Efficacy of intravenous patient-controlled analgesia after supratentorial intracranial surgery: a prospective randomized controlled trial

Clinical article

*Athir H. Morad, M.D.,1 Bradford D. Winters, M.D., Ph.D.,1 Myron Yaster, M.D.,1 Robert D. Stevens, M.D.,1 Elizabeth D. White, R.N.,1 Richard E. Thompson, Ph.D.,2 Jon D. Weingart, M.D.,3 and Allan Gottschalk, M.D., Ph.D.1

Departments of 1Anesthesiology and Critical Care Medicine, 2Biostatistics, and 3Neurosurgery, Johns Hopkins Medical Institutions, Baltimore, Maryland

Object. Opioid administration following major intracranial surgery is often limited by a presumed lack of need and a concern that opioids will adversely affect postoperative outcome and interfere with the neurological examination. Nevertheless, evidence is accumulating that these patients suffer moderate to severe postoperative pain and that this pain is often undertreated. The authors hypothesized that intravenous patient-controlled analgesia (PCA) would safely and more effectively treat postoperative supratentorial craniotomy pain than conventional as needed (PRN) therapy.

Methods. Following a standardized course of general anesthesia, adult patients who underwent elective supratentorial intracranial surgery were randomized in the neuroscience intensive care unit to receive either PRN intravenous fentanyl 25–50 μg every 30 minutes or PCA intravenous fentanyl 0.5 μg/kg every 15 minutes (maximum 4 doses/hour). The authors measured pain (self-reported scale score [0–10]), sedation (Ramsay Sedation Scale score), Glasgow Coma Scale score, fentanyl use, and major adverse events (excessive sedation, respiratory depression, pruritus, nausea, or vomiting) hourly.

Results. Sixty-four patients with a mean age of 48 years (range 22–77 years) were randomized to intravenous PCA (29 patients) or PRN fentanyl (35 patients) groups. There were no statistically significant demographic differences between the 2 groups. Patients receiving intravenous PCA had significantly lower pain scores than those receiving intravenous PRN fentanyl (2.53 ± 1.96 vs 3.62 ± 2.11 [p = 0.039]) and received significantly more fentanyl than the PRN group (44.1 ± 34.5 vs 23.6 ± 23.7 μg/hour [p = 0.007]). There were no differences between the 2 groups regarding the number of patients with adverse events.

Conclusions. Intravenous PCA more effectively treats the pain of supratentorial intracranial surgery than PRN fentanyl, and patients in the former group did not experience any untoward events related to the self-administration of opioids. (DOI: 10.3171/2008.11.JNS08797)

Key Words • acute pain • analgesia • craniotomy • neurosurgery • opioids • patient-controlled analgesia

Abbreviations used in this paper: ANOVA = analysis of variance; GCS = Glasgow Coma Scale; NCCU = Neuroscience Critical Care Unit; PCA = patient-controlled analgesia; PRN = as needed.

* Drs. Morad and Winters contributed equally to this study.
ies have reported that pain following intracranial surgery is in fact common, often intense, and undertreated. Failure to adequately treat pain in other postoperative conditions is not only associated with poor patient satisfaction but worse functional outcomes. Indeed, aggressive assessment and treatment of pain for other conditions is now routine and the standard of care. One of the most common and safest methods of effectively treating pain in adults and children is intravenous PCA. However, this method of pain management has rarely been used following craniotomy. Although intravenous PCA has been used in several studies to compare different analgesics following craniotomy, the efficacy and safety of intravenous PCA has not been studied in comparison with conventional PRN therapy. We hypothesized that intravenous PCA would safely and more effectively treat the pain of supratentorial craniotomy than PRN therapy.

Methods

After obtaining approval from the institutional review board, eligible patients presenting for elective supratentorial craniotomy were recruited on the day of surgery. Those eligible needed to be opioid-naive, nonpregnant, English-speaking adults, and able to use an intravenous PCA delivery system. Exclusion criteria included a history of substance abuse, obstructive sleep apnea, and epilepsy.

