Anesthesiology
2000; 93:48-54

Relation between Perioperative Hypertension and Intracranial Hemorrhage after Craniotomy

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Background: **Previous data suggest that systemic hypertension (HTN) is a risk factor for postcraniotomy intracranial hemorrhage (ICH). The authors examined the relation between perioperative blood pressure elevation and postoperative ICH using a retrospective case control design.**

Methods: **The hospital's database of all patients undergoing craniotomy from 1976 to 1992 was screened. Coagulopathic and unmatchable patients were excluded. There were 69 evaluable patients who developed ICH postoperatively (n = 69). A 2-to-1 matched (by age, date of surgery, pathologic diagnosis, surgical procedure, and surgeon) control group without postoperative ICH was assembled (n = 138). Preoperative, intraoperative, and postoperative blood pressure records (up to 12 h) were examined. Incidence of perioperative HTN (blood pressure ≥ 160/90 mmHg) and odds ratios for ICH were determined.**

Results: **Of the 11,214 craniotomy patients, 86 (0.77%) suffered ICH, and 69 fulfilled inclusion criteria. The incidence of preoperative HTN was similar in the ICH (34%) and the control (24%) groups. ICH occurred 21 h (median) postoperatively, with an interquartile range of 4–52 h. Sixty-two percent of ICH patients had intraoperative HTN, compared with only 34% of controls ($P < 0.001$). Sixty-two percent of the ICH patients had prehemorrhage HTN in the initial 12 postoperative hours *versus* 25% of controls ($P < 0.001$), with an odds ratio of 4.6 ($P < 0.001$) for postoperative ICH. Hospital stay (median, 24.5 *vs.* 11.0 days), and mortality (18.2 *vs.* 1.6%) were significantly greater in the ICH than in the control groups.**

Conclusions: **ICH after craniotomy is associated with severely prolonged hospital stay and mortality. Acute blood pressure elevations occur frequently prior to postcraniotomy ICH. Patients who develop postcraniotomy ICH are more likely to be hypertensive in the intraoperative and early postoperative periods. (Key words: Anesthesia; complications; morbidity; neurosurgery.)**

This article is highlighted in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

THE perioperative course of patients undergoing intracranial procedures is frequently complicated by the occurrence of systemic hypertension (HTN).[1-8] Intraoperatively, acute hypertensive episodes may occur during brain manipulation[9,10] but more often are produced by events such as epinephrine-containing local anesthetic administration, head-pin application, periosteal dissection, and emergence.[1,2,4,11] HTN may be associated with a number of adverse pathophysiologic consequences. When cerebral autoregulation is disturbed[12,13] or its limits are exceeded,[14,15] blood flow passively increases with blood pressure (BP). This in turn can increase intracranial pressure or cause breakdown of the blood-brain barrier with resultant transudation of intravascular fluid.[16-18] Bleeding and signs of encephalopathy may ensue. After intracranial surgery, acute HTN may also increase morbidity and mortality by exacerbating cerebral edema, raising intracranial pressure, or disrupting the delicate postoperative hemostatic state.[9,19] Intracranial hemorrhage (ICH) can be a serious and sometimes fatal complication when it occurs during or after intracranial surgery.

Previous reports have suggested that perioperative HTN and coagulopathy[20-23] are factors that predispose to intracranial bleeding, yet the relation between perioperative HTN and ICH following craniotomy has not been investigated in a large group of patients. To assess whether preoperative, intraoperative, and postoperative HTN are related to the development of postoperative ICH, we examined all patients who suffered ICH after

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Received from the Cleveland Clinic Foundation and the Cleveland Clinic Foundation Health Science Center of the Ohio State University, Cleveland, Ohio. Submitted for publication February 26, 1999. Accepted for publication February 3, 2000. Supported by institutional or departmental sources. Presented in part at the 1994 Annual Meeting of the American Society of Anesthesiologists, San Francisco, California, October 15-19, 1994.

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craniotomy during a 17-yr period at The Cleveland Clinic Foundation and compared them to a double-matched control group who did not have ICH.

