SUMMARY

OBJECTIVES. To evaluate the hemodynamic responses to nociceptive stimuli in children submitted to videolaparoscopic appendectomy under balanced anesthesia with isoflurane and dexmedetomidine.

METHODS. Randomized, double-blind and placebo-controlled study involving 26 children submitted to videolaparoscopic appendectomy carried out at Hospital São Lucas (PUCRS) between May 2004 and February 2005. Patients were assigned to two groups: (a) Dexmedetomidine group (n=13): infusion of 1μg/kg over 10 minutes and maintenance dose of 0.5μg/kg/h) as an adjuvant to inhaled isoflurane anesthesia; (b) Control group (n=13): normal saline infusion at a similar rate and volume of the dexmedetomidine infusion. During the different surgical and anesthetic periods, groups were compared regarding heart rate, systolic and diastolic arterial blood pressures as well as need of supplemental fentanyl infusion. Student’s t test, ANOVA, and Finner’s procedure were used for statistical analysis.

RESULTS. During the strongest nociceptive stimuli (airway access and abdominal catheter placement), the heart rate and systolic blood pressure increased significantly (p<0.001) in the control group compared to the dexmedetomidine group. Compared to baseline levels, the hemodynamic responses to nociceptive stimuli were more stable when dexmedetomidine was used in combination with inhaled isoflurane anesthesia. The need for supplemental doses of fentanyl and the hemodynamic parameters were similar for both groups.

CONCLUSION. Dexmedetomidine combined with inhaled isoflurane for anesthesia of children submitted to videolaparoscopic appendectomy, efficiently blocks the hemodynamic responses to nociceptive stimuli. When compared to placebo, the use of dexmedetomidine did not change the need for supplemental doses of fentanyl for maintenance of hemodynamic parameters during the intraoperative period.

Only patients graded as American Society of Anesthesiologists (ASA) I and II were included in the study. The study protocol was submitted to and approved by the Research Ethics Committee of Hospital São Lucas (PUCRS). Parents or legal surrogates were informed of the study objectives and signed a consent form for inclusion of their children in the research. Children with a history of allergy to midazolam, fentanyl, propofol, atracurium, isoflurane, or dexmedetomidine were excluded.

On admission to the surgical ward, patients were assigned to the following groups: (a) Dexmedetomidine group: use of dexmedetomidine as adjuvant to inhaled isoflurane anesthesia. Intravenous (IV) Dexmedetomidine (2 μg/ml) was infused during 10 minutes (1 μg/kg – rapid phase) followed by a maintenance infusion (0.5 μg/kg/h) until the end of surgery; (b) Placebo - control group: normal saline solution (0.9%) infusion as adjuvant to inhaled isoflurane anesthesia, at the same rate and volume used for dexmedetomidine administration.

All children underwent a fasting period of at least six hours. Preoperative intravenous hydration and antibiotic coverage (gentamicin plus clindamycin) were prescribed by the on-duty emergency pediatrician and/or by the pediatric surgeon. Hydration with normal saline solution at 0.9% was maintained during surgery. The anesthesia stages were as follows:

1) **Preanesthetic medication:** on admission to the surgical ward all patients received intravenous midazolam infusion (0.1 mg/kg; maximum of 5mg).

2) **Anesthesia monitoring:** A Datascpe Passport II- 5LXG monitor was used to control hemodynamic parameters (continuous ECG, phase II; noninvasive blood pressure monitoring; pulse oximetry) and anesthetic gas analysis. Assisted ventilation was provided by a Takaoka Monterey respirator with the tidal volume and/or respiratory frequency adjusted to maintain PaCO₂ at less than 45mmHg, with an oxygen flow of 2L/min.

3) **Induction and maintenance of anesthesia:** Anesthetic induction was performed after 10 minutes of intravenous administration of isoflurane or placebo. Concurrently, sevoflurane 1% was inhaled in order to blind the surgical team to the induction agent. Sevoflurane was interrupted after five minutes of IV dexmedetomidine or placebo administration. With this procedure the end-tidal concentration could be equivalent to 0% at the time of induction.

