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Intensive Care Admission and Management of Patients with Acute Ischemic Stroke: A Cross Sectional Survey of the European Society of Intensive Care Medicine

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Results of this survey have been partially presented at the European Society of Intensive Care Meeting LIVESin December 2020.

Abstract

Background: No specific recommendations are available regarding the intensive care management of critically ill acute ischemic stroke (AIS) patients, and questions remain regarding optimal ventilatory, hemodynamic and general ICU therapeutic targets in this population. We performed an international survey to investigate intensive care unit (ICU) admission criteria and management of AIS patients.

Methods: An electronic questionnaire including 25 items divided into 3 sections was available on the European Society of Intensive Care Medicine (ESICM) website between 1st November 2019 and 30th March 2020 and advertised through the Neurointensive Care (NIC) section newsletter. This survey was emailed directly to the NIC members and was endorsed by the ESICM.

Results: There were 214 respondents from 198 centers, with response rate of 16,5% of total membership (214/1296). In most centers (67%), the number of AIS patients admitted to respondents' hospitals in 2019 was between 100 and 300, and, among them, fewer than 50 required ICU admission per hospital. The most widely accepted indication for ICU admission criteria was a requirement for intubation and mechanical ventilation. A standard protocol for arterial blood pressure (ABP) management was utilized by 88 (58%) of the respondents. For patients eligible for iv thrombolysis, the most common ABP target was < 185/110 mmHg (n=77 [51%]), while for patients undergoing mechanical thrombectomy it was $\leq$ 160/90 mmHg (n=79 [54%]). The preferred drug for reducing ABP was labetalol (n=84 [55,6%]). Other frequently used therapeutic targets included: blood glucose 140-180 mg/dl (n=65 [43%]) maintained with intravenous insulin infusion in most institutions (n=110 [72,4%]); enteral feeding initiated within 2-3 days from stroke onset (n=142 [93,4%]); oxygen saturation (SpO_2) >95% (n=80 [53%]), and tidal volume 6-8 ml/kg of predicted body weight (n=135 [89%]).

Conclusions: The ICU management of AIS, including therapeutic targets and clinical practice strategies, importantly varies between centers. Our findings may be helpful to define future studies and create a research agenda regarding the ICU therapeutic targets for AIS patients.

Keywords: acute ischemic stroke; intensive care unit; mechanical ventilation; arterial blood pressure; thrombolysis

Introduction

Acute ischemic stroke (AIS) is a major cause of mortality and morbidity wordwide.[1] A substantial proportion of patients with AIS require admission to an intensive care unit (ICU) for neurological monitoring and management of general or poststroke complications that cannot be delivered on a stroke unit.[2]

The overarching goal of AIS management in both stroke units and ICUs is to target therapeutic efforts to restore blood flow to the penumbra before irreversible tissue injury has occurred in order to minimize secondary brain injury and improve long-term functional outcomes and quality of life.[3,4] This is accomplished by conceptually optimizing brain perfusion and compensating for associated dysfunction in systemic organ systems. Because of the rapid and irreversible nature of ischemic brain injury, it is crucial for neurocritical care management to begin as early as possible in appropriate patients.[2,5,6.] A number of medical, surgical, and endovascular treatment are associated with improved long-term outcomes.[6] However, evidence regarding general management of AIS is scarce; therapeutic strategies are often based on specific locally agreed criteria, and questions remains regarding the optimal ventilatory, hemodynamic and general ICU management.[2,5-7]

We therefore conducted an international survey: "Indication**S** of ICU admission and in**T**ensive ca**R**e management of pat**I**ents with acute ischemic stro**KE**: the STRIKE survey" to assess current criteria for admission to ICU, clinical practice variability, and critical care management of AIS patients. Our hypothesis is that ICU indications and management vary significantly among centers.

Methods

The questionnaire underwent a peer-review process within the European Society of Intensive Care Medicine (ESICM) Research Committee. This international survey was endorsed by the ESICM and promoted by the Neuro-intensive Care (NIC) section of ESICM. The survey was registered with the ESICM Survey portfolio, and no ethics approval was required. The questionnaire was distributed by the ESICM office, thus protecting data confidentiality and anonymity using a specific database.

