THE EFFECTS OF DEXMEDITOMIDINE ON PERIOPERATIVE HEMODYNAMICS IN CRANIOTOMY

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Abstract: OBJECTIVE In this prospective randomized placebo controlled study, we investigated the effects of Dexmedetomidine as an adjuvant in craniotomy on the following hemodynamic changes and brain edema during the perioperative period, and additional opioid requirement.

MATERIALS AND METHODS Twenty patients of ASA physical status and undergoing craniotomy were randomly divided into two groups as Group D (Dexmedetomidine group) and group P (placebo group). In the Group D (n=10), Dexmedetomidine was infused as bolus dose of 1 microgram per kg over 10 minutes before induction of anaesthesia, maintained with 0.4-0.5 microgram per kg per hour during the surgery and stopped at the initiation of skin suture. At the time of induction, fentanyl was given as a 2 microgram per kg dose in both the groups. Hemodynamic changes, cerebral relaxation scores, and additional intraoperative opioid requirement were recorded.

RESULTS In Group D, HR and MAP values were significantly lower than the placebo group after induction.
Dexmeditomodine thus may be a suitable anaesthetic adjuvant to neurosurgical anaesthesia. We designed this study to assess the efficacy of Dexmeditomodine on perioperative hemodynamics, intracranial pressure and additional opioid requirements in patients undergoing craniotomy.

**AIM OF THE STUDY**
The aim of the study is analysis of the effects of Dexmeditomodine on perioperative hemodynamics, intracranial pressure and opioid requirements in patients undergoing craniotomy.

**PHARMACOLOGY OF DEXMEDITOMIDINE**
Dexmeditomidine is a pharmacologically active d-isomer of medetomidine. It was first synthesized in late 1980s, Phase 1 studies in early 1990s and clinical trials in late 1990s. It has approximately 8-fold greater $\alpha_2:\alpha_1$ selectivity than clonidine. It also has a shorter elimination half-life than clonidine 2-3 vs 8-12 hr. It is FDA approved for ICU sedation in adults.

**PHARMACOKINETICS**
The metabolites are inactive and eliminated through kidney. Its half life is significantly increased ifThe intravenous distribution $t_{1/2}$ is 6 minutes and elimination $t_{1/2}$ is 2 hrs. It has a volume of distribution of 118 liters and 94% protein bound. It undergoes almost 100% biotransformation by glucuronidation and cytochrome-P450 enzymes hepatic failure (7.5 hr). Renal impairment has no significant effect on its pharmacokinetics.

**MECHANISM OF ACTION**
In general, presynaptic activation of the alpha-2 adrenoceptor inhibits the release of norepinephrine, terminating the propagation of pain signals. Postsynaptic activation of $\alpha_2$ adrenoreceptors in the central nervous system inhibits sympathetic activity and thus can decrease blood pressure and heart rate. Combined, these effects can produce analgesia, sedation, and anxiolysis. Dexmedetomidine combines all these effects.
independent of cAMP and protein phosphorylation. It is mediated by $G_{0}$ proteins. These two mechanisms represent two very different ways of effecting analgesia— in the first, the nerve is prevented from ever firing and in the second, it cannot propagate its signal to its neighbour. One of the highest densities of alpha-2 receptors has been detected in the locus ceruleus, the predominant noradrenergic nucleus in the brain and an important modulator of vigilance. The hypnotic and sedative effects of $\alpha$-adrenoceptor activation have been attributed to this site in the CNS. The locus ceruleus is also the site of origin for the descending medullospinal noradrenergic pathway, known to be an important modulator of nociceptive neurotransmission. In this region of the brain, alpha-2 adrenergic and opioidergic systems have common effector mechanisms, indicating that dexmedetomidine has a supraspinal site of action. The substantia gelatinosa of the dorsal horn of the spinal cord contains receptors which when stimulated inhibit the firing of nociceptive neurons stimulated by peripheral A and C fibers and also inhibit the release of the nociceptive neurotransmitter substance P. This spinal mechanism is most likely why anesthesiologists have found success in using clonidine as an epidurally administered agent in addition to its primary use as an intravenous drug. Alpha-2 adrenergic receptors are widely distributed within the cerebral vasculature. Noradrenergic neurons in the locus ceruleus project widely throughout the brain, also targeting the intracerebral capillaries and microarterioles (i.e., intrinsic adrenergic innervation). Thus, systemic administration of alpha-2 agonists could decrease cerebral blood flow via direct alpha-2 mediated vascular smooth muscle constriction and indirectly via effects on the intrinsic neural pathways modulating vascular effects.

