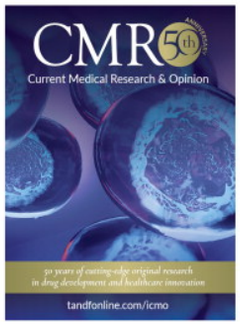

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ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/icmo20

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To cite this article: Sebastian Goss, Jan Jedlicka, Elisabeth Strinitz, Sebastian Niedermayer, Daniel Chappell, Klaus Hofmann-Kiefer, Ludwig C. Hinske & Philipp Groene (2024) Association between intraoperative hypotension and postoperative nausea and vomiting: a retrospective cohort study, Current Medical Research and Opinion, 40:8, 1439-1448, DOI: 10.1080/03007995.2024.2373885

To link to this article: https://doi.org/10.1080/03007995.2024.2373885

CURRENT MEDICAL RESEARCH AND OPINION
2024, VOL. 40, NO. 8, 1439–1448
https://doi.org/10.1080/03007995.2024.2373885
Article ST-0264/2373885

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RESEARCH ARTICLE

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Association between intraoperative hypotension and postoperative nausea and vomiting: a retrospective cohort study

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ABSTRACT

Objective: Postoperative nausea and vomiting (PONV) occurs in up to 30% of patients and its pathophysiology and mechanisms have not been completely described. Hypotension and a decrease in cardiac output are suspected to induce nausea. The hypothesis that intraoperative hypotension might influence the incidence of PONV was investigated.

Material and methods: The study was conducted as a retrospective large single center cohort study. The incidence of PONV was investigated until discharge from post anesthesia care unit (PACU). Surgical patients with general anesthesia during a 2-year period between 2018 and 2019 at a university hospital in Germany were included. Groups were defined based on the lowest documented mean arterial pressure (MAP) with group H50: MAP <50mmHg; group H60: MAP <60mmHg; group H70: MAP <70mmHg, and group H0: no MAP <70mmHg. Decreases of MAP in the different groups were related to PONV. Propensity-score matching was carried out to control for overlapping risk factors.

Results: In the 2-year period 18.674 patients fit the inclusion criteria. The overall incidence of PONV was 11%. Patients with hypotension had a significantly increased incidence of PONV (H0 vs. H50: 11.0% vs.17.4%, Risk Ratio (RR): 1.285 (99%CI: 1.102–1.498), $p < 0.001$; H0 vs. H60: 10.4% vs. 13.5%, RR: 1.1852 (99%CI: 1.0665–1.3172), $p < 0.001$; H0 vs. H70: 9.4% vs. 11.2%, RR: 1.1236 (99%CI: 1.013 – 1.2454); $p = 0.0027$).

Conclusion: The study demonstrates an association between intraoperative hypotension and early PONV. A more severe decrease of MAP had a pronounced effect.

ARTICLE HISTORY
Received 8 March 2024
Revised 18 June 2024
Accepted 25 June 2024

KEYWORDS
Nausea; vomiting; hypotension; intraoperative; blood pressure; mean arterial pressure

1. Introduction

Postoperative nausea and vomiting, or PONV, describes a multifactorial, undesirable but frequent condition seen in patients in the first 24–48 h after surgery and general anesthesia[1]. To date more than 10,000 publications examining the causes, pathophysiology, and treatment of PONV have been published.

Despite intensive scientific effort concerning the "phenomenon" of PONV and its treatment, it is still one of the most common issues in clinical daily practice. If no preventive actions are taken, up to 30% of patients suffer from PONV following an operative procedure. Individual and procedural risk factors for PONV have been identified and transposed into scoring systems[2]. The fear of PONV is one of the most common concerns patients have before surgery[3]. Besides discomfort, PONV can directly impair the surgical outcome e.g. by rupturing bowel anastomoses or compromising wound closure. As a result, PONV can cause prolonged hospital stay, unplanned hospitalization of outpatients and increased treatment costs[4,5]. Successful PONV prophylaxis is cheaper than the treatment of PONV itself, and by far cheaper than a prolonged hospitalization caused by PONV[6,7].

To date, the pathophysiology and mechanisms of action of PONV are still not fully understood. However, in recent years, significant progress has been made in understanding PONV followed by the development of a multi-causal model that combines the influence of multiple intrinsic patient and procedural factors.

Hypotension and a decrease in cardiac output are known to induce nausea, quite independently of anesthesia[8]. Medical research, especially perioperative medicine, has so far barely addressed this aspect. Several studies were carried out in obstetric anesthesia concerning the influence of hypotension on the occurrence of peri-interventional nausea after spinal anesthesia[9,10]. Studies in more generalized, less

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/03007995.2024.2373885.

specific populations are rare and, so far, have reported heterogeneous results[11–13].

Therefore, the present study investigated the hypothesis of an association between intraoperative arterial hypotension and the occurrence of PONV in the early postoperative period, up to the time of transfer from the PACU.

2. Methods

2.1. Data collection and subject selection

After approval by the ethics committee of the Ludwig-Maximilians University (No.: 20-211), which waved the need for written informed consent, the software used to generate the department's electronic anesthesia records (NarkoData®, IMESO® GmbH, Giessen, Germany) was accessed. This software collects anesthesia-relevant perioperative data for all patients undergoing surgery. In addition, the hospital's patient data management system (KAS®, SAP Deutschland SE & Co. KG, Walldorf, Germany) was used. This software package captures administrative data and some medical information like patients' comorbidities. Data were collected from 01.01.2018 to 31.12.2019 at the university hospital.

