

Intranasal dexmedetomidine to facilitate mask induction and prevent emergence delirium.

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1 **Intranasal dexmedetomidine to facilitate mask induction**
2 **and prevent emergence delirium.**

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22 **Abstract**

23 **Background**

24 As children are exposed to stress and anxiety during the perioperative period, pre-anaesthetic
25 medication to facilitate induction of anaesthesia without prolonging recovery is needed.
26 Dexmedetomidine is increasingly being used for sedation in the intensive care units and for
27 procedural anaesthesia outside the operating room. However, the effectiveness of pre-operative
28 sedation with intranasal dexmedetomidine in paediatric patients undergoing ambulatory surgery
29 has not yet been well characterised.

30 **Aims**

31 To identify the effectiveness of intranasal dexmedetomidine in facilitating mask induction and
32 preventing emergence agitation.

33 **Methods**

34 In a single centre retrospective implementation study, we compared intranasal dexmedetomidine
35 (2 µg/kg) administration, sequentially in all paediatric patients undergoing minor urological
36 surgery between January 2019 and July 2019 with a period in which dexmedetomidine was not
37 administered. The outcome measures were tolerance of mask induction, post-operative sedation
38 and the Paediatric Anaesthesia Emergence Delirium scale (PAED) score.

39 **Results**

40 The 53 children in the control group were compared with 50 children in the dexmedetomidine
41 group during implementation. The incidence of sedation on mask induction was greater in patients
42 given dexmedetomidine compared to those who did not receive premedication (60% versus 0%,
43 $p < 0.0001$). The proportion of children who were asleep but easily arousable in the recovery room
44 and in day-care hospital was greater in the dexmedetomidine group compared to the control group.
45 (32% versus 7% in the recovery room; $p = 0.004$, and 20% versus 2% in day-care hospital, $p =$

46 0.002). The *PAED* scores did not differ between the two groups, neither in the recovery room nor
47 in day-care hospital.

48 **Conclusion**

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

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63 **KEY WORDS**

64 Dexmedetomidine – Premedication – Paediatric – Administration, intra-nasal – Delirium

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67 **Background**

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

76 Pre-anaesthetic medication in children should aim at relieving this anxiety, facilitating the
77 induction of anaesthesia, without prolonging recovery.(4) Several drugs and routes of
78 administration have been intensively studied and proven useful for this indication. Since
79 intravenous administration requires an invasive access, this is not preferable in young children.
80 Rectal administration of the pre-anaesthetic, such as benzodiazepines, is hampered by low
81 bioavailability, a wide scatter of pharmacokinetic and pharmacological results, and poor
82 predictability of the clinical effect. Many studies have shown that an intranasal route is an
83 effective way to administer premedication and sedation to children.(5-6) With the use of older
84 sedatives such as benzodiazepines and/or opioids, there is a potential risk of respiratory
85 depression or paradoxical agitation. Benzodiazepines, particularly midazolam, have a very low
86 pH which makes the administration also a stressful moment for the child.

87 Dexmedetomidine is a newer and potent, highly selective and specific alpha-2 adrenoceptor
88 agonist with sedative, anxiolytic, sympatholytic and analgesic effects.(7-8) When
89 dexmedetomidine is administered through the nasal mucosa, it is an easy and non-invasive
90 alternative with a high bioavailability and relative few side effects. (9) Many studies have already
91 established the sedative effects and safety of dexmedetomidine. Intranasal dexmedetomidine is
92 relatively easy to administer and reduces first-pass effect.(10) A recent systematic review

93 demonstrated that intranasal dexmedetomidine may be more effective at sedating children than
94 oral choral hydrate and diazepam. (11) Dexmedetomidine seems to have the safest profile for
95 neurotoxicity on the developing brain.(23) We therefore examined the effect of intranasal
96 dexmedetomidine administration on patient comfort measures during the perioperative period in
97 a well-defined patient population through a “before-after” implementation study.

98

99 **Methods**

100 Patients population

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

106

107 Dexmedetomidine administration and mask sedation

108 Dexmedetomidine was administered intranasally at least 15 minutes preoperatively in a dose of
109 2µg/kg. Total dose was distributed equally over both nostrils and patients remained in the lying
110 supine position for at least 2 min to facilitate dexmedetomidine absorption. If necessary, normal
111 saline was added to acquire a minimum of 0,3 mL per nostril. Every patient received mask
112 induction and maintenance of anaesthesia with N₂O and Sevoflurane and were ventilated with a
113 laryngeal mask.

114

115

116 Outcome measures

117 We retrospectively compared both groups in terms of the following endpoints: 1) level of agitation
118 upon arrival in the operating theatre, 2) acceptance of mask induction, 3) Paediatric Anaesthesia
119 Emergence Delirium scale (PAED) in the recovery room and at day-care hospital postoperatively,
120 4) whether patients were asleep in the recovery room or at day-care hospital postoperatively and
121 5) length of hospital stay. We also evaluated the acceptance of intranasal injection of
122 dexmedetomidine in the treatment group, maximal MAC (sevoflurane + N₂O) and the use of
123 atropine, vasopressive drugs or opioids perioperatively.