Methods

This study was approved by the Institutional Review Board of The Cleveland Clinic Foundation. All patients who underwent intracranial procedures at this institution from January 1976 through December 1992 were screened for a diagnosis of postoperative ICH using the hospital's abstract database system and departmental morbidity and mortality records. We excluded patients with documented coagulopathy or a history of anticoagulant therapy, as well as those who could not be matched.

Blood pressure records from the preoperative, intraoperative, emergence (defined as the last 30 min of the anesthesia record), and immediate postoperative periods were examined. Preoperative HTN was defined as a history of HTN documented in the medical record. Postoperative HTN was defined as at least one recorded episode of systolic BP greater than 160 mmHg or diastolic BP greater than 90 mmHg occurring prior to ICH. For the intraoperative period, during which BP was monitored at 5-min intervals, we defined HTN as at least two consecutive occurrences of BP greater than 160/90 mmHg. Published criteria for systolic and diastolic HTN were used.[24,25]

The timing of a postoperative intracranial bleeding episode was estimated by a change in neurologic status preceding the diagnostic computed tomography (CT) or, if this was unavailable, by the time a physician ordered the diagnostic CT scan. Additional information collected included the type of anesthetic administered, estimated surgical blood loss, intraoperative fluids given, selected preoperative laboratory data, operative duration, and body temperature at the end of the procedure.

A control group, matched by patient age ± 5 yr, year of surgery ± 2.5 yr, pathologic diagnosis (meningioma, primary brain neoplasm, metastatic neoplasm, aneurysm, arteriovenous malformation, or other), surgical procedure (stereotactic, nonstereotactic, or transsphenoid), and each of the 11 surgeons who practiced during the study period, was similarly studied. For each patient with ICH, two matching control patients were selected using information from the hospital abstract database and pathologic diagnosis databanks. If more than two matching patients were available, the two patients whose date of surgery most closely matched that of the ICH patient were selected as controls, provided all other criteria were fulfilled. The ICH and control groups were compared with regard to demographics; baseline laboratory data; occurrence of preoperative, intraoperative, and postoperative HTN; and timing of postoperative hypertensive events.

Statistical Analysis

This study featured a retrospective case control design with a 1:2 matching scheme which was designed to examine the relation between ICH and perioperative HTN. Conditional logistic regression was used to examine the association between ICH and the prognostic factors of preoperative, intraoperative, emergence, and postoperative HTN. Odds ratios (OR) for ICH and their 95% confidence intervals (CI) were calculated. Quantitative variables are reported as mean ± SD or as median with the interquartile range representing the difference between the 25th and 75th percentiles. Categorical variables are reported as frequency and percent. A significance level of $P < 0.05$ was used for each hypothesis.

Results

A total of 11,214 intracranial operations were performed by the neurosurgical service at the Cleveland Clinic Foundation from 1976 to 1992. From this population, 86 patients (0.77%) suffered clinically important ICH, as indicated by hospital course and discharge diagnosis. Four patients were excluded because of coagulopathy. Another 13 cases were excluded for failure to be matched. Consequently, the total number of analyzable patients for this study was 69 (ICH group) with a matched control group of 138 patients. The sample size was sufficient to yield 80% power at the 0.05 significance level to detect an absolute difference in the incidence of HTN of 20% or greater, assuming that about 30% of the controls would be hypertensive.

The anatomic site of ICH was intracerebral in 70%, epidural in 13.5%, subdural in 13.5%, and intrasellar in 3%. All ICH episodes were confirmed by CT or magnetic resonance imaging scan. In 78.2% of patients, the onset of ICH was identified by a change in neurologic status. In the remaining 21.8%, it was determined by the time of a physician's order for the diagnostic CT or magnetic resonance imaging.

