Research paper

Estimating patients' risk for postoperative delirium from preoperative routine data - Trial design of the PRe-Operative prediction of postoperative DElirium by appropriate SCreening (PROPDESC) study - A monocentre prospective observational trial

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ABSTRACT

Background: Postoperative Delirium (POD) is the most common complication of elderly patients after surgery associated with increased postoperative morbidity, persistent care dependency and even mortality. Prevention of POD requires detection of patients at high risk prior to surgery. PROPDESC intends to provide an instrument for preoperative routine screening of patients' risk for POD.
Methods: PROPDESC is a monocentric prospective observatory trial including 1000 patients older than 60 years from various disciplines of a university hospital planned for surgery of at least 60 min. To develop a score predicting the risk for POD, anesthesiological stratifications, laboratory values, medication and known risk factors as well as quality of life and cognitive performance are taken into account. POD assessment is performed daily on the first five days after the operation respectively the end of sedation in the intensive care units and normal wards. The score is evaluated from 600 data sets and subsequently validated internally. The most appropriate predictors are determined by a component-wise gradient boosting approach.
Discussion: Based on retrospective investigations, etiology of POD is considered multifactorial. By a prospective analysis of various factors, PROPDESC intends to provide an applicable tool to predict the risk for POD from preoperative routine data and assessment of cognitive function. Objective is to establish an automatically generating score in preoperative routine to screen patients for increased risk of POD as starting point for POD reduction and management. Model compilation requires a high significance and enhancement within compound as well as regular availability of the selected predictors.
Trial registration: DRKS, DRKS00015715. Registered 13 December 2018 - Retrospectively registered, https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00015715.

1. Introduction

Postoperative delirium (POD) is the most common postoperative complication in elderly patients [1]. The incidence of POD in surgical populations ranges from 11 to 51%. In medically geriatric patients, delirium occurs in 18–35% and even in 40% of nursing home residents during hospitalization [3].

According to the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association [4], delirium is characterized by acutely developing and fluctuating disturbances of awareness, attention and cognition caused by an organic pathophysiology. POD occurs as a hyperactive form with agitation and motor restlessness, as a hypoactive form with apathy and lethargy and as a mixture of both.

Although POD is an acute and transient condition, it has a serious impact on the outcome and prognosis of patients. Adverse outcomes

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include functional and cognitive decline or persistent dysfunction, up to permanent need for care and increased mortality [5–20]. POD often prolongs hospital treatment and leads to higher treatment efforts and costs. Considering additional personnel- and material-costs, including the impact on the length of stay in hospital Weinrebe et al. retrospectively calculated costs associated with hyperactive POD up to 1200 € per patient [21]. In Germany, the number of elderly people (>65 years) in the population is predicted to rise from 21% in 2016 to 29% in 2040 [22]. That increases the necessity and challenge to address POD as the most common complication of this population and to work on solutions to prevent or treat it.

The development of a delirium seems to be caused multifactorial. In this context, predisposing (non-influenceable) and precipitating (influenceable) factors are distinguished as promoters of delirium. Predisposing factors include functional, cognitive and sensory impairment, age, comorbidities, severity of disease as well as delirium and alcohol abuse in patient history. Medication, invasiveness of the operation and monitoring, infections and disorders of homeostasis, as well as physical restraint can affect patients and trigger POD as precipitating factors [3].

The risk for POD results from the amount and impact of several risk factors that should be considered in the screening process. Patient history, operative and anesthesiological risk stratification, laboratory values as well as testing and family assessment of cognitive performance are taken into account to develop a predictive score for the POD risk from preoperative routine data.

2. Methods

2.1. Study population

Within 12 months 1000 patients from different surgical disciplines of the University Hospital Bonn are included in a monocentric prospective observational trial. Patients older than 60 years with planned operations of at least 60 min duration are eligible (Inclusion criteria).

Exclusion criteria are emergency procedures, language barriers, diseases that could affect the safety of the patient or the compliance with the study protocol and incapacity to participate in the study as determined by the investigator.

2.2. Study plan

Screening and recruitment is conducted by the Department of Anesthesiology of the University Hospital Bonn. Study physicians include eligible patients in PROPDESC after receiving written informed consent to participate and to contact patients and their relatives for a postoperative telephone follow-up 180 days after the operation (Table 1). In this process, data of participants and relatives are entered in the patient list of the study team and a pseudonymized data record is created in the REDCap database. Password protected access to the patient list and the database is restricted to the study staff.Reasons for leaving the study are both the withdrawal of the patient's consent or the cancellation of the planned surgery as well as violations of the study protocol. Patients who have received less than three postoperative visits for delirium assessment are excluded from the statistical evaluation to determine predictors for POD, unless they were discharged without POD before reaching the third visit. Completeness of the preoperative data set is attempted, but sporadically lacking parameters are not a strict exclusion criterion. Handling this way evaluates the regular availability of preoperative data in clinical routine that might be predictive for POD. A follow-up after 180 days is also not mandatory for the evaluation of predictors of POD, but investigates the long-term consequences of this complication.

