Comparison of Robot-assisted versus Conventional Laparoscope on Incidence and Risk Factors of Postoperative Delirium for Patients undergoing radical prostatectomy: A single-center retrospective analysis

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Abstract

Background

Robot-assisted laparoscopic radical prostatectomy (RALRP) has better effects than conventional laparoscopic radical prostatectomy (LRP). However, limited data is available regarding the incidence and risk factors for developing postoperative delirium in patients undergoing these two procedures. This study aimed to assess the incidence of postoperative delirium in patients undergoing RALRP and LRP, and evaluated the risk factors for developing postoperative delirium

Methods

From June 2013 to December 2019, 81 cases of RALRP patients and 71 cases of LRP patients were included in this study. The unpaired Student *t* tests, repetitive measure analysis of variance and chi-square test were used to compare several different parameters. The binary logistic regression analysis was used to explore the independent risk factors of postoperative delirium .

Results

The incidences of postoperative delirium in group RALRP and LRP were (17.3% *VS* 32.4%, $P = 0.03$), IAP was (12.72 ± 1.87 *VS* 13.37 ± 1.12 mmHg; $P = 0.01$), $PaCO_2$ at post-pneumoperitoneum and after loosening pneumoperitoneum were (47.89 ± 10.89 *VS* 38.65 ± 16.32 mmHg; $P < 0.001$; 40.77 ± 5.34 *VS* 43.57 ± 4.54 mmHg; $P = 0.001$), the overall cost was (8.29 ± 5.55 *VS* 5.18 ± 1.51 Ten thousand RMB, $P < 0.001$). The incidence of postoperative delirium increased 1.17 times, 1.13 times, and 1.66 times for each unit increase recovery time (T_r), post-pneumoperitoneum $PaCO_2$ and IAP.

Conclusion

The RALRP group had a lower IAP, lower incidence of postoperative delirium and shorter recovery time compared with the LRP group, but the overall cost was higher. IAP was the main factor affecting the incidence of postoperative delirium.

Background

Prostate cancer continues to be one of the most common cancers among men worldwide. Throughout the last few decades, advances in treatment including surgical technique have helped curtail the potentially devastating effects of prostate cancer on patients. In 1997, the da Vinci system was the first robotic surgical system to progress to human trials, with the first patient undergoing a cholecystectomy[26]. By 2000, the da Vinci robotic system was approved by the Food and Drug

Administration (FDA) for use. Robotic surgery has since been increasingly used in procedures spanning several different surgical specialties. From 2012–2018, it was found that the use of robotic surgery increased from 1.8–15.1% for all general surgery with a concomitant decrease in laparoscopy and open surgery [24]. This trend is also observed among the different radical prostatectomy techniques, including robotic procedures where the volume of cases was found to increase from 2010–2017 [23].

Previous studies have shown that compared with open or laparoscopic radical prostatectomy, RALRP has fewer postoperative complications and is a safe alternative for radical prostatectomy [1]. The laparoscopic approach, whether via classic laparoscopy only or combined with robotic technique, significantly influences a patient's physiology. Laparoscopy involves pneumoperitoneum which subsequently increases hypercapnia, decreases preload venous return, increases afterload, increases intra-abdominal pressures which subsequently reduce renal blood flow, may result in increased vagal stimulation, and may require steep Trendelenburg (ST) positions to provide effective operating space. These physiologic changes may affect the incidence of postoperative delirium.

CO_2 pneumoperitoneum as used during laparoscopic procedures can promote the inflammatory response during surgery[2], which negatively affects patient outcomes and has been specifically implicated in the development of lung injury in laparoscopic patients. The effect of organ injury varies with the change of intra-abdominal pressure (IAP) such that laparoscopic procedures using lower pressure pneumoperitoneum evoke a reduced stress response as measured by changes in heart rate, blood pressure, and levels of stress hormones [3]. While RALRP and LRP are similar in that they use a laparoscopic approach, it is important to note that RALRP uses a computer to precisely control the robotic arm during surgery. Robotic surgical approaches are therefore able to provide a better surgical field of vision and three-dimensional anatomical structure for the surgeon in comparison with alternative techniques[4]. RALRP has been shown to require shorter operation time, and has been shown to be successfully performed with lower IAP requirements [1, 28]. Collectively, these differences suggest that RALRP may have less physiological impact and facilitate faster patient recovery and less postoperative adverse events than with LRP. This retrospective study seeks to compare the effects of these two different procedures on operation time, IAP, partial pressure of arterial CO_2 (P_aCO_2), postoperative outcomes and the incidence and risk factors of developing postoperative delirium.

