Clinical Interventions in Aging

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ORIGINAL RESEARCH

Association Between Intraoperative Noradrenaline Infusion and Outcomes in Older Adult Patients Undergoing Major Non-Cardiac Surgeries: A Retrospective Propensity Score-Matched Cohort Study

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Background: Noradrenaline (NA) is commonly used intraoperatively to prevent fluid overload and maintain hemodynamic stability. Clinical studies provided inconsistent results concerning the effect of NA on postoperative outcomes. As aging is accompanied with various diseases and has the high possibility of the risk for postoperative complications, we hypothesized that intraoperative NA infusion in older adult patients undergoing major non-cardiac surgeries might potentially exert adverse outcomes.
Methods: In this retrospective propensity score-matched cohort study, older adult patients undergoing major non-cardiac surgeries were selected, 1837 receiving NA infusion during surgery, and 1072 not receiving NA. The propensity score matching was conducted with a 1:1 ratio and 1072 patients were included in each group. The primary outcomes were postoperative in-hospital mortality and complications.
Results: Intraoperative NA administration reduced postoperative urinary tract infection (OR:0.124, 95% CI:0.016–0.995), and had no effect on other postoperative complications and mortality, it reduced intraoperative crystalloid infusion (OR:0.999, 95% CI:0.999–0.999), blood loss (OR: 0.998, 95% CI: 0.998–0.999), transfusion (OR:0.327, 95% CI: 0.218–0.490), but increased intraoperative lactate production (OR:1.354, 95% CI:1.051–1.744), and hospital stay (OR:1.019, 95% CI:1.008–1.029).
Conclusion: Intraoperative noradrenaline administration reduces postoperative urinary tract infection, and does not increase other postoperative complications and mortality, and can be safely used in older adult patients undergoing major non-cardiac surgeries.
Keywords: noradrenaline, outcome, older adult, non-cardiac surgery

Introduction

Noradrenaline (NA), a strong adrenergic α1 and mild β1 agonist, can counteract the vasodilation induced by general anesthesia and treat intraoperative hypotension,[1] and it is commonly used intraoperatively to prevent fluid overload and maintain hemodynamic stability. Clinical studies revealed that NA increased postoperative wound infection and mortality in high-risk surgeries,[2–4] but others showed that intraoperative restrictive fluid therapy combined with NA administration decreased postoperative complications and hospital stay in radical cystectomy,[5] and NA infusion was not the risk factor for postoperative acute kidney injury.[6] Animal studies revealed that NA impaired microcirculation and inhibited tissue oxygen extraction,[7,8] These inconsistent results may result from the heterogeneity of NA on microcirculation and organ function,[9] but whether NA can be safely used intraoperatively is still an unresolved issue.

Received: 18 September 2023
Accepted: 31 January 2024
Published: 9 February 2024

Older adult patients are more likely to suffer hypotension during surgery.[10] Aging is accompanied with various diseases and has the high possibility of the risk for postoperative complications, and many adverse events are associated with major surgeries, including stroke, myocardial infarction (MI), or even death.[11] We hypothesized that intraoperative NA infusion in older adult patients might cause adverse outcomes.

Thus, in this study, we investigated the association between NA and postoperative in-hospital outcomes, tried to figure out the safety of intraoperative NA administration in older adult patients undergoing major non-cardiac surgery.

Materials and Methods

This retrospective cohort study was conducted at Chongqing University Cancer Hospital, and approved by the Ethics Committee of Chongqing University Cancer Hospital (approval number: CZLS2018-024; approval date: 2018-1-30), the informed consent was waived due to the anonymous nature of data.

Participants

The eligible participants included older adult patients who underwent major non-cardiac surgeries. Major non-cardiac surgery referred to the surgical procedure associated with significant fluid shifts that required postoperative hospitalization,[12] which included open resection of organs, thoracic surgery, intracranial surgery, spinal surgery, large joint replacement, laparoscopic surgery. The inclusion criteria included: patients age ≥65 years, surgical duration ≥2 hours, and elective surgery under general anesthesia. The exclusion criteria included emergency operation, intraoperative massive bleeding (>2000mL), and patients with preexisting organ failure.

