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Original Contribution

Ketamine vs. haloperidol for prevention of cognitive dysfunction and postoperative delirium: A phase IV multicentre randomised placebo-controlled double-blind clinical trial

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ABSTRACT

Study objective: Delirium is frequently observed in the postoperative and intensive care unit (ICU) population. Due to the multifactorial origin of delirium and according to international guidelines (e.g., American Geriatrics Society; Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption (PADIS) guideline), there are several but no incontestable options for prevention and symptomatic treatment.

The purpose of the Baden PRIDe (Prevention and Reduction of Incidence of postoperative Delirium) trial was to determine whether postoperative cognitive dysfunction and delirium could be prevented by the combination of possible preventive agents such as haloperidol and ketamine. In addition, pre- and postoperative levels of the biomarkers cortisol, neuron specific enolase (NSE) and S100β were measured to investigate their dynamics in delirious and non-delirious patients after surgery.

Design: The Baden PRIDe Trial was an investigator-initiated, phase IV, two-centre, randomised, placebo-controlled, double-blind clinical trial.

Setting: Perioperative care.

Patients: 182 adult patients that underwent elective or emergency surgery under general or combined (i.e., general and regional) anaesthesia.

Interventions: Pre-anaesthetic, pharmacologic prevention of postoperative brain dysfunction with haloperidol, ketamine, and the combination of both vs. placebo.

Measurements: Assessment of cognitive performance pre- and postoperatively with the MMSE, the DOS, the Nursing Delirium Screening Scale (Nu-DESC) or the Intensive Care Delirium Screening Checklist (ICDSC) during ICU stay.

Main results: None of the three study arms – haloperidol, ketamine, or both drugs combined - was significantly superior to placebo for prevention of postoperative brain dysfunction and delirium ($P = 0.39$). Measured levels of postoperative cortisol were significantly higher in delirious patients. S-100β levels were significantly higher in

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all postoperative outcome groups (cognitive impairment, delirium, no cognitive decline), whereas postoperative NSE levels declined in all groups.
Conclusions: The study results offer no possibility for a novel recommendation for prevention of postoperative cognitive decline including delirium. Perioperative S-100β trajectories in patients with cognitive deterioration suggest affection of glial cells in particular.
Trial registration: ClinicalTrials.gov NCT02433041; registered on April 7, 2015.

1. Introduction

Delirium was first described roughly 2500 years ago. [1] Numerous risk factors for delirium have been detected over the last decades, [2] emphasising the importance of delirium prevention in patients undergoing surgery. International guidelines can at most suggest perioperative pharmacologic adjustments, as evidence recommending or opposing specific drugs remains insufficient. [3] Accordingly, the challenge of creating reliable hospital algorithms for prevention and treatment of delirium persists and routine use of risk-prediction tools is not recommended either. [4] While the American guidelines for sedation, analgesia and delirium oppose the use of haloperidol and ketamine for delirium prevention, [5] the European Society of Anaesthesiology suggests haloperidol for delirium treatment only. [6] Despite growing evidence against the use of haloperidol for delirium prevention, [7,8] uncertainty remains due to contradictory results. [9,10] Similar findings are reported for and against the use of ketamine. [11–13] The anti-inflammatory properties of ketamine may explain its beneficial effect on limiting the development of delirium. To the author's knowledge, haloperidol and ketamine have never been investigated in combination to assess their synergistic potential for delirium prevention.

This randomised, double-blinded, placebo-controlled study aimed to compare haloperidol and ketamine separately and in combination to prevent the incidence of postoperative delirium. In addition, the association between postoperative delirium and three biomarkers that were frequently investigated in the context of neurocognitive disorders was evaluated: Cortisol [14,15], neuron specific enolase (NSE) [16,17] and S-100 calcium-binding protein B (S−100B, S-100β or S-100). [16] The investigated biomarkers have been previously linked to delirium [18], but their relevance remains unclear.

2. Materials and methods

2.1. Study design

The Baden prevention and reduction of incidence of postoperative delirium (PRIDe) trial was a prospective, interventional, Swiss two-Centre cohort study of 200 patients. The study was performed in accordance with good clinical practice standards and the tenets of the Declaration of Helsinki 2002, was approved by the local ethical committees and was registered on ClinicalTrials.gov (NCT01367093)

The study protocol was previously published [19]. Participating patients were randomly allocated to one of four study groups: one receiving haloperidol (5 μg/kg BW (body weight)), one receiving ketamine (1 mg/kg BW), one receiving both haloperidol and ketamine using the same dosing, and one receiving placebo. Patients were administered the active comparator or placebo only once right before the induction of anaesthesia. Patients were followed for the duration of three days beginning on the first postoperative day. If the study participant was discharged from the hospital before termination of the three scheduled follow-up days, he or she was contacted by telephone.

