Analysis Plan

Study title:

Safe and sustainable balanced anaesthesia – identifying potentials in daily clinical routine (SAFE-SUSTAIN)

Version:

V1.0 based on protocol version V1.5 06.05.2024

Protocol version:

V1.5 06.05.2024

Software

R version 4.4.1 (2024-06-14) -- "Race for Your Life" or later

Platform: x86_64-w64-mingw32/x64 (64-bit)

Packages used: ggplot2 version 3.3.6. or higher

Database

Microsoft Excel 2016

Study design

Prospective, multi-centre observational study. (See Protocol section 4.1.)

Study objectives

1. to determine sevoflurane consumption during anaesthesia induction and to identify modifiable factors of influence.

2. to investigate the safety of applied FGF settings by assessing narcotic depth and hemodynamic stability.

3. to compare different ways of sevoflurane consumption measurements (vaporizer weight as gold standard vs. sevoflurane consumption displayed by Draeger® anaesthesia machine vs. sevoflurane consumption calculated by a widely-used formula vs. sevoflurane consumption calculated by the simulation software GasMan®).

4. to compare the gathered real-world data to a simulated anaesthesia induction (software GasMan®) with optimized FGF and vaporizer settings in order to develop a safe low flow algorithm with minimized sevoflurane consumption and maintained narcotic depth.

The current document describes the analysis plan for the first two objectives.

Primary endpoint

Sevoflurane consumption in ml during induction measured as cumulative amount in the first 7 minutes after opening of vaporizer. It is measured as the difference in the vaporizer weight before and after use.

Secondary endpoints

The following are secondary outcomes of interest:

- Sevoflurane consumption in ml during maintenance (cumulative amount after induction)
- Ventilation settings:
    - Fresh gas flow (FGF) (amount in l/min and duration)
    - Sevoflurane vaporizer setting (%)
    - Fraction of inspiratory oxygen (FiO2)
- End-tidal sevoflurane concentration
- Age-related minimal alveolar concentration (shown as xMAC in Dräger menu or calculated using the following equation: xMAC = MAC40 * 10 ^ (-0.00269 * (age - 40)) [1])
- Ventilation complications
    - Laryngospasm, bronchospasm
- Neuromonitoring (PSI, Narcotrend Index or BIS)
- Need for additional propofol bolus
- Hemodynamic stability:
    - episode and time of mean arterial blood pressure (MAP) < 65mmHg
    - need for vasopressors
    - episode and time of bradycardia (defined as <45 bpm)
    - episode and time of tachycardia (defined as >100 bpm)

Study Flow

See Protocol section 4.7

Study Population

The full analysis set includes all cases from whom any of the outcome data has been recorded. Analyses of outcome data and patient characteristics will be performed on this set.

Target variables

Data type and unit of recorded variables are tabulated in table 1 and table 2.

Variable(s) code	Description	Data type	Unit	Response set
Patienten-ID	Patient identifier	nominal		character
Zentrumsnummer	Site identifier	nominal		1; 2; 3
Surgery-Specialty_neu	Surgical specialty	nominal		General; Gynaecology; Neurosurgery; Orthopaedic; Trauma; Urology; Other
Classification_neu	Surgical classification following “the Johns Hopkins Medical Institutions”	nominal		I; II; III; IV; V
Approach_neu	Surgical approach	nominal		DaVinci; Laparoscopic
Sex_neu	Patient´s sex	nominal		female; male

