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Universitätsklinik für Anästhesiologie und Schmerztherapie
Direktor und Chefarzt
Prof. Dr. med. F. Stüber

Co-administration of dexmedetomidine in carotid endarterectomy (CEA) with intraoperative SSEP and MEP monitoring: A single-centre prospective randomised controlled trial

Clinical Study Protocol

SHORT TITLE: Dexdor Study, 2018-00220

Study Type:	Clinical trial with drugs
Study Categorisation:	Risk category A
Study Registration:	Clinical trials.org
Study Identifier:	Vetter2017
Sponsor-Investigator:	Christian Vetter
Principal Investigator:	Christian Vetter christian.vetter@insel.ch
Investigational Product:	Dexmedetomidine
Protocol Version and Date:	V4.20, 9.08.2018

Signature Page(s)

Study number	Study registry and registration number (at clinicaltrials.gov)
Study Title	Co-administration of dexmedetomidine in carotid endarterectomy (CEA) with intraoperative SSEP and MEP monitoring. A single-centre prospective randomized controlled trial.

The Sponsor-Investigator and trial statistician have approved protocol version 4.20, 09.08.2018, and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm if applicable and the local legally applicable requirements.

Sponsor: Dr. med. Christian Vetter

Bern, 09th August 2018 _____

Place/Date Signature

Principal Investigator
I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

Principal investigator: Dr. med. Christian Vetter

Bern, 09th August 2018 _____

Place/Date Signature

Study Investigator: PD Dr. med. Vladimir Krejci

Bern, 15th January 2018 _____

Place/Date Signature

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STUDY SYNOPSIS

Sponsor-Investigator	Dr. med. Christian Vetter, Dept. of Anaesthesia and Pain Medicine, Inselspital Bern University Hospital, University of Bern, Bern, Switzerland
Study Title:	Co-administration of dexmedetomidine in carotid endarterectomy (CEA) with intraoperative SSEP and MEP monitoring. A single-centre prospective randomised controlled trial.
Short Title / Study ID:	Dexdor
Protocol Version and Date:	Version 4.20 of 09.08.2018
Trial registration:	Anticipated registry: www.clinicaltrials.gov
Study category and Rationale	Clinical trial with drugs. Risk category A. Interventional RCT comparing the effective concentration (Cet) of propofol required for EEG burst suppression and maintenance thereof by the co-administration of dexmedetomidine
Clinical Phase:	4
Background and Rationale:	In our institution, as a neuroprotective measure, all neurosurgical patients undergoing operation for carotid endarterectomy (CEA) are routinely operated on under deep anaesthesia with suppression of the electrical activity of the electroencephalogram (EEG). The rationale for BS is to decrease oxygen consumption. To achieve this suppression of the EEG activity (burst suppression, BS), high effector concentrations (Cet) of propofol doses are needed. However, a protracted infusion of large amounts of propofol to reach a BS during the operation can lead to accumulation and a protracted wake-up phase with poorer neurological assessability. Somatosensitive evoked potentials (SSEPs) are used to test the functional integrity of the nervous system. Standardised surgical and anaesthesiological measures at the CEA, with defined EEG endpoints and depending on the anaesthetic effect, can – in normal EEG and SSEPs – effectively exclude severe global ischaemia. The effects of burst suppression and the volatile anaesthetics on SSEPs have also been investigated and showed no significant difference. Since 2016, motor-induced evoked potentials (MEPs) have also been used, but they may be suppressed even by low dose of volatile anaesthetics. On the other hand, dexmedetomidine in combination with propofol seems to suppress only insignificantly the MEPs[10)]. Somatosensory evoked potentials (SSEP) and trans-cranial Doppler (TCD) flow velocity in the middle cerebral artery are measured to detect ischaemia. A significant decrease in TCD velocity and/or SSEP amplitudes during cross-clamping of the internal carotid artery (ICA) is treated with an adapted Median nerve somatosensory evoked potentials (SEPs) were performed by stimulation at the wrist with a pair of needle electrodes (Inomed Germany®).

This is a single pulse stimulation with 0.5 ms pulse duration and a low repetition rate ranging from 0.7 - 2.3 Hz. Recording is performed via corkscrew electrodes placed according to the 10-20-EEG system on the patient's scalp. SEP C3´/Fz is chosen as standard derivation for the right median nerve and SEP C4´/Fz is chosen for the left median nerve. Alternatively, Cz' or the contralateral Cp' served as a reference to improve quality of recording. To improve the signal-to-noise ratio the responses are averaged 150-200 times. Latencies and amplitudes as shown in Figure 1 are measured and recorded in the protocol at the defined critical events[7)].

Figure 1:

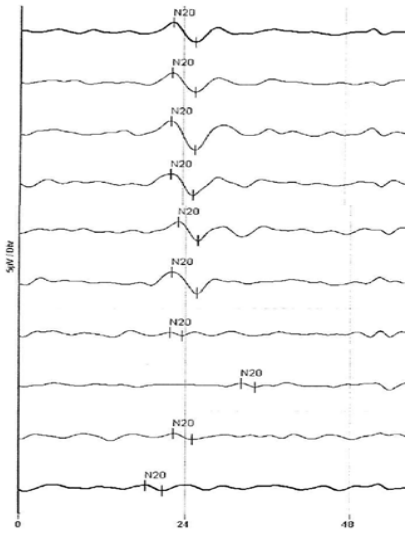


Figure 1: Illustration of SEP latencies and amplitudes recorded from the corkscrew electrodes on the patient's head after averaging. Ten consecutive recordings are presented. In this example the SEP amplitude changed drastically between line 6 and 7, with a complete loss of the signal at time of ICA clamping (from Dr. med. K. Seidel, Dept. of Neurosurgery, Inselspital Bern).

The indication spectrum for the centrally acting α_2-agonist dexmedetomidine has been increasingly expanded since its approval in Switzerland. In addition to its use in intensive care units, dexmedetomidine is also increasingly being used perioperatively up to premedication in children. In some studies, an anaesthetic reduction of 40%–60% could be achieved or the opioid consumption after the addition of an α_2-agonist could be reduced by 50%–75%[11)]. The blood pressure response to a dexmedetomidine dose depends on the rate of infusion[4)]. In addition, administration of dexmedetomidine does not result in respiratory depression or compromise of the respiratory tract. It has been shown that dexmedetomidine can cause a "sleep-like" sedation state, and this state can be interrupted by verbal stimuli[2)]. Huupponen et al. 2008[3)] examined the EEG activity in sedated volunteers compared to a control group with physiological sleep patterns. In this study, it was shown that the EEG spindle activity in subjects with dexmedetomidine infusion was comparable to that of a physiological non-

	rapid eye-movement (nonREM) sleep stage II in the control tests. The authors concluded from their investigations that a "sleep-like state" (stage II non-REM) can be achieved by the Dexmedetomidine infusion. However, no data currently exist for practical use in carotid endarterectomy with propofol and dexmedetomidine in conjunction with electrophysiological studies (somatosensory evoked potentials (SSEP) and motor evoked potentials (MEP)). In addition, there is a high risk of postoperative delirium (POD) in many of these patients undergoing CEA. This was examined in a recently published Lancet study by Xian Su and colleagues in 700 elderly patients with non-cardiac interventions[8]. A reduction of the delirium incidence from 23% to 9% was found after a low-dose dexmedetomidine dose of 0.1 µg/kg body weight/h. In addition, a neuroprotective effect against ischemic and hypoxic influences is attributed to dexmedetomidine[5]. Other experimental studies in animals have indicated neuroprotection in ischemic insult and subsequent reperfusion[6].
Objective(s):	Primary study objectives are to evaluate the maximum dose of propofol leading to the attainment of EEG burst suppression (measured and interpreted by the anaesthesiologist) for the co-administration of dexmedetomidine in combination with propofol compared to propofol alone as the standard therapy. The secondary study objectives are the intraoperative propofol requirement and consumption per unit of time, duration from the end of surgery to reaching the extubation criteria (extubation), intraoperative electrophysiological parameters (latency and amplitude of evoked potentials, measured and interpreted by the neurosurgery team), intraoperative haemodynamic parameters, vasoactive substances, and fluid management. We will also measure vigilance (Glasgow Coma Scale = GCS, Richmond Agitation Sedation Scale = RASS) before beginning of anaesthesia and directly before the patient is transferred to the intensive care unit and the development of delirium (CAM-ICU) and muscle force measured in the extremities as described by Janda (M0-M5) in the first 24 hours after the end of the operation in the intensive care unit (ICU). Further measurements will include: perioperative urinary output; patients' use of painkillers; the need for rescue analgesics; and postoperative nausea and vomiting (PONV).
Outcome(s):	The primary study outcome is to determine whether the intervention reduces the effect size concentration of propofol. Secondary endpoints are the intraoperative propofol requirement or consumption per unit of time, duration from the end of surgery to extubation (measured by extubation criteria), intraoperative electrophysiological parameters (latency and amplitude of evoked potentials), intraoperative haemodynamic parameters, vasoactive substances, and fluid management. We will also measure vigilance (Glasgow Coma Scale = GCS, Richmond Agitation Sedation Scale = RASS), criteria for the development of delirium (CAM-ICU) and muscle force of the extremities as described by Janda (M0-

