Patient safety and cost-effectiveness of general anaesthesia

PhD thesis

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1. Introduction

Patient safety and cost-effectiveness are two frequently discussed topics in anaesthesiology. Recent conditions in the Hungarian health sector increasingly call for more cost-effective procedures and products without compromising patient safety. The task of the anaesthetist is to ensure adequate and safe environment for the patient during the operation in such a way that he/she supports and supplements the surgeon's work. The cost indicators of anaesthesiologic activities are always high within an institute, so the cost-effective management of narcosis (e.g. applying cost-effective procedures, and cost-effective medicine use) and the perioperative treatment are of paramount importance. The ethical and legal principles are also shall be observed when expenses are planned - the patient's safety and the patient's rights shall not be infringed. These also should be taken into consideration when operating procedures for cost-reduction purposes are developed.

1.1. The professional and legal background of patient care in perioperative anaesthesiology

Patient safety is one of the main points of anaesthesiology in the perioperative period. An essential part of patient safety is safe medication to provide an optimal therapy. Another vital part of patient safety is knowing and preventing the intervention-related risk factors, possible complications, as well as their professional treatment, if they develop. It is important to elaborate action plans with using the analysis of the complications and the results, to mitigate the harmful effects of the developed event. The continuous patient monitoring, precise interpretation of changes in parameters and recognizing the warning signs may lead to prevent the intraoperative anaesthesiologic complications and their frequency may be reduced.

1.2. Patient care: ethics and cost-effectiveness

The patient care is the responsibility of the government in Hungary. The principle of charity / greatest benefit and justice / available for everyone, the principle of treatment without discrimination is important morally. Cost-effectiveness means the most

effective distribution and use of available resources in order to reach the maximal health gain, so it is not equal to a simple cost-cutting. The cost-effectiveness is characterized by cost-effectiveness treshold (cost-effectiveness rate), which is the ratio of costs and Quality-Adjusted Life Years (QALY).

1.3 *Costs of anaesthesia in the perioperative period*

Anaesthesiology belongs to the high-cost professional areas from device and medicine use aspects. Personnel and equipment shall be ensured in accordance with the requirements of the Hungarian Society of Anaesthesiology and Intensive Therapy. Effectiveness, more optimal medicine use, the introduction and application of techniques which require materials and medicines of lower price, frequently require the improvement of equipment. In this question a study could be useful, which is conducted according to a generally acceptable and professionally approved, commonly used methodology within Hungary.

In summary, when the cost-effectiveness of anaesthesia is investigated, both professional and ethical-legal requirements should be considered. Throughout the clinical trials, as part of the cost-effectiveness analysis of the perioperative period, costs of medicines and devices used for narcosis, costs due to complications and short-term postoperative costs also should be included in the calculation. Throughout the comprehensive cost-effectiveness analysis (determination of standard and varying costs) of narcosis it is necessary to involve professionals from different areas (pharmacist, statistician, health economic analyst).

2. Aims

1. The examination of intraoperative haemodynamic parameters and their comparison in cases of otorhinolaryngological anaesthesia with sevoflurane and propofol.

2. The objective examination and comparison of intraoperative medicine use for the two types of narcosis.

3. The examination of intraoperative and postoperative complications due to anaesthesia.

4. The comparison of medicine and device use of the perioperative period.

5. The effect of intraoperative monitoring of the depth of anaesthesia and neuromuscular blockade on the costs of narcosis.

6. The examination of the effect of otorhinolaryngological narcosis on cognitive functions.

3. Methods

*3.*1*. Analysis of the cost-effectiveness of anaesthesia (I.)*

In this study we compared combined anaesthesia (sevoflurane) and total intravenous anaesthesia (propofol) during otorhinolaryngological surgeries from the following aspects: the use of medicines and single-use devices, perioperative complications and the costs of these.

We enrolled patients with 18-65 years from ASA I and II classes into the prospective, randomized study. Exclusion critera were the followings: the lack of informed consent from the patient; allergy to any of the agents used in the study; ASA (American Society of Anesthesiologists Physical Status) III-IV; asthma bronchiale, chronic obstructive pulmonary disease in the medical history; factors that risks the validity of Bispectral Index (BIS) value (cerebral apoplexy in medical history, encephalomalacia, brain injury; dementia, paradoxical delta waves, epilepsy, the use of anticonvulsive agents, uremic or hepatic encephalopathy). The study was accepted and approved by the Regional Research Ethics Committee of the Medical Center, University of Pécs (approval number: 316-2336/KK15/2011.). The trial was recorded in the international register also (ClinicalTrials.gov ID: NCT02920749).

The patients were enrolled to one of the four main anaesthesia groups. In SEVO, SEVO+ groups the agent for maintaining anaesthesia was sevoflurane, while in PROP, PROP+ groups it was propofol. In SEVO+ and PROP+ groups we supplemented the general monitoring of vital signs with BIS and Train-of-Four (TOF) monitors (**Table 1**).

