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Intranasal dexmedetomidine to facilitate mask induction and prevent emergence delirium

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Abstract: As children are exposed to stress and anxiety during the perioperative period, pre-anesthetic medication to facilitate induction of anesthesia without prolonging recovery is needed. Dexmedetomidine is increasingly being used for sedation in the intensive care units and for procedural anesthesia outside the operating room. However, the effectiveness of pre-operative sedation with intranasal dexmedetomidine in pediatric patients undergoing ambulatory surgery has not yet been well characterized. Therefore, the aim was to identify the effectiveness of intranasal dexmedetomidine in facilitating mask induction and preventing emergence agitation.

In a single center retrospective implementation study, we compared intranasal dexmedetomidine (2 µg/kg) administration, sequentially in all pediatric patients undergoing minor urological surgery between January 2019 and July 2019 with a period in which dexmedetomidine was not administered. The outcome measures were tolerance of mask induction, post-operative sedation and the Pediatric Anesthesia Emergence Delirium scale (PAED) score.

The 53 children in the control group were compared with 50 children in the dexmedetomidine group during implementation. The incidence of sedation on mask induction was greater in patients given dexmedetomidine compared to those who did not receive premedication (60% versus 0%, p<0.0001). The proportion of children who were asleep but easily arousable in the recovery room and in day-care hospital was greater in the dexmedetomidine group compared to the control group. (32% versus 7% in the recovery room; p=0.004, and 20% versus 2% in day-care hospital, p = 0.002). The *PAED* scores did not differ between the two groups, neither in the recovery room nor in day-care hospital.

In pediatric patients undergoing small urologic surgery, premedication with intranasal dexmedetomidine in a dose of 2µg/kg provides adequate sedation and anxiolysis on mask induction and in the postoperative period. These results from an implementation study need to be confirmed in a multicenter blinded randomized controlled trial.

Keywords: Dexmedetomidine; premedication; pediatric; administration, intra-nasal; delirium.

Introduction

Children undergoing surgical procedures can experience significant stress, anxiety and distress during the perioperative period, which may be due to separation from parents, fear of injections or fear of the operating theatre. This may lead to agitation or excess crying, which also make the management of such patients difficult during induction of anesthesia for patient, caregiver and parents (1). Additionally, anxiety at induction of anesthesia is associated with distress on awakening in the recovery area and with later postoperative agitation (2-3). Premedication in children may thus be helpful to reduce the child's stress and anxiety, as well as facilitate smooth mask induction of anesthesia.

Pre-anesthetic medication in children should aim at relieving this anxiety, facilitating the induction of anesthesia, without prolonging recovery (4). Several drugs and routes of administration have been intensively studied and proven useful for this indication. Since intravenous administration requires an invasive access, this is not preferable in young children. Rectal administration of the pre-anesthetic, such as benzodiazepines, is hampered by low bioavailability, a wide scatter of pharmacokinetic and pharmacological results, and poor predictability of the clinical effect. Many studies have shown that an intranasal route is an

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effective way to administer premedication and sedation to children (5-6). With the use of older sedatives such as benzodiazepines and/or opioids, there is a potential risk of respiratory depression or paradoxical agitation. Benzodiazepines, particularly midazolam, have a very low pH which makes the administration also a stressful moment for the child.

Dexmedetomidine is a newer and potent, highly selective and specific alpha-2 adrenoceptor agonist with sedative, anxiolytic, sympatholytic and analgesic effects (7-8). When dexmedetomidine is administered through the nasal mucosa, it is an easy and non-invasive alternative with a high bioavailability and relative few side effects. (9). Many studies have already established the sedative effects and safety of dexmedetomidine. Intranasal dexmedetomidine is relatively easy to administer and reduces first-pass effect (10). A recent systematic review demonstrated that intranasal dexmedetomidine may be more effective at sedating children than oral choral hydrate and diazepam. (11). Dexmedetomidine seems to have the safest profile for neurotoxicity on the developing brain (23). We therefore examined the effect of intranasal dexmedetomidine administration on patient comfort measures during the perioperative period in a well-defined patient population through a "before-after" implementation study.