A recruitment period of approximately 12 months is planned to include 1000 patients in PROPDESC. Dropout of 5% of recruited patients will be tolerated. If this rate will be exceeded, a further recruitment will be conducted in order to obtain the intended statistical power. The study interval will be terminated after the last scheduled follow-up.

The participants' timeline from screening to follow-up is shown in Table 1.

2.3. Data

Preoperative data (Table 2) are acquired in the course of the preoperative evaluation by the Clinic for Anesthesiology and is supplemented by cognitive testing of patients and by conducting surveys of relatives by the study staff.

Treatment data (Table 3) are collected postoperatively by the study team from the anesthesia protocols and the patient records.

2.4. Tests

The occurrence of POD is assessed in daily morning visits by trained doctoral students on each of the first five days after surgery respectively on the first five days after ending of sedation. For this purpose, different tests, as listed in Table 4 are used. In order not to miss the delirium diagnosis in the context of spot examinations, the delirium observation scale (DOS) is additionally applied by interviewing the nursing staff. In this context we retrospectively consider the previous 24 h.

Table 1
PROPDESC participants' timeline.

Examinations	Screening	Inclusion	Visit 0 6 weeks before surgery up to day of surgery	SURGERY	Visit 1 Day 1 after surgery or sedation	POD testing Day 1-5 after surgery or sedation	Follow-up Day 180 after surgery or sedation
Inclusion criteria	X						
Exclusion criteria	X						
Informed consent		X					
Registration		X					
Anamnesis/risk stratification/routine laboratory values			X				
MOCA/EQ-5D-5L/IQCODE			X				
Data of surgery, anesthesia, intensive care and pain therapy					X		
CAM-ICU, DOS (ICU/IMC)						X	
CAM, DOS, 4AT, ASE (normal ward)						X	
Vital parameters, pain scores, postoperative complications						X	
EQ-5D-5L/IQCODE (phone call)							X

Table 2
Preoperative data.

Preoperative data	Items
Demographic data	age, gender, height, weight, BMI
Risk classification	ASA, RCRI, NYHA, MET
Surgical discipline	orthopedics, breast surgery, gynecology/obstetrics, urology/kidney, upper gastrointestinal tract, lower gastrointestinal tract, hepato-biliary, vascular surgery, head/neck, plastic/dermatological surgery, cardiac surgery, thoracic surgery (lungs/esophagus), others
Surgical risk	low, intermediate, high
Routine-laboratory	hemoglobin, hematocrit, HbA1c, leukocyte count, sodium, potassium, creatinine, total protein, C-reactive protein, troponin, NT pro-BNP
Long-term medication	anticholinergics, benzodiazepines, tricyclic antidepressants, SSRI, hypnotics, opioids, others, number of medications
Delphi score	age, physical activity, alcoholism, hearing impairment, history of delirium, emergency surgery, open surgery, ICU admission, C reactive protein
Alcohol consumption	AUDIT-C
Quality of life	EQ-5D-5L
Cognitive impairment	MOCA (patient testing), IQCODE (survey of relatives)

BMI: Body Mass Index, ASA: American Society of Anesthesiology, RCRI: revised Cardiac Risk Index, NYHA: New York Heart Association, MET: Metabolic Equivalent of Task, ICU: Intensive Care Unit, SSRI: Selective serotonin reuptake inhibitor, AUDIT-C: Alcohol Use Disorders Identification Test-Consumption.

Table 3
Treatment data.

Treatment data	Item
Premedication	amount of midazolam
Anesthesia technique	general, spinal, epidural, analgo-sedation, local, other regional
Operation	conducted operation, planned/actual duration, duration of CPB
Fluid balance	infusion, transfusion, blood loss, urine volume
Ventilation	duration of ventilation in the OR/ICU
Postoperative care	duration of stay in PACU, ICU admission, cause of ICU admission
Postoperative pain therapy	opioids, peripheral analgesic, regional, other
POD testing	start of testing after operation/sedation

CPB: Cardio Pulmonary Bypass, OR: Operating Room, ICU: Intensive Care Unit, PACU: Post Anesthesia Care Unit.

Table 4
POD assessment.

