



Original Contribution

Intraoperative hypotension is not associated with postoperative cognitive dysfunction in elderly patients undergoing general anesthesia for surgery: results of a randomized controlled pilot trial



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ABSTRACT

Study objective: To assess the effect of different intraoperative blood pressure targets on the development of POCD and test the feasibility of a larger trial.

Design: Randomized controlled pilot trial.

Setting: Perioperative care in a tertiary care teaching hospital with outpatient follow-up.

Patients: One hundred one patients aged ≥ 75 years with ASA physical status < 4 , undergoing elective, non-cardiac surgery under general anesthesia and 33 age-matched healthy controls.

Interventions: Randomization to a personalized intraoperative blood pressure target, mean arterial pressure (MAP) $\geq 90\%$ of preoperative values (*Target group*), or to a more liberal intraoperative blood pressure management (*No-Target group*). Strategies to reach intraoperative blood pressure target were at discretion of anesthesiologists.

Measurements: An experienced neuropsychologist performed a validated battery of neurocognitive tests pre-operatively and 3 months after surgery. Incidence of POCD at three months and postoperative delirium were assessed. Intraoperative time spent with MAP $\geq 90\%$ of preoperative values, recruitment and drop-out rate at 3 months were feasibility outcomes.

Main results: The Target group spent a higher percentage of intraoperative time with MAP $\geq 90\%$ of preoperative values ($65 \pm 25\%$ vs. $49 \pm 28\%$, $p < 0.01$). Incidence of POCD (11% vs. 7%, relative risk 1.52; 95% CI, 0.41 to 6.3; $p = 0.56$) and delirium (6% vs. 14%, relative risk, 0.44; 95% CI, 0.12 to 1.60; $p = 0.21$) did not differ between groups. No correlation was found between intraoperative hypotension and postoperative cognitive performance ($p = 0.75$) or delirium ($p = 0.19$). Recruitment rate was of 6 patients/month (95% confidential interval (CI), 5 to 7) and drop-out rate at 3 months was 24% (95% CI, 14 to 33%).

Conclusions: Intraoperative hypotension did not correlate with postoperative cognitive dysfunction or delirium occurrence in elderly patients undergoing general anesthesia for non-cardiac surgery.

A multicenter randomized controlled trial is needed in order to confirm the effect of intraoperative blood pressure on the development of POCD.

Trial registration number: NCT02428062 www.clinicaltrials.gov.

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1. Introduction

The world population is both growing and aging, causing a steady increase in surgical procedures performed in elderly patients [1]. In these patients, postoperative complications are more common [2] and correlate with age [3]. Postoperative cognitive dysfunction (POCD) is a frequent, often under-recognized complication posing elderly patients at higher risk for long-term disability and, possibly, mortality [4,5]. The pathophysiology of POCD is complex and multifactorial [6,7]. Non-modifiable risk factors, such as age, educational level [5,8] and type and duration of surgery [9] have been identified. On the other hand, any cerebral insult possibly encountered during the perioperative period is a potentially modifiable risk factor. The major *intraoperative* cerebral insults could be pharmacological neurotoxicity and cerebral tissue hypoxia. Indeed, general anesthetics are associated, both in experimental and neonatal literature, with neurotoxicity [10] and impaired neurological development [11]. On the other side, intraoperative cerebral tissue hypoxia can be the consequence of systemic hypoxemia and/or hypotension. While intraoperative hypoxemia is a relatively rare event [12], hypotension is frequent [13] and more often observed in elderly and hypertensive patients [14]. Few studies have explored the role of intraoperative hypotension on POCD development. Gold et al. [15] randomly assigned patients to two absolute pressure targets, during on-pump cardiac surgery, without finding any difference in cognitive function between the two groups. Moller et al. found no association between intra- and postoperative hypotension and POCD [8]. Several factors, including the use of absolute rather than relative values for the definition of hypotension in the study by Gold et al., and the observational nature of Moller's study, do not allow us to draw conclusions on the hemodynamic hypothesis of POCD pathogenesis. Especially for hypertensive patients, in which a rightward shift of cerebral autoregulation has been documented [16], absolute pressure values, adequate for healthy subjects, could lead to cerebral hypoperfusion [17].

Another cognitive disorder frequently encountered in surgical patients is postoperative delirium [18]. Also for this complication a role for intraoperative blood pressure has been hypothesized [19,20].