	M5) in the intensive care unit (ICU) in the first 24 hours after the end of the operation at. Furthermore, we will examine the perioperative urinary output in these patients during the operation and during their stay in the intensive care unit. Additionally, we want to examine the patients' use of painkillers and the need for rescue analgesics as well as the postoperative nausea and vomiting (PONV) direct after the patient has been extubated and once during the stay in the intensive care unit.
Study design:	Randomised controlled prospective trial in two groups. Group 1 will receive anaesthesia with propofol and co-administration of dexmedetomidine in conjunction with electrophysiological studies measuring somatosensory evoked potentials (SSEPs) and motor evoked potentials (MEPs). Group 2 will receive standard anaesthesia with propofol alone, in conjunction with electrophysiological studies measuring SSEPs and MEPs.
Inclusion / Exclusion criteria:	We will include patients undergoing surgery of carotid endarterectomy requiring general anaesthesia at the Inselspital, Bern University Hospital, University of Bern, Department of Neurosurgery. Inclusion criteria are: age ≥18 years, ASA physical status 1-4, and written informed consent provided. Exclusion criteria are: Age <18 years, higher grade atrioventricular block without pacemaker, severe hypovolaemia or bradycardia, uncontrolled hyper or hypotension, hypersensibility concerning the active substance dexmedetomidine or any other component, serve liver disease, known malignant hyperthermia, cardiovascular instability or severe heart failure (> NYHA III), limited peripheral autonomic activity, pregnancy, rejection or lack of consent of the patient or their relatives.

Measurements and procedures:	The study participants must be undergoing carotid endarterectomy (CEA) of the internal carotid artery (ICA). All patients will receive anaesthetic care according to the standard operation procedure of the institution. This includes preoperative assessment by an anaesthesiologist (premedication) before surgery, the NIHSS (National Institutes of Health Stroke Scale) Score and obtainment of written informed consent. The patients will not receive any sedatives before surgery as premedication. On arrival in the operating room, patients are monitored and recorded according to the clinical standards. An intravenous catheter is inserted in a peripheral vein and a catheter in the radial artery for continuous blood pressure monitoring and for analysis of arterial blood gases. Either the Bispectral Index (BIS) or Narcotrend® will be used to measure the frontal EEG (brain activity) before and during the anaesthesia procedure. The results are measured and interpreted by by the treating anesthesiologist. The effects of propofol will be detected with EEG burst suppression. The study participants are divided into two groups: Group 1 starts with a bolus of dexmedetomidine 0.4 µg/kg over 10 minutes, followed by continuous infusion of dexmedetomidine 0.4 µg/kg/h until the end of burst suppression. Group 2 receives the standard anaesthesia management. Patients are intubated and ventilated. Inspiratory and end-tidal concentrations of oxygen and carbon dioxide are measured. All patients receive intravenous propofol as a target-controlled infusion for induction and maintenance of general anaesthesia. Remifentanil is given as a continuous intravenous infusion and additional boli of fentanyl are administered as needed. Neuromuscular blocking agents are given to facilitate endotracheal intubation. The effect-site concentration of propofol (Cet) is set based on the clinical evaluation and the processed EEG (target BIS of 40-60, Narcotrend®, Narcotrend-Gruppe Hannover, Germany, corresponding 25-65). The data and curves will be analysed and interpreted by the attending anaesthesiologist. Before cross-clamping of the internal carotid artery, the effect-site concentration of propofol is gradually increased until a burst suppression pattern is established in the frontal EEG (max. 1 burst every 10 seconds, which is approximately 70% of isoelectric EEG). After reperfusion of the internal carotid artery, Cet of propofol is decreased and guided by clinical appreciation and EEG. At the end of burst suppression, dexmedetomidine is discontinued. Somatosensory evoked potentials (SSEP) and Doppler flow velocity in the middle cerebral artery are measured and interpreted by the neurosurgeon team to detect ischaemia. A significant decrease in Doppler velocity and/or SSEP amplitudes during cross-clamping of the internal carotid artery (ICA) is treated with an adapted increase of arterial blood pressure or placement of a shunt. Every patient undergoing CEA median nerve SEPs and MCA flow velocity is constantly monitored by an additional technician who has been trained and certified in the assessment of intraoperative monitoring. The median nerve SEP amplitudes are recorded at least at these time points: baseline value before skin incision, EEG burst suppression before cross clamping of the internal carotid artery, at the time of ICA cross clamping, 10 minutes after cross clamping or immediately after placement of a shunt (ICA clamping 2), on reperfusion of ICA, and when haemostasis is reached (end

of surgery). The predefined criterion for temporary shunting is the reduction of more than 50% of the SEP amplitude.
Median nerve somatosensory evoked potentials (SEPs) were performed by stimulation at the wrist with a pair of needle electrodes (Inomed® Germany). This is a single pulse stimulation with 0.5 ms pulse duration and a low repetition rate ranging from 0.7 -2.3 Hz. Recording is performed via corkscrew electrodes placed according to the 10-20-EEG system on the patient's scalp. For the right median nerve SEP C3´/Fz and for the left median nerve SEP C4´/Fz is chosen as standard derivation. Alternatively, Cz' or the contralateral Cp' served as reference to improve quality of recording. To improve the signal-to-noise ratio the responses are averaged 150–200 times. Latencies and amplitudes as shown in Figure 1 are measured and recorded in the protocol at the defined critical events[7)].

Figure 1:

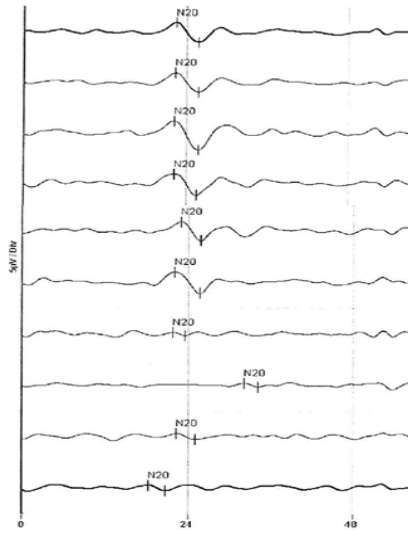
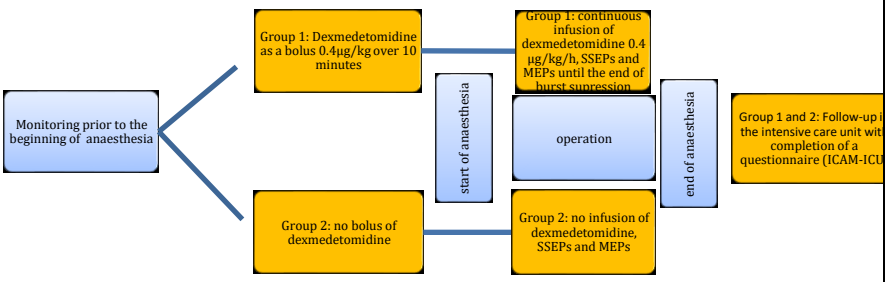


Figure 1: Illustration of SEP latencies and amplitudes recorded from the corkscrew electrodes on the patient's head after averaging. Ten consecutive recordings are presented. In this example the SEP amplitude changed drastically between lines 6 and 7, with complete loss of the signal at the time of ICA clamping (from Dr. med. K. Seidel, Dept. of Neurosurgery, Inselspital Bern).

Particular attention will be paid to haemodynamic management. The last three blood pressure values are averaged and used to determine a baseline. During the operation and until clamping, blood pressure is kept in a range of baseline +/- 10%. If this value is undershot or exceeded, then vasopressors or antihypertensives are used, following the preference of the supervising anaesthesiologist. Before clamping of the ICA, arterial blood pressure is usually increased to levels slightly above normal systolic values (150-160 mmHg) and subsequently decreased before reperfusion. Until the end, and after the procedure, arterial systolic blood pressure is maintained below values of 100-140 mmHg to prevent hyperperfusion oedema. Concentrations of intravenous anaesthetics are gradually decreased and discontinued on

	completion of skin closure. Patients are extubated and discharged to the ICU. A postmedication interview will be performed before ICU discharge with a CAM-ICU Test (see appendix) and the medication given at the ICU will be registered in our database.

