



Anesthetic Dose Correction in Hospital Pharmacology Using Bispectral Index Monitoring Technology*

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SUMMARY

Background Modern clinical pharmacology insists on the valorization of individual patient's characteristics that influence pharmacokinetic and pharmacodynamics medicine effects. The objective of this work is evaluation of anesthetic doses in patients with larynx benign tumors, operated by applying endoscopic surgical methods and where was used bispectral index monitoring technology during general endotracheal anesthesia.

Material and Methods Patients were divided in two groups. Group A was made out of ten patients in which are applied recommended anesthetic doses, while inspection in bispectral index values was possible only after closed anesthesia. Group B was made out of twenty patients with corrected anesthetic doses according to the bispectral index numerical values.

Results In the Group A, waking up lasted averagely 120 ± 10 seconds, and in Group B 70 ± 9 seconds ($p < 0.01$). In the Group B, induction dose was 25% lower ($p < 0.01$), observance dose was 15% lower, and total propofol consumption was 25% lower than in Group A ($p < 0.01$).

Conclusions It is possible without bispectral index monitoring technology to apply higher anesthetic dose than it is regular. Bispectral index monitoring should become standard in clinical anesthesia.

Keywords: BIS monitoring technology; anesthetics – application and dosage; clinical hospital pharmacology; dose; medicine response ratio

*Bispectral Index Monitoring Technology was first established in the Clinical Center of Serbia in 2007 by Prof. Dragan Vučović, MD, PhD, Prim. Dragana A. Kastratović, MD, PhD, and Prim. Nadežda N. Radošić, MD.

NOTE

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INTRODUCTION

In everyday clinical practice, the physicians are well aware of the fact that besides professional qualification and equipment of medical team and objective clinical parameters, the development of clinical situation depends upon patient's individual characteristics. Clinical pharmacologists insist on valorization of patient's individual characteristics which affect the pharmacokinetic and pharmacodynamic effects of drugs [1].

Bispectral index (BIS) is a monitoring of the depth of anesthesia, which originated from bispectral analysis of electroencephalogram, a direct measure of the effects of anesthetics and sedatives on brain, a new "vital sign" allowing the clinicians to perform anesthesia more precisely, to assess the changes of patient's condition during the surgical intervention and react more efficient to them [2]. Numerical values of BIS range from hundred to zero, where the general anesthesia is achieved within the range of 60 to 40 [3].

Clinical studies have shown that the use of BIS monitoring technology provides better performance of anesthesia, what implies lesser consumption of anesthetics and faster recovery from it [4]. Literature data have demonstrated that the use of BIS monitoring technology not only contributes to improvement of the clinical practice but also to cost-effectiveness, and therefore, it deserves to become a routine procedure [5].

Endoscopic surgical interventions in pharyngolaryngeal region are characterized by medium degree of anesthesiological stress (minimal bleeding in the surgical field, with predominating reflex irritability over painful stimulation), with an average duration of about 60 minutes. General endotracheal anesthesia (GETA) is performed by means of endotracheal small diameter tubes providing an optimal workspace for the endoscopist.

The specificities of anesthesia in these procedures, providing that these are ASA I and II patients (according to American Society of Anesthesiologists classification, i.e. a group at low, tolerable operative risk), allow for good monitoring of effects of general anesthetics on target organ – brain using the BIS technology. The group of patients selected in this way is a good basis of qualitative and yet simple analysis of effects of the applied anesthetic doses recorded by BIS monitoring technology.

According to available references, we supposed that the anesthetic doses would be corrected if BIS monitoring technology is used during general anesthesia of the endoscopic larynx surgery [6, 7].

The aim of this paper was the evaluation of used anesthetic doses in patients with the benign tumors of larynx, operated on by means of endoscopic surgical procedures, where BIS monitoring technology was used during the GETA.