Methodology

Patients population

All ASA I children below the age of 6 years, who underwent small urologic procedures under general anesthesia (circumcision, inguinal hernia repair) from January 2019 until July 2019 were included in the analysis. Patients with a history of major cardiovascular, pulmonary or renal disease and children with any nasal disorder that may interfere with nasal administration of drugs were excluded.

All methods were carried out in accordance with relevant guidelines and regulations. All experimental protocols were approved by the institutional board of Ziekenhuis Oost-Limburg. Informed Consent was waived by institutional board and ethical committee of Ziekenhuis Oost-Limburg due to retrospective nature of the study.

Dexmedetomidine administration and mask sedation

Dexmedetomidine was administered intranasally at least 15 minutes preoperatively in a dose of 2µg/kg. Total dose was distributed equally over both nostrils and patients remained in the lying supine position for at least 2 min to facilitate dexmedetomidine absorption. If necessary, normal saline was added to acquire a minimum of 0,3 mL per nostril. Every patient received mask induction and maintenance of anesthesia with N_20 and Sevoflurane and were ventilated with a laryngeal mask.

Outcome measures

We retrospectively compared both groups in terms of the following endpoints: 1) level of agitation upon arrival in the operating theatre, 2) acceptance of mask induction, 3) Pediatric Anesthesia Emergence Delirium scale (PAED) in the recovery room and at day-care hospital postoperatively, 4) whether patients were asleep in the recovery room or at day-care hospital postoperatively and 5) length of hospital stay. We also evaluated the acceptance of intranasal injection of dexmedetomidine in the treatment group, maximal MAC (sevoflurane + N_20) and the use of atropine, vasopressive drugs or opioids perioperatively.

A 4-point scale to determine level of agitation upon arrival in the operating theatre (1 = awake, 2 = light sedation, 3 = deep sedation, 4 = anesthesia) was used and a 3-point scale (1 = no resistance, 2 = moderate resistance, 3 = strong resistance) to assess the degree of mask acceptance. The assessments were done by the attending anesthetist.

In the recovery room, patients were monitored for non-invasive blood pressure, heart rate and pulse oxygen saturation. Children were continuously assessed for agitation by nursing staff and maximal PAED scores were recorded. The patients were discharged when the modified Aldrete score was > 9. In day-care hospital PAED scores were also registered. Any adverse event including bradycardia, hypotension, nausea of vomiting and respiratory depression was recorded during the entire hospital stay.

Statistical analysis

Data were analyzed using JMP version 15.0.0 (SAS Institute, Cary, NC, USA). Results were expressed as either mean +/- standard deviation (SD) or median + interquartile range (IQR) for continuous data and compared by either unpaired t-test or Mann-Whitney U test, respectively. Numbers (percentages) were compared by a chi-square test. A p-value of <0,05 was considered statistically significant.

Results

General characteristics

A total of 103 ASA I patients undergoing small urologic procedures were included in this study. Fifty patients received preoperative dexmedetomidine intranasally and 53 did not being defined as the control group. The weight and age of all patients did not differ between both groups. The administered dose of dexmedetomidine in the treatment group was mean 2.01 ± 0.08 mg/kg

Arrival in the operation theatre and mask acceptance

All patients in the control group were fully awake upon arrival in the operation theatre. In comparison, 46% of the patients in the dexmedetomidine group were slightly sedated and 12% were deeply sedated (p<0.001). (Table 1) However, mask acceptance did not differ between the dexmedetomidine and control group (p=0.17). (Table 2) Time between dexmedetomidine administration and arrival in the operating room was 31 (IQR 21.5-61) min in level 1 sedation (awake), 30 (IQR 25-59) min in level 2 light sedation and 85.5 (IQR 56.5-146.75) min in level 3 deep sedation (p=0.04).

