Robot-Assisted versus Open Pancreatoduodenectomy: Identifying Perioperative Anesthetic Factors associated with Postoperative Morbidity. A retrospective cohort study.

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Abstract

Background

Robot-assisted pancreatoduodenectomy (RAPD) poses several challenges concerning perioperative anesthetic guidance compared to open pancreatoduodenectomy (OPD), e.g. combined pneumoperitoneum with reversed-Trendelenburg positioning. The primary objective of this observational study is to specify these anesthetic differences of RAPD versus OPD and secondly to identify independent anesthetic factors associated with patient morbidity following RAPD.

Methods

All consecutive patients who underwent either RAPD or OPD between 2017 and 2018 were included for analysis. Patient records were screened for intraoperative vasopressor and fluid administration as well as for results of perioperative arterial blood gas analysis. Variables were compared for the groups RAPD versus OPD, major morbidity following RAPD versus non-major morbidity following RAPD (resp. Clavien-Dindo score $\geq$ III vs. $<$ III) and high versus low intraoperative blood loss during RAPD. Perioperative factors associated with major postoperative morbidity (Clavien-Dindo $\geq$ III) were identified using a logistic regression model.

Results

N=64 RAPD and n=62 OPD patients were included for retrospective analysis. RAPD was associated with higher administration of intraoperative norepinephrine (9.5% of operative time vs. 0% in OPD, $p=0.005$) and a higher net intraoperative fluid balance (2497.6 vs. 1572.3 ml, $p<0.001$). During OPD, patients received more frequent and higher doses of colloid fluids compared to RAPD (79.0% vs. 51.6%, $p<0.001$, median 1000.0 vs. 500.0 ml, $p<0.001$). Colloid administration during surgery and hyperlactatemia 12 hours postoperatively were associated with major morbidity after RAPD (OR 5.06, 95% CI 1.49-17.20, $p=0.009$ and OR 3.18, 95% CI 1.01-9.91, $p=0.047$, respectively).

Conclusions

RAPD is a challenging procedure for the anesthesiologist, e.g. considering a higher demand for vasopressors. Inotropic/vasopressor administration as well as the intraoperative fluid balance are associated with (major) morbidity following RAPD. However, it remains unclear whether and in which direction a causal relationship exists.

Trial registration: Not applicable.

Background

The robot-assisted approach for pancreatoduodenectomy was first described in 2003 by Giulianotti et al. and has gained momentum as an established minimally invasive technique for pancreatoduodenectomy

surgery [1]. Various cohort studies already compared surgical outcomes of robot-assisted pancreatoduodenectomy (RAPD) with conventional open pancreatoduodenectomy (OPD). Despite increased surgical times, RAPD is characterized by lower intraoperative blood loss with equal postoperative mortality and similar oncological outcome [2–4]. Although the surgical feasibility of RAPD is extensively reported in literature, little is known about perioperative anesthetic concerns of the robotic approach and how perioperative anesthetic factors affect postoperative outcome.

Determining optimal intraoperative fluid regimens during abdominal surgery in relation to postsurgical morbidity is part of ongoing scientific debate. The 2018 RELIEF trial described an association between a more restrictive intraoperative net fluid balance (median 3.7 liters) and an increased rate of kidney injury following major abdominal surgery [5]. However, Grant et al. reported no differences in postoperative major morbidity after randomizing between either a net liberal (12 ml kg/hr) versus net restrictive (6 ml kg/h) intraoperative fluid balance for pancreatic surgery (irrespective of the surgical approach) [6]. RAPD presents several specific challenges concerning the perioperative anesthetic guidance. The patient is exposed to pneumoperitoneum, reversed-Trendelenburg positioning during the majority of surgical time, increasing central venous pressure, expected higher blood carbon dioxide levels and decreasing cardiac output [7–9]. We therefore hypothesize differences between RAPD and OPD in perioperative demands for vasopressor and fluid administration.

The primary objective of this retrospective cohort study is to evaluate perioperative anesthetic differences of RAPD versus OPD. Secondly, this study aims to identify independent anesthetic factors associated with patient morbidity following RAPD.

Methods

The Medical Ethics Committee approved a waiver for informed consent on February 14th 2019 (MEC-2019-0090, Medical Ethics Committee, Erasmus MC University Hospital, P. Box 2040, 3000 CA, Rotterdam, the Netherlands), given the retrospective nature of this observational study. All consecutive patients who underwent either RAPD or OPD between January 1st 2017 and December 31st 2018 were included for analysis. RAPD has been performed in our center (tertiary referring hospital for pancreatic diseases) since January 2017. All procedures were undertaken by a dedicated team of two pancreatic surgeons or a pancreatic surgeon together with a pancreatic surgical fellow. RAPD was executed using the Da Vinci Model S robotic surgical device, which was later switched to the Model Xi (Intuitive Surgical Inc., Sunnyvale, CA, USA). OPD was performed by or under direct supervision of three experienced consultant pancreatic surgeons. Several consultant anesthesiologists were involved in both surgical modalities. Patients were assigned to RAPD based on patient preference and availability of both the robot and the robotic surgical team, the sole exclusion criterion for RAPD was locally advanced pancreatic cancer.

RAPD was characterized as full-robotic surgery, meaning both the resection and the reconstruction phase were conducted in a robotic fashion. A central venous catheter was incidentally inserted based on the anesthesiologist's discretion. All patients were postoperatively admitted to a High Dependency Unit (HDU)

or incidentally to an Intensive Care Unit (ICU). Protocols for postoperative management were identical for HDU and ICU. Standard postoperative analgesic regimen comprised paracetamol (1000mg 4 times daily) and naproxen (750mg 3 times daily). OPD was preferably performed under additional epidural analgesia (routinely using ropivacaine 0.2% combined with sufentanil 1 µg/ml). For RAPD a patient-controlled analgesia (PCA) device (morphine based) was used for postoperative analgesia. Once oral intake was possible again, epidural or PCA analgesia was if necessary converted to oral oxycodone.