Anesthetic agent	Groups	BIS	TOF
sevoflurane	SEVO	no	no
	SEVO+	yes	yes
propofol	PROP	no	no
	PROP+	yes	yes

Table 1 *Characteristics of groups*
BIS=Bispectral index; TOF=Train-of-Four; SEVO=sevoflurane-based combined anaesthesia; SEVO+=sevoflurane-based combined anaesthesia supplemented with BIS and TOF monitoring; PROP=propofol-based total intravenous anaesthesia; PROP+=propofol-based total intravenous anaesthesia supplemented with BIS and TOF monitoring.

3.2. The methodology we followed during general anaesthesia cases

As premedication 7.5 mg of midazolam was administered orally to the patients 1.5 hours prior to narcosis. In the intraoperative period we invasively monitored mean arterial pressure (MAP), pulse rate, electrocardiography (ECG), end-tidal carbon-dioxide ($EtCO_2$), peripheral oxygen saturation (SpO_2), and anaesthetic agents. In patients of SEVO+ and PROP+ group we supplemented the intraoperative monitoring with the monitoring of the extent of the depth of anaesthesia (BIS™ Quatro Brain Monitoring Sensor, Aspect Medical Systems, Inc, 95% Norwood, MA, USA) and neuromuscular blockade (Infinity®, Trident® NMT SmartPod®, Dräger Medical Systems, Inc., Danvers, MA, USA).

3.3. The protocol of anaesthesia

Following preoxygenation, the patients received 1 μg/kg intravenous (IV) fentanyl in each group. In SEVO and PROP groups the administration of propofol for induction took place till the eyelash reflex disappeared (2-3 mg/kg, IV), while in SEVO+ and PROP+ groups it took place till reaching BIS value of 90. We used atracurium for neuromuscular blockade in each of the four groups, its intubating IV dose was 0.5 mg/kg. We waited for 4 minutes in SEVO and PROP groups prior to the intubation. While in SEVO+ and PROP+ groups the time of intubation was determined by the depth of anaesthesia (BIS≤60) and the neuromuscular blockade (TOF=0). In SEVO and SEVO+ groups, the minimum alveolar concentration (MAC) of sevoflurane was 1.0, the fraction of inspired oxygen (FiO_2) is 0.50, the fresh gas flow (FGF) was 1.0 L/min. In PROP and PROP+ groups, the administration of propofol took place according to Roberts "10-8-6" scheme and FiO_2 value was 0.50, FGF was 1.0 L/min

[49]. The target value of intraoperative MAP was in the range of 60-85 mmHg. We reduced intraoperative pain in each group with boluses containing 50 μg fentanyl, according to the MAP values (if MAP elevated by >20%). In SEVO+ and PROP+ groups it was an additional expectation that BIS value is between 40 and 60 at the same time. The repeat maintenance dose of atracurium during anaesthesia was 0.15 mg/kg. Repeat took place in SEVO and PROP groups every 30 minutes, in SEVO+ and PROP+ groups the criterion for administration was a TOF value of 2. Before extubation the patients received neostigmine and atropin combination (2.5 mg and 1.0 mg, respectively) to suspend the effect of the neuromuscular blocker. Then we extubated the patients with good vital signs. The criterion for extubation in PROP and PROP+ groups was TOF rate being above 95%. After extubation, the patients with good vital signs were transferred to the postoperative recovery room, where we continuously checked and recorded these parameters for additional two hours. For postoperative pain management we used diclofenac (75 mg, in IV infusion) and nalbuphine (5-10 mg, in IV infusion). In the records we included the minor postoperative complications [hypotension, postoperative nausea and vomiting (PONV), headache, restlessness, tremor, postoperative delirium and postoperative cognitive dysfunction (POCD), visual disturbance, muscle pain, somnolence] and their treatment, if it was necessary.

3.4. The applied supplementary monitoring techniques (I.)

3.4.1. Intraoperative monitoring of the depth of anaesthesia

When the narcosis is induced, during the administration of anaesthetics and checking the patient's condition, the fact should be taken into consideration that the patient monitors display data with 10-20 sec delay, and in certain patients the pharmacodynamic and phamacokinetic parameters of the administered medicines may be different. The aim of monitoring the depth of anaesthesia is to avoid and prevent unintended intraoperative awareness and awakening. Recently, the most frequently used monitoring method for the depth of anaesthesia is based on electroencephalography (EEG). The point in BIS monitor is, that real-time and continuous EEG monitoring takes place during anaesthesia. With bispectral, power spectral and suppression analyses, the computer of the BIS monitor converts the signs

to a dimensionless number ranging from 0 to 100. The value of 0 is equivalent to the absence of the electrical activity in the brain (EEG silence), while the value of 100 is characteristic for totally alert patients. If BIS value is between the range of 40 and 60 , the anaesthesia is adequate, is of appropriate depth. If the BIS value is in the range of 60-70 (or even higher), then the narcosis is shallow and the risk of intraoperative awakening is higher.

