UNIVERSITY OF MEDICINE AND PHARMACY

"VICTOR BABEȘ" TIMIȘOARA

FACULTY OF MEDICINE
10TH DEPARTMENT

ANCA RALUCA DINU

DOCTORAL THESIS SUMARY

IMPLICATIONS OF GENERAL ANESTHESIA MULTIMODAL MONITORING COMPRISING OF ENTROPY (RE/SE) IN ON THE CLINICAL PROGNOSIS AND NEUROCOGNITIVE RECOVERY

Scientific coordinator

PROF. UNIV. DR. DOREL SĂNDESC

T i m i ș o a r a 2020

Introduction

Worldwide, anaesthesia and intensive care services are considered to be the clinical departments with the highest mortality rates in a hospital (30-40%) and are the largest consumers of budgetary resources (over 15% of hospitals' budgets). One of the main challenges of the anesthesia and ICU medical specialty is given by the multidisciplinary caseload. During the development of this medical field a series of new and modern monitoring techniques have appeared. Moreover, in order to increase patient safety and the integrity of the medical service it is necessary to interconnect these systems with modern IT technology. In these clinics specialists have implemented in a very short time modern diagnosis and therapeutic methods. This has been confirmed by performance parameters and by a significant reduction in mortality rates. However, paradoxically the development of monitoring thechniques and the implementations of good practice guidelines, that complication rate still remains high. Taking into account the medical progress as well as the progress as a society, there is a permanent pressure from the patients and the authorities for the reduction of complications related to the medical act, with the final goal being an increased survival and a better prognosis for different patient groups. Another important aspect is given by the fact that together with the introduction of new and modern technologies capable of storing numerous data and clinical parameters, their interpretations has deemed necessary in different contexts, influencing clinical decisions and scientific research.

Anesthesia and intensive care have a new momentum regarding the development of monitoring techniques. Regarding general anesthesia, in the last years the literature has discussed a series of parameters capable of measuring the degree of hypnosis, the level of nociception, and the neuromuscular transmission. If we were to talk about adapting the general anesthesia to the needs of each patient, a newly developed parameter that can be used in order to achieve this goal is the Entropy. Entropy encompasses two other parameters, that together can offer answers regarding the dynamics of general anesthesia. We are talking hear about State Entropy SE and Response Entropy RE (4-6). This is made possible by analyzing the EEG signals and FEMG signals. From a clinical point of view, entropy can be interpreted as being a) deep

anesthesia when SE=0 and superficial anesthesia/awake patient SE=`100. Regarding the reference interval for RE, the values are similar, with RE=0 showing deep anesthesia and RE=`100 for the awake patient. One of the major benefits for entropy is given by the individualized dosage of inhalator or intravenous anesthetics. The constant use of these parameters leads to obtaining a degree of hypnosis tailored for each patient, avoiding therefore an general anesthesia that is too light or too profound. Moreover one can avoid intraoperative awareness as well as the suppression of cortical EEG. Another aspect that should not be omitted is the faster recovery of the patient from the general anesthesia and the lower doses of anesthetic substances used. Similarly, this gives rise to a better future for critically ill patients needing general anesthesia. This technique can improve guidelines and protocols, reduce mortality as well as reduce OR times, leading to a individualized approach for each patient and reducing adverse effects such as inflammation, oxidative stress, and respiratory failure.

MAIN OBJECTIVES:

1. Dynamic changes regarding systolic blood pressure relative to baseline values. These changes have been analyzed from the perspective of the numbers of hypotension or hypertension episodes. The values of hemodynamic parameters have been analyzed and recorder at every 15 minutes.
2. Dynamic changes regarding heart rate relative to baseline values. These changes have been analyzed from the perspective of the numbers of bradycardia or tachycardia episodes. The values of hemodynamic parameters have been analyzed and recorder at every 15 minutes.

SECONDARY OBJECTIVES:

1. Adapting the consumption and reducing the consumption of inhalatory anesthetic gas.
2. Improving hemodynamic stability by quantifying:

- Consumption of vasopressors.
- Resuscitation fluids consumption.