**REVIEW OF LITERATURE**

P. E. Tanskanen, J. V. Kytta, T. T. Randell and R. E. Aantaa et al - Dexmedetomidine as an anaesthetic adjuvant in patients undergoing intracranial tumour surgery—a double-blind, randomized and placebo-controlled study. Br J Anaesth 2006, 97, 658–65. Fifty-four patients scheduled for elective surgery of supratentorial brain tumor were randomly divided into three groups as, placebo group (n=18), dexmedetomidine 0.2 group (n=17) and dexmedetomidine 0.4 group (n=18). The results of the study was the median times from the termination of N2O to extubation were 6 (3–27), 3 (0–20) and 4 (0–13) minutes in placebo, DEX-0.2 and DEX-0.4 groups, respectively (P<0.05 ANOVA all-over effect). The median percentage of time points when systolic blood pressure was within more or less than 20% of the intraoperative mean was 72, 77 and 85 respectively (P<0.01). DEX-0.4 group differed significantly from the other groups. DEX blunted the tachycardic response to intubation (P<0.01) and the hypertensive response to extubation (P<0.01). DEX-0.4 group differed in the heart rate variability from placebo (93 vs 82%, P<0.01). The authors concluded that Dexmedetomidine increased perioperative haemodynamic stability in patients undergoing brain tumour surgery. Bristow A, Shalev D, Rice B, Lipton JM,
Giesecke AH jr et al - Low dose synthetic narcotic infusions for cerebral relaxation during craniotomies. Anesth Analg 1987; 66:413-6. Thirty patients undergoing craniotomies were administered infusions of fentanyl 1 microgram/kg/hr (n=10), sufentanil 0.1 microgram/kg/hr (n=10) and normal saline (n=10) in a double-blind study of cerebral relaxation. Significantly better relaxation scores were achieved in patients given a narcotic infusion, but there was no difference between the scores with the two narcotics. Infusions of narcotics at these low rates did not delay recovery or alter the requirement for other anesthetic agents.

Narcotic infusion rates that do not delay recovery or alter the depth of anesthesia significantly improve cerebral relaxation.

Alex Bekker, Mary Sturaitis, Marc Bloom, Mario Moric, John Golfinos, Erik Parker, Ramesh Babu, Abishabeck Pitti et al - The Effect of Dexmedetomidine on Perioperative Hemodynamics in Patients Undergoing Craniotomy (Anesth Analg 2008, 107, 1340 –7). Fifty six patients scheduled for elective craniotomy were randomly assigned to receive either sevoflurane–opioid (n=28) or sevoflurane–opioid–DEX anesthesia (n=28). The results were, Area under the curve-SBP for above the targeted range was significantly lower for patients in the DEX group (P=0.044). The coefficient of variation for SBP or HR did not differ between groups. A significantly smaller proportion of patients in the DEX group required treatment with antihypertensive medications (12 of 28, 42% vs 24 of 28, 86%, P=0.0008). The DEX group required fewer opioids in the intraoperative period, but there were no differences in the use of sevoflurane. In the postanesthesia care unit, patients in the DEX group had fewer hypertensive episodes (1.25±1.55 vs 2.50±2.00, P=0.0114) and were discharged earlier (91±17 vs 130±27 min, P<0.0001). There were no differences in the requirement for postoperative opioids or antiemetics.

The Authors concluded that intraoperative Dexmedetomidine infusion was effective for blunting the increases in SBP perioperatively. The use of Dexmedetomidine did not increase the incidence of hypotension or bradycardia.

Osman Ilhan, Senem Koruk, Gokcen Serin, Ibrahim Erkutlu, Unsal Oner et al - Dexmedetomidine in the Supratentorial Craniotomy. EAJM 2010, 42, 61-5. Thirty patients of ASA physical status I-II undergoing intracranial tumor surgery were randomly divided in two groups as Group D-receiving Dexmedetomidine infusion (n=15) and Group F-receiving Fentanyl infusion (n=15). The result was in group D, MAP and HR values after intubation, after skull clamp insertion and after extubation were lower than in group F (p<0.05). In group D, cerebral relaxation scores were also significantly lower. Recovery times were found to be shorter in group D as compared to group F; the same trend was observed for the supplemental opioid requirement. During the postoperative period, there was no shivering, nausea or vomiting in group D. But in group F, 3 patients complained of shivering and 2 patients experienced nausea and vomiting. The conclusion was Dexmedetomidine controlled the hemodynamic changes better than fentanyl perioperatively, after extubation and during the early postoperative period.

