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CLINICAL RESEARCH

Impact of intraoperative hypotension and blood loss on acute kidney injury after pancreas surgery

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KEYWORDS
Acute kidney injury;
Hypotension;
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Abstract
Purpose: This study aimed to investigate factors associated with postoperative Acute Kidney Injury (AKI) focusing on intraoperative hypotension and blood loss volume.
Methods: This was a retrospective cohort study of patients undergoing pancreas surgery between January 2013 and December 2018. The primary outcome was AKI within 7 days after surgery and the secondary outcome was the length of hospital stay. Multivariate analysis was used to determine explanatory factors associated with AKI; the interaction between the integrated value of hypotension and blood loss volume was evaluated. The differences in length of hospital stay were compared using the Mann-Whitney*U*-test.
Results: Of 274 patients, 22 patients had experienced AKI. The cube root of the area under intraoperative mean arterial pressure of < 65 mmHg (Odds Ratio = 1.21; 95% Confidence Interval 1.01–1.45; $p = 0.038$) and blood loss volume of > 500 mL (Odds Ratio = 3.81; 95% Confidence Interval 1.51–9.58; $p = 0.005$) were independently associated with acute kidney injury. The interaction between mean arterial hypotension and the blood loss volume in relation to acute kidney injury indicated that the model was significant ($p < 0.0001$) with an interaction effect ($p = 0.0003$). AKI was not significantly related with the length of hospital stay (19 vs. 28 days, $p = 0.09$).
Conclusion: The area under intraoperative hypotension and blood loss volume of > 500 mL was associated with postoperative AKI. However, if the mean arterial pressure is maintained even in patients with large blood loss volume, the risk of developing postoperative AKI is comparable with that in patients with small blood loss volume.

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PALAVRAS-CHAVE
Lesão renal aguda;
Hipotensão;
Volume de perda sanguínea

Impacto da hipotensão e perda sanguínea intraoperatórias na lesão renal aguda após cirurgia de pâncreas

Resumo
Justificativa: O presente estudo teve como objetivo examinar os fatores associados à Lesão Renal Aguda (LRA) no pós-operatório, centrando-se na hipotensão e perda de sangue intraoperatórias.
Método: Estudo de coorte retrospectivo de pacientes submetidos a cirurgia de pâncreas entre janeiro de 2013 e dezembro de 2018. O desfecho primário foi a ocorrência de LRA em até 7 dias após a cirurgia e o secundário, o tempo de hospitalização. A análise multivariada foi usada para determinar os fatores explicativos associados à LRA; a interação entre o valor integrado da hipotensão e volume de perda de sangue foi avaliada. As diferenças no tempo de hospitalização foram comparadas pelo teste U de Mann−Whitney.
Resultados: Dos 274 pacientes, 22 pacientes apresentaram LRA. A raiz cúbica da área sob a pressão arterial média intraoperatória < 65 mmHg (Odds Ratio = 1,21; Intervalo de Confiança de 95% 1,01−1,45;p = 0,038) e volume de perda sanguínea > 500 mL (Odds Ratio = 3,81; Intervalo de Confiança de 95% 1,51−9,58; p = 0,005) estavam independentemente associados à lesão renal aguda. A interação entre hipotensão arterial média e volume de perda sanguínea em relação à lesão renal aguda apontou o modelo como significante (p < 0,0001) com efeito de interação (p = 0,0003). A LRA não apresentou relação significante com o tempo de hospitalização (19 *vs.* 28 dias, p = 0,09).
Conclusões: A área sob hipotensão arterial e o volume de perda sanguínea > 500 mL no intraoperatório apresentaram associação com LRA no pós-operatório. Entretanto, se a pressão arterial média se mantém, mesmo em pacientes com grande volume de perda sanguínea, o risco de desenvolver LRA no pós-operatório é comparável ao risco dos pacientes com pequeno volume de perda sanguínea.

