An Approach for Controlling Emergence Hypertension in Cranial Surgery Using Dexmedetomidine Infusion

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Abstract

Background: Systemic hypertension often accompanies emergence from anesthesia that may lead to serious neurologic, cardiovascular, or surgical-site complications and which requires urgent management. Dexmedetomidine is a highly selective α2-adrenoceptor agonist with sedative, anxiolytic and analgesic properties that may prevent catecholamines release and development of hypertension.

Patients and Methods: Patients scheduled for craniotomy for supratentorial tumors, were divided randomly into 2 equal groups with 25 patients in each group, both received standard anesthetic technique the rate of the infusion in both groups was 0.5ml/kg/hr and started after dural closure, Group D received dexmedetomidine infusion in a rate of (0.5 µg/kg/hr). Group C received normal saline infusion. Nitroglycerine at a dose starting from (1 µg/kg/min) added if systolic blood pressure exceeded 25% of its preinduction value. Hemodynamic parameters were recorded intra-and postoperatively, Number of patients needing nitroglycerine infusion in each group recorded together with total amount infused and time to extubation.

Results: Dexmedetomine in a dose of 1 µg/kg/hr started after dural closure reduces the incidence and the extent of emergence hypertension as the number of patients needing nitroglycerine was 8 representing 32% of patients in dexmedetomidine group and 22 representing 88% of patients in control group without significant prolongation the time to extubation.

Conclusion: Dexmedetomine in a dose of 1 µg/kg/hr started after dural closure had a significant effect in reducing the incidence and the extent of emergence hypertension without prolonging the time needed for extubation.

Key Words: Hypertension – Cranial surgery – Dexmedetomidine.

Introduction

The perioperative course of patients undergoing intracranial tumours may be complicated by the occurrence of hypertension, coughing and ventilatory insufficiency. The incidence of emergence hypertension which is systemic hypertension during emergence from anesthesia and extubation may reach up to 57% in cranial surgeries [1]. This may lead to a number of adverse pathophysiological consequences, as when cerebral autoregulation is disturbed or its limits are exceeded blood flow passively increases with blood pressure, this in turn can increase Intracranial Pressure (ICP) or causes breakdown of the blood brain barrier [2].

Activation of the sympathetic nervous system appears to be a fundamental component of periextubation hypertension, as evidenced by elevated plasma catecholamine concentrations in these patients, other factors have been suggested which include pain, shivering [3]. Suppression of this response after release of endogenous catecholamines can be done with anti-hypertensive drugs which are not devoid of side effects [2].

Dexmedetomidine is a highly selective α2-adrenoceptor agonist with sedative, anxiolytic and analgesic properties that has minimal effects on respiratory drive. Its sedative and hypotensive effects are mediated via central α2A and imidazoline type 1 receptors while activation of peripheral α2B-adreno receptors result in an increase in arterial blood pressure and Systemic Vascular Resistance (SVR) [4].

Patients and Methods

After gaining approval of the ethics committee of the Anesthesia Department, Cairo University, and obtaining written informed consents from all patients participating in the study, fifty patients scheduled for supratentorial craniotomy under general anesthesia were included. The study was carried out in neurosurgical theatre in Cairo Uni-
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versity Hospital during the period between January 2014 and June 2015.

Inclusion criteria were patients from 18 to 50 years old, ASA I and II, scheduled for craniotomy for supratentorial tumour. Exclusion criteria were impaired renal functions, systemic hypertension, dysrhythmia, heart failure, glasco coma scale less than 12, the need for postoperative ventilation, history of allergy to the study drugs, surgeries lasting more than 6 hours.

Fifty patients were randomly allocated by a computer-generated table into one of the 2 study groups; the randomization sequence was concealed in sealed envelopes.

Study groups:
The two study groups were:
• Group D (dexmedetomidine group): 25 patients.
• Group C (control group): 25 patients.

Anaesthetic technique:
All chronic patient medications were continued (e.g., dexamethasone, anticonvulsants) until the morning of surgery.

In the preparation room, all patients were cannulated with an 18 gauge venous cannula, afterwards monitors were applied in the form of ECG lead II (with ST segment analysis), pulse oximetry, non-invasive blood pressure and invasive blood pressure was measured by a transducer connected to arterial catheter. These monitors were applied to all patients.