Table 1. Clinical Characteristics of ICH and Control Groups (Mean ± SD)

	ICH Group (n = 69)	Control Group (n = 138)	*P* Value
Biologic data*			
Age (yr)	51 ± 17	50 ± 17	†
Gender (female [%])	59.4	53.6	0.43
Weight (kg)	69 ± 19	69 ± 17	0.99
Height (cm)	163 ± 13	166 ± 16	0.07
PT (s)	12.3 ± 1.5	12.4 ± 1.9	0.78
PTT (s)	24.9 ± 3.3	24.8 ± 3.1	0.71
Platelet count	273 ± 82	297 ± 78	0.053
BUN (mg/dl)	16.6 ± 5.7	16.6 ± 6.6	0.81
Serum creatinine (mg/dl)	1.0 ± 1.0	1.0 ± 0.6	0.96
Duration of surgery (h)	6.7 ± 3.4	6.2 ± 3.2	0.16
Intraoperative fluids			
Crystalloid (ml)	2,075 ± 1,900	2,000 ± 1,200	0.54
Hetastarch (% receiving > 500 ml)	4.8	5.4	0.99
PRBC (% receiving > 1,500 ml)	7.9	3.1	0.16
Temperature at end of surgery (°C)	35.7 ± 1.1	35.7 ± 1.1	0.42
Vasodilator therapy (%)‡	31	20	0.09
Intubated at time of ICH (%)	29	5	<0.001
Pathologic diagnosis (count [%])			
Tumor			
Primary neoplasm	32 [46.4]	64 [46.4]	†
Meningioma	12 [17.4]	24 [17.4]	
Metastatic	4 [5.8]	8 [5.8]	
Vascular—aneurysm or AVM§	17 [24.6]	34 [24.6]	†
Other	4 [5.8]	8 [5.8]	
Surgical procedure (count [%])			
Nonstereotaxic	56 [81.2]	112 [81.2]	†
Stereotaxic	11 [15.9]	22 [15.9]	
Transsphenoid	2 [2.9]	4 [2.9]	

* Laboratory data are from the preoperative period.

† Matching variable—no *P* value given.

‡ Percent of patients receiving any vasodilator 12 h before ICH or equivalent period in matched controls.

§ Aneurysms and AVMs were matched separately.

ICH = intracranial hemorrhage; PT = prothrombin time; PTT = partial thromboplastin time; BUN = blood urea nitrogen; PRBC = packed red blood cells; AVM = arteriovenous malformation.

Table 1 provides relevant biologic and perioperative data. More ICH patients were intubated at the time of ICH than controls (29% *vs.* 5%, respectively; $P < 0.001$); each control was evaluated at the same temporal distance from surgery as the corresponding ICH patients. Moreover, hospitalization was significantly longer (median, 24 days; interquartile range, 16-48 days *vs.* 11 days; interquartile range, 8-11 days), and mortality was higher (18.2% *vs.* 1.6%; $P < 0.001$) in ICH than in control patients.

Table 2 shows the incidence of preoperative, intraoperative, and postoperative HTN in the control and study groups. Denominators for specific analyses vary based on the number of nonmissing values available. Patients with postoperative ICH were more likely to have intraoperative HTN (OR = 8; 95% CI = 2-30), to be hyper-

Table 2. Univariate Group Comparisons with Respect to the Incidence of Hypertension

	ICH Group (n = 69)	Control Group (n = 138)	*P* Value
Preoperative hypertension	23/68 (34%)	32/135 (24%)	0.10
Intraoperative hypertension	39/63 (62%)	42/125 (34%)	<0.001
Emergence hypertension	18/65 (28%)	15/130 (12%)	0.005
Early postoperative hypertension*	42/68 (62%)	35/136 (26%)	<0.001

* First 12 h after surgery but before intracranial hemorrhage (ICH).