	Flow chart: The graphic shows the course of the study. The orange fields relate to the study-related measures. The light blue fields contain all study-independent procedures. 
Study Intervention:	Group 1: Co-administration of dexmedetomidine and propofol in conjunction with electrophysiological studies (somatosensory evoked potentials (SSEPs) and motor evoked potentials (MEPs)) Group 2: Standard anaesthesia with propofol in conjunction with electrophysiological studies (somatosensory evoked potentials (SSEPs) and motor evoked potentials (MEPs))
Control Inter-vention:	Group 2: Standard anaesthesia with propofol in conjunction with electrophysiological studies (somatosensory evoked potentials (SSEPs) and motor evoked potentials (MEPs)).
Number of Participants with Rationale:	We will include 46 patients, 23 patients each group. Assuming an effect size concentration (Cet) of 6 mg/ml with a SD of +/- 3 mg/ml in the control arm, a minimal clinically important difference of 3 mg/ml and an alpha of 0.05, at least 23 patients per group would be needed to reach a power of 90%.
Study Duration:	24 months
Study Schedule:	Study begin: July 2018. Study end: July 2020
Investigator (s):	Dr. med. Christian Vetter and PD Dr. med. Vladimir Krejci, both Dept. of Anaesthesiology and Pain Medicine, Inselspital, Bern University Hospital, University of Bern Christian Vetter, Christian.vetter@insel.ch, phone: 031 632 69 78, Address: Inselspital Bern, Freiburgstrasse, 3010 Bern Vladimir Krejci, vladimir.krejci@insel.ch, phone: 031 632 90 53, Address: Inselspital Bern, Freiburgstrasse, 3010 Bern

Study Centre:	Inselspital Bern, Freiburgstrasse, 3010 Bern
Statistical Considerations:	Null hypothesis (H0): We will test the null hypothesis that the effect concentration (Cet) of propofol (Propofol®, Fresenius, Switzerland) for EEG burst suppression and maintenance thereof remains unchanged through the co-administration of Dexmedetomidine (Dexdor®, Orion Pharma, Switzerland) against a two-sided alternative. Parametric distribution and equal variances will be confirmed. ANOVA and Student's t-test will be used to verify differences between mean, with Tukey's correction factor for multiple comparison where appropriate. No interim analysis is planned.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements.

STUDY SUMMARY IN LOCAL LANGUAGE

Am Inselspital wird als neuroprotektive Massnahme bei allen neurochirurgischen Carotis Endarterektomien (CEA) routinemässig die elektrische EEG-Aktivität mit hohen Effektortkonzentrationen (Cet) von Propofol unterdrückt (Burst-Suppression; BS). Eine protrahierte Infusion grosser Mengen an Propofol zum Erreichen eines BS während der Operation kann jedoch zu einer Kumulation und einer protrahierten Aufwachphase mit schlechterer neurologischen Beurteilbarkeit führen.

Zur Überprüfung der funktionellen Integrität des Nervensystems werden somatosensensorisch evozierte Potentiale eingesetzt (SSEP). Standardisierte Massnahmen aus chirurgischer und anästhesiologischer Sicht bei der CEA mit definierten EEG-Endpunkten und in Abhängigkeit von der Anästhetikawirkung, können bei normalem EEG und SSEP eine schwere, globale Ischämie praktisch ausschliessen. Darüber hinaus werden seit 2016 zusätzlich motorisch evozierte Potentiale (MEP) intraoperativ erhoben. Die intraoperative EEG-Aktivität wird durch den betreuenden Kaderarzt der Anästhesie beurteilt und interpretiert. Die MEPs und SSEPs werden durch das Team der Neurochirurgie erhoben und beurteilt.

Die somatosensorisch evozierte Potenziale (SSEP) und die Fliessgeschwindigkeit in der mittleren zerebralen Arterie werden mittels Doppler gemessen, um eine Ischämie zu detektieren. Eine signifikante Abnahme der Flussgeschwindigkeit und / oder der SSEPs-Amplitude während dem vorübergehendem Verschluss der Arteria carotis interna (ICA) wird mit einer angepassten Erhöhung des arteriellen Blutdrucks oder der Platzierung eines Shunts behandelt.

Das Team der Neurochirurgie überwacht und zeichnet die Daten bei jedem Patienten auf, der sich einer CEA unterzieht. Die SSEPs und MEPs sowie die Flussgeschwindigkeit der Arteria cerebri media werden intraoperativ permanent von einem intraoperativen Monitoring (IOM-)Techniker überwacht, der speziell in der Beurteilung der Überwachung der SEPs-Signale geschult und zertifiziert wurde.

Die SEP-Amplituden des N. medianus werden kontinuierlich aufgezeichnet. Dies ist insbesondere bei folgenden kritischen Ereignissen der Fall: Ausgangswert als Baseline vor Hautinzision, EEG-Burstunterdrückung vor dem Abklemmen der A. carotis interna, 10 Minuten nach Abklemmung der ACI oder unmittelbar nach Platzierung des Shunts (ICA Abklemmung 2), Reperfusion der ICA und Hämostase / Ende der Operation. Das vordefinierte Kriterium für den temporären Shunt ist eine Reduktion von mehr als 50% der SEP-Amplitude.
Die somatosensorisch evozierte Potentiale (SEPs) Nervus medianus wurden durch Stimulation am Handgelenk mit einem Paar Nadelelektroden (Inomed Germany®) durchgeführt. Hierbei

erfolgt eine Einzelimpulsstimulation mit einer Pulsdauer von 0,5 ms und einer niedrigen Wiederholrate von 0,7-2,3 Hz. Die Aufnahme erfolgt über Korkenzieherelektroden, die entsprechend dem 10-20-EEG-System auf der Kopfhaut des Patienten platziert sind. Für den rechten Nervus medianus SEP C3' / Fz und für den linken N. medianus wird der SEP C4' / Fz als Standardableitung gewählt. Alternativ diente Cz 'oder das kontralaterale Cp' als Referenz, um die Aufzeichnungsqualität zu verbessern. Um das Signal-Rausch-Verhältnis zu verbessern, werden die Antworten im Mittel 150-200-mal gemittelt. Bei den kritischen Ereignissen werden die Latenzen und Amplituden gemessen und aufgezeichnet (vgl. Abbildung 1)[7].

Abbildung 1:

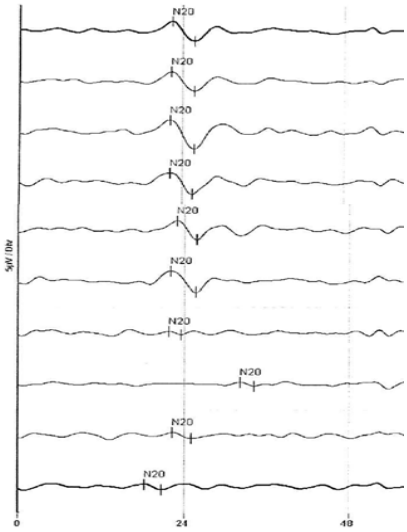


Abbildung 1: Darstellung der SEP-Latenzen und -Amplituden, die von Korkenzieherelektroden am Patientenkopf nach der Mittelung aufgenommen wurden. Zehn aufeinander folgende Aufnahmen werden vorgestellt. In diesem Beispiel änderte sich die SEP-Amplitude drastisch zwischen den Zeilen 6 und 7 mit einem vollständigen Verlust des Signals zum Zeitpunkt der ICA-Abklemmung (von Dr. med. K. Seidel, Klinik für Neurochirurgie, Inselspital Bern).

Der additive Effekt von Propofol und Sevoflurane auf die EEG-Suppression wurde 2009 von Schumacher und al. beschrieben und in unserer Klinik angewendet, jedoch unterdrücken volatile Anästhetika dosisabhängig MEPs, so dass die volatilen Anästhetika sich nur bedingt bei Operationen bei denen die SSEPs bzw. MEPs gemessen werden wie z.B. bei Carotis Endarterektomien (CEAs) eigenen. Hingegen scheint Dexmedetomidine in Kombination mit Propofol SSEPs und MEPs nur unwesentlich zu unterdrücken.