3.4.2. Intraoperative monitoring of the extent of neuromuscular blockade

With the use of TOF the level of muscle relaxation of patients being under the effect of neuromuscular blockers can be assessed easily, precisely and objectively (with the electrical stimulation of a peripheral nerve). This assessment technique is a fourfold stimulation, it consists of four series of impulses, and gives TOF-ratio (%, between 0 and 1.0) or TOF-score (0, 1, 2). TOF monitoring may help to administer the neuromuscular blockers more precisely during general anaesthesia and to determine, when their effect should be antagonized. With the help of this, the postoperative incidence of neuromuscular weakness during awakening and complications caused by them can be decreased.

3.5. Intraoperative medicine consumption (I.)

3.5.1. Method for determining medicine use

The amount of painkillers and neuromuscular blockers used during narcosis can be easily determined from the anaesthesia records. When calculating the costs, in case of single administrations we assigned the cost to a given value, while during the maintenance of narcosis we calculated the cost of medicines in HUF/hour units. The quantity of propofol used and its cost can be determined on the basis of the quantity missing from the syringe and the perfursor. It is not easy to determine the quantity of used sevoflurane. In our study we used a simplified formula developed by us to determine the used amount of sevoflurane and its cost.

Determination of the quantity of used sevoflurane:

$$\frac{\text{FGF (L/min) x v/v\% x duration (min)}}{\text{liquid to vapour ratio*}}$$

Determination of the cost of sevoflurane:

$$\frac{\text{FGF (L/min) x v/v\% x duration (min) x cost of 1 bottle (HUF)}}{\text{liquid to vapour ratio* x volume of a bottle**}}$$

FGF=Fresh Gas Flow; v/v%=sevoflurane concentration; duration=time of anaesthesia; *=liquid to vapour ratio (the volume of vapour produced from 1 mL liquid for inhalation, that is 183 mL for sevoflurane); ** the volume of 1 sevoflurane bottle (0.25 L); HUF=Hungarian Forint

At the costs of single-use devices we included the followings: syringes, needles, cannules, infusion line, adhesive plasters, three-way stopcock, ECG-electrodes, nasogastric suction catheter, Mayo tube, endotracheal tube and BIS sensor. When we calculated the amount of used medicine, we took into account the used quantity and not the open vial (this would have cause bias in actual data). The costs of medicines and single-use devices used for anaesthesia is determined according to the official product price list of University of Pécs.

3.6. Examination of perioperative cognitive functions (II.)

3.6.1. Cognitive functions, delirium and cognitive dysfunction

The elements of cognitive functions are memory, association, planning, pattern recognition, language, attention, perception, acting, problem solving and mental imagery. The postoperative cognitive dysfunction (POCD) means the deterioration of these skills. The Montreal Cognitive Assessment (MoCA) test was developed by Nassreddine et al. in 1996. The translation of 7.2 and 7.3 versions of the test into Hungarian, the linguistic validation of the test, as well as its validation under clinical conditions took place at PTE Clinical Center Department of Neurology, in cooperation with the Department of Behavioural Sciences University of Pécs, Medical School. In our study we applied the Hungarian versions of 7.1 and 7.2 MoCA.

3.6.2. Clinical trial

In our study we compared the two main types of general anaesthesia, combined and total intravenous anaesthesia, from the aspect of changes in perioperative cognitive functions. We enrolled patients above 18 years from ASA I and II classes into the prospective, randomized study, who underwent otorhinolaryngological surgery in controlled hypotension. Exclusion criteria were the followings: the absence of informed consent form; cerebral infarction in medical history; other disorder of the cerebral circulation; epilepsy; dementia; as well as defective hearing to such an extent, that significantly affects the communication. The study was accepted and approved by the Regional Research Ethics Committee of the Medical Center, University of Pécs, document ID: 4913.

As premedication each patient received 7.5 mg midazolam orally. Anaesthesia was maintained with sevoflurane-fentanyl-atracurium, as well as propofol-fentanyl-atracurium combinations. In the intraoperative period we took vital signs [blood pressure (BP), pulse rate, SpO_2, $EtCO_2$] every 5 minutes in both groups. We performed the first test (MoCA 7.1 version) prior to the surgery, while the control test (MoCA 7.2 version) was taken 2 hours following the surgery, when the patient were already fully awake, the GCS value was 15. The test took approx. 10 minutes. At the evaluation of the MoCA tests we organized the obtained scores and the parameters recorded during anaesthesia.

4. Results

4.1. Cost-effectiveness analysis (I.)

We randomized 30 patients into each group. Demographic data were similar in each of the four groups. During data analysis we had to exclude one patient from the PROP+ group due to unsuitable BIS values.

