Identifying Perioperative Anesthetic Factors associated with Postoperative Morbidity in Robot-Assisted vs. Open Pancreatoduodenectomy: A Cohort Study

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Abstract

Background: Robot-assisted pancreatoduodenectomy (RAPD) is a challenging procedure for the perioperative anesthesiologist, e.g. because of prolonged pneumoperitoneum exposure and reversed-Trendelenburg positioning. Purpose of this retrospective cohort study is to identify differences in perioperative anesthesia-related factors between RAPD and open pancreatoduodenectomy (OPD) and to determine perioperative anesthetic factors associated with major morbidity (Clavien Dindo ≥ III) after RAPD.

Methods: All consecutive patient undergoing pancreatoduodenectomy were retrospectively included during a two year inclusion period. Anesthesia charts were studied on fluid management details, rates of vasopressor administration and arterial blood gas results. All factors were compared between both surgical approaches. Within RAPD, factors were subsequently compared between patients with major (Clavien Dindo ≥ III) vs. without major postoperative morbidity and between procedures with high and low intraoperative blood loss. Perioperative factors associated with considerable postsurgical morbidity (Clavien Dindo ≥ III) were identified by constructing a logistic regression model.

Results: RAPD was associated with higher administration of intraoperative vasopressors (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). OPD patients more frequently and quantitatively received colloids compared to RAPD patients (79.0% vs. 51.6%, p<0.001, 1000.0 vs. 500.0 ml, p<0.001). Intraoperative erythrocyte transfusion rate was 6.3% (4/64) for RAPD compared to 30.6% (19/62) for OPD (p<0.001). Colloid administration during surgery and hyperlactatemia after 12 hour postoperative admission were associated with major (Clavien Dindo ≥ III) morbidity after RAPD (OR 5.06 with 95% CI 1.49-17.20, p=0.009 and OR 3.18 with 95% CI 1.01-9.91, p=0.047, respectively).

Conclusions: RAPD is a challenging procedure for the perioperative anesthesiologist e.g. considering a higher perioperative demand for vasopressors. Perioperative anesthetic factors, including hemodynamics and fluid strategy might alter postoperative morbidity. However, current data is insufficient to make specific recommendations.

Background

The robot-assisted approach of pancreatoduodenectomy was first described in 2003 by Giulianotti et al. and has gained momentum as a minimally invasive technique for pancreatoduodenectomy surgery [1]. Robot-assisted pancreatoduodenectomy (RAPD) was already compared with conventional open pancreatoduodenectomy (OPD) for surgical outcomes by various cohort studies. Despite longer duration of surgery, RAPD is characterized by lower intraoperative blood loss with equal postoperative mortality rates and similar oncological outcome [2–4]. Although the surgical feasibility of RAPD is extensively reported, little is known about specific anesthesiologic concerns of RAPD and how perioperative anesthesia-related factors affect postoperative outcome after RAPD.

The optimal intraoperative fluid regimen during abdominal (including pancreatic) surgery in relation to postsurgical morbidity is part of ongoing scientific debate. E.g., the 2018 RELIEF trial described an association between a more restrictive intraoperative net fluid balance (median 3.7 liters) and an increased rate of postsurgical kidney injury after major abdominal surgery [5]. Grant et al. however observed no differences in postoperative major morbidity rate after randomizing between either a net liberal (12 ml kg^{-1} hr^{-1}) vs. net restrictive (6 ml kg^{-1} hr^{-1}) intraoperative fluid balance for pancreatectomy surgery, both in a conventional and minimally-invasive approach [6]. RAPD presents several specific perioperative challenges. The patient is exposed to pneumoperitoneum and placed in reversed-Trendelenburg position during the most of the surgical time. This specific sequence has previously been described to alter central venous pressure, to increase blood carbon dioxide levels as well as to decrease cardiac output [7–9]. Compared to OPD, RAPD is expected to differ in perioperative vasopressor demands and levels of fluid administration.

The objective of this retrospective study was firstly to evaluate anesthesia-related differences of RAPD compared to OPD and secondly to identify independent anesthesia-related factors associated with post-RAPD morbidity.

Methods

Population and study characteristics

The local Medical Ethics Committee approved the study with waiver for informed patient consent with reference MEC-2019-0090 (Medical Ethics Committee, Erasmus MC University Hospital, Rotterdam, the Netherlands). The study protocol is performed in accordance with the relevant guidelines.

All consecutive patients who underwent pancreatoduodenectomy (either RAPD or OPD) between January 1st 2017 and December 31st 2018 have been retrospectively included for analysis. RAPD has been performed in our tertiary referral center 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). OP was performed by or under direct supervision of three experienced consultant pancreatic surgeons. Different consultant anesthesiologists (n = 39) were involved in both surgical modalities.