Das Indikationsspektrum für den zentral wirkenden α_2-Agonist Dexmedetomidine wurde seit seiner Zulassung in der Schweiz zunehmend ausgeweitet. Neben dem Einsatz von Dexmedetomidine auf den Intensivstationen wird Dexmedetomidine zunehmend auch perioperativ bis hin zur Prämedikation bei Kindern eingesetzt. In einigen Studien konnte eine Anästhetikareduktion von 40-60% erzielt oder der Opioidverbrauch nach Zugabe eines α2-Agonisten um 50-75% reduziert werden. Die Blutdruckantwort auf eine Dexmedetomidinegabe ist abhängig von der Infusionsgeschwindigkeit[4]. Darüber hinaus führt die Gabe von Dexmedetomidine zu keiner Atemdepression oder einer Kompromittierung der Atemwege. Nachdem gezeigt werden konnte, dass Dexmedetomidine einen „Schlaf ähnlichen“ Sedationszustand herbeiführen und dieser Zustand durch verbale Stimuli unterbrochen werden kann[2], untersuchte Huupponen et al. 2008[3] die EEG-Aktivität bei Sedation an freiwilligen Probanden im Vergleich zu einer Kontrollgruppe mit physiologischem Schlafmuster. In dieser Studie konnte gezeigt werden, dass die EEG-Spindel-Aktivität bei Probanden mit

Dexmedetomidine-Infusion derjenigen eines physiologischem non rapid eye movement (nonREM)-Schlafes Stadium II bei den Kontrollprobanden vergleichbar war. Die Autoren folgerten aus ihren Untersuchungen, dass durch die Dexmedetomidine-Infusion ein „schlafähnlicher Zustand“ (Stadium II Non-REM) erreicht werden kann. Momentan sind jedoch keine Daten zur praktischen Anwendung bei Carotis Endarterektomien mit Propofol und Dexmedetomidine in Verbindung mit elektrophysiologischen Untersuchungen (somatosensibel evozierten Potentialen (SSEPs) und motorisch evozierte Potentialen (MEPs)) bekannt.

Darüber hinaus besteht bei einer Vielzahl dieser Patienten ein hohes Risiko für ein postoperatives Delir (POD). Dies wurde in einer kürzlich publizierten Lancet Studie von Xian Su und Kollegen an 700 Patienten mit nicht kardialen Eingriffen bei älteren Patienten untersucht[8)]. Hierbei zeigte sich eine Reduktion der Deliriumsinzidenz von 23% auf 9% nach einer niedrig dosierten Dexmedetomidine-Gabe von 0.1µg/kg/h. Zusätzlich wird Dexmedetomidine ein neuroprotektiver Effekt gegenüber ischämischen und hypoxischen Einflüssen zugeschrieben[5)]. Weitere tierexperimentelle Studien weisen auf eine Neuroprotektion bei ischämischem Insult und anschliessender Reperfusion hin[6)].

Ziel der Studie:
Durchführung einer prospektiv kontrollierten Studie, welche die Quantität von Propofol mit der Co-Administration von Dexmedetomidine im Vergleich zum Propofol alleine untersucht. Hierbei sind der intraoperative Propofol-Bedarf und -Verbrauch pro Zeiteinheit, die Dauer vom Ende der Operation bis zum Erreichen der Extubationskriterien (Extubation), intraoperative elektrophysiologische Parameter (Latenz und Amplitude evozierter Potentiale (SSEPs und MEPs), intraoperative hämodynamische Parameter, Quantität an Vasoaktiva, sowie das Flüssigkeitsmanagement.

Darüber hinaus wird die Vigilanz mittels GCS (= Glasgow Coma Scale) und RASS (= Richmond Agitation Sedation Scale) vor der Narkose und kurz bevor der Patient auf die Intensivstation verlegt wird und kurz vor Verlegung von der Intensivstation auf die Normalstation untersucht. Kriterien für die Entwicklung eines Delirs gemäss CAM-ICU Fragebogen und Objektivierung der Muskelkraft der Extremitäten nach Janda (M0-M5) in den ersten 24 Stunden nach dem Ende der Operation und in den ersten 24 Stunden auf der Intensivstation. Darüber hinaus untersuchen wir die perioperative Urinausscheidung bei diesen Patienten intra- und während der folgenden 24h postoperativ. Darüber hinaus wollen wir den Schmerzmittelbedarf, den Bedarf an Reserveanalgetika, sowie das Auftreten von postoperativen Übelkeit- und Erbrechen (PONV) und den Antiemetikabedarf während des Aufenthaltes auf der Intensivstation untersuchen.

Abbreviations

AE	Adverse Event
CA	Competent Authority (e.g. Swissmedic)
CEC	Competent Ethics Committee
BS	burst supression
CEA	carotid endarterectomy
EEG	electro encephalogram
CRF	Case Report Form
Cet	effector concentrations
GCP	Good Clinical Practice
HFG	Humanforschungsgesetz (Law on human research)
HFNCT	High Frequency Nasal Cannula Therapy
HMG	Heilmittelgesetz
HRA	Federal Act on Research involving Human Beings
ICA	internal carotid artery
IIT	Investigator-initiated Trial
ITT	Intention to treat
KlinV	Verordnung über klinische Versuche in der Humanforschung (in English: ClinO)
PI	Principal Investigator
POD	postoperative delirium
SDV	Source Data Verification
SOP	Standard Operating Procedure
SSEP	Somatosensory evoked potentials

Study schedule

July 2018: Start clinical part of the study, first patient included
March 2019: last patient included
Mayr 2019: data analysed and manuscript drafted
July 2020: end of study

1. STUDY ADMINISTRATIVE STRUCTURE

All persons mentioned are members of the Department of Anaesthesiologie and Pain Medicine at the Inselspital, Bern University Hospital, Freiburgstrasse, 3010 Bern. Contact details for the PI Christian Vetter, Dr. med., christian.vetter@insel.ch; Tel: 031 632 69 78

1.1 Sponsor, Sponsor-Investigator

Dr. med. Christian Vetter will oversee the entire study, drafting and finalisation of the protocol, the analysis of the results, and the writing of the manuscript for publication. Contact details: christian.vetter@insel.ch, Tel: 031 632 69 78

1.2 Principal Investigator(s)

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1.3 Statistician ("Biostatistician")

PD Dr. med. Vladimir Krejci, vladimir.krejci@insel.ch; Tel: 031 632 90 53

1.4 Monitoring Institution

A study nurse from our department who is not involved in the study will control all data for its validity and completeness on a weekly basis. External monitoring will not occur, as this is an investigator-initiated study with no external funding.

2. ETHICAL AND REGULATORY ASPECTS

Before the study is conducted, the protocol, the proposed patient consent form as well as other study-specific documents will be submitted to the Cantonal Ethics Committee Bern. Any amendment to the protocol must be approved by this institution as well.
The decision of the CEC concerning the conduct of the study will be communicated in writing to the Sponsor-Investigator before commencement of the study. The clinical study can only begin after approval from all required authorities has been received. Any additional requirements imposed by the authorities shall be implemented.

Ethical considerations

a. The potential gain of new knowledge obtained with this study, and its meaning for patients/society:

In Switzerland, Stroke is a major cause of mortality and disability, and accounts for a large part of healthcare expense, and suffering. One cause of stroke is untreated significant, or symptomatic stenosis of the internal carotid artery. Carotid artery endarterectomy may be performed in select patients to decrease the risk of stroke. General, as well as loco-regional anaesthesia are equally accepted and safe for this type of procedure. While loco-regional anaesthesia allows better neurological assessment of the awake patient, general anaesthesia provides more comfort for both the surgeon and the patient. In addition, the risk of unexpected complications, such as loss of the airway, or sudden movement of the patient are greatly reduced with general anaesthesia. However, assessment of neurological function is more difficult. For this reason, in our institution the integrity of the nervous system in patients undergoing CEA under general anaesthesia is assessed with neurophysiological monitoring. Cross-clamping of the internal carotid artery bears the risk of cerebral ischemia and infarction.

Although electrophysiological monitoring may detect ischemia, cerebral oxygen consumption is decreased to a „maintenance“ level with high doses of anaesthetics for neuroprotection, the end-point being electroencephalographic burst suppression. High amounts of anaesthetics may result in delayed recovery and difficult neurological assessment. While most patients recover from this type of general anaesthesia within acceptable limits, in some patients a significant delay of one hour and more was observed. The aim of this study is to test a combination of intravenous anaesthetics, which may decrease the risk of delayed recovery. Published data from other procedures suggest, that electrophysiological monitoring will not be impaired with the type of anaesthesia used in the present study.

