ORIGINAL ARTICLE

Medicine Science International Medical Journal

Is intraoperative remifentanil infusion associated with early postoperative hypertension in intracranial tumor surgery?

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Abstract

Hemodynamic instability may cause serious complications such as intracranial hemorrhage, stroke, and brain edema in the postoperative period in intracranial tumor surgery. This study investigated the relationship between remifentanil infusion used for anesthesia maintenance in intracranial tumor surgery and postoperative early hypertension. Hemodynamic parameters were recorded in the first 24 hours after intracranial tumor surgery in the postoperative intensive care unit. Hypertension rate, causes, and treatment methods of hypertension in our clinic were compared with the literature. The study included 113 patients. In 83 patients (73.4%), hypertension was detected in the first 24-hour period during the intensive care follow-up. The hypertensive attack was controlled with intravenous opioids administered in 69 (83.1%) of 83 patients with hypertension, and with additional intravenous antihypertensive in 14 (16.9%) patients. Analgesia use was higher in hypertensive patients in the first 24 hours postoperatively (83.1% vs. 30%, P<.01). Ultra-short-acting remifentanil infusion used for maintenance of anesthesia may cause hypertensive episodes in the early postoperative period.

Keywords: Remifentanil, intracranial tumor surgery, hypertension

Introduction

Hemodynamic stability, cerebral perfusion pressure maintenance, and intracranial pressure control are the primary anesthetic targets in craniotomy procedures. Selection of the method of anesthesia must also target gentle and rapid recovery from anesthesia for early neurological examination. In addition, the ideal anesthetic agent must maintain cerebral blood flow and reduce the cerebral metabolic rate without affecting the surgical procedure [1].

In general, intravenous (IV) induction agents, except for ketamine, decrease cerebral metabolic rate and cerebral blood flow. As a result, intracranial pressure either remains stable or decreases. Inhalation anesthetics (isoflurane, sevoflurane, desflurane, and halothane) are dose-dependent cerebral vasodilators and reduce the cerebral metabolic rate. In addition, inhalation agents may increase cerebral blood flow and, accordingly, the intracranial pressure.

Due to these reasons, intravenous anesthetic agents may be considered a more suitable option for the induction and maintenance of anesthesia during intracranial procedures [2].

Total intravenous anesthesia (TIVA), in combination with remifentanil, has begun to be frequently used as a suitable induction and maintenance method in craniotomy surgery [3]. Remifentanil is a powerful and ultra-short-acting opioid used for general anesthesia and sedation. While remifentanil offers various advantages in clinical practice, it is also associated with the development of "opioid-induced hyperalgesia (OIH)," a paradoxical increase in sensitivity to painful stimulants that develops after opioid infusion (hyperalgesia, allodynia, or both) [4]. Acute opioid tolerance (AOT) is another undesirable opioid-induced clinical effect that must be differentiated from OIH [5].

The pain that occurs during and after craniotomy increases heart rate (HR) and mean arterial pressure (MAP) [6]. High blood pressure can cause severe complications, especially after intracranial surgery. The pain-related hypertensive response has been reported in many patients after craniotomy [7].

Our study aimed to investigate the relationship between

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hypertension, possible facilitating factors, and remifentanil infusion in the first 24 hours after anesthesia in patients who received remifentanil infusion for anesthesia maintenance in intracranial tumor surgery.

Materials and Methods

Study plan

Our study was planned retrospective cross-sectional after approval from the Ethics Committee of our hospital (KAEK 2019/699). Patients over 18, with an ASA (American Society of Anesthesiologists) score of 3 and below, who underwent elective intracranial tumor surgery between January 2017 and January 2019, were followed in our postoperative intensive care unit and received remifentanil infusion for intraoperative anesthesia maintenance were included in the study. The exclusion criteria were determined as emergency intracranial tumor surgery and missing patients' data.