MATERIAL AND METHODS

This paper is a part of the prospective academic (non-commercial) phase IV study, carried out in the Clinical Center of Serbia (CCS), at the Clinic for Otorhinolaryngology and Maxillofacial Surgery (ENT and MFS). Study has been approved by the CCS Ethics Board and conducted in compliance with the EU clinical trials directives [8]. Informed consent was obtained from all patients.

GETA was used as a routine anesthesiological procedure in ENT surgery and MFS. During the surgical intervention, the anesthesiological depth was assessed by standard clinical monitoring – blood pressure, pulse, peripheral blood oxygen saturation, electrocardiography and capnometry. BIS monitoring was used simultaneously (BIS module – *Aspect®* and monitor *Infinitive Delta®* – *Draeger*).

The patients were surgically treated in day hospital of the CCS Clinic for ENT and MFS. Thirty patients aged 18 to 65 years of both sexes, having ASA I benign laryngeal tumor, indicated for endoscopic surgical intervention, were divided in two groups: A (ten patients) and B (twenty patients). Both groups were monitored by BIS monitoring technology. The patient Group A was anesthetized by recommended anesthetic doses, and the access to BIS monitoring values was possible only after the completion of anesthesia. In patient Group B, the anesthetic doses were corrected according to numerical values of BIS monitoring technology. All data were stored in the study database, and BIS strips and data obtained from anesthesia chart were used for data processing.

Premedication for all patients included: i.v. midazolam 1 mg (*Dormicum®* 5 mg/5 ml, amp. i.v., *Roche*) and i.v. Fentanyl 0.05 mg (*Fentanyl®*, 0.1 mg/2 ml, amp. i.v., *Janssen*). For introduction to anesthesia, we used propo-

fol (*Recofol*®, 20 mg/ml; Bayer-Schering) and relaxant rocuronium-bromide (*Esmeron*®, 50 mg/5 ml, inj. i.v. inf., *Organon*). Anesthesia was maintained by propofol (*Recofol*®, 20 mg/ml; Bayer-Schering), using the infusion pump for propofol – *Diprifuzor Pilot 2* and reduced dose of intravenous narcotic Fentanyl 0.1 µg/kg.

Immediately upon the completion of anesthesia, BIS numerical values and graphical recordings were analyzed for patient Group A. Upon review of these values, we concluded to make a correction of recommended anesthetic doses. This clinical experience was applied in such a way that 20 patients from Group B were administered corrected anesthetic doses according to BIS values, and these were monitored continuously during the anesthesia.

The results were processed by the following statistical methods: descriptive statistics (tabular and graphic presentation) and analytical statistics (T-test for two small independent samples).

RESULTS

Mean age of Group A patients was 46.62 ± 6.7 years and Group B patients 49.12 ± 4.5 years. There was no significant difference of age between these two groups of patients ($p > 0.5$) (Table 1).

They were working age patients, without any sociopathological characteristics (alcohol or psychoactive drug addiction). All belonged to ASA I group.

The patients of both groups were well-nourished, without any extreme deviations. Mean weight of Group A patients was 74 ± 16.7 kg and Group B patients 71 ± 12 kg. There was no significant difference of weight between these two groups ($p > 0.5$) (Table 1).

Groups A and B included six women each and four and fourteen men, respectively.

Mean duration of surgical treatment was 20 minutes and 44 seconds in Group A and 21 minutes and 25 seconds in Group B. There was no significant difference of surgical treatment duration between two groups ($p > 0.5$) (Table 2).

In Group A and B, mean time of awakening from anesthesia was 120 ± 10 seconds and 70 ± 9 seconds, respectively. Statistically, awakening was significantly shorter in Group B than in Group A ($p < 0.01$) (Table 2).