2.2. Study inclusion and exclusion criteria

Briefly, all patients admitted to the two participating hospitals in Switzerland who were scheduled for both elective and emergency surgery under general or combined (i.e., general and regional) anaesthesia were screened for eligibility. The inclusion criteria were patients aged ≥65 years and scheduled for visceral, orthopaedic, vascular, gynaecological, cardiac, or thoracic surgery. The exclusion criteria were delirium upon hospital admission or development of delirium prior surgery, Mini Mental State Examination (MMSE) score < 24 points, Delirium Observation Scale (DOS) ≥3 points, dementia, high risk for postoperative treatment in the intensive care unit (ICU; standard procedure excluded), known haloperidol or ketamine intolerance, lack of cooperation or lack of ability to communicate (i.e., speech disorders, isolation, aphasia, coma, terminal illness, drug or alcohol abuse), QT interval (QTc) prolongation (≥460 ms in men, ≥470 ms in women) or drugs influencing QT interval, Parkinson's disease, parkinsonism, intake of dopaminergic drugs (levodopa, dopamine agonists), epilepsy, delay of surgery for > 72 h after set indication for surgery, body weight > 100 kg, or inability to read German.

2.3. Assessment and definition of cognitive function

Cognitive performance was tested pre- and postoperatively with the MMSE, the DOS, the Nursing Delirium Screening Scale (Nu-DESC) or the Intensive Care Delirium Screening Checklist (ICDSC) during ICU stay. [19] A physician obtained the MMSE score once daily upon study inclusion as well as on the three immediate postoperative days. Nu-DESC score once daily, and DOS score three times per day were obtained from the caring nurse. The ICDSC score (nurse), and if possible the MMSE score (physician), were obtained when patient was treated in the ICU after surgery. All scores were documented in the paper and electronic case report form.

The MMSE may serve as a screening tool for delirium, [20] even though it was originally designed to assess cognitive impairment. [21] Moreover, significant correlation between a widely established assessment tool (Confusion Assessment Method (CAM)) and the MMSE was confirmed in a recently published article. [22] The term “delirium” was used in the protocol [19] to summarize both types of postoperative brain dysfunction after surgery assessed in the PRIDe trial: Cognitive impairment and fully developed delirium. Inferiority of one of the active comparator treatment arms in patients after surgery for prevention of postoperative cognitive impairment was defined as a two-point drop in MMSE score when assessed during one of the three postoperative days (primary outcome measure). [19].

To comply with tools used in Swiss hospitals the Nu-DESC (sensitivity 42%, specificity 98% [23]) and the DOS (sensitivity 90%, specificity 91% [24]) were implemented as screening tools for postoperative delirium parallel to the assessment of the MMSE. Of note, patients with a conspicuous Nu-DESC or DOS score prior surgery were not included in the study.

2.3.1. Postoperative cognitive impairment

As outlined above, postoperative brain dysfunction was further divided into postoperative cognitive impairment (CI) and postoperative delirium in this trial. Cognitive impairment was defined as drop of at least two points in MMSE score when below 27 on one of the first three postoperative days, or as an MMSE score below 24. [25,26]

2.3.2. Postoperative delirium

Postoperative delirium was defined by a conspicuous NuDESC / DOS / ICDSC (i.e., DOS ≥3, NuDESC ≥2, ICDSC ≥4) score on one of

the three postoperative days. CI prior surgery was defined by an MMSE score < 27 (with an MMSE score < 24 representing an exclusion criterion).

2.3.3. Postoperative cognitive improvement

Postoperative cognitive improvement was defined by an MMSE score < 27 prior to surgery with an improvement of at least two points during one of the three postoperative days independent from any drop in MMSE score below the preoperative level on one of the three postoperative days. In case of overlap of CI preoperatively and CI improvement postoperatively, the patient was assigned to the second group (i.e., CI improvement postoperatively).

2.4. Delirium biomarkers

Pre- and postoperative cortisol, NSE, and S-100β levels were measured using electrochemilumiscence kits on an E170 immunoanalyser (Roche Diagnostics, Switzerland). Blood for preoperative biomarker measurements was withdrawn directly before anaesthesia induction. For postoperative biomarker levels, blood was withdrawn between 6 a.m. and 8 a.m. on the first morning after surgery. Blood samples were centrifuged 2000 x*g* for 10 min and aliquots of patient sera were stored in a − 70 °C freezer until analysis. The coefficient of variation (CV) from the Baden lab was 1.8% for S-100β, 4% for NSE, and 7% for cortisol with an inaccuracy of around 5% for all measurements. For the Basel lab the CV of S-100β and NSE was < 9%, and for cortisol it was < 5% with corresponding inaccuracies of < 5%, < 4%, and < 6%, respectively.