ASA_Score_neu	American Society of Anesthesiologists score	nominal		I; II
Age_neu	Patient´s age	ratio	years	positive integer
Height [cm]_neu	Patient´s height	ratio	cm	positive integer
Weight [kg]_neu	Patient´s weight	ratio	kg	positive integer
BMI_neu	Body mass index	ratio	kg/m2	positive real
MAC: 0min_neu through MAC: 7min_neu	xMAC values from 0 min to 7 min	ratio	%	positive real
BPM: before_neu and BPM: 0min_neu through BPM: 7min_neu	Beats per minute	ratio	per minutes	positive integer
MAP: before_neu and MAP: 0min_neu through MAP: 7min_neu	Median arterial pressure	ratio	mmHg	positive integer
Propofol?_neu	Additional propofol within first 7 minutes	nominal		ja
Total [mg]_neu	Propofol dose within first 7 minutes	ratio	mg	positive integer
BIS-Index: 7min_neu	BIS Index at 7 min	ratio		positive integer
Narcotrend: 7min_neu	Narcotrend Index at 7 min	ratio		positive integer
PSI: 7min_neu	PSI Index at 7 min	ratio		positive integer
Tubes_neu	Breathing circuit	nominal		Dahlhausen; Intersurgical; VentStar 1.8m; VentStar 2.8m
Substance_neu...34	Opioid	nominal		Sufentanil; Remifentanyl
Dose [µg]_neu	Opioid dose	ratio	µg	positive real
Substance_neu...50	Opioid – perfusor	nominal		Remifentanyl
Perfusor_Total [µg]_neu...54	Opioid dose	ratio	µg	positive real
Substance_neu...106	Opioid – pre intubation	nominal		Sufentanil
Dose [µg]_neu...110	Opioid dose	ratio	µg	positive real
Substance_neu...222	Opioid – pre-vapor-opening	nominal		Sufentanil; Remifentanyl
Dose [µg]_neu...226	Opioid dose	ratio	µg	positive real
Substance_neu...238	Opioid – pre-vapor-opening in perfusor	nominal		Remifentanyl

Perfusor_Total [µg]_neu...242	Opioid dose	ratio	µg	positive real
Substance_neu...62	Hypnotic	nominal		Propofol
Dose [mg]_neu...66	Hypnotic dose	ratio	mg	positive integer
Substance1_neu	Hypnotic – pre intubation	nominal		Propofol
Dose1 [mg]_neu	Hypnotic dose	ratio	mg	positive integer
Substance_neu...202	Hypnotic – pre-vapor-opening	nominal		Propofol
Dose [mg]_neu...206	Hypnotic dose	ratio	mg	positive integer
vasopressor prä-intubation?_neu	Vasopressor pre intubation	nominal		ja
vasopressor prä-Vapor-Opening?_neu	Vasopressor pre-vapor-opening	nominal		ja
Vapor 1 Opening-Time_neu	Time at vaporizer 1 opening	Time	h:m:s	0-23:0-59:0-59
Vaporswitch-Time_neu	Time at vaporizer switch	Time	h:m:s	0-23:0-59:0-59
Vapor 2 Closing-Time_neu	Time at vaporizer 2 closing	Time	h:m:s	0-23:0-59:0-59
Duration Intubation-Extubation [h:mm:ss]_neu	Time from intubation to extubation	Time	h:m:s	0-23:0-59:0-59
Bolus_Total [µg]_neu	Opioid dose in first 7 minutes	ratio	µg	positive real
Bolus?_neu	Opioid - bolus in first 7 minutes	nominal		ja
Perfusor_Total [µg]_neu	Opioid dose in first 7 minutes	ratio	µg	positive real
Perfusor?_neu	Opioid –perfusor in first 7 minutes	nominal		ja
Substance_neu	Vasopressor –perfusor within first 7 minutes	nominal		Noradrenalin
Perfusor_Total [µg]_neu	Vasopressor dose - perfusor within first 7 minutes	ratio	µg	positive real
Substance1_neu	Vasopressor – bolus within first 7 minutes	nominal		Akrinor; Noradrenalin
Bolus1_Total [µg]_neu	Vasopressor dose – bolus within first 7 minutes	ratio	µg	positive real
Substance2_neu	Vasopressor – bolus within first 7 minutes	nominal		Akrinor
Bolus2_Total [µg]_neu	Vasopressor dose – bolus within first 7 minutes	ratio	µg	positive real

Sev_Weight_Induction [ml]_neu	Sevoflurane consumption during induction based on vaporizer weight	ratio	ml	positive real
Sev_Weight_Maintenance [ml]_neu	Sevoflurane consumption during maintenance based on vaporizer weight	ratio	ml	positive real

Table 1: Data types of data recorded in CRF. (Data type indicates expected data type)

Variable	Description	Data type	Unit	Response set
Time	Time of setting or measurement	Time	h:m:s	0-23:0-59:0-59
Date/Time	Date and time of setting or measurement	Date/time	YYYY-mm-dd h:m:s	[0000-9999]-[01-12]-[01-31] 0-23:0-59:0-59
Label	Type of recorded data	nominal		Vaporizer setting; FG flow
Current value	Vaporizer setting or FG value	ratio	L/min or %	non-negative real
FiO2	Fraction of inspiratory oxygen	ratio	%	positive integer
etSev	Endtidal sevoflurane concentration	ratio	%	non-negative real

Table 2: Data type of data recorded by and exported from the anaesthetic machine (files *1-002_Excel.xlsx* through *3-096_Excel.xlsx).* (Data type indicates expected data type)

Data handling

Data will be merged into a one-row per patient table.