Oda Y, Toriyama S, Tanaka K, Matsuura T, Hamaoke N, Morino M, Asada A et al - The effect of dexmedetomidine on electrocorticography in patients with temporal lobe epilepsy under sevoflurane anesthesia. Anesth Analg 2007 Nov, 105(5), 1272-7. The results were, median frequency of Electrocorticogram in 88 leads from all leads from all patients was significantly decreased by 1.5 ng/mL of dexmedetomidine.
compared with those at baseline and 0.5 ng/mL (P =0.003 and 0.03, respectively). However, spectral power densities in the frequency bands: delta (<4 Hz), theta (> or =4 and <8 Hz), alpha (> or =8 and <13 Hz), and beta (> or =13 Hz), were not changed. Neither the number of leads with spikes nor the number of spikes in all leads and in the lead with highest number of spikes at baseline was affected by dexmedetomidine. The inference was, Dexmedetomidine at plasma concentrations of 0.48 and 1.60 ng/mL decreased the median frequency of Electrocor-ticogram, but did not affect spike activity in patients with temporal lobe epilepsy anae-sthetized with 2.5% sevoflurane. B.-S. Chen, H. Peng and S.N. Wu et al- Dexmede-tomidine, an a2-adrenergic agonist, inhibits neuronal delayed-rectifier potassium current and sodium current British Journal of Anaes-thesia 103 (2), 244–54 (2009). The result was Dexmedetomidine suppressed the amplitude of delayed rectifier K+ current [IK(DR)] in a concentration-dependent manner with an IC50 value of 4.6 mM in NG108-15 cells. No change in the steady-state inactiva-tion of IK(DR) was evident in the presence of DEX. A minimal binding scheme was also used to evaluate DEX-induced block of I K(DR). Inhibition of IK(DR) by Dexmedetomidine was still observed in cells preincubated with yohimbine (10 mM) or efaroxan (10 mM). Dexmedetomidine depressed the peak amplitude of Na+ current (INa), whereas it had minimal effect on L-type Ca2+ current. Under current-clamp configuration, DEX increased the duration of action potentials. IK(DR) and INa in response to AP waveforms were more sensitive to block by Dexmedetomidine than those elicited during rectangular pulses. In isolated cerebellar granule cells, Dexmedetomidine also effectively suppressed IK(DR). The inference was, the effects of Dexmedetomidine are not limited to its interactions with a2-adrenergic receptors

Inhibitory effects on IK(DR) and INa constitute one of the underlying mechanisms through which Dexmedetomidine and its structurally related compounds might affect neuronal activity in the brain.

STUDY METHOD
The study was undertaken entirely in the Department of Anaesthesiology, Government Stanley Medical College and Hospital, Chennai during the period from January 2011 to June 2011 with due permission from the Institutional Ethical committee. It was a prospective randomized placebo controlled study. The target population was 10 in each group. Though the sample size is small, the target population was decided upon based on the study by Bristow A, Shalev D, Rice B, Lipton JM, Giesecke AH jr et al7 on Low dose synthetic narcotic infusions for cerebral relaxation during cranioto-mies, in which the sample size was 10 in each group. Randomisation was done in our study was done by using sealed envelopes.

INCLUSION CRITERIA: Ø Any patient aged 20–65 yr, with Glasgow Coma Scale score 14 or 15 and scheduled for elective intracranial surgery under general anaesthesia in our institution, was considered eligible for the study. EXCLUSION CRITERIA: Ø Pregnant or nursing woman Ø Premeno-pausal woman without reliable contra-ception Ø Morbid obesity Ø Preoperative heart rate (HR)<45 beats/min Ø First second or third degree AV block Ø Anti-hypertensive medication with alphamethyldopa, clonidine or other alpha2-adrenergic agonist Ø Participation in another drug study during the preceding 1 month period.