Data Extraction

The data were extracted from the medical database of Chongqing University Cancer Hospital from January 2018 to December 2021, which included sex, age, ASA (American Society of Anesthesiology) physical status classification, surgical types, comorbidities, fluid replacement, transfusion, urinary output, NA dosage, lactate production (the difference of lactate level between the end of surgery and baseline), postoperative in-hospital complications and mortality and hospital stay. In NA group, a bolus of Ringer's solution was administered at a dose of 4–6 mL/kg during the induction of general anesthesia, and norepinephrine was infused till the end of surgery, the infusion rate was 0.04–0.1μg/kg/min, Ringer's solution was infused at 5–6mL/kg/h intraoperatively, and the mean artery pressure (MAP) target was set above 60 mmHg, when hypotension (MAP < 60mmHg) occurred at any time during surgery and anesthesia, the primary strategy was to adjust NA infusion rate, a bolus of crystalloid (200–250 mL) was administered if needed, which was decided by the attending anesthesiologist. In non-NA group, a bolus of Ringer's solution was administered at a dose of 8–10 mL/kg during the induction of general anesthesia, and Ringer's solution was infused at 8–12mL/kg/h afterwards till the end of surgery, when MAP < 60 mmHg at any time during surgery and anesthesia, a bolus of 200–250 mL of Ringer's solution was administered and repeatedly when necessary, ephedrine was administered if needed. In all patients, colloid was infused when blood loss exceeding 500mL or managing hypotension if necessary.

A balanced salt crystalloid solution of 1000–1500 mL and 500 mL 5% glucose was routinely infused postoperatively for the surgical patients per day until the normal oral intake recovered.

Outcomes

The primary outcomes were postoperative in-hospital mortality and complications, including stroke, myocardial infarction (MI), arrhythmia, pulmonary edema, pulmonary infection, respiratory failure, acute kidney injury (AKI), urinary tract infection, wound infection, anastomotic leakage, and thrombosis. AKI was defined according to the classification of the Acute Kidney Injury Network (AKIN) based on changes in plasma creatinine levels over 72 postoperative hours.[13] The secondary outcomes were intraoperative crystalloid infusion, blood loss, transfusion, lactate production, and hospital stay.

Statistical Analysis

The patients were grouped as receiving NA and not receiving NA, the basic characteristics between groups were balanced using propensity score matching (PSM) with R program language 4.1.2. PSM was performed using a one-to-one nearest neighbor matching algorithm without replacement, the caliper was 0.2. The predictors for PSM were age, sex, BMI, smoking, ASA physical status, comorbidities, and surgical types. Categorized variables were presented as absolute numbers and proportions, and were compared using Fisher exact test. Continuous variables were presented as median (interquartile range), those of normal distribution were compared using *t* test, and those of non-normal distribution were compared using Mann–Whitney test. Logistic regression was performed for intraoperative fluid replacement, transfusion, blood loss, urinary output, intraoperative lactate increase, postoperative in-hospital complications and mortality. Odds ratio (OR) and 95% confidence interval (CI) were achieved. A *P* value less than 0.05 was considered statistically significant, and the statistical analysis was conducted using Stata MP 14 (64-bit) software.

Results

Figure 1 showed the procedure of patients selection. A total of 3466 older adult patients undergoing elective major non-cardiac surgery were identified, and 2909 patients were eventually included. Of those, 1837 receiving intraoperative NA