Anesthesia was induced by propofol (1-2mg/kg, (fentanyl 2µg/kg) and intubation was facilitated by the use of atracurium (0.5mg/kg) to induce muscular relaxation and done after disappearance of second twitch of train of 4 using Peripheral Nerve Stimulator (PNS), anesthesia was maintained with isoflurane (1.2% end tidal) and 100% O₂. Further fentanyl was given as 1µg/kg at the time of skin incision and again at the time bur hole. All patients were mechanically ventilated to maintain an end tidal CO₂ between 30-35mmhg. Muscle relaxation was maintained by an infusion of atracurium (0.5mg/kg/hr.). All patients received intraoperative fluid in the form of normal saline infusion (3ml/kg/hr.) and voluven (10ml/kg).

After dural closure. Group D patients received dexmedetomidine infusion in a rate of (0.5mg/kg/hr). Group C patients received normal saline infusion. The rate of the infusion in both groups was 0.5ml/kg/hr. The attending anesthetist was blinded to the type of solution injected. Atracurium infusion was discontinued after closure of the dura, while isoflurane was discontinued after skin closure is completed.

Management of hypertension was done using nitroglycerine at a dose starting from (1 µg/kg/min) if mean arterial blood pressure exceeded 25% of its preinduction value. When hypotension (MAP <25% from preinduction value) occurred ephedrine 3mg increments were given whereas atropine (0.5mg IV bolus) was given for bradycardia (HR <45min).

PNS was used to detect neuromuscular recovery, neuromuscular blockade was reversed with neo-stigmine (0.05mg/kg) and atropine 0.01mg/kg. Patients were extubated upon localization to pain. The study infusions were stopped at the time of extubation.

The patients were then transferred to the PACU where all haemodynamic parameters (heart rate, blood pressure and O₂ saturation) were monitored and patients received O₂ supplementation until discharge to the ward.

Data collection:
Heart Rate (HR), Mean (MAP) arterial blood pressure were recorded at the following times: Before induction of anesthesia, before dural closure, 5 minutes after drug administration, every 5 minutes intraoperative till extubation, at the time of extubation, every 30 minutes for 1 hour were recorded in the PACU.

Number of patients needing nitroglycerine infusion in each group was recorded together with total amount infused. And extubation time (defined as the time between the discontinuation of inhalation agents and extubation) was also measured.

Statistical analysis:
Data were coded and entered using the statistical package SPSS version 22. Values were expressed as mean and SD for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between different groups were carried out by unpaired t-test.

Sample size estimation:
Based on two-tailed a error probability of 0.05 and b error probability of 0.2 (power of 80%), a total sample size of 42 patients randomly allocated into two equal groups (21 patients in each group).
was required to detect a minimum clinically significant difference of 10% (effect size d=1) in mean arterial blood pressure. Statistical power calculations was performed using computer program G*Power 3 for Windows. (Franz Faul, Universität Kiel Germany). We enrolled 50 patients in the study (25 in each group) for the possible drop out.

For comparing categorical data, Chi square ($\chi^2$) test was performed. Exact test was used instead when the expected frequency is less than 5. $p$-values less than 0.05 were considered as statistically significant.

**Results**

The demographic data of the patients including age, weight and gender did not show statistical significance between the two groups. Values are Mean ± standard deviation (Table 1).

There was no statistically significant difference ($p>0.05$) between both groups as regard blood loss and ephedrine administration duration of surgery however there was a statistically significant difference in the amount of nitroglycerin received, dexmedetomidine and the number of patients received nitroglycerin was 22 (88%) mean while only 8 patients of dexmedetomine group received Nitroglycerin.

As regards the hemodynamics, baseline values of HR and MAP were comparable in both groups. Intraoperatively, the HR and MAP were significantly lower in Group D relative to Group C after starting drug infusion as shown in Figs. (1,2).

Table (1): Inhibition zone diameters interpretive standards for Enterobacteriaceae.

<table>
<thead>
<tr>
<th></th>
<th>Dex group</th>
<th>Control group</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>42.52±12.12</td>
<td>40.56±11.49</td>
<td>0.560</td>
</tr>
<tr>
<td>Weight</td>
<td>74.56±16.47</td>
<td>79.00±11.18</td>
<td>0.270</td>
</tr>
<tr>
<td>Height</td>
<td>168.56±11.75</td>
<td>164.92±6.03</td>
<td>0.18</td>
</tr>
<tr>
<td>Gender:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Female/Male)</td>
<td>17/8 (68%/32%)</td>
<td>12/13 (48%/52%)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Table (2): Duration of surgery, blood loss, nitroglycerin, ephedrine administration and time to extubation.data presented as Mean ± SD or n (%).

