

Usage of Alpha-2 Agonists and Opioids in Neuroanesthesia: Twenty Years of Experience

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Pain stimulation is perceived only during manipulations of the skin, periosteum, and dura mater in intracranial surgical procedures. The main part of surgical intervention is performed on the brain, which does not have pain receptors. That is why pain relief does not seem to be an essential problem of anesthesia management during neurosurgical procedures. In our opinion, the creation of a certain level of stabilization of the autonomic nervous system, by preventing redundant hemodynamic and neuroendocrine response to surgical stimulation and preserving adaptive mechanism of cerebral autoregulation, determines the adequacy of anesthesia during neurosurgical procedures. Surgical stage of anesthesia can be reached by electroanesthesia and conventional inhalation agents. We chose to investigate a combination of alpha-2 agonists and opioids during neurosurgical procedures. These agents affect two types of receptors: opiate and adrenoreceptors, still preserving their adaptive mechanisms, and with few side effects. The results of 20 years of experience with the above-mentioned methods are shown in this article.

MATERIALS AND METHODS

During the last 20 years, more than 20,000 patients undergoing different neurosurgical procedures were anesthetized by using drug combination of alpha-2 agonists and opioid analgesic. These procedures included 14,000 craniotomies for tumor removal, 4000 procedures for severe head trauma, 1600 interventions on children (1 month to 16 years of age) with hydrocephalus and inherited

malformations, and 400 surgeries for cerebral aneurysms and arteriovenous malformations. Analysis and data processing in each group were done according to certain criteria. Patients with intracranial tumors were divided into groups according to their tumor size and localization, degree of intracranial hypertension, patient's age, coexisting diseases, type and severity of complications, stage of operation, and changes of vital signs. Standard monitoring was used, including EKG, pulse oximetry, plethysmography, noninvasive blood pressure monitoring, temperature, and capnography. Urine output, blood loss, hemoglobin level, hematocrit value, glucose level, acid-base balance, and hemocoagulation were monitored on an hourly basis (monitors SC 6002 and 7000 "Siemens", capnograph "Novometrics", coagulograph "Organon"). Mechanical ventilation was performed with ventilators Siemens 900c or Kion. Patients were moderately hyperventilated to ETCO_2 of 35-38 mm Hg. Fluid management was aimed to keep patients adequately hydrated and included hydroxyethyl-starch solutions and normal saline; blood was transfused when blood loss exceeded 20% of blood circulating volume (BCV). Neurological status of the patients was evaluated at the time of emergence from anesthesia and on the first postoperative day.

This clinical research was approved by the Institute Ethics Committee, informed consent was obtained, and patients were distributed into groups. Blood pressure was measured by direct invasive method through a catheter inserted into radial artery, central venous pressure was obtained through catheter inserted into superior v. cava, and ICP measured via a catheter inserted into one of the lateral ventricles (monitors SC-7000, Dinamap plus "Criticon"). Electroencephalogram was registered via intracutaneous electrodes using international system 10-20. Auditory and optic somatosensory evoked potentials were recorded (Nichon Cohdem, Endeavor "Nicolet"). Cardiac index, stroke volume, and peripheral vascular resistance were measured with NICO "Novometrix" device.

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Table 1.

Figures	Stage of Anesthesia and Operation				
	Before Induction of Anesthesia	After fentanyl-clonidine Injection	Laryngoscopy	Tracheal Intubation	Opening Dura Mater
ICP (mm Hg)	17.7 ± 2.8	9.9 ± 1.7	10.1 ± 1.6	10.1 ± 1.9	3.8 ± 0.78
MAP (mm Hg)	98.5 ± 3.6	83 ± 5.1	82.5 ± 5.3	85.4 ± 4.7	82.4 ± 4.8
ICP/MAP (H. Shapiro et al. 1972)	0.18	0.12	0.12	0.1	0.046
CCP (mm Hg)	80.8 ± 4.9	73.1 ± 4.6	72.4 ± 5.1	75.3 ± 4.9	78.2 ± 5.1

Various statistical programs were used to process the results.