The aim of the present pilot randomized controlled trial was to assess the effect of an individualized intraoperative blood pressure target ($\geq 90\%$ of baseline mean arterial pressure, MAP) on the incidence of POCD and postoperative delirium in elderly patients undergoing elective non-cardiac surgery under general anesthesia, as compared to usual practice (no target specified).

2. Materials and methods

2.1. Study design

This prospective, single center, pilot randomized controlled trial was approved by the ethics committee (N°336/2013) of the Policlinico Ca' Granda Hospital in Milan, Italy and registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (ID [NCT02428062](https://clinicaltrials.gov/ct2/show/study?term=NCT02428062)). Patients were recruited between November 2014 and April 2016, inclusive, and each participant gave written informed consent. Patients were randomly assigned in a 1:1 ratio on the day of surgery with a dedicated software using the minimization technique [21] to balance groups for (i) age, (ii) expected duration of surgery and, (iii) educational level. The anesthesiologists in the operating rooms were necessarily aware of group assignment, while patients and research personnel were blinded to the study-group assignment.

An age-matched Control group was also recruited from patients' and staff members' relatives to gather normative material for POCD definition (see below). Every control subject gave written informed consent to the study and underwent the same multidimensional geriatric assessment and neuropsychological evaluation (see [Data collection](#)) of the enrolled patients.

This manuscript adheres to the applicable CONSORT guidelines.

2.2. Study patients

Inclusion criteria were age ≥ 75 years and scheduled general anesthesia for elective non-cardiac surgery. Exclusion criteria consisted of a pre-existing cognitive impairment (preoperative mini-mental state examination (MMSE) < 24), neurologic or vascular surgery and general anesthesia in the previous 6 months. Furthermore, patients with metastatic cancer, American Society of Anesthesia (ASA) physical status classification ≥ 4 , or patients with difficult geographical accessibility were excluded.

The only inclusion criterion for the Control group was age ≥ 75 years. General anesthesia in the previous 6 months, scheduled surgery/hospitalization in the subsequent 3 months and pre-existing cognitive impairment (MMSE < 24) constituted exclusion criteria.

2.3. Study treatment

Study patients were assigned either to a targeted intraoperative blood pressure management (*Target group*), in which the anesthesiologist was provided with a personalized intraoperative blood pressure target (90% of baseline MAP, see below), or to a liberal intraoperative blood pressure management (*No-Target group*), in which no target was specified. In the *Target group*, the strategy to reach the hemodynamic target was at the discretion of the anesthesiologist.

2.4. Data collection

2.4.1. Preoperative phase

The preoperative evaluation was performed at the pre-anesthesia outpatient clinic before the scheduled surgery.

An anesthesiologist recorded baseline demographic/medical data and vital parameters. Blood pressure was measured with an automated device and the average MAP of three recordings was considered the patient's baseline MAP, subsequently employed for intraoperative blood pressure target definition.

A multidimensional geriatric assessment was performed, including MMSE and physical frailty [22] measurements. The definition of physical frailty considers five items: unintentional weight loss, weakness (grip strength), self-reported exhaustion, slow walking speed and low physical activity. Patients were defined as Non-frail (0 items), Pre-frail (1–2 items) or Frail (≥ 3 items).

Finally, an experienced neuropsychologist (S.I.) performed a neuropsychological evaluation, including the Trail Making Test (TMT) part A and B, the Stroop test (time and errors), the Symbol Digit Modalities Test (SDMT), the Free and Cued Selective Reminding Test (FCSRT), immediate and delayed recall, the Verbal Phonemic Fluency Test (VPFT) and the Denomination test. Time measurements (TMT A and B and Stroop time) were transformed to a logarithmic scale as suggested by Rasmussen [23].

2.4.2. Intraoperative phase

In patients in which a radial artery catheter was placed for clinical reasons, blood pressure was measured using disposable transducers and recorded every minute. In the remaining patients, blood pressure was non-invasively measured and recorded every 3 min. Other cardiorespiratory variables and administered drugs were recorded every 30 min. When available, the non-invasive cerebral regional oxygen saturation, i.e., rSO_2 (INVOS 5100C, Covidien, Mansfield MA, USA), and the depth of anesthesia based on the Bispectral index (BIS VISTA, Covidien, Mansfield MA, USA), were monitored every minute. Since these monitoring techniques are not routinely used in our hospital, the anesthesiologist was blinded to both values to avoid any change in current clinical practice.

2.4.3. Postoperative phase and follow-up

For the first postoperative week, or until discharge (whatever came

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