Table 3. Incidence of Intraoperative Hypertension by History of Preoperative Hypertension

Preoperative Hypertension	ICH Group	Control Group
Yes	56.5% (12/23)	53.1% (17/32)
No	54.3% (25/46)	28.1% (19/103)*

* $P < 0.05$ *versus* preoperatively hypertensive controls and both intracranial hemorrhage (ICH) groups stratified by preoperative hypertension.

tensive during emergence (OR = 3.4; 95% CI = 1.4–8.1), and to have HTN within the 12 h after surgery (OR = 24; 95% CI = 5–127) when compared with the control group. Two of these relations were still significant after adjusting for presence of tracheal intubation at the time of ICH as a covariate (emergence: $P = 0.016$; first 12 h: $P = 0.006$). In a multivariable conditional logistic regression model, ICH was also associated with intraoperative and early postoperative HTN, as it was with the interaction between these two factors ($P = 0.021$).

The incidence of intraoperative HTN by preoperative HTN and study group is shown in table 3. The timing of postoperative ICH in the early postoperative period is illustrated in figure 1. Approximately 50% of ICH episodes occurred in the immediate postoperative period, 0–20 h from the end of surgery. Within the 12-h interval that preceded ICH, 39 of 69 (57%) patients had at least one hypertensive episode, for a total of 130 hypertensive episodes. For these 39 patients, the hypertensive episode closest to ICH occurred a median of 2 h before ICH, with 50% occurring 1–4 h prior to ICH. Most (65%) of the hypertensive episodes during the 12-h period prior to ICH occurred within 6 h of ICH. Figure 2 shows the percentage of hypertensive readings that occurred in temporal proximity to ICH in the 69 study patients. Except for the early postoperative period (within 12 h),

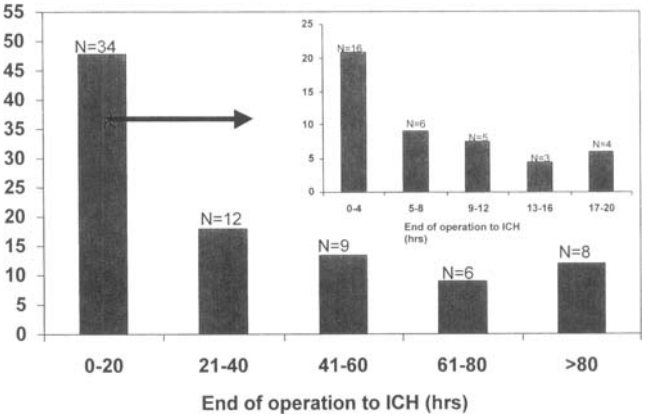

Fig. 1. Temporal distribution of postoperative intracranial bleeding episodes for all 69 intracranial hemorrhage (ICH) patients.

the number of BP readings available for control patients was insufficient to reliably compare them with ICH patients at a similar postoperative time.

Discussion

To our knowledge, the current study for the first time systematically reports evidence of an association between perioperative HTN and postcraniotomy ICH in noncoagulopathic patients screened from a large cohort. The data suggest that patients who develop intraoperative and early postoperative HTN are at increased risk for postoperative ICH after craniotomy, a complication which is associated with a markedly increased mortality and commitment of hospital resources.

Postoperative intracranial bleeding may develop at the operative site or in remote locations[20,23,26] and can be an

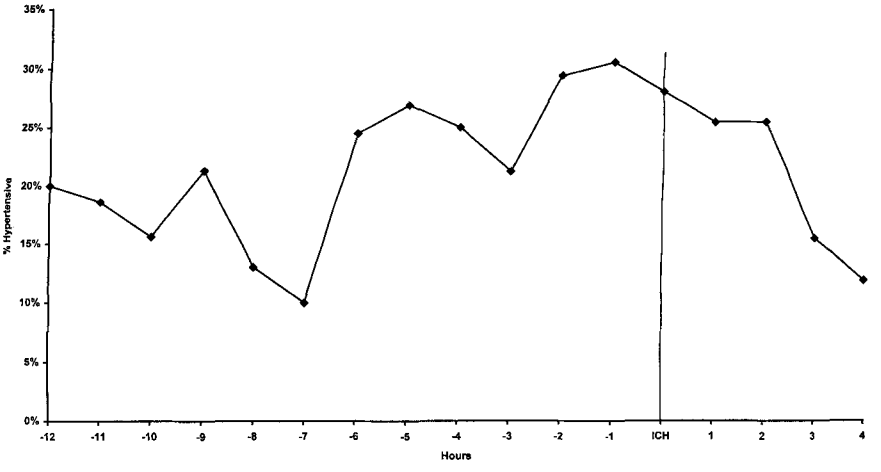

Fig. 2. Percent hypertensive readings in intracranial hemorrhage group immediately before and after intracranial hemorrhage.

