A Comparison of the Effects of Urapidil and Remifentanil on Hemodynamics and Extubation Quality in Intracranial Surgery

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Abstract

Aim: Maintaining stable hemodynamics during emergence is crucial for reducing cerebral perfusion pressure and minimizing risk of bleeding. We aimed to compare effects of urapidil and remifentanil on extubation quality and hemodynamics during extubation.

Methods: 90 patients aged 18-65 years, ASA 1-3 included. Anesthesia was maintained with remifentanil 0.125-0.25 μg/kg/min and sevoflurane 1-2% for all groups. In group I, remifentanil infusion is reduced to 0.02-0.03 μg/kg/min last 15 min of surgery. In group II, remifentanil infusion is stopped 15 min before end of surgery. After 5 min, bolus dose of urapidil (12.5mg) is given and urapidil infusion (3.2-4.8μg/kg/min) is started. In group III, remifentanil infusion is stopped 15 min before end of surgery and urapidil infusion (3.2-4.8 μg/kg/min) is started. Hemodynamics, entropy values and Glasgow Coma Scale were recorded last 15 min and up to 5 min after extubation.

Results: Statistically significant differences observed between the mean values of SAP (systolic arterial pressure), MAP (mean arterial pressure) and DAP (diastolic arterial pressure) before and after extubation ($p<0.05$). In group I, the mean values of SAP, MAP and DAP at baseline were lower than the mean values at 1-3 and 5 min after extubation. In groups II-III, SAP, MAP and DAP at baseline were higher than 1-3-5 min after extubation.

Conclusion: Both infusion and bolus+infusion of urapidil administration at end of intracranial surgery, effectively prevents haemodynamic reactions secondary to extubation and controls blood pressure without affecting heart rate. In addition, quality of extubation, extubation time were similar.

***Keywords**: Urapidil, remifentanil, hemodynamics, intracranial surgey*

1. Introduction

During neurosurgery, large amounts of catecholamines may be released because of the sympathetic activity caused by surgical stress. Hemodynamic changes such as tachycardia and hypertension may occur during intubation and extubation. These sympathetic responses can lead to bleeding and postoperative cardiac events during the perioperative period[1-3]. Hypertension is associated with increased postoperative risk and major adverse cardiac events within seven postoperative days[4].

To avoid sympathetic responses, agents such as opioids, dexmedetomidine, lidocaine, and β-blockers can be administered perioperatively[5-8].

Remifentanil is an opioid with rapid onset of action and belongs to the class of short-acting opioids.

It is hydrolyzed from blood and tissues by non-specific esterases. Remifentanil can suppress sympathetic responses and provide hemodynamic stabilization and is therefore considered an effective drug for the management of hemodynamic parameters in neurosurgery[9-18]. Urapidil is a selective α-1 antagonist used to control hypertension. Urapidil mainly antagonizes postsynaptic alpha-1 adrenergic receptors; but also stimulates 5-HT1A receptors, resulting in vasodilation and blood pressure reduction without reflex tachycardia. After intravenous administration, urapidil has a rapid onset and short duration of action, and the dose can be easily adjusted according to the hemodynamic response[19-26].

Our primary aim was to compare the results of urapidil and remifentanil in suppressing hemodynamic responses during extubation, and secondarily to assess their effects on the quality of extubation and depth of anesthesia in intracranial surgery.

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2. Materials and Methods

This study was approved by Institutional Review Board (IRB Number:166/11, Date:07/04/2022) and written informed consent was obtained from all patients before enrolment in the trial. It was aimed to include 30 patients per group who American Society of Anesthesiologist (ASA) physical status classification I-III, 18 -65 years. Exclusion criterias were aged >65 years, ASA physical status IV-V, greater than first-degree AV block, history of pulmonarry disease, drug allergy, uncontrolled hypertension, bronchospasm, coronary artery disease, renal or hepatic disease, presence of cerebral vasospasm, elevated intracranial pressure and pregnancy or lactation. In addition, patients with heart rate (HR) <50 bpm before drug administration and systolic blood pressure <80 mmHg and patients with elevated blood pressure levels (systolic blood pressure >160 mmHg) despite treatment with antihypertensive drugs were excluded from the study.