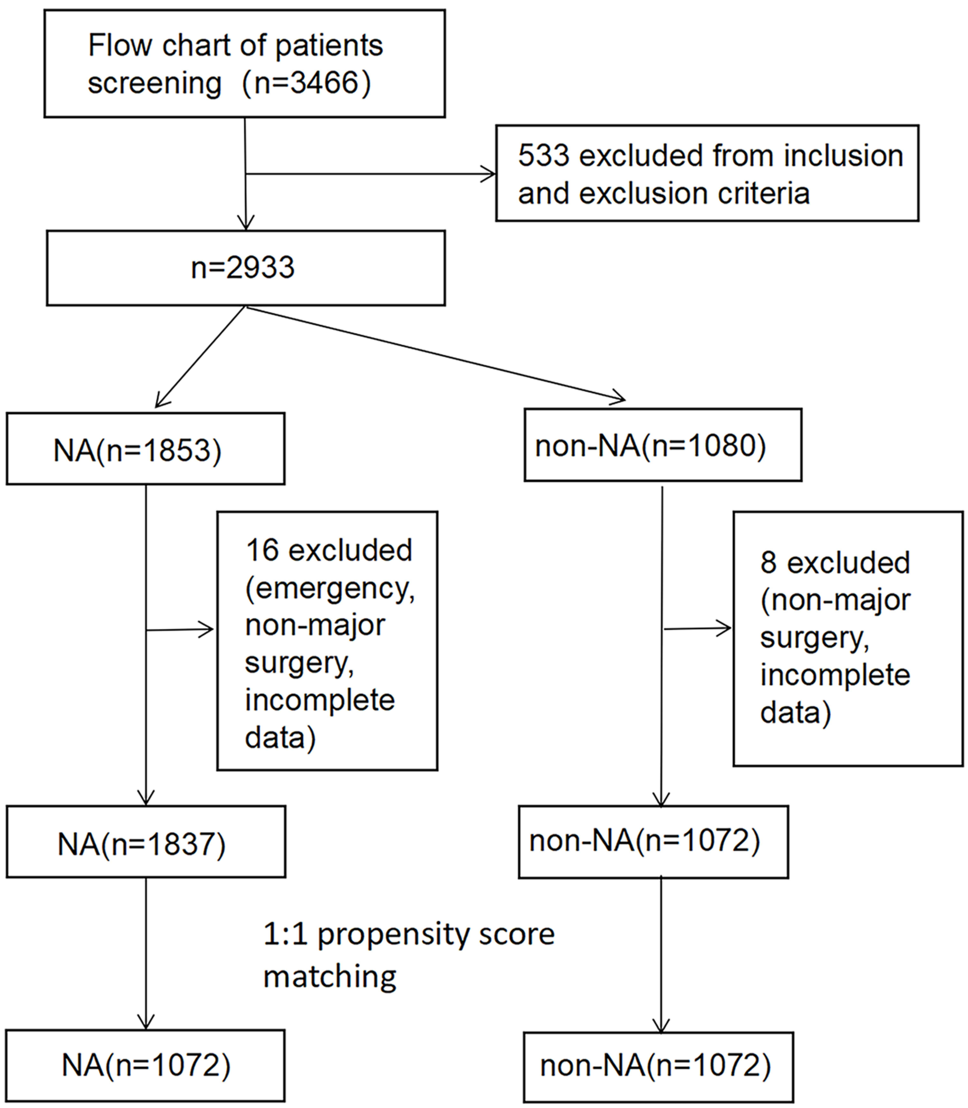

Figure 1 Flowchart of patients screening.

infusion, and 1072 not receiving NA infusion. The propensity score matching was conducted with a 1:1 ratio, and 1072 patients were eventually included in either group.

The baseline characteristics before and after propensity score matching were presented in Table 1. The sex composition, age, ASA composition, the proportions of patients with diabetes mellitus (DM), smoking, gynecological surgery, orthopedic surgery, gastrointestinal surgery, thoracic surgery, and neurosurgery were significantly different between groups; after propensity score matching, the patients characteristics were well balanced.

The in-hospital mortality and complications after surgery in the unmatched and matched cohort were presented in Table 2. No difference existed in in-hospital mortality between NA and non-NA group (*P*=0.506). NA reduced postoperative urinary tract infection (*P*=0.019), but had no impact on other postoperative in-hospital complications. The OR with 95% CI in NA group with reference to non-NA in the logistic regressions for in-hospital mortality and postoperative complications in the matched cohort were shown in Figure 2 and Supplemental Table 1. Patients receiving NA had a lower likelihood of urinary tract infection (OR: 0.124, 95% CI: 0.016–0.995).