In the four groups there was no significant difference in terms of MAP and pulse rate measured at the commencement of anaesthesia. The intraoperative pulse rate was significantly lower in SEVO group compared to the PROP group (SEVO vs. PROP+ 64.1 ± 15.1 vs. 73.4 ± 10.1 bpm, p=0.019). The intraoperative average MAP value remained within the target range of controlled hypotension in each group. The MAP values were significantly lower in SEVO and SEVO+ groups compared to propofol groups (SEVO vs. PROP+ 70.9 ± 9.6 vs. 78.3 ± 9.5 mmHg, p=0.026) (SEVO+ vs. PROP+ 70.0 ± 7.6 vs. 84.3 ± 11.4 mmHg, p=0.001). The postoperative values of MAP and pulse rate did not differ significantly in the four groups. The intraoperative BIS and TOF average values did not show significant difference when SEVO+ and PROP+ groups were compared.

4.2. Medication use and perioperative data (I)

4.2.1. Sevoflurane anaesthesia

The induction dose of fentanyl and atracurium was similar at the comparison of SEVO and SEVO+ groups, we did not experience significant difference. The quantity of propofol used during induction was significantly lower in SEVO+ group (SEVO vs. PROP+ 196.3 ± 46.9 vs. 166.4 ± 35.2 mg, p<0.001). The extent of intraoperative fentanyl use was higher, while we used sevoflurane and atracurium to a lower extent in SEVO+ group compared to SEVO group, the differences were not significant.

The duration of surgery, the duration of anaesthesia and time to reach intraoperative controlled hypotension was similar in SEVO and SEVO+ groups. In SEVO+ group, time between finishing anaesthesia and extubation was significantly shorter than in SEVO group (SEVO vs. PROP+ 14.5 ± 3.9 vs. 11.1 ± 4.7 min, p=0.002). MAP values recorded in the postoperative period returned sooner to the value (±5%)

measured at the start of narcosis in SEVO+ group compared to SEVO group, the difference was not significant. There was no difference in terms of the antidote (neostigmine, atropin) antagonising the effect of the neuromuscular blocker used in the early postoperative period, as well as in terms of minor anaesthesiologic complications.

4.2.2. Propofol anaesthesia

When we compared PROP and PROP+ groups, there was no significant difference regarding the quantities of fentanyl and atracurium used at the induction of narcosis. The quantity of propofol used during induction was significantly lower in PROP+ group compared to PROP group (PROP vs. PROP+ 194.3 ± 18.9 vs. 147.3 ± 30.2 mg, $p<0.001$). The extent of intraoperative fentanyl and atracurium use was higher, while we used propofol to a lower extent in PROP+ group, the differences were statistically not significant.

The duration of surgery, the duration of anaesthesia and time to reach intraoperative controlled hypotension was similar in PROP and PROP+ groups. In PROP+ group, time between finishing narcosis and extubation was significantly shorter than in PROP group (PROP vs. PROP+ 15.2 ± 4.7 vs. 12.6 ± 5.4 min, $p<0.001$). MAP values recorded in the postoperative period returned sooner to the value (±5%) measured at the start of narcosis in PROP+ group, the difference was not significant. There was no significant difference between PROP and PROP+ groups in terms of the antidote (neostigmine, atropin) antagonising the effect of the neuromuscular blocker used in the early postoperative period and in terms of minor anaesthesiologic complications.

4.3. Cost-effectiveness analysis of anaesthesia (I)

4.3.1. Sevoflurane anaesthesia

The cost of propofol used for induction was significantly lower in SEVO+ group compared to SEVO group (SEVO vs. SEVO+ 359.6 ± 49.6 HUF vs. 291.4 ± 58.9 HUF, $p=0.016$). There was no statistically significant difference between the two groups regarding the cost of fentanyl and atracurium used for induction. The hourly cost of intraoperative pain alleviation increased, while the hourly cost of used sevoflurane and atracurium was lower in SEVO+ group compared to SEVO group – the difference was

not statistically significant. The total hourly cost of medication was significantly lower in SEVO+ group (SEVO vs. SEVO+ 2740.4 ± 1274.1 vs. 2436.6 ± 1097.4 HUF/hour, p=0.002). The cost of single-use devices was significantly higher in SEVO+ group compared to SEVO group (SEVO vs. SEVO+ 2011.9 ± 34.1 vs. 7207.5 ± 37.2 HUF, p=0.001). In SEVO+ group, the total cost of narcosis calculated for one hour was significantly higher compared to SEVO group (SEVO vs. SEVO+ 3766.5 ± 1649.2 vs. 6184.5 ± 2644.3 HUF/hour, p=0.001).

4.3.2. Propofol anaesthesia

The cost of propofol used for induction was significantly lower in PROP+ group compared to PROP group (PROP vs. PROP+ 353.4 ± 24.8 vs. 251.1 ± 62.0 HUF, p<0.001). There was no significant difference between the PROP and PROP+ groups regarding the cost of fentanyl and atracurium used for the induction of narcosis. The hourly cost of intraoperative pain alleviation increased, while the hourly cost of used propofol and atracurium was lower in PROP+ group compared to PROP group. The hourly total cost of medicines was significantly lower in PROP+ group compared to PROP group (PROP vs. PROP+ 2582.3 ± 936.2 vs. 2332.2 ± 771.9 HUF/hour, p<0.001). The cost of single-use devices was significantly higher in PROP+ group (PROP vs. PROP+ 2507.9 ± 21.7 vs. 7675.6 ± 58.9 HUF, p<0.001). The total cost of narcosis was significantly higher in PROP+ group (PROP vs. PROP+ 4101.3 ± 1311.3 vs. 6854.1 ± 2504.8 HUF/hour, p<0.001).