Digital patient records were reviewed for patient demographics, intra- and postoperative management and postoperative morbidity. Extracted baseline data included age, sex, body mass index (BMI) and medical history (comprising diabetes mellitus, any pulmonary, cardiac or vascular disease, any history of cerebrovascular accident (CVA) or transient ischemic attack (TIA), hypertension or prior kidney or liver failure). Besides, records were reviewed regarding any history of previous malignancy, abdominal as well as non-abdominal surgery or neoadjuvant chemotherapy. Baseline comorbidity was graded according to the American Society of Anesthesiologist's (ASA) score and Charlson Comorbidity Index (CCI) [10]. Baseline hemoglobin (Hb), platelet count, estimated glomerular filtration rate (e-GFR) and levels of albumin, total bilirubin, creatinine and tumor-marker CA 19-9 were also extracted from patient records.

According to our center's protocol, norepinephrine (NE) was routinely used as first choice perioperative vasopressor. Perioperative anesthesia records were screened for the NE dose on start and end of surgery as well as the amount of times NE dose perioperative exceeded 0.2 µg kg/min (considered the cut-off for the administration of NE over a central instead of peripheral intravenous cannula). The amount of times NE dosage exceeded 0.2 µg kg/min was expressed as time span in minutes and as percentage of operating room time (time between entering versus leaving the surgical theatre). The operative time was defined as the time interval between skin incision and wound closure, time to detubation as the time interval between wound closure and removal of the endotracheal tube.

Fluid balances, including the necessity of erythrocyte transfusion, were studied up to 24 hours following surgery. Types of intravenous fluid used were NaCl 0.9% (Baxter, Deerfield, United States of America) and Sterofundin ® (Braun, Melsungen, Germany) as crystalloids, Voluven ® and Volulyte ® (Hydroxyethylstarch 130/0.4, Fresenius Kabi, Bad Homburg vor der Höhe, Germany) as colloids. Besides, arterial blood gas (ABG) analyses (including blood pH, partial CO₂ (pCO₂) pressure, lactate and Hb count) were studied at 3 points in time: first available sample results during surgery, first available results upon HDU/ICU admission and first available results after a minimum of 12 hour HDU/ICU admission. The perioperative pCO₂ levels were subsequently compared to the corresponding end tidal (et) CO₂ level.

Patient records were screened for the total hours of postoperative HDU/ICU stay and the rate of prolonged HDU/ICU admission, the latter defined as a HDU/ICU stay exceeding 24 hours. The length of postoperative hospital stay was counted in days starting from the first day following surgery. Postoperative morbidity was assessed 90 days after surgery using the Clavien Dindo (CD) morbidity score as well as the Comprehensive Complication Index [11, 12]. Major morbidity was defined as a CD score ≥ III. Kidney failure was graded according to European Society of Anesthesiologists' (ESA)

European Perioperative Clinical Outcome (EPCO) standards [13]. Pain scores, expressed as Numeric Rating Scale (NRS), were analyzed on postoperative days 1 and 3. Mortality rates were studied on postoperative days 30 and 90.

Baseline and perioperative variables were analyzed for RAPD versus OPD, RAPD patients suffering major postoperative morbidity ($CD \geq III$) vs. absence of major postoperative morbidity ($CD < III$) and RAPD patients above versus below median intraoperative blood loss (high and low intraoperative blood loss, respectively). Normal distribution of data was assessed using a combination of visual inspection of histograms and Q-Q plots and the Shapiro-Wilk test. Numerical data were presented as mean (standard deviation, SD) or median (interquartile range, IQR), as appropriate. Categorical data were presented with frequencies and percentages. An independent sample T-test or Mann-Whitney U-test was performed in comparing numerical data, a χ^2 or Fisher's exact test in categorical data. In order to identify independent predictors of major morbidity following RAPD ($CD \geq III$), a logistic regression model was constructed using a backward stepwise approach. Baseline and perioperative variables showing a significant difference between minor ($CD < III$) versus major ($CD \geq III$) morbidity after RAPD and of suspected clinical relevance in predicting major morbidity after RAPD were included in the regression model. Results herein were presented as odds ratio (OR) with corresponding 95% confidence interval (CI). Throughout the study two-tailed P-values of < 0.05 were considered statistically significant. Statistical analysis was carried out using IBM SPSS Statistics (version 24.0, Armonk, NY, USA; IBM Corp.).

Results

126 consecutive patients were included in this study during the two-year inclusion period (n=64 RAPD, n=62 OPD).

RAPD vs. OPD

The only significant difference in baseline patient characteristics was a lower baseline hemoglobin level for OPD (12.6 vs. 13.2 g/dl, $p=0.049$) (Table 1, additional file 1). Operative time was 441.5 min. in RAPD compared to 318.0 min. in OPD ($p<0.001$, Table 2, additional file 2). No RAPD procedures were converted to OPD. Net intraoperative fluid balance was higher in RAPD (2497.6 vs. 1572.3 ml in OPD, $p<0.001$). OPD patients more frequently and quantitatively received colloids compared to RAPD patients (79.0% vs. 51.6%, $p<0.001$, median 1000.0 vs. 500.0 ml, $p<0.001$). Average intraoperative blood loss was 250.0 ml for RAPD compared to 1150.0 ml for OPD ($p<0.001$) with an intraoperative erythrocyte transfusion rate of 6.3% (4/64) for RAPD compared to 30.6% (19/62) for OPD ($p<0.001$). Within the RAPD group, intraoperative Hb levels were higher during surgery, upon HDU/ICU admission and after a minimum of 12 hour of HDU/ICU admission (12.6 vs. 11.9 g/dl, $p=0.017$, 12.6 vs. 11.3 g/dl, $p<0.001$ and 12.1 vs. 11.0 g/dl, $p<0.001$, respectively).