After 10 minutes, IV propofol (2.0 mg/kg) combined with lidocaine 1% (1/3 of its volume) (13); IV fentanyl (1.5 μg/kg) and IV atracurium (0.5 mg/kg) were infused. Tracheal intubation was performed after two minutes. Anesthesia was maintained with isoflurane 1.2%, supplemented with IV fentanyl (1 μg/kg) if the systolic blood pressure or heart rate was 20% higher than the baseline levels. For adequate surgical relaxation, subsequent doses of atracurium (1/3 of the initial dose) were given every 30 minutes during maintenance of the pneumoperitoneum.

4) **Intraoperative maintenance of hemodynamic parameters:** Adjustments were predefined to prevent hypotension and low cardiac output, as well as to provide adequate analgesia.

- a) If blood pressure decreased (equal to or greater than 20% of baseline levels) normal saline (according to the hourly baseline requirement4) was infused for 3 minutes and repeated up to three times, if hypotension persisted;

- b) If systolic blood pressure decreased (equal to or greater than 30% of baseline levels) isoflurane concentration was reduced from 1.2% to 0.5% with a concomitant normal saline infusion (same as in the previous item). If the blood pressure still remained low, dexmedetomidine infusion was reduced by 50%. If blood pressure levels did not reach at least 20% of baseline levels, intravenous administration of dexmedetomidine was discontinued and the patient excluded from the study and considered a treatment failure;

- c) If the heart rate decreased more than 30% from baseline levels, a dose of 0.01 mg/kg intravenous atropine was administered. It could be repeated within five minutes if the heart rate did not reach levels above the minimum acceptable value of a 30% reduction. Patients were excluded from the study if they did not respond to atropine infusion or if reduction in the heart rate resulted in hypotension and/or low cardiac output;

- d) If systolic blood pressure and/or heart rate increased more than 20% from baseline levels, fentanyl (1 μg/kg) was given at five-minute intervals. The endpoint was a maximal acceptable increment of 20% from baseline levels.

Data were collected using a standardized protocol, which included demographic data, fluid infusion before and during surgery, infused drugs, length of surgery and isoflurane volume administered. The author defined heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) as major parameters to assess the hemodynamic response to nociceptive stimuli during the following periods:

- **Baseline (M0):** after premedication (midazolam) and prior to anesthetic induction;

- **Moment 1 (M1):** after the administration of the anesthetic drugs and prior to tracheal intubation;

- **Moment 2 (M2):** after tracheal intubation. The highest HR recorded during tracheal intubation was considered. SBP and DBP were measured immediately after tracheal intubation;

- **Moment 3 (M3):** HR, SBP and DBP measured immediately before surgical incision;

- **Moment 4 (M4):** HR, SBP and DBP measured immediately after surgical incision and during videolaparoscopic transumbilical trocar placement;

- **Moment 5 (M5):** HR, SBP and DBP measured at maximum pneumoperitoneum insufflation of 12mmHg of CO₂;

- **Moments 6 and 7 (M6 and M7):** HR, SBP and DBP measured during placement of the second and third videolaparoscopy trocars on the right and left abdominal sides, respectively;

All unexpected events which took place during the anesthetic induction and surgery time were recorded as adverse effects as well as the need for supplemental doses of fentanyl for maintenance of intraoperative hemodynamic parameters at a maximum 20% increase from baseline levels (M0).

For sample size calculation, researchers considered the systolic blood pressure in M4 as the major parameter. They presumed that in
order to obtain a significant difference between the two groups there should be a difference greater than 15% in systolic blood pressure, in addition to a standard deviation (SD) of 10 mmHg and a power of 90%. Therefore, at least 11 patients would be required per group. The comparison between the means (general characteristics) was made using Student’s t test. Behavior between the groups regarding the comparison between the means (general characteristics) was made using Finner’s procedure (16) was used to compare specific moments (M2, M4, M6 and M7) between the two groups as well as behavior of the means between these moments and the baseline values (M0), within the same group. The SPSS 11.0 (Statistical Package for the Social Sciences) was used for statistical analysis.