SPECIAL PART

2. MATERIALS AND METHODS

2.1. STUDY POPULATION

This is a prospective, observational, randomized study and was carried out in the Clinic for Anesthesia and Intensive Care of the “Pius Brinzeu” Emergency County Hosptial in Timisoara, Romania between January 2019-December 2019. The study was part of a larger group of studies carried out by the Department of Medical Education and Research of the Romanian Society of Anesthesia and Intensive Care (www.srati.ro). The identification code in the ClinicalTrials.gov database is NCT03210077. The approval from the Ethics Committee of the institution was received before starting the study as it respects the Declaration from Helsinki regarding clinical studies and patient safety.

Two study groups were created, Group A or the target group that received the multimodal monitoring protocol (heart rate HR, bpm; blood pressure BP, mmHg, peripheral oxygen saturation SpO_2, capnography $EtCO_2$; state entropy SE; response entropy RE; fraction of inspired oxygen FiO_2; minimum alveolar concentration MAC) and Group B, or the control group for which general anesthesia was guided based on standard monitoring (heart rate HR, bpm; blood pressure BP, mmHg, peripheral oxygen saturation SpO_2, capnography $EtCO_2$; fraction of inspired oxygen FiO_2; minimum alveolar concentration MAC). In accordance with the study protocol the inclusion and exclusion criteria were: age over 18, both genders, surgical intervention – laparoscopic cholecystectomy, general anesthesia with Sevoflurane. The exclusion criteria were: pregnancy, septic shock, and massive hemorrhage. Allocation to the study group was made in a randomized manner, using online software (http://www.randomization.com) (Figure 7).