Every patient aged over 18 years who received general anesthesia or general anesthesia combined with regional anesthesia preceding general surgery, urologic surgery, orthopedic surgery, gynecologic surgery, or maxillofacial surgery was included. Patients undergoing neurosurgery were excluded because these patients usually underwent special positioning maneuvers and/or were usually transferred directly to the ICU; ENT patients were also excluded because PONV prophylaxis differed from the clinic's standard in most cases (patients received a broader preoperative PONV prophylaxis including atropine to suppress hypersalivation and marked vagal stimuli). Additionally, patients experiencing procedures with extreme intraoperative positioning, for example Trendelenburg position in robot-assisted urologic surgery could not participate in the study, because these positions may increase the risk of PONV[14]. Patients undergoing urologic procedures requiring high amounts of intravesical flushing solutions were excluded as well because the calculation of an exact fluid balance was critical in these cases. Patients who could not be extubated after surgery or had to be transferred to an ICU were also excluded from the investigation. Patients' length of stay in the postoperative anesthesia care unit (PACU) had to be longer than 20 min but not to exceed 360 min. Stays longer than 360 min were interpreted to be equivalent to an intermediate care (IMC) or ICU stay, and the corresponding patients were excluded as well. Only the first surgery for each patient in the corresponding quarter of the year was included. For the resulting patient cohort, data was extracted from the NarkoData® database using Python 3 (Version 3.6.9) [15]. Patient characteristics included age, body mass index (BMI), sex and American Society of Anesthesiology(ASA)-classification. Time between induction of anesthesia and extubation was collected as well as the balance of fluids. For each opioid given, the total dose was recorded, and a corresponding morphine equivalent dose was calculated[16]. Concerning maintenance of general anesthesia, differentiation was made between total intravenous anesthesia (TIVA) and balanced anesthesia. The smoker status of the patient was also recorded. If a patient received one of the following substances prior to extubation, this was considered as administration of a PONV prophylaxis: dimenhydrinate, ondansetron, haloperidol, metoclopramide, dexamethasone, and droperidol, irrespective of the dose. All patients received propofol for anesthesia induction, regardless of whether maintenance of anesthesia was carried out as balanced anesthesia or TIVA.

To examine a possible relationship with PONV, three "severity levels" of arterial hypotension were defined[17–19]. First, a single MAP measurement below 70 mmHg (Group: H70), second, a single MAP measurement below 60 mmHg (Group: H60) and third, a single MAP measurement below 50 mmHg (Group: H50)[17–19]. As there is no generally accepted definition of hypotension, we have oriented ourselves on previously published studies and clinically relevant blood pressure limits[17]. If patients experienced at least one of these predefined episodes (regardless of its duration) they were assigned to the corresponding hypotension group. The time duration was not added as a variable since this is only inaccurately reflected in the anesthesia protocol (documentation of the value every 3 min automatically regardless of non-invasive or invasive measurement). An H50 episode was defined as most important, followed by H60 and H70. Thus, patients were assigned to the H50 group if an H50 episode occurred, regardless of additional H60 and/or H70 episodes during the same operation. Similarly, patients were assigned to the H60 group if an H60 episode was recorded, regardless of additional H70 episodes. If no hypotensive event according to the definitions H50 to H70 was recorded, the patient was assigned to the H0 group.

Blood pressure measurement was done using non-invasively (cuff) or invasively, mostly using radial artery.

The occurrence of PONV after surgery was defined as the primary endpoint of the study. Patients were considered PONV-positive if the mandatory documentation of PONV at the end of PACU showed PONV and/or if a patient had received a medication against nausea and vomiting (PONV prophylaxis as defined above) after extubation (in order to close the electronic combined anesthesia/PACU protocol an entry concerning the presence or absence of PONV needs to be submitted). The incidence of the primary endpoint in cohorts H0 to H70 was examined.

2.2. Statistical analysis

For all data analyses SPSS version 23 (IBM Corporation, Armonk, New York, USA), Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA), the free software package "R©" version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria) including the packages "matchit," "cor" and "car" as well as the "glm"-function and Python 3 (Version 3.6.9, Python Software Foundation, Delaware, USA) with the libraries Sklearn 0.23.2, Matplotlib 3.0.3, and Numpy 1.18.1. were used.

The existence of a Gaussian distribution of data was evaluated using the Kolmogorov-Smirnov test; skewed data are displayed as median ± interquartile range, otherwise they are given as mean ± standardized deviation of the mean. For group comparisons, the Mann-Whitney U-test was used if data was not normally distributed, otherwise, a Student's T-test or Welch's test was applied. Associations regarding categorical demographic and outcome variables were assessed using Pearson's chi-square test or Fisher's exact test if necessary. Concerning the primary outcome parameter, the risk ratio and their corresponding 99% confidence intervals (CI), as well as the corresponding p-values were calculated. P-values were used as a measure of overall significance. For all comparisons, a value of $p < 0.05$ was considered significant.

In order to eliminate overlapping risk factors and differences in the frequency of the already known risk factors for PONV in the individual hypotension and control groups, propensity score matching was carried out following analysis of the uncorrected data set. Prior to the matching process, potential confounders influencing PONV frequency were identified with the help of a systematic literature analysis. Only risk factors that are well accepted in the majority of studies (gender, age, PONV history, total intravenous anesthesia (versus balanced anesthesia), duration of anesthesia, PONV prophylaxis given (versus not given), dose of opioids given, fluid balance, smoker (versus non-smoker)) were used as confounding variables in the matching process, whereas risk factors labeled as "unproven" or "conflicting" (for example BMI) were not included[20]. In order to get the best matching results, the "nearest neighbor method" was applied. In addition, a caliper of 0.2 was applied to further harmonize study groups. Matching was done with a ratio of 1:3 with replacement[21–23]. Data concerning the quality of the matching process is displayed in the supplemental material (Tables A1/1–A1/3).