We summarized and assigned the total costs of narcosis to determined lengths of surgery. The hourly anaesthesia costs are inversely proportional to the duration of surgery (**Figure 1**). The major difference experienced at a 60-minute-long intervention became negligible in the 240th minute, there was no significant difference between the groups. The longer interventions required lower total cost calculated for time units.

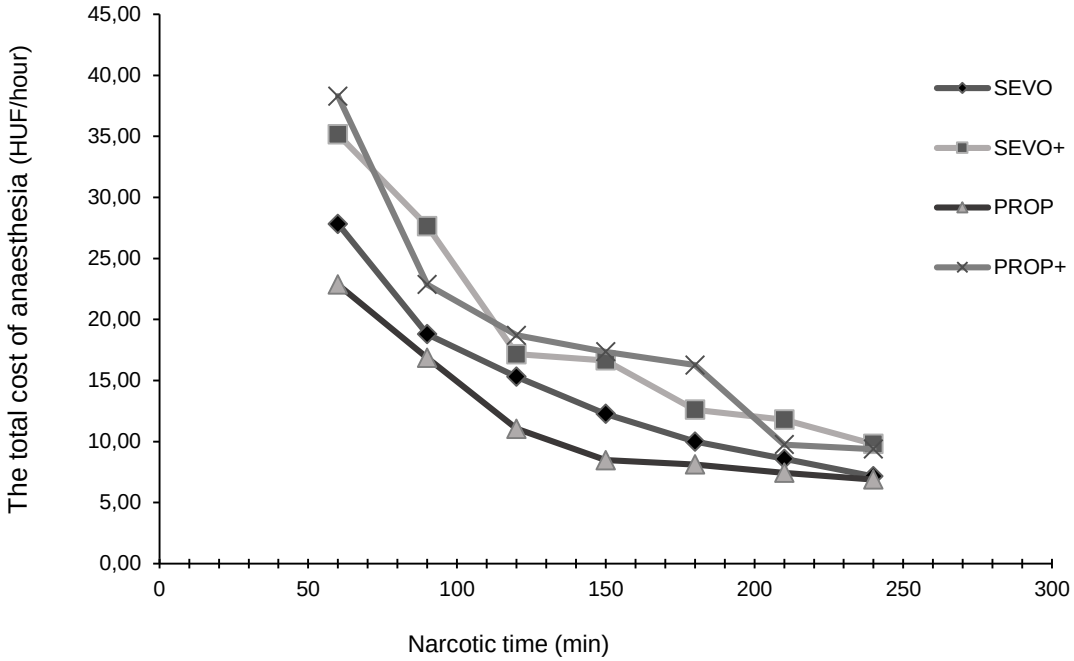

Figure 1 *The total cost of anaesthesia*
SEVO=sevoflurane-based anaesthesia; SEVO+=sevoflurane-based anaesthesia supplemented with BIS and TOF monitoring; PROP=propofol-based anaesthesia; PROP+=propofol-based anaesthesia supplemented with BIS and TOF monitoring; HUF=Hungarian Forint.

4.4. The effect of narcosis on cognitive functions (II)

In the study we examined patients, who underwent otorhinolaryngological interventions, in 30 cases combined (sevoflurane anaesthesia) and in 30 cases total intravenous (propofol anaesthesia) anaesthesia was performed. The enrolled patient did not show significant differences in terms of age, educational stage (completed school years), other information in the medical history (hypertony, smoking, alcohol consumption) and surgery characteristics (duration of surgery, duration of narcosis).

The two types of narcosis showed significant difference regarding the checked vital signs (p<0.05), except for the value of peripheral oxygen saturation (N.S.) and maximum diastolic blood pressure (p=0.05). We did not find significant difference in the age and educational level of patients participating in the study, however, the educational level influenced the understanding and completion of the tests. The Pearson correlation shows that between the patients' test results and educational level there is a positive correlation, while test results and age are negatively related.

After the result analysis, we can conclude that the cognitive functions were significantly worse 2 hours after the examined anaesthesia cases (short-term analysis) compared to the preoperative status. There is a significant difference between the total scores of pre-and postoperative tests in both sevoflurane and propofol anaesthesia cases. Taking into consideration certain components of the test, the results of visual spatial and orientation skills, attention, memory, and language skills were significantly worse in the postoperative tests compared to the preoperative ones (p<0.01). The change in abstract functioning was not significant. The skills of naming subjects and orientation did not deteriorate after the surgery. The values of Pearson correlation were between 0.19 and 0.42 when we analysed the relationship among the intraoperative pulse rate, BP values, the duration of anaesthesia, the duration of surgery and the change in cognitive functions.