Table 1
Demographic and baseline details for RAPD and OPD patients

Variables	RAPD vs. OPD			Post-RAPD morbidity		
	RAPD (n=64)	OPD (n=62)	<i>P</i>	RAPD without major morbidity (CD < III, n=36)	RAPD with major morbidity (CD ≥ III, n=28)	<i>P</i>
Age (yr)	67.8 ± 9.8	65.5 ± 10.1	0.188	66.8 ± 9.7	69.1 ± 9.9	0.340
Sex (M:F)	1.0:0.9	1.0:0.9	0.424	1.0:1.0	1.0:0.9	0.806
BMI (kg/m ²)	25.0 (18.9- 37.9)	24.6 (16.7- 40.7) ²	0.179	25.9 ± 5.0	26.0 ± 3.3	0.909
Medical history						
Diabetes mellitus	17 (26.6)	22 (35.5)	0.337	12 (33.3)	5 (17.9)	0.254
Pulmonary disease	13 (20.3)	9 (14.5)	0.484	7 (19.4)	6 (21.4)	1.000
Cardiac disease	17 (26.6)	15 (24.4)	0.839	9 (25.0)	8 (28.6)	0.782
Vascular disease	2 (3.1)	5 (8.1)	0.269	1 (2.8)	1 (3.6)	1.000
CVA or TIA	5 (7.8)	6 (9.7)	0.761	3 (8.3)	2 (7.1)	1.000
Hypertension	28 (43.8)	25 (40.3)	0.721	11 (30.6)	17 (60.7)	0.023
Kidney or liver failure	10 (15.6)	10 (16.1)	1.000	4 (11.1)	6 (21.4)	0.312
Previous malignancy	19 (29.7)	18 (29.0)	1.000	9 (25.0)	10 (35.7)	0.256
Previous abdominal surgery	35 (54.7)	36 (58.1)	0.723	21 (58.3)	14 (50.0)	0.615
Previous non-abdominal surgery	41 (64.1)	43 (69.4)	0.574	22 (61.1)	19 (67.9)	0.610
ASA						
I	8 (12.5)	4 (6.9) ⁴	0.543	6 (16.7)	2 (7.1)	0.460
II	45 (70.3)	41 (70.3) ⁴		25 (69.4)	20 (71.4)	

Variables	RAPD vs. OPD			Post-RAPD morbidity		
	RAPD (n=64)	OPD (n=62)	<i>P</i>	RAPD without major morbidity (CD < III, n=36)	RAPD with major morbidity (CD ≥ III, n=28)	<i>P</i>
III	11 (17.2)	13 (22.4) ⁴		5 (13.9)	6 (21.4)	
IV	0	0		0	0	
Charlson Comorbidity Index						
Score	5.4 ± 2.0	5.4 ± 1.9	0.900	5.1 ± 1.9	5.8 ± 2.0	0.161
Charlson = 0	0	0		-	-	-
Charlson = 1-3	12 (18.8)	10 (16.1)	0.332	8 (22.2)	4 (14.3)	0.492
Charlson = 4-6	34 (53.1)	35 (56.5)		18 (50.0)	16 (57.1)	
Charlson = 7	18 (28.1)	17 (27.4)		10 (27.8)	8 (28.6)	
Preoperative chemotherapy	4 (6.3)	11 (17.7)	0.057	2 (5.6)	2 (7.1)	0.593
Baseline laboratory						
Hemoglobin level (mmol/L)	8.2 ± 0.9	7.8 ± 1.0	0.049	8.0 ± 0.9	8.4 ± 0.8	0.116
Platelet count (x 10 ⁹ /L)	266 ± 83	293 ± 78	0.063	264 (114-556)	236 (135-402)	0.365
e-GFR (ml/min/1.73 m ²)	81.3 ± 18.1	82.9 ± 17.5	0.610	84.4 ± 17.2	77.3 ± 18.7	0.123
Albumin level (g/L)	42.1 ± 7.2 ²	41.8 ± 4.6 ⁶	0.757	41.0 (24.0-50.0) ¹	42.0 (32.0-75.0) ¹	0.564
Total bilirubin level (umol/L)	11.5 (3.0-214.0)	9.0 (3.0-208.0) ¹	0.218	12.5 (3.0-214.0)	10.5 (5.0-51.0)	0.542
Creatinine level (umol/L)	77.0 ± 23.7	75.4 ± 18.8	0.675	73.5 ± 17.3	81.4 ± 29.7	0.216

Variables	RAPD vs. OPD		<i>P</i>	Post-RAPD morbidity		
	RAPD (n=64)	OPD (n=62)		RAPD without major morbidity (CD < III, n=36)	RAPD with major morbidity (CD ≥ III, n=28)	<i>P</i>
Ca 19-9 (kU/L)	33.0 (1.0- 5146.0)	29.0 (1.0- 7408.0) 5	0.880	35.0 (1.0-5146.0)	33.0 (1.0-1908.0)	0.946
<p>Values are presented as number (proportion) or depending on normality distribution of cases as mean ± SD or median (interquartile range). Xⁿ where n represents the number of missing cases. ASA, American Society of Anesthesiologists Classification; BMI, Body Mass Index; CD, Clavien Dindo; CVA, Cerebro Vascular Accident; e-GFR, Estimated Glomerular Filtration Rate; OPD, Open Pancreatoduodenectomy; RAPD, Robot-Assisted Pancreatoduodenectomy; TIA, Transient Ischemic Attack.</p>						

Table 2
Perioperative anesthesia-related factors, RAPD vs. OPD

Variables	RAPD vs. OPD		
	RAPD (n=64)	OPD (n=62)	P
Operating room time (min)	513.5 (377.0-836.0)	392.5 (240.0-802.0)	<0.001
Operative time (min)	441.5 (326.0-756.0)	318.0 (188.0-753.0)	<0.001
Intraoperative fluid balance			
Net positive fluid balance (ml)	2497.6 (544.0-5535.0) ¹	1572.3 (50.0-25925.2) ³	<0.001
Crystalloid dose (ml)	2100.0 (51.0-5137.0) ¹	1896.0 (0.0-8337.4) ³	0.069
Colloid dose (ml)	500.0 (0.0-2000.0) ¹	1000.0 (0.0-5700.0) ³	<0.001
Colloid administration	33.0 (51.6) ¹	49.0 (79.0) ³	<0.001
Blood loss (ml)	250.0 (0.0–2500.0)	1150.0 (0.0-11585.0) ³	<0.001
Intraoperative erythrocyte transfusion	4 (6.3) ¹	19 (30.6)	<0.001
NE regimen			
NE dose on surgery's start (ug/kg/min)	0.05 (0.00-0.20) ²	0.03 (0.00-0.72) ²	0.021
NE dose on surgery's end (ug/kg/min)	0.06 (0.00-0.38) ¹	0.06 (0.00-0.80)	0.821
NE dose > 0.2 ug/kg/min (min)	1 (0-5) ¹	0 (0-3) ¹	0.005
Time span NE dose > 0.2 ug/kg/min (min)	4.1 (0.0-610.0) ¹	0.0 (0.0-393.0) ¹	0.002
Operative time NE dose > ug/kg/min (%)	9.5 (0.0-96.2) ¹	0.0 (0.0-56.5) ¹	0.005
First arterial BGA during surgery			
Blood pH	7.32 ± 0.06 ⁷	7.35 ± .0.06 ²	0.021
Partial CO ₂ pressure (kPa)	6.2 (4.3-24.2) ⁷	5.6 (4.5-7.1) ²	<0.001
Corresponding end-tidal CO ₂ (kPa)	5.0 ± 0.6 ¹⁵	4.7 ± 0.3 ⁸	0.001
Lactate level (mmol/L)	0.7 (0.3-1.9) ⁷	0.7 (0.3-2.7) ²	0.884