Arterial hypotension is a known cause of morbidity in patients with cerebrovascular disease. Uncontrolled hypertension during emergence may result in complications such as bleeding, or brain edema. Our preliminary experience with this anaesthetic regimen suggestes, which it will possibly contribute to hemodynamic stability, both at induction, and during emergence.

Delirium is another cause of postoperative morbidity, mortality, and prolonged hospital stay. Published data strongly suggest, that Dexmedetomidine, may reduce the risk of postoperative delirium.

Overall, CEA is very safe procedure. However, in our experience, CEA is performed the longer the more often in patients with very recent stroke, who may be more vulnerable to hemodynamic instability and ischemia, and who may benefit from pharmacological prevention of delirium.

b. Assessment of the benefit/risk relationship for the patient

Study participants must be undergoing either emergency or elective surgery of the internal carotid artery (ICA). All patients will receive anaesthetic care according to their institution’s standard operation procedure. This includes preoperative assessment by an anaesthesiologist (premedication) before surgery, the NIHSS (National Institutes of Health Stroke Scale) Score and written informed consent. For this operation, standard operating procedure has been developed and is applied regularly.
Every patient in this study will be monitored according to our clinical standards as well as the recommendations of the specialist company. Postoperatively, patients’ blood pressure must be closely monitored and managed; invasive blood pressure measurement will provide the corresponding values in real time. The treating anaesthesiologist can react promptly and initiate necessary measures. All anaesthesiologists who supervise patients in this study are familiar with the drug dexmedetomidine and use it regularly. Dexmedetomidine has been approved by Swissmedic for the sedation of patients with a dose of up to 1.4 µg/kg/h. The dose we will use in this study, 0.4 µg/kg/h, is in the lower third.

Two theoretical risks are involved when dexmedetomidine is used as a bolus or continuous infusion. First, severe bradycardia can occur. However, the amount of dexmedetomidine to be administered in our study is relatively small. On the other hand, studies with higher dexmedetomidine concentrations do not indicate a heightened occurrence of severe bradycardia nor has this been described in the literature. Second, there is the possibility of severe hypotension, which requires therapy. Since patients will already be receiving invasive blood pressure measurement as standard, and the anaesthesiologist can intervene at an early stage, this risk is also very small.

We cannot use healthy people or animals as a substitute for this patient group.

c. The methodology is ethically appropriate to gain new generalizable knowledge

Our patients will be blinded to the randomisation. The responsible anaesthetist cannot influence the bolus of dexmedetomidine started prior to the induction of anaesthesia (very low risk of creating bias). The two groups will be statistically and clinically equivalent with regard to age, weight, health status and elective or emergency status. The trial method is well suited to study the research question, and the participating anaesthesiologists are familiar with all possible side effects and comfortable treating them.

2.1 Study registration

The study will be registered at www.clinicaltrials.gov and in the database of the Inselspital Bern through the University of Bern's Clinical Trials Unit, as well as with the Swiss Federal Office of Public Health's portal for human research, KOFAM (www.kofam.ch).

2.2 Categorisation of study

Risk category A.
Rationale: The medications we will use in this study are approved as sedatives by Swissmedic (registration number: 62183). We compare two therapeutic strategies in one experimental and one standard therapy arm (= propofol is routinely used as an anaesthetic in modern anaesthesia procedure).

2.3 Competent Ethics Committee (CEC)

Kantonale Ethikkommission Bern (KEK), Institut für Pathophysiologie, Hörsaaltrakt Pathologie, Eingang 43A, Büro H372, Murtenstrasse 31, 3010 Bern. According to Art. 38 KlinV: completion of the study must be reported to the responsible ethics committee within 90 days or interruption (including details of reasons) within 15 days. In addition, a final report must be submitted to the Ethics Committee within one year after completion or interruption of the study.

2.4 Ethical conduct of the study

The study will be carried out in accordance with the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH , Swiss law, and the Swiss regulatory authority's requirements. The CEC and regulatory authorities will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements. A final report will be sent to the CEC at latest one year after the study ends.

2.5 Declaration of conflicts of interest

None of the investigators reports a conflict of interest.

2.6 Patient information and informed consent

The investigators will explain to the patients the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits, and any discomfort it may entail. Each patient will be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect subsequent medical assistance and treatment. Patients must be informed that their medical records may be examined by authorised individuals (e.g., CEC) other than their treating physician.

All study participants will receive a consent form along with an information sheet describing the study and providing sufficient information to make an informed decision about their participation.

The study information sheet and consent form will be submitted to the CEC for review and approval. In elective patients the formal consent must be obtained from the participant before the participant undergoes any study procedures.
According to our numbers of patients, we assume 13% of emergencies in this patient group each year. In case of emergencies, a distinction is made as to whether they are even able to give informed consent. If this is the case and the patient has enough time (time to participate in the study to the operation > 6 hours) to take a decision, the consent form will be obtained from the patient himself. If this is not the case, as the patient is not able to consent at the time of the information, the next family members will be informed and the consent of one of the patient family members will be obtained in a writing form. In addition, an independent doctor is consulted. Once the patient is able to consent, the informed consent is obtained retrospectively.

Study participants should read before signing and dating the informed consent form and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or his designee) and retained as part of the study records.

2.7 Participant privacy and confidentiality

The investigators affirm and uphold the principle of the participant's right to privacy and agree that they will comply with applicable privacy laws. In particular, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.
Medical information about individual subjects obtained through this study is considered confidential, and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification codes to correspond to treatment data in the computer files.
The codes will be stored in the lockable office of the principal investigator in a lockable cupboard where no one else has access.
For data verification purposes, authorised representatives of a competent authority (e.g. Swissmedic) or the cantonal ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.

2.8 Early termination of the study

The Sponsor-Investigator may terminate the study prematurely under certain circumstances, for example:

- ethical concerns,
- insufficient participant recruitment,
- when the safety of the participants is in doubt or at risk,
- when alterations in accepted clinical practice make the continuation of a clinical trial unwise,
- when there is early evidence of harm of the intervention

2.9 Protocol amendments

Substantial amendments can only be implemented after approval of the CEC. Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of the study participants may proceed without prior approval of the sponsor and the CEC. Such deviations shall be documented and reported to the sponsor as soon as possible.
All non-substantial amendments are communicated to the CEC within the Annual Safety Report (ASR).

3. BACKGROUND AND RATIONALE

3.1 Background and rationale

In our clinic, as a neuroprotective measure, all neurosurgical patients undergoing operation for carotid endarterectomy (CEA) are routinely operated on under deep anaesthesia with suppression of the electrical activity of the electroencephalogram (EEG). To achieve this suppression of the EEG activity (burst suppression, BS), high effector concentrations (Cet) of propofol doses are needed. However, a protracted infusion of large amounts of propofol to reach a BS during the operation can lead to accumulation and a protracted wake-up phase, with poorer neurological assessability. Somatosensory evoked potentials (SSEPs) are used to verify the functional integrity of the nervous system. Intraoperative monitoring and recording of data in every patient undergoing CEA median nerve SEPs and MCA flow velocity is constantly monitored by an additional intraoperative monitoring (IOM) technician who has been trained and certified in the assessment of intraoperative monitoring.

The median nerve SSEP amplitudes are recorded at least at these events:

- Baseline value before skin incision
- EEG burst suppression before cross clamping of the internal carotid artery
- At time of ICA cross clamping
- 10 minutes after cross clamping or immediately after placement of shunt (ICA clamping 2)
- Reperfusion of ICA
- Haemostasis/end of surgery

The predefined criterion for temporary shunting is the reduction of more than 50% of the SEP amplitude.

Median nerve SSEPs are measured by stimulation at the wrist with a pair of needle electrodes (Inomed® Germany). This is a single pulse stimulation with 0.5 ms pulse duration and a low repetition rate ranging from 0.7 -2.3 Hz. Recording is performed via corkscrew electrodes placed according to the 10-20-EEG system on the patient's scalp. For the right median nerve SEP C3´/Fz and for the left median nerve SEP C4´/Fz is chosen as standard derivation. Alternatively, Cz' or the contralateral Cp' served as reference to improve quality of recording. To improve the signal-to-noise ratio the responses are averaged 150-200 times. Latencies and amplitudes as shown in Figure 1 are measured and recorded in the protocol at the defined critical events[7)].