Introduction

Despite improvements in surgical and anesthetic techniques, pancreaticoduodenectomy and distal pancreatectomy remain invasive procedures with a high rate of postoperative complications.[1,2] Clavien-Dindo classification has been commonly used to assess postoperative complications, although this classification does not allow the evaluation of postoperative Acute Kidney Injury (AKI), which is associated with prolonged hospital stay and worse mortality.[3–5]

Previous studies revealed that the factors associated with postoperative AKI are advanced age, obesity, chronic obstructive pulmonary disease and pre-existing chronic kidney disease; however, several of these factors are difficult to modify.[6–8] In recent years, modifiable factors including intraoperative arterial pressure and preoperative hematologic markers such as Neutrophil-to-Lymphocyte Ratio (NLR) have been reported as independent predictors of AKI following noncardiac surgery.[9,10] In a large retrospective study including 57,315 patients undergoing noncardiac surgery, it was reported that the longer cumulative times of intraoperative mean arterial pressure of < 65 mmHg significantly increased postoperative AKI.[9] In addition, intraoperative bleeding is one of the most common complication and can cause hypotension during major abdominal surgery. However, intraoperative hypotension and its relation with postoperative AKI are poorly documented. Therefore, we examined the development of AKI and associated factors after pancreaticoduodenectomy and distal pancreatectomy in patients at a high-volume Japanese medical center. In addition, we investigated the interaction between the area under intraoperative mean arterial hypotension and blood loss volume with respect to postoperative AKI.

Methods

Ethical approval for this retrospective study (Approval nº 2131) was provided by the Nara Medical University Institutional Review Board, Kashihara, Nara, Japan (Chairperson Prof. M Yoshizumi) on February 18, 2019.

We included patients aged ≥ 20 years who underwent pancreaticoduodenectomy and distal pancreatectomy with a diagnosis of malignant tumor at Nara Medical University between January 2013 and December 2018. Individuals aged < 20 years and those with end-stage renal disease (i.e. estimated glomerular filtration rate of < 15 $mL.min^{-1}.1.73\,m^{-2}$ determined using a formula validated in Japan or a receipt of hemodialysis) were excluded from the study.[11] We also excluded patients in whom surgery could not be completed (e.g. in-operable patients) and those who underwent other procedures in addition to pancreaticoduodenectomy and distal pancreatectomy. Further, patients with incomplete data were excluded from analysis.

The primary outcome was the development of AKI within 7 days after surgery. The secondary outcomes were fac-

tors associated with postoperative AKI and postoperative length of stay. The occurrence and severity of postoperative AKI were determined by changes in serum creatinine between preoperative and postoperative values according to the KDIGO definition.[12] The preoperative value was the concentration determined at a time closest to the surgery. The postoperative value recorded was the highest concentration measured during 7 days postoperatively.

Data of the study patients, including sex, age, height, weight, comorbidities (hypertension, respiratory function and diabetes mellitus), treatment with preoperative chemotherapy and the American Society of Anesthesiologists (ASA) physical status, were procured from the electronic medical records. Patients with hypertension and diabetes mellitus were defined as those taking antihypertensive drugs and oral diabetes drugs or injectable insulin, respectively. Patients were considered to be suffering from obstructive respiratory dysfunction if their forced expiratory volume 1.0 (s)% was < 70%; restrictive respiratory dysfunction was defined as a vital capacity of < 80%. Patients with both obstructive and restrictive respiratory dysfunction were considered to have mixed respiratory dysfunction. Additionally, we collected preoperative laboratory data, including hemoglobin, serum albumin, serum amylase, serum creatinine, hemoglobin A1c levels and platelet count. The NLR was calculated as the neutrophil count divided by the lymphocyte count.[13]

Intraoperative data were recorded by the anesthesiologist; it included the type of surgery (pancreaticoduodenectomy and distal pancreatectomy), the type of anesthetic used (inhalation or propofol), water volume, urine volume, fluid balance, blood loss volume, transfusion, the area under intraoperative mean arterial hypotension, duration of surgery and postoperative analgesic management (epidural analgesia or intravenous patient–controlled analgesia).

Similar to a previous study, mean arterial pressure values were recorded at 1-minute intervals when an arterial catheter was used or at 2.5-minute intervals when blood pressure was oscillometrically measured.[14] In our institution, an arterial catheter was inserted after the induction of anesthesia and before tracheal intubation. Mean arterial pressure values were considered to be artefactual and were excluded when the recorded value was < 30 mmHg or > 250 mmHg.[14] A previous large retrospective cohort study showed that mean arterial pressure of $\leq$ 65 mmHg was related to postoperative AKI; therefore, in our study, the cutoff value of mean arterial pressure was 65 mmHg.[9] Next, the area under intraoperative mean arterial hypotension was calculated.