<table>
<thead>
<tr>
<th></th>
<th>Dex group</th>
<th>Control group</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of surgery.</td>
<td>256±66</td>
<td>243±69</td>
<td>0.69</td>
</tr>
<tr>
<td>Blood loss (ml).</td>
<td>764.00±110.42</td>
<td>782.00±116.26</td>
<td>0.296</td>
</tr>
<tr>
<td>Nitroglycerin dosage* (mg).</td>
<td>.13±.22</td>
<td>8.08±11.28</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Number of patients received nitroglycerin*.</td>
<td>.8±.32%</td>
<td>.22±.88%</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Ephedrine dosage (mg).</td>
<td>1.44±3.98</td>
<td>.00±.00</td>
<td>0.018</td>
</tr>
<tr>
<td>Number of patients received ephedrine.</td>
<td>3±12%</td>
<td>0±0%</td>
<td>0.12</td>
</tr>
<tr>
<td>Time to extubation.</td>
<td>15.28±4.99</td>
<td>15±4.55</td>
<td>0.85</td>
</tr>
</tbody>
</table>

**Fig. (1): Heart rate HR for the two groups over time.**
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Discussion

The present study was designed in patients undergoing cranial surgery for supratentorial tumors to compare the effects of dexmedetomidine infusion in a dose of 1 µg/kg/h and a control group (equivalent volume of saline) all started after dural closure. Several aspects were investigated including patients developing hypertension exceeding 25% of baseline value and requiring the use of nitroglycerin, also nitroglycerin dosage was calculated, and hypotension (MAP < 25% from baseline value) requiring ephedrine, variable hemodynamic data recorded, time to emergence also documented.

The present study highlights an important observation. That dexmedetomine in a dose of 1 µg/kg/hr started after dural closure had a significant effect in reducing MAP during emergence as the number of patients needing nitroglycerin was 8 representing 32% of patients in dexmedetomidine group while 22 patients representing 88% of patients needed nitroglycerine in the control group. This was without significantly prolonging the time to emergence and.

Regarding the hemodynamics the main effects throughout the drug infusion and postoperative periods were lower MAP in dexmedetomidine group in comparison to other group.

Guler et al., studied the effect of single dose of the alpha agonist dexmedetomidine on airway and circulatory reflexes during emergence from anesthesia in sixty patients who received a standard anesthetic. Five minutes before the end of surgery, they were randomly allocated to receive either dexmedetomidine 0.5 g/kg (n30) or saline placebo (n30) intravenously over 60s in a double-blind design. Guler et al., found that there was less significant increase in HR, SBP and DBP at extubation with dexmedetomidine with no difference in the time for tracheal extubation and for emergence from anesthesia. This is consistent with the present study. The difference is that the use of dexmedetomidine in the present study was in the form of infusion at a dose of 1 µg/kg that started at dural closure continued to the time of extubation [5].

Bindu et al., studied the effect of an intravenous infusion of dexmedetomidine 0.75 mcg/kg against control group, over 15 minutes before anticipated time of end of surgery in fifty patients scheduled for elective general surgical, urological and gynecological. Heart rate, systolic, diastolic, mean arterial pressures were recorded at the start of injection, at 1, 3, 5, 10, 15 minutes till extubation, at 1, 3, 5 minutes after extubation, and thereafter every 5 minutes for 30 minutes. They were significantly higher in control group. This is in concurrence with the present study taking in consideration the difference in surgical group, dosing and the time of start of infusion [6].

Kothari et al., compared the effect of dexmedetomidine versus lignocaine in attenuation of circulatory and airway responses during endotracheal extubation in craniotomies. The drugs were given 5min before the extubation over a period of 60s, dexmedetomidine in a dose of 0.5mcg/kg and lignocaine in a dose of 1.5mg/kg. Kothari et al., found that single dose of dexmedetomidine given 5min before extubation produced significant attenuation of circulatory and airway responses produced.
during extubation as compared to lignocaine in craniotomies which comes in agreement with the present study though there is a difference in the dose used, the time and the way of administration [7].