Materials And Methods

1. Patients and groups

This single-center, retrospective study was approved by the Ethics Committee of the General Hospital of Southern Theater command, and written informed consent was obtained from all patients. All methods and procedures were carried out in accordance with the principles contained in the Declaration of Helsinki. 152 patients undergoing radical prostatectomy performed in the Department of Anesthesiology of General Hospital of Central Theater Command from June 2013 to December 2019 were included.

Overall cohorts were divided into two groups according to the surgical method they received: 81 cases were included in the group RALRP and 71 cases were included in the group LRP.

The inclusion criteria was that the anesthesia documents were recorded in detail, including airway pressure, P_aCO2 before pneumoperitoneum, post-pneumoperitoneum, and after loosening pneumoperitoneum. All surgical procedures were performed by a single surgeon. Patients with heart, lung, liver, kidney, respiratory insufficiencies, disorders of consciousness, preoperative MMSE less than 27 points, or conversion to open surgery during operation were excluded from the data set.

2. Measurements

Demographic variables (age, height, weight, ASA classification, blood pressure, heart rate), the time of preparation for surgery (T_p), time of operation (T_o), time of anesthesia maintenance (T_a), emergence time (time from cessation of intravenous anesthetic to endotracheal extubation, T_e), recovery time (time from endotracheal extubation to discharge from post-anesthesia care unit, T_r), anesthetic dosage (propofol, sufentanil, remifentanil), P_aCO2, plasma lactate level, airway pressure at different points (before pneumoperitoneum, post-pneumoperitoneum, after loosening pneumoperitoneum), the incidences of postoperative delirium, utilization of mannitol, IAP, dosage of vasoactive agents (ephedrine, methoxamine and atropine), fluid infusion volume, blood transfusion volume, blood loss, time of postoperative hospitalization(T_h) and overall cost were recorded.

3. Methods of anesthesia

In the operating room, all patients were monitored with standard ASA monitors and an upper extremity vein was used for intraoperative infusion. A radial artery cannula was inserted under local anesthesia to monitor blood pressure directly and for arterial blood gas analysis. Nasopharyngeal temperature was monitored by nasal temperature probe. Neuromuscular function was measured using a TOF-Watch acceleromyograph. All patients were induced with etomidate 0.3 mg/kg, sufentanil 0.5 μg/kg and rocuronium 0.9 mg/kg. When TOF ratio was at 0, intubation is performed. After intubation, ventilation was performed to maintain P_aCO_2 between 35 and 45 mmHg. General anesthesia was maintained with propofol, remifentanil and rocuronium. Vasoactive drugs (ephedrine 5 mg or methoxy 0.5-1 mg) were administered when blood pressure was 20% below patient baseline, and atropine 0.5 mg was administered when heart rate was below 45 beats/min. Esmolol (5mg) was commonly used to treat tachycardia, and nicardipine (0.2-0.5 mg) was used for hypertension. Red blood transfusion was typically initiated with hemoglobin values were lower than 7.0g/dL. 15 minutes before the end of the operation, propofol infusion was stopped and the rate of remifentanil infusion was reduced. When the operation was over, remifentanil infusion was stopped, patients were given dolasetron 12.5mg to prevent vomiting, and 40 mg parecoxib sodium was administered to relieve pain. Extubation occurred when the patient was conscious, spontaneously ventilation recovered, TOF value >90%, SPO_2>95%, and with normal vitals. After endotracheal extubation, the patients were continued to be monitored until they were fully conscious, able to cooperative, and vital signs were stable. If postoperative delirium occurred, mannitol was administered to improve cerebral oxygen metabolism, or propofol was given for its sedating effects.

4. Surgical Procedure

After general anesthesia, the patients were kept in the supine. Pneumoperitoneum was induced with CO2 insufflation pressure of 15 mmHg. Following trocar insertion, an IAP of 8 mmHg was set from the previous 15 mmHg, and a remote control was used to place the patients in a ST position. IAP was gradually increased until the surgeon was satisfied with the surgical space. The IAP was recorded throughout the procedure.

5. Statistical analysis

Statistical analysis was performed using SPSS version 25.0. Measurement data are described as mean ± standard deviation. Demographic variables, T_p, T_o, T_a, T_e, T_r, dosage of anesthetic (propofol, sufentanil, remifentanil), IAP, dosage of vasoactive drugs (ephedrine, methoxamine and atropine), infusion volume, blood transfusion volume, blood loss, T_h and overall cost were compared using unpaired Student *t* tests. P_aCO2, lactic acid value and airway pressure at different points are repeated measurement data, using repetitive measure analysis of variance. The incidence of postoperative delirium and utilization of mannitol, and ASA scores are count data, using chi-square test. Binary logistic regression analysis was performed with postoperative delirium as the dependent variable, T_a, T_e, T_r, P_aCO_2, and IAP as independent variables, to explore the risk factors for postoperative delirium. A p value < 0.05 was considered statistically significant.