Continuous data are presented as medians with 25th to 75th percentiles and categorical variables as number. To identify which variables were significantly associated with postoperative AKI, data were examined using the chi-square test or Fisher's exact test for dichotomous variables or Mann-Whitney *U*-test for continuous variables. In addition, explanatory factors with a significant univariate association ($p \leq 0.1$) were used as explanatory variables for multivariate analysis with stepwise selection (significant level of $p \geq 0.1$ for both incorporation and preservation in the model). Discrimination of the final model was assessed using the likelihood ratio test. Calibration of the model was tested using the Hosmer-Lemeshow test. The area under the receiver operating characteristic curve was computed as a descriptive tool for measuring model bias. The interaction between the area under the intraoperative mean arterial hypotension and blood loss volume was evaluated with nonlinear restricted cubic spline in the regression model. The postoperative length of stay was compared using Mann-Whitney *U*-test. All data were analyzed with SPSS version 22.0 (IBM Inc, Armonk, NY, USA) and the rms package for R version 2.13.0 (R Foundation for Statistical Computing, Vienna, Austria). A value of $p < 0.05$ was considered statistically significant.

Results

Out of 308 patients reviewed, 274 patients were included in the final analysis (Fig. 1) and postoperative AKI was detected in 22 of those patients. One patient was excluded from the analysis because AKI was due to vancomycin administration. The maximal AKI stage in the remaining 21 patients was as follows: 18 patients had Stage 1 and three patients had Stage 2 AKI. Table 1 summarizes patient characteristics and operative variables stratified by postoperative AKI status. Univariate analysis revealed that respiratory function, duration of surgery, blood loss volume and the area under intraoperative mean arterial hypotension were suitable as explanatory variables in multiple logistic regression. However, the Kolmogorov-Smirnov test showed that both blood loss volume and the area under intraoperative mean arterial hypotension were not normally distributed. Therefore, we transformed the data using the root transformation, cubic root transformation and log transformation.[15] However, any transformations of blood loss volume were allowed to distribute normally (Supplementary Fig. S1). Therefore, we decided to include blood loss volume as three categorical variables ($\leq$ 100; 100–500; > 500). With regard to the area under intraoperative mean arterial hypotension, the cubic root transformation provided normal disturbance (Supplementary Fig. S2).

Explanatory variables in multiple logistic regression were as follows: respiratory function (obstructive respiratory dysfunction, restrictive respiratory dysfunction and mixed respiratory dysfunction), duration of surgery, blood loss volume (< 100, 101–500; > 500 mL) and the cubic root of the area under intraoperative mean arterial hypotension. Multiple logistic regression identified the cubic root of the area under intraoperative mean arterial hypotension and blood loss volume of > 500 mL as factors that were independently associated with postoperative AKI (Table 2). Figure 2 shows the interaction between the cubic root of the area under intraoperative mean arterial hypotension and the presence or absence of blood loss volume of > 500 mL in relation to AKI, which indicated that the model was significant ($p < 0.0001$) with an interaction effect ($p = 0.0003$). Finally, AKI was not significantly related to postoperative length of stay (19 [15–29] vs. 28 [18–37] days, $p = 0.09$).

Discussion and conclusion

This retrospective analysis showed that the incidence rate of AKI after pancreaticoduodenectomy and distal pancreatectomy was 7.6% in the study cohort and large

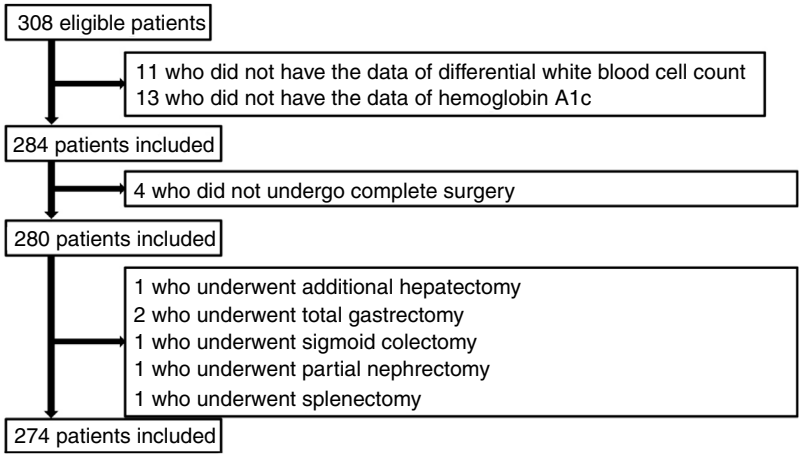

Figure 1 The interaction between the cubic root of the area under intraoperative mean arterial hypotension and the presence or absence of blood loss volume of > 500 mL in relation to acute kidney injury.