Variables	RAPD vs. OPD		
	RAPD (n=64)	OPD (n=62)	P
Hemoglobin count (mmol/L)	7.8 ± 0.8 ⁷	7.4 ± 1.0 ²	0.017
First arterial BGA upon HCU/IDU admission			
Blood pH	7.33 ± 0.04 ¹	7.35 ± 0.05	0.013
Partial CO ₂ pressure (kPa)	5.8 (4.7-20.1) ¹	5.5 (4.0-6.7)	0.002
Lactate level (mmol/L)	1.3 (0.1-6.3) ¹	1.3 (0.4-11.7)	0.517
Hemoglobin count (mmol/L)	7.8 ± 0.9 ¹	7.0 ± 1.0	<0.001
First arterial BGA after ≥ 12 hours HCU/IDU admission			
Blood pH	7.39 (7.29-7.48) ⁴	7.39 (7.23-7.47) ¹	0.981
Partial CO ₂ pressure (kPa)	5.8 (4.7-7.0) ⁴	5.5 (3.8-7.9) ¹	0.019
Lactate level (mmol/L)	1.1 (0.5-2.9) ⁴	1.0 (0.4-5.6) ¹	0.803
Hemoglobin count (mmol/L)	7.5 ± 0.9 ⁴	6.8 ± 1.0 ¹	<0.001
Values are presented as number (proportion) or depending on normality distribution of cases as mean ± SD or median (interquartile range). Xⁿ where n represents the number of missing cases. BGA, Blood Gas Analysis; HDU, High Dependency Unit; ICU, Intensive Care Unit; NE, Norepinephrine; OPD, Open Pancreatoduodenectomy; RAPD, Robot Assisted Pancreatoduodenectomy.			

On average, NE administration during the start of surgery was higher in RAPD (0.05 vs. 0.03 µg kg/min in OPD, p=0.021). During the intraoperative course of RAPD, NE dosage exceeded 0.2 µg kg/min more frequently compared to OPD with a median time span of 48 vs. 0 min (p=0.002) equaling 9.5 vs. 0 percent of operating room time (p=0.005). RAPD was characterized by a more acidotic blood pH during surgery (7.32 vs. 7.35 in OPD, p=0.021) with high pCO₂ pressures and corresponding etCO₂ levels (6.2 vs. 5.6 kPa, p<0.001 and 5.0 vs. 4.7 kPa, p=0.001, respectively). A similar trend was observed in RAPD patients upon HDU/ICU arrival (arterial blood pH 7.33 vs. 7.35 in OPD, p=0.013 and pCO₂ 5.8 vs. 5.5 kPa, p=0.002, Table 2, additional file 2).

No differences were observed in major morbidity (CD ≥ III) following RAPD versus OPD (28/64, 43.8% in RAPD vs. 33/62, 53.2% in OPD, p=0.373, Table 3). Average Comprehensive Complication Index was 32.7 for RAPD vs. 49.9 in OPD (p=0.012). Postoperative acute kidney injury was present in 9/64 (14.5%) of RAPD patients vs. 6/62 (9.7%) of OPD patients (p=0.583). Six patients entered the procedure with pre-existing renal impairment (e-GFR < 60 ml/min, n=3 in RAPD and n=3 in OPD): no further deterioration of kidney injury was observed in any of these patients. Average NRS on postoperative day 1 was 3 for RAPD

compared to 1 for OPD ($p < 0.001$). On postoperative day 3, average NRS was 2 for both RAPD and OPD ($p = 0.894$).

Table 3
Postoperative outcome after RAPD vs. OPD

Variables	RAPD (n=64)	OPD (n=62)	<i>P</i>
Time to detubation (min)	32.0 (0.0-931.0) ¹¹	21.0 (1.0-21714.0) ⁹	0.381
Stay HCU/IDU (hours)	19.5 (14.6-97.4)	21.6 (15.6-478.4) ¹	<0.001
Prolonged HDU/ICU admission	5 (7.8)	12 (19.7) ¹	0.069
Hospital stay (days)	11.5 (4.0-61.0)	14.5 (6.0-200.0) ¹	0.277
Comprehensive Complication Index	32.7 (0.0-100.0)	49.9 (8.7-100.0)	0.012
CD morbidity rates			
Grade III	20 (31.1)	23 (37.1)	0.574
Grade IIIA	15 (23.4)	14 (22.6)	1.000
Grade IIIB	5 (7.8)	9 (14.5)	0.268
Grade IV	8 (12.5)	10 (16.1)	0.617
Grade IVA	3 (4.7)	4 (6.5)	0.715
Grade IVB	5 (7.8)	6 (9.7)	0.761
=> Grade III	28 (43.8)	33 (53.2)	0.420
Acute Kidney failure	9 (14.5)	6 (9.4)	0.583
30-day mortality	1 (1.6)	2 (3.2)	0.616
90-day mortality	5 (7.8)	4 (6.5)	1.000
NRS Postoperative day 1	3 (0-7) ⁸	1 (0-7) ³	<0.001
NRS Postoperative day 3	2 (0-7) ⁹	2 (0-5) ¹⁶	0.894
Values are presented as number (proportion) or depending on normality distribution of cases as mean $\pm$ SD or median (interquartile range). Xⁿ: where represents the number of missing cases. CD, Clavien Dindo; HDU, High Dependency Unit; ICU, Intensive Care Unit; NRS, Numeric Rating Scale; OPD, Open Pancreatoduodenectomy; RAPD, Robot Assisted Pancreatoduodenectomy.			