Results
Between May 2004 and February 2005, 35 videolaparoscopic pediatric appendectomies were performed at the Hospital São Lucas (PUCRS). Of these patients, 27 children were anesthetized by the main researcher (MCS) and one was not included in the study because parents refused to sign the consent form. Subsequently, 13 were allocated to the dexmedetomidine group and another 13 to the placebo group.

Both groups were homogeneous (Table 1) in terms of age, weight, gender and baseline hemodynamic parameters. The only exception was the length of preoperative fasting, which was longer (p=0.03) in the dexmedetomidine group. It should be highlighted that in both groups an extremely small volume (approximately 36ml/m²/h) of parenteral hydration was used preoperatively.

Results regarding systolic blood pressure, diastolic blood pressure and heart rate at the different moments of analysis are shown in Table 2 and Figure 1.

The behavior of hemodynamic parameters assessed during videolaparoscopic appendectomy in the dexmedetomidine and placebo-control groups is next described.

Systolic blood pressure (SBP): There was a remarkable increase in systolic blood pressure in the control group when compared to the dexmedetomidine group (p=0.009). (Figure 1). Comparing both groups at the different moments, significant differences in SBP levels at M2, M4, M6 and M7 (p=0.03 ;<0.01;<0.01 and <0.01, respectively) were found; the mean values at these moments were higher in the control group than in the dexmedetomidine group.

Diastolic blood pressure (DBP): No statistically significant differences were observed between the groups regarding DBP levels, in the comparison between groups (p=0.32), or in the assessment of specific moments M2, M4, M6 and M7 (p=0.20; 0.07; 0.15 and 0.12, respectively) (Figure 1).

Heart rate: The mean heart rate values were higher in the control group (p=0.001), as well as at moments M2, M4, M6 and M7 when compared to the dexmedetomidine group (p<0.01, at all moments) (Figure 1).

By comparing the moments of highest stimulation (M2, M4, M6 and M7) in relation to the baseline levels (M0) within the group, it was observed that:

### Table 1- General characteristics of the patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DMD</th>
<th>PLACEBO</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>9.2±1.6</td>
<td>9.2±2.0</td>
<td>p=0.93</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>37.3±11.2</td>
<td>38.8±13.9</td>
<td>p=0.76</td>
</tr>
<tr>
<td>Gender F/M</td>
<td>3/10</td>
<td>3/10</td>
<td>p=1.00</td>
</tr>
<tr>
<td>ASA I/II</td>
<td>0/13</td>
<td>0/13</td>
<td>p=1.00</td>
</tr>
<tr>
<td>SBP M0 (mmHg)</td>
<td>111±11.4</td>
<td>115±8.3</td>
<td>p=0.30</td>
</tr>
<tr>
<td>DBP M0 (mmHg)</td>
<td>62±8.8</td>
<td>68±8.6</td>
<td>p=0.14</td>
</tr>
<tr>
<td>HR M0 (bpm)</td>
<td>96±14.5</td>
<td>101±14.6</td>
<td>p=0.33</td>
</tr>
<tr>
<td>Length of surgery (min)</td>
<td>101.5±27.1</td>
<td>84.1±14.6</td>
<td>p=0.05</td>
</tr>
<tr>
<td>Pre-anesthetic fasting (h)</td>
<td>17.8±6.7</td>
<td>12.2±6.0</td>
<td>p=0.03</td>
</tr>
<tr>
<td>Pre-anesthesia hydration (ml/m²/h)</td>
<td>36.0±26.9</td>
<td>33.8±19.8</td>
<td>p=0.80</td>
</tr>
<tr>
<td>Use of analgesic in the last six hours</td>
<td>4</td>
<td>3</td>
<td>p=0.50</td>
</tr>
<tr>
<td>Vomiting in the last 24 hours</td>
<td>5</td>
<td>4</td>
<td>p=0.50</td>
</tr>
</tbody>
</table>

ASA: American Society of Anesthesiology classes; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; M0: baseline measurements (admission to the surgical ward, after administration of midazolam).