Standard ASA monitoring (electrocardiogram (ECG), noninvasive blood pressure, pulse oximeter, and temperature) was applied to patients who were admitted to the operating room without premedication. An entropy probe was placed in all patients to preoperatively monitor the depth of anesthesia. Baseline hemodynamic variables (systolic arterial blood pressure (SAP), mean arterial blood pressure (MAP), diastolic arterial blood pressure (DAP), and HR) were recorded. Before anesthesia induction, intravenous access was obtained, and fluid therapy was started with 5-10 ml/kg NaCl or Lactated Ringer's solution. Propofol 2 mg/kg, rocuronium 0.6 mg/kg and remifentanil 0.5 µg/kg were used for anesthesia induction and endotracheal intubation was performed after adequate muscle relaxation was achieved.

Central venous catheterization was performed via the subclavian or jugular vein, and invasive right radial artery catheterization was performed to continuously monitor arterial blood pressure and blood gas, hemoglobin and blood sugar values. In all patients, the lungs were ventilated with 40% 0_2 and 60% N_2O, maintaining the end-tidal carbon dioxide concentration in the range of 30-35 mmHg. Anesthesia was maintained with remifentanil 0.125-0.25 µg/kg/min and sevoflurane 1-2%. The depth of anesthesia adjusted with entropy between 40-60 values. The target MAP was 75-95 mmHg during the intraoperative period.

Mannitol 2.5 ml/kg alone or mannitol/hypertonic saline combination (1.25 ml/kg mannitol, 1.25 ml/kg hypertonic saline) and dexamethasone (16 mg) were administered for brain relaxation. If the brain was edematous during the dural incision, hyperventilation ($PaCO_2$ at 30 mmHg), intravenous bolus propofol (30-40 mg), and cerebrospinal fluid (CSF) drainage were performed.

During the last 15 min of surgery (during subcutaneous suturing), the sevoflurane concentration was reduced to 0.4-0.6% and patients were randomly assigned to three groups using a random number table.

Group 1; (remifentanil group); remifentanil infusion was reduced to 0.02-0.03 µg-kg-min and continued until extubation.

Group II; (Urapidil bolus + infusion group); remifentanil infusion was stopped and after 5 min bolus of urapidil (12.5 mg) was given, then urapidil infusion (3.2-4.8 µg/kg/min) was administered until extubation, and urapidil infusion was stopped at extubation.

Group III; (Urapidil infusion group); remifentanil infusion was stopped and then urapidil infusion (3.2.-4.8 µg/kg/min) was administered (without bolus urapidil) until extubation, urapidil infusion was stopped at extubation.

Tramadol 2 mg/kg (at last 45 min) and paracetamol 10 mg/kg (at last 20 min) were administered to all patients for postoperative analgesia.

At the end of the operation, sevoflurane was discontinued; and all participants were ventilated with 100% oxygen at 6 L/min. Atropine (15 µg/kg and neostigmine (40 µg/kg) were used for decurarisation. The patient met the extubation criteria which were defined as sustained tetanus for more than 5 s, a respiratory rate of less than 12 breaths per minute, positive head lift, hand grip, and eyes following commands.

Extubation time was defined as the time from the cessation of the inhaled agent to the removal of the endotracheal tube. Hemodynamic parameters, entropy values, and possible side effects were recorded during extubation and during the first 5 minutes (1st, 3rd and 5th minutes) after extubation.

The patients' response status during extubation was assessed using an adapted 5-point scale. On this scale, 1 point indicated no cough and muscle rigidity, 2 points indicated mild cough for easy extubation, 3 points indicated moderate cough, 4 points indicated severe cough or muscle rigidity, and 5 points indicated too agitated to be extubated. After extubation, when the patients were fully conscious and hemodynamically stable, they were transferred to the neurosurgical intensive care unit.

2.1. Statistical analyses

A prior power analysis determined that a minimum of 20 patients in each group was required to detect a difference in MAP of 15 mmHg at a significance level of 0.05 (type I error) and 80% power.

The IBM SPSS 25 program was used for the statistical analyses applied in the study. Continuous variables are presented as mean±standard deviation and median (1st quartile-3rd quartile), while categorical variables are presented as frequencies and percentages. The one-way ANOVA test was used for group comparisons on normally distributed data, the Kruskal-Wallis test for group comparisons of non-normally distributed data, and the dependent samples t-test and Wilcoxon signed-rank test were used to examine the difference between two related measures. Where there were differences between the groups, multiple comparison tests were used to determine which groups differed from each other. The relationship between categorical variables was examined using the chi-square test and was considered statistically significant if the p-value was <0.05.