Postoperative morbidity after RAPD: major (CD $\geq$ III) vs. non-major (CD < III)

A higher rate of baseline hypertension was observed in the RAPD subgroup with major postoperative morbidity (17/28, 60.7% vs. 11/36, 30.6%, $p = 0.023$, Table 1). Median intraoperative colloid administration

and blood loss were higher in the RAPD group with major postoperative morbidity (500.0 vs. 0.0 ml, $p=0.002$ and 350.0 vs. 200.0 ml, $p=0.047$, respectively, Table 4, additional file 3). Average NE dose was higher at the end of surgery for the RAPD subgroup with major postoperative morbidity (0.09 vs. 0.04 $\mu\text{g/kg/min}$, $p=0.726$). Upon HDU/ICU admission, lower arterial blood pH as well as higher lactate levels were observed in the RAPD subgroup with major postoperative morbidity (7.32 vs. 7.34, $p=0.017$ and 1.7 vs 1.3 mmol/l, in the RAPD subgroup without major postoperative morbidity, respectively). A similar trend was observed after a minimum of 12 hour HDU/ICU stay (7.37 vs. 7.39, $p=0.016$ and 1.4 vs. 0.9 mmol/l, respectively). Hospital stay was more than doubled in the patients with major postoperative morbidity compared to patients (18.0 vs. 7.0 days, $p<0.001$, Table 5). Within 90 days following surgery, $n=2$ RAPD patients deceased due to early recurrence of malignant disease (one in both RAPD subgroups).

Table 4
Perioperative anesthetic factors in RAPD

Variables	RAPD (n=64)	Post-RAPD morbidity			Intraoperative blood loss (RAPD)		<i>P</i>
		RAPD with major morbidity (CD ≥ III, n=28)	RAPD without major morbidity (CD < III, n=36)		High (≥ 250 ml, n=33)	Low (< 250 ml, n=31)	
Operating room time	513.5 (377.0- 836.0)	527.5 (397.0- 749.0)	513.5 (377.0- 836.0)	0.690	580.0 (397.0- 750.0)	478.0 (377.0- 836.0)	0.001
Operative time	441.5 (326.0- 756.0)	463.5 (353.0- 691.0)	441.5 (326.0- 756.0)	0.671	516.0 (353.0- 691.0)	410.0 (326.0- 756.0)	0.001
Intraoperative fluid balance							
Net positive fluid balance (ml)	2497.6 (544.0- 5535.0) ¹	2777.1 ± 1046.9 ¹	2688.0 ± 806.3	0.704	3057.0 (544.0- 5535.0) ¹	2288.9 (1525.6- 4346.9)	0.012
Crystalloid dose (ml)	2100.0 (51.0- 5137.0) ¹	2267.4 ± 1110.4 ¹	2294.4 ± 702.2	0.906	2478.7 ± 1048.7 ¹	2080.6 6 ± 51.6	0.076
Colloid dose (ml)	500.0 (0.0- 2000.0) ¹	500.0 (0.0- 2000.0) ¹	0.0 (1.0- 1000.0)	0.002	500.0 (0.0- 2000.0) ¹	0.0 (0.0- 1250.0)	<0.001
Colloid administration	33.0 (51.6) ¹	20 (71.4) ¹	13 (36.1)	0.005	25 (75.8) ¹	8 (25.8)	<0.001
Blood loss (ml)	250.0 (0.0- 2500.0)	350.0 (0.0- 2500.0)	200.0 (30.0- 2000.0)	0.047	500.0 (250.0- 2500.0)	150.0 (0.0- 200.0)	<0.001
Intraoperative erythrocyte transfusion	4 (6.3) ¹	2 (7.1) ¹	2 (5.6)	1.000	4 (12.1) ¹	0	0.113
NE regimen							
NE dose on surgery's start (ug/kg/min)	0.05 (0.00- 0.20) ²	0.05 (0.01- 0.20) ¹	0.05 (0.00- 0.20) ¹	0.472	0.05 (0.00- 0.19) ²	0.05 (0.00- 0.20)	0.692

Variables	RAPD (n=64)	Post-RAPD morbidity			Intraoperative blood loss (RAPD)		
		RAPD with major morbidity (CD ≥ III, n=28)	RAPD without major morbidity (CD < III, n=36)		High (≥ 250 ml, n=33)	Low (< 250 ml, n=31)	P
NE dose on surgery's end (ug/kg/min)	0.06 (0.00-0.38) ¹	0.09 (0.00-0.22) ¹	0.04 (0.00-0.38)	0.726	0.09 (0.00-0.38) ¹	0.04 (0.00-0.25)	0.518
NE dose > 0.2 ug/kg/min (min)	1 (0-5) ¹	1 (0-5) ¹	1 (0-3)	0.471	1 (0-4) ¹	1 (0-5)	0.374
Time span NE dose > 0.2 ug/kg/min (min)	4.1 (0.0-610.0) ¹	133.0 (0.0-610.0) ¹	22.5 (0.0-550.0)	0.262	134.0 (0.0-600.0) ¹	15.0 (0.0-610.0)	0.283
Operative time NE dose > ug/kg/min (%)	9.5 (0.0-96.2) ¹	20.4 (0.0-96.2) ¹	5.0 (0.0-9.1)	0.298	20.8 (0.0-86.2) ¹	4.0 (0.0-96.2)	0.431
First arterial BGA during surgery							
Blood pH	7.32 ± 0.06 ⁷	7.34 ± 0.06 ³	7.31 ± 0.06 ⁴	0.135	7.31 ± 0.06 ³	7.33 ± 0.06 ⁴	0.361
Partial CO ₂ pressure (kPa)	6.2 (4.3-24.2) ⁷	6.1 (4.3-8.1) ³	6.3 (5.3-24.2) ⁴	0.681	6.3 (4.3-8.4) ³	6.1 (5.1-24.2) ⁴	0.695
Corresponding end-tidal CO ₂ (kPa)	5.0 ± 0.6 ¹⁵	5.0 ± 0.7 ⁵	5.0 ± 0.5 ¹⁰	0.895	5.0 (3.9-6.5) ⁸	5.0 (3.9-6.6) ⁷	0.703
Lactate level (mmol/L)	0.7 (0.3-1.9) ⁷	0.8 (0.3-1.9) ³	0.7 (0.4-1.3) ⁴	0.403	0.8 (0.3-1.6) ³	0.7 (0.4-1.9) ⁴	0.411
Hemoglobin count (mmol/L)	7.8 ± 0.8 ⁷	7.9 ± 0.8 ³	7.8 ± 0.9 ⁴	0.526	7.7 ± 0.9 ³	8.0 ± 0.8 ⁴	0.180
First arterial BGA upon HDU/ICU admission							
Blood pH	7.33 ± 0.04 ¹	7.32 ± 0.04	7.34 ± 0.04 ¹	0.017	7.33 ± 0.05 ¹	7.33 ± 0.04	0.588