RAPD is characterized as full-robotic surgery, meaning both the resection and the reconstruction phase were conducted robotically-assisted. Patients were assigned to RAPD based on patient preference and availability of both the robot and the robotic surgical team. Patients were only excluded for RAPD in case of locally advanced pancreatic cancer. 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 both units. Digital patient records were reviewed for patient demographics, intra- and postoperative management and postoperative outcome.

Demographic and baseline details

Extracted baseline data included age, sex, body mass index (BMI) and medical history (comprising preoperative 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, data were extracted on preoperative rates of any previous malignancy, (non-) abdominal surgery or neoadjuvant chemotherapy. Baseline comorbidity was graded according to American Society of Anesthesiologist's (ASA) score and Charlson Comorbidity Index (CCI) [10]. Laboratory results (including hemoglobin (Hb), platelet count, estimated glomerular filtration rate (e-GFR) and levels of albumin, total bilirubin, creatinine and CA 19 – 9) were also extracted.

Perioperative factors and postoperative outcome

According to local protocol norepinephrine (NE) was routinely used as perioperative vasopressor adjunct. Anesthesia records were screened for NE doses on start and end of surgery as well as the frequency of an NE dosage exceeding 0.2 µg kg^{-1} min^{-1} (this dosage was chosen within our center as a cut-off for NE-administration via a central venous catheter instead of via a peripheral intravenous cannula). A central venous catheter was incidentally inserted based on preoperative anesthesiologist's assessment. The amount of times NE dosage exceeded 0.2 µg kg^{-1} min^{-1} was expressed as time span in minutes and as percentage of operating room time (time span between entering and leaving the operating theatre). Operative time was defined as the time interval between skin incision and wound closure.

Fluid balances, including the necessity of erythrocyte transfusion, were studies up to 24 hours postoperatively. Results of arterial blood gas (ABG) analyses (including blood pH, partial CO_2 (pCO_2) pressure, lactate and Hb count) were evaluated 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 ABG results were also compared with the corresponding end tidal (et) CO_2 level.

Time to detubation was defined as the time interval between wound closure and removal of the endotracheal tube. Pain scores, expressed as Numeric Rating Scale (NRS), were analyzed on postoperative days 1 and 3. Standard postoperative analgesic regimen comprised paracetamol (1000 mg 4 times daily) and naproxen (750 mg 3 times daily). OPD was preferably performed under additional epidural analgesia (routinely using ropivacaine 0.2% combined with sufentanil 1 µg ml^{-1}). 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.

Patient records were analyzed for the total hours of postoperative HDU/ICU stay and the rate of prolonged HDU/ICU admission (defined as exceeding 24 hours). Length of hospital stay was determined starting from the first day after surgery. Postoperative morbidity was graded on a 90-day postsurgical interval using the Clavien Dindo (CD) score as well as the Comprehensive Complication Index [11, 12]. A CD score ≥ III was defined as major postsurgical morbidity. Kidney failure was graded according to

European Society of Anesthesiologists' (ESA) European Perioperative Clinical Outcome (EPCO) standards [13]. Mortality rates were calculated on postoperative days 30 and 90.

Data processing and statistical analysis

Baseline and perioperative factors were primarily analyzed for RAPD and OPD totals. Factors were subsequently compared for RAPD patients with major postsurgical morbidity (CD ≥ III) vs. RAPD patients without major postsurgical morbidity. In order to determine whether anesthetic factors were influenced by intraoperative blood loss, factors ware also compared for RAPD patients with above vs. below median intraoperative blood loss (referred to as groups of high and low blood loss, respectively).

Normal distribution of numerical data was assessed using a combination of visual inspection of histograms and Q-Q plots and the Shapiro-Wilk test. Numerical data on averages 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. A logistic regression model was constructed using a backward stepwise approach to identify independent prognostic factors of major morbidity (CD ≥ III) after RAPD. Results herein were presented as odds ratio (OR) with corresponding 95% confidence interval. 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

During the inclusion period, 126 Consecutive patients underwent pancreatoduodenectomy (n = 64 RAPD, n = 62 OPD).

