This premedication was mixed with 3–5 ml of syrup. An anaesthesiologist not involved in the clinical protocol prepared the randomization envelopes. For each child included in the study, the anaesthesiologist responsible for the protocol (NT) drew the sealed envelope and administered the premedication.

Anaesthetic regimen

Premedication was administered in the recovery room in the presence of the parents. The anaesthetist who administered the premedication was excluded from the perioperative management and the postoperative assessment of the child.

A strict anaesthetic protocol was applied. Parents were absent from the anaesthetic room at the time of induction. The child was maintained with facemask and bag ventilation throughout the surgery. Anaesthesia was induced with inspired sevoflurane 8% in a 40:60% mixture of oxygen/nitrous oxide and a fresh gas flow of 6 litre min^{-1}. In children <15 kg, a Jackson–Rees circuit was used, whereas in children weighing ≥15 kg a circle system was used. Once a sufficient depth of anaesthesia (Guedel phase 3) was achieved, inspired sevoflurane concentration was reduced to 4% and a venous catheter was inserted. Neither a Guedel airway nor a harness was used in any of the children. Ringer's lactate solution was infused according to the child's weight.[13] A penile block with bupivacaine 0.5% 0.3 ml kg^{-1} (maximum volume: 8 ml) was performed by another anaesthetist. All the regional blocks were carried out by two experienced anaesthetists (FdG, AdV). After the block had been performed, the inspired sevoflurane concentration was reduced to 1.5% and paracetamol 30 mg kg^{-1} was administered rectally. Surgery was allowed to start 10 min after the injection of bupivacaine. At the beginning of skin suture, the inspired sevoflurane concentration was reduced to 0.7% and stopped at the time of the last suture while maintaining a 40:60% mixture of oxygen/nitrous oxide until the end of the wound dressing. Then the child was allowed to breathe 100% oxygen until complete recovery of his reflexes. The child was transferred to the recovery room where one of the parents was waiting.

As pain is known to promote agitation, all the children who had an inadequate penile block were excluded from the study. A penile block was considered inadequate if, under an inspiration fraction of sevoflurane 1.5%, systolic arterial pressure and heart rate increased to >15% above baseline values at surgical incision. If this was the case, the child received i.v. sufentanil (0.1 μg kg^{-1}) and was excluded from the study.

The anaesthetist in charge of the child evaluated the quality of induction as either good or bad. Systolic and diastolic arterial pressures, heart rate, and oxygen saturation were measured every 5 min throughout the procedure.

Assessment in the recovery room

An independent observer evaluated the child in the recovery room for 2 h after surgery, in the presence of one of the parents, using the objective pain scale. The state of agitation was assessed every 15 min for the first hour by means of a modified objective pain scale.[14] The full objective pain scale includes five items (Table 1); of which, the items movement, tears, and behaviour were used to assess agitation.[8 15] For these three items, which constituted the modified objective pain scale, the total possible score was 6. Agitation was defined by a total score of ≥3 for these three items.[8 15] Prolonged agitation was defined as a score of ≥3 lasting >15 min after arrival in the recovery room.

Arterial pressure, heart rate, and oxygen saturation were measured every 15 min during the 2-h postoperative observation period. Occurrence of hypotension or bradycardia was recorded. Hypotension and bradycardia were defined as a value of at least 15% less than the normal mean value for the child's age.[13] The time of the first urine output and of the first drink was also recorded. The child was discharged from the recovery room when all of the following

Table 1 The objective pain scale[14]

	Score
Arterial pressure	
<10% increase from preoperative value	0
>20% of preoperative value	1
>30% of preoperative value	2
Tears	
Absent	0
Present, but child can be consoled	1
Present and child cannot be consoled	2
Movements	
Absent	0
Moderate agitation (does not sit still)	1
Intense agitation (risk of trauma)	2
Behaviour	
Sleeping or calm	0
Grimacing, trembling voice, can be calmed down	1
Frightened, sticks to parents, cannot be calmed down	2
Verbal or bodily expression	
Sleeping or calm	0
Moderate, non-localized pain, general discomfort or positioned with flexed legs and arms crossing the tummy	1
Localized pain expressed verbally or pointed out by finger	2