Table 1 The Characteristics in NA and Non-NA Cohort Before and After Matching

	Unmatched Cohort		*P* value	Matched Cohort		*P* value
	NA(n=1837)	Non-NA (n=1072)		NA(n=1072)	Non-NA (n=1072)	
Sex[b]			0.034			0.861
Male	1122(61.1%)	612(57.1%)		616(57.5%)	612(57.1%)	
Female	715(38.9%)	460(42.9%)		456(42.5%)	460(42.9%)	
Age (y)[a]	69(67,73)	69(66,73)	0.028	69(66,73)	69(66,73)	0.373
BMI(kg/m^2)[a]	23.1(21.0,25.0)	23.3(21.1,25.3)	0.110	23.2(21.2,25.1)	23.2(21.1,25.3)	0.954
ASA[b]			0.000			0.704
II–III	1769(96.3%)	1059(98.8%)		1057(98.6%)	1059(98.8%)	
IV–V	68(3.7%)	13(1.2%)		15(1.4%)	13(1.2%)	
Comorbidity[b]						
Hypertension	556(30.3%)	318(29.7%)	0.732	327(30.5%)	318(29.7%)	0.672
CAD	235(12.8%)	122(11.4%)	0.263	141(13.2%)	122(11.4%)	0.211
DM	112(6.1%)	45(4.2%)	0.029	42(3.9%)	45(4.2%)	0.743
COPD	84(4.6%)	34(3.2%)	0.065	39(3.6%)	34(3.2%)	0.552
Asthma	10(0.5%)	6(0.6%)	0.957	7(0.7%)	6(0.6%)	0.781
Renal disease	17(0.9%)	8(0.8%)	0.614	11(1.0%)	8(0.8%)	0.489
Smoking	501(27.3%)	233(21.7%)	0.001	225(21.0%)	233(21.7%)	0.673
Stroke	59(3.21%)	22(2.05%)	0.067	21(2.0%)	22(2.1%)	0.878
Surgical type[b]						
Gynecological surgery	120(6.5%)	129(12.9%)	0.000	118(11.0%)	129(12.0%)	0.457
Orthopedic surgery	42(2.3%)	99(9.2%)	0.000	42(3.9%)	99(9.2%)	0.000
Gastrointestin-al surgery	495(27.0%)	370(34.5%)	0.000	397(37.0%)	370(34.5%)	0.224
Thoracic surgery	628(34.2%)	206(19.2%)	0.000	250(23.3%)	206(19.2%)	0.020
Neurosurgery	173(9.4%)	45(4.2%)	0.000	37(3.5%)	45(4.2%)	0.368
Hepatobiliary surgery	181(9.9%)	97(9.05%)	0.476	97(9.1%)	97(9.1%)	1.000
Urologic surgery	198(11.1%)	126(11.8%)	0.420	131(12.2%)	126(11.8%)	0.740
NA (mg)[c]	0.600±0.630	0		0.566±0.012	0	
HR						
Baseline	77(69,85)	76(69,84)	0.488	77(70,86)	76(69,84)	0.077
Average value[d]	71(66,77)	69(64,76)	0.000	71(65,77)	69(64,76)	0.003
MAP						
Baseline	95(87,103)	95(87,103)	0.206	95(87,103)	95(87,103)	0.451
Average value[d]	90.4(76.1,85.4)	81.7(76.9,87.1)	0.000	80.4(76.5,85.2)	81.7(76.9,87.1)	0.000

Notes: [a]Median (interquartile range); [b]frequency (percentage); [c]: mean ± standard deviation; [d]:intraoperative average value.
Abbreviations: CAD, coronary artery disease; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; NA, noradrenaline; HR, heart rate; MAP, mean atrery pressure.