2.5. Perioperative course

Duration of anaesthesia was defined as the period from anaesthesia induction until discontinuation of anaesthetic drugs. Time to extubation was defined as the period from discontinuation of anaesthetic drugs until extubation.

2.6. Statistical analysis

To increase the quality of data analyses, each set of data was tested for normal distribution (D'Agostino and Pearson omnibus normality test) and for homogeneity of variances (Levene's test) before statistical analyses. To detect differences between two groups, a paired *t*-test (paired, normal data) with Welch's correction in case of unequal variances, a Mann-Whitney test (unpaired, non normal data) or a Wilcoxon matched-pairs signed rank test (paired, non normal data) was used. Differences between multiple groups were compared using one-way ANOVA with subsequent Tukey's test to correct for multiple comparisons using statistical hypothesis testing. *P*-values reported from one-way ANOVAs are reported as multiplicity adjusted P-values to account for multiple comparisons, whereas the family-wise significance and confidence level were set to 0.05 (95% confidence interval). Differences between number of patients in different groups were compared using Pearson's chi-squared test with Bonferroni correction for alpha inflation and the Monte Carlo simulation method if the expected frequency was lower than 5.

Statistical analyses were performed using IBM SPSS Statistics (Version 24, IBM SPSS, Chicago, IL, USA) and GraphPad Prism (Version 7.04, GraphPad Software, La Jolla, CA, USA). Significance was accepted at $P < 0.05$ (two-sided for *t*-tests). Data in the text and tables are given as mean ± standard deviation (SD) or as median and confidence interval (CI).

Sample size calculation and randomisation are described in a previously published study protocol (Riegger et al., Trials 2018). [19]

2.7. CONSORT statement

The manuscript was written according to the CONSORT (CONsolidated Standards of Reporting Trials) 2010 guideline and a CONSORT checklist included within the submission. [27]

3. Results

During the recruitment period from July 2013 until December 2018, a total of 200 patients were randomly assigned to one of the four study

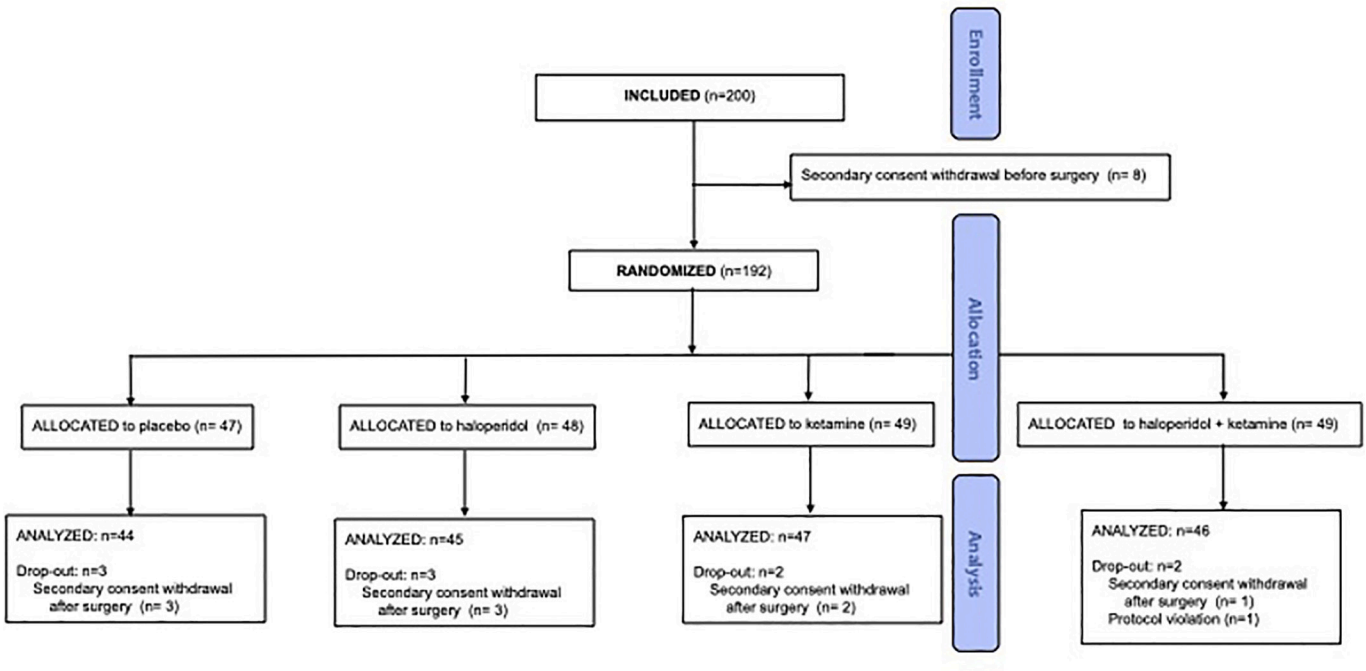

Fig. 1. Study flow chart.