Patient data

Induction of anesthesia in intracranial tumor surgery patients included in the study, Thiopental Sodium (Pentothal Sodium®) 3-5mg/kg IV bolus, rocuronium (Esmeron®) 0.6-0.9mg/kg IV bolus, fentanyl (Talinat®) 0.5-1µg/kg was provided by IV bolus. Anesthesia was maintained with 2-10 mg/kg/h 2% Propofol (Propofol Fresenius®) infusion and 0.05-2 µg/kg/min remifentanil (Ultiva®). Central venous catheterization with a 7F 15 cm central catheter (Certofix® Trio, Bbraun, Melsungen AG, Germany) from the right internal jugular vein; Invasive artery follow-up was performed from the right radial artery with a 20G (Vasofix® Bbraun Melsungen AG, Germany) peripheral cannula. The drug concentrations used in the maintenance of anesthesia were arranged in line with the intraoperative hemodynamic parameters.

All patients are followed up in the intensive care unit after intracranial tumor surgery. In our intensive care unit, hemodynamically stable craniotomy patients are followed by blood pressure monitoring on the first postoperative day for 15 minutes for the first 6 hours, 30 minutes for the second 6 hours, and hourly for the next 12 hours. Hemodynamic changes in the first 24 hours after surgery; development and frequency of hypertension (systolic blood pressure 140mmHg; diastolic blood pressure more than 80mmHg and increase in mean blood pressure more than 20mmHg according to preoperative blood pressure values), development and frequency of hypotension (systolic blood pressure, 90mmHg; diastolic blood pressure, measurement below 60mmHg; and mean blood pressure, more than 40mmHg decrease from preoperative blood pressure values), bradycardia and its frequency (heart rate, below 60 pulses/min), tachycardia and its frequency (heart rate, 100 pulses/min), arrhythmia development was recorded. Demographic data that may affect hemodynamic parameters in the first 24 hours postoperatively, the relationship between intraoperative and postoperative variables, hemodynamic instability and mortality, length of stay in the intensive care unit, and the need for mechanical ventilation were evaluated. After the first admission to our intensive care unit, after intracranial tumor surgery, all patients considered to be hemodynamically stable postoperatively are followed for heart rate and rhythm monitoring, blood pressure monitoring, and peripheral oxygen saturation in line with the 2014 ESC/ESA guidelines [8]. Considering the possible need for analgesia, an IV bolus of 0.05-0.1mg/kg morphine

(Morphine HCI®)is administered to hypertensive patients after admission to the postoperative ICU. If high blood pressure persists in the follow-ups, blood pressure is regulated with 500µg/kg/min loading in 1 minute and 25-200 µg/kg/min infusion esmolol (Brevibloc Premiks®) treatment.

Demographic data of patients (age, weight, height, and body mass index (BMI), history of chronic disease (hypertension, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), comorbidities), duration of surgery, preoperative and postoperative Glasgow Coma Score) (GCS), drugs used in induction and maintenance of anesthesia and their doses (mg-mcg/kg/min), amount of fluid used intraoperatively (ml), blood and blood products (IU), inotropic and antihypertensive drugs and their doses (mg-mcg). /kg/min), intraoperative vital signs [arterial blood pressure (mmHg), pulse (bpm), body temperature (^{0}C), $Sa0_2$ (%)], intraoperative mechanical ventilation values were recorded. Postoperative vital functions [blood pressure (mmHg), heart rate (bpm), body temperature (^{0}C), SaO_2(%)], total fluid balance (ml), blood and blood product transfusions, inotropic and antihypertensive drugs and their doses, sedation applied, mechanical ventilation parameters, additional postoperative complications, intensive care unit durations and mortality rates reviewed.

Statistical analysis

Data were analyzed using IBM SPSS V23. Linear regression analysis was used to examine independent variables that affected the duration of stay in the intensive care unit and the frequency of hypertension. Variables divided into 3 or more subgroups for patients with postoperative early hypertension were evaluated with the Kruskal Wallis H test, and variables divided into 2 subgroups were evaluated with the Mann Whitney U test. Binary logistic regression analysis was preferred for the examination of hypertension and the independent risk factors with effects on it. The level of significance was set at $P<.05$.