Results

A total of 152 patients were assessed for eligibility. Demographic variables (age, weight, height, ASA grading, blood pressure and heart rate) of patients in the two groups showed no significant difference (Table 1).

Table 1
Patient characteristics

	RALRP group	**LRP group**	**statistics**	***p* values**	**95% *CI***
sample	81	71			
age (yr)	67.56 ± 6.82	68.85 ± 6.37	1.20	0.232	-0.84−3.81
weight (kg)	68.04 ± 10.13	66.68 ± 9.06	0.86	0.389	-4.45−1.74
height (cm)	169.78 ± 5.56	168.97 ± 4.95	0.94	0.350	-2.50−0.89
ASA scores n(%)	28(34.6%)	31(43.7%)	1.32	0.251	
□	53(65.4%)	40(56.3%)			
□					
systolic pressure(mmHg)	146.59 ± 17.03	142.85 ± 18.93	1.29	0.201	-9.51−2.02
diastolic pressure(mmHg)	81.51 ± 8.09	79.62 ± 9.37	1.33	0.185	-4.68−0.91
heart rate (beats/min)	73.46 ± 10.85	74.62 ± 11.85	0.63	0.529	-2.48−4.80

T_p, T_o and T_a in group RALRP were significantly longer than those in group LRP; T_e was significantly shorter than that in group LRP; There was no statistical difference between T_r and T_h (Table 2).

Table 2
Comparison of T_p, T_o, T_a, T_e, T_r, and T_h between two groups

	RALRP group	**LRP group**	**statistics**	***p* value**	**95% *CI***
sample	81	71			
T_p	39.10 ± 6.34	32.15 ± 6.95	6.44	<0.001	4.81−9.07
T_o	235.58 ± 38.21	216.82 ± 39.50	2.97	0.003	6.29−31.23
T_a	280.89 ± 41.55	264.56 ± 42.10	2.40	0.018	2.90−29.75
T_e	31.52 ± 9.89	38.65 ± 16.32	3.20	0.002	2.72−11.54
T_r	30.65 ± 10.07	32.37 ± 11.50	0.98	0.329	-1.74−5.17
T_h	13.11 ± 6.34	14.52 ± 8.07	1.21	0.230	-0.90−3.72

T_p was defined as time from the start of anesthesia to the start of surgery; T_o was defined as time from the surgery start to end; Ta was defined as time from anesthesia start to end; T_e was defined as time from cessation of intravenous anesthesia to tracheal endotracheal extubation; T_r was defined as time from endotracheal extubation to time of leaving the post-anesthesia care unit; Th was defined as time from the day after surgery to day of discharge.

The dosage of propofol and remifentanil in the group RALRP were higher than those in the group LRP; IAP was lower in group RALRP than that in the group LRP; overall cost was higher in group RALRP than that in group LRP. The incidence of delirium and utilization of mannitol were lower in group RALRP than those in group LRP. There was no significant difference in dosage of sufentanil, vasoactive agents, fluid infusion volume, blood transfusion volume, and blood loss between the two groups (Table 3).

Table 3
Intraoperative and Postoperative Observation Indexes

	RALRP group	**LRP group**	**statistics**	***p* value**	**95% *CI***
sample	81	71			
propofol(g)	1.37 ± 0.27	1.26 ± 0.30	2.35	0.020	0.02–0.20
remifentanil(mg)	5.30 ± 1.10	4.68 ± 1.03	3.58	<0.001	0.28–0.97
sufentanil(μg)	49.51 ± 10.74	46.69 ± 10.79	1.61	0.110	-6.27–0.64
Vasoactive drugs ephedrine(mg) methoxamine(mg) atropine(mg)	1.88 ± 3.33 0.06 ± 0.30 0.21 ± 0.28	2.13 ± 3.36 0.08 ± 0.25 0.28 ± 0.64	0.46 0.35 0.91	0.646 0.727 0.364	-0.82–1.32 -0.07–0.10 -0.08–0.23
IAP(mmHg)	12.72 ± 1.87	13.37 ± 1.12	2.63	0.010	0.16–1.14
incidence of delirium(%)	14(17.3%)	23(32.4%)	4.69	0.030	
incidence of utilization of mannitol(%)	6(7.4%)	15(21.1%)	5.98	0.014	
Overall cost(Ten thousand RMB)	8.29 ± 5.55	5.18 ± 1.51	4.57	<0.001	1.77–4.45
infusion volume(ml)	2286.05 ± 581.44	2143.61 ± 473.44	1.65	0.10	-314.91–28.02
blood transfusion volume(ml)	51.85 ± 230.37	25.35 ± 87.37	0.91	0.362	-83.82–30.82
blood loss(ml)	183.33 ± 109.26	203.5 ± 123.15	1.07	0.286	-17.06–57.43