Table 1
Patient characteristics according to study group.

Patient characteristics	All n = 182	Placebo n = 44	Haloperidol n = 45	Ketamine n = 47	Haloperidol + Ketamine n = 46	MV
Demographics	n = 182	n = 44	n = 45	n = 47	n = 46	
Age (years)	73.7 (6.1)	74.8 (6.6)	73.4 (6.3)	73.4 (6.1)	73.2 (5.2)	0
Gender (female, %)	79 (43.4)	25 (54.5)	16 (35.6)	21 (44.7)	17 (37)	0
Weight (kg)	76.8 (13.8)	72.1 (13.2)	78.2 (14.1)	78.2 (13.8)	78.6 (13.7)	0
Height (m)	1.69 (0.09)	1.66 (0.08)	1.70 (0.09)	1.68 (0.09)	1.70 (0.08))	0
BMI (kg/m^2)	26.9 (4.3)	26.1 (4.3)	26.8 (4.4)	27.6 (4.3)	27.1 (4.2)	0
Electrocardiogram						
QTc pre (ms)	422.2 (20.5)	423.0 (4.3)	421.4 (23.1)	424.0 (19.2)	420.2 (22.0)	1.6
QTc post (ms)	433.5 (26.7)	431.7 (21.9)	439.4 (30.5)	434.5 (30.8)	428.5 (22.2)	4.9

Data are displayed as mean (standard deviation) or percentage. MV, missing values (%); pre, preoperative.

groups. Among the 200 patients enrolled, 18 could not be followed due to secondary withdrawal from the study or protocol violation (Fig. 1): 44 patients were allocated to the placebo group, 45 patients were allocated to the haloperidol group, 47 patients were allocated to the ketamine group, and 46 patients were allocated to the mixed group (haloperidol + ketamine). Of the 182 patients with complete follow-up, baseline characteristics were similar among groups (Table 1). Apart from orthopaedic surgery distribution of surgical procedures varied considerably among groups (Supplementary Table 1), whereas anaesthesia procedures were comparable (Supplementary Table 2). There was no evidence for higher perioperative opioid use in patients suffering from delirium (Supplementary Table 3). One, and in most cases, two simple analgesics were given to all patients. Many patients without cognitive decline after surgery suffered from chronic pain (i.e., preoperative use of pregabalin, tramadol, buprenorphine, oxycodone), but among patients with postoperative cognitive improvement there were no chronic pain patients. 14 patients (7.7%) were discharged from the hospital before completion of the three follow-up days of whom seven (50%) could be reached by phone. None of these patients reported any signs of cognitive decline and all were satisfied with their clinical course after surgery.

None of the three interventional study arms – haloperidol, ketamine or both – was superior to placebo for postoperative delirium prevention (P = 0.39; Table 2). Accordingly, assessment methods did not differ among groups (Supplementary Table 4). Also, no significant difference was found (P = 0.1881) when patients without cognitive decline (no cognitive decline postoperatively, NCD) were compared to postoperative CI and delirium combined. Despite significant differences in the durations of anaesthesia and surgery, the lengths of PACU (post-anaesthesia care unit) stay were comparable among the studied groups (Table 3).

Biomarker assessments are presented in Table 4 and Figs. 2 and 3. Change of preoperative and postoperative Cortisol levels was significant in the placebo group only, whereas change of preoperative and postoperative NSE levels was significant in the ketamine group. These changes were significant for S100β levels among all study groups (Fig. 2). When comparing preoperative and postoperative biomarker levels according to outcome the only significant difference was seen in preoperative cortisol levels among NCD, cognitive impairment, and delirium (Table 4a, Fig. 3). Changes in cortisol and S-100β levels were significant in delirious patients (Table 4b). However, S-100β levels were also significantly higher in the other two groups (i.e., NCD and CI; Table 4b). NSE levels were lower in all groups after surgery, and were significantly lower among NCD individuals alone (Table 4a and 4b). When comparing preoperative and postoperative biomarker levels according to outcome the only significant difference was seen in preoperative cortisol levels among NCD, cognitive impariment, and delirium (Table 4a, Fig. 3), also when only comparing two outcome groups each (i.e., NCD and CI, Table 4c).

Table 2
Postoperative outcome according to study group.