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

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

134 Statistical analysis

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

140

141 **Results**

142 **General characteristics**

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

147 **Arrival in the operation theatre and mask acceptance**

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

155 *Table 1: Comparison of the sedation scale upon arrival in the operating theatre.*

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

156 *The scale of sedation was compared between both groups and was expressed as 1 (awake), 2 (slightly sedated) or 3*
157 *(deeply sedated/anaesthesia).*

158 *Table 2: Mask acceptance scale.*

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

159 *The scale of mask acceptance was compared between both groups and was expressed as 1 (no resistance), 2*
160 *(moderate resistance) or 3 (strong resistance).*

161 Postoperative emergence agitation

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

168 *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%)

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

171

172 *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%)

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

175

176 Adverse events

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

179

180

181 **Discussion**

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

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

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

206 In our study, we could demonstrate that the sedative effect of pre-operatively, intranasally
207 administered dexmedetomidine lasts until postoperatively by showing less agitation in the
208 recovery room and day-care hospital, without a longer hospitalisation. Other studies obtained
209 comparable results in different types of paediatric surgery and using different routes of
210 administration. Although we could show a postoperative sedative effect of dexmedetomidine
211 sedation, this effect could not be demonstrated using the Paediatric Anaesthesia Emergence
212 Delirium scale. Inconsistency in the PAEDS scoring by the large number of nurses may at least
213 partially explain this.

214 Furthermore, there is increasing and compelling evidence that most general anaesthetic agents are
215 associated with neuroapoptosis and neurodegeneration in animal models (20). Clinical evidence
216 is still limited because this phenomenon is difficult to study in human subjects. A recent
217 retrospective cohort study has suggested that multiple exposure to anaesthesia before the age of
218 4 years old is a risk factor of learning difficulties later in children (21). In animals,
219 dexmedetomidine did not induce histologic injury and did show a beneficial effect when
220 administered with another anaesthetic. (22) No long-term effects of dexmedetomidine in children
221 have been identified yet.

222

223 **Conclusion**

224 The intranasal administration of dexmedetomidine in children undergoing minor urologic surgery
225 resulted in better sedation on arrival in the operating theatre, the recovery room and in day-care
226 hospital without any adverse side effects or prolonged hospital stay.

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

230

231 **Declarations**

232 Ethics approval and consent to participate

233 All methods were carried out in accordance with relevant guidelines and regulations. All
234 experimental protocols were approved by the institutional board of Ziekenhuis Oost-Limburg.

235 Informed Consent was waived by institutional board and ethical committee of Ziekenhuis Oost-
236 Limburg due to retrospective nature of the study.

237 Consent for publication

238 Not applicable

239 Availability of data and materials

240 The datasets used and/or analysed during the current study are available from the corresponding
241 author on reasonable request.

242 Competing interests

243 The authors certify that they have no affiliations with or involvement in any organization or entity
244 with any financial interest in the subject matter or materials discussed in this study.

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249 Authors' contributions

250 MD performed the general anesthesia, interpreted the data and was a major contributor in writing
251 the manuscript. HG contributed in writing the manuscript. EV analyzed the patient data and
252 contributed in writing the manuscript. DM analyzed and interpreted the patient data and was a

253 major contributor in writing the manuscript. JV was responsible for the study design, interpreted
254 the data, performed the general anesthesia and was a major contributor in writing the manuscript.
255 All authors read and approved the final manuscript.