Study population

The target audience consisted of Neurointensive Care (NIC) section members of the ESICM who had agreed to participate in ESICM surveys at the time of their membership registration, and who manage patients with AIS in their clinical practice. Participants did not receive compensation for their participation in the survey, and response to the survey questionnaire was deemed as implied consent for participation.

Survey development

The survey was developed by three investigators (C.R., G.C. and M.S.), following a narrative review of the literature on the management of stroke in the ICU.[7] An electronic questionnaire including 25 items divided into 3 sections was emailed to the NIC members of the ESICM through the section newsletter, and was available on the ESICM website, accessible only by NIC members (1296 members), between 1st November 2019 and 30th March 2020. Multiple responders from each institution were allowed. Two mass reminders were sent during the study period.

The survey questionnaire is shown in the supplementary material (Supplemental digital content (SDC) 1: Survey questionnaire).

The survey participants were asked to score (on a scale of 0 to 10 according to the priority of their management) responses to different factors aimed to guide specific clinical decisions during AIS patients' management (e.g. ICU admission criteria, neuromonitoring choices, indication for tracheostomy). Single-answer questions were asked about specific area of management, including glycemic control, ventilation, temperature, arterial blood pressure, thrombotic risk, management of dysphagia and speech disturbance. The questions allowed only one single answer, and multiple answers were accepted only for the following questions: Section 2, question 4; Section 3, question 1, 16,17 (SDC 1: Survey questionnaire).

The survey was designed to identify (within 3 sections):

Section 1: Survey participants' demographics, type of hospital/ICU, catchment area population for AIS, number of ICU beds, medical and nurse staffing, and the presence of neurointerventional service or stroke unit.

Section 2: General information and criteria for ICU admission of AIS patients in the respondents' institution.

Section 3: Specific aspects of the ICU management of AIS patients in the respondents' institution.

Statistical analysis

Variables are reported as percentages of the total responses; if a "none" response was allowed in the questionnaire, percentage was calculated using only reported values. Numerical variables are presented as median and interquartile range (IQR), as they were not normally distributed. Results are presented according to micro-macro geographical areas to test our hypothesis. Descriptive analysis was performed using statistical package of "R" software ver. 4.0.2. Level of significance was considered as $p<0.05$.

Results

There were 214 responses from 198 centers and 54 countries around the world, with a response rate of 214/1296 (16,5%) of total registered members of the NIC section. A significant proportion of the respondents (n=73,3%) did not provide complete information, and only partial responses were included in the analysis.

More than one half of the respondents were from European countries (n=130 [61%]); Spain was the country with the highest number of respondents (n=18), followed by India (n=16), United Kingdom (n=15), Italy (n=14) and France (n=12) (SDC 2, Supplementary Table S1: Countries of respondents). The majority of respondents were general intensivists (n=126 [59%]), and 27% (n=57) worked in dedicated neuro-intensive care units. Baseline characteristics of the respondents are summarized in the supplementary material (Table1, and SDC 3, Supplementary figure S1: Geographic areas of respondents). Large variability was observed between centers and countries.

The number of patients with AIS admitted to the hospital in 2019 was between 100 and 300 according to the majority of the responders (n=90;67%); among these, fewer than 50 required ICU admission in most cases (n=64, 35,5%). In half of the centers (n=82; 51,2%) less than 20% of AIS patients underwent intravenous thrombolysis in 2019, while fewer than 10% (n=68; 49,3%) of AIS patient were eligible for mechanical thrombectomy, with large variability among countries (SDC 4, Supplementary Figure S2: Percentage of patients undergoing thrombolysis and mechanical thrombectomy).

The most widely accepted ICU admission criteria were need for intubation and mechanical ventilation (median score on scale 0-10: 10, IQR 9-10), need for systemic organ support (10, IQR 9-10) and management of intracranial complications (10, IQR9-10) (Figure 1). Table 2, and SDC 5 (Supplementary Table S3: General ICU management) summarize the details of key ICU targets and management principles.