### Table 2- Hemodynamic parameters recorded during different surgical moments: dexmedetomidine (DMD) versus placebo groups

<table>
<thead>
<tr>
<th>SBP M0</th>
<th>DMD</th>
<th>PLACEBO</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline levels DBP</td>
<td>62±8.79</td>
<td>68±8.60</td>
<td>p=0.60</td>
</tr>
<tr>
<td>Pre-intubation DBP</td>
<td>53±16.81</td>
<td>54±12.50</td>
<td>p=0.50</td>
</tr>
<tr>
<td>Intubation DBP</td>
<td>57±16.09</td>
<td>65±13.79</td>
<td>p=0.20</td>
</tr>
<tr>
<td>Pneumoperitoneum DBP</td>
<td>57±12.65</td>
<td>65±15.23</td>
<td>p=0.05</td>
</tr>
</tbody>
</table>

HR: heart rate (bpm); p= comparisons made using Finner’s procedure

DBP: diastolic blood pressure (mmHg); SBP: systolic blood pressure (mmHg); ASA: American Society of Anesthesiology classes; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; M0: baseline measurements (admission to the surgical ward, after administration of midazolam).
Systolic blood pressure: Comparing to the baseline values (M0), a remarkable decrease in SBP levels in the dexmedetomidine group at M2 and M4 (p=0.01 and <0.01, respectively); and non-significant differences at M6 and M7 were observed.

However, the control group showed a significant increase in SBP at M6 and M7, when compared to the baseline levels (p=0.04 and 0.03, respectively), whereas no significant difference was observed at M2 and M4 (p=0.71 and 0.60, respectively).

Diastolic blood pressure: No significant differences were observed in the dexmedetomidine and control groups, when DBP was compared in M2, M4, M6 and M7 with the baseline levels (p=0.35; 0.06; 0.48 and 0.46 respectively, in the dexmedetomidine group; and, p=0.50; 0.75; 0.98 and 0.76, in the control group).

Heart rate: No significant heart rate increase was observed in the dexmedetomidine group at M2, M4 and M6 compared to the baseline levels (p= 0.07; 0.18, and 0.15, respectively). However, there was a remarkable decrease in heart rate at M7 (p=0.01) when compared to baseline levels. On the other hand, the control group showed a heart rate increase at M2, M4, M6 and M7 when compared to the baseline levels (p<0.01; =0.03; <0.01 and < 0.01, respectively).

Use of fentanyl as isoflurane adjuvant in general anesthesia during the surgery corresponded to 2.6 ± 1.1 μg/kg in the control group and 1.9 ± 0.5 μg/kg in the dexmedetomidine group (p=0.053). No significant difference between the two groups was found in relation to isoflurane consumption (Dexmedetomidine group=12.6 ± 3.4 ml versus 14.9 ±3.3 ml in the control group; p=0.1) as well as in arterial saturation of oxygen during the time of surgery.

One patient in the dexmedetomidine group (at the end of the infusion of 1μg/Kg for 10 minutes) showed a decrease of more than 30% in heart rate in comparison to baseline levels. Bradycardia was treated prior to the end of anesthetic induction, with immediate response. Two other patients in the dexmedetomidine group had a decrease in systolic blood pressure below the 30% established for the intervention. The first patient regained a normal blood pressure after receiving normal saline infusion and the second required normal saline infusion plus a 0.5% reduction of the isoflurane concentration until blood pressure levels returned to normal. In the control group, two patients presented agitation during sevoflurane inhalation. One patient reacted to tracheal intubation and another moved during abdominal closure, before isoflurane inhalation was discontinued.