Results

We analyzed 148 adult patients who had undergone intracranial tumor surgery. 18 patients who required emergency craniotomy were excluded from the study. Study data for 17 patients could not be reached. Complete data of 113 patients were evaluated. In the first 24 hours postoperatively (Figure 1).
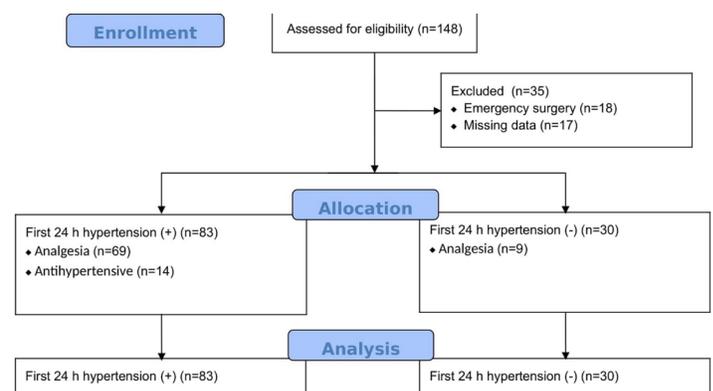

Figure 1. Flow chart of the patients included in the study

In the first 24 hours, hypertension was detected in 83 patients (73.4%), arrhythmia in 12 patients (10.6%), bradycardia in 5

patients (4.4%), tachycardia in 20 patients (17.7%), hypotension in 3 patients (2.7%).

Demographic data, systemic diseases, and outcomes of patients are summarized in Table 1.

The mean intensive care unit stay was 3.1 days (1-39), and the mortality rate was 5.3%. There was no significant effect of hypertension in the early postoperative period on the length of stay in the intensive care unit, the duration of mechanical ventilation, and mortality (Table 1).

Patients' surgery time, intraoperative mean remifentanil infusion, intraoperative fluid balance, blood/blood product transfusion, and intraoperative hypertension variables did not significantly affect postoperative hypertension (Table 2).

The number of patients with hypertension once in the first 24 hours after admission to the intensive care unit was 30 (36.1%), the number of patients with hypertension twice was 33 (39.7%), and the number of patients with three or more hypertensive measurements was 20 (24%).

According to the correlation between demographic data, chronic diseases of patients, ASA classification, and postoperative hypertension, the risk of hypertension increased with age (P=.009; hypertension increased by 1.037 times per unit increase in age). Hypertension risk in those with an ASA classification of 3 was 11.5 (P=.02) times higher than those with an ASA classification of 1. The postoperative hypertension risk in patients with the known hypertensive disease was 13.448 times (P=.026) higher than those without hypertension (Table 3).

IV analgesia was used in 69 (83.1%) of 83 patients with hypertension in the first 24 hours postoperatively, and antihypertensive medical treatment was used in 14 (16.9%) patients to control the hypertensive attack. Analgesia use was significantly higher in patients with hypertension in the first 24 hours postoperatively (83.1% vs. 30%, P<.01, Figure 2).
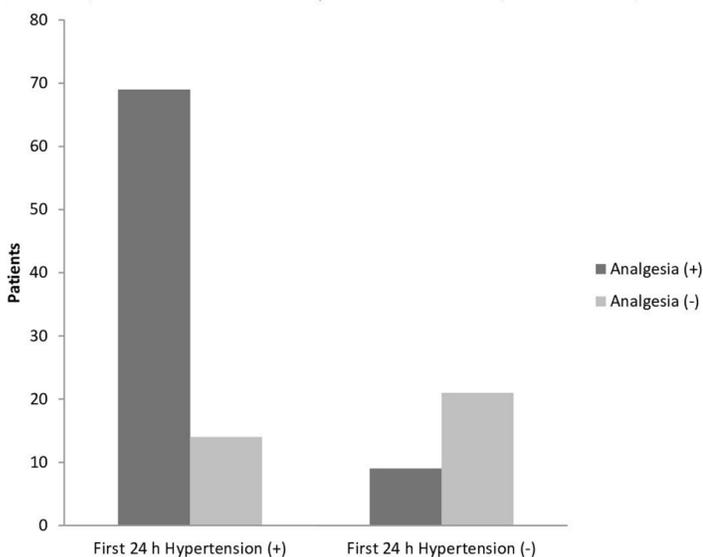
with hypertension in the first 24 hours postoperatively, and to 3 (10%) of 30 patients without hypertension within the first 24 hours. There was no significant relationship between hypertension and sedation in the first 24 hours (P=.467)