Test	CAM	CAM-ICU	DOS	4 AT + ASE
ICU		X	X	
IMC		X	X	
Normal ward	X		X	X

CAM: Confusion Assessment Method, CAM-ICU: Confusion Assessment Method for Intensive Care Unit, DOS: Delirium Observation Scale, 4 AT: Alertness, Attention, Acute Change and Abbreviated Mental Test-4, ASE: Attention Screening Examination.

In addition to the POD assessment, vital parameters (respiratory rate, heart rate, blood pressure, oxygen saturation), pain evaluation using numeric rating scale (NRS) and verbal rating scale (VRS) as well as postoperative complications are registered on the postoperative study visits and from the medical records. The assessments are performed as spot checks at the time point of the daily visits.

2.5. Endpoints/sub-group analysis

Primary endpoint is the occurrence of postoperative delirium during any of the first five days after surgery respectively during the first five days after ending of postoperative sedation. The endpoint is considered to be fulfilled if POD is detected by at least one of the applied assessment methods (Table 4).

In addition, the study protocol offers the possibility to capture the course and outcome of treatment as well as their consequences in the follow-up after 180 days and sub-group analysis. The endpoints are listed in Table 5.

2.6. Sample size considerations

In order to investigate the correlation of several preoperative parameters with postoperative delirium at a sufficient number of events under the assumption of a delirium incidence of 20–30% in the study group, the sample size was determined to be 1000 patients. Based on 120–180 expected events in the evaluation cohort (n = 600), 8–12 parameters should be tested for significance in a multivariate analysis in order to form a risk score.

2.7. Evaluation cohort/interim analysis

The evaluation cohort consists of the first 600 data sets with completed postoperative study visits. First, an interim analysis is performed to identify predisposing risk factors for POD from the preoperative study data. Subsequent development of the PROPDESC score is based on significant correlations found in this preceding multifactorial univariate analysis. Strength of the correlations and overlapping effects of the parameters as well as clinical considerations and estimation of data availability and applicability are considered in the development.

2.8. Validation cohort

The obtained PROPDESC score is to be validated internally on the last 400 data sets of the observational study.

2.9. Statistical analysis

In the evaluation step different approaches will be used and evaluated to derive predictive models for POD based on preoperative information. The final model will be set up based on the results of intensive cross validation for the models resulting from these analyses based on the evaluation data set, taking also into account the practicability of the score to be developed.

One of the approaches will be based on logistic regression analysis to predict POD. In a first step, unifactorial logistic regression will be used to fit linear, nonlinear and threshold models to the data. The predictors resulting from this step will be included into various stepwise strategies (e.g. forward and backward selection) to reveal a first multifactorial model. Finally this model will be checked for improvement by the inclusion of interaction terms.

A second approach will follow a component-wise gradient boosting approach [23]. These types of algorithms are able to estimate and select the most informative variables for prediction models based on gradient descent in function space [24]. The algorithm fits the negative gradient of the loss one-by-one to weak learners (e.g. simple univariate regression

Table 5
Primary and secondary endpoints.

Endpoints	
Primary	POD
Secondary	course and outcome of treatment, pain therapy, postoperative complications, length of stay (LOS), intrahospital mortality, mortality after 180 days, postoperative cognitive dysfunction (POCD) 180 days after surgery, preoperative quality of life and quality of life 180 days after surgery, posthospital care, sensitivity and feasibility of the test methods for POD and pain assessment

models) for each potential predictor and selects in each iteration only the best-performing one. The final model consists of the sum of the estimated and selected predictors effects: The resulting prediction model follows hence an additive structure and is in the same way interpretable as more classical approaches. The main tuning parameter is the number of boosting iterations to be carried out, which is selected via resampling procedures on the evaluation cohort based on prediction accuracy [25].

2.10. Clinical study monitoring

According to good clinical practice (GCP) guidelines, this observational trial includes a monitoring concept to ensure data quality and safety. Therefore, training of the study nurses and student assistants as well as regular database checks for missing or inaccurate data (query reports) and regular team meetings (recording) are components of PROPDESC. The intentions of training, supervision and meetings are to achieve high protocol compliance and data quality, as well as to ensure patients' safety and rights.

3. Discussion

POD is the most common complication of elderly patients after surgery. It occurs acutely in the first few postoperative days and compromises the success of treatment by enhanced morbidity, persistent need for care and even increased mortality. Due to demographic developments towards a larger proportion of the elderly in the population of industrialized countries, a strategy for counteracting this complication is becoming increasingly important in perioperative medicine.

Knowledge of the promoting (predisposing) and triggering (precipitating) factors is initially required to reduce the incidence and the harm of POD. The aim is to identify patients at risk before their treatment in order to protect them from adverse effects of POD by prophylaxis or early treatment.