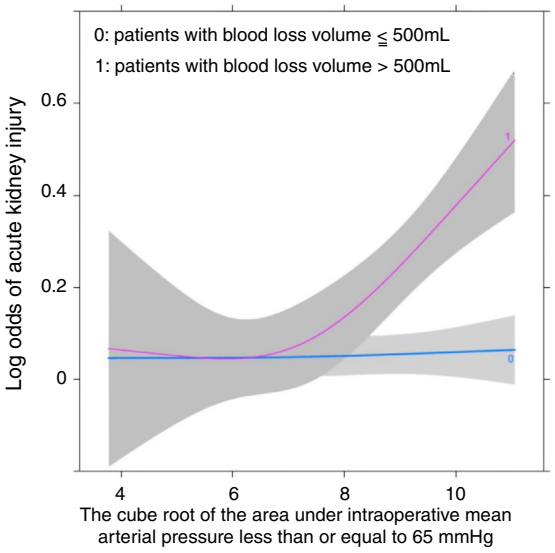

Figure 2 Log odds of acute kidney injury.

integrated values of arterial mean pressure, time and large blood loss volume were significantly associated with the development of postoperative AKI. Further, it was revealed that for patients with blood loss volume of ≤ 500 mL, the risk of developing AKI does not increase even when area under intraoperative mean arterial hypotension increases. However, the risk of developing AKI increases when the area under intraoperative mean arterial hypotension increases following a blood loss volume of > 500 mL during pancreaticoduodenectomy and distal pancreatectomy.

Some studies using the KDIGO criteria have reported incidences of postoperative AKI ranging from 7.4–9.1% after pancreatic surgery, consistent with the current findings.[16,17] Previous studies have demonstrated that a longer length of stay is related to postoperative AKI; however, our results do not support this.[4,18] Moreover, a 9-day difference in median length of stay would be significant in clinical practice.

Our results are consistent with the reports in previous studies that intraoperative hypotension and increased blood loss volume is associated with the development of postoperative AKI, although there are no studies which have evaluated the interaction between intraoperative hypotension and blood loss volume.[9,16,19] Our study showed that prolonged intraoperative hypotension caused by bleeding is associated with postoperative AKI. There are some mechanism of intraoperative hypotension, including the reduction of stroke volume and systemic vascular resistance. Our results suggest that a reduction in stroke volume due to bleeding increases the incidence of postoperative AKI but is not related with a decrease in systemic vascular resistance. The exact mechanism, which is beyond the scope of this study, remains unclear because we did not measure stroke volume and systemic vascular resistance during surgery. However, by understanding the factors associated with the development of postoperative AKI, it is possible to identify the patients who would likely benefit from specific interventions. Therefore, our study aimed to help guide prospective interventional studies.

A retrospective study, including 473 burn-injured patients, showed that preoperative NLR can provide useful information for the early detection of postoperative AKI at a cutoff value of 11.7.[10] In our cohort, the median NLR was 2.56 (1.74–4.00), which is lower than the cutoff value considered in previous studies and may thus reflect a low inflammation status. Consequently, preoperative NLR might not be identified as a significant indicator of postoperative AKI.

Our study had several limitations. First, the retrospective study design may have resulted in selection bias; thus, important factors associated with postoperative AKI may have been missed. Second, the generalizability of our findings may be limited due to the nature of a single-center study. Third, in spite of high-volume center of pancreas surgery, our sample size was too small to limit the number of covariates for multivariate regression analysis. In the future, the further study including large population is needed.

Finally, intraoperative management, including the use of vasoactive agents and fluid therapy, was at the discretion of each anesthesiologist.

Table 1 Patients' demographics and intraoperative data.