In 7 of 34 patients with a known history of hypertension and 7 of 79 patients without a history of hypertension, hypertension in the first 24 hours was controlled with antihypertensive medication. It was observed that the history of hypertension known in the preoperative period was not associated with the need for antihypertensive medication in the postoperative period (P=.083).

Table 1. Demographic data, systemic diseases and outcomes of patients

	First 24 h Hypertension (+)(n=83)	First 24 h Hypertension (-)(n=30)	P
Age, (year) mean ± SD	54.5±14.5	45.4±16.7	.009
Gender (Female) n (%)	44(53)	16(53.3)	.648
Systemic Disease n (%)			
Diabetes Mellitus	15(18.1)	183.3)	.135
Hypertension	27(32.5)	7(23.3)	.020
COPD	3(3.6)	-	.999
Coronary Artery Disease	12(14.4)	3(10)	.248
ASA Classification n (%)			
I	18(23.7)	9(32.2)	.614
II	37(46.6)	18(62.2)	.840
III	23(29.7)	1(5.4)	.026
Outcomes			
Mechanical Ventilation (hours) mean±SD	4.8±6	7.6±15.5	.581
ICU time (day) mean ± SD	3.2±4.8	2.9±2.3	.915
Mortality n (%)	3(3.6)	3(10)	.181

ASA: American Society of Anesthesiologists, **COPD:** Chronic Obstructive Pulmonary Disease, **ICU:** Intensive Care Unit

Table 2. Effects of intraoperative data on postoperative first 24 h hypertension

	First 24h Hypertension (+)(n=83)	First 24h Hypertension (-)(n=30)	P
Surgery time (min) mean ± SD	236.9±68.9	246.8±70.1	.213
Remifentanil (µg/kg/min) mean ± SD	0.98±0.56	0.85±0.54	.792
Fluid balance (ml) mean ± SD	1125±665	1281±722	.200
Intraoperative RBCT n (%)	5(6)	-	.999
Intraoperative FFPT n (%)	2(2.4)	-	.999
Intraoperative hypertension n (%)	24(28.9)	5(16.7)	.366

RBCT: Red blood cells transfusion, **FFPT:** Fresh Frozen Plasma transfusion

Table 3. Effects of preoperative variables on postoperative first 24 h hypertension

	Beta	SD	OR (%95 CI)	p
Age	0.036	0.014	1.037 (1.009 - 1.066)	.009
ASA 3	2.442	1.100	11.5 (1.331 - 99.329)	.026
Hypertension	2.599	1.117	13.448 (1.507 - 120.036)	.02

ASA: American Society of Anesthesiologists

Figure 2. Analgesia in the first 24 hours in patients

It was observed that sedation was applied to 5 (6%) of 83 patients

Discussion

It may cause severe systemic complications such as hemodynamic instability, intracranial hemorrhage, stroke, brain edema, acute kidney injury, and myocardial infarction after craniotomy [9,10]. Close hemodynamic and neurological follow-up in the intensive care unit after craniotomy can reduce possible complications. Hyperacute elevation in blood pressure is quite common, especially after craniotomy [11]. In the literature, the rates of early hypertension developing after intracranial tumor surgery have been reported in a wide range of 21-90% [12]. Bilotta et al. reported that significant tachycardia and hypertension developed immediately after extubation in 49 (82%) of 60 patients who received propofol-remifentanil TIVA in the maintenance of anesthesia for intracranial tumor surgery, and they stated that these patients could control their hypertensive attacks with esmolol infusion [13]. In our study, the rate of hypertension in the first 24 hours after intracranial tumor surgery was similar to the high rates in the literature.