Induction anesthetic dose was 2 mg/kg and 1.5 mg/kg in Group A and B, respectively,

Table 1. Demographic variables in patient groups

Variable	Group	\bar{X}	SD	Min.	Max.	t	p
Age (years)	A	46.6	6.7	30	55	-1.218	0.233
	B	49.1	4.5	37	55		
Weight (kg)	A	74.0	16.7	55	99	0.505	0.621
	B	71.0	12.0	49	95		

\bar{X} – mean value; SD – standard deviation; Min – minimum value; Max – maximum value

Table 2. Time characteristics of general anesthesia

Variable	Group	\bar{X}	SD	Min.	Max.	t	p
Surgical treatment (min.)	A	20.4	0.8	19	22	-1.884	0.07
	B	21.3	1.4	19	23		
Waking up (s)	A	120.0	10.0	105	135	13.801	<0.001
	B	70.0	9.0	50	80		

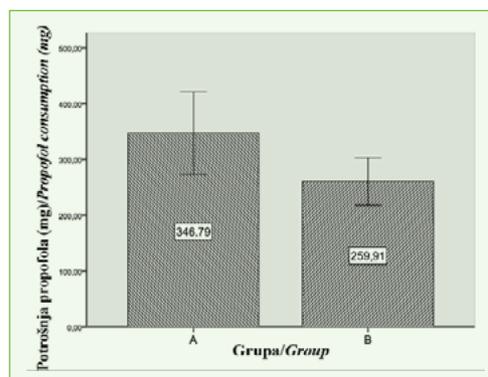
Table 3. Anesthetic doses characteristics (propofol)

Variable	Group	\bar{X}	SD	Min.	Max.	t	p
Induction dose (mg/kg)	A	2.0	0.0	2.0	2.0	26.049	<0.001
	B	1.5	0.1	1.4	1.6		
Maintenance dose (mg/kg/h)	A	7.0	0.2	6.8	7.3	17.039	<0.001
	B	6.0	0.1	5.9	6.2		
Total consumption (mg)	A	346.8	73.7	260.2	474.6	3.454	0.005
	B	259.9	42.5	178.5	341.6		

meaning that induction dose was 25% lower in Group B, what was a highly significant difference ($p < 0.01$) (Table 3).

Mean maintenance dose was 7 mg/kg/h and 6 mg/kg/h in Groups A and B, respectively. This means that maintenance dose was 15% lower in Group B, what was a highly significant difference ($p < 0.01$) (Table 3).

Total consumption of propofol during surgery was 346.7 mg and 260.50 mg in Group A and B, respectively. Total propofol consumption was 25% lower in Group B than in Group A, what was a highly significant difference ($p < 0.01$) (Table 3, Graph 1).



Graph 1. Total consumption of propofol in patient groups

Table 4. Bispectral index monitoring values during anesthesia when using recommended (group A) and corrected (group B) anesthetic doses

Variable	Group	\bar{X}	SD	Min.	Max.	t	P
Induction	A	25.0	1.5	23	27	-12.269	<0.001
	B	35.0	2.3	31	38		
Maintenance	A	35.0	1.5	33	37	-13.015	<0.001
	B	42.0	1.3	40	44		

Using BIS monitoring technology, the effects of propofol on the brain were recorded all time during the general anesthesia. Mean induction BIS was 25 ± 1.5 in Group A and 35 ± 2.3 in Group B, what was a highly significant difference ($p < 0.001$) (Table 4).

During the maintenance of anesthesia, BIS was 35 ± 1.5 in Group A and 42 ± 1.3 in Group B, what was also a highly significant difference ($p < 0.001$) (Table 4).

DISCUSSION

There were no complications during surgery of studied patients; therefore, its duration was within limits for this type of surgical intervention in both groups. The patients were ASA I group, with approximately similar body mass and age. The standard clinical monitoring parameters indicated that our work would be simple and adequate anesthetic doses would be approximate to recommended ones.

For successful outcome and quality of general anesthesia, it is wake-up duration that is important. In Group B, where following the BIS monitoring values the anesthetic doses were corrected, the awakening of patients was significantly faster, what was compatible with reference data [4, 8].