adverse prognostic indicator for the patient's hospital course. In our patients, ICH greatly increased hospital cost, as shown by the more than doubled hospital stay. The incidence of postcraniotomy ICH in our study was 0.77%, which is similar to that previously reported by our institution[20] but less than the 3.9% incidence of medium-sized to large ICH from a survey of postcraniotomy CT scans.[26] Our lower ICH incidence is explained by the fact that we studied only clinically significant ICH noted in the hospital morbidity database.

The frequency of postoperative HTN has been reported to be 6% after general surgery[27] and 35–50% after cardiac surgery.[28] We report an incidence of 57% for postcraniotomy HTN. This figure is relatively low compared with previous reports noting incidences from 54–91% during the perioperative course of intracranial surgery.[1,2,5,7,8,17,29]

Our definition of HTN as BP greater than 160/90 mmHg bears comment. This level was chosen arbitrarily but is based on previously accepted criteria.[24,25] A sensitivity analysis showed that our observations would have yielded similar conclusions had the BP criterion been 180/100 or 150/90 mmHg. We did not define HTN as a function of baseline BP because we presumed a certain absolute mechanical vulnerability of intracranial blood vessels postcraniotomy regardless of preoperative BP. Furthermore, because of the short presurgical contact period and the paucity of preoperative BP readings, it was impractical to obtain an accurate representation of baseline BP behavior from our elective surgical patients. Using a criterion that depends on preoperative baseline, BP, therefore, seemed fraught with a high possibility of error. An absolute BP criterion has also been previously used by our group for evaluation of a similar neurosurgical patient population.[20] We might be criticized for relying on single BP readings in a portion of this study. However, in the intraoperative and emergence periods, we required two consecutively elevated BPs for a patient to be considered hypertensive. In addition, only 20% of elevated BP readings occurred in isolation, which should have limited the confounding effect of isolated BP measurements.

HTN may be both the harbinger of ICH and its consequence. Although systemic HTN is a plausible contributory cause of ICH, systemic HTN can also be precipitated by cerebral injury such as ischemia,[30] ICH,[31] intracranial HTN,[32] and operative intervention.[10] Previous reports implicating HTN in the development of ICH have shed little light on this issue. Waga *et al.*[23] have noted that labile HTN and intraoperative changes in BP may contribute to the development of ICH remote from the operative site following neurosurgical procedures, although actual BP readings and temporal relations were not detailed in any of the four reported cases. In a survey of 4,992 intracranial procedures, Kalfas and Little[20] reported that 16% of patients who developed ICH had arterial HTN greater than 160 mmHg preceding ICH. However, a comparison with the BP behavior of patients without ICH was not available, and the temporal relation between HTN and ICH was not further defined.

The odds ratios calculated from our data appear to demonstrate a higher incidence of intraoperative and early postoperative HTN in patients who develop postcraniotomy ICH. The likelihood of a causal relation between systemic HTN and postoperative ICH requires consideration. Epidemiologically, an association is said to be more likely causal if it is strong, appropriately temporal, specific, dose-related, consistent, plausible, and coherent.[33] We demonstrated a substantive but not necessarily strong association between intraoperative or immediate (12 h) postoperative HTN and postoperative ICH. Because most (65%) of the hypertensive episodes 12 h prior to ICH occurred in the first 6 h prior, a reasonable temporal relation could have existed. The observation that the incidence of HTN 4 h before ICH was higher than that during the 4 h interval after ICH might argue against ICH having caused the observed HTN. However, it might also have been the result of aggressive BP control following the diagnosis of ICH. We could not address whether the tendency for ICH was related to the magnitude of HTN, because we evaluated patients only for the presence or absence of HTN, as previously defined. Therefore, a "dose response" was not demonstrated. An important argument against HTN as a cause for ICH in postcraniotomy patients is the lack of specificity of our findings; 38% of ICH patients did not have hypertensive BPs recorded during the 12-h period after surgery, whereas 26% of control patients (table 2) in turn became hypertensive during the same period. Nevertheless, the differences in the incidence of HTN prior to ICH between the study and control groups are substantial and are unlikely due to chance. Furthermore, the study's double-matched design and exclusion criteria allowed reasonable control over several potentially confounding variables, such as type of intracranial lesion,[20] surgical technique, and patient age.[34]