In a second step, we tried to answer the question whether a PONV-prophylaxis given to patients experiencing a relevant drop in blood pressure (H50, H60, and H70 groups) was suitable to prevent PONV. Because six different antiemetic drugs were administered to the complete study cohort in various combinations, we did not aim to analyze the effect of a single drug or drug combination in this context but concentrated on the number of antiemetics a patient had received. Thus, we examined patients who had received up to three antiemetics, one antiemetic and two antiemetic drugs versus any antiemetic drug, respectively. Patients who had received three antiemetic drugs were not processed solely, because numbers were too small to do reasonable statistics ($n = 171$). First, a chi-square test was carried out to examine unadjusted data. Second, to gain a set of adjusted data, a further propensity score matching (nearest neighbor method, 1:1 ratio, no caliper) was initiated with PONV-prophylaxis being the binary variable to test in the H50, H60 and H70 groups. Gender, age, PONV history, total intravenous anesthesia (versus balanced anesthesia), duration of anesthesia, dose of opioids given, fluid balance, smoker (versus non-smoker) were considered as risk factors. Data concerning the quality of the matching process are displayed in the appendix (Tables A2.1–A2.3). To test for significant differences in the resulting adjusted groups, a chi-Square test was used, too. In this case we abstained from forming subgroups and only examined patients who did receive an antiemetic medication (regardless of the number of antiemetics) versus those who had received none, because, again, patient numbers, especially in the H50-group were too small to perform a valid propensity score matching in the potential subgroups.

3. Results

In the 2-year time frame 84.387 surgeries were registered at the University Hospital of Munich. Out of these 18.674 matched the inclusion criteria and were enrolled in the study. The complete process of patient inclusion is demonstrated in Figure 1. Patient characteristics are described in Table 1.

In the total unmatched cohort, 2,157 (11.6%) patients met the primary endpoint of PONV. Of these, 1366 (63.3%) had PONV documented prior to PACU discharge and 1526 (70.7%) received rescue antiemetics between extubation and PACU discharge. PONV incidence in the different study groups is outlined in Table 2. PONV prophylaxis was given in 49.7% of the patients and 18.7% received at least two different agents for PONV prophylaxis. It was carried out with ondansetron ($n = 3123$), dexamethasone ($n = 8147$), droperidol ($n = 203$), haloperidol ($n = 1361$), dimenhydrinate ($n = 22$) and metoclopramide ($n = 93$).

Group comparisons after matching are displayed in Table 2. All data concerning the matching process is presented in the appendix (Table A1.1–A1.3).

A PONV-prophylaxis given in patients suffering from relevant hypotension during anesthesia tended to be advantageous in preventing PONV in the H50 group (unadjusted data). Nevertheless, we did not observe a significantly reduced frequency of PONV, in hypotensive patients who had received anti-emetic drugs, neither in the raw, nor in the adjusted data groups (exception: in group H70 two anti-

Table 1. Patients' characteristics.

	All	H0	H50	H60	H70
N	18,674	5,249	1,132	4,585	7,708
Age [Y]	55 (38/69)	55 (39/69)	65 (52/74)	55 (39/69)	53 (36/67)
BMI	25.0 (22.2/28.4)	26.0 (23.2/29.4)	24.5 (21.6/27.8)	24,4 (21.6/27.8)	24.8 (22.1/28.1)
ASA III/IV [%/n]	40/7536	38/1997	65/741	44,2/2028	36/2770
Female [%/n]	52/9815	45/2354	49.3/559	57.7/2650	55/4252

Data are given as numbers (median (Q1/Q3)) and/or proportion. All: All groups; H0: group without hypotension period; H: group with any hypotension period, H50, H60, H70: groups with hypotension periods following the given definitions; N: number of patients in this specific group; Age is given in years; BMI: Body-Mass-Index given in kg/m^2; ASA: American Society of Anesthesiology Classification Score; Female: proportion of female patients.

Table 2. Statistical results in the different study groups after propensity score matching.

	Group					
	H50 versus H0		H60 versus H0		H70 versus H0	
	H50	*H0*	*H60*	*H0*	*H70*	*H0*
[n]	1132	1511	4585	3840	7708	4766
PONV [n]	197	167	619	399	860	451
No PONV [n]	935	1344	3966	3441	6848	4315
PONV [%]	17.4	11.0	13.5	10.4	11.2	9.4
Risk Ratio PONV detected [hypotension versus no hypotension]	1.285		1.1852		1.1236	
99% CI Risk Ratio	1.102–1.498		1.0665–1.3172		1.013–1.2454	
PONV detected [hypotension versus no hypotension]	$p < 0.001$		$p < 0.001$		$p = 0.0027$	

PONV: postoperative nausea and vomiting. Data are presented as numbers [n] or percentages; H0: group without hypotension period; H50-H70: groups with a hypotension period according to the given definitions. CI: Confidence-Interval.

Table 3. Influence of PONV prophylaxis on incidence of PONV in the different groups of hypotension.