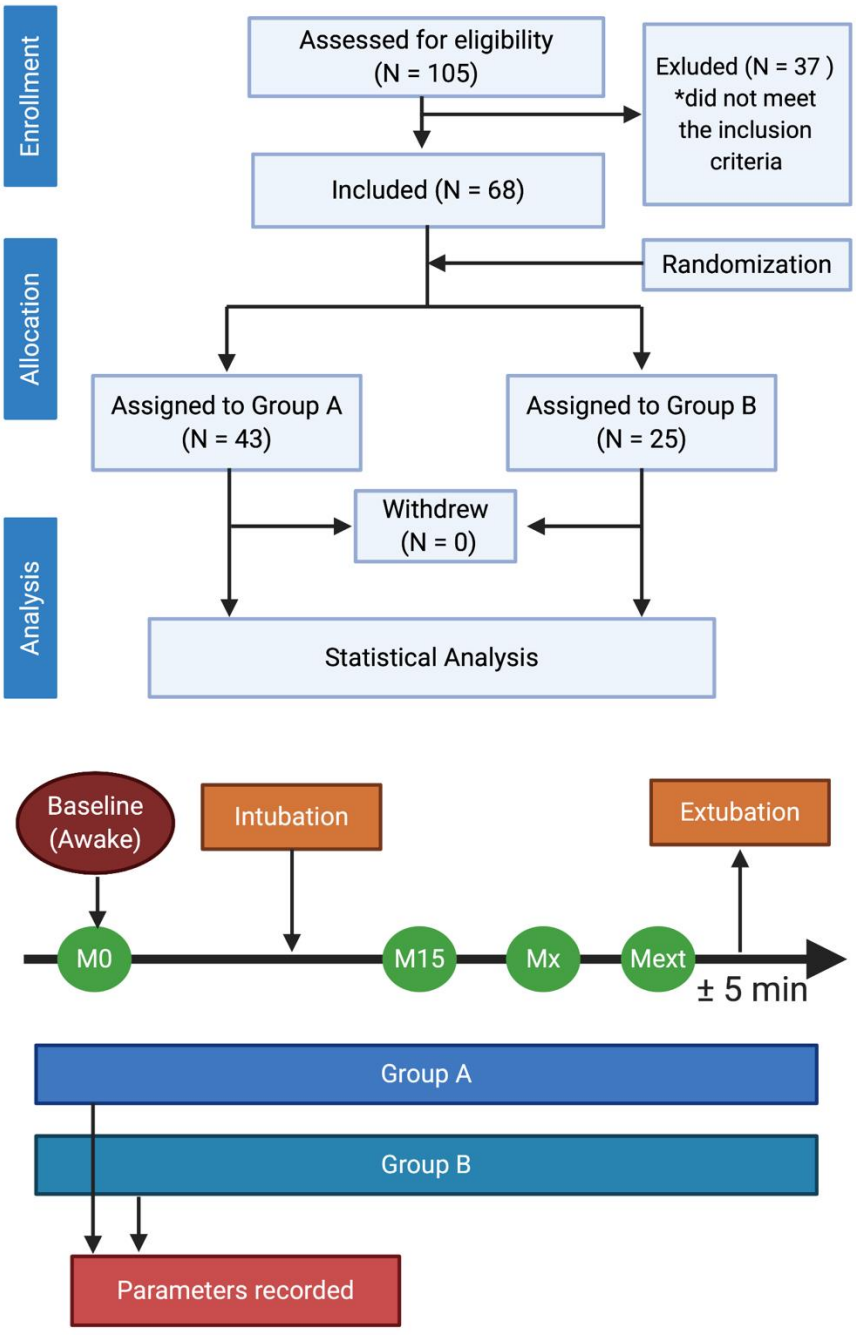

Figure 7. Study Flowchart

3. RESULTS AND STATISTICAL ANALYSIS

3.1. CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF PATIENTS ENROLED IN THE STUDY

Between January 2019 and December 2019 the patients eligible for the study have been registered based on the inclusion and exclusion criteria, with a total number of 68 patients. After applying the randomization protocols 43 patients were allocated to Group A and 25 patients to Group B. None of the patients in either group have presented with certain phenomena that could have led to the exclusion from the study.

For the statistical analysis at first the demographical and clinical data have been compared (Table 2) for patients in Group A and Group B, with no statistically significant differences between the two groups. Distribution based on gender was analyzed by applying the Chi square test with 1 d.f. For the comparison of all the other characteristics the Student's t test was used (two-tailed, unpaired). Moreover, for all the analyzed data the Confidence Interval (95%) has been stated.

Table 2. Clinical and demographical characteristics of the study groups

Characteristic	Group A (N=43)	Group B (N=25)	95% Confidence Interval	p value
Age, years, mean ± SD	51 ± 16.51	52.20 ± 13.79	-6.620 to 9.020	0.7603
Sex, M, N (%)	7 (16.28)	6 (24)	-10.8233% to 28.7947 %	0.4384
ASA Score, I, N (%)	10 (23)	3 (12)	-0.5716% to 27.4520%	0.2680
ASA Score, II, N (%)	24 (56)	17 (68)	-11.9231% to 32.8672%	0.3328
ASA Score, III, N (%)	6 (14)	5 (20)	-11.3628% to 26.5172%	0.5205
HR at M0, bpm, mean ± SD	78.48 ± 13.87	75.32 ± 14.28	-10.46 to 3.616	0.3351
SBP la M0, mmHg, mean ± SD	136.5 ± 22.47	134 ± 17.51	-12.97 to 7.917	0.6305
	SD, standard deviation; M, male; N, number of patients; HR, heart rate; SBP systolic blood pressure; M0, moment zero; p, statistically significant at $p < 0.05$			

In the two study groups the age distribution was homogenous, without any statistical extremes (p = 0.7603). The minimum value for age in Group A was 22 years vs. 23 years in Group B. The median in the two groups was as follows: 53 for Grop A and 51 for Group B. Another statistical parameter that proves group homogeneity regarding age was the variation coefficient that was 32.37% for Group A and 26.41% for Gorup B. Moreoever the 25% percentile was 39 in Group A and 46 in Group B. The Lower 95% CI was 45.99 for Group A vs. 46.51 for Group B. In contrast, the Upper 95% CI of the mean was 56.08% in Group A and 57.89% in Group B. (Figure 9).