Table 2 The Incidence of Postoperative in-Hospital Complications in Unmatched and Matched Cohorts

	Unmatched Cohort		*P* value	Matched Cohort		*P* value
	NA(n=1837)	Non-NA (n=1072)		NA(n=1072)	Non-NA (n=1072)	
Mortality	41(2.2%)	20(1.9%)	0.506	11(1.0%)	20(1.9%)	0.103
Stroke	36(2.0%)	18(1.7%)	0.589	17(1.6%)	18(1.7%)	0.865
MI	4(0.2%)	1(0.1%)	0.434	1(0.1%)	1(0.1%)	1.000
Arrhythmia	108(5.9%)	71(6.6%)	0.421	60(6.1%)	71(6.6%)	0.321
Pneumonia	263(14.3%)	120(11.2%)	0.016	128(11.6%)	120(11.2%)	0.589
Respiratory failure	38(1.7%)	10(0.9%)	0.020	13(1.2%)	10(0.9%)	0.529
Urinary tract infection	7(0.4%)	8(0.8%)	0.185	1(0.1%)	8(0.8%)	0.019
AKI	102(5.6%)	49(4.6%)	0.250	60(5.6%)	49(4.6%)	0.279
Wound infection	12(0.7%)	12(1.1%)	0.180	8(0.8%)	12(1.1%)	0.369
Anastomotic leakage	12(0.7%)	12(1.1%)	0.180	10(0.9%)	12(1.1%)	0.668
Thrombosis	97(5.3%)	39(3.6%)	0.043	54(4.3%)	39(3.6%)	0.112

Note: Data are frequency (percentage).
Abbreviations: NA, noradrenaline; MI, myocardial infarction; AKI, acute kidney injury.

The ORs in NA with reference to non-NA from logistic regression model for intraoperative infusion, transfusion, bleeding, arterial lactate levels, and hospital stay were presented in Figure 3 and Supplemental Table 2 after propensity score matching. NA infusion reduced intraoperative crystalloid infusion (OR: 0.999,95% CI:0.999–0.999), colloid infusion (OR:1.000,95% CI: 0.999–1.000), blood loss (OR: 0.998, 95% CI: 0.998–0.999), transfusion (OR: 0.327, 95% CI: 0.218–0.490), and urinary output (OR: 0.999, 95% CI: 0.999–0.999), but increased intraoperative lactate production (OR: 1.354, 95% CI: 1.051–1.744) and hospital stay (OR: 1.019, 95% CI: 1.008–1.029).

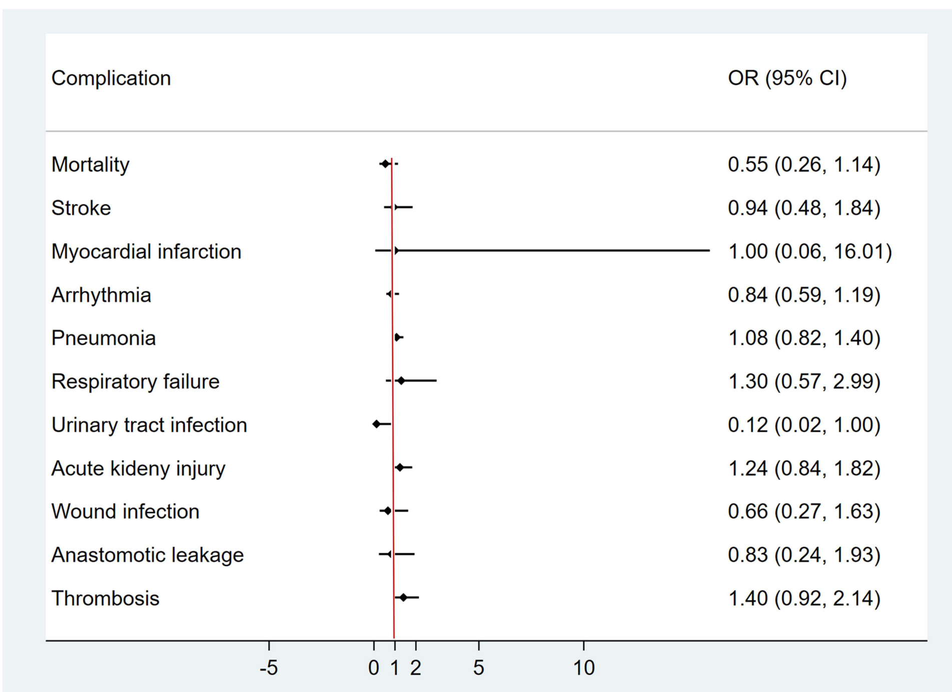

Figure 2 The Odds ratios (ORs) in matched cohorts for NA with reference to non-NA in postoperative in-hospital complications. NA reduced the risk of urinary tract infection.