		Not-adjusted data									Adjusted data		
		1–3 antiemetic drugs			One antiemetic drug			Two antiemetic drugs			1–3 antiemetic drugs		
		%	n	p	%	n	p	%	n	p	%	n	p
H50 group	Prophylaxis given	7.6	a	0.380	6.1	55	0.860	3.6	29	0.128	8,1	87	0.417
	Prophylaxis not given	9.7	110		12.1	110		13.6	110		9,1	97	
H60 group	Prophylaxis given	7.3	336	0.914	5.7	207	0.953	4.9	123	0.812	7.2	301	0.421
	Prophylaxis not given	6.1	283		7.8	283		9.4	283		6.7	283	
H70 group	Prophylaxis given	5.7	441	0.762	4.9	331	0.216	2.5	108	0.040	5.6	416	0.912
	Prophylaxis not given	5.4	419		6.7	419		8.1	419		5.6	419	

PONV: postoperative nausea and vomiting. Data are presented as numbers [n] or percentages; H0: group without hypotension period; H50-H70: groups with a hypotension period according to the given definitions.

emetic drugs turned out to be more effective than none; $p = 0.04$, see Table 3).

4. Discussion

The present study demonstrates an association between intraoperative hypotension and early PONV. Patients belonging to a specific group of hypotension (H50, H60, H70) showed a significant increase in the occurrence of PONV compared to patients without intraoperative hypotension.

Hypotension has been studied as a risk factor for PONV for several years. However, to date, most studies investigating this topic have focused on obstetric populations. In these populations, short-lasting hypotension frequently occurs during or immediately after spinal anesthesia. George et al. demonstrated that prophylactic administration of vasoconstrictors is able not only to minimize hypotension but also to reduce nausea and vomiting in obstetric patients[10]. Likewise, an evaluation of treatment quality concerning cases of maternal hypotension after spinal anesthesia from a current Cochrane analysis showed that (i) PONV is a common problem and that (ii) a reduced frequency of hypotensive events also led to fewer patients suffering from PONV[24].

Nevertheless, there are few studies on the relationship of PONV with intraoperative hypotension in general surgical populations. In an actual study on 247 patients undergoing thyroidectomy, a significant influence of hypotension on the occurrence of PONV was noted[25]. Two further prospective observational studies carried out by Pusch et al. also showed a positive association between hypotension and PONV[11,12]. A significant increase in the rate of PONV was noted in patients whose systolic blood pressure dropped more than 35% compared to induction. Interestingly, it was irrelevant whether the decrease in blood pressure occurred during induction or maintenance of general anesthesia. A subsequent study with a similar group of patients observed a significantly higher rate of PONV in patients with orthostatic dysregulation. However, it must be noted that in these studies there were some group differences with regard to known PONV risk factors, which was officially commented in a reply to the authors[26].

Maleczek et al. investigated the association of PONV and intraoperative hypotension in a recent retrospective analysis of more than 30.000 patients and identified a MAP $<$ 50 mmHg to be a risk factor for PONV in the PACU[13].

To identify PONV risk factors (other than hypotension) in the study groups, we carried out an extensive literature research and chose only well-established factors (gender, age, PONV history, total intravenous anesthesia (versus balanced anesthesia), duration of anesthesia, PONV prophylaxis given (versus not given), dose of opioids given, fluid balance, and smoker (versus non-smoker)). Using the identified factors as "confounders," we performed propensity score matching. As a result, the examined post-analysis groups were comparable with regard to pre-described PONV risks and demographic data[27]. Statistics calculated in the post-analysis groups only displayed minimal bias despite their retrospective structure. Therefore, they should be suitable to confirm the suspected connection between PONV and intraoperative hypotension in a large population.

In many studies, the definition of intraoperative hypotension is a point of criticism, especially given the growing evidence that blood pressure values should be defined more individualized than with general values[28–30]. A current review found 140 different definitions of perioperative hypotension used in