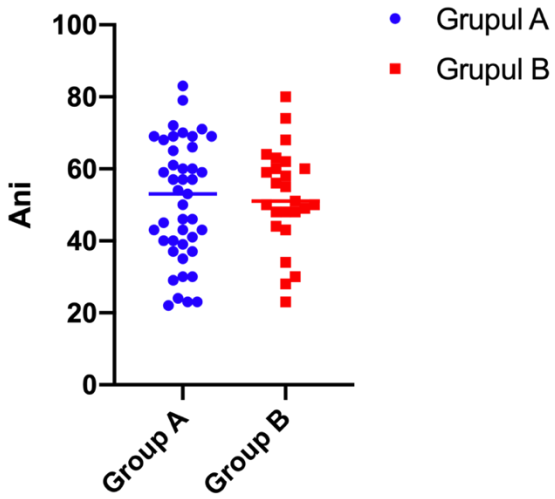

Figure 9. Age distribution in the study groups

Another important parameter that characterizes homogeneity of the two groups was the gender distribution for the patients enrolled in the study. Group A included 16.28% male patients (N=7), while Group B included 24% male patients (N=6), 95% CI -10.8233% to 28.7947%, p = 0.4384.

Due to the fact that the main objective of the study was to determine the impact of advanced monitoring on hemodynamic stability, the starting values for heart rate (HR, bpm) and blood pressure (SBP, mmHg) have been statistically analyzed for further statistical comparison of the hemodynamic profiles in the two study groups.

Patients in Group A presented a minimum value for heart rate at moment zero of 60 bpm, while patients in Group B 51 bpm. Group A had a maximum HR of 112 bpm, while Group B 110 bpm. The mean variation coefficient was 17.61% in Group A vs.

18.96% in Group B. Complex statistical analysis did not show statistically significant differences between the two groups, the 25% Percentile being 70.00 vs. 66.50, 75% Percentile being 85.00 vs. 85.00, Lower 95%CI of the mean 74.48 vs. 69.43, and Upper 95%CI was 83.01 vs. 81.21 (Table 3, Figure 10).

Table 3. Descriptive statistical analysis of heart rate at starting moment

	Group A	**Group B**
Minimum	60,00	51,00
25% Percentile	70,00	66,50
Mean	74,00	72,00
75% Percentile	85,00	85,00
Maximum	112,0	110,0
Mean	78,74	75,32
Std. Deviation	13,87	14,28
Std. Error of the mean	2,115	2,856
Lower 95% CI	74,48	69,43
Upper 95% CI	83,01	81,21

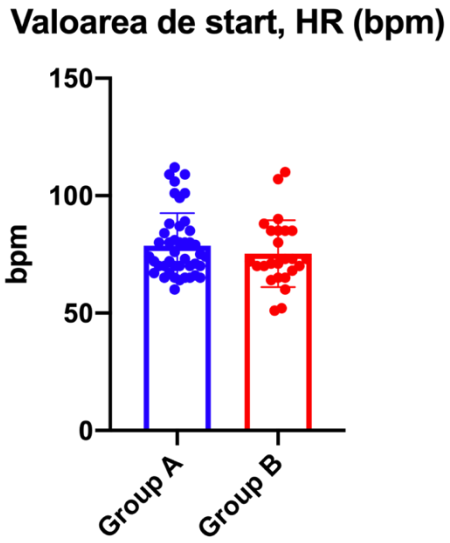

Figure 10. Starting value for heart rate (HR, bpm) in the two study groups

Regarding the starting value for blood pressure (SBP, bpm) the statistical results are similar, without any significant statistical differences between the two study groups ($p > 0.05$). Group A had a minimum value of 100 mmHg vs. 110 mmHg in Group B. The median for blood pressure values in the two groups presented no numerical difference, with 136 for Group A and 130 for Group B. Advanced statistical analysis showed a standard deviation of 22.47 for Group A, 25% Percentile of 120, 75% Percentile of 147, Lower 95% CI of 129.6, and Upper 95% CI 143.4. For Group B the standard deviation was 22.47%, 25% Percentile was 121.5, 75% Percentile was 145.5, Lower 95% CI 126.7, and Upper 95% CI 141.2 (Figure 11, Table 4).