There was statistically significant difference of P_aCO_2 between groups; P_aCO_2 at time points of post-pneumoperitoneum and after loosening pneumoperitoneum in group RALRP was lower than that in group LRP (Fig. 1). There was no statistically difference of plasma lactate concentration between two groups, but there was statistically significant difference of plasma lactate concentration within groups and the change of that in group RALRP was smaller than that in group LRP (Fig. 2). There was no statistically difference of airway pressure between groups, but there was statistically significant difference of airway pressure within groups and the change of airway pressure in group RALRP was smaller than that in group LRP (Fig. 3).

Binary logistic regression analysis was performed with postoperative delirium as the dependent variable; T_a, T_e, T_r, P_aCO_2 (Pp, Alp), and IAP as independent variables. Using the Enter method, $p < 0.05$ was entered into the equation and $p > 0.1$ was removed from the equation. The results showed that T_e, $PaCO_2$ (Pp)and IAP were entered into the equation and the formula was obtained as follows: Logit (P) =-18.55 + $0.11 \times T_r + 0.12 \times$ PaCO2(Pp) + $0.50 \times$IAP. The result showed the incidence of postoperative delirium increased 1.17 times (95% *CI* 1.06–1.17), 1.13 times (95% *CI* 1.03–1.24), and 1.66 times (95% *CI* 1.02–2.70) for each unit increase in T_e, $PaCO_2$(Pp) and IAP. With the prediction probability 0.5 as the cut-off point, the sensitivity of judging the incidence of postoperative delirium was 67.6%, the specificity was 95.7%, and the total correct rate was 88.8% (Table 4,5).

Table 4
The results of binary logistic regression

	B	*SE*	*Wald*	*p*	*OR*	*95% CI*
T_e	0.11	0.03	19.90	<0.001	1.12	1.06–1.17
$PaCO_2$(Pp)	0.12	0.05	6.49	0.011	1.13	1.03–1.24
IAP	0.50	0.25	4.07	0.044	1.66	1.02–2.70

Table 5
Model classification table with the prediction probability 0.5 as the cut-off point

		delirium		
Observed		**NO**	**YES**	**Correct percentage(%)**
delirium	NO	110	5	95.7
	YES	12	25	67.6
Overall Percentage(%)				88.8
Bp = before pneumoperitoneum, Pp = post-pneumoperitoneum, Alp = after loosening pneumoperitoneum				

Discussion

While prostate cancer remains one of the most common diseases in elderly men over 60 years of age, there has been a 51% overall decline in death rate in prostate cancer from 1993 to 2014[5]. Advances in early detection and treatment, including advances in surgical techniques, have contributed to the decline in prostate cancer mortality. For several years, open radical prostatectomy has been the reference standard of treatment for prostate cancer. In more recent years, open surgical approaches to prostate cancer treatment have been replaced by minimally invasive techniques such as LRP and RALRP[6]. Previous studies have shown that in comparison with LRP and open radical prostatectomy, RALRP improves patient outcomes in areas such as achieving enhanced surgical margins, decreasing rate of erectile dysfunction and incontinence postoperatively, as well as shortening total hospital stays[1].

As the utilization of robotic surgery continues to be widespread across several surgical specialties, it is critical that we continue to explore the benefits of robotic assisted surgical procedures, especially as it is implicated in the incidence of postoperative delirium. The development of postoperative delirium has been associated with longer hospital stay, increased rates of mortality, and higher rates of readmission and adverse events[25]. Previous studies in thoracic surgery have shown that the incidence of postoperative delirium in robotic assisted esophagectomy was significantly lower than in open esophagectomy[8]. Similarly, our study found that the incidence of postoperative delirium in the group RALRP was 17.3% as compared to 32.4% in the LRP group.