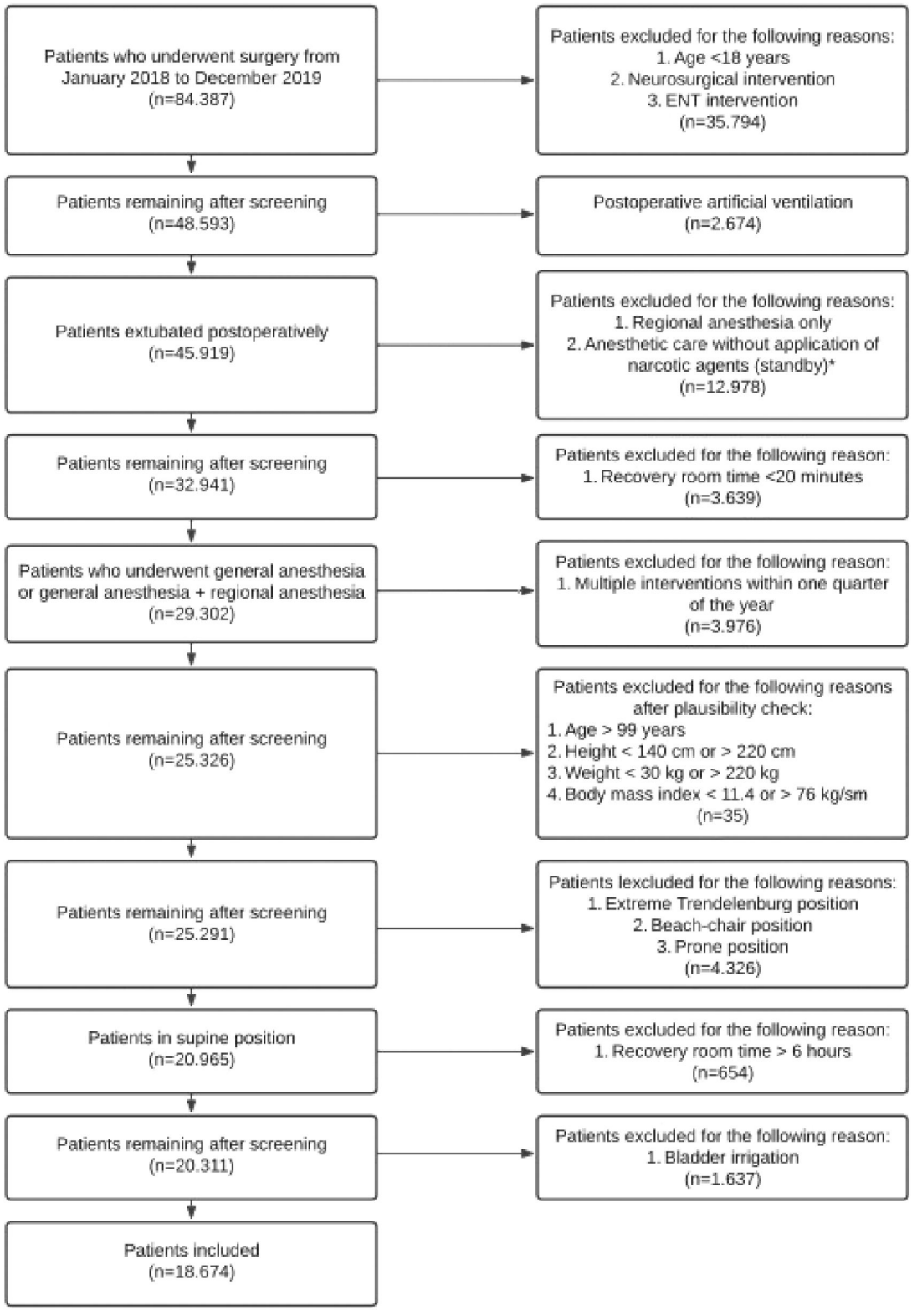

Figure 1. Process of patient inclusion.
*Central venous catheter installation, dialysis catheter installation, vascular embolization, etc.
ENT: ear, nose and throat surgery.

different trials, which, according to Bijker et al. limits the comparability of research results[17]. The most common definition of perioperative hypotension is a systolic blood pressure lower than 80 mmHg or a decrease of systolic blood pressure of more than 20% compared to values before induction of anesthesia[17]. If MAP decreases more than 55% compared to pre-anesthetic values, damage to the myocardium and renal tissue is probable[19]. However, besides the mere severity of a reduction in blood pressure, the duration of intraoperative hypotensive episodes is also a relevant factor[18].

In the current study, the various definitions of hypotension given in the literature were taken into account by defining three different hypotension groups. We found that all three defined types of hypotension increased the frequency of PONV. Pronounced, albeit short-lived, hypotension with a MAP <60 mmHg had a particularly pronounced effect. These results are comparable to the findings of Maleczek et al. which were carried out in a comparable study setting[13].

We also considered investigating the duration of hypotension as a possible influencing factor but decided not to do this because long-lasting periods of severe hypotension were very rare in this cohort (data not shown). Blood pressure values are transferred to the digital anesthesia protocol every 3 min and are thus only a very inaccurate representation of the temporal component of hypotension. All in all, despite large patient numbers, our data were not suitable to study the effect of prolonged hypotension on PONV incidence.

If one considers the negative effects of intraoperative hypotension on various organ systems, which are well known and have been repeatedly demonstrated, this study adds another negative aspect[30–32]. PONV primarily affects postoperative patient comfort, but can also have an outcome-influencing character.

Different types of PONV prophylaxis were shown to be effective in various investigations[7]. In our clinic mostly dexamethasone and/or ondansetron are given as a PONV-prophylaxis. Nevertheless, the number of different antiemetic drug combinations administered was too large to carry out a differentiated analysis concerning only dexamethasone and ondansetron. Interestingly, a prophylaxis with two antiemetics was effective in the H70 group. However, in groups with a more pronounced hypotension (H50; H60), PONV-prophylaxis was not helpful and was presumably overshadowed by the low blood pressure effect.

4.1. Limitations

The current investigation has some limitations. Due to the retrospective nature of the study, it is possible that unmeasured confounders could have influenced the results despite propensity score matching. Propensity score matching can compensate for some limitations associated with retrospective investigations, but data quality is not comparable to a RCT.

Second, compared to many other studies, a PONV rate of around 11% in the current population seems rather low. This might be due to the relatively short observation interval (compared to other studies), which only lasted until the end of care in the PACU. Unfortunately, our digital documentation goes only up to this point. After that, the data was no longer accessible in a standardized and structured manner with regard to this issue. Additionally, it may be attributed to the fact that 49.6% of the patients received a PONV prophylaxis, that induction of general anesthesia was carried out with propofol (propofol was not administered in most patients during early PONV research in the 1990s) and that total intravenous anesthesia was applied in 55%[2,33]. Additionally, the exclusion criteria might have influenced the occurrence of PONV. A large number of patients who received anesthesiological care within the 2-year observation period were excluded. The reasons for doing so are given in the methods section. The inclusion of these special populations (for example patients with extreme positioning) could have altered the PONV rates and, thus, the results, but from our point of view also could have generated relevant bias with regard to more general surgical populations.

A very small number of patients might have been classified as "PONV positive" because intraoperative PONV prophylaxis was forgotten and erroneously administered immediately after extubation, which would be recognized as a rescue administration in our algorithm. This may have occurred in any group but should have been leveled out by the matching and group-building process.

