

Flurbiprofen and hypertension but not hydroxyethyl starch are associated with post-craniotomy intracranial haematoma requiring surgery

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Editor's key points

- Intracranial haematomas are a rare but serious complication of craniotomy surgery.
- The authors analysed a large neurosurgical database to assess risk factors for haematomas requiring surgery.
- Hypertension during craniotomy, after craniotomy, or both were significant factors.
- Administration of flurbiprofen during, but not after, craniotomy was associated with haematoma development.

Background. Post-craniotomy intracranial haematoma is one of the most serious complications after neurosurgery. We examined whether post-craniotomy intracranial haematoma requiring surgery is associated with the non-steroidal anti-inflammatory drugs flurbiprofen, hypertension, or hydroxyethyl starch (HES).

Methods. A case-control study was conducted among 42 359 patients who underwent elective craniotomy procedures at Beijing Tiantan Hospital between January 2006 and December 2011. A one-to-one control group without post-craniotomy intracranial haematoma was selected matched by age, pathologic diagnosis, tumour location, and surgeon. Perioperative blood pressure records up to the diagnosis of haematoma, the use of flurbiprofen and HES were examined. The incidence of post-craniotomy intracranial haematoma and the odds ratios for the risk factors were determined.

Results. A total of 202 patients suffered post-craniotomy intracranial haematoma during the study period, for an incidence of 0.48% (95% CI=0.41–0.55). Haematoma requiring surgery was associated with an intraoperative systolic blood pressure of >160 mm Hg (OR=2.618, 95% CI=2.084–2.723, $P=0.007$), an intraoperative mean blood pressure of >110 mm Hg (OR=2.600, 95% CI=2.312–3.098, $P=0.037$), a postoperative systolic blood pressure of >160 mm Hg (OR=2.060, 95% CI= 1.763–2.642, $P=0.022$), a postoperative mean blood pressure of >110 mm Hg (OR=3.600, 95% CI= 3.226–4.057, $P=0.001$), and the use of flurbiprofen during but not after the surgery (OR=2.256, 95% CI=2.004–2.598, $P=0.005$). The intraoperative infusion of HES showed no significant difference between patients who had a haematoma and those who did not.

Conclusions. Intraoperative and postoperative hypertension and the use of flurbiprofen during surgery are risk factors for post-craniotomy intracranial haematoma requiring surgery. The intraoperative infusion of HES was not associated with a higher incidence of haematoma.

Keywords: flurbiprofen; hydroxyethyl starch; hypertension; postoperative haemorrhage

Accepted for publication: 31 March 2014

Post-craniotomy intracranial haematoma is one of the most serious complications after neurosurgery. Intracranial haematomas cause increased intracranial pressure, oedema, local and then global cerebral ischaemia, and life-threatening cerebral herniation. Even a small-sized haematoma in the posterior fossa can be fatal.¹ There are few studies describing the incidence and risk factors for the development of post-craniotomy haematoma. Reports of patients between 1976 and 1992 have suggested an association with age, pre-existing, intraoperative and postoperative hypertension, coagulopathies, intraoperative

blood loss, specific types of tumours, chronic subdural haematomas, and inadequate haemostasis.^{2–5}

Non-steroidal anti-inflammatory drugs (NSAIDs) like flurbiprofen are effective analgesics, but a major concern is their antiplatelet effects and this is the main reason for the reluctance by some to routinely use them.^{6,7} There are numerous studies in major surgery showing that patients receiving NSAIDs, especially chronic use, have a higher risk of bleeding than patients receiving placebo.^{3,8} Conversely, there are studies showing that acute perioperative use does not

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significantly increase bleeding.^{9,11} This issue has not been well investigated in the neurosurgical literature.

Colloids are commonly used for acute restoration and stabilization of systemic intravascular volume and improved tissue perfusion during surgery.¹² However, the infusion of hydroxyethyl starch (HES) solution is associated with haemostatic alterations by inhibiting platelet function, reducing von Willebrand factor, and fibrin polymerization.¹³ Whether the intraoperative infusion of HES is associated with post-craniotomy intracranial haematoma is not known.