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258

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- 321

322 **Figure legends**

323 **Figure 1: PAED recovery room**

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

328 **Figure 2: PAED day-care hospital**

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

Figures

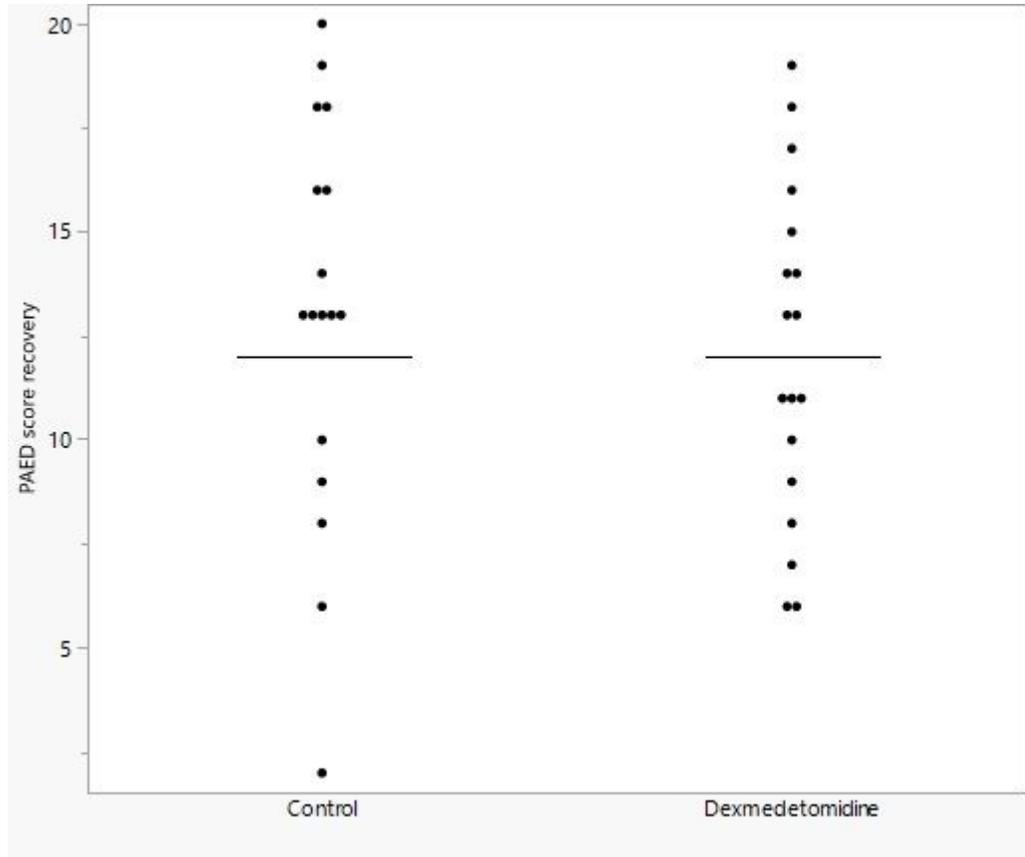


Figure 1

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.

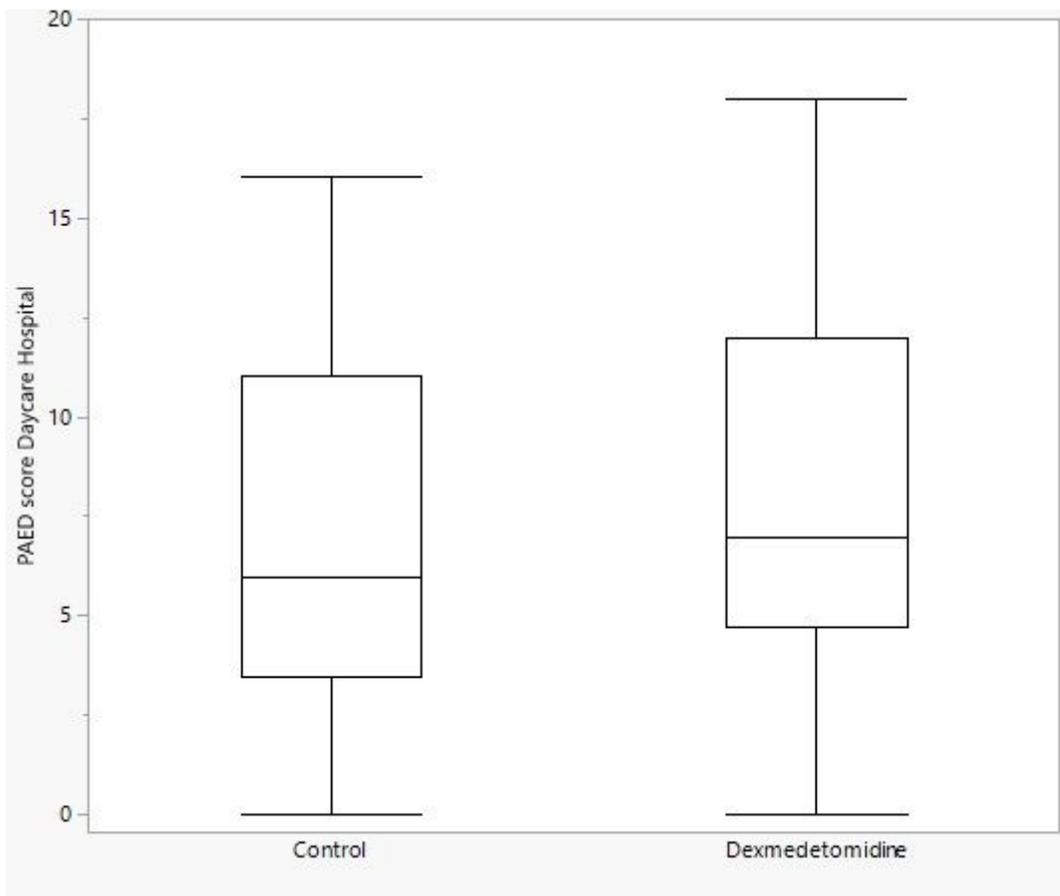


Figure 2

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.