Table 1

Demographic Values and Operation Characteristic in Groups.

Variables	mean±SS	Min-Max
Age (year)	47.70±13.80	18-65
Weight (kg)	76.34±1.92	45-130
Operation time (h)	3.57±1.07	1.5-7.5
Extubation time (min)	10.71±2.34	5-17
Gender	n	(%)
·Female	47	%52.2
·Male	43	%47.8
ASA		
·ASA I	44	%48.9
·ASA II	46	%51.1
Comorbidite		
·Yes	46	%51.1
·No	44	%48.9
Operation Type		
·Supratentorial	59	%65.6
·Infratentorial	31	%34.4

3. Results

Demographic variables and operative data were not significantly different between groups (p>0.05), (Table 1).

3.1. Hemodynamic Variables Before Extubation

This data presented in Table 2. The mean SAP in Group 1 at 1, 2, 3, and 5 min before extubation was higher than that in Groups 2 and 3 (p<0.05). The mean SAP at 7th min was significantly higher in group 1 than in Group 2 (p<0.05). At 12 min, the mean SAP of Group 2 was higher than that of Groups 1 and 3 (p<0.05). In addition, the mean DAP of Group 1 was higher than that of Groups 2 and 3 at the 1st, 2nd, 3rd and 5th min before extubation. At 12 min, the mean DAP of Group 2 was higher than the mean DAP of Groups 1 and 3. The MAP of group 1 at the 1st, 2nd, 3rd, 5th and 7th min before extubation was higher than that of groups 2 and 3 before extubation. There were no statistically significant differences between the groups in heart rate, peripheral oxygen saturation and entropy RE values at any time before extubation.

3.2. Hemodynamic Variables after Extubation

This data presented in Table 3. After extubation, the mean SAP, DAP, and MAP were higher in Group 1 than in Groups 2 and 3 at various time points (at the 0th, 1st, 3rd and 5th minutes after extubation). However, there was no difference in heart rate, entropy RE values, or peripheral oxygen saturation between the groups at any time after extubation.

3.3. Extubation Quality Score and Side Effects

Extubation quality was similar between the groups, and no severe coughing or straining was observed in any of the groups. The Glasgow Coma Score was 14-15 in all patients postoperatively, indicating good neurological status. Furthermore, no complications or side effects were observed in the early postoperative period.

Table 2

Systolic, Diastolic and Mean Arterial Pressure and HR Values in Groups

Before the ext.	Group I	Group II	Group III	p
1.min				
·SAP	131.93±14.70	108.33±12.65	111.30±11.33	0.000
·DAP	75.70±12.38	62±9.58	61.43±8.81	0.000
·MAP	97.07±12.96	78.90±9.42	79.63±7.33	0.000
·HR	69.03±15.28	66.7±15.09	64.63±13.52	0.503
2. min				
·SAP	126.97±14.42	107.03±12.70	110.43±11.26	0.000
·DAP	72.90±12.19	60.97±8.93	60.63±8.31	0.000
·MAP	93.53±12.51	78.13±8.85	78.67±7.54	0.000
·HR	64.60±11.77	65.17±14.80	63.73±14.56	0.721
3. min				
·SAP	124.93±15.44	107.17±13.34	110.40±12.24	0.000
·DAP	72.07±13.16	61.63±9.56	61.5±9.53	0.000
·MAP	92.53±13.83	78.37±10.04	79.10±8.92	0.000
·HR	64.60±11.77	65.17±14.80	63.73±14.56	0.939
5. min				
·SAP	119.47±16.71	107.47±12.17	108.67±10.63	0.001
·DAP	68.93±11.85	62.47±9.35	60.10±8.88	0.003
·MAP	88.47±13.30	79.47±9.52	77.80±7.94	0.001
·HR	63.40±11.68	63.70±15.42	63±14.26	0.823
7. min				
·SAP	115.93±15.49	105.60±11.33	109.43±12.55	0.012
·DAP	67.63±10.99	61.97±9.55	60.60±8.54	0.015
·MAP	86.43±12.32	79.20±9.54	78.17±8.86	0.005
·HR	64.23±13.02	64.0±14.15	63.3±14.62	0.899
10. min				
·SAP	111.20±13.56	110.5±11.03	109.37±13.64	0.855
·DAP	65.5±11.09	64.40±9.21	60.77±9.41	0.161
·MAP	82.80±11.38	81.77±9.83	78.17±9.57	0.193
·HR	62.5±10.68	67.07±15.04	62.53±14.48	0.362
12. min				
·SAP	107.60±12.74	121.17±14.15	11037±15.25	0.001
·DAP	63.17±10.91	70.73±13	61.30±10.33	0.005
·MAP	79.70±10.93	89.47±13.06	79.53±11.45	0.002
·HR	62.17±11.13	68.23±16.20	62.63±14.74	0.284
15. min				
·SAP	103.43±12.03	107.07±13.93	110.03±14.08	0.166
·DAP	60±9.42	63.70±10.98	62.30±11.92	0.413
·MAP	76.43±9.81	79.77±12.18	79.73±12.17	0.435
·HR	61.10±10.74	65.67±15.56	64.47±16.44	0.451