STUDY MATERIALS:
1. Dexmeditomidine infusion prepared by diluting 200 microgram of the drug in 50 ml of 0.9% normal saline. 2. Placebo infusion - 50 ml of 0.9% normal saline. 3. Drugs for general anaesthesia. 4. Emergency drugs. 5. Airway equipments. 6. Monitors - Pulse oximeter, Invasive blood pressure, Electrocardiogram, End tidal carbon dioxide. It was observed from the Pilot study that the incidence and severity of hypotension was less, and it was treatable with crystalloid fluid boluses. None of the patients required ephedrine. So, a central venous catheter was not placed. The response to bradycardia and hypotension was assessed with the invasive arterial blood pressure monitor. An accurate quantitative assessment of the Intracranial pressure can be done only with an intraventricular or subdural catheter pressure monitoring system. After opening the duramater, quantitative assessment of the Intracranial pressure is not possible. Only a qualitative assessment of the cerebral relaxation or brain edema can be done. Qualitative assessment of cerebral relaxation has been employed in various studies too. So, hemodynamic response was assessed with IBP and qualitative assessment of the ICP was done with the Cerebral relaxation score. Preoperative general and systemic examination was done and Glasgow coma scale was assessed (only 14 and 15 included in the study). Preoperative investigations - Complete blood count, blood grouping and typing, blood sugar, urea, creatinine, Chest-X ray and ECG were done. On the day of surgery, a complete systemic examination was done. A written informed consent was obtained from the patients. After shifting to the operation theatre, intravenous access was obtained with 18G venflon. Monitors - SPO2, NIBP, ECG, ETCO2 were connected to the patient. An invasive arterial line was placed before induction. The Patients were premedicated with Inj.Glycopyrrolate 0.2 mg, Inj.Midazolam 70 microgram/kg, Inj.Fentanyl 2 microgram/kg. In Group D, Dexmeditomodine was administered 1 microgram/kg bolus slow IV over 10 minutes, before induction. The patients were induced with Inj.Thiopentone 5 mg/kg and Inj.vecuronium 0.1 mg/kg and ventilated with 100% O2 for 3 minutes. Under direct laryngoscopy, intubation was done with appropriate size endotracheal tube. During the time of skin incision or skull clamp placement Inj.Fentanyl 2 microgram/kg IV was given to patients in both the groups. The surgeons were asked to infiltrate the scalp with Inj.Lignocaine with adrenaline before incision. Intraoperatively, anaesthesia was maintained with N2O/O2-60%:40%, Isoflurane 0.2-1% and Inj.Vecuronium 0.03 mg/kg. To avoid positional effects on the study, all the patients were uniformly positioned in a 30 degree head up position. Hyperventilation was done to maintain an ETCO2 of 35-40 mmhg. In group D, Dexmeditomidine infusion was started at 0.4-0.5 microgram/kg/hr and in Group P 0.9% isotonic saline infusion was started. The following parameters were monitored intraoperatively - HR, SBP, DBP, MAP, SPO2. These values were recorded at the time of - baseline, after premedication, 1 min after induction, 5 min after induction, before skull clamp placement, 1 min after skull clamp placement, before skin incision, 1 min after skin incision, intraop once in 15 mins, before extubation, 1 min after extubation and 10 mins after extubation. Intraoperatively, if HR and SBP are 20% of baseline Inj.Fentanyl 2 microgram/kg was given. If HR 50/min, Inj.Atropine 0.6 mg was given in increments. If SBP 90 mmhg or a fall in MAP of 20% from the baseline values, it was treated with fluid bolus of crystalloid (200 ml of 0.9% normal saline).
If not responding, Inj.Ephedrine was given in 5mg increments. Before opening the dura, Inj.Mannitol 1g/kg IV was given over 15 mins. The surgeon was asked to evaluate cerebral relaxation on a five-point scale from excellent (1) to poor (5). The score was based on five factors - tenseness of the brain tissue and 2 or Fisher’s exact test, as appropriate. Values of p<0.05 were accepted as significant. The minimum age in group D was 30 and the maximum age was 53. In Group P the minimum age was 28 and the maximum age of 2 was awarded if retraction was not ideal and blood vessels were not fully constricted. A score of 3 indicated tense brain tissue that significantly hindered the procedure, combined with flat sulci and dilated blood vessels. A score of 4 represented a further deterioration in these factors with significant bulging of brain tissue from the skull and the worst possible conditions for surgery. So, the scoring was done as follows: 1-perfect, no swelling; 2-minimal swelling; 3- substantial swelling, no medication required and 4-severe swelling, medication required. Additional intraoperative opioid requirements in both the groups was also recorded. Both the infusions were stopped at the initiation of skin suture. After spontaneous respiratory attempts, the patients were reversed with Inj.Neostigmine 0.05mg/kg and Inj.Glycopyrrolate 0.01mg/kg and extubated. All the patients were shifted to an Intensive care unit for observation.