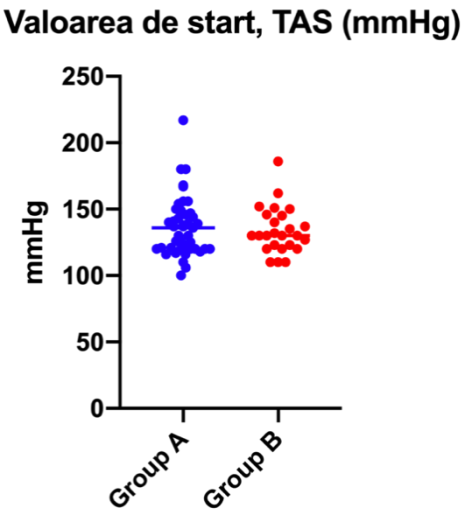

Figure 11. Starting value of systolic blood pressure (TAS, mmHg) in the two study groups

Table 4. Descriptive statistical analysis of blood pressure at starting moment

	Group A	Group B
Minimum	100,0	110,0
25% Percentile	120,0	121,5
Median	136,0	130,0
75% Percentile	147,0	145,5
Maximum	217,0	186,0
Media	136,5	134,0
Std. Deviation	22,47	17,51
Std. Error of the mean	3,426	3,502
Lower 95% CI	129,6	126,7
Upper 95% CI	143,4	141,2

Another parameter analyzed at moment zero was the peripheral oxygen saturation (SpO_2, %). No statistically significant differences were noticed between the two study groups regarding SpO_2 de start ($p > 0.05$) (Figure 12).

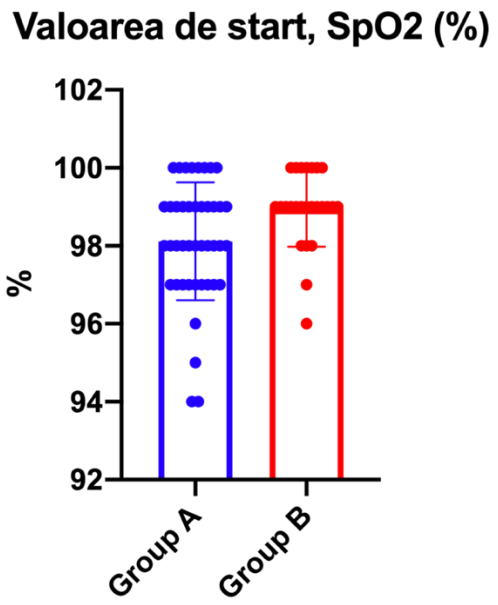

Figure 12. Starting value of peripheral oxygen saturation (SpO2, %) in the two study groups

3.3. PERIOPERATIVE HEMODYNAMIC PROFILE

Hemodynamic stability has been analyzed through a series of different parameters. In this regard we discussed the HR (bpm) dynamics and the SBP (mmHg) dynamics, as well as the number of hemodynamic events such as hypertension, hypotension, tachycardia, and bradycardia. For Group A we recorded a total number of 1.6/N (N=43) of hemodynamic events, out of which 17 (24.4%) were hypertension, 19 (28.4%) hypotension, 12 (17.9%) tachycardia și 19 (28.4%) bradycardia. In Group B there was 2.84/N (N=25) hemodynamic events: 21 (29.6%) hypertension, 14 (19.7%) hypotension, 21 (29.6%) tachycardia, and 15 (21.1%) bradycardia. For a correct appreciation of the number of hemodynamic events they were expressed relative to the number of patients in each group (Table 9).