Our observations cannot establish HTN as a causative factor. However, perioperative HTN may represent a marker of patients at risk for ICH, possibly as an epiphenomenon of an as yet undiscovered primary process.

ICH is likely the result of many predisposing conditions (*e.g.,* surgical hemostasis, venous pressure, coagulation status, genetic predisposition, hemodynamic state), only one of which may be systemic HTN. Of particular interest is our observation of a very strong association (estimated OR = 24) with ICH when BP remained lower than 160/90 mmHg intraoperatively but became hypertensive postoperatively compared with those with HTN in neither period. One plausible explanation for this might be that patients with this combination were not adequately "tested" (by allowing BP to rise) for bleeding intraoperatively, leaving them with vessels that were sealed less than optimally and later bled when BP was higher.

Other confounding factors could also account for the observed association between ICH and HTN. First, and most important, ICH patients were tracheally intubated more frequently than controls, although several of the associations remained significant even after accounting for intubation as a covariable. Tracheal intubation is associated with frequent coughing and straining, which may increase cerebral venous pressure and predispose to ICH. Pharmacologic antihypertensive therapy may have resulted in cerebral vasodilation, cerebral edema, shearing of vessels, or rebleeding of previously constricted vessels. However, vasodilator therapy was not associated with ICH in any of the time intervals reported. Although different pathogenic mechanisms may be responsible for intracerebral compared with subdural or epidural bleeding, our observations in the subgroup of intracerebral bleeds (n = 47) are the same as those in the entire data set.

We deliberately did not match for existence of preoperative HTN, although its prevalence was similar in both the ICH and control groups. Furthermore, the incidence of intraoperative HTN was significantly lower in controls who were normotensive preoperatively compared with ICH patients who were normotensive preoperatively (table 3). The observed differences in the incidence of intraoperative and postoperative HTN were therefore not primarily determined by the existence of preoperative HTN, as has been found in patients undergoing carotid endarterectomy.[30] One might conclude, however, that the inclusion of preoperatively hypertensive patients could have understated the relation between intraoperative HTN and ICH in our study. The effect of every possible confounder could not be completely eliminated given the chosen study design. However, we believe that the data gleaned from our study show a substantial and believable association of ICH with intraoperative and early postoperative hypertensive tendencies.

Our data should be interpreted with a realization of the limitations of a retrospective design, the most serious of which is the loss of data not recorded in the medical record. The incidence and severity of perioperative HTN may therefore actually have been higher than that reported. However, this factor should have been equally operant in either group and therefore likely did not affect the results of our comparisons. Conversely, the timing of ICH *via* chart review was no doubt somewhat inaccurate. Therefore, some post-ICH HTN may have been included in the 12-h postoperative data, perhaps falsely increasing our estimate of hypertensive frequency. Because of the inability to find sufficient control BP readings during and before later-occurring ICH events, further assessment of the temporal relation between HTN and ICH was not feasible. Whether prevention of systemic HTN can reduce the incidence of postcraniotomy ICH is an issue that could not be addressed by the present study.

Our double-matched case control study of postcraniotomy ICH screened from 11,214 patients over 17 yr shows that postoperative ICH is associated with severely prolonged hospital stay and increased mortality. Postcraniotomy ICH was also associated with acute intraoperative and early postoperative HTN, although a causal relation could not be demonstrated.

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