To further understand this statistically significant decrease in the development of postoperative delirium among RALRP patients in comparison with LRP patients, several different perioperative parameters were compared. We found that the reduced anesthesia recovery time in RALRP group was accompanied by a decreased incidence of postoperative delirium. T_e in group RALRP and LRP was 31.5 ± 9.8 and 38.6 ± 16.3 min, respectively. Historically speaking, operation times of RALRP have been longer than those of LRP but more recent data suggests that operation times of RALRP may now be shorter than LRP[1]. Nonetheless, at our institution, it was found that the T_p, T_o, T_a of RALRP was significantly longer than that of LRP, and the dosages of propofol and remifentanil required intraoperatively were also higher in the RALRP group than in the LRP group. These differences may be attributed to technical skills of the practicing surgeon, as well as the more recent utilization of the daVinci surgical system which only became available in this institution a few years prior to this data collection. Further contrasting with other studies that suggest that decreased blood loss and shorter hospital stays are seen with robotic techniques, our study did not find such differences [1, 22]. The cost of RALRP in our institution is higher than LRP, which may further hinder the development of RALRP in other countries such as China, despite its advantageous possibilities.

Similarly to LRP, RALRP also requires insufflation of the abdomen with carbon dioxide (CO2) pneumoperitoneum and steep Trendelenburg (ST) positioning to optimize surgical exposure. Steep Trendelenburg positioning has been associated with increased postoperative intracranial pressure after RALRP and compromised postoperative cognitive function [17]. Laparoscopy has certainly limited the need for more invasive open surgical procedures but it is important to keep in mind that the associated pneumoperitoneum with this surgical approach causes a number of physiological derangements with potential complications. These include hypercapnia, organ ischemia, increased stimulation, increased intraabdominal pressures, decreased venous return, increased intracranial pressure, and brain edema.

Hypercapnia affects cerebral autoregulation, which may explain why pneumoperitoneum has been observed to prolong postoperative recovery time and increase the incidence of postoperative delirium[9]. Furthermore, rapid CO_2 insufflation or high pressure pneumoperitoneum accompanied by increased intraabdominal pressure and systemic CO_2 absorption can lead to organ ischemia, increased postoperative pain, and delay in recovery of certain normal bodily functions[10]. CO_2 negatively impacts various organs by promoting oxidative stress and inflammatory response through the inactivation of nitric oxide and subsequent increase in inflammatory cytokines[2]. In the central nervous system, these neuroinflammatory responses which result in microglial activation have been linked to cognitive dysfunction[15, 16]. Reduction of intra-operative IAP and P_aCO_2 may attenuate stress and inflammatory response and help curtail adverse cognitive effects[3]. Our study has found that post-pneumoperitoneum PaCO2 and IAP in group RALRP were significantly lower than those in group LRP, which may explain the lower incidence of postoperative delirium and shorter recovery time of the RALRP group.

Small doses of mannitol have been successfully used to improve cerebral oxygen metabolism and protect cognitive function postoperatively[9]. Increased rates of reintubation, ICU readmission, and longer hospital stays were observed in patients who did not receive intraoperative mannitol and later developed postoperative delirium relative to patients who received mannitol and did not develop delirium[27]. In patients with severe delirium after surgery, we first administered a small dose of mannitol. We also sedated patients with propofol and gradually removed the endotracheal tube after the delirium remission. T_e in the group RALRP was significantly lower than in the LRP group, and the RALRP group also exhibited a lower incidence of postoperative delirium. However, there was no difference in T_e between RALRP and LRP—this can be attributed to the process of only extubating awake patients without delirium. Patients were discharged from the post-anesthesia care unit with the same criteria—vital signs of patients in both groups after endotracheal extubation were similar and the dosage of vasoactive drugs in the two groups were also comparable.

Postoperative delirium likely also relates to postoperative pain as evident by a lower incidence in less invasive surgery with minor incisions[18]. In procedures that employ lower IAP, reduced postoperative pain has been observed[19–21]. Our study found that the IAP of patients in the group RALRP was significantly lower than that in the group LRP (12.72 ± 1.87 VS 13.37 ± 1.12 mmHg, $P < 0.05$) thus alluding that decreased IAP is accompanied by a decrease in pain and hence a lower incidence of postoperative delirium. Through binary logistic regression analysis, our study also found that with each unit increase of IAP, there was a subsequent increase in the rate of development of postoperative delirium by 1.66 times.