5. Summary and conclusions

5.1.Haemodinamic parameters és drug consumption (I.)

The results of our study show that the intraoperative pulse rate and MAP were lower in SEVO and SEVO+ groups than in PROP and PROP+ groups. The pulse rate and MAP values were significantly lower in case of sevoflurane-based anaesthesia cases (p<0.05), when SEVO/PROP and SEVO+/PROP+ groups were compared. The difference was not significant between the two types of anaesthesia when we analysed the length of time to reach intraoperative hypotension. In PROP and PROP+ groups the hypotension was reached sooner than in SEVO and SEVO+ groups.

Our results suggest that the total perioperative medicine use decreased in SEVO+ and PROP+ groups. The amount of propofol used at the induction of anaesthesia was significantly less in SEVO+ and PROP+ groups (p<0.001). The amount of fentanyl used during surgery was higher, the amount of used anaesthetic was lower in SEVO+ and PROP+ groups (the difference is insignificant). We needed less neuromuscular blockers in SEVO+ and PROP+ groups. However, the amount of intraoperatively used atracurium increased in PROP+ group. The pulse rate reached a relatively higher value in the SEVO+ group, while MAP slightly increased in comparison with SEVO group. In PROP+ group the intraoperative pulse rate was lower, contrary to this, MAP increased compared to the PROP group. Such changes in haemodynamic parameters can be caused by the anaesthetics, the effect of painkillers and neuromuscular blockers exerted on the circulation, as well as the modified medicine use. The needed amount of anaesthetic decreased in SEVO+ and PROP+ groups, thus cardiovascular effects and fentanyl-atracurium use have changed accordingly.

BIS and TOF monitors also help in the administration of anaesthetic drugs, so there is a high probability that the underdosing or overdosing of medicines is avoided. Due to the expanded monitoring, the anaesthesia management is more targeted, the use of BIS and TOF monitors contribute to the interpetation of haemodynamic parameters. In SEVO+ and PROP+ groups we experienced that the extent of anaesthetic use decreased, while the extent of painkiller use increased. The intraoperative dose of neuromuscular blockers varied in SEVO+ and PROP+ groups.

The previously mentioned effect may be responsible for this (different effect of sevoflurane and propofol on the neuromuscular junction).

Our results suggest that with the use of sevoflurane we can reach a controlled hypotension which develops at a slower speed but it is deeper. The use of BIS and TOF monitors are beneficial to the extent of anaesthetic use but as a consequence the use of painkillers and neuromuscular blockers may change (it decreases in case of sevoflurane, while increases in case of propofol).

5.2. Perioperative complications (I.)

Based on our study data, the frequency of complications during the perioperative period were similar in case of sevoflurane and propofol anaesthesia. In the awakening phase, the length of time between the end of surgery and extubation was similar for both anaesthesia types (SEVO vs. PROP and SEVO+ vs. PROP+). This length of time was significantly shorter in SEVO+ and PROP+ groups than in SEVO and PROP groups (p<0.01).The postoperative MAP returned to the initial (preoperative) blood pressure value (±5%) in SEVO+ and PROP+ groups sooner than in SEVO and PROP groups (p<0.01). The frequency of PONV was higher in SEVO+ and PROP+ groups, the higher need for intraoperative painkillers and use may be in the background.

Our results show that there is no significant difference between sevoflurane and propofol in terms of perioperative complications. The use of BIS and TOF monitors may accelerate the awakening after anaesthesia and may accelerate recovery.

5.3. The anaesthesiologic costs of the perioperative period (I.)

The results of our analyses suggest that the SEVO group had the highest cost of intraoperative medicine use among the four groups. FGF influences the intraoperative costs of sevoflurane. If FGF is lower than 1.0 L/min during the combined anaesthesia, the difference between the cost of sevoflurane and propofol anaesthesia will not be significant. In our study FGF was 1.0 L/min, this might have influenced our results. Furthermore, we can conclude that the total cost of medicines/hour in SEVO+ and PROP+ groups was lower than in SEVO and PROP groups (SEVO vs. SEVO+ p=0.002; PROP vs. PROP+ p<0.001). The trends in medicine costs refer to the changes in used medicines. According to our results, the cost of single-use devices,

hence the hourly cost of anaesthesia in total was significantly higher in SEVO+ and PROP+ groups compared to SEVO and PROP groups (p<0.001).

As we analysed the hourly total costs (taking into consideration the used quantities of medicines), we can conclude that –observing the requirements of a sterile environment– the cost of anaesthesia was the same within the first hour, independently of the time elapsed. In the second hour the “hourly” total cost significantly decreased, while in cases of longer narcosis than this, the hourly cost yet slightly changed. The total cost of perioperative medicine use (e.g. antidotes: neostigmine, atropine, naloxon, flumazenil; including the cost of potential complications) per one anaesthesia case provides more exact information and the obtained sum of money reflects better the expected costs.