Table 9. Hemodynamic changes in Group A and Group B

	Group A (N=43)			Group B (N=25)		
	Nr. Hemodynamic ev	**Nr. Hemodynamic ev / Patient**	**% hemo d.ev.**	**Nr. Hemodynamic ev**	**Nr. de Hemodynamic ev / Patient**	**% hemo d.ev.**
Hypertension	17	0,4	25,4	21	0,84	29,6
Hypotension	19	0,5	28,4	14	0,56	19,7
Tachycardia	12	0,3	17,9	21	0,84	29,6
Bradycardia	19	0,5	28,4	15	0,6	21,1
Total	67	1,6		71	2,84	

Regarding the statistical analysis in the two groups the results have shown a statistically significant decrease in the number of hypotensive events in Group A ($p = 0.011$; 95% CI 0.1851 to 0.7042; min 0: max 2; 25% Percentile 0, 75% Percentile 1; Range 2). Statistically significant differences have also been recorded for bradycardia in Group A, with a reduction in the incidence ($p < 0.0001$; 95% CI 0.3296 to 0.7923; min 0 : max 1; 25% Percentile 1, 75% Percentile 1; Range 1). There were no statistically significant differences in the number of hypertensive events ($p = 0.3547$; 95%CI -0.1349 to 0.3712; min 0 : max 1; 25% Percentile 0, 75% Percentile 1; Range 1), or for tachycardia ($p = 9.2866$; 95%CI -0.1357 to 0.4520; min 0 : max 1; 25% Percentile 0, 75& Percentile 1; Range 1). The distribution of the number of hemodynamic events in the two groups shows that in the case of bradycardia most of the patients included in study Group A presented no bradicardic events. A low number presented one moment of bradycardia (N=10, 83.33%), with an isolated case that presented two episodes (N=1, 8.37%). On the other hand in Group B a high number of patients presented one bradycardia episode (N=21, 84%). The same trend was followed by hypotension, with

Group A showing that most of the patients presented one single episode 76.47% (N= 13) and 11.77% (N=2) presented two hypotensive episodes. In contrast, 86% (N=21) of patients in Group B presented one episode of hypotension. Although the distribution of tachycardia and hypertension events is different, these differences were not statistically significant. Therefore, in the case of tachycardia 84.21% (N=16) of Group A presented one episode, 5.26% (N=1) three episodes, while for Group B 60% (N=15) presented one episode. Hypertension events follow a similar pattern with 100% (N=19) of Group A and 56% (N=14) of Group B presenting one episode (Figures 22-25).