All patients from both groups emphasized that they felt safer during narcotization, being aware of the fact that the effects of anesthetics would be monitored by BIS monitoring technology during anesthesia. It is significant because the doctors know that study design provides the correction of anesthetic dose in Group B, while Group A receives commonly recommended anesthetic doses. Presented considerably higher medical care upgraded subjective feeling of patient safety in both groups. After the operation, all patients were satisfied, but Group A patients manifested bradypsychia, while Group B reported that "it was kind of easy" [9, 10]. It was an unexpected gain we could not plan, but their praise has been good to us.

In compliance with study objective, the largest attention of the whole team, and particularly the hospital clinical pharmacologist, was focused on the analysis of dose values and anesthetic consumption [11]. Induction anesthetic dose was 25% lower, with highly significant difference ($p < 0.01$) found, what was also compatible with reference data [12].

Maintenance dose was 15% lower in Group B, what was highly significant ($p < 0.01$). When dose reduction over 10% to relatively low drug consumption is discussed in clinical pharmacology, it is very beneficial reduction from the clinical aspect, significant for more qualitative performance of anesthesia. It is early to analyze side-effects and recommendations, because the sample was small, and, in addition, the results obtained from other surgical techniques of the head-neck region [13] as well as possible ethnic characteristics need to be summarized.

The value of the total propofol consumption is the most illustrative datum obtained from this study for evaluation of BIS monitoring technology effectiveness. Total propofol consumption was 25% lower in Group B than in Group A, what was highly significant ($p < 0.01$).

Besides such illustrative results compatible with literature data [12], our analysis was facilitated by the fact that the patients belonged to ASA I group, what also underscored the significance of the obtained results. In patients with severe conditions, due to existing comorbidity, there are several drug interactions and consequently more side-effects.

Modern hospital pharmacology implies an individual pharmacotherapeutic approach to patients. It means that the use of BIS monitoring technology may provide the monitoring of the achieved effect of propofol to effectory organ – brain, because the same concentration of this anesthetic may produce different hypnotic effect in different patients, as well as in the same person under different conditions. Clinical efficiency of BIS monitoring technology is reflected in three elements: lesser side-effects of anesthetics, more explicit decision-making, and accomplishment of pharmacotherapeutic objective. Current pharmacovigilance reports side-effects of anesthetics after several days, weeks or even months from surgical intervention. Making of efficient clinical decisions and timing of their implementation is very important in the operating room, since sudden changes of blood pressure and heart action, embolization, hemorrhage, convulsion, etc. are quite possible [14,

15, 16]. The achievement of the best therapeutic effect is, unquestionably, most definite clinical benefit produced by BIS. The absence of BIS monitoring technology may result in overlooking the information important for performance of top-quality clinical anesthesia.

Application of recommended anesthetic doses, along with classical clinical monitoring, resulted in low BIS values in Group A patients. Anesthetic dose correction by BIS monitoring technology in Group B brought about the numerical BIS values to desired ones (40-60). Accordingly, awakening was significantly faster in Group B, and the patients were hemodynamically more stable during the entire GETA (the subject of detailed analysis in pharmacokinetic part of our study).

The use of BIS monitoring technology enables objective inspection of the depth of anesthesia by monitoring the effects on target organ – brain, provides an individual dose-clinical approach to patient, and as a result, more safer and qualitative anesthesia and surgical treatment [4]. This secures more operative work of the team – anesthesiologist, hospital clinical pharmacologist and ENT surgeon. BIS monitoring technology uplifts the spirit of the medical team because it gives answer best so far to eternal question: “Is my patient adequately anesthetized?” [17] “Can patient individual differences be an advantage in drug dosing?”, “May better anesthesia lead to improvement of my surgical results?” Naturally, this makes the physicians more perceptive during their clinical practice, what in turn develops the applied medical science. Now we know that without the BIS monitoring technology we can miss helpful information on patient’s condition.