Third, the number of prophylactically administered antiemetics was not considered for integration in the general propensity score matching process. In our clinic, we first administer dexamethasone prophylactically. If the PONV risk is high, ondansetron is added towards the end of the surgery. If the risk is very high, inhaled anesthetics are not used at all. Due to the high number of cases, differences in the number of prophylactics administered should almost balance out in the propensity score matching.

Fourth, the definition of hypotension is inconsistent around the world and a universal definition is still being debated. We tried to accommodate for this problem by "creating" different hypotension groups.

Furthermore, one cannot rule out the fact that – despite mandatory electronic documentation – the documentation of PONV might not have been completely consistent. To further improve documentation, we also interpreted the postoperative administration of certain medications as a sign of PONV. Finally, the reduction of PONV is defined as one of the quality goals of our clinic and is therefore a focal point for all anesthesiologists involved.

5. Conclusion

This study demonstrates an association between intraoperative hypotension per se and the occurrence of early PONV prior to transfer from the PACU. As most observed episodes of hypotension were brief, a relationship concerning the duration of these episodes and PONV frequency could not be established.

Transparency

Declaration of funding

This paper was not funded.

Declaration of financial/other relationships

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

Sebastian Goss: This author helped to analyze the results and to draft the manuscript. Jan Jedlicka: This author helped to supervis the study and to draft the manuscript. Elisabeth Strinitz: This author helped to conduct the study, to analyze the results, and to draft the manuscript. Sebastian Niedermayer: This author helped to plan the study. Daniel Chappell: This author helped to plan and to supervise the study. Klaus Hofmann-Kiefer: This author helped to plan and to supervise the study and he helped to analyze the results and to draft the manuscript. Ludwig C. Hinske: This author helped to plan and to supervise the study. Philipp Groene: This author helped to plan, conduct and supervise the study and he helped to draft the manuscript.

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Appendix

1. Tables A1/1–A1/3 matching protocols

1.1. Group H50

Table A1/1. Summary of balance for all data before and after matching.

Summary of balance for all data:

Variable	Means treated	Means control	Std. mean diff	Var. ratio	eCDF mean	eCDF max
Distance	0.4340	0.1221	0.9973	5.7081	0.3392	0.5238
Gender	0.4938	0.4485	0.0907	.	0.0453	0.0453
Age	61.6060	54.1892	0.4398	0.8958	0.0927	0.2106
PONV-History	0.0548	0.0640	−0.0406	.	0.0092	0.0092
TIVA	0.3860	0.6239	−0.4886	.	0.2379	0.2379
Anesthesia-Time	201.9655	97.6729	0.9152	3.9353	0.2291	0.4738
PONV-Prophylaxis	0.4700	0.4302	0.0797	.	0.0398	0.0398
Opioid-Dose	142.7037	67.9124	0.4112	7.5671	0.1626	0.2193
Smoker y/n	0.1555	0.1351	0.0563	.	0.0204	0.0204
Fluid-Balance	1769.3825	881.8926	0.6730	2.3979	0.1723	0.3704

Summary of balance for matched data:

Variable	Means treated	Means control	Std. mean diff	Var. ratio	eCDF mean	eCDF max	Std. pair dist
Distance	0.4340	0.4334	0.0019	1.0033	0.0006	0.0345	0.0088
Gender	0.4938	0.5188	−0.0501	.	0.0250	0.0250	0.9842
Age	61.6060	59.4476	0.1280	1.0056	0.0320	0.0922	1.0988
PONV-History	0.0548	0.0509	0.0168	.	0.0038	0.0038	0.4543
TIVA	0.3860	0.3731	0.0266	.	0.0130	0.0130	0.8964
Anesthesia-Time	201.9655	205.4906	−0.0309	0.8375	0.0145	0.0406	0.4700
PONV-Prophylaxis	0.4700	0.5174	−0.0950	.	0.0474	0.0474	1.0012
Opioid-Dose	142.7037	157.2677	−0.0801	0.8735	0.0214	0.0610	0.7277
Smoker y/n	0.1555	0.1428	0.0349	.	0.0127	0.0127	0.7062
Fluid-Balance	1769.3825	1627.9470	0.1072	1.4768	0.0242	0.0922	0.6623

SD: standard deviation for all variables, where applicable. Std. Mean Difference: standardized mean difference for all variables. Var. Ratio: variance ratio. eCDF: empirical cumulative distribution function. Std. Pair. Dist.: standardized pair distance. Opioid-Dose as mg morphine equivalent.

1.2. Group H60

Table A1/2. Summary of balance for all data before and after matching.

Summary of balance for all data

Variable	Means treated	Means control	Std. mean diff	Var. ratio	eCDF mean	eCDF max
Distance	0.5670	0.3782	0.8744	1.5507	0.2505	0.3672
Gender	0.5780	0.4485	0.2622	.	0.1295	0.1295
Age	53.9252	54.1892	−0.0141	1.1005	0.0101	0.0303
PONV-History	0.0735	0.0640	0.0364	.	0.0095	0.0095
TIVA	0.4844	0.6239	−0.2792	.	0.1395	0.1395
Anesthesia-Time	158.0951	97.6729	0.6357	2.7379	0.1274	0.2989
PONV-Prophylaxis	0.5448	0.4302	0.2302	.	0.1146	0.1146
Opioid-Dose	107.4553	67.9124	0.3102	3.7178	0.0961	0.1432
Smoker y/n	0.1583	0.1351	0.0637	.	0.0233	0.0233
Fluid-Balance	1389.7760	881.8926	0.4895	1.4844	0.1015	0.2169