**STATISTICAL ANALYSIS**

A target population of 10 per group was decided based on the study by Bristow A, Shalev D, Rice B, Lipton JM, Giesecke AH jr et al7 on Low dose synthetic narcotic infusions for cerebral relaxation during craniotomies, in which the sample size was 10 in each group. Randomisation of subjects to the two groups was done by using sealed envelopes. The statistical data were recorded with SPSS 13.0. Mean ± standard deviation values were determined using descriptive analyses. Comparisons of the two groups with regard to hemodynamic and recovery periods were carried out with the Mann-Whitney U-test, the Wilcoxon sign test was used for intragroup comparisons. Gender, side effects and need for additional medication were analyzed via Fisher’s exact test, as appropriate. Values of p<0.05 were accepted as significant. The minimum age in group D was 30 and the maximum age was 53. In Group P the minimum age was 28 and the maximum age was 52. The minimum surgical time was 193 minutes and 200 minutes in Group P. The maximum time was 238 minutes in Group D and 250 minutes in Group P. Both the groups were comparable in terms of age, sex and duration of surgery.

In group D, the HR values for dexmedetomidine after a loading infusion of 10 minutes were lower with respect to the values observed prior to sedation. It was statistically significant (p<0.033). However, these decreases were less than 20% and within physiological limits. The HR values were lower one minute after intubation, after the skull clamp and after extubation in group D and this was also statistically significant (p-0.024). In Group F, the HR values at one minute after the intubation, after the skin incision, after the skull clamp and after extubation were significantly higher as compared to the values obtained before the induction of anesthesia (p-0.042).
### Table 1: Demographic Variables

<table>
<thead>
<tr>
<th></th>
<th>Group D (n=10)</th>
<th>Group P (n=10)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>41±10.8</td>
<td>39±11.2</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>4/6</td>
<td>5/5</td>
<td>NS</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>215.12±20.34</td>
<td>218.43±30.33</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Table 2: Cerebral Relaxation Score

<table>
<thead>
<tr>
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<th>Group D (n=10)</th>
<th>Group P (n=10)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No swelling (score 1)</td>
<td>8 (80%)</td>
<td>1 (10%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Minimal swelling (score 2)</td>
<td>2 (20%)</td>
<td>3 (30%)</td>
<td>NS</td>
</tr>
<tr>
<td>Substantial swelling (score 3)</td>
<td>0 (0%)</td>
<td>6 (60%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Severe Swelling (score 4)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Overall CRS (median(range))</td>
<td>1 (1-2)</td>
<td>3 (1-3)</td>
<td>&lt;0.0001</td>
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### Table 3: Additional Opioid Requirement

<table>
<thead>
<tr>
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<th>Group D (n=10)</th>
<th>Group P (n=10)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients required additional intraop fentanyl</td>
<td>2 (20%)</td>
<td>10 (100%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

### Table 4

<table>
<thead>
<tr>
<th></th>
<th>Group D (n=10)</th>
<th>Group P (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

An Initiative of The Tamil Nadu Dr. M.G.R. Medical University
University Journal of Medicine and Medical Sciences
In group D, the mean arterial pressure values for dexmedetomidine after a loading infusion of 10 minutes were significantly lower with respect to the values observed prior to sedation (p<0.027). In group D as compared to group F, there was a statistically significant decrease in MAP value measurements after induction, one minute after intubation, after the skull clamp and after extubation (p<0.042). In Group F, higher values were observed after the induction, intubation, skull clamp and after extubation (p<0.04). In Group D, 8 out of 10 patients had no cerebral swelling, whereas in Group P it was only 1 out of 10 patients, which is statistically significant (p<0.0001). None of the patients in Group D had a substantial cerebral swelling. In Group P, 6 patients had a substantial cerebral swelling and the results are statistically significant (p<0.001). Patients in both the group did not have severe cerebral swelling, requiring medication. The overall median score was 1 in Group D and 3 in Group P, which is statistically significant (p<0.0001).