	All	Haloperidol	Ketamine	Haloperidol + Ketamine	Placebo	P value
Cogn impairment (%)	14.3	15.6	21.3	6.6	13.6	0.16[1]
Delirium (%)	7.7	11.1	6.4	4.3	9.1	
No cogn decline (%)	78	73.3	72.3	89.1	77.3	
Cogn improvement (%)	8.8[2]	4.4[3]	14.9[3]	10.9[3]	4.5[3]	0.25[4]

BMI, body mass index; Cogn impairment, cognitive impairment; Cogn improvement, cognitive improvement; No cogn decline, no cognitive decline after surgery.
[1] P value according to comparison among “healthy”, “cognitive impairment”, and “delirium” postoperatively.
[2] Percentage of cognitive improvement among all patients (n = 182).
[3] Percentage of cognitive improvement among all patients within the study group.
[4] P value according to comparison among “cognitive improvement” and “no cognitive improvement” postoperatively.

Table 3
Perioperative data according to study group.

	All	Haloperidol	Ketamine	Haloperidol + Ketamine	Placebo	P value
Duration of surgery (min)	164.7 (100.9)	202.9 (133.6)	165.4 (78.8)	141.5 (94.3)	153.1 (83.4)	0.03*
Duration of anaesthesia (min)	242.9 (112.8)	282.4 (146.6)	238.4 (89.3)	216.6 (106.0)	236.8 (96.2)	0.05*
Time to extubation (min)	16.8 (32.5)	13.2 (8.8)	19.3 (56.6)	13.7 (8.3)	20.52 (30.1)	0.65
Duration of PACU stay (min)	332.5 (370.1)	284.5 (324.2)	398.6 (399.2)	322.8 (373.0)	320.2 (380.0)	0.58

Data are displayed as mean (standard deviation) or as the p-value (* marks statistically significant values). min, minutes; PACU, post-anaesthesia care unit.

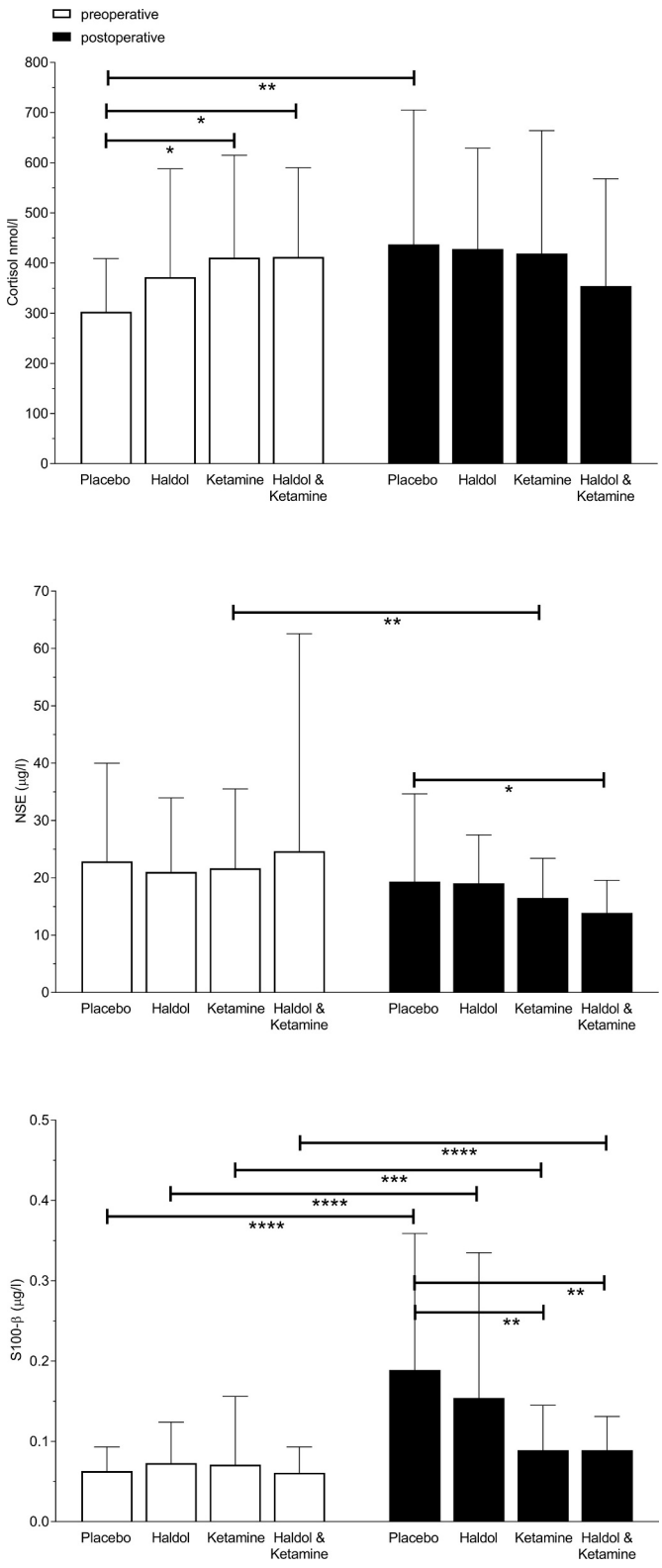

Fig. 2. Level of pre- and postoperative biomarkers divided by premedication. Horizontal lines show significant differences within and between pre- and postoperative levels. * < 0.05, ** < 0.01, *** < 0.001, **** < 0.0001; NSE, neuron specific enolase; S100, S-100 calcium-binding protein B.