Table 3

Hemodynamic Variables during and after the Extubation

(mmHg)	Group I	Group II	Group III	P valeu
During extubation				
·SAP	144.20±14.14	116.47±11.60	121.93±11.74	0.001
·DAP	82.37±12.34	66.67±10.12	65.33±9.35	0.001
·MAP	105.90±13.52	85.20±9.26	86.47±8.92	0.001
1. min after ext.				
·SAP	145.50±15.60	120.47±12.28	123.63±12.34	0.001
·DAP	83.87±11.78	67.90±8.86	64.87±8.82	0.001
·MAP	107.07±13.39	87.77±9.20	86.43±9.36	0.001
3. min after ext.				
·SAP	144.17±14.98	122.5±12.57	124.8±11.24	0.001
·DAP	80.97±11.48	68.33±10.16	66.63±9.35	0.001
·MAP	104.60±12.71	88.27±10.15	88.23±9.44	0.001
5. min after ext.				
·SAP	145.63±15.28	123.03±11.03	125.10±11.47	0.001
·DAP	80.83±13.37	69.13±9.96	66±8.89	0.001
·MAP	105±13.99	89.63±9.28	87.63±8.65	0.001

4. Discussion

In our study, both bolus urapidil plus infusion and urapidil infusion alone resulted in a greater reduction in blood pressure during extubation than remifentanil alone.

Increased stress, catecholamine release, tachycardia, and hypertension can observe during neurosurgery. In particular, during laryngoscopy and intubation, pinholder application, skin incision, dural incision, and extubation, increases in heart rate and blood pressure and may result in sudden and dangerous increases in intracranial pressure. Low-dose hypnotics, opioid analgesics, lidocaine, and adrenergic blockers can suppress the hemodynamic responses during extubation[8,10,11,17,18,25]. Guy et al. compared remifentanil and fentanyl in patients who underwent craniotomy for space-occupying supratentorial lesions[11]. They reported that the effects of both drugs on intracranial and cerebral perfusion pressure were similar. Balakrishnan et al. compared fentanyl and remifentanil with isoflurane in intracranial surgery, and reported that hemodynamic data and side effects were similar in both agents, and extubation was performed faster with remifentanil[12]. Gesztezi et al. reported that an infusion rate of 0.125 µg/kg/min was appropriate for intracranial surgery[1]. In our study, remifentanil was planned to be administered at a dose range of 0.125 - 0.25 µg/kg/min with sevoflurane, but mostly used at a dose of 0.125 µg/kg/min. Nho et al. reported that maintaining a remifentanil infusion (remifentanil maintained at a target organ concentration of 1.5 ng ml-1) reduced the hemodynamic changes and cough associated with tracheal extubation almost without significantly delaying recovery from anesthesia[13]. In addition, Aouad et al. showed that during emergence, the remifentanil infusion (0.014+/-0.011 µg/kg/min) had a significantly lower incidence and less severe coughing compared with the control group (40% vs 80%)[14]. Urapidil has fewer hypotensive and side effects than most antihypertensive agents. The hypotensive effect of urapidil is achieved through a peripheral α1-adrenoceptor blockade and central hypotensive activity, resulting in a reduction in systemic vascular resistance[19,20]. Van Aken et al. show that no change in intracranial pressure or intracranial compliance after the administration of urapidil with or without intracranial hypertension in dogs (50 mg plus an infusion of urapidil 8.2±1.2 mg/min)[21]. There is no consensus in the literature on perioperative doses of urapidil. Mentioned studies report different dosing regimens and their effects. For example, Scafuro et al. found that urapidil administration during induction and preoperatively caused a 25% decrease in MAP[22]. Steib et al. reported a 16% decrease in blood pressure compared to the initial value in cases where they used 0.4 mg/kg urapidil to suppress the cardiovascular response to tracheal intubation[23]. Quéré et al. also found that the decrease in blood pressure was 12%[24]. Hernández-Palazón et al. compared urapidil and lidocaine to prevent cardiovascular responses during laryngoscopy and intubation in patients undergoing intracranial mass surgery, and found that it did not prevent an increase in heart rate[25]. Ye et al. reported that a low dose (0.4 mg/kg) or high dose of urapidil (0.6 mg/kg) could be used under general anesthesia to control fluctuating blood pressure during intubation and extubation[26]. Tauzin-Fin et al. reported the perioperative management of pheochromocytoma with intravenous urapidil to prevent haemodynamic instability[27]. They used a continuous intravenous infusion of urapidil with a stepwise increase in dose (started at 5 mg/h and increased by 1 mg/h every hour) until the onset of dizziness or orthostatic hypotension.