In Group D, 1 patient developed bradycardia and two patients developed hypotension. Bradycardia (HR-45) occurred post induction and was treated with Inj. Atropine 0.6mg IV. The mean arterial pressure was 50 mmhg in one patient and 52 mmhg in the other patient. In both the patients hypotension was observed in the postinduction period. Hypotension was treated with crystalloid (0.9% normal saline) fluid bolus of 200ml. The mean arterial pressure raised to 65mmhg and 69mmhg respectively. Both the patients did not require ephedrine. In Group P none of the patients developed bradycardia or hypotension.

**DISCUSSION**

In neuroanaesthesia, the appropriate surgical conditions ensure that the brain is minimally affected by the procedure, without jeopardizing autoregulation of the cerebral circulation. Rapid recovery from neuroanaesthesia and early neurological examination are also required. Alpha-2 adrenergic agonists have properties that reduce sympathetic, sedative and anaesthetic requirements as well as provide hemodynamic stabilization. It is also known that dexmedetomidine exhibits an analgesic effect without inducing respiratory depression. The final common pathway leading to perioperative hypertension appears to be activation of the sympathetic nervous system, as evidenced by increased plasma catecholamine concentrations in patients after craniotomy. Dexmedetomidine decreases plasma epinephrine and norepinephrine level perioperatively. In this study, we investigated the effects of Dexmedetomidine in neurosurgical patients in an attempt to find a clinically feasible combination of anaesthetics that would ensure perioperative haemodynamic stability and fast recovery. All the patients were comparable in terms of age, sex and duration of surgery. Tanskanen et al used dexmedetomidine on patients undergoing intracranial tumor surgery. He showed that dexmedetomidine depresses tachycardia and the hypertensive response developing at intubation and at extubation better than placebo. Lawrence et al showed that dexmedetomidine...
given before the induction as a single dose of 2 microgram/kg IV controls the hemodynamic responses to tracheal intubation and extubation as well as HR changes during the intraoperative period, which is due to the decrease in cerebral blood flow. Even though we did not have the opportunity to directly measure the effects of dexmedetomidine on cerebral blood flow in our study, cerebral swelling (as a reflection of cerebral blood flow in combination with the cerebral relaxation score) was higher in Group P as compared to group D (p<0.0001). Therefore, dexmedetomidine treatment resulted in improved cerebral relaxation.

Tanskanen et al\textsuperscript{1} observed that in the intraoperative period, dexmedetomidine reduced systolic blood pressure by 20% in comparison to control group levels. Lawrence et al\textsuperscript{9} showed that dexmedetomidine given before the induction as a single dose of 2 microgram/kg IV controls the pressure responses to tracheal intubation and extubation in comparison to control treatment. Taittonen et al\textsuperscript{10} showed that, after premedication with dexmedetomidine, HR decreased by 18%. Osman ilhan et al\textsuperscript{21} observed a decrease of 9% in HR after the bolus infusion of dexmedetomidine for 10 minutes. In our study, tachycardia attacks were more effectively controlled in the dexmedetomidine group, especially during the periods when the stress response was pronounced (p=0.024). Although these changes represented statistically significant differences, each parameter remained at physiologically acceptable levels. Although the hemodynamic measurements before the skull clamp placement were similar, after the skull clamp was placed, we recorded lower values for HR in group D.

Bekker et al\textsuperscript{8} reported that dexmedetomidine administered during neuroanesthesia reduces the need for opioids, leads to fewer antihypertensive treatments and provides better hemodynamic stability during incision. Aantaa et al\textsuperscript{19} showed that when 1 microgram/kg of dexmedetomidine was used as premedication, the thiopental dose necessary for the induction of anesthesia was reduced by 55%. In a similar study, the authors reported that dexmedetomidine, administered as premedication, reduced the dose of IV anesthetic agents required, as well as the need for opioids during the intraoperative period\textsuperscript{10}. In our study, the amount of additional narcotics required was significantly lower in group D as than group F (p<0.0001).