A standard protocol for ABP management was utilized by 88 (58%) of respondents. For patients eligible for iv thrombolysis, the most common ABP target was $\leq$ 185/110 mmHg (n=77 [51%]), the same as for those ineligible for this procedure (n=64 [43%]). For patients undergoing mechanical thrombectomy, the most common ABP target was $\leq$ 160/90 mmHg (n=79 [54%]). The preferred drugs for reducing ABP were continuous intravenous administration of labetalol (n=84 [55,6%]) and nicardipine (n=25 [16,6%]) (Table 2).

Blood glucose levels were most frequently monitored every 4 hours (n=61 [40%]), and the most frequently used glycemic target was 140-180 mg/dl (n=65 [43%]) (Figure 2). Glycemic control was achieved by intravenous insulin infusion in most institutions (n=110 [72,4%]). Enteral feeding was started between days 2-3 from stroke onset in 142 (93.4%) respondents' centers (SDC 6, Figure S3: Insulin use and time to start

of enteral feeding). With regard to respiratory management, the most common oxygen saturation (SpO_2) target was > 95% (n=80 [53%]), the most common end tidal carbon dioxide ($EtCO_2$) target was 35-40 mmHg (n=89 [59%]), and the most commonly used tidal volume in mechanically ventilated patients was 6-8 ml/kg of predicted body weight (n=135 [89%])(SDC 7, Supplementary Figure S4: Ventilator targets and management). A target temperature $\leq$ 37,5°C (n=99 [65%]) was preferred in most centers, and the most used treatment for fever was antipyretic drugs (n=129 [85%]).

Thromboembolic prophylaxis was most frequently initiated within 2 days from stroke onset (n=121 [79,6%]); most respondents (n=89 [58,6%]) used intermitted pneumatic devices as the preferred physical method for prophylaxis (SDC 8, Supplementary Figure S5: Thromboprophylaxis). The most common hemoglobin trigger for transfusion was 7-8 mg/dl (n=107 [70,4%])(SDC 9, Figure S6: Transfusion thresholds).
According to most of the respondents (n=126 [78%]), fewer than 10% of AIS patients underwent decompressive craniectomy in 2019 (SDC 10 - Figure S7: Decompressive craniectomy rates).

Clinical observation was considered the most important “neuromonitoring” technique for AIS patients in the ICU (median score 10, IQR 10-10), followed by intermitted electroencephalography (EEG) (median score 5, IQR 3-10) and transcranial Doppler ultrasound (5, IQR1-8) (SDC 11, Figure S8: Neuromonitoring).

Access to speech and language therapists was reported by 82 (54%) respondents; stroke-related dysphagia was mostly assessed clinically (102 [67%]), with a bolus of food (Figure 3). The main indications for tracheostomy in AIS patients in the ICU were poor neurological status (median score 9, IQR 8-10), followed by repeated extubation failures (9, IQR 7-10). Tracheostomy was typically performed after 8 days from the event in most institutions (n=91 [60%])(SDC 12, Figure S9: Timing and indication for tracheostomy).

Discussion

This international survey provides information regarding ICU admission criteria and ICU management of patients with AIS. Our results provide an overview of current clinical practices and their variation across several countries and stroke centers, thus representing the current state of affairs regarding the ICU management of AIS patients, which may be influenced by location (country), local, regional and national guidelines. Although variability between centers might potentially lead to innovation, the development of specific and universal guidelines may assist clinicians in their practice.

This survey reports a high variability among respondents with regard to type of ICU, hospital and number of general vs neuro ICU beds, type of medical staff and management of AIS patients, with consequent different availability of resources, standardization of care at institutional care, performance measures, public reporting of data etc.

Indications for ICU admission

The indications for ICU admission of patients with AIS are variable; this likely depends on several factors, including the level of care that can be provided in the institution's stroke unit, availability of intermediate care units (such as step-up of step-down from ICU) and local preferences.[7-10]

The availability of more aggressive treatments and interventional approaches has led to an increasing number of AIS patients being admitted to the ICU.[11] The literature suggests that common indications for ICU admission include the need for intubation and/or mechanical ventilation due to respiratory failure and/or decreased level of consciousness with loss of airway protection, blood pressure management, systemic organ system support (e.g. for cardiac failure, acute kidney injury) management of cerebral complications (seizures, post-intervention or anticoagulation hemorrhage, malignant infarction or post decompressive craniectomy). [7,12-15] The results of our survey are in line with these previous reports, with the most common indication for ICU admission being a need for airway management or systemic organ support or monitoring and management of intracranial complications that cannot be managed in the stroke units. ICU admission indications are likely related on the level of care provided by stroke units, and number of specialized neurocritical care units; in fact, in some countries, staffing and care of patients in a stroke unit be a satisfactory replacement to the ICU.