Predictive models such as Delphi [2] or PreDEliric [26] include preoperative predisposing factors for POD as well as parameters of intraoperative course and postoperative physical status. PROPDESC intends to develop a risk score for the detection of POD endangered patients prior to elective surgery based on preoperative routine data and cognitive assessment. The goal is to identify high-risk patients preoperatively during treatment planning.

Lindroth et al. give advice for further research on that topic in their "Systematic review of prediction models for delirium in the older adult inpatient" [27]. As we agree with their suggestions we designed the trial only with parameters that available prior to the onset of delirium and are readily available in clinical practice, we plan to conduct a structured delirium assessment 7 days a week by trained study staff. We hope that we can avoid the weaknesses of the past trials to get a reliable risk score for the preoperative prediction of postoperative delirium.

After identifying significant predictors for POD from the preoperatively collected data, a screening instrument for application in clinical routine will be developed. In compiling the prediction model, not only the significance of the individual factors, but also their enhancement of predictive power in compound as well as their regular availability in routine will be addressed. For example, it makes little sense to integrate frequently available hemoglobin concentrations and hematocrit both as predictors into the score, as their clinical implications are too similar. On the other hand, time-consuming, comprehensive cognitive tests could not be performed as routine screening and therefore their results would not be available for every patient. In order to identify cognitive impairment as a risk factor preoperatively, a short routine test with good prediction for POD should be used. PROPDESC examines the separate items of MOCA, IQCODE and EQ-5D-5L for their predictive power regarding POD in order to select the most appropriate ones for the instrument.

PROPDESC intends to develop a predictive risk score for POD that is automatically generated from routine preoperative data. The resulting

screening instrument should be easily integrated into the routine of preoperative evaluation to provide consistent detection of patients at risk and thus to enable a targeted application of protective efforts for prophylaxis of this complication.The results of PROPDESC should provide useful support for further research in the field of perioperative management of patients at risk for delirium. Measures to protect patients from POD could be the avoidance of drugs and treatments that promote delirium on the one hand and on the other hand the support of reorientation through visual and hearing aids as well as cognitive stimulation in the postoperative routine. Assistance for adequate oral nutrition and mobilization seems to be equally important in order to regain health and return to everyday life, as described in mHELP (Modified Hospital Elder Life Program) [28].

The PROPDESC study group intends to conduct a multicenter external validation of the predictive score and an intervention study to reduce the incidence and adverse effects of POD. Besides the preoperative detection of patients at risk for delirium, PROPDESC investigates secondary objectives. These include the development of brief and simple tests to detect preoperative cognitive and functional impairments derived from more comprehensive procedures such as MOCA, IQCODE and EQ-5D-5L.

POD often remains unrecognized. Short cognitive tests and focused clinical observation are required to detect it. In this context, the key diagnostic features such as acute onset and fluctuating course of symptoms, inattention, impaired level of consciousness, and disturbance of cognition (e.g., disorientation, memory impairment, alteration in language) need to be addressed [29,30]. For this purpose, the Confusion Assessment Method (CAM) was validated as the most widely used instrument in many studies with a sensitivity of 94% and a specificity of 89% [29,31–33]. It is very closely oriented to the diagnostic criteria of delirium according to the Fifth Edition Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-V) as a reference standard [4]. Translations into several languages as well as a variant adapted for use on intensive care unit (CAM-ICU) have been validated [34].

Other useful assessment tools are the Delirium Observation Scale (DOS) which is based on observation during regular care and the clinical rapid test 4 AT involving Alertness, Attention, Acute Change and Abbreviated Mental Test-4 [35,36] designed in 2011 by Mac Lullich (Edinburgh Delirium Research Group) Ryan and Cash.

The sensitivity of various POD assessments will also be investigated to reduce the existing high number of unreported delirium diagnoses and to enable early treatment by reliable detection. In addition to the spot checks by CAM-ICU, CAM, 4AT and ASE, the DOS is used under involvement of the nursing staff in order not to miss any POD diagnosis.

Adverse long-term effects of POD, such as POCD and decline in quality of life, are assessed in a 180-day telephone follow-up using EQ-5D-5L and IQCODE after surgery.

In preparation for the planned interventional study, perioperative influences from surgery, anesthesia, intensive and pain therapy will be captured to form a likely protective treatment bundle.

The comprehensive data set of the PROPDESC study allows subanalyses to be performed on various questions concerning the perioperative care of elderly patients. Due to the size of the study sample and the detailed records, we hope to obtain statistically significant results that will be useful for their treatment.