RALRP is similar to LRP in that the surgical approach requires the use of CO2 to provide effective operating exposure, however the crucial differences in the two procedures are elucidating key reasons for the superiority of RALRP. The computerized electromechanical controls of RALRP give the surgeon much more precision and stability for the dissection of critical structures. The robotic console has tridimensional vision, which provides increased depth of field and helps immensely with surgical precision and orientation[4]. Because of these advances in surgical technique that the robot provides, RALRP can be performed with lower IAP while still gaining the same surgical access. We show that IAP is the most important factor affecting the incidence of postoperative delirium, and controlling IAP may help reduce the incidence of postoperative delirium. The underlying mechanism of this link between IAP and postoperative delirium requires further study to better understand its etiology.

It should be noted that the incidence of postoperative delirium is complex and influenced by many factors. For instance, even marital status is among the influencing factors as it appears that single, widowed, or divorced patients are more susceptible to postoperative delirium[29]. Confounding bias from the many factors that affect postoperative delirium should be considered when deciding on the surgical approach for radical prostatectomy[30].

Abbreviations

RALRP: Robot-assisted laparoscopic radical prostatectomy; LRP: laparoscopic radical prostatectomy; LAP: intraabdominal pressure; ST: steep Trendelenburg; P_aCO_2: partial pressure of arterial CO_2; TOF: train of four stimulation; ASA; american society of anesthesiologists.

Declarations

Acknowledgement:. None

Authors' contributions

H-GJ, XB and MX contributions to study conception and design, data analysis and

interpretation, and preparation of the manuscript. S-WD, L-BX, RN and MC participated in data collection and analysis. All authors read and approved the final manuscript.

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Availability of data and materials

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

Declarations

Ethics approval and informed consent

This study was approved by the Medical Ethics Committee of the General Hospital of Southern Theater command and was conducted in accordance with principles of the Declaration of Helsinki of the World

Medical Association. The informed consent requirement was waved.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