After obtaining written informed consent, all patients underwent standardized general anesthesia. Anesthesia was induced using intravenous propofol (2–3 mg/kg), fentanyl (2–5 μg/kg), and vecuronium (0.1 mg/kg) and maintained with isoflurane, nitrous oxide, oxygen, and fentanyl up to a maximum of 2 μg/kg/hr as needed. All patients received a scalp block or infiltration of the surgical site with bupivacaine. At the conclusion of surgery, neuromuscular blockade was antagonized with neostigmine and glycopyrrolate, and patients were taken to the NCCU for recovery. In the NCCU, patients were neurologically assessed for new immediate postoperative neurological deficits, the ability to communicate, and the ability to physically use a PCA button before they were permitted to continue with randomization. Patients with new deficits or those who had communication problems, who could not manipulate the PCA device, or had received naloxone in the operating room were excluded from continuing in the study.

Patients were randomized to receive either 25–50 μg intravenous fentanyl every 30 minutes PRN or intravenous PCA 0.5 μg/kg fentanyl with a lock-out interval of 15 minutes and a maximum of 4 demand doses/hour. Additionally each patient was given acetaminophen 650 mg rectally every 4 hours while they were unable to take oral medication, followed by 1 g acetaminophen orally every 6 hours thereafter.

While in the NCCU, study patients were routinely assessed (hourly for the first 10 hours then every 2 hours until discharge from the intensive care unit) for the following outcome variables: changes in neurological status, pain scores, incidence of uncontrolled pain (defined as a pain score ≥ 5/10 for > 2 hours), incidence of respiratory depression requiring an opioid antagonist or institution of ventilatory support, the number of emergency postoperative CT or MR imaging studies obtained for evaluation of neurological changes, incidence of pruritus, and the incidence, duration, and intensity of nausea and vomiting. Vital signs were continuously measured. All data were entered into a Microsoft Access database by a researcher coordinator for analysis.

Statistical Methods

Our previous investigation in adult patients undergoing major intracranial surgery found that 69% of 187 patients treated with PRN fentanyl experienced moderate to severe pain (self-report score ≥ 4 on a 10-point pain scale). For this study, we assumed that the use of intravenous PCA would reduce by 50% the number of patients with moderate to severe pain when compared with conventional PRN fentanyl therapy. Using a 2-sided alpha of 0.05, 32 patients per treatment group would give an 80% power to detect at least a 50% decrease in the percentage of patients with pain scores ≥ 4.

Frequency data were analyzed using the Fisher exact test or log-linear analysis (when frequency tables were other than 2 × 2), ordinal data were analyzed using Kruskal-Wallis ANOVA, and continuous data were analyzed using ANOVA and, where appropriate, techniques for longitudinal data analysis. Most outcome variables (pain, fentanyl use, respiratory rate, oxygen saturation, systolic blood pressure, heart rate, GCS score, and Ramsay Sedation Scale score) were treated as continuous variables, whose average over the entire NCCU length of stay was analyzed using 1-way ANOVA. With the exception of the fentanyl data, the initial hour was not included in the analysis because, for these variables, there would have been no differences between the control and intervention groups. Furthermore, for these variables, longitudinal data analysis was also carried out using a general estimating equation approach whose results were also confirmed using a mixed-model approach. Results obtained from longitudinal data analysis are reported only for the data displayed in the figures because the results were not materially different from results obtained using 1-way ANOVA. Ordinal data for nausea and vomiting and pruritus were reduced to simple frequency tables representing the presence of the symptom at any time during the study period. These symptom scales were also summed for each patient over the entire study period and analyzed using Kruskal-Wallis ANOVA, and the result was reported only if it was materially different from that obtained from the frequency data. Additional power analysis of safety data was performed using the binomial distribution to compute confidence intervals as a function of study size. Data were analyzed with Statistica 6.0 (StatSoft, Inc.) and, for longitudinal data analysis, Stata 10 (StataCorp. LP). Probability values ≤ 0.05 were considered significant.