Variables	RAPD (n=64)	Post-RAPD morbidity			Intraoperative blood loss (RAPD)		
		RAPD with major morbidity (CD ≥ III, n=28)	RAPD without major morbidity (CD < III, n=36)		High (≥ 250 ml, n=33)	Low (< 250 ml, n=31)	<i>P</i>
Partial CO ₂ pressure (kPa)	5.8 (4.7- 20.1) ¹	5.8 (4.8- 20.1)	5.8 (4.6- 10.7) ¹	0.241	5.8 (4.7- 20.1) ¹	5.8 (5.0- 10.7)	0.588
Lactate level (mmol/L)	1.3 (0.1- 6.3) ¹	1.7 (0.5- 6.3)	1.3 (0.1- 6.3) ¹	0.021	1.6 (0.5- 6.3) ¹	1.0 (0.1- 3.7)	0.008
Hemoglobin count (mmol/L)	7.8 ± 0.9 ₁	7.8 ± 0.9	7.8 ± 0.9 ¹	0.874	7.5 ± 0.9 ¹	8.1 ± 0.8	0.007
First arterial BGA after ≥ 12 hours HDU/ICU admission							
Blood pH	7.39 (7.29- 7.48) ⁴	7.37 ± 0.04 ¹	7.39 ± 0.03 ₃	0.016	7.38 ±0.04 ³	7.40 ± 0.04 ¹	0.131
Partial CO ₂ pressure (kPa)	5.8 (4.7- 7.0) ⁴	5.8 ± 0.5 ¹	5.6 ± 0.5 ³	0.190	5.8 (4.8- 6.3) ³	5.7 (4.9- 7.0) ¹	0.906
Lactate level (mmol/L)	1.1 (0.5- 2.9) ⁴	1.4 (0.6- 2.8) ¹	0.9 (0.5- 2.9) ³	0.014	1.2 (0.7- 2.8) ³	1.0 (0.5- 2.9) ¹	0.282
Hemoglobin count (mmol/L)	7.5 ± 0.9 ₄	7.7 (5.2- 8.7) ¹	7.6 (6.1- 9.5) ³	0.864	7.1±0.9 ₃	7.9 ± 0.7 ¹	<0.001
Values are presented as number (proportion) or depending on normality distribution of cases as mean ± SD or median (interquartile range). X ⁿ where n represents the number of missing cases. BGA, Blood Gas Analysis; HDU, High Dependency Unit; ICU, Intensive Care Unit; NE, Norepinephrine; OPD, Open Pancreatoduodenectomy; RAPD, Robot Assisted Pancreatoduodenectomy.							

Table 5
Postoperative outcome after RAPD

Variable	RAPD (n=64)	Post-RAPD morbidity			Intraoperative (RAPD) blood loss		
		RAPD with major morbidity (CD $\geq$ III, n=28)	RAPD without major morbidity (CD < III, n=36)	P	High ($\geq$ 250 ml, n=33)	Low (< 250 ml, n=31)	P
Time to detubation (min)	32.0 (0.0- 931.0) 11	49.5 (0.0- 403.0) ⁶	24.0 (0.0- 931.0) ⁵	0.316	55.0 (0.0- 931.0) 8	22.5 (0.0- 185.0) 3	0.327
Stay HDU/ICU (hours)	11.5 (4.0- 61.0)	20.0 (15.3- 97.4)	19.1 (14.6- 44.0)	0.140	18.8 (14.0- 97.4)	19.7 (14.6- 44.9)	0.122
Prolonged HDU/ICU admission	5 (7.8)	4 (14.3)	1 (2.8)	0.159	3 (9.1)	2 (6.5)	1.000
Hospital stay (days)	10.5 (4.0- 61.0)	19.0 (5.0- 61.0)	8.0 (4.0-37.0)	<0.001	17.0 (5.0- 61.2)	9.0 (4.0- 48.0)	0.002
Comprehensive Complication Index	32.7 (0.0- 100.0)	64.5 (0.0- 100.0)	21.8 (0.0- 100.0)	<0.001	51.5 (12.2- 100.0)	24.2 (0.0- 99.9)	<0.001
CD $\geq$ Grade III	28 (43.8)	-	-	-	20 (60.6)	8 (25.8)	0.006
NRS Postoperative day 1	3 (0-7) 8	3 (0-7) ¹	2 (0-7) ⁷	0.248	3 (0-7) 3	2 (0-7) 5	0.255
NRS Postoperative day 3	2 (0-7) 9	2 (0-7) ³	2 (0-4) ⁶	0.071	2 (0-7) 4	2 (0-7) 5	0.562
Values are presented as number (proportion) or median (interquartile range). Xⁿ where n represents the number of missing cases. CD, Clavien Dindo; HDU, High Dependency Unit; ICU, Intensive Care Unit; NRS, Numeric Rating Scale; OPD, Open Pancreatoduodenectomy; RAPD, Robot Assisted Pancreatoduodenectomy.							