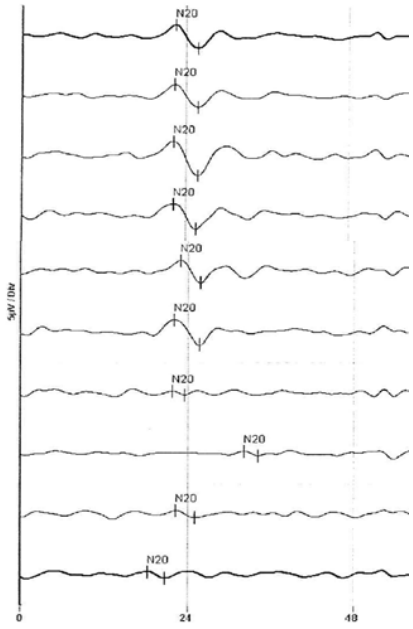


Figure 1: Illustration of SEP latencies and amplitudes recorded from the corkscrew electrodes on the patient's head after averaging. Ten consecutive recordings are presented. In this example the SEP amplitude changed drastically between lines 6 and 7, with complete loss of the signal at the time of ICA clamping (from Dr. med. K. Seidel, Neurosyrgery, Inselspital Bern).

Standardised surgical and anaesthesiological measures at the CEA with defined EEG endpoints and depending on the anaesthetic effect can, in normal EEG and SSEPs, effectively exclude severe global ischaemia. The effects of burst suppression and volatile anaesthetics on SSEPs have also investigated and showed no significant difference. Since 2016, motor-induced evoked potentials (MEPs) have also been used, but they are suppressed by volatile anaesthetics in a dose-dependent manner. On the other hand, dexmedetomidine in combination with propofol seems to suppress only insignificantly.

The indication spectrum for the centrally acting α_2-agonist dexmedetomidine has been increasingly extended since the drug's approval in Switzerland. In addition to being used in intensive care units, dexmedetomidine is also increasingly being used perioperatively up to premedication in children. In some studies, an anaesthetic reduction of 40-60% could be achieved, or opioid consumption after the addition of an α_2-agonist could be reduced by 50-75%. The blood pressure response to a dexmedetomidine dose depends on the rate of infusion[4]. In addition, administration of dexmedetomidine does not result in respiratory depression or compromise of the respiratory tract. It has been shown that dexmedetomidine can cause a "sleep-like" sedation state, and this state can be interrupted by verbal stimuli[2].

Huupponen et al. 2008[3] examined the EEG activity in sedated volunteers compared to a control group with physiological sleep patterns. In this study, it was shown that the EEG spindle activity in subjects with dexmedetomidine infusion was comparable to that of a physiological non-rapid-eye-movement (nonREM) sleep stage II in the control tests. The authors concluded from their investigations that a "sleep-like state" (stage II non-REM) can be achieved with dexmedetomidine infusion. However, no data are currently available for practical use in carotid endarterectomy with propofol and dexmedetomidine in conjunction with electrophysiological studies (somatosensory evoked potentials and motor-evoked potentials).

In addition, there is a high risk of postoperative delirium (POD) in many of these patients. This was examined in a recently published Lancet study by Xian Su and colleagues in 700 elderly patients with non-cardiac interventions. A reduction of the delirium incidence from 23% to 9% was found after a low-dose dexmedetomidine dose of 0.1 µg/kg body weight/h. In addition, a neuroprotective effect against ischaemic and hypoxic influences has been attributed to dexmedetomidine[5)]. Other experimental studies in animals indicate neuroprotection in ischemic insult and subsequent reperfusion[6)].

3.2 Investigational product (treatment, device) and indication

Dexmedetomidine (Dexdor®).

3.3 Clinical evidence to date

All relevant available evidence is summarized under 3.1

3.4 Dose rationale: rationale for the intended purpose in study

The drug dexmedetomidine is approved by Swissmedic for the sedation of patients. The most common dose in the previously published studies is between 0.5 and 0.7 µg/kg/h. Since patients usually have relevant comorbidities and thus belong to ASA class III and higher, and due to the substantial exclusion of side effects, we have a bolus of 0.4 µg/kg over 10 minutes followed by a continuous infusion of 0.4 µg/kg/h until the end of the operation. The dose of 0.4 µg/kg/h we plan to use in this study is in the lower third of the maximum dosage approved by Swissmedic. The Risk for adverse events is very little.

3.5 Explanation of choice of comparator (or placebo)

We will not use a placebo for this study, as the current standard for treating patients undergoing carotid endarterectomy (CEA) is propofol. We will test whether co-administration of dexmedetomidine and propofol is superior to the standard therapy with propofol alone.

3.6 Risks/benefits

The study participants must undergo either an emergency or elective surgery on the internal carotid artery (ICA). Standard operating procedure has been developed for this operation and is applied regularly.

Every patient in this study will be monitored according to our clinical standards as well as the recommendations of the specialist company. Postoperatively, patients' blood pressure must be closely monitored and managed; invasive blood pressure measurement will provide the corresponding values in real time. The treating anaesthesiologist can react promptly and initiate necessary measures. All anaesthesiologists who supervise patients in this study are familiar with the drug dexmedetomidine and use it regularly. Dexmedetomidine has been approved by Swissmedic for the sedation of patients with a dose of up to 1.4 µg/kg/h. The dose we will use in this study, 0.4 µg/kg/h, is in the lower third. According to the product information of dexmedetomidine, there is currently no adequate experience with the use of dexmedetomidine in pregnant women. Therefore, a pregnancy test must be performed on women of childbearing potential prior to enrolment.

Two theoretical risks are involved when dexmedetomidine is used as a bolus or continuous infusion. First, severe bradycardia can occur. However, the amount of dexmedetomidine to be administered in our study is relatively small. On the other hand, studies with higher dexmedetomidine concentrations do not indicate a heightened occurrence of severe bradycardia nor has this been described in the literature. Second, there is the possibility of severe

hypotension, which requires therapy. Since patients will already be receiving invasive blood pressure measurement as standard, and the anaesthesiologist can intervene at an early stage, this risk is also very small.

All patients undergoing general anaesthesia have at least a small risk of perioperative complications. Although this risk is multifactorial, it depends on the clinical condition of the patient as well as the type of intervention. But these conditions have a great influence on the perioperative outcome. High effector concentrations (Cet) of propofol suppress the electrical EEG activity up to burst suppression (BS). However, protracted infusion of large amounts of propofol to reach BS during a carotid endarterectomy (CEA) can lead to accumulation and a protracted wake-up phase, with poorer neurological assessability.

With this study, we hypothesize that the spearing effect of propofol caused by the co-administration of dexmedetomidine will reduce the dose of anaesthetics required to achieve and sustain anaesthesia without influencing the SSEPs and MEPs during the operation. If we can show with this study both that patients awaken faster from anaesthesia and that neurological assessability improves with a lower risk of postoperative complications – such as postoperative delirium (POD) – we will greatly improve patient safety.

3.7 Justification of choice of study population

The study participants must undergo either an emergency or elective surgery on the internal carotid artery (ICA). Standard operating procedure has been developed for this operation and is applied regularly.

Every patient in this study will be monitored according to our clinical standards as well as the recommendations of the specialist company. Postoperatively, patients' blood pressure must be closely monitored and managed; invasive blood pressure measurement will provide the corresponding values in real time. The treating anaesthesiologist can react promptly and initiate necessary measures. All anaesthesiologists who supervise patients in this study are familiar with the drug dexmedetomidine and use it regularly. Dexmedetomidine has been approved by Swissmedic for the sedation of patients with a dose of up to 1.4 µg/kg/h. The dose we will use in this study, 0.4 µg/kg/h, is in the lower third.

Two theoretical risks are involved when dexmedetomidine is used as a bolus or continuous infusion. First, severe bradycardia can occur. However, the amount of dexmedetomidine to be administered in our study is relatively small. On the other hand, studies with higher dexmedetomidine concentrations do not indicate a heightened occurrence of severe bradycardia nor has this been described in the literature. Second, there is the possibility of severe hypotension, which requires therapy. Since patients will already be receiving invasive blood pressure measurement as standard, and the anaesthesiologist can intervene at an early stage, this risk is also very small.

We cannot use healthy people or animals as a substitute for this patient group.

4. STUDY OBJECTIVES

4.1 Overall objective

This study investigates the co-administration of dexmedetomidine and propofol for carotid endarterectomy under controlled conditions. In our clinic, as a neuroprotective measure, all neurosurgical patients undergoing operation for carotid endarterectomy (CEA) are routinely operated on under deep anaesthesia with suppression of the electrical activity of the electroencephalogram (EEG). To achieve this suppression of the EEG activity (burst suppression, BS), high effector concentrations (Cet) of propofol doses are needed. However, a protracted infusion of large amounts of propofol to reach a BS during the operation can lead to accumulation and a protracted wake-up phase with poorer neurological assessability.