RAPD vs. OPD

No differences in age, BMI and baseline medical history could be demonstrated between RAPD and OPD patients (Table 1). Baseline hemoglobin level was lower for OPD (12.6 vs. 13.2 g dl^{-1}, p = 0.049). Operative time was 441.5 min. in RAPD compared to 318.0 min. in OPD (p < 0.001, Table 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, 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). For RAPD, Hb levels were higher during surgery, upon HDU/ICU admission and after a minimum of 12 hour HDU/ICU admission (12.6 vs. 11.9 g dl^{-1}, p = 0.017, 12.6 vs. 11.3 g dl^{-1}, p < 0.001 and 12.1 vs. 11.0 g dl^{-1}, 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)	*P*	RAPD without major morbidity (CD < III, n = 36)	RAPD with major morbidity (CD ≥ III, n = 28)	*P*
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)	
III	11 (17.2)	13 (22.4) [4]		5 (13.9)	6 (21.4)	

Variables	RAPD vs. OPD			Post-RAPD morbidity		
	RAPD (n = 64)	OPD (n = 62)	*P*	RAPD without major morbidity (CD < III, n = 36)	RAPD with major morbidity (CD ≥ III, n = 28)	*P*
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}·1.73^{-1} 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
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

Variables	RAPD vs. OPD			Post-RAPD morbidity		
	RAPD (n = 64)	OPD (n = 62)	*P*	RAPD without major morbidity (CD < III, n = 36)	RAPD with major morbidity (CD ≥ III, n = 28)	*P*

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. 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.

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^{-1}·min^{-1})	0.05 (0.00-0.20) [2]	0.03 (0.00-0.72) [2]	0.021
NE dose on surgery's end (ug·kg^{-1}·min^{-1})	0.06 (0.00-0.38) [1]	0.06 (0.00-0.80)	0.821
NE dose > 0.2 ug·kg^{-1}·min^{-1} (min)	1 (0–5) [1]	0 (0–3) [1]	0.005
Time span NE dose > 0.2 ug·kg^{-1}·min^{-1} (min)	4.1 (0.0-610.0) [1]	0.0 (0.0-393.0) [1]	0.002
Operative time NE dose > ug·kg^{-1}·min^{-1} (%)	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

Variables	RAPD vs. OPD		
	RAPD (n = 64)	OPD (n = 62)	*P*
Lactate level (mmol/L)	0.7 (0.3–1.9) [7]	0.7 (0.3–2.7) [2]	0.884
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). 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.

On average, NE was administered in a higher dose at procedure's start in RAPD (0.05 vs. 0.03 µg kg^{-1} min^{-1} in OPD, p = 0.021). During the intraoperative course of RAPD, NE dosage exceeded 0.2 µg kg^{-1} min^{-1} more frequently compared to OP with a net time span of 48 vs. 0 min (p = 0.002) and 9.5 vs. 0 percent of operating room time (p = 0.005). RAPD was characterized by lower average blood pH during surgery (7.32 vs. 7.35 in OPD, p = 0.021) with high pCO_2 pressures and corresponding $etCO_2$ levels (6.2 vs. 5.6 kPa in OPD, p < 0.001 and 5.0 vs. 4.7 kPa in OPD, p = 0.001, respectively). A similar trend is observed in RAPD patients upon HDU/ICU arrival (arterial blood pH 7.33 vs. 7.35 in OPD, p = 0.013 and pCO_2 5.8 vs. 5.5 kPa in OPD, p = 0.002, Table 2).

No differences were observed in major postoperative morbidity rate (CD ≥ III) between both surgical modalities (28/64, 43.8% in RAPD vs. 33/62, 53.2% in OPD, p = 0.373, Table 3). An average Comprehensive Complication Index of 32.7 was observed in RAPD vs. 49.9 in OPD (p = 0.012). Rates of postoperative acute kidney injury were 9/64 (14.5%) for RAPD vs. 6/92 (9.7%) for OPD (p = 0.583). Six

patients entered the procedure with pre-existing renal impairment (e-GFR < 60 ml min-1, n = 3 in RAPD and n = 3 in OPD). No further deterioration of kidney injury was observed in any of these patients. Average pain score on postoperative day 1 was 3 for RAPD compared to 1 for OPD (p < 0.001). On postoperative day 3, average pain score 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)	*P*
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)`	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 ± SD or median (interquartile range). X^n: 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.