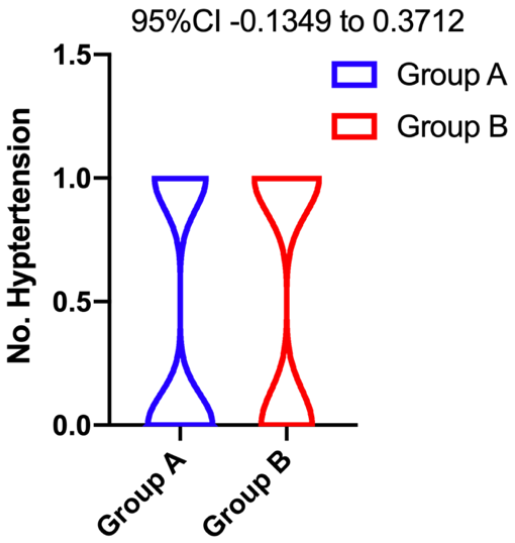

Figure 22. Statistical analysis of hemodynamic events - hypertension

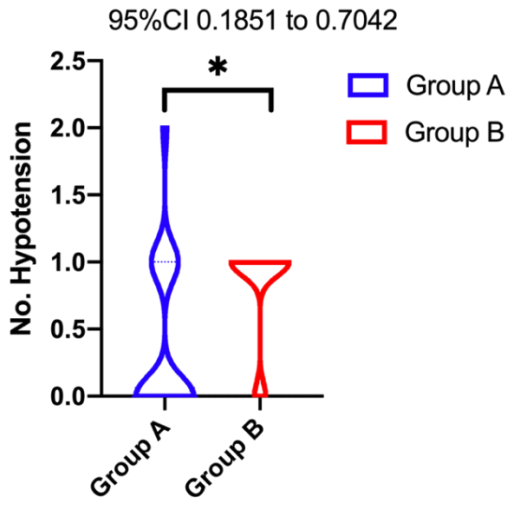

Figure 23. Statistical analysis of hemodynamic events - hypotension

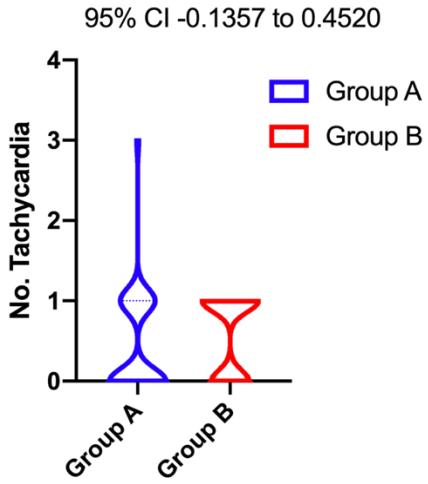

Figure 24. Statistical analysis of hemodynamic events - tachycardia

CONCLUSION AND PERSONAL CONTRIBUTION

This study has proven benefic changes from a clinical point of view given by general anesthesia guided with multimodal monitoring based on Entropy. One of the most specific characteristics of volatile anesthetics is represented by induced hypotension and changes in the hemodynamic balance. This study the Entropy parameters SE and RE were kept at target values between 40 and 60 based on data in the literature. We have observed a reduction in Sevoflurane consumption in Group A, in contrast with general anesthesia solely guided by the hemodynamic measurements. This has brought benefits in regard with the prognosis of these patients by reducing the incidence of hypotension episodes, as well as the incidence of tachycardia episodes. Taking into account the increased hemodynamic instability of patients undergoing laparoscopic surgery, the individualized titration of anesthetic drugs is needed. By achieving this target one can reduce both the incidence of complications and perioperative adverse reactions, leading to increased patient safety.

Inadequate anesthesia can lead to vasoplegia with hemodynamic imbalance and can increase the need for vasopressors, as well the need for crystalloids or colloids. In our study, titrating anesthesia based on advanced monitoring has led to a statistically significant decrease in the need for vasopressors ($p < 0.00010$). Regarding perioperative fluid resuscitation needed to achieve hemodynamic stability, the patients in the target group received a volume of crystalloids and colloids with a 500.00 ± 100.00 mL lower than the patients in the control group. This is a valid argument for proving that Entropy guided general anesthesia increases hemodynamic stability in patients undergoing laparoscopic cholecystectomy.

In conclusion, we can state that multimodal monitoring including both classical parameters and parameters monitoring the depth of anesthesia (Entropy) leads to a better perioperative hemodynamic stability. Our study has shown a decrease in the incidence of hypotension and bradycardia in the patients who benefited from individualized titration of anesthetic dosage based on Entropy. Furthermore, we have reported a decrease in Sevoflurane consumption in the study group, where general anesthesia was guided based on the Entropy.

We can therefore conclude that, by tailoring general anesthesia based on the individual needs of each patient one can achieve an individualized anesthetic technique with a positive impact on perioperative hemodynamic stability, as well as on volatile agent consumption. Last but not least we can highlight the increased patient safety and a better therapeutic management by adapting and reorienting the clinical practice towards a more personalized medicine.

Study results

1. Evaluation of the degree of hypnosis by monitoring “”State Entropy” and ”Response Entropy” can bring personalized information when administering general anesthesia.
2. Volatile anesthetic agents titration based on Entropy values significantly reduces the number of hemodynamic events (hypotension and bradycardia).
3. By implementing a multimodal monitoring protocol patient safety can be increased.
4. Perioperative monitoring quality is increased in patients benefiting from Entropy monitoring.
5. Patients undergoing laparoscopic cholecystectomy under general anesthesia guided with entropy have a shorter recovery time and a decreased incidence of adverse effects.
6. OR times are shorter with adequate titration of general anesthetics.
7. Opioid consumption and analgesic drugs consumption in the postoperative period is decreased in patients that benefited from an adequate degree of hypnosis during surgery, based on SE and RE values.
8. The risks associated with general anesthesia and the risk for complications was significantly reduced in patients benefiting from multimodal monitoring.
9. Better patient flow with shorter times between cases in the same OR.