Total intravenous anesthesia was administered to all patients undergoing these procedures. Pre-medication included midazolam or diazepam. Dose was selected according to patient's age and was administered the night before and an hour before surgery. Anesthesia induction started with intravenous injection of nondepolarizing neuromuscular blocking agents (pipercuronium, pancuronium, or vecuronium) in recommended doses. Immediately following injection of a nondepolarizing muscle relaxant, an anesthetic drug was given (sodium thiopental dosed from 1 to 2.5 mg per kg of body weight or propofol dosed at 3-4 mg per kg), and fentanyl (0.3-0.6 mg per kg) infusion was started. Clonidine and fentanyl doses were adjusted to patient's age and vital signs. Aged and/or hypovolemic patients due to use of diuretics, or who otherwise were showing symptoms of dehydration, received reduced doses. For patients with head injury, dose correction was dependent on a blood loss. Anesthesia was maintained by constant intravenous infusion of sodium thiopental or propofol (dosed from 1.5 to 3 and from 1.0 to 3 mg per kg, respectively), clonidine, and fentanyl (dosed from 0.05 to 0.15 and from 0.07 to 0.15 mg per kg of body mass, respectively). Muscle relaxant agent was given by bolus injections or continuous infusion (vecuronium) in recommended dose. Use of fentanyl and clonidine was stopped 1 hour or 40 minutes before the end of the procedure. Propofol was stopped as soon as skin had been closed. After emergence from anesthesia, patients were transported to PACU.

RESULTS

Intracranial hypertension usually accompanies intracranial pathological processes, and anesthetic management is essentially complicated in this case.

In order to maintain stable cerebral perfusion pressure (CPP), it is important to eliminate factors contributing to additional increase of intracranial pressure and destabilizing the autoregulatory process. The increase of intracranial pressure during laryngoscopy and intubation of the trachea is a well-known event. Different methods were described to blunt this reaction. The intracranial and blood pressure changes during laryngoscopy and tracheal intubation in our study are presented in Table 1. Obviously, these measurements present parallel changes. CPP remained stable when the above-mentioned anesthetic technique was used. Data also showed that, during anesthesia induction, arterial and intracranial pressures decreased in a parallel way. Dynamics of measurement proposed in 1972 by Shapiro et al⁷ reflected the trend of mean arterial and intracranial pressures and also demonstrated this phenomenon. The analysis of numerous factors (without direct intracranial pressure) indicates preservation of adequate CPP when a clonidine and fentanyl combination was used. These factors include EEG stability during arterial pressure changes, absence of dura mater tension after removal of bone flap, and hemodynamic stability after dura mater has been opened. Following induction of anesthesia, arterial pressure decreased by 20% from initial level in 92% of the cases, by 25% in 6% of the cases, and by 35% in 2% of the cases. More than 20% blood pressure reduction from initial level was observed when the patients were fluid resuscitated or had misdiagnosed hypovolemia. The changes attributed to medication used were registered on EEG, but there were no bioelectrical signs of cerebral hypoperfusion. Dura mater was relaxed in 89% of cases after bone flap removal, and in 11% of cases, it was moderately tensed. This tension was explained by reasons of "mass effect," such as large tumor, cyst, or intracranial hematoma. No case of brain edema was

noticed after opening the dura mater. No additional blood pressure reduction was observed during cranial decompression.

As a result, induction of anesthesia with a fentanyl-clonidine increase of intracranial pressure during laryngoscopy and tracheal intubation is prevented, and the physiological relationship between intracranial and arterial pressure is preserved.

After opening the dura, the intracranial pressure equaled the atmospheric pressure. Problems related to intracranial hypertension disappeared. The anesthesiologist's main task during this phase of surgery is to provide cerebral volume stability and relaxation and optimal homeostasis. Mainly, these conditions depend on cerebral blood flow, which is directly related to volume status and brain activity.⁹ In addition to the local biochemical and neurotransmitter changes, vasa vasorum reactions were accompanied by efferent impulses caused by direct nerve tissue irritation (shortened reflexes). According to our experience, the higher arterial pressure and heart rate deviations during the first hour of surgery, the more difficult to preserve viscous-elastic cerebral features and more often hyperventilation and dehydration are required. This tendency was obvious during long surgical procedures (more than 3 hours). That is why hemodynamic stability is an important indicator of adequate anesthesia management. Hemodynamic profile of the operation remained rather stable when fentanyl-clonidine combination was used. When compared with neuroleptanalgesia, deviations higher than 15% from the base line of systolic blood pressure were registered three to four times less often during 1 hour of surgery. The statistic analysis showed that, in 89% of the cases with fentanyl-clonidine technique, no supplemental method to provide adequate stability of brain was necessary. In 11% of cases, furosemide and hyperventilation to PaCO₂ 25-28 mm Hg were applied. Most of those patients had severe head injury and brain tumors with risk of brain herniation. Surgical hemostasis was adequate in all the cases. At the end of surgery, all patients regained consciousness up to level of verbal response. Adequate spontaneous breathing was also regained except for those patients admitted unconscious before surgery (patients with severe head injury or brain herniation in cases of intracranial tumors). Decision to proceed with extubation was always taken individually case by case. Only 8% of patients—mostly with pri-

mary (head injury) or secondary (diffuse axonal injury) brainstem damage—required postoperative mechanical ventilation. In all cases, complete amnesia of the intraoperative period was obtained. Pain control was not required during the first 4 hours after operation. Patients were calm, adequate, and arousable during neurological examination.