High vs. low intraoperative blood loss in RAPD

Average intraoperative blood loss was 250 ml in RAPD (Table 2, additional file 2), n=33 RAPD procedures were characterized by high ($\geq$ 250 ml) vs. n=31 RAPD procedures with low (< 250 ml) intraoperative blood loss. Both operating room and operative times were longer in the RAPD group with high

intraoperative blood loss (580.0 vs. 487.0 min., $p=0.001$ and 518.0 vs. 410.0 min., $p=0.001$, respectively, Table 4, additional file 3). Average NE dose at the end of surgery was higher for the RAPD group with high intraoperative blood loss (0.09 vs. 0.04 $\mu\text{g kg/min}$ in the RAPD group with low intraoperative blood loss). NE-dose tended to exceed 0.2 $\mu\text{g kg/min}$ more frequently in the RAPD group of high intraoperative blood loss (134.0 vs. 15.0 min, $p=0.283$, and 20.8% vs. 4.0% of operative time, $p=0.431$). Upon HDU/ICU admission, lactate levels were higher in the RAPD group of high intraoperative blood loss (1.6 vs. 1.0 mmol/l in the RAPD group of low intraoperative blood loss, $p=0.008$). Length of hospital stay was doubled for the RAPD group of high intraoperative blood loss (16.0 vs. 8.0 days in the RAPD group of low intraoperative blood loss, $p=0.002$, Table 5). A higher rate of postoperative morbidity was observed in the RAPD group with high intraoperative blood loss (Comprehensive Complication Index of 51.5 vs. 24.2 in the RAPD group with low intraoperative blood loss, $p<0.001$). Besides, a higher rate of major postoperative morbidity ($\text{CD} \geq \text{III}$) was found in the RAPD group characterized by high intraoperative blood loss (20/33, 60.6% vs. 8/31, 25.8% in the RAPD group of low intraoperative blood loss, $p=0.006$).

Predictors of major morbidity following RAPD

After performing univariate logistic regression, variables independently associated with major morbidity ($\text{CD} \geq \text{III}$) following RAPD were baseline medical history of hypertension (OR 3.51, 95% CI 1.24-9.92, $p=0.018$), colloid administration during surgery (OR 5.06, 95% CI 1.69-15.14, $p=0.004$), lactate level upon HDU/ICU admission (OR 2.47, 95% CI 1.27-4.82, $p=0.008$) and lactate level after 12 hour HDU/ICU admission (OR 3.66, 95% CI 1.29-10.44, $p=0.015$, Table 6). After carrying out backward stepwise regression, colloid administration during surgery and lactate level after 12 hour HDU/ICU admission remained independently associated with major morbidity after RAPD (OR 5.06, 95% CI 1.49-17.2, $p=0.009$ and OR 3.18, 95% CI 1.01-9.91, $p=0.047$, respectively).

Table 6

Logistic regression analysis : anesthesia-related factors independently associated with major morbidity (CD $\geq$ III) after RAPD

Variable	Univariable analysis			Backward stepwise regression		
	OR	95% CI	<i>P</i>	OR	95% CI	<i>P</i>
Medical history of hypertension	3.51	1.24 to 9.92	0.018	3.28	0.97 to 11.13	0.057
Intraoperative colloid administration	5.06	1.69 to 15.14	0.004	5.06	1.49 to 17.20	0.009
Blood loss during surgery (ml)	1.12	1.00 to 1.26	0.058			
Operating room time (min)	1.00	1.00 to 1.01	0.599			
Lactate level in first BGA after HDU/ICU admission (mmol/L)	2.47	1.27 to 4.82	0.008			
Lactate level in BGA after $\geq$ 12 hour HDU/ICU admission (mmol/L)	3.66	1.29 to 10.44	0.015	3.18	1.01 to 9.91	0.047
BGA, Blood Gas Analysis; CI, confidence interval; CD, Clavien Dindo; HDU, High Dependency Unit; ICU, Intensive Care Unit; NE, Norepinephrine; OR, Odds Ratio; RAPD, Robot Assisted Pancreatoduodenectomy.						

Discussion

RAPD is characterized by higher perioperative vasopressor administration as well as a higher intraoperative net fluid balance, compared to OPD. However, colloid administration and erythrocyte transfusion were more often used in OPD compared to RAPD. Rates of major postoperative morbidity following surgery (CD $\geq$ III) were similar for RAPD and OPD. Patients who developed major morbidity (CD $\geq$ III) after RAPD required vasopressor administration in higher doses and more often received intraoperative colloids than those without major postoperative morbidity. Administration of colloids as well as increased postoperative lactate levels, were independently associated with major morbidity (CD $\geq$ III) following RAPD.

When interpreting outcomes following RAPD versus OPD, patient-related factors are more likely to affect postoperative morbidity compared to the surgical modality. We report a relatively small portion of patients marked ASA class III and higher (11/64, 17.2% in RAPD and 13/62, 22.4% in OPD), compared to earlier studies reporting percentages up to 43.1 and 82.4% [14, 15]. This discrepancy might suggest an underrating of ASA grading, in contrast with the 2017 strengthened ASA classifications [16]. ASA scores

in our series are however in concordance with recent findings of van Roessel et al., reporting a fraction of 21.8% ASA III patients in a cohort of n=3341 pancreatic surgeries, based on the Dutch Nationwide Pancreatic Cancer Audit data [17, 18]. Van Roessel et al. predicts worse outcome following pancreatoduodenectomy in patients allocated ASA $\geq$ III (OR 0.59, 95% CI 0.44-0.80, for achieving 'optimal outcome' after pancreatic surgery). In our study ASA class itself was not an individual predictor for postoperative major morbidity (CD $\geq$ III) as baseline hypertension was (OR 3.51, 95% CI 1.24-9.92). This finding, along with higher vasopressor demands in RAPD, implies an association between elemental hemodynamic and cardiovascular condition and postoperative outcome following RAPD. This observation illustrates the necessity of adequate perioperative cardiovascular risk management, e.g. suggesting lower postoperative morbidity following RAPD in case of optimal baseline antihypertensive therapy, invasive monitoring of circulatory status and prompt intervention in case of any deterioration. However, having a medical history of hypertension might include several other conditional factors posing an increased risk for developing (major) postoperative morbidity (e.g. increased BMI, vascular remodeling or pre-existing renal insufficiency) by itself.

The higher use of intraoperative vasopressors in RAPD versus OPD can be explained by differences in patient positioning (reversed-Trendelenburg in RAPD vs. supine in OPD) as well as exposure to pneumoperitoneum, increasing cardiac afterload and decreasing cardiac output [7–9]. A higher demand for vasopressor administration in RAPD was not necessarily reflected by worse baseline physical condition. Except for the fact that OPD patients more often received neoadjuvant chemotherapy and baseline hemoglobin levels were lower, no differences in baseline medical conditions could be demonstrated between RAPD and OPD patients. Although the intraoperative use of vasopressors was evident, we feel supported by recently published data that the routine insertion of a central venous catheter is not mandatory in neither RAPD nor OPD patients [19, 20].