https://doi.org/10.2147/CIA.S440902

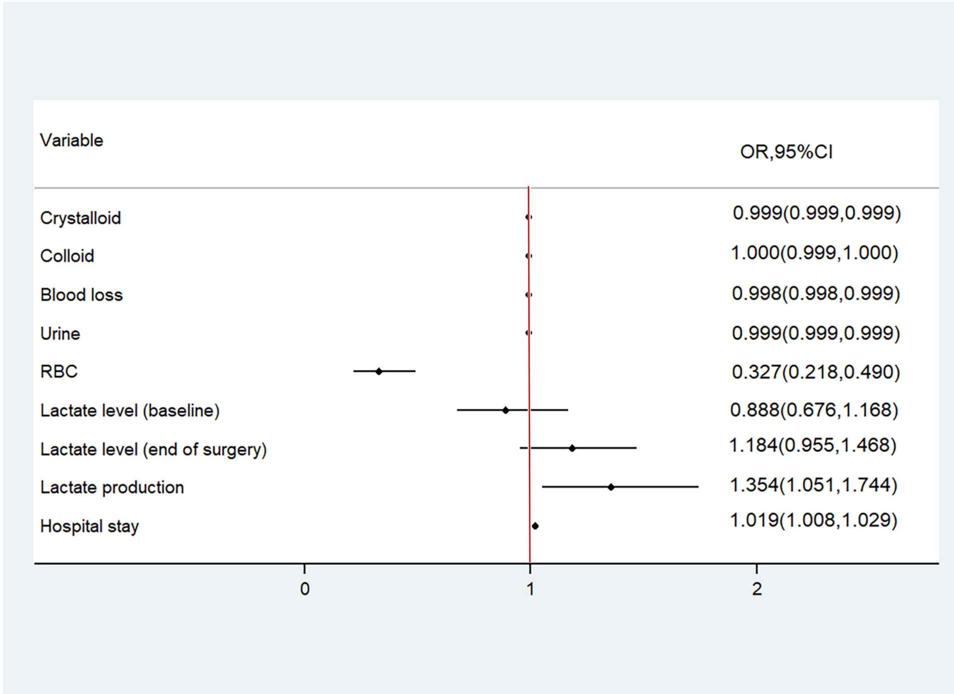

Figure 3 The Odds ratios (ORs) in matched cohort for NA with reference to non-NA in intra- and post-operative outcomes.
Abbreviation: RBC, red blood cell.

Discussion

In this retrospective propensity score-matched cohort study, we investigated the association between intraoperative NA infusion and postoperative in-hospital outcomes in older adult patients undergoing major non-cardiac surgeries. From the results, intraoperative NA administration could reduce the volume of intraoperative fluid therapy, blood loss and RBC transfusion, and postoperative urinary tract infection, but had no effect on other postoperative complications despite the increased intraoperative lactate production and extended hospital stay.

Clinical studies have confirmed that intraoperative NA administration prevents fluid overload and counteract intraoperative hypotension,[1] and promotes platelet aggregation and clot firmness in surgical patients.[14] Adrenergic α1 receptor exists on the surface of platelets, and NA can promote platelet aggregation by activating α1 receptor and ADP pathway,[13] so as to reduce surgical bleeding. Our previous meta-analysis showed that intraoperative restrictive fluid therapy reduced postoperative infectious complications in abdominal surgery.[15] In this study, intraoperative NA administration significantly reduced the volume of fluid therapy, which might contribute to the lower rate of urinary tract infection in NA cohort.

It was reported that intraoperative NA administration at a rate of 0.05 or 0.075 μg/kg/min could maintain blood pressure more stable than 0.025 μg/kg/min after spinal block in cesarean section.[16] In this study, the intraoperative NA infusion rate was 0.04–0.1μg/kg/min, which could maintain the stability of blood pressure and reduce fluid replacement, but increased intraoperative lactate production. NA infusion at 0.05 μg/kg/min in cesarean section could slightly increase maternal lactate level after delivery, although there did not exist significance.[17] In our study, intraoperative NA infusion at 0.04–0.1μg/kg/min significantly increased lactate production. As the duration of cesarean section was short and NA was infused for a very short period, but the infusion was much longer in our study. NA activates α1 receptor, contracts arterioles, and impairs mesenteric microcirculation,[18] in addition, NA inhibited oxygen extraction in tissues in animal studies.[8] All these mechanisms might contribute to the increased lactate production during surgery.