Postoperative emergence agitation

Only 7% of the patients in the control group were asleep but easily arousable in the recovery room, in contrast to the 32% in the dexmedetomidine group (p = 0.004). (Table 3) In day-care hospital, more patients were asleep in the dexmedetomidine group in comparison to the control group (10/50 (20%) and 1/53 (2%) respectively. p = 0.002). (Table 4) However, the Pediatric Anesthesia Emergence Delirium scale (PAED) scores did not differ between the two groups, neither in the recovery room nor in day-care hospital. (Fig. 1, Fig. 2).

Table 1

Comparison of the sedation scale upon arrival in the operating theatre

Group	1	2	3
Control, n (%)	53 (100%)	0 (0 %)	0 (0%)
Dexmedetomidine, n (%)	21 (42%)	23 (46%)	6 (12%)

The scale of sedation was expressed as 1 (awake), 2 (slightly sedated) or 3 (deeply sedated/anaesthesia).

Table 2

Mask acceptance scale

Group	1	2	3
Control, n (%)	26 (49%)	16 (30%)	11 (21%)
Dexmedetomidine, n (%)	30 (60%)	16 (32%)	4 (8%)

The scale of mask acceptance was expressed as 1 (no resistance), 2 (moderate resistance) or 3 (strong resistance).

Table 3

Asleep in recovery room

Group \ Status sleep	Unknown	Asleep	Not asleep
Control, n (%)	29 (55%)	4 (7%)	20 (38%)
Dexmedetomidine, n (%)	17 (34%)	13 (32%)	17 (34%)

The status of sleep was compared between both groups in the recovery room. The sleep status was expresses as unknown, asleep or not asleep.

Table 4

Asleep in day-care hospital

Group \ Status sleep	Unknown	Asleep	Not asleep
Control, n (%)	0 (0%)	1 (2%)	52 (98%)
Dexmedetomidine, n (%)	1 (2%)	10 (20%)	9 (78%)

The status of sleep was compared between both groups in the day-care hospital. The sleep status was expressed as unknown, asleep or not asleep.

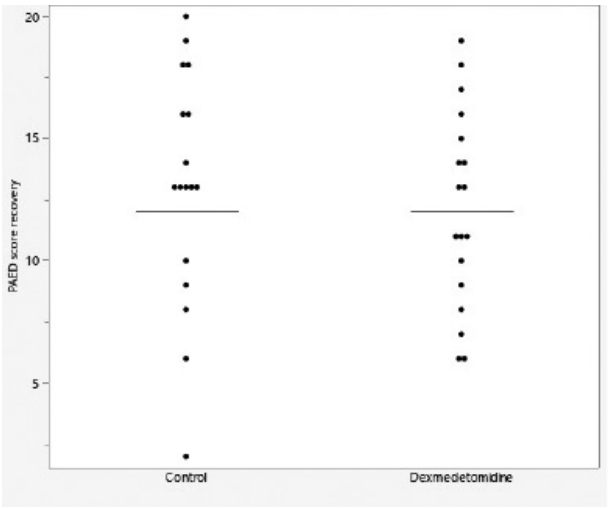

Fig. 1. — PAED recovery room. Comparison of PAED scores between the control and dexmedetomidine group in the recovery room. The box depicts the interquartile range (IQR) and the line represents the median. The tails mark the upper and lower bounds of 1.5 times the IQR. PAED, Pediatric Anesthesia Emergence Delirium.