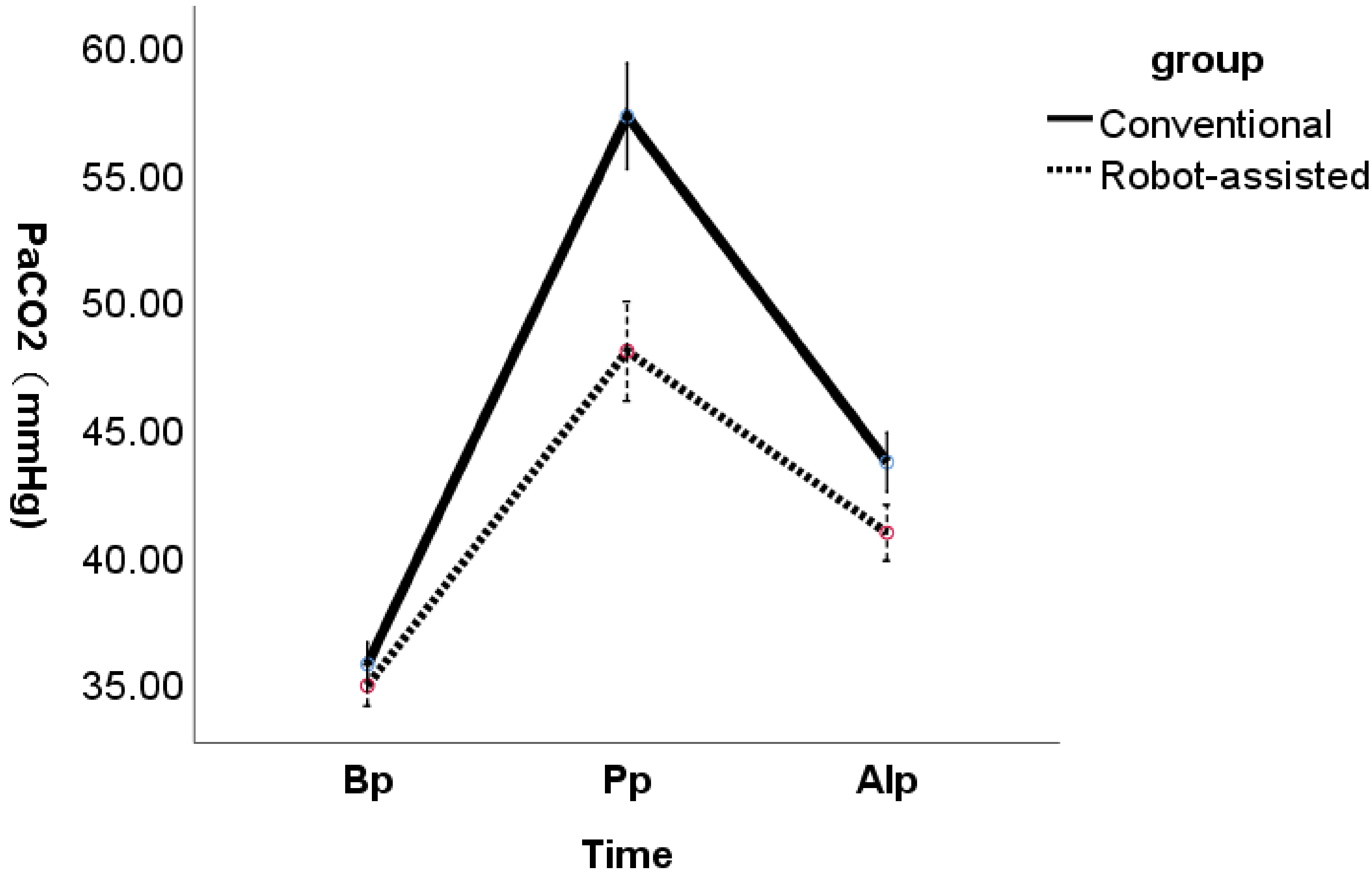

Figure 1

PaCO2 at different time points in the two groups . Bp = before pneumoperitoneum, Pp = post-pneumoperitoneum, Alp = after loosening pneumoperitoneum