As presented in Table 1, the total number of dedicated neurocritical care units according to our responders is low, and the ICUs are small to moderate size. This suggests that ICU admission criteria are stricter and use ICU resource only for the sickest patients, and not for monitoring or routinely after mechanical thrombectomy.

Neuromonitoring

Limited data are available regarding the role of neuromonitoring after AIS. Most patients are not sedated, thus making clinical assessment the most useful monitoring tool in this cohort.

Transcranial Doppler (TCD) ultrasonography is a safe, bedside tool able for the assessment of cerebral blood flow and potentially useful in the detection of acute vessels occlusion and to assess cerebral and vasoreactivity[16,17] TCD and near-infrared spectroscopy allow assessment of autoregulatory indexes that have been reported to identify individualized optimal ABP/ cerebral perfusion pressure targets.[18]

EEG can be useful to detect subclinical seizures which may occur after AIS.[19] Routine ICP monitoring is not recommended after AIS but can be considered in patients with large infarct areas or hemorrhagic complications and significant midline shift.[20] Finally, evidence on the utility of brain tissue oxygen tension (PtiO2) and pupillometry are lacking and are currently not routinely used.

As no neuromonitoring technique can be considered the gold standard, and has limitations, a multimodal approach- according to availability of resources, standardization of care at institutional care- is warranted.

Ventilation

Patients with AIS often require intubation and mechanical ventilation because of airway or respiratory compromise or pharyngeal dysfunction, [6,21-25] Hypoxemia should be avoided to minimize secondary brain damage,[26] but a randomized controlled trial found no benefit on 90-days functional outcome of oxygen administration with SpO2 >93% versus ≤93%;[27] the most recent guidelines suggest maintenance of SpO2 >94% and avoidance of supplemental oxygen in non-hypoxemic patients[6]. No specific recommendations are available regarding PaCO2 targets and ventilator management, but the use of protective ventilation strategies, including low tidal volume (while maintaining normocapnia) and positive end expiratory pressure titrated to optimize systemic oxygenation while avoiding hemodynamic instability and alveolar overdistension have been suggested.[21]

Similarly, the indications for performing a tracheostomy in AIS patients include both respiratory (more than one extubation failure) and neurological (impaired brainstem reflexes or level of consciousness) factors. No specific guidelines are available regarding the optimal time for performing a tracheostomy after AIS, but recent evidence in traumatic brain injured patients suggest that early tracheostomy might be associated with reduced ICU length of stay.[28,29] In contrast, the results from our survey suggest that late tracheostomy (>8 days) is favored, although with large variability among centers, possibly because of the potential risk of intracranial instability in the early phases. This suggests that the decision to perform a tracheostomy is mostly driven by local policies and resources.

Blood pressure

Patients with AIS often present with systemic hypertension. Strict management of ABP is mandatory in order to reduce the risks of hypertension (hemorrhagic complications, cerebral edema, cardiovascular complications), while avoiding hypoperfusion and the risk of inadequate blood flow to the ischemic penumbra.[7,30,31] Hypertension is also associated with several complications after endovascular treatment.[32] Guidelines recommend that patients with elevated blood pressure who are eligible for endovascular treatment with alteplase should have ABP reduced <185/110 mm Hg before intravenous (iv) fibrinolytic therapy is initiated.[6] There is no clear evidence to guide ABP targets in the post procedural phase or in cases of mechanical thrombectomy, but most of the responders suggested an ABP target of 160/90. In the absence of specific recommendations, according to our responder, labetalol is the first drug of choice for blood pressure control, followed by nicardipine.