10. Clinical prognosis was better in the case of patients who benefited from optimized general anesthesia based on multimodal monitoring with RE and SE.

We consider the first goal of our study to have been achieved after demonstrating the positive impact of the multimodal monitoring protocol based on both standard parameters and Entropy, expressed as increased hemodynamic stability and a reduction in anesthetic drugs consumption.

Originality of the study:

- Complementing the standard monitoring protocol with two new parameters: State Entropy and Response Entropy;
- Secondary objective – the identification of hemodynamic adverse events and the links between these events and the dynamic titration of anesthetic drugs dosage;
- Multimodal evaluation of general anesthesia in patients undergoing laparoscopic surgery;
- Developing a standard monitoring protocol to be applied to all patients needing general anesthesia;

FUTURE DIRECTIONS OF THE RESEARCH

1. The development of new clinical studies that can evaluate both the expression of entropy and of the bispectral index;
2. Introducing multimodal monitoring guidelines in general anesthesia;
3. Establishing exact correlations between the expression of entropy and the consumption of volatile anesthetics;
4. Establishing statistical correlations between the RE/SE expression and MAC value;
5. Establishing a concise protocol regarding minimum perioperative monitoring standards;

LIST OF PUBLISHED ARTICLES

1. **Anca Raluca Dinu**, Alexandru Florin Rogobete, Tiberiu Bratu, Sonia Elena Popovici, Ovidiu Horea Bedreag, Marius Papurica, Lavinia Melania Bratu, Dorel Sandesc. Cannabis Sativa Revisited—Crosstalk between microRNA Expression, Inflammation, Oxidative Stress, and Endocannabinoid Response System in Critically Ill Patients with Sepsis. Cells 2020, 9, 307; doi:10.3390/cells9020307 (impact factor 5.657)

2. **Dinu, Anca Raluca;** et al. Impact of General Anaesthesia - guided by State Entropy (SE) and Response Entropy (RE) on Perioperative Stability in Elective Laparoscopic Cholecystectomy Patients. A Prospective Observational Randomized Monocenter Study. Entropy 2020, Preprints, DOI code: 2020020130 (doi: 10.20944/preprints202002.0130.v1). (impact factor 2.3)

3. Ivan MV, Rogobete AF, Bedreag OH, Papurica M, Popovici SE, **Dinu A**, Sandesc M, Beceanu A, Bratu LM, Popoiu CM, Sandesc D, Boruga O, Fulger L. New Molecular and Epigenetic Expressions as Novel Biomarkers in Critically Ill Polytrauma Patients with Acute Kidney Injury (AKI). Clin Lab. 2018 May 1;64(5):663-668. doi: 10.7754/Clin.Lab.2018.171226. Review. PubMed PMID: 29739062 (impact factor 0.980) (Impact factor 0.950)

4. Sandesc M, Rogobete AF, Bedreag OH, **Dinu A**, Papurica M, Cradigati CA, Sarandan M, Popovici SE, Bratu LM, Bratu T, Stan AT, Sandesc D. Analysis of oxidative stress-related markers in critically ill polytrauma patients: An observational prospective single-center study. Bosn J Basic Med Sci. 2018 May 20;18(2):191-197. doi: 10.17305/bjbms.2018.2306. PubMed PMID: 29310566; PubMed Central PMCID: PMC5988539. (Impact Factor 1.540)

5. Sandesc M, Dinu A, Rogobete AF, Bedreag OH, Sandesc D, Papurica M, Bratu LM, Negoita S, Vernic C, Popovici SE, Corneci D. Circulating microRNAs Expressions as Genetic Biomarkers in Pancreatic Cancer Patients Continuous Non-Invasive Monitoring. Clin Lab. 2017 Oct 1;63(10):1561-1566. doi: 10.7754/Clin.Lab.2017.170608. Review. PubMed PMID: 29035444. (Impact factor 0.950)