Summary of balance for matched data:

Variable	Means treated	Means control	Std. mean diff	Var. ratio	eCDF mean	eCDF max	Std. pair dist
Distance	0.5670	0.5669	0.0003	1.0005	0.0003	0.0100	0.0027
Gender	0.5780	0.5863	−0.0168	.	0.0083	0.0083	0.9038
Age	53.9252	53.1371	0.0422	1.1168	0.0175	0.0505	1.1098
PONV-History	0.0735	0.0726	0.0036	.	0.0009	0.0009	0.5118
TIVA	0.4844	0.4843	0.0001	.	0.0001	0.0001	0.8963
Anesthesia-Time	158.0951	159.5117	−0.0149	0.9520	0.0082	0.0279	0.4676
PONV-Prophylaxis	0.5448	0.5785	−0.0676	.	0.0337	0.0337	0.9257
Opioid-Dose	107.4553	111.1537	−0.0290	0.9334	0.0132	0.0565	0.7119
Smoker y/n	0.1583	0.1553	0.0084	.	0.0031	0.0031	0.7193
Fluid-Balance	1389.7760	1289.1151	0.0970	1.5427	0.0205	0.0635	0.6723

SD: standard deviation for all variables, where applicable. Std. Mean Difference: standardized mean difference for all variables. Var. Ratio: variance ratio. eCDF: empirical cumulative distribution function. Std. Pair. Dist.: standardized pair distance. Opioid-Dose as mg morphine equivalent.

1.3. Group H70

Table A1/3. Summary of balance for all data before and after matching.

Summary of balance for all data:

Variable	Means treated	Means control	Std. mean diff	Var. ratio	eCDF mean	eCDF max
Distance	0.6274	0.5472	0.5915	1.1375	0.1662	0.2432
Gender	0.5516	0.4485	0.2074	.	0.1032	0.1032
Age	51.9751	54.1892	−0.1186	1.0972	0.0279	0.0576
PONV-History	0.0685	0.0640	0.0178	.	0.0045	0.0045
TIVA	0.5624	0.6239	−0.1240	.	0.0615	0.0615
Anesthesia-Time	130.9528	97.6729	0.4188	1.9135	0.0754	0.1871
PONV-Prophylaxis	0.5176	0.4302	0.1750	.	0.0875	0.0875
Opioid-Dose	90.0845	67.9124	0.2123	2.4942	0.0584	0.0972
Smoker y/n	0.1526	0.1351	0.0487	.	0.0175	0.0175
Fluid-Balance	1130.5627	881.8926	0.2891	1.0200	0.0507	0.1064

Summary of balance for matched data:

Variable	Means treated	Means control	Std. mean diff	Var. ratio	eCDF mean	eCDF max	Std. pair dist
Distance	0.6274	0.6273	0.0003	1.0013	0.0002	0.0030	0.0021
Gender	0.5516	0.5545	−0.0058	.	0.0029	0.0029	0.8489
Age	51.9751	51.5749	0.0214	1.1101	0.0136	0.0349	1.0814
PONV-History	0.0685	0.0661	0.0096	.	0.0024	0.0024	0.4876
TIVA	0.5624	0.5483	0.0283	.	0.0141	0.0141	0.9478
Anesthesia-Time	130.9528	130.5449	0.0051	0.9990	0.0037	0.0110	0.5064
PONV-Prophylaxis	0.5176	0.5333	−0.0314	.	0.0157	0.0157	0.8918
Opioid-Dose	90.0845	90.7828	−0.0067	1.0242	0.0055	0.0331	0.6636
Smoker y/n	0.1526	0.1542	−0.0046	.	0.0016	0.0016	0.7105
Fluid-Balance	1130.5627	1081.8883	0.0566	1.4449	0.0112	0.0322	0.7403

SD: standard deviation for all variables, where applicable. Std. Mean Difference: standardized mean difference for all variables. Var. Ratio: variance ratio. eCDF: empirical cumulative distribution function. Std. Pair. Dist.: standardized pair distance. Opioid-Dose as mg morphine equivalent.

2. Tables A2/1–A2/3 matching protocols regarding PONV prophylaxis

2.1. Group H50

Table A2/1. Summary of balance for all data before and after matching.

Summary of balance for all data:

	Means treated	Means control	Std.mean diff.	Var. ratio	eCDF mean	eCDF max
Distance	0.5549	0.3946	0.8648	1.0541	0.2326	0.3462
Gender	0.6485	0.3567	0.6112	n.a.	0.2918	0.2918
Age	58.7124	64.1717	−0.3080	1.2848	0.0699	0.1456
Ponv-History	0.0883	0.0250	0.2232	n.a.	0.0633	0.0633
TIVA	0.3064	0.4567	−0.3260	n.a.	0.1503	0.1503
Anaesthesia-TIme	200.1617	203.5650	−0.0309	0.8844	0.0119	0.0465
Opioid-Dose	123.5649	159.6735	−0.2389	0.5494	0.0475	0.0890
Smoker Y/n	0.1504	0.1600	−0.0269	n.a.	0.0096	0.0096
Fluid-Balance	1705.4474	1826.0717	−0.1027	0.6708	0.0330	0.0739

Summary of balance for matched data:

	Means treated	Means control	Std. mean diff.	Var. ratio	eCDF mean	eCDF max	Std. pair dist.
Distance	0.5549	0.4260	0.6957	1.2265	0.1886	0.3064	0.6958
Gender	0.6485	0.4023	0.5158	n.a.	0.2462	0.2462	0.6417
Age	58.7124	63.1353	−0.2495	1.2264	0.0566	0.1165	1.0691
Ponv-History	0.0883	0.0282	0.2119	n.a.	0.0602	0.0602	0.3179
TIVA	0.3064	0.3910	−0.1835	n.a.	0.0846	0.0846	0.9256
Anaesthesia-TIme	200.1617	204.0677	−0.0354	0.8740	0.0134	0.0489	1.1200
Opioid-Dose	123.5649	148.0072	−0.1617	0.6411	0.0330	0.0658	0.8880
Smoker Y/n	0.1504	0.1654	−0.0421	n.a.	0.0150	0.0150	0.7362
Fluid-Balance	1705.4474	1795.3571	−0.0766	0.6507	0.0295	0.0639	1.1851

Sample sizes:	Control	Treated
All	600	532
Matched	532	532
Unmatched	68	0
Discarded	0	0

2.2. Group H60

Table A2/2. Summary of balance for all data before and after matching.

Summary of balance for all data:

	Means treated	Means control	Std. mean diff.	Var. ratio	eCDF mean	eCDF max
Distance	0.6095	0.4674	0.8369	0.9216	0.2181	0.3379
Gender	0.7106	0.4193	0.6424	.	0.2913	0.2913
Age	51.1829	57.2075	−0.3232	1.0458	0.0744	0.1609
Ponv-History	0.1141	0.0249	0.2805	.	0.0892	0.0892
TIVA	0.4460	0.5304	−0.1699	.	0.0845	0.0845
Anaesthesia-TIme	155.9303	160.6862	−0.0504	0.9672	0.0126	0.0469
Opioid-Dose	103.4040	112.3045	−0.0739	0.7901	0.0142	0.0313
Smoker Y/n	0.1437	0.1759	−0.0916	.	0.0321	0.0321
Fluid-Balance	1375.1181	1407.3206	−0.0330	0.7751	0.0182	0.0376

Summary of balance for matched data:

	Means treated	Means control	Std. mean diff.	Var. ratio	eCDF mean	eCDF max	Std. pair dist.
Distance	0.6637	0.4674	1.1564	0.5079	0.3024	0.4763	1.1564
Gender	0.8495	0.4193	0.9488	.	0.4303	0.4303	1.0037
Age	48.8275	57.2075	−0.4496	0.9979	0.1035	0.2199	1.1094
Ponv-History	0.1366	0.0249	0.3512	.	0.1116	0.1116	0.3662
TIVA	0.4552	0.5304	−0.1513	.	0.0752	0.0752	1.0266
Anaesthesia-TIme	153.8620	160.6862	−0.0724	0.9874	0.0160	0.0517	1.0699
Opioid-Dose	100.2848	112.3045	−0.0999	0.7440	0.0193	0.0364	0.8805
Smoker Y/n	0.1275	0.1759	−0.1380	.	0.0484	0.0484	0.7253
Fluid-Balance	1349.6603	1407.3206	−0.0591	0.7126	0.0246	0.0508	1.0209

Sample sizes:	Control	Treated
All	2087	2498
Matched	2087	2087
Unmatched	0	411
Discarded	0	0

2.3. Group H70

Table A2/3. Summary of balance for all data before and after matching.

Summary of balance for all data:

	Means treated	Means control	Std.mean diff.	Var. ratio	eCDF mean	eCDF max
Distance	0.5964	0.4331	0.8767	1.0447	0.2323	0.3496
Gender	0.7033	0.3889	0.6881	.	0.3143	0.3143
Age	49.2479	54.9018	−0.3087	0.9704	0.0698	0.1478
Ponv-History	0.1170	0.0164	0.3130	.	0.1006	0.1006
TIVA	0.5278	0.5995	−0.1436	.	0.0717	0.0717
Anaesthesia-TIme	133.5995	128.1124	0.0673	1.1178	0.0123	0.0374
Opioid-Dose	91.6674	88.3858	0.0316	0.9717	0.0125	0.0652
Smoker Y/n	0.1406	0.1654	−0.0714	.	0.0248	0.0248
Fluid-Balance	1154.3737	1105.0097	0.0604	0.8190	0.0106	0.0423

Summary of balance for matched data:

	Means treated	Means control	Std. mean diff.	Var. ratio	eCDF mean	eCDF max	Std. pair dist.
Distance	0.6226	0.4331	1.0174	0.8144	0.2699	0.4029	1.0174
Gender	0.7547	0.3889	0.8007	.	0.3658	0.3658	0.8737
Age	47.9508	54.9018	−0.3795	0.9382	0.0858	0.1813	1.1257
Ponv-History	0.1256	0.0164	0.3397	.	0.1092	0.1092	0.3464
TIVA	0.5137	0.5995	−0.1719	.	0.0858	0.0858	1.1179
Anaesthesia-TIme	134.7265	128.1124	0.0811	1.1643	0.0148	0.0436	1.0322
Opioid-Dose	92.1050	88.3858	0.0359	1.0161	0.0114	0.0586	0.7880
Smoker Y/n	0.1374	0.1654	−0.0805	.	0.0280	0.0280	0.7614
Fluid-Balance	1163.2765	1105.0097	0.0713	0.7498	0.0108	0.0414	0.9663

Sample sizes:	Control	Treated
All	3718	3990
Matched	3718	3718
Unmatched	0	272
Discarded	0	0