Major (CD ≥ III) vs. without major morbidity after RAPD

A higher rate of baseline hypertension was observed in the RAPD group with major postoperative morbidity (17/28, 60.7% vs. 11/36, 30.6% for the RAPD group without major morbidity, $p = 0.023$, Table 1). 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). Average NE dose was higher at the end of surgery for the RAPD group with major postoperative morbidity (0.09 vs. 0.04 µg kg^{-1} min^{-1} for the RAPD group without major postoperative morbidity, $p = 0.726$). Upon HDU/ICU admission, lower arterial blood pH as well as higher lactate levels were observed in the RAPD group with major postoperative morbidity (7.32 vs. 7.34, $p = 0.017$ and 1.7 vs 1.3 mmol l^{-1}, in the RAPD group without major postoperative morbidity, respectively). A similar trend was observed after a minimum of 12 hour HDU/ICU admission (7.37 vs. 7.39, $p = 0.016$ and 1.4 vs. 0.9 mmol l^{-1}, respectively). Hospital stay was doubled in the RAPD group with major postoperative morbidity compared to the RAPD group without major postoperative morbidity (18.0 vs. 7.0 days, $p < 0.001$, Table 5). Within the 90-day inclusion period, n = 2 (RAPD) patients deceased due to early recurrence of malignant disease.

Table 4
Perioperative anesthetic factors in RAPD

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*
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 ($ug \cdot kg^{-1} \cdot min^{-1}$)	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^{-1}·min^{-1})	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^{-1}·min^{-1} (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^{-1}·min^{-1} (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^{-1}·min^{-1} (%)	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)	*P*
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 ≥ III, n = 28)	RAPD without major morbidity (CD < III, n = 36)	*P*	High (≥ 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 ≥ 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). X^n 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), n = 33 RAPD procedures were characterized by high (≥ 250 ml) vs. 31 RAPD procedures by low (< 250 ml) intraoperative blood loss. Both operating room and operative time 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) compared to the RAPD group with low intraoperative blood loss. Average NE dose was higher at the end of surgery for the RAPD group with high intraoperative blood loss (0.09 vs. 0.04 μg kg^{-1} min^{-1} in the RAPD group with low intraoperative blood loss). NE-dose trended to exceed 0.2 μg kg^{-1} min^{-1} 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 in the RAPD group of low intraoperative blood loss, 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^{-1} 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 (CD ≥ III) was observed in the RAPD group of 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 after RAPD

After univariate logistic regression analysis, anesthesia-related factors independently associated with major morbidity (CD ≥ III) after RAPD were a 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 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 ≥ III) after RAPD

Variable	Univariable analysis			Backward stepwise regression		
	OR	95% CI	*P*	OR	95% CI	*P*
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 admisison (mmol/L)	2.47	1.27 to 4.82	0.008			
Lactate level in BGA after ≥ 12 hour HDU/ICU admisison (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

After comparing perioperative anesthetic factors for RAPD and OPD, RAPD is characterized by higher demands of vasopressor support and higher intra- and postoperative pCO_2 and Hb-levels. Although net intraoperative fluid balance and vasopressor demands are higher in RAPD, levels of colloid and erythrocyte transfusion are lower for RAPD compared to OPD. Rates of major postoperative morbidity (CD ≥ III) were similar for the surgical approaches. Within patients who developed major morbidity (CD ≥ III) after RAPD, vasopressor demands and necessity of colloid administration tended to be higher. The need for intraoperative colloid administration and increased postoperative lactate levels were independently associated with major morbidity (CD ≥ III) after RAPD.

Comparing outcomes, the surgical modality itself influences the development of major morbidity less than patient-related variables. We report a small fraction of patients marked ASA class III and above (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 21.8% ASA III patients in a cohort of n = 3341 pancreatoduodenectomy and distal pancreatectomy procedures, using Dutch Nationwide Pancreatic Cancer Audit data [17, 18]. Van Roessel et al. predict worse outcome after pancreatoduodenectomy in ASA ≥ III patients (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 ≥ III) where baseline hypertension was (OR 3.51, 95% CI 1.24–9.92). This finding, compared with higher vasopressor demands in RAPD, implies as association between baseline cardiovascular condition and postoperative outcome after RAPD. However, a medical history of hypertension might comprise several baseline conditional factors with itself a possible influence on postoperative morbidity (e.g. increased BMI, vascular remodeling or pre-existing renal insufficiency).

A higher need for intraoperative vasopressor administration in RAPD could be explained by differences in patient positioning (reversed-Trendelenburg in RAPD vs. supine in OPD) as well as exposure to pneumoperitoneum, affecting cardiac afterload and cardiac output [7–9]. Higher demand for vasopressor administration in RAPD was not necessarily reflected by worse baseline physical condition. Although OPD patients more often received neoadjuvant chemotherapy and baseline hemoglobin levels were lower, no differences in baseline medical condition could be demonstrated between both surgical approaches. Although the intraoperative use of vasopressors was evident, we feel supported by recently published data that routinely insertion of a central venous catheter is not mandatory in RAPD or OPD patients [19, 20].