In our literature review, we found that the effects of remifentanil and urapidil on hemodynamic status during extubation have not been previously compared. In our study, it was found that urapidil bolus plus infusion or urapidil infusion alone lowered the blood pressure more than remifentanil infusion. And also, SAP during extubation was higher in Group 1 than in the other groups (respectively; it was determined as 144.20±14.14 mmHg, 116.47±11.60 mmHg, 121.93±11.74 mmHg). It was observed that remifentanil infusion administered at a dose of 0.02-0.03 µg/kg/h alone did not prevent blood pressure increases during extubation. In addition, the SAP values in the first 5 min after extubation were higher in the remifentanil group than in the urapidil group. In Groups 2 and 3, a rapid decrease in DAP was observed from the first minute, followed by a stable course. The mean DAP of the patients until extubation was significantly higher in Group 1. Mean DAP values during extubation were 82.37±12.34 mmHg, 67±10.12 mmHg, 65.33±9.35 mmHg for Group 1, Group 2 and Group 3, respectively. The DAP showed a rapid decrease in Groups 2 and 3 (urapidil groups) from the first minute

after extubation, followed by a stable course. In contrast, the mean DAP of Group 1 remained significantly higher until extubation and continued to increase for 5 min after extubation. The MAP showed a pattern similar to that of systolic and diastolic arterial pressures.

A previous study reported tachycardia in patients administered urapidil, which was believed to be secondary to hypotension[26]. However, in the current study, heart rate values were similar in both groups, and tachycardia was not observed in any patient. Regarding extubation time and extubation quality, it is mentioned that they were similar between the groups, with most patients experiencing extubation without severe coughing or straining.

The Entropy RE values, which indicate the depth of anesthesia, were not significantly different between the groups, indicating that the different drug regimens administered with remifentanil and urapidil had similar effects on extubation time and wakefulness.

This study had some limitations, including being conducted at a single center with a small number of cases. Additionally, the follow-up period was limited to the first 5 min after extubation, and extending the observation time could provide more comprehensive evaluation of the effects of the drugs on intracranial pressure, complications, and postoperative outcomes.

5. Conclusion

Urapidil administered at various doses during intracranial surgery effectively prevents hemodynamic responses secondary to extubation and controls blood pressure without affecting heart rate. In addition, the quality of extubation, extubation time, and wakefulness were similar to those achieved using remifentanil. However, this study highlights the need for larger sample sizes in future research to establish and update standard regimens for hemodynamic control in neuroanesthesia practice.

Statement of ethics

This study was approved by Institutional Review Board (IRB Number:166/11, Date:07/04/2022) and written informed consent was obtained from all patients before enrolment in the trial.

Source of Finance

The authors declare that they have received no financial support for this study

Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request. https://tez.yok.gov.tr/UlusalTezMerkezi/TezGoster?key=qVqOZFj2DwNmvdf1oGFYiAI0XZXQEbFvgHBYPs9i4EGiHVnk8Z1QbJfp02g9U_Ul

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