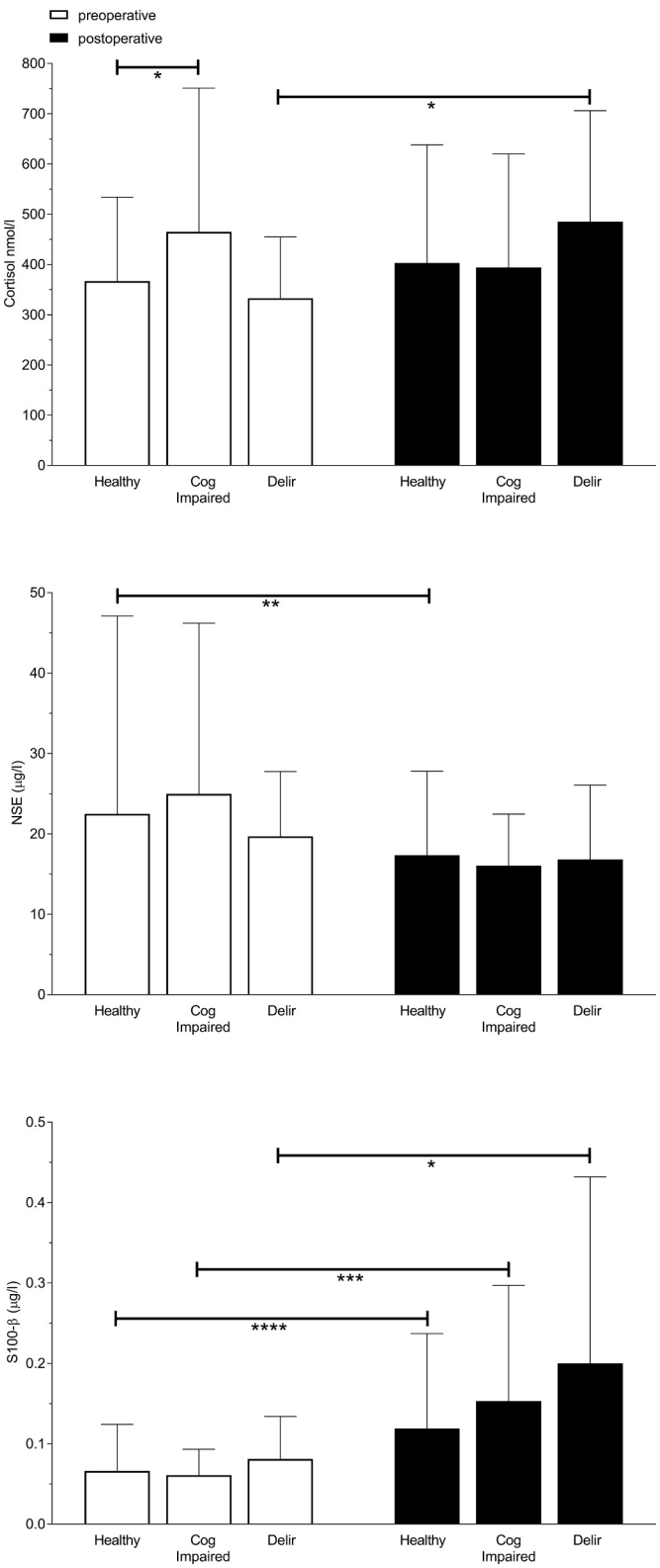

Fig. 3. Level of pre- and postoperative biomarkers divided by outcome of patients. Horizontal lines show significant differences within and between pre- and postoperative levels. * < 0.05, ** < 0.01, *** < 0.001, **** < 0.0001; NSE, neuron specific enolase; S100, S-100 calcium-binding protein B.

Table 4a
Biomarker values according to postoperative outcome.