The 2018 RELIEF Study reported on postoperative outcome after distinct intraoperative fluid strategies during major abdominal surgery, differentiating between an either restrictive (median crystalloid + colloid 2177) or liberal (median crystalloid + colloid 3500 ml) net intraoperative fluid balance [5]. Whereas no differences were observed in general postoperative outcome between both fluid approaches, a liberal intraoperative fluid strategy was associated with lower rates of postoperative kidney failure (17/1439, 5.0% for liberal vs. 124/1443, 8.6% for restrictive, $p < 0.001$). In comparison, we report a median intraoperative fluid balance of 2800 ml and a 9/64 (14.5%) rate of postoperative acute kidney injury in RAPD patients. Bannone et al. observed an increased rate of post pancreatoduodenectomy pancreatitis in patients exposed to a near-zero net perioperative fluid regime, suggesting a more restrictive perioperative fluid balance to be associated with an increased risk of 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 post pancreatoduodenectomy surgery after following a more restrictive intraoperative fluid strategy [22]. The optimal intraoperative fluid regime in pancreatoduodenectomy remains point of debate and prospective research should extrapolate this topic to minimally-invasive vs. conventional pancreatoduodenectomy 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, reporting an OR of 1.86 (95% CI 1.03–4307) for development of major postoperative morbidity after the intraoperative administration of colloids (n = 308 elective surgeries for abdominal malignancies,

including n = 22 pancreatic surgical procedures) [23]. In our RAPD series of low intraoperative blood loss, 8/31 (25.8%) of patients vs. 25/33 (75.8%) of patients in the RAPD group of high intraoperative blood loss intraoperative received colloids. It is important to consider which patient category requires intraoperative colloid transfusion. Since colloid administration is part of therapy for major blood loss in our center's protocol, the association of intraoperative colloid administration and development of major postoperative morbidity (CD ≥ III) does not necessarily have to reflect a direct causative effect.

Over the perioperative course, pH values were higher in RAPD compared to OPD (7.35 vs. 7.32 on beginning of surgery, p = 0.021 and 7.35 vs. 7.33 upon HDU/ICU arrival, p = 0.013). These differences in pH levels do not reflect clinical relevance and moderately higher perioperative pH levels in RAPD can well be explained by exposure to pneumoperitoneum and (retroperitoneal) absorption of CO_2. In our series a higher lactate level after a minimum 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 attributable 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 comprises 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 n = 39 different consultant anesthesiologists who followed available protocols with different levels of adherence.

Conclusions

Specific differences exist in perioperative anesthesia-related factors between RAPD and OPD. RAPD is associated with higher levels of vasopressor drug administration as well as higher net perioperative fluid balance. Besides, levels of colloid and erythrocyte transfusion are lower for RAPD compared to OPD. Baseline hypertension, perioperative colloid administration and increased lactate levels after surgery were associated with higher rates of major morbidity (CD ≥ III) after RAPD. A more restrictive intraoperative fluid regime has previously been shown to increase postoperative (nephrogenic) morbidity, present evidence is however contradictory. Current data is insufficient to make specific recommendations on perioperative anesthetic guidance in RAPD. However, intraoperative hemodynamics including fluid strategy might influence postoperative morbidity and should be the focus of future prospective research.

Abbreviations

ABG = Arterial Blood Gas

ASA = American Society of Anesthesiologists

BMI = Body Mass Index

CCI = Charlson Comorbidity Index

CD = Clavien Dindo

CVA = Cerebro Vascular Accident

e-GFR = Estimated Glomerular Filtration Rate

EPCO = European Perioperative Clinical Outcome

ESA = European Society of Anesthesiology

ET = End Tidal

Hb = Hemoglobin

HDU = High Dependency Unit

ICU = Intensive Care Unit

IQR = Inter Quartile Range

NE = Norepinephrine

NRS = Numeric Rating Scale

OPD = Open Pancreatodudoenectomy

OR = Odds Ratio

PCA = Patient Controlled Analgesia

pCO_2 = Partial Carbon dioxide

pO_2 = Partial Oxygen

RAPD = Robot Assisted Pancreatoduodenectomy

SD = Standard Deviation

TIA = Transient Ischemic Attack

Declarations

Ethics approval and consent to participate

The local Medical Ethics Committee approved the study with waiver for informed patient consent with reference MEC-2019-0090 (Medical Ethics Committee, Erasmus MC University Hospital, Rotterdam, the Netherlands).

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

AE was responsible for data acquisition, methodology, formal analysis and visualization of data. Conceptualization was performed by BGK and MK. Writing of the original draft was conducted by AE. BGK, MMV and MK reviewed and edited the manuscript. The final manuscript was read and approved by all authors.

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