Glucose/insulin/nutrition

Strict monitoring of blood glucose is mandatory in AIS patients, as both hypo and hyperglycemia are associated with adverse outcomes, particularly in relation to the potential effect of glycemic derangements and cerebral blood flow.[33] A blood glucose concentration of 140-180 mg/dL is the most used target worldwide, as recommended by the latest guidelines.[6] However, optimal glycemic management after AIS remain controversial. The recent Stroke Hyperglycemia Insulin Network Effort (SHINE) study[34] demonstrated that intensive glucose control (80–130 mg/dL) with insulin infusion has no beneficial effect on 90-day functional outcomes when compared with standard control (< 180 mg/dL) with intermittent subcutaneous insulin. As consequence, different strategies for glucose control are being used worldwide (including continuous glucose monitors), with large variability among centers and countries. Regardless of the strategy used, frequent checks of glucose values (every 4 hours) to reduce the risk of hypoglycemia are warranted.

Enteral feeding started within 7 days from admission has a favorable effect on outcome, with a reduction of 5.8% in mortality after AIS.[35] Specifically, most clinicians prefer very early initiation of enteral feeding (within 2-3 days), with the early insertion of a nasogastric tube in case of dysphagia.

Temperature control

Fever is common after AIS, with temperature > 37.5 °C occurring in up to 25% of patients in the first 6 hours after stroke onset and in about 30% in the first 24 h.[2,7] Fever may have an infective or neurogenic origin, and is associated with poor outcome.[36] However, whether targeted temperature management (TTM) policies improve outcome has not been investigated. Further, no clear evidence is available

regarding the threshold of temperature for TTM after AIS; a recent consensus in brain injured patients suggested starting TTM when temperature is >37.5 degrees, which is consistent with the results from our survey.[37] Antipyretic drugs are first-line therapy for fever after AIS, although treatment with paracetamol seems not to be effective.[38] Secondary interventions include external and intravascular cooling methods. Type and timing of temperature management are strongly influenced by local policies and resources.

Other issues

According to our survey, a hemoglobin concentration of 7-8 mg/dL is generally accepted as the trigger for red cell transfusion of to optimize cerebral oxygen delivery and minimizing the adverse effects of transfusion.

Venous thromboembolism (VTE) is very common after AIS (10-75%) and is potentially a life-threatening complication.[39] VTE prophylaxis should always be considered when and initiated when the potential benefits outweigh bleeding risks.[6] The use of intermittent pneumatic compression in stroke patients without contraindications is strongly recommended. The Clots in Legs Or sTockings after Stroke (CLOTS)3 trial found that, compared to routine care, intermittent pneumatic compression can significantly reduce the incidence of deep-vein thrombosis and improve outcomes.[40] Our survey revealed that low molecular weight heparin is generally started within 1-2 days from stroke, and intermittent pneumatic compression is the preferred option for deep venous thrombosis prophylaxis.

Finally, dysphagia occurs in 23–50% of AIS patients and increases the risks of aspiration pneumonia, affecting morbidity and mortality.[7] Recent guidelines suggest an early nurse-led swallow assessment followed by fibreoptic evaluation in those at risk for aspiration.[6] In our survey, we found that clinical evaluation is the preferred method for dysphagia assessment, with very low use of fiberoscopy, vidoefluoroscopy or clinical scores, but also with large variability between centers.

Limitations

There are several limitations to this study. First, the number of respondents is relatively small, making it difficult to generalize the findings of the study. The low response rate may be due to the fact that the survey was started just before the first peak of the first Covid-19. However, the response rate is similar to a previously published survey from the ESICM.[41] Unfortunately, the response rate cannot be precisely calculated as NIC-ESICM members were invited to forward the invitation to relevant colleagues, thus making it impossible to obtain the total number of people who received the survey. Second, this survey was developed after conducting a narrative review of the literature rather than a systematic review. Third, this survey was not previously validated, and the impact of the results is therefore reduced; pilot testing of the questionnaire was not conducted in a smaller sample of participants prior to the survey. Furthermore, important information is missing, including the presence of triage mechanisms or institutional ICU

admissions policies among countries, details regarding the type treatment and location of ischemic strokes, data on hemorrhagic transformation, and post stroke vascular reserve or collateralization. Moreover, the processes and clinical practices that identified by this survey are those before the start of the COVID-19 pandemic and some treatment pathways and management policies may be different now. Finally, this survey only describes the perception of the clinical practice according to the respondents, without inclusion of patient data, and more than one responder per center was allowed to answer, thus making the results less generalizable.