Preoperative risk factors that cause hemodynamic instability after intracranial tumor surgery are stated as known hypertension, advanced age, high BMI, and diabetes mellitus [14-16]. In our study, age, high ASA score, and known history of hypertension were associated with high blood pressure in the first 24 hours postoperatively.

Another cause of postoperative hypertension and tachycardia is pain. Pain seen after craniotomy may increase morbidity and mortality rates by increasing pulmonary or cardiac complications due to sympathetic discharge [6]. The incision, traction, and hemostasis processes used for craniotomy stimulate nerve fibers and specific nociceptors, causing postoperative pain [17]. Contrary to the belief that pain is minimal following intracranial surgery, new data argues the opposite. Moderate to severe pain can be seen in most patients in the first few days after the craniotomy procedure [18]. Poorly controlled pain after craniotomy may adversely affect hemostasis and cerebral hemodynamics. However, excessive use of analgesics may also negatively affect rapid neurological assessment and increase morbidity [19]. In our center, medical preemptive analgesia protocol is not used due to the concerns of possible complications and inadequate neurological evaluation after intracranial tumor surgery.

Remifentanil is preferred for maintaining anesthesia in many surgical procedures, and remifentanil is held responsible for opioid-induced hyperalgesia. In a systematic review, it was reported that perioperative use of remifentanil is a risk factor for the development of severe postoperative pain [20]. Most studies have documented the development of AOT and OIH after infusion of remifentanil >0.1 µg/kg/min. [21,22]. Our study aimed to investigate the effect of AOT and OIH developing after remifentanil infusion on the hypertensive attack developing in the first 24 hours postoperatively. Although the mean infusion dose of intraoperative remifentanil was higher in patients with hypertension in the first 24 hours, this difference was not statistically significant. We could not find a significant difference in the development of hypertension in the first 24 hours between the patients who were given an intraoperative remifentanil >0.1 µg/kg/min infusion and those who were given a lower remifentanil infusion.

It has been reported that the need for early antihypertensive treatment after craniotomy is between 30% and 90% in studies [16,23]. In our study, hypertension was controlled in 69 (83.1%) of 83 patients with hypertension in the first 24 hours after analgesia, and in 14 (16.9%) patients with additional antihypertensive agents. Antihypertensive use was required in 14 (12.3%) of 113 patients included in the study. Our study found that Bilotta et al. required a much lower antihypertensive treatment (82-12.3%) than the need for antihypertensive therapy after propofol-remifentanil infusion in the maintenance of anesthesia in intracranial tumor surgery [13]. We have seen that we can control hypertension, which we see at a high rate in the first 24 hours postoperatively, with analgesia treatment to a large extent.

Basali et al., in their study with 11.214 patients, showed that hypertensive episodes cause a serious increase in risk for postoperative intracranial hematoma, increasing hospital stay and mortality rates [23]. In our study, with patients who developed early hypertension, no significant difference was found between the duration of mechanical ventilation, period of intensive care unit, and mortality rates.

Limitations

Our study has several limitations. First of all, reviewing a small number of retrospective patient data is one of these limitations. Various results have been tried to be interpreted after a single type of anesthesia application. Due to the investigation of the early hemodynamic effects after anesthesia, various late complications may not have been evaluated. Since the patients included in the study were in the early postoperative period, intubated, mechanically ventilated, and in the recovery period from anesthesia due to intracranial surgery, cognitive functions and pain assessment could not be performed optimally. In addition, preoperative hypertension treatments of patients with a history of hypertension and how these treatments were arranged in the preoperative period were not evaluated.

Conclusion

Remifentanil infusion used for maintenance of anesthesia may cause hypertensive attacks in the early postoperative period. Prospective studies of remifentanil, widely used in TIVA protocols, will provide important information about episodes of OIH and AOT-related hypertension.

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