DISCUSSION

In this clinical, randomized and double-blind study, in which dexmedetomidine was compared to a placebo as an adjuvant anesthetic to inhaled isoflurane in children submitted to videolaparoscopic appendectomy, it was observed that: a) the hemodynamic response to nociceptive stimuli was lower in the dexmedetomidine group when compared to the control group; b) hemodynamic changes were especially due to heart rate oscillations during nociceptive stimulation; c) diastolic blood pressure levels remained unchanged in both groups, without oscillation when compared to the baseline levels; d) supplemental doses of fentanyl for maintaining the hemodynamic parameters stable during surgery were not different between groups; and, e) the amount of preoperative hydration given to both groups was smaller than the recommended baseline requirements.14,15

Suppression of hemodynamic response to nociceptive stimuli, with concomitant reduction of hormone release, is one of the major goals of an adequate “anesthetic state.”13 Blood pressure and heart rate are the hemodynamic variables habitually used to assess the adequate block of the response to surgical stimulation17,18. Similarly to what happens in adult patients, it was observed that during tracheal intubation dexmedetomidine induces lower increases of blood pressure levels and of the heart rate when compared to the placebo.6,8 The same result was noted during placement of the trocars for laparoscopy. However, the greater differences were related to the heart rate: in the control group, the heart rate showed a remarkable increase, whereas in the dexmedetomidine group, it remained below baseline values.

Dexmedetomidine is known to have a sedative, analgesic and sympatholytic action.2,3,4 Plasma concentration of 1.2 ng/ml, close to
I and II) 17, who were normovolemic 26 and did not have severe water loss, during surgery, thus requiring additional hydration.

Only two patients who received dexmedetomidine showed a decrease in norepinephrine levels by up to 50% 20. These levels remained low and were suppressed with supplemental opioid doses. Unfortunately, with this finding might have been influenced by the hypotensive effect of propofol21 used for anesthetic induction, since behavior of the other stimuli was different and the variations between groups were greater.

Use of dexmedetomidine did not disclose any difference in diastolic blood pressure between groups. However, other studies22 revealed a remarkable increment of diastolic blood pressure, mostly when isoflurane doses of 0.6% had been used. 22 This effect, attributed to the high peripheral vascular resistance caused catecholamine release in response to the nociceptive stimulus, would be blocked with the infusion of dexmedetomidine. 22

In the current study, infusion of 0.5 μg/kg/h of dexmedetomidine as isoflurane adjuvant at 1.2% allowed control of the hemodynamic response to stimuli with values equal to or less than those of the baselines, reflecting adequate control of the sympathetic stimulus. However, the need for supplemental fentanyl during surgery, for maintenance of the hemodynamic parameters, was not different between groups when isoflurane was used in constant concentrations of 1 MAC (minimum alveolar concentration). Some studies have described a remarkable decrease in the MAC of isoflurane, with lessening of consumption, when combined with the continuous infusion of dexmedetomidine, in plasma concentrations of 0.3 and 0.6 ng/ml. 7

It should be underscored that inadequate analgesia is not the only factor interfering with hemodynamic parameters during laparoscopy. The increase in abdominal pressure during laparoscopy, automatically maintained at 10mmHg via CO2 insufflations, increases peripheral vascular resistance and decreases stroke volume. 21,24,25 In this case, increment of systolic blood pressure and of heart rate would not be suppressed with supplemental opioid doses. Unfortunately, with this sample size a correct alternative for this answer cannot be defined.

An occasional finding that merits special attention concerns preoperative hydration which was obtained using smaller amounts than the recommended baseline requirements (75ml/m²/h). 14,15 Additionally, patients with an abdominal infectious process have a greater water loss due to ileum, vomiting and fever. 26 Nevertheless, only two patients who received dexmedetomidine showed a decrease in blood pressure during surgery, thus requiring additional hydration. An explanation may be that only patients with a good health status (ASA I and II) 27,28 who were normovolemic 26 and did not have severe water loss, were included in the study. Hypovolemia of hypovolemic children may be intensified due to the vasodilation caused by anesthesia. 29,30 These children require less anesthesia, greater intravascular volume, or both, to ensure an adequate cardiac output. 9 Blood volume losses, greater than 20% would be needed to cause sinus tachycardia and a decrease in blood pressure. 27,28

A limitation of this study is that no specific equipment was used to monitor the depth of anesthesia (BIS), and also the possible correlation with the control of hemodynamic disorders caused by nociceptive stimuli (29-33).