	Total (n = 273)	non-AKI (n = 252)	AKI (n = 21)	*p*-value
Age (years)	72.0 (66.0–76.0)	71.5 (66.0–76.0)	72.0 (61.0–77.0)	0.57
Male/Female	177/96	161/91	16/5	0.34
Body Mass Index (kg. m^{-2})	22.0 (20.0–24.0)	22.0 (20.0–24.0)	22.4 (20.3–23.6)	0.80
< 18.5	25	25	0	
18.5 ≤ 25	194	187	17	
25 ≤ 30	39	36	3	
≥ 30	5	4	1	
Hypertension	122	111	11	0.49
Respiratory function				0.021
Normal	209	198	11	
Obstructive	49	41	8	
Restrictive	11	10	1	
Mixed	4	3	1	
Diabetes Mellitus	105	100	5	0.16
Preoperative chemotherapy	151	142	9	0.25
Hemoglobin (g.dL^{-1})	11.7 (10.5–12.9)	11.6 (10.5–12.9)	11.7 (11.1–12.0)	0.89
Platelets (10$\hat{4}$ μL^{-1})	20.1 (15.1–25.7)	19.9 (15.0–25.5)	22.7 (7.3–28.2)	0.271
Serum albumin (g.dL^{-1})	3.9 (3.6–4.2)	3.9 (3.6–4.2)	3.8 (3.5 4.1)	0.27
Serum Amylase (U.L^{-1})	64 (44–101)	64.5 (44.7–100.2)	59.0 (37.0–106.0)	0.69
Serum creatinine (mg.dL^{-1})	0.73 (0.61–0.87)	0.72 (0.61–0.86)	0.77 (0.69–0.95)	0.24
Hemoglobin A1c (%)	6.3 (5.7–7.2)	6.3 (5.7–7.3)	6.1 (5.7–6.6)	0.29
Neutrophil-to-lymphocyte ratio	2.56 (1.71–4.00)	2.57 (1.71–4.00)	2.55 (1.92–3.50)	0.98
ASA physical status classification				
I	17	17	0	0.38
II	223	203	20	
III	33	32	1	
Types of surgery				
PD/DP	174 / 89	168/ 84	16 / 5	0.47
Water volume (mL. kg^{-1}. h^{-1})	8.4 (6.9–9.9)	8.4 (6.9–9.9)	8.3 (7.4–9.9)	0.43
Urine volume (mL. kg^{-1}. h^{-1})	0.84 (0.57–1.29)	0.85 (0.57–1.29)	0.77 (0.57–1.46)	0.89
Fluid balance (mL. kg^{-1}. h^{-1})	6.8 (5.5–8.4)	6.8 (5.5–8.4)	6.6 (5.9–8.4)	0.77
Anesthesia				
Inhalation/Intravenous	251/22	231/21	20/1	1
Postoperative pain management				
EPI/IVPCA	213/50	206/46	17/4	1
Duration of surgery (min)	296 (231–364)	293 (229–360)	321 (278–429)	0.071
Transfusion	42	38	6	0.12
Blood loss (mL)	205 (93–447)	197 (84–396)	500 (195–1240)	0.001
≤ 100	76	74	2	
100 ≤ 500	140	131	9	
> 500	57	47	10	
The area under intraoperative hypotension time	749 (376–1369)	736 (400–1295)	1592 (348–1762)	0.026

Median (first quartile to fourth quartile) or number. ASA, America Society of Anesthesiology; DP, Distal Pancreatectomy; EPI, Epidural Analgesia; IVPCA, Intravenous Patient-Controlled Analgesia; PD, Pancreatoduodenectomy.

Table 2 Multivariate logistic regression model for acute kidney injury.

	Odds ratio	95% Confidence Interval	*p*-value
Cube root of intraoperative mean arterial hypotension	1.21	1.01 – 1.45	0.038
Blood loss volume > 500 mL	3.81	1.51 – 9.58	0.005

Discrimination of the final model assessed by the likelihood ratio test was significant ($p = 0.016$). The Hosmer-Lemeshow test did not reject a logistic regression model fit ($p = 0.11$). The explanatory model based on these variables had an area under the receiver operating characteristic curve of 0.68 (95% Confidence Interval, 0.54–0.82). No value exceeded the expected value by 3 ± standard deviation.

This retrospective study showed that intraoperative hypotension with large blood loss is a significant risk factor for postoperative AKI in patients undergoing pancreaticoduodenectomy and distal pancreatectomy for malignancy.

Conflicts of interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi: https://doi.org/10.1016/j.bjane.2020.07.001.

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