During 20 years, we did not notice any case of complication directly connected to fentanyl-clonidine combination use. Excessive hypotension in case of hypovolemia is possible practically with any anesthesia technique. Adequate fluid resuscitation before induction of anesthesia, prophylactic glucocorticoids, and inotropic support make it possible to prevent excessive arterial hypotension. It is necessary to emphasize that only the combination of fentanyl-clonidine was used and never clonidine alone. We have no evidence that the above combination causes more hypotension than fentanyl and droperidol. In cases with unstable hemodynamics, fentanyl-clonidine dose should be reduced up to 50% of recommended; drugs should be injected slowly and fractionally. Relative contraindications to use the combination opioid and alpha-2 agonists could be brainstem dysfunction and vascular tonus regulation failure. In case of unstable hemodynamics, as in severe head injury when, during surgery, the patient requires vigorous hemodynamic support, use of the fentanyl-clonidine combination is not reasonable.

An absolute contraindication for fentanyl-clonidine combination probably can be only individual hypersensitivity to mentioned preparations. We prefer to use propofol, which smoothly regulates the level of consciousness and makes anesthesia easy to control.

DISCUSSION

Central alpha-2 agonists carry their effects by changing neuronal excitability and exert many effects, including sedation, anxiolysis, analgesia, reduction of requirement in anesthetics, and antisialagogue effect. That is why these medications are widely used in different branches of anesthesiology. Specific information can be found in several literature reviews.^{4,10} Clonidine improves outcome from incomplete ischemia in rats.¹¹ This effect is probably connected to the fact that alpha-2 agonists inhibit voltage-sensitive calcium channels, which in turn suppress influx of calcium into the

nerve terminals.^{4,5} In volunteers, clonidine (0.5 mg orally) decreases flow velocity and slightly attenuates CO₂ reactivity. Clonidine reduces slope of the PaCO₂-CBF response curve, but does not affect cerebral autoregulation.¹² In patients scheduled for surgery for cerebral tumor, clonidine has sparing effect on anesthetic requirement. In the same study, suppression of central hemodynamics, adrenal cortical response to surgery, and lower blood pressure level were found.¹³ The hypertensive response during laryngoscopy and application of Mayfield clamp was much less in clonidine-pretreated patients.¹⁴ Increase in total body oxygen consumption and CO₂ production were attenuated, and reduction in shivering was observed in post-operative period.¹⁵ Other studies indicate that post-operative pain was eliminated.¹⁶ The data correspond with the results of our researches mentioned above as well as previous publications.¹⁻³ The information about alpha-2 agonists influence on sympathetic impulsation is of special interest. Administered intrathecally or intravenously, clonidine has depressant effect on both the sympathetic outflow and the afferent A- and C-fiber-mediated somatosympathetic reflexes.⁸ The site of action of alpha-2 agonists is supposed to be the locus ceruleus, which receives afferents mainly from the nucleus paragigantocellularis, the nucleus prepositus hypoglossi, the hypothalamus, and the spinal cord. Efferents from locus ceruleus project to the reticular formation and several cranial nerve nuclei.⁶ Also, the dorsal raphe nucleus is enhanced by noradrenaline, and this effect is attenuated by clonidine.¹⁷ More detailed information about this problem can be found in the review by G.E. Cold and B.L. Dahl.¹⁰ It is important to understand that the modulating sympathetic system activity effect of alpha-2 agonists occurs with the contribution of several brainstem structures. This manner of action results in modulation of the reactions but preserves at the same time the basic adaptational reactions in which the system functions. In other words, alpha-2 agonists in a definitive dose range prevent excessive spontaneous and evoked sympathetic activity and thus preserve adaptive processes of autoregulation necessary to guarantee cerebral vitality.

Stable CPP in the phase before dura mater opening, moderate quantity of deviation of hemody-

namic parameters during manipulations on brain, good characteristics of anesthesia recovery period all together serve as an indirect proof of alpha-2 agonists significance for neuroanesthesiology.

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