Individualization of dose regime is also present in relation to operative region, surgical diagnosis and applied surgical technique, which is a distinct characteristic of surgical procedures performed in head-neck region and not only of patient’s individual features. This undoubtedly suggests that BIS monitoring technology should be a standard in operating theatres where surgery of head-neck region is carried out.

Propofol pharmacokinetics is complicated and intriguing [18]. The issue of adequate propofol concentration that will produce targeted BIS monitoring value will be clarified by

population pharmacokinetics which is taking place at our Clinic.

In a large number of academic clinical trials of a kind, it is necessary to acquire knowledge and experience on approximately recommended dose regime, with definitely emphasized characteristics of the whole anesthesiological-surgical treatment affecting the dose regime as well as to focus on issues requiring special attention. For this reason, large-scale study and support by pharmaceutical industry are needed. In this medical assignment, team work is the only solution. Hospital clinical pharmacology has its right place herein, and sophistication of the required staff profile is completely appropriate to the task. This would contribute to best possible level of the quality of the course and outcome of anesthesia and surgical intervention in the head-neck region.

CONCLUSIONS

The specificity of anesthesia in otorhinolaryngology and maxillofacial surgery is one reason more for implementation of the BIS monitoring technology as a standard in everyday clinical practice. Individually adjusted anesthetic dose upgrades the patient’s safety, comfort and the quality of work of the whole medical team, contributing to safety and quality of anesthesia from the patient’s aspect. Not providing BIS index monitoring technology may lead to overdosing of anesthetic.

Applied science deserves its place in the best medical institutions. Perennial trials on a large number of patients are needed to establish the dosing regime and its explanation in relation to surgical treatment, anesthesiological technique and side-effects of anesthetic.

Using the BIS monitoring technology, the anesthesiologist has a trace in writing on the course of general anesthesia, what is, in some cases, of priceless significance to doctors. Accordingly, we insist on continuous education and training of hospital clinical pharmacologist, anesthesiologist and surgeon.

Conflict of Interest Statement

Authors declare no conflict of interest.

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Korekcije doza anestetika u bolničkoj farmakologiji primenom tehnologije monitoringa bispektralnog indeksa

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KRATAK SADRŽAJ

Uvod Savremena bolnička farmakologija insistira na valorizaciji individualnih odlika bolesnika koje utiču na farmakokinetičke i farmakodinamičke efekte lekova. Cilj rada bila je procena doza anestetika kod bolesnika s benignim tumorima larinksa operisanih primenom endoskopskih hirurških metoda kod kojih je tokom opšte endotrahealne anestezije korišćena tehnologija monitoringa bispektralnog indeksa.

Materijal i metode rada Ispitanici su svrstani u dve grupe. Grupu A činilo je deset bolesnika kod kojih su primenjene preporučene doze anestetika, a uvid u vrednosti bispektralnog indeksa bio je moguć tek nakon završetka anestezije. Grupu B činilo je dvadeset bolesnika kod kojih su doze anestetika korigovane prema numeričkim vrednostima bispektralnog indeksa.

Rezultati U grupi A buđenje bolesnika trajalo je prosečno 120 ± 10 sekundi, a u grupi B 70 ± 9 sekundi ($p < 0,01$). U grupi B indukciona doza je bila 25% manja ($p < 0,01$), doza održavanja 15% manja, a ukupna potrošnja propofola 25% manja nego u grupi A ($p < 0,01$).

Zaključak Bez tehnologije monitoringa bispektralnog indeksa moguće je primeniti veću dozu anestetika nego što treba. Monitoring bispektralnog indeksa treba da bude standard u kliničkoj anesteziji.

Ključne reči: BIS monitoring tehnologija; anestetici – primena i doziranje; bolnička klinička farmakologija; odnos doze i odgovora na lek

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