Data validation

All patient records will be double-checked by trained study staff for data entry errors.

Data transformations

The following derived variables will be created using syntax in file `clean.R`.

Vasopressor_ja_nein = Substance_neu!="n.a" | Substance1_neu!="n.a" | Substance2_neu!="n.a"

Remifentanyl = Dose [µg]_neu + Perfusor_Total [µg]_neu...54 + Perfusor_Total [µg]_neu...242 if Substance_neu...34 == “Remifentanyl” , Substance_neu...50 == “Remifentanyl”, Substance_neu...238 == “Remifentanyl”

Sufentanil = Dose [µg]_neu + Dose [µg]_neu...110 if Substance_neu...34 == “Sufentanil” , Substance_neu...106 == „Sufentanil“

Remifentanyl_yes = TRUE if Substance_neu...34==”Remifentanyl” | Substance_neu...50==”Remifentanyl” | Substance_neu...106==”Remifentanyl” | Substance_neu...222==”Remifentanyl” | Substance_neu...238==”Remifentanyl”

Sufentanil_yes = TRUE if Substance_neu...34==”Sufentanil” | Substance_neu...50==”Sufentanil” | Substance_neu...106==”Sufentanil” | Substance_neu...222==”Sufentanil” | Substance_neu...238==”Sufentanil”

Propofol_mg = Dose [mg]_neu...66 + Dose1 [mg]_neu + Dose [mg]_neu...206

Propofol_total = Propofol_mg + Total [mg]_neu

Remifentanyl_total = Remifentanyl + Perfusor_Total [µg]_neu

Sufentanil_total = Sufentanyl + Bolus_Total [µg]_neu

Mean vaporizer setting for each patient will be calculated and stored in variable *vapor_mean* from the *current_value* for *label*=”Vaporizer setting” using syntax in file `Transform_vapor_setting.R`.

Mean FGF for each patient will be calculated and stored in variable *meanFGF* from *current_value* for *label*=”FG flow” using syntax in file `Tranform_FG_flow.R`.

Mean FiO2 and mean etSev for each patient will be calculated and stored in variables *meanFiO2* and *meanetSev* using syntax in file `Transform_FiO2_etSev.R`.

Descriptive Statistics

Descriptive statistics of continuous characteristics will be tabulated using number of observations, mean, standard deviation, minimum, maximum, and quartiles. Categorical variables will be described using number of observations and frequencies. Variables will also be tabulated by centers. Other visualization methods will also be considered.

Sevoflurane consumption during induction

Descriptive statistics of the primary endpoint sevoflurane consumption will be performed by age, weight, mean MAP, mean MAC, mean FGF, total propofol, and mean vaporizer setting. For graphical presentation scatter plots or similar graphical techniques will be used.

Secondary outcome variables

All secondary outcome variables will be analysed using descriptive methods as described in section Descriptive Statistics.

Models

Linear regression models will be used to model sevoflurane consumption during induction. The following variables will be considered in univariable and multivariable models: centre (categorical), weight (continuous), age (continuous), propofol (continuous), mean MAP in first 7 minutes (continuous), vasopressor use during induction (categorical; yes/no), mean MAC in first 7 minutes (continuous), mean FGF in first 7 minutes (continuous), mean vaporizer setting in first 7 minutes (continuous), volume of breathing circuit (categorical), dosage of remifentanil (continuous), and dosage of sufentanil (continuous). Predictor levels occurring less than 1% in the dataset will not be

used. In multivariable models we will include interactions between centre and remifentanil and sufentanil dosage.

The model assumptions and model fit will be checked using graphical methods and the multivariable model will be adapted using transformation of variables, including non-linear terms and using generalized linear models.

Missing data

Frequency of missing data will be tabulated.

Other analyses

Analyses of other predefined secondary endpoints, such as economic efficiency, sustainability, and comparison of different sevoflurane consumption measurements as well as comparison of real-world data to simulated anaesthesia induction are described elsewhere.

Future analyses

Additional analyses of the collected data may be planned in the future. All analyses planned and carried out after finalizing data collection will be distinguished from the pre-planned analyses.

Literature

1. Nickalls R W, Mapleson W W. Age-related iso-MAC charts for isoflurane, sevoflurane and desflurane in man. *Br J Anaesth* 2003; **91**: 170-174.