Clinical trials involving use of dexmedetomidine in children are restricted to sedation for magnetic resonance imaging exams24 and as preanesthetic to reduce the incidence of agitation caused by sevoflurane. 25 Other findings in literature are described in case reports, which show the intraoperative use of dexmedetomidine, its use as an adjuvant in assisted ventilation in the ICU, and in the treatment of opioid dependency. 10,11,12,36 The authors believe that presumably this is the first double-blind study to assess the use of dexmedetomidine in pediatric surgical patients in this setting.

The current study showed that an initial dose of dexmedetomidine (1 μg/kg) followed by a maintenance dose of 0.5 μg/Kg/h, as an adjuvant to isoflurane anesthesia, in children submitted to videolaparoscopic appendectomy, kept the heart rate and blood pressure stable, also in periods of heightened surgical stimulation. On the other hand, the hemodynamic effects of decreased heart rate and blood pressure were not clinically relevant even when patients received less hydration than recommended.

Conflict of interest: none

RESUMO

DEXMEDETOMIDINA NA ANESTESIA DE CRIANÇAS SUBMETIDAS À APENDECTOMIA POR VIDEOLAPAROSCOPIA: UM ESTUDO DUPLO CEGO RANDOMIZADO E PLACEBO-CONTROLADO

OBJETIVOS. Avaliar a resposta hemodinâmica aos estímulos nociceptivos em crianças submetidas à apendicectomia por videolaparoscopia sob anestesia balanceada com isoflurano e dexmedetomidina.

MÉTODOS. Estudo randomizado, duplo cego e placebo controlado envolvendo 26 crianças submetidas à apendicectomia por videolaparoscopia no Hospital São Lucas da PUCRS entre maio de 2004 a fevereiro de 2005. Os pacientes foram alocados: a) Grupo Dexmedetomidina (n=13), administrada 1μg/kg em 10 minutos e manutenção de 0,5μg/Kg/h como coadjuvante à anestesia inalatória com isoflurano; b) Grupo Controle (n=13), que recebia solução fisiológica com volume e velocidade de infusão semelhante ao grupo anterior. Durante os diferentes tempos cirúrgicos e anestésicos os grupos foram comparados em relação à frequência cardíaca, pressão arterial sistólica e diastólica, assim como necessidade de doses suplementares de fentanil. Os grupos foram comparados pelo teste T, Qui quadrado, a ANOVA e Finner.

RESULTADOS. Nos momentos de maior estímulo doloroso (entubação, colocação dos trocateres abdominais), a frequência cardíaca e tensão arterial sistólica aumentaram significativamente (p<0,001) no grupo placebo em comparação ao grupo dexmedetomidina. Houve maior estabilidade hemodinâmica aos estímulos nociceptivos quando a dexmedetomidina foi empregada na complementação anestésica ao isoflurano. A necessidade de doses adicionais de fentanil na manutenção dos parâmetros hemodinâmicos estáveis foi semelhante entre os dois grupos.

CONCLUSÃO. A dexmedetomidina, utilizada como coadjuvante ao isoflurano na anestesia de crianças submetidas à apendicectomia por videolaparoscopia sob anestesia balanceada com isoflurano e dexmedetomidina, não apresentou diferença significativa em relação às parâmetros de hemodinâmica quando comparada com o placebo. No entanto, foram necessárias doses adicionais de fentanil no grupo placebo para manter a estabilidade hemodinâmica, o que pode ser explicado pela efetividade do adjuvante éfem mediado por mecanismos locais.
videolaparoscopia, bloqueia de forma efetiva a resposta hemodinâmica aos estímulos nociceptivos. No entanto, quando comparada ao placebo a dexmedetomidina não modificou a necessidade de doses complementares de fentanil para manutenção de parâmetros hemodinâmicos estáveis, durante o período intraoperatorio. [Rev Assoc Med Bras 2008; 54(4): 308-13]


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