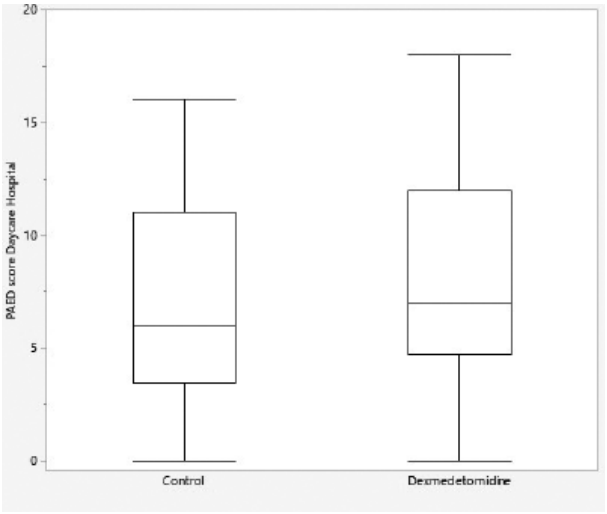

Fig. 2. — PAED day-care hospital. Comparison of PAED scores between the control and dexmedetomidine group in day care hospital. The box depicts the interquartile range (IQR) and the line represents the median. The tails mark the upper and lower bounds of 1.5 times the IQR. PAED, Pediatric Anesthesia Emergence Delirium.

Adverse events

In both groups no adverse events occurred. None of the patients in the dexmedetomidine group needed atropine or any form of vasopressive medication.

Discussion

Despite the evolutions in anesthetic products and techniques, many children still refuse mask induction partly due to the uncommon smell of the mask and inhalational anesthetic. Moreover, this resistance has been demonstrated to contribute to postoperative agitation (2-3). Any form of sedation would thus be preferable prior to mask induction. Older products such as benzodiazepines and opiates have shown their use, but all have serious side effects such as hypotension, respiratory depression, longer extubating times and paradoxical agitation. There is now also a trend of opiate-free anesthesia.

In the present single center implementation study, we demonstrated that intranasally dexmedetomidine in a dose of 2 µg/kg provided adequate sedation on arrival in the operating theatre without causing any of the potential harmful side effects. It appears that the dexmedetomidine administration ideally occurs minimal 30 minutes preoperatively for maximal effect. Even though patients were more sedated upon arrival in the operating room, dexmedetomidine administration did not result in a better acceptance of mask induction. This is in contrast with other small studies. (12-13). A recent systematic review on the other hand was consistent with the findings of our study and could not show a significant effect of sedation at mask induction. The authors reason that dexmedetomidine sedation has a mechanism like natural sleep. Thus, dexmedetomidine leads to sedation without extreme drowsiness, and the resulting sedation is prone to easy and rapid arousal, like natural sleep (12). Therefore, it is not unforeseen that patients react to external stimuli such as mask ventilation.

Another significant perioperative application of dexmedetomidine is its role in prevention of emergence delirium. This is a known side effect after sevoflurane anesthesia, although there is no clinical evidence that agitation influences long-term outcome. At least six prospective clinical trials have shown that dexmedetomidine lowers the incidence of emergence delirium, when it was given to children prior to recovery from sevoflurane or desflurane anesthesia (14-19).

In our study, we could demonstrate that the sedative effect of pre-operatively, intranasally administered dexmedetomidine lasts until post-operatively by showing less agitation in the recovery room and day-care hospital, without a longer hospitalization. Other studies obtained comparable results in different types of pediatric surgery and using different routes of administration. Although we could show a postoperative sedative effect of dexmedetomidine sedation, this effect could not be demonstrated using the Pediatric Anesthesia Emergence Delirium scale. Inconsistency in the PAEDS scoring by the large number of nurses may at least partially explain this.

Furthermore, there is increasing and compelling evidence that most general anesthetic agents are associated with neuroapoptosis and neurodegeneration in animal models (20). Clinical evidence is still limited because this phenomenon is difficult to study in human subjects. A recent retrospective cohort study has suggested that multiple exposure to anesthesia before the age of 4 years old is a risk factor of learning difficulties later in children (21). In animals, dexmedetomidine did not induce histologic injury and did show a beneficial effect when administered with another anesthetic. (22). No long-term effects of dexmedetomidine in children have been identified yet.

Conclusion

The intranasal administration of dexmedetomidine in children undergoing minor urologic

surgery resulted in better sedation on arrival in the operating theatre, the recovery room and in day-care hospital without any adverse side effects or prolonged hospital stay.

This implementation study strongly suggests a positive sedative effect of intranasal dexmedetomidine administration, but needs to be confirmed in large, blinded multicenter randomized controlled trials.

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