In the current study, we tested the hypothesis that post-craniotomy intracranial haematoma requiring surgery is associated with perioperative hypertension, the use of flurbiprofen, and the infusion of HES. We conducted a case-control study, examining all patients who suffered post-craniotomy intracranial haematoma during a 6-yr period at Beijing Tiantan Hospital and comparing them with a matched control group who did not have an intracranial haematoma. Beijing Tiantan Hospital is a single medical centre affiliated to Capital Medical University and one of Asia's busiest neurosurgical hospitals performing ~8000 neurosurgical procedures a year.

Methods

The study was approved by the Institutional Review Board at Beijing Tiantan Hospital. Because patients were not subjected to investigational actions and only de-identified retrospective data would be used, no written informed consent was required. For similar reasons, this study was not registered with a clinical trials registry. We performed a retrospective case-control study. All patients who underwent elective craniotomy at Beijing Tiantan Hospital from January 2006 to December 2011 were screened (M.J.) in the hospital's database system for a diagnosis of 'haematoma' and 'post-craniotomy intracranial haematoma' which was confirmed by computed tomography scan and required surgery. Then another anaesthesiologist (X.L.) searched the anaesthetic record system for all the patients admitted to the operating room with the diagnosis of post-operative intracerebral haematoma. By searching two separate databases, we are confident that all the patients were included. Thereafter, we excluded patients for whom complete medical records could not be obtained.

Perioperative patient data were collected from medical records. All the electronic medical records were reviewed by two reviewers both of whom were anaesthesiologists (M.J., X.L.) to ensure the validity of the data. These consisted of patients' age, gender, ASA grade, past medical history, preoperative laboratory data, location and histology of the brain tumour, date of first operation, operative details such as the type of anaesthetic administered, occurrence of preoperative, intraoperative and postoperative hypertension, the use of flurbiprofen, estimated surgical blood loss, intraoperative crystalloid and colloid fluids given and operative duration, date of second operation, and the site and volume of the haematoma. Outcomes of patients were assessed according to the length of hospital stay and Karnofsky performance status (KPS)¹⁴ score at discharge.

Preoperative hypertension was defined as a history of hypertension recorded in the medical record. Intraoperative and postoperative hypertension were defined as the maximum blood pressure both absolute, >160/90 mm Hg or mean (MBP) >110 mm Hg, and relative to the baseline (>20% increase from the baseline). All the blood pressures during the surgery were measured through an arterial line and recorded every 5 min. We also compared the use of vasodilator drugs between the two groups. The baseline blood pressure was defined as the blood pressure measured at preoperative evaluation the day before surgery.

Flurbiprofen is the only injected i.v. NSAIDs in our hospital. The use of flurbiprofen included bolus i.v. administration during surgery and continuous i.v. administration after surgery. The dose of flurbiprofen during surgery was 50 mg; the dose of flurbiprofen after surgery was 1.5 mg kg⁻¹ day⁻¹.

For every patient with a post-craniotomy haematoma, one control patient was matched by age (5 yr) and date of surgery (1 week), the same pathologic diagnosis (meningioma, glioma, aneurysm, pituitary tumour, metastatic neoplasm, or other), tumour location, and attending surgeon.

Statistical analysis

Categorical variables are reported as frequency and per cent. The rates of occurrence of perioperative hypertension and the use of flurbiprofen were compared using the Pearson chi-square test and are presented as odds ratios (ORs) for post-craniotomy intracranial haematoma and 95% confidence intervals (CIs). Normally distributed continuous variables are reported as mean (SD) and compared using the two-sample *t*-test. Continuous variables, not normally distributed, are reported as median with the interquartile range representing the difference between the 25th and 75th percentiles and compared using the Mann-Whitney test.

Conditional logistic regression was used to examine the association between haematoma and the occurrence of perioperative hypertension and the use of flurbiprofen and HES. A significance level of $P \leq 0.05$ was used for each hypothesis. The statistical analysis was performed with the SPSS software version 13.0.

Results

There were 42 359 patients who underwent craniotomy at Beijing Tiantan hospital from January 2006 to December 2011. Of these patients, there were 202 (0.48%) post-craniotomy haematoma surgeries according to our anaesthetic record system. After we reviewed these cases one by one, it turned out that 13 patients underwent a third surgery, mainly decompressive craniectomy for brain oedema, after the second surgery. Therefore, there were 189 patients who suffered a post-craniotomy haematoma in our study. Five patients were excluded for incomplete medical records, so the total number of patients that could be analysed for this study was 184 with post-craniotomy intracranial haematoma and a matched control group of 184 patients. These data were also confirmed by hospital medical records and discharge diagnosis.

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