To sum up, the propofol anaesthesia (with or without BIS and TOF monitor) has higher costs regarding the single-use devices and the total cost of narcosis than sevoflurane anaesthesia (under similar patient monitoring conditions). We can also conclude that the intraoperative use of BIS and TOF monitors increases the cost of single-use devices, this way it increases the total cost, but may reduce the cost of perioperative medicines (**Figures 2-4**).

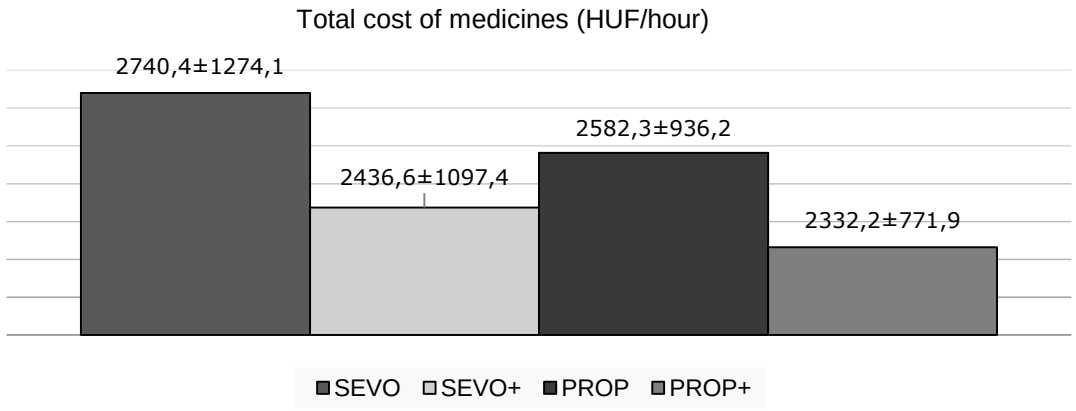

Figure 2 *Total cost of medicines (HUF/hour) in the studied groups*
Main ± SD; SEVO=sevoflurane-based anaesthesia; SEVO+=sevoflurane-based anaesthesia supplemented with BIS and TOF monitoring; PROP=propofol-based anaesthesia; PROP+=propofol-based anaesthesia supplemented with BIS and TOF monitoring; HUF=Hungarian Forint; SEVO vs. SEVO+ p=0.002; PROP vs. PROP+ p<0.001.

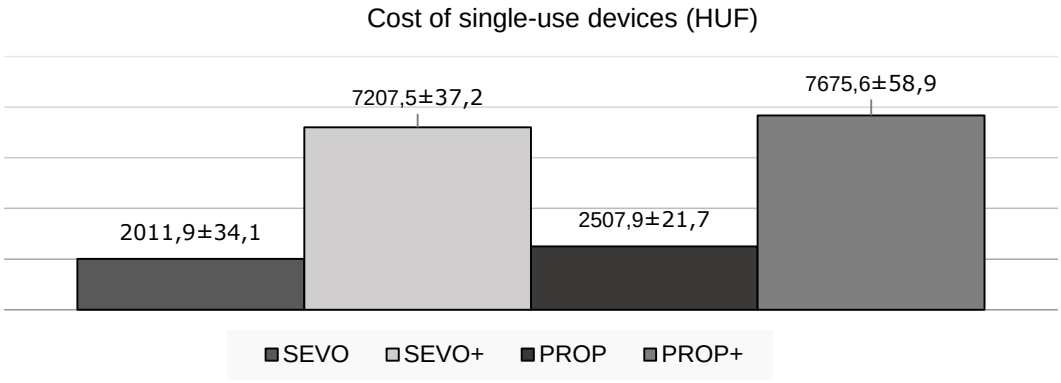

Figure 3 *Cost of single-use devices (HUF)*
Main ± SD; SEVO=sevoflurane-based anaesthesia; SEVO+=sevoflurane-based anaesthesia supplemented with BIS and TOF monitoring; PROP=propofol-based anaesthesia; PROP+=propofol-based anaesthesia supplemented with BIS and TOF monitoring; HUF=Hungarian Forint; SEVO vs. SEVO+ p=0.001; PROP vs. PROP+ p<0.001.