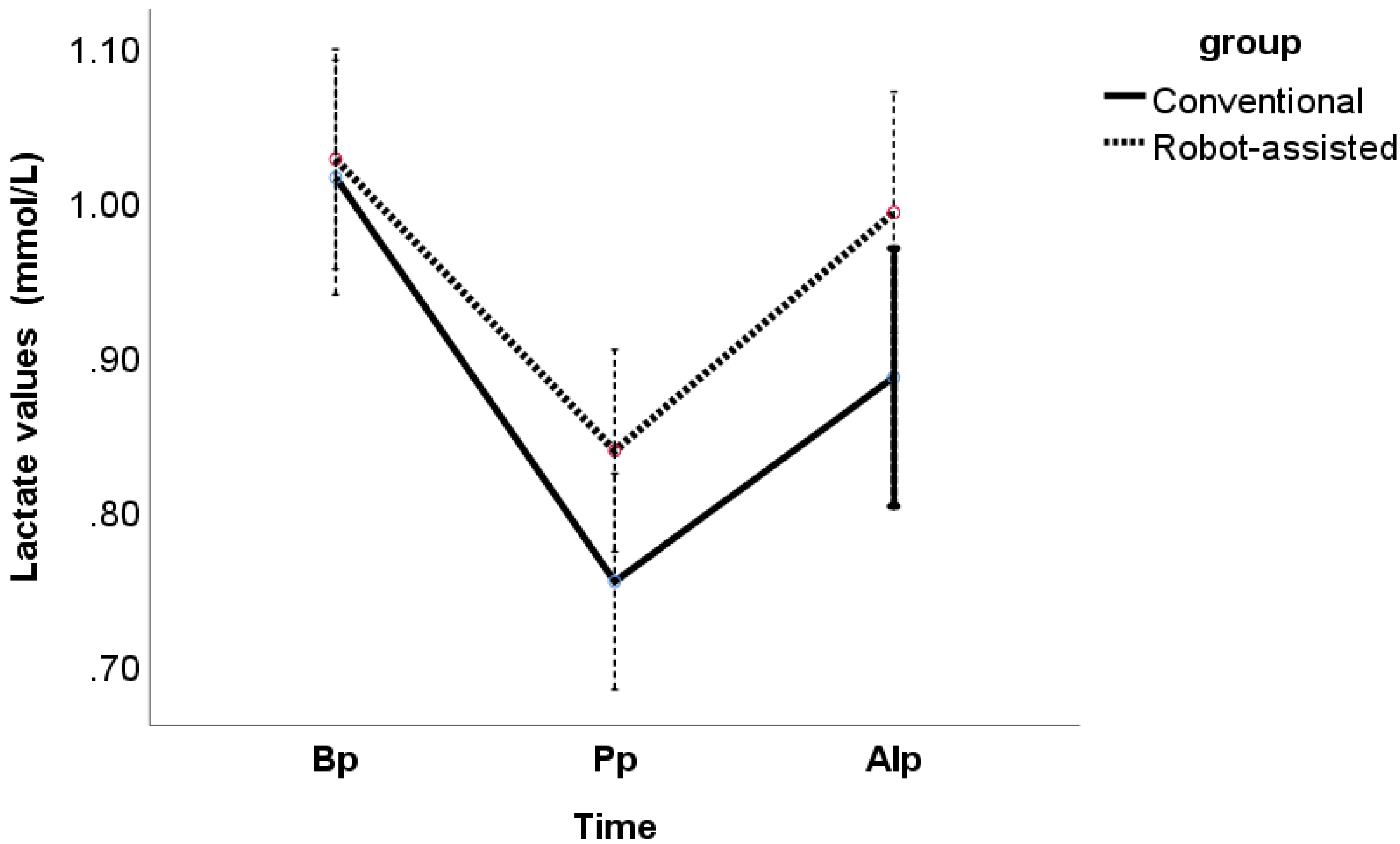

Figure 2

Plasma lactate concentration at different time points in the two groups

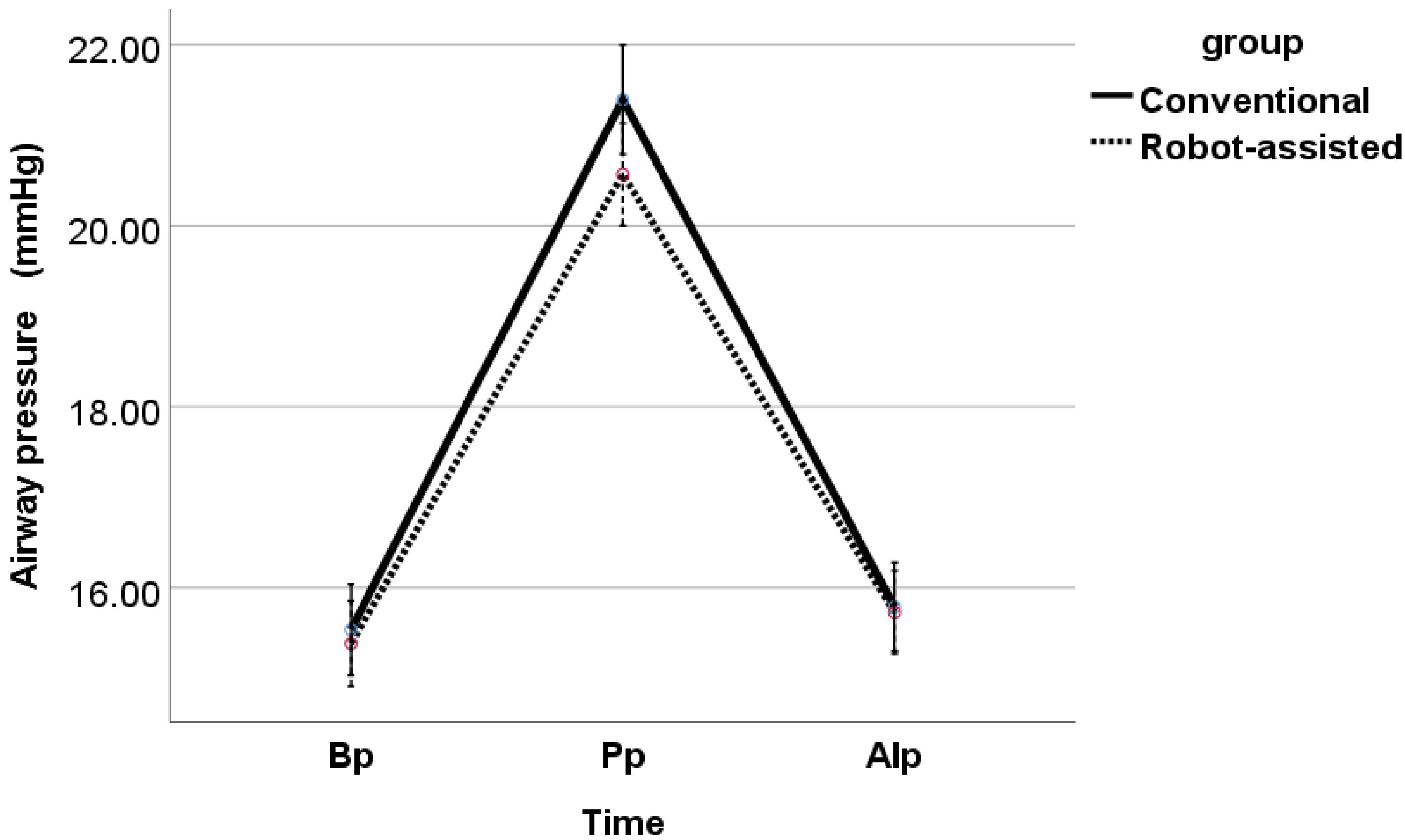

Figure 3

Airway pressure at different time points in the two groups