The 2018 RELIEF Study focused on postoperative outcomes after distinct intraoperative fluid strategies during major abdominal surgery, differentiating between an either restrictive (median crystalloid + colloid 2177 ml) or liberal (median crystalloid + colloid 3500 ml) net intraoperative fluid balance [5]. Whereas no differences were observed in general postoperative outcomes between both fluid approaches, a more liberal intraoperative fluid strategy was associated with lower rates of postoperative acute kidney failure (17/1439, 5.0% for liberal vs. 124/1443, 8.6% for restrictive, $p < 0.001$). In our study, median intraoperative net fluid balance was 2800 ml and 9/64 (14.5%) of RAPD patients suffered from postoperative acute kidney injury. Bannone et al. suggested an association between a more restrictive perioperative fluid balance and an increased risk for developing postoperative pancreatic fistula [21]. On the contrary, the 2019 meta-analysis by Garland et al. reported an OR of 0.54 (95% CI 0.31–0.94) for major morbidity following pancreatoduodenectomy surgery after adopting a more restrictive intraoperative fluid strategy [22]. The optimal intraoperative fluid regime in pancreatoduodenectomy remains point of debate: current insights are contradictory and prospective research in this area should distinguish between laparoscopic and open pancreatic surgery.

We observed an association between the intraoperative administration of colloids and development of major morbidity after RAPD (OR 5.06, 95% CI 1.96-15.14, $p=0.009$). This finding is in accordance with Simões et al., reporting an OR of 1.86 (95% CI 1.03-4.307) for major morbidity following the intraoperative administration of colloids (including $n=308$ elective surgical procedures for abdominal malignancies, including $n=22$ pancreatic surgeries) [23]. In our series, 8/31 (25.8%) RAPD patients with low intraoperative blood loss vs. 25/33 (75.8%)

RAPD patients with high intraoperative blood loss received colloids during surgery. Of note, it is important to consider who are the patients requiring intraoperative colloid administration. Since colloid fluid administration is an integral part of the treatment in case of major blood loss in our center, the association of intraoperative colloid administration and development of major postoperative morbidity ($CD \geq III$) does not necessarily have to reflect a direct causative effect.

During the perioperative course, pH values were lower in RAPD compared to OPD (7.32 vs. 7.35 on beginning of surgery, $p=0.021$ and 7.33 vs. 7.35 upon HDU/ICU arrival, $p=0.013$). Differences in pH levels of this magnitude do not reflect clinical relevance. In our series a higher lactate level after a minimal admission of 12 hours on HDU/ICU was associated with major morbidity after RAPD (OR 3.18, 95% CI 1.01-9.91, $p=0.047$). This is in accordance with De Schryver et al., reporting an OR of 3.58 (95% CI 1.22-10.18, $p=0.020$) for 6-hour post pancreatic (laparotomic) surgery hyperlactatemia and development of postoperative pancreatic fistula [24]. Average postoperative pain scores during the first postoperative day were higher in RAPD compared to OPD. The reported first postoperative day NRS of 3 in RAPD compared to a NRS of 1 in OPD is of limited clinical relevance and therefore not likely to attribute to major morbidity. Besides, this moderate difference can well be explained by the routine application of additional epidural analgesia in OPD, in accordance with previously reported studies on additional epidural analgesia during pancreatoduodenectomy [25].

Our study has several limitations. First the retrospective single-center study design covering a relatively high, but still limited number of procedures. Due to the limited number of surgeons, the surgical approach was very standardized. This is in contrast to the perioperative anesthetic care, which was provided by several consultant anesthesiologists who followed the available protocols with different levels of adherence. We consider this variability in the anesthesiological approach a mirror of clinical practice and an aspect which deserves special attention in possible prospective trials. Also, although locally advanced pancreatic disease was considered the only exclusion criteria for RAPD, study results could be biased by patient selection for RAPD either OPD surgery.

Conclusions

There are specific differences and challenges regarding the perioperative anesthetic strategy between RAPD and OPD. RAPD is associated with higher levels of vasopressor administration during surgery and net perioperative fluid balance is higher. Contrarily, the levels of colloid and erythrocyte transfusion are higher for OPD compared to RAPD. Baseline hypertension, perioperative colloid administration and

increased lactate levels after surgery are associated with higher rates of major morbidity (CD $\geq$ III) following RAPD. A more restrictive intraoperative fluid regime has previously been shown to increase postoperative (nephrogenic) morbidity, present evidence is nonetheless contradictory. Current data is insufficient to make specific recommendations to optimal perioperative anesthetic guidance in RAPD. However, perioperative hemodynamic management including preoperative optimization and intraoperative fluid- and vasopressor- strategy are suggested to influence postoperative morbidity and should be the focus of future prospective studies.

Abbreviations

ASA = American Society of Anesthesiologists

BGA = Blood Gas Analysis

BMI = Body Mass Index

CCI = Charlson Comorbidity Index

CD = Clavien Dindo

CI = Confidence Interval

CVA = Cerebral Vascular Accident

e-GFR = Estimated Glomerular Filtration Rate

EPCO = European Perioperative Clinical Outcome

ESA = European Society of Anesthesiologists

et = End Tidal

Hb = Hemoglobin

HDU = High Dependency Unit

ICU = Intensive Care Unit

IQR = Interquartile Range

NE = Norepinephrine

NRS = Numeric Rating Scale

OPD = Open Pancreatoduodenectomy

OR = Odds Ratio

PCA = Patient Controlled Analgesia

pCO₂ = Partial CO₂

RAP = Robot-Assisted Pancreatoduodenectomy

SD = Standard Deviation

TIA = Transient Ischemic Attack

Declarations

- Ethics approval and consent to participate: The Medical Ethics Committee approved a waiver for informed consent on February 14th 2019 (MEC-2019-0090, Medical Ethics Committee, Erasmus MC University Hospital, P. Box 2040, 3000 CA, Rotterdam, the Netherlands), given the retrospective nature of this observational study.
- Consent for publication: not applicable.
- Availability of data and materials: the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.
- Competing interests: the authors declare that they have no competing interests.
- Funding: departmental funding only.
- Authors' contributions: All authors contributed to the study conception and design. Data collection and subsequent analysis were performed by AvdE. The first draft of the manuscript was written by AvdE and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.
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