With the co-administration of dexmedetomidine and propofol during anaesthesia we will try to show that both the outcome and the complication rate can be improved, resulting in improved safety and better patient management during the operation.

4.2 Primary objective

The primary study objective is to determine whether the intervention reduces the effect size concentration of propofol.

4.3 Secondary objectives

The secondary study objectives are the intraoperative propofol requirement and consumption per unit of time, duration from the end of surgery to reaching the extubation criteria (extubation), intraoperative electrophysiological parameters (latency and amplitude of evoked potentials), intraoperative hemodynamic parameters, vasoactive substances, fluid management. We also measure the vigilance (Glasgow Coma Scale = GCS, Richmond Agitation Sedation Scale = RASS) before anaesthesia and directly before the patient is transferred to the intensive care unit. Criteria for the development of delirium (CAM-ICU) and muscle force of the extremities as it was described by Janda (M0-M5) in the first 24 hours after the end of the operation at the intensive care unit (ICU). Furthermore, we examine the perioperative urinary output in these patients. Additionally, we want to examine the patient's use of painkillers and the need for rescue analgesics as well as the postoperative nausea and vomiting state (PONV).

4.4 Safety objectives

According to the recommendations of the SGAR (Schweizerische Gesellschaft für Anästhesiologie und Reanimation), all patients are monitored and a radial artery for continuous blood pressure monitoring and for analysis of arterial blood gases, electrolytes and metabolites is inserted prior starting with the induction of anaesthetics. The brain activity is monitored by Bispectral Index or Narcotrend®. Both are assessed and analysed by the treating anesthesiologist. The SSEPs, MEPs and MCA flow velocity Doppler are analysed and assessed by the treating neurosurgery team.

5. STUDY OUTCOMES

5.1 Primary outcome

The primary study outcome is to determine whether the intervention reduces the effect size concentration of propofol.

5.2 Secondary outcomes

Secondary endpoints are the intraoperative propofol requirement or consumption per unit of time, duration from the end of surgery to extubation (measured by extubation criteria), intraoperative electrophysiological parameters (latency and amplitude of evoked potentials), intraoperative haemodynamic parameters, vasoactive substances, and fluid management. We will also measure vigilance (Glasgow Coma Scale = GCS, Richmond Agitation Sedation Scale = RASS), criteria for the development of delirium (CAM-ICU) and muscle force of the extremities as described by Janda (M0-M5) in the intensive care unit (ICU) in the first 24 hours after the end of the operation at. Furthermore, we will examine the perioperative urinary output in these patients during the operation and during their stay in the intensive care unit. Additionally, we want to examine the patients' use of painkillers and the need for rescue analgesics as well as the postoperative nausea and vomiting (PONV) direct after the patient has been extubated and once during the stay in the intensive care unit.

5.3 Safety outcomes

Presence of severe refractory hypotension and bradycardia during surgery will be identified by the continuous blood pressure measurement and treated immediately.

6. STUDY DESIGN

6.1 General study design and justification of design

Single-blinded randomised controlled prospective trial (Co-administration of dexmedetomidine in carotid endarterectomy with intraoperative SSEP and MEP monitoring. A single-centre prospective randomised controlled trial).

In total we will include 46 patients; at least 23 patients in each group. Patients will be blinded as to their group allocations.

Double-blinding is not intended. The sequence is described above.

6.2 Methods of minimising bias

6.2.1 Randomisation

Patients will be assigned to their respective groups using a computer-generated randomisation list. Randomisation will be stratified according to use of propofol alone as standard therapy (group 2) and propofol with the co-administration of dexmedetomidine (group 1), with 23 patients in each group. Group allocation will be kept in a sealed opaque envelope opened before induction of anaesthesia until the patient is motorised. The Patients won't be informed about this result. Patients excluded from the study before opening of the randomisation envelope will be replaced, as if they were not eligible for the study.

6.2.2 Blinding procedures

Patients are under general anaesthesia and therefore blinded to the treatment group, but personnel in the operating room are not blinded.

6.3 Unblinding procedures (code break)

Unblinding procedure: The randomization code is placed in a locked drawer in the office of the study sponsor from Dr. med. C. Vetter. Only the study leader has a key for it.

7. STUDY POPULATION

7.1 Eligibility criteria

To be included are all patients undergoing elective and emergency carotid endarterectomy under general anaesthesia with intubation in the neurosurgery clinic at the Inselspital, Bern University Hospital.

Additional inclusion criteria are: Age ≥18 years, ASA physical status 1-4, a pregnancy test must be performed on women of childbearing potential prior to enrolment, provision of written informed consent.

Exclusion criteria are: Age <18 years, higher grade atrioventricular block without pacemaker, severe hypovolaemia or bradycardia, uncontrolled hyper or hypotension, hypersensibility concerning the active substance dexmedetomidine or any other component, serve liver disease, known malignant hyperthermia, cardiovascular instability or severe heart failure (> NYHA III), limited peripheral autonomic activity, pregnancy, rejection or lack of consent of the patient or their relatives.

Patients will be screened and asked to participate in the study during the pre-anaesthesia visit before surgery. If they are willing to take part they will sign the informed consent form, there.

7.2 Assignment to study groups

Patients will be randomly assigned to their respective groups using www.randomisation.com.

7.3 Criteria for withdrawal/discontinuation of participants

The patient will be withdrawn from the study if there is no surgical intervention or if a decision is made to change the anaesthesia procedure (i.e., general anaesthesia is not needed). A therapy-refractory hypotension and/or bradycardia which does not respond to vasoactive or sympathomimetic drugs will also lead to exclusion of the patient from the study.
A pregnancy test must be performed on women of childbearing potential prior to enrolment, if its possitiv, we will exclude the patient from this study.

8. STUDY INTERVENTION

8.1 Investigational treatment

8.1.1 Experimental intervention

The effect-site concentration of propofol (Fresenius Kabi, Switzerland) (Cet) in co-administration with dexmedetomidine (Dexdor®, Orion Pharma, Switzerland) was set based on the clinical evaluation and the processed EEG.

8.1.2 Control intervention (routine treatment)

Comparator: The effect-site concentration of propofol (Fresenius Kabi, Switzerland) (Cet) was set based on the clinical evaluation and the processed EEG.

8.2 Administration of experimental and control interventions

8.2.1 Experimental intervention

The effect-site concentration of propofol (Fresenius Kabi, Switzerland) (Cet) in co-administration with dexmedetomidine (Dexdor®, Orion Pharma, Switzerland) was set based on the clinical evaluation and the processed EEG.

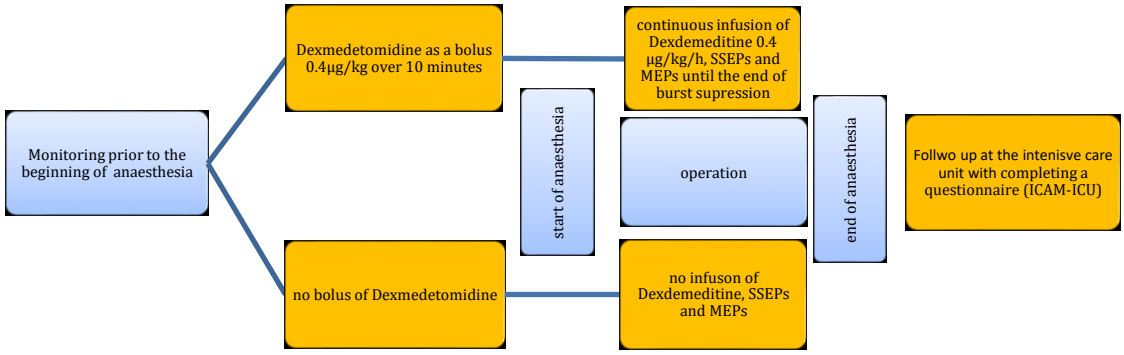
8.2.2 Control intervention

Comparator: The effect-site concentration of propofol (Fresenius Kabi, Switzerland) (Cet) was set based on the clinical evaluation and the processed EEG.

8.3 Data collection and follow-up for withdrawn participants

No further data will be collected after withdrawal from the study. Data already collected will be analysed and after data evaluation anonymised

Study flow chart(s) / table of study procedures and assessments: The graphic shows the course of the study. The orange fields relate to the study-related measures. The light blue fields contain all study-independent procedures**.**



8.4 Assessments of outcomes

8.4.1 Assessment of primary outcome

The primary study outcome is to determine whether the intervention reduces the effect size concentration of propofol.