Conclusions

This international survey identified important institutional differences in the ICU management of AIS patients, and many questions about optimal management remain. The survey highlights specific areas with large practice variability among centers, and those areas with clinical equipoise with regard to the management of critically ill AIS patients. Individualized arterial blood pressure management, protective ventilation strategies and hemoglobin targets are areas that have been increasingly developed over the last years. The findings of this survey might be useful to inform the design of future randomized clinical studies and comparative effectiveness research, as well as more specific recommendations/guidelines on this topic.

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Figures

Figure 1

Indications for ICU admission

Values are presented as median value and interquartile range. Circles represent outlier values.

Stroke severity; according to clinical and radiological characteristics; phys*, physiological*

ABP, arterial blood pressure; ICU, intensive care unit; MCA, middle cerebral artery

Figure 2

Glucose targets in acute stroke patients the intensive care unit

Figure 3

Methods to assess dysphagia in the ICU in acute ischemic stroke patients

ICU, intensive care unit

SUPPLEMENTARY MATERIAL

Supplemental digital content 1

Survey Questionnaire

SDC 1.pdf

Supplemental digital content 2

Table S1: Countries of respondents

SDC 2. pdf

Supplemental digital content 3

Figure S1: Geographic areas of the responders

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Figure S2: Thrombolysis and mechanical thrombectomy. The zero level corresponds to the threshold of “10%” of patients undergoing mechanical thrombectomy. The values below 0 both include the ‘<10%’ and ‘unknown’ responses, to differentiate small hospitals from first level referral hospitals.

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Table S3: General ICU Management

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Supplemental digital content 6

Figure S3: Insulin use and timing for start of enteral feeding SDC 6. pdf

Supplemental digital content 7

Figure S4: Ventilator targets and management

SDC 7. pdf

Supplemental digital content 8

Figure S5: Thromboembolic prophylaxis

SDC 8. pdf

Supplemental digital content 9

Figure S6: Hemoglobin threshold for transfusions
SDC 9. pdf

Supplemental digital content 10

Figure S7: Decompressive craniectomy in acute ischemic stroke

SDC 10. pdf

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Figure S8: Type of neuromonitoring. Values are presented as median value and interquartile range.

Circles represent outlier values.

SDC 11. pdf

Supplemental digital content 12

Figure S9: Indications and timing for tracheostomy

SDC 12. pdf

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Table 1. Arterial blood pressure (ABP) Management (reported as absolute values, % on total answers and % on answers with perceived values)

Table 1.			
ABP target in patients eligible for iv thrombolysis			
	n	TOT=214	TOT=151
<185/110	77	36%	51%
<160/90	60	28%	39,7%
Reduction of 15% *	11	5,1%	7,3%
Other	3	1,4%	2%
Not Answered	63	29,4%	
ABP target in patients not eligible for iv thrombolysis			
	n	TOT=214	TOT=149
<185/110	64	29,9%	43%
<160/90	38	17,8%	25,5%
<220/120	14	6,5%	9,4%
Reduction of 15% *	29	13,6%	19,5%
Other	4	1,9%	2,7%
Not Answered	65	30,4%	
ABP target in patients after mechanical thrombectomy			
	n	TOT=214	TOT=147
<185/110	40	18,7%	27,2%
<160/90	79	36,9%	53,7%
Reduction of 15% *	23	10,7%	15,6%
Other	5	2,3%	3,4%
Not Answered	67	31,3%	
Preferred Drugs for reducing ABP			
	n	TOT=214	TOT=151
Labetalol	84	39,2%	55,6%
Nicardipine	25	11,7%	16,6%
Clevepine	3	1,4%	2%
Enalapril	9	4,2%	6%
Hydralazine	6	2,8%	4%
Other	24	11,2%	15,9%
Urapidil	16	7,5%	10,6%
Nifedipine	2	0,9%	1,3%
Nitroprusside	3	1,4%	2%
Captopril	1	0,5%	0,7%
Amlodipine	1	0,5%	0,7%
Azamethonium	1	0,5%	0,7%
Not Answered	63	29,4%	

* of the initial arterial blood pressure