One study reported that intraoperative restrictive fluid therapy combined with NA administration decreased postoperative complications and hospital stay in radical cystectomy,[5] but our study showed that intraoperative NA infusion extended the hospital stay by 1 day compared with non-NA cohort, and a further study is needed to explore the reason.

Another study found that combination of intraoperative restrictive fluid therapy and NA infusion increased the risk of AKI after radical cystectomy, and NA was not a risk factor.[6] In our study, intraoperative NA infusion and restrictive fluid therapy did not affect cardiac, pulmonary, and other in-hospital complications. So, NA infusion at a rate of 0.04–0.1μg/kg/min is relatively safe during major non-cardiac surgery in older adult patients despite the increased intraoperative lactate production and hospital stay.

Various definitions of intraoperative hypotension exist in different studies when using the absolute level of MAP, the criteria included MAP <70 mmHg, or <65mmHg, or <60 mmHg, or <55mmHg.[19] According to Perioperative Quality Initiative consensus statement, MAP <60–70 mmHg was defined as hypotension, and associated with postoperative adverse outcomes.[20] So we used MAP < 60 mmHg as intraoperative hypotension in our study.

The incidence of perioperative stroke is 0.1–1.0% in non-cardiac, nonvascular, nonneurological surgeries.[21,22] In our study, the incidence of postoperative in-hospital stroke was 1.6% in NA cohort, and 1.7% in non-NA cohort, which were higher than those in previous studies. Several reasons might be involved in it, the patients undergoing neurosurgery were included in our study, and it is higher in patients undergoing neurosurgery (1.5%),[23] the patients underwent major non-cardiac surgeries, and most of them were cancer patients, and the patients were from Southwest of China, who might be at a higher risk of perioperative stroke, but it needs to be testified.

As NA is a strong adrenergic α1 agonist and has a very high property of constricting arteries and veins, the major concern of peripheral administration is extravasation which might cause severe and long-lasting skin damage.[24] One recent retrospective cohort study found that peripherally administered NA did not result in more adverse events including skin necrosis.[25] In our study, NA was administered mostly via a central venous line, we might be cautious to use peripheral route for NA infusion.

This study has some limitations, the advanced monitoring parameters such as cardiac output and pulse pressure variation are not common in our clinical practice, and the related data cannot be presented; the consistency within each cohort cannot be completely ensured, such as the infusion rate of NA or crystalloid during surgery, the strategy to manage hypotension in each cohort, and this is a single-center retrospective cohort study, the results cannot be extrapolated to other centers; in this study, we only investigated postoperative in-hospital complications, which was a relatively short-term period, and further studies are needed to explore long-term complications associated with intraoperative NA infusion.

Conclusions

Intraoperative noradrenaline administration reduces postoperative urinary tract infection, and does not increase other post-operative complications and mortality, and can be safely used in older adult patients undergoing major non-cardiac surgeries.

Abbreviations

NA, Noradrenaline; MI, myocardial infarction; MAP, mean artery pressure; AKI, acute kidney injury; ASA, American Society of Anesthesiology; DM, diabetes mellitus.

Data Sharing Statement

All the data can be obtained by contacting the corresponding author.

Ethics Approval and Informed Consent

This retrospective cohort study was conducted at Chongqing University Cancer Hospital, and approved by the Ethics Committee of Chongqing University Cancer Hospital (approval number: CZLS2018-024; approval date: 2018-1-30), the informed consent was waived due to the anonymous nature of data. This study complies with the Declaration of Helsinki for medical studies.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the Key R & D project of Chongqing Science and Technology Bureau, No: cstc2020jscx-dxwtB0010 and the Key R & D project of the Ministry of Science and Technology of China, No: 2018YFC0116704.

Disclosure

The authors report no conflicts of interest in this work.

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