8.5 Secondary outcomes

The secondary study outcomes are the intraoperative propofol requirement and consumption per unit of time, duration from the end of surgery to reaching the extubation criteria (extubation), intraoperative electrophysiological parameters (latency and amplitude of evoked potentials), intraoperative haemodynamic parameters, vasoactive substances, and fluid management. We will also measure vigilance (Glasgow Coma Scale = GCS, Richmond Agitation Sedation Scale = RASS) before starting anaesthesia and directly before the patient is transferred to the intensive care unit and the development of delirium (CAM-ICU) and muscle force measured in the extremities as described by Janda (M0-M5) in the first 24 hours after the end of the operation in the intensive care unit (ICU). Further measurements will include: perioperative urinary output; patients' use of painkillers; the need for rescue analgesics; and postoperative nausea and vomiting (PONV).

8.5.1 Assessment of secondary outcomes

This is a standard procedure used very often in the anaesthesia and intensive care units.

8.5.2 Assessment of safety outcomes

According to the product information of dexmedetomidine, there is currently no adequate experience with the use of dexmedetomidine in pregnant women. Therefore, a pregnancy test must be performed on women of childbearing potential prior to enrolment.

Possible hypotension and bradycardia will be monitored as described before.

8.5.2.1 Adverse events

Any adverse events during the study period will be recorded.

All SAEs will be reported immediately or within a maximum of 24 hours to the Sponsor-Investigator of the study.

SAEs resulting in death should be reported to the local ethics committee within 7 days.

SUSARs will be reported to the local ethics committee within 15 days.

8.5.2.2 Laboratory parameters

We will not draw blood for testing in this study.

8.5.2.3 Vital signs

During anaesthesia, standard non-invasive and invasive monitoring of vital signs will be recorded, as defined by the American Society of Anaesthesiologists and the Swiss Society for Anaesthesia and Reanimation. This includes: ECG, end-tidal CO_2, invasive blood pressure, pulse oximetry, heart frequency, and body temperature and urinary output.

8.6 Procedures at each visit

The first visit will take place during the pre-anaesthesia visit. A follow-up visit will be performed (structured post-medication interview) before the patient leaves the ICU, including completion of an ICAM-ICU form.

9. SAFETY

Adverse events during the anaesthesia procedure will be treated according to current departmental guidelines at the discretion of the attending anaesthesia consultant. If severe, therapy-refractory problems persist, the study can be stopped at any time points without delay and the study patient will be treated according to the departmental guidelines.

Adverse event (AE):
Any unintentional medical incident in a patient or subject who is has received pharmaceutical preparation. The undesirable event does not have to necessarily be causally related to treatment. Thus, an undesirable event may be any unwanted or unintended sign, symptom or any illnesses that are temporary with the administration of the investigational medicinal product is independent whether a causal link with the investigational medicinal product is being considered.

Serious Adverse Event (SAE):
Every AE, that

- leads to death
- is life threatening
- Hospitalization or extension of existing hospitalization
- leads to permanent and significant disability
- is a hereditary deviation / birth defect
- requires medical intervention to avert the above consequences

Fatal SAEs will be sent to the responsible ethics committee within 7 days. SAEs without fatal outcome will be reported as part of the annual safety report.

Suspected unexpected serious adverse reaction (SURAS):
As SUSAR are called such side effects that are unexpected at the same time and serious. SURAS with death must be reported to the ethics committee within 7 days, all other SURAS within 15 days

10. STATISTICAL METHODS

10.1 Hypothesis

Null hypothesis: We will test the null hypothesis that the effect concentration (Cet) of propofol (Propofol®, Fresenius, Switzerland) for EEG burst suppression and maintenance thereof remains unchanged through the co-administration of Dexmedetomidine (Dexdor®, Orion Pharma, Switzerland) against a two-sided alternative.

Second outcome hypothesis: secondary outcome hypothesis are the intraoperative Propofol requirement and consumption per unit of time, duration from the end of surgery to reaching the extubation criteria (extubation), intraoperative electrophysiological parameters (latency and amplitude of evoked potentials), intraoperative hemodynamic parameters, vasoactive substances, fluid management. We also measure the vigilance (GCS = Glasgow Coma Scale, RASS = Richmond Agitation Sedation Scale) before the anaesthesia and directly before the patient will be transferred to the intensive care unit, Criteria for the development of a delirium (CAM-ICU) and muscle force of the extremities as it was described by Janda (M0-M5) in the first 24 hours after the end of the operation at the intensive care unit (ICU). Furthermore, we examine the perioperative urinary output in these patients. Additionally, we want to examine the patient's use of painkillers and the need for rescue analgesics as well as the postoperative nausea and vomiting state (PONV).

10.2 Determination of sample size

Assuming an effect size concentration of 6 mg/ml with a SD of +/- 3 mg/ml (Ref) in the control arm, a minimal clinically important difference of 3 mg/ml and an alpha of 0.05, at least 23 patients per group would be needed to reach a power of 90%.

10.3 Planned analyses

10.3.1 Datasets to be analysed, analysis populations

The main analysis set will include all randomized patients. Parametric distribution and equal variances confirmed, ANOVA and Student's t-test will be used to verify differences between mean with Tukey's correction factor for multiple comparison where appropriate, no interim analysis is planned.

10.3.2 Safety analysis

According to the product information of dexmedetomidine, there is currently no adequate experience with the use of dexmedetomidine in pregnant women. Therefore, a pregnancy test must be performed on women of childbearing potential prior to enrolment.

Presence of severe refractory hypotension or bradycardia during surgery will be identified immediately by the continuous blood pressure and heart frequency measurement and will be compared with known results from the literature.

10.3.3 Deviation(s) from the original statistical plan

Any deviation from the planned analyses will be listed and justified in the study report.

10.4 Handling of missing data and drop-outs

Any missing data or drop-outs will be listed and justified in the study report. With the rather small sample size we will take care to have no missing data or drop-outs in the study.

11. QUALITY ASSURANCE AND CONTROL

11.1 Data handling and record keeping/archiving

11.1.1 Case report forms

Demographic data (age, weight, sex, type of surgery) will be obtained from the departmental electronic anaesthesia information system (AIS). Consent forms will be obtained at the pre-anaesthesia visit. All study data will be directly recorded in the CRF, which should also be considered as source data. These data will be transferred into the departmental research documentation system – LabKey.

11.1.2 Recordkeeping/archiving

All study data will be archived for a minimum of 10 years after study termination or premature termination of the clinical trial.
Data will be transferred to a secure, web-based data integration platform (LabKey, LabKey Software, Seattle, WA, USA, Version 14.3) and controlled independently by two members of the study team. Additionally, data will be double-checked by comparing the screening records with the digital anaesthesia documenting system of the hospital.

11.2 Data management

11.2.1 Data management system

11.2.2 Data security, access and back-up

The LabKey Server provides web application security. It can be configured for Secure Socket Layer (SSL) encrypted data transfer if needed.
The application has a group-based and a role-based security model. Each user belongs to one or more security groups with specific sets of permissions in relation to folders or projects in the system. Only dedicated site administrators have access to the admin console enabling user management and changes to security settings.
Data are stored and visualised in data grids either in the format of datasets, lists or assays. Each change of data is tracked and documented in corresponding audit log files.
The system can only be accessed by entering a user name and password. All events are recorded in the user event list of the audit log files.
The application runs on a productive server with an image on a backup server. In addition, a regular backup of the whole database is implemented using storage servers (darwinnas0001 and darwinnas0002) hosted at the darwin.insel.ch domain.

11.2.3 Analysis and archiving

The LabKey server provides data analysis by integrated tools for creating filtered views and charts.
All data can be exported in various formats (excel, text, queries) suitable for transfer to a preferred statistical software package. In addition, data can be analysed by creating R views.
All data will be archived and secured in the database if required by legislation.

11.2.4 Electronic and central data validation

Data are validated by the primary investigator and the sponsor when evaluating the results.

11.3 Monitoring:

A study nurse from our department who is not involved in the study will control all data for its validity and completeness on a weekly basis. External monitoring will not occur, as this is an investigator-initiated study with no external funding.

12. PUBLICATION AND DISSEMINATION POLICY

The results will be published in a peer-reviewed journal. The final decision on publishing the results will be made by the project leaders. Authors of the publication are team members who contributed to the design, conduct or analysis of the study and who approved the final version of the manuscript.

13. FUNDING

13.1 Funding

This study is solely financed by a departmental research grant from the departmental anaesthesia research fund. There is no funding or financial influence through any other company.

14. INSURANCE

Insurance will be provided by the Inselspital Bern through Zürich Versicherungs-Gesellschaft AG.

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