Results

Between March 2006 and December 2007, we identified 601 eligible patients of whom 79 were randomized to receive either PRN or intravenous PCA analgesia (Fig. 1). Both groups were similar with respect to demographic
variables, intraoperative variables, and pain levels on admission to the NCCU (Table 1). Data collection was terminated prematurely for 6 patients, but not before the criterion of ≥ 10 hours of data collection (Table 1). Of these 6 patients, 2 were withdrawn from the study because of uncontrolled pain (both in the PRN group), 1 because of uncontrolled nausea and vomiting (intravenous PCA group), and 3 patients (1 in the PRN and 2 in the intravenous PCA group) because of neurological deterioration unrelated to opioid administration.

There were no significant differences in pain scores at the time (Hour 0) of admission to the NCCU (p = 0.875) (Table 1 and Fig. 2). Thereafter, longitudinal data analysis demonstrated significant differences between the 2 groups over the course of the study (p = 0.015) (Fig. 2). Patients in the intravenous PCA group had lower pain scores than those in the PRN group (2.53 ± 1.96 vs 3.62 ± 2.11 [p = 0.039]) during the 16 hours after their admission to the NCCU (Table 1 and Fig. 2). Consistent with this, patients in the intravenous PCA group also received significantly more fentanyl than those in the PRN group (44.1 ± 34.5 vs 23.6 ± 23.7 μg/hour; Table 1 and Fig. 3). There were no differences between the 2 groups in sedation scores, GCS scores, respiratory rate, or oxygen saturation (Table 2). Although heart rate and blood pressure were lower in the intravenous PCA group than the PRN group, this dif-
ference was significant only for blood pressure (Table 2). Finally, there were no statistically significant differences in the number of unscheduled brain imaging studies performed to evaluate patients for neurological deterioration. Of those who did suffer neurological deterioration or required unscheduled brain imaging, none of these were attributable to opiate administration.

Although there was a trend toward more nausea and vomiting in the intravenous PCA group, this did not reach significance (Table 1). This adverse event was examined in further detail, and although there were no differences in the actual incidence of nausea and vomiting, when either did occur the overall intensity and duration was significantly worse in the PCA group (summed scores over time: 1.46 ± 2.89 and 2.79 ± 3.20 for PRN and PCA, respectively [p = 0.022]).

**Discussion**

This prospective, randomized controlled trial clearly demonstrated the superiority of intravenous PCA over conventional PRN therapy in treating postcraniotomy pain,
Use of PCA following major intracranial surgery

Fig. 2. Graph showing the hourly pain scores (discrete 0–10 scale) presented as the mean ± standard error of the mean. There were no significant differences in pain scores obtained at Hour 0, the time of admission to the NCCU (p = 0.875). Thereafter, longitudinal data analysis demonstrates significant differences between the 2 groups over the course of the study period (p = 0.026), which was more apparent when initial pain was used as a covariant (p = 0.015).

without major adverse events in either group. Although only a few studies have been performed evaluating PCA therapy in the management of postcraniotomy pain, we believe that this is the first randomized controlled trial directly comparing standard intravenous PCA fentanyl with PRN therapy in this patient population. Furthermore, the use of intravenous PCA in this study neither altered the neurological examination nor increased the incidence of neurological deterioration. These results are not consistent with the widely held belief that opioid administration in general, and intravenous PCA therapy in particular, is unsafe in this patient population.

The need for postoperative analgesia and the degree of pain associated with craniotomy surgery has been disputed in the past. Only recently has a sufficiently coherent picture developed to reconsider the traditional teaching that this pain is minimal. Building on several earlier studies, a large prospective study of pain following major intracranial surgery recently demonstrated some period of moderate to severe pain (≥ 4 on a 0–10 scale) in 69% of patients on the 1st postoperative day and in 48% of patients on the 2nd postoperative day. In contrast to other studies, patient satisfaction varied significantly with the quality of pain relief. Demographic and clinical factors linked to increased pain following intracranial surgery have included sex, younger age, surgical site, surgical approach, and use of perioperative neural blockade. Pain intensity is also a significant factor in studies evaluating the quality of recovery from intracranial surgery.