**SUMMARY**

We conducted this prospective randomized placebo controlled study to examine whether an addition of Dexmedetomidine to a commonly administered balanced anesthetic regimen improves global hemodynamic stability in patients undergoing craniotomy. The results of the study was, Ø Patients in both the groups were comparable in terms of age, sex and duration of surgery. Ø The heart rate values after induction, intubation, skull clamp placement and extubation were significantly lower...
in the Dexmedetomidine group than the placebo group. There was a significant decrease in mean arterial pressure with dexmedetomidine after induction, intubation, skull clamp placement and extubation. Dexmedetomidine reduced the intraoperative requirement of opioids significantly.

CONCLUSION
In conclusion, dexmedetomidine is effective in craniotomy for controlling perioperative hemodynamic responses, inducing cerebral relaxation and for reducing opioid consumption during the perioperative period.

ANSWERS TO THE QUERIES
1. Yes sir the sample size is small. I chose the same sample size that was chosen in the references I have provided:–
   a. Bristow A, Shalev D, Rice B, Lipton JM, Giesecke AH jr. Low dose synthetic narcotic infusions for cerebral relaxation during craniotomies. Anesth Analg1987; 66:413-6. Thirty patients undergoing craniotomies were administered infusions of fentanyl 1 microgram/kg/hr (n=10), sufentanil 0.1 microgram/kg/hr (n=10) and normal saline (n=10) in a double-blind study of cerebral relaxation. The effect of two narcotic drugs – fentanyl and sufentanil on cerebral relaxation was compared with the placebo group. In this study also, statistically significant results were obtained with a sample size of 10 in each group.
   b. Osman ilhan, Senem koruk, Gokcen serin, Ibrahim erkuulu, Unsal oner - Dexmedetomidine in the supratentorial craniotomy-The Eurasian journal of medicine-2010,vol 42,number 2. Thirty patients of ASA physical status I-II undergoing intracranial tumor surgery were randomly divided in two groups as Group D-receiving Dexmedetomidine infusion (n=15) and Group F-receiving Fentanyl infusion (n=15). The effects of Dexmedetomidine and fentanyl on perioperative hemodynamic parameters (HR and MAP) was analysed. A statistically significant result was obtained with a target population of 15 in each group. Statistically significant results were obtained with a small sample size of 20 and 30 in the above mentioned studies. Based on the inferences of the above studies and also from the results of the pilot study, the statistician decided the sample size as 20 (10 in each group) in our study.

Hypotension occurred immediate post Induction as shown in the Figure no.5. It was treated with a bolus of 200ml of crystalloid (0.9% normal saline). It did not require Inj. Ephedrine. Moreover, hypotension was treated based on the response in the IBP in the following references:
   c. Alex Bekker, Mary Sturaitis, Marc Bloom, Mario Moric, John Golfinos, Erik Parker, Ramesh Babu, Abishabeck Pitt-The Effect of Dexmedetomidine on Perioperative Hemodynamics in Patients Undergoing Craniotomy international anaesthesia research society vol 107,number 4,October 2008. In the above mentioned studies hypotension was treated initially with a crystalloid bolus of 200ml (0.9% normal saline). Inj. ephedrine was used in some patients in whom the
hypotension did not respond to a fluid bolus. In the above mentioned studies CVP was not used and hemodynamic response was assessed with an Invasive Blood Pressure. So, in our study also the hemodynamic responses was assessed with IBP. Moreover, in our pilot study hypotension was not severe enough to be treated with Inj.ephedrine. Hence, a CVP was not used.

Bradycardia occurred in the postinduction period as shown in Figure no.4. It was treated with Inj.Atropine 0.6mg IV.

The scoring system used to evaluate cerebral relaxation is a clinical scoring system as used in the following references –


The intracranial pressure can be quantitatively measured by an intraventricular, intraparenchymal or subdural catheter. It can be assessed qualitatively by the Cerebral Relaxation Score. In our Institution we do not use intraventricular or subdural catheters regularly to measure the intracranial pressure.

5. In the above mentioned studies 20 or 30 degree head up position was maintained throughout the procedure and so the positional effects were not studied. In our study also, throughout the procedure a 30 degree head up was maintained, that's the reason the positional effects were not studied.

I hope I have satisfactorily answered all your queries, Sir.

BIBLIOGRAPHY


21 Alex Bekker, Mary Sturaitis, Marc Bloom, Mario Moric, John Golfinos, Erik Parker, Ramesh Babu, Abishabeck Pitt. The Effect of Dexmedetomidine on Perioperative Hemodynamics in Patients Undergoing Craniotomy international anaeesthesia research society vol 107,number 4,October 2008.