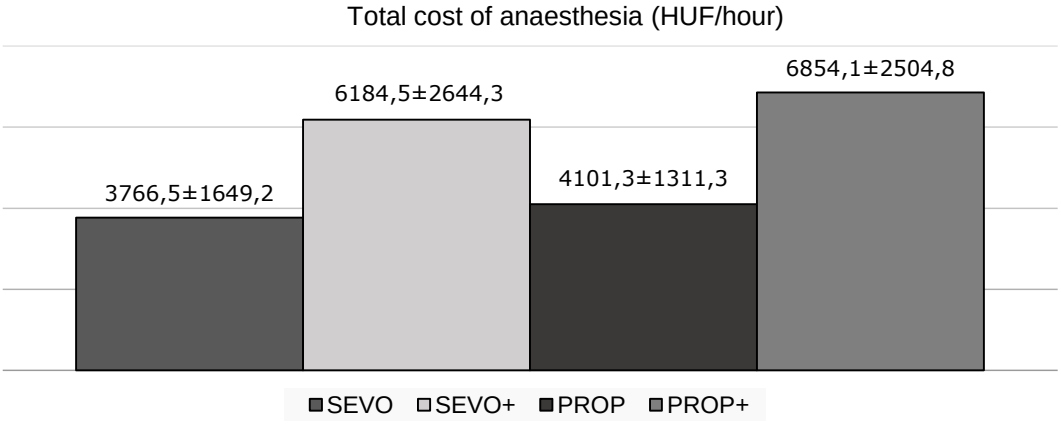

Figure 4 *Total cost of anaesthesia (HUF/hour)*
Main±SD;SEVO=sevoflurane-based anaesthesia; SEVO+=sevoflurane-based anaesthesia supplemented with BIS and TOF monitoring; PROP=propofol-based anaesthesia; PROP+=propofol-based anaesthesia supplemented with BIS and TOF monitoring; HUF=Hungarian Forint. SEVO vs. SEVO+ p=0.001; PROP vs. PROP+ p<0.001.

5.4. The intraoperative monitoring of the extent of anaesthetic depth and the neuromuscular blockade and their effect on the costs of narcosis (I.)

The breakdown of the anaesthesia costs per hour show that the costs of medicines used during anaesthesia changed as a result of the expanded monitoring. The pharmacological effects and interactions of the anaesthetic, the painkiller and the neuromuscular blocker influence the used quantity of a certain agent (direct and indirect effect). The performed study suggests that the awakening is faster, the vital

signs return to baseline values sooner after those anaesthesia cases, where the anaesthetic depth and the neuromuscular funcion was intraoperatively monitored, independently from the applied anaesthetic. The use of BIS and TOF monitors influence certain items of the total cost to varying extent and direction. After having summarized our results, we deem that BIS and TOF monitors are suitable to reduce medicine use. The applied cost calculation methods are easy to follow and carry out in practice. In terms of the cost-effectiveness of anaesthesia, there is a need for further supplementary studies to find out the impact of BIS and TOF monitors on QALY.

5.5. The effect of sevoflurane and propofol on cognitive functions (II)

Based on the assessments we can conclude that narcosis has an impact on cognitive functions in the short term. Sevoflurane and propofol anaesthesia also worsens cognitive functions, however, at their comparison we did not find statistically evaluable difference. Certain cognitive functions (visual spatial skills, attention, memory, language skills) were significantly worse in both groups in the second hour following anaesthesia. Test completion was influenced by age (negative correlation) and educational level (positive correlation). Due to the short follow-up period, the study observes those changes of cognitive functions that occurred only few hours following anaesthesia. No conclusion can be drawn on reversibility due to the lack of longer-term follow-up.

6. Novel findings

1. In our study we elaborated a methodology for anasthesia maintenance and cost calculation, this may be the part of an effective perioperative cost analysis.
2. We are the first to conduct perioperative cost analysis study under validated conditions, with the comparison of sevoflurane and propofol anaesthesia, in Hungary.
3. We are the first to conduct and publish a prospective, randomized study in which sevoflurane and propofol anaesthesia were compared with the concomitant use of BIS and TOF monitoring techniques, in Hungary.
4. We can draw the following conclusions based on our study results:
    - with the use of sevoflurane we can reach a controlled hypotension that develops at a slower speed but it is deeper;
    - in overall, the use of BIS and TOF monitors are beneficial to the extent of anaesthetic agent use, but as a consequence, the use of painkillers (may increase in case of both anaesthetics) and neuromuscular blockers (it may decrease in case of sevoflurane, while may increase in case of propofol) may change;
    - there is no significant difference between sevoflurane and propofol in terms of perioperative complications;
    - the use of BIS and TOF monitor may accelerate the awakening following anaesthesia and the recovery (shorter time till extubation, after surgery MAP returns to baseline faster);
    - when BIS and TOF monitors are used, PONV may be more frequent following anaesthesia;
    - the total intravenous anaesthesia (propofol anaesthesia) with or without BIS and TOF monitors has higher costs than sevoflurane anaesthesia under similar patient monitoring conditions;
    - the intraoperative use of BIS and TOF monitors increases the cost of single-use devices, this way it increases the total cost, but may reduce the cost of perioperative medicines;

- the use of BIS and TOF monitors are suitable to directly reduce certain agents in medicine use (sevoflurane, propofol, atracurium);
- the applied cost calculation method can be followed easily and can be used in everyday practice;
- in terms of the cost-effectiveness of anaesthesia, there is a need for further supplementary studies to determine the impact of BIS and TOF monitors on QALY;
- independently from the type of the anaesthetic agent, the cognitive functions significantly worsened after the narcosis in the early postoperative period, when we compared the anaesthetics, there was no significantly evaluable difference;
- test completion was influenced by age (negative correlation) and educational level (positive correlation).