Bekker et al., designed a study in which patients scheduled for elective craniotomy were randomly assigned to receive either sevoflurane-opioid or sevoflurane-opioid-dexmedetomidine anesthesia. Bispectral index was used to maintain a similar level of hypnosis in both groups (40-50). Opioids, sevoflurane, and vasoactive medications were titrated in a routine manner, Bekker et al., by using indices, which assess a global hemodynamic stability of the anesthetics concluded that intraoperative dexmedetomidine infusion was effective for blunting the increases in SBP perioperatively, which is consistent with the present study, however there is a difference in the design between the present study and bekker study as in the present study dexmedetomidine was given as infusion only started at the time of dural closure, while in bekker study, dexmedetomidine started as loading and maintenance from start of the operation and opioid dosing controlled by BIS [8].

Also Ilhan et al., studied in double-blind prospective clinical study, the effects of fentanyl and dexmedetomidine as adjuvant agents in supratentorial craniotomies on the: Hemodynamic changes during perioperative and recovery periods, recovery times and side effects, thirty patients undergoing intracranial tumor surgery divided in two groups. In one group (n= 15), dexmedetomidine was infused as a 1 \( \mu \text{g/kg} \) bolus dose 10 minutes before induction of anesthesia and maintained with 0.4-0.5 \( \mu \text{g/kg/min} \) during the operation, fentanyl was given as a 2\( \mu \text{g/kg} \) at induction. In the other group (n=15), patients were given fentanyl 0.02 \( \mu \text{g/kg/min} \) as an infusion for anesthesia maintenance and bolus at induction a 4 \( \mu \text{g/kg} \) dose Ilhan concluded that dexmedetomidine controlled the hemodynamic changes better than fentanyl perioperatively, after extubation and during the early postoperative period, which supports the results of the present study results [9].

**Conclusion:**

From the present study we concluded that dexmedetomine in a dose of 1 \( \mu \text{g/kg/hr} \) started after dural closure had a significant effect in reducing the incidence and the extent of emergence hypertension without prolonging the time needed for extubation.

**References**

الخلاص العربي

ارتفاع ضغط الدم يصاحب عادة الاضطرابات من التخدير بعد إجراء جراحة المخ وقد يؤدي لحدوث تجمع نموي داخل الجمجمة على الرغم من أن هناك العديد من الأدوية التي تم تقييمها، مازال ارتفاع ضغط الدم في هذه المجموعة من المرضى بشكل تحدي لطباء التخدير.

تقليل الجهاز العصبي الودي يبدو عنصراً أساسيًا في ظهور ارتفاع ضغط الدم، كما يتضح من ارتفاع تركيزات الكاتيكولامين في هؤلاء المرضى، وعلى ذلك فإن منع إطلاق الكاتيكولامينين يبدو أكثر استحصالاً من الأدوية الخافضة للضغط.

وقد تم تصميم هذه الدراسة في المرضى الذين يخضعون لإجراءات الجمجمة للأورام فوق الخيمة، للمقارنة بين أثار ضغع عقار النيكسيدوتوميدين بجرعة 1 ميكروغ/كُغ/ساعة ضد مجموعة ضابطة كما يبدأ ضغع الأندوبين بعد إغلاق الأم الجافية.

بعد التخدير بطريقة قياسية لإجراءات الدم للأورام فوق الخيمة، وصولاً نهاية العملية الجراحية وبدء إغلاق الأم الجافية، تم تقسيم المرضى عشوائياً إلى مجموعتين في كل مجموعة، المجموعة الأولى تلقى ضغع النيكسيدوتوميدين في معدل 1 ميكروغ/كُغ/ساعة، تلقت المجموعة الثانية حجماً معاكساً من محلول الملح. كان معدل الضغ في جميع المجموعات 60 مل/كُغ/ساعة.

وقد أظهرت الدراسة أن النيكسيدوتوميدين في معدل 1 ميكروغ/كُغ/ساعة بدأ من بعد إغلاق الأم الجافية كان له أثر كبير في الحد من عدد المرضى المصابين بارتفاع ضغط الدم المصاحب للفتق وبدخ هذا الارتفاع وابتهاج تخفيف عدد المرضى المحتاجين الى التيتروجيلسين وكبيتة وهو أمر مفيد نظراً لأثاره الجانبية ومن إعادة اعمالات الأدوية لنزع الأندوبين.