	Cortisol (mmol/l)		NSE (µg/l)		S-100β (µg/l)	
	pre	post	pre	post	pre	Post
NCD	367 (167)	403 (235)	22.5 (24.6)	17.4 (10.5)	0.07 (0.05)	0.12 (0.12)
	n = 134	*n* = 97	*n* = 128	*n* = 94	*n* = 127	*n* = 92
Cognitive impairment	465 (286)	394 (226)	25 (21.2)	16 (6.4)	0.06 (0.03)	0.15 (0.14)
	n = 22	*n* = 15	n = 22	n = 15	n = 22	n = 15
Delirium	333 (122)	485 (221)	19.7 (8)	16.8 (9.3)	0.08 (0.05)	0.2 (0.23)
	n = 14	*n* = 10	n = 14	n = 10	n = 14	n = 10
P value	*0.05**	*0.55*	*0.8*	*0.9*	*0.56*	*0.15*
Cognitive improvement	359 (197)	416 (203)	15.7 (7.4)	14.4 (4.5)	0.08 (0.13)	0.12 (0.06)
	n = 16	n = 14	n = 16	n = 14	n = 16	n = 14
P value (no)	*0.53*	*0.53*	*0.09*	*0.59*	*0.53*	*0.82*

Data are displayed as number of patients with measured biomarker levels (n), or as mean (standard deviation). Abbreviations: pre, preoperative value; post, postoperative value. *P* values (*marks statistically significant values).
of "delirium" and "cognitive improvement" have been calculated by comparing delirium/cognitive improvement.
"yes" or "no" (i.e., compared to the rest of the study population) before and after surgery. NCD, no cognitive decline.
after surgery; NSE, neuron specific enolase; S100β, S-100 calcium-binding protein B.

Table 4b
Significance of changes of perioperative biomarker levels according to outcome.

	NCD	Cognitive impairment			Delirium	
Cortisol (nmol/l)	32 [−33; 117]	H, 0.31	−18 [−343; 159]	L, 0.45	142 [13; 331]	H, 0.03*
NSE (µg/l)	−2.7 [−4.9; −1.1]	L, 0.002*	−2.1 [−4.4; −0.4]	L, 0.06	−5.1 [−9; 14.3]	L, 0.56
S-100β	0.03 [0.02; 0.05]	H, < 0.0001*	0.08 [0.03; 0.13]	H, 0.001*	0.06 [−0.02; 0.42]	H, 0.03*

Data are displayed as median of differences with corresponding 95% confidence interval, and *P* value (* marks statistically significant values) of the change of preoperative and postoperative biomarker level (H = higher after surgery; L = lower after surgery). NCD, no cognitive decline after surgery; NSE, neuron specific enolase; S100β, S-100 calcium-binding protein B.

Table 4c
Changes of perioperative biomarker levels according to outcome compared among outcome groups.

	Cortisol (nmol/l)		NSE (µg/l)		S-100β	
	Pre	Post	Pre	Post	Pre	Post
NCD vs. CI	0.04*	0.98	0.87	0.81	0.9	0.46
NCD vs. delirium	0.79	0.42	0.91	0.98	0.59	0.08
CI vs. delirium	0.08	0.47	0.77	0.97	0.51	0.54
No CImpr vs. CImpr	0.53	0.53	0.09	0.59	0.53	0.82

Data are displayed as the *P* value (*marks statistically significant values) of significant differences of preoperative and postoperative biomarker level when comparing certain outcomes. CI, cognitive impairment; CImpr, cognitive improvement; D, delirium; H, healthy; NCD, no cognitive decline after surgery; NSE, neuron specific enolase; S100β, S-100 calcium-binding protein B.

4. Discussion

The PRIDe study investigated three pharmacological prevention strategies – haloperidol, ketamine, and both combined – compared to placebo for prevention of postoperative delirium in 182 patients. None of which was superior to placebo for delirium prevention. Patients receiving both, haloperidol and ketamine upon anaesthesia induction showed the lowest incidence of postoperative brain dysfunction (i.e., CI and delirium). Interestingly, delirious patients did not receive more opioids [2,28] and were pain-naïve compared to the number of patients suffering from chronic pain in the NCD group. Of note, patients receiving ketamine were the most likely to reveal cognitive improvement after surgery.

Gender seems to display different sensitivity to delirium. [29,30] The male–female ratio in PRIDe was lower compared to the often reported distribution among the ICU patient population (i.e., male patients admitted represent two thirds of the ICU population). [31–33]