Trial status

This study was registered under German Clinical Trials Register/ Deutsches Register Klinischer Studien (DRKS-ID: DRKS00015715) on 13th of December 2018 - Retrospectively registered, https://www.drks. de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRK S00015715.

The feasibility of the study protocol was previously evaluated by including 5 patients in July 2018 – First patient was enrolled on 9th of July 2018. The planned 12-month interval with frequent recruitment

and enrolment began on the 3rd of September 2018. Until 30th of April 2019, 700 patients were enrolled in PROPDESC, so the recruitment plan is likely to be fulfilled.

Declarations

Declaration of Helsinki

The work described has been carried out in accordance with The Code of Ethics of the World Medical Association for experiments involving humans.

Ethics approval and consent to participate

A positive ethics vote was obtained by the Ethics Commission of the Medical Faculty of the Rheinische Friedrich-Wilhelms-Universität Bonn on 18.09.2017 under application number 255/17 (Ethical Approval Document 1). The study protocol including amendments was finalized on 2nd of May 2018 as version 2.1 (Ethical Approval Document 2). Each patient must give written informed consent (Patient) to participate in the study. Relatives must give written informed consent to be contacted for telephone follow-up.

Consent for publication

All authors consented with this publication.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request after the end of the trial. A fulfilled SPIRIT 2013 Checklist is available as an Additional file (Appendix).

Funding

Authors' contributions

Vera Guttenthaler and Jan Menzenbach have substantially contributed to the interpretation of current specific knowledge, which resulted in the conception and design of the present trial. Jan Menzenbach is sponsor and principle investigator of the present trial and participated in the acquisition of funding.

Maria Wittmann and Jan Menzenbach have been involved in drafting the manuscript, revising it critically for important intellectual content, and approved the final manuscript.

The study team consists of physicians and non-physicians from the Clinic for Anesthesiology at the University hospital of Bonn as well as doctoral students who are supervised by Professor Dr. Maria Wittmann and Dr. Jan Menzenbach. Listed authors (Acknowledgements) contribute to the collection of data. Andrea Kirfel, Jan Menzenbach and Maria Wittmann are responsible for project management. Rolf Fimmers and Andreas Mayr wrote the statistical methods.

Inclusion in the study is performed by the physicians of the study staff after receiving written informed consent.

Primary sponsor and principle investigator of the PROPDESC Study is Dr. Jan Menzenbach.

Statistical processing of the study data is supported and performed by the Institute for Medical Biometry, Informatics and Epidemiology (IMBIE) at the University of Bonn supervised by Dr. Rolf Fimmers and Professor Dr. Andreas Mayr.

The authors listed below have access to the database, the final study data and study results. The authors are entitled to publish study results, including subgroup analyses and investigations of secondary endpoints. All authors have read and approved the manuscript.

Declaration of competing interest

None.

Acknowledgements

List of abbreviations

4 AT	Alertness, Attention, Acute Change and Abbreviated Mental Test-4
ASA	American Society of Anesthesiologists' Physical Status
ASE	Attention Screening Examination
AUDIT-C	Alcohol Use Disorders Identification Test—Consumption
BMI	Body-mass index
CAM	Confusion Assessment Method
CAM-ICU	Confusion Assessment Method for use on intensive care unit
CPB	Cardiopulmonary bypass
CRP	C-reactive protein
Delphi score	DELirium Prediction Based on Hospital Information Score
DOS	Delirium Observation Scale
DRKS	Deutsches Register Klinischer Studien (German Clinical Trials Register)
DSM-V	Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders
EQ-5D-5L	EuroQol-5 Dimensions-5 Levels
FKS	Funding Program Clinical Studies
GCP	Good Clinical Practice
HbA1c	Glycated hemoglobin (hemoglobin A1c)
ICU	Inrtensive Care Unit
IMC	Intermediate Care Unit
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
LOS	Length Of Stay
MET	Metabolic Equivalent of Task
mHELP	Modified Hospital Elder Life Program
MOCA	Montreal Cognitive Assessment
NRS	Numeric Rating Scale
NT pro-BNP	N-terminal pro brain natriuretic peptide.
NYHA	New York Heart Association Classification
OR	Operating Room
PACU	Post-Anesthesia Care Unit
POCD	POstoperative Cognitive Dysfunction
POD	Postoperative Delirium
PROPDESC	PRe-Operative Prediction of postoperative DElirium by appropriate SCreening
RCRI	Revised Cardiac Risk Index
REDCap	Research Electronic Data Capture
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SSRI	Selective Serotonin Reuptake Inhibitor
SZB	Studienzentrum Bonn
UKB	University Hospital Bonn
VRS	Verbal Rating Scale

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