Inflammation is considered an important mechanism in the pathophysiology of delirium. [18,34] Surgical trauma leads to an increase of inflammatory markers such as CRP (C-reactive protein), which can stimulate formation of reactive oxygen species. [34] Those may cause disruption of the blood-brain barrier (BBB) and provoke delirium. [34] While S-100β level trajectory was significant among all outcomes (i.e., NCD, CI and delirium), which can be considered as evidence for elevated BBB permeability, only cortisol might be of interest for early assessment of postoperative brain dysfunction. This finding supports most data on the role of cortisol in delirium and may once again substantiate the importance of stress reduction as a key strategy to manage patients in the perioperative setting. [18] Considering the anti-inflammatory properties of ketamine, this hypothesis may on one hand be supported by the fact that cortisol remained basically the same after surgery in the ketamine group, as opposed to the changes in biomarker levels within the placebo group where an unimpeded inflammatory reaction due to surgery could lead to damage of glial cells. On the other hand, cortisol levels did not differ significantly before and after surgery also in the haloperidol group, and S100β levels did also significantly differ in the ketamine group. Interestingly, there was a significant difference between postoperative NSE and S100β levels within the placebo and the combined group. These findings may suggest a certain protective effect of ketamine administered prior surgery on neurons and astrocytes. This may correspond with the suggested glial protection of ketamine due to its N-Methyl-D-Aspartat (NMDA) antagonism. [35–37] The finding that postoperative biomarker levels are always highest in the placebo group and lowest in the combined group was also observed with postoperative cortisol values, but without significance.

Preoperative biomarker values were assessed to analyze their trajectory and to be able to detect significant baseline differences as well. Comparison of preoperative cortisol levels revealed significant changes among study groups. However, due to the circadian rhythm of cortisol secretion and withdrawal of blood upon anaesthesia induction (i.e.,

different time-points) this finding cannot be interpreted.

The high standard deviations of preoperative NSE levels in patients with and without any type of CI after surgery may question adequacy of use of the measured parameters in the context of delirium. It is highly interesting that postoperatively one biomarker of cell death is lower (NSE) and another is higher (S-100β) in patients suffering from CI and delirium after surgery. These results may apply to a novel theory of predominant astrocyte death as a precursor to postoperative delirium while neurons seem to remain mostly intact. However, since postoperative S-100β levels after surgery were significantly elevated in all outcome groups glial injury alone may not be sufficient to cause delirium. Moreover, the only cerebral biomarkers that were assessed in our trial were NSE and S-100β. Thus, an association between biomarker trajectories and neuroinflammation cannot be proven.

We acknowledge that the study has several limitations. First, the study may not be sufficiently powered to detect a reduced incidence of delirium in one of the three interventional arms. Moreover, the sample size was determined at 188 participants and increased to 200 to account for drop-outs, which was lower than the number of drop-outs found in our investigation. Second, study patients underwent surgeries of various disciplines with assumed widely differing postoperative management. Detailed information on perioperative medication was obtained, but not on fluid balance (imprecise when not documented in the ICU), mobilization or nutrition protocols. However, all of these factors are relevant for a multi-component approach to prevent and treat delirium. Third, study patients were only followed for the first three postoperative days. Fourth, biomarker levels were not measured postoperatively in roughly one third of the included patients. Finally, despite that the investigation of haloperidol and ketamine combined was a new approach in the presented trial, overall lack of evidence for pharmacologic delirium intervention did diminish the power of the trial rationale to some extent. Furthermore, the ketamine dose for adequate cerebral protection may be higher.

Nevertheless, inclusion of patients aged 65 and older representing the age cohort most susceptible for delirium as well as baseline evaluation of the presented scores (i.e., MMSE, DOS, Nu-DESC) can be considered major strengths of the Baden PRIDe trial.

5. Conclusion

The study results offer no possibility for a novel recommendation for the prevention of postoperative cognitive decline including delirium using haloperidol, ketamine, or both drugs administered together. Perioperative S-100β and NSE trajectories point towards a protective effect of ketamine on neurons and astrocytes when administered prior surgery. Perioperative S-100β trajectories in patients with postoperative brain dysfunction suggest affection of glial cells in particular.

Contributorship statement

The authors have contributed to this study, its conductance and publication of study results as follows:

- Substantial contributions to the conception or design of the work: Alexa Hollinger (AH), Martin Siegemund (MS).
- Statistics: Christoph Rüst (CR).
- Planning, conduct and reporting of the work: Jonas Brügger (JB), Bianca Gysi (BG), Alexa Hollinger (AH), Jan Huber (JH), Harriet Riegger (HR), Martin Siegemund (MS), Luzius A. Steiner (LS), Madlen Surbeck (MSu), Fabian Tran (FT), Katharina Toft (KT).
- Biomarker measurement: Katharina Rentsch (KR), Hans-Ruedi Schmid (HS).
- Drafting the manuscript: Alexa Hollinger (AH), Martin Siegemund (MS).
- Critical revision of the article: all declared authors.
- Final approval of the version published: all declared authors.
- Agreement to be accountable that all aspects of the work were appropriately investigated and resolved: all declared authors.

Ethics and dissemination

This study has been approved by the Ethics Committee of Northwestern and Central Switzerland and was 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.

Patient/public involvement

Neither patients nor the public were involved in the design of our research, and were not involved in the conduct, or reporting, or dissemination of our research.

Disclosures

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Declaration of Competing Interest

All authors declare that there are no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinane.2020.110099.

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