Despite the great advances that have occurred over the past 2 decades in neurosurgery, neuroanesthesia, and neurosurgical intensive care, analgesic therapy following intracranial surgery has remained a therapeutic conundrum. On one hand, there is a basic desire by all physicians to alleviate pain and, on the other, there is a fundamental requirement to do no harm. Opioids, the analgesics most often prescribed for moderate to severe pain, have had a limited role in the analgesic therapy of patients who have undergone major intracranial surgery because of a concern that opioid administration can adversely affect the postoperative neurological examination and outcome. This concern has a reasonable degree of face validity but has not previously been well examined to determine if it is legitimate.

Perhaps not surprisingly, we found that intravenous PCA was superior to PRN opioid administration in terms of pain relief. In the traditional PRN approach, a patient must complain of pain and ask for pain relief. The responding nurse must respond to and assess the patient, then locate, prepare, and administer the ordered medication at a fixed dose and time interval. Dosing and time intervals are often inadequate because of prescriber's lack of familiarity with the pharmacology of opioids, fear of opioid-induced side effects, an under-appreciation of pain, and an irrational fear of inducing drug addiction.

Thus, even in the best of circumstances, there is a lag time inherent in asking for and receiving analgesia. Patient-controlled analgesia permits patients to treat their pain by direct activation of a device that administers predetermined, intermittent aliquots of analgesics. In this study, we used intravenous administration of the relatively potent and rapidly acting opioid fentanyl.

Individual analgesic needs are accommodated by the diverse dosing patterns and immediate response that the PCA device permits. Patients typically receive < 50% of the total allowable, and already inadequate, PRN prescription. In this study, we observed a more generous administration of PRN opioid than noted in other studies as well as our previous observational study. Several factors may have contributed to this increased use of fentanyl in the PRN group. This was an unblinded study, and the institutional investigational review board mandated in their approval process that the PRN treatment group receive effective analgesia at doses that were greater and more frequent than usually used in the NCCU. Further-

Fig. 3. Graph showing the hourly fentanyl use. Hour 0 indicates the amount of fentanyl administered from the time of admission until the end of the 1st hour. Longitudinal data analysis demonstrates significant differences between the 2 groups (p = 0.004), which were more apparent when initial pain was also considered (p = 0.001).
more, the bedside nurses were mandated by the protocol to frequently assess and treat pain, and this may have affected their behavior. The nurses may also have been aware of the results of our previous study showing a high level of ineffectively treated pain in these patients, leading to a Hawthorne effect. Despite the PRN dosing being more generous and frequent than in our previous study, we were still able to demonstrate significant improvements in analgesia in the intravenous PCA arm.

A potential criticism of this study is that more fentanyl was used in the PCA group because more opioids were available to that group. However, the converse argument can be made that the increased use of opioids, when given the opportunity, attests to the degree of pain suffered by the postcraniotomy patient population and the inferiority of the PRN approach. Assuming that patients received the maximum dose possible, the PRN arm would get 100 μg fentanyl/hour, and the PCA group could get as much as 200 μg/hour. Although the patients in the PCA arm used nearly twice as much fentanyl per hour as those in the PRN arm, both had average doses well below the maximum total hourly dose (44.1 vs 23.6 μg/hour). This difference in maximum allowable opioid may explain the improved pain scores with PCA and suggests that how much opioid a patient receives is as important as the method of delivery. Patient-controlled analgesia may optimize the delivery and the total dose to achieve more effective pain relief.

When discussing the safety of PCA, the distinction must be made between the complications arising from the PCA as a modality of delivering analgesics and problems resulting from the opioids used in treating pain. There are actually few complications with PCA as a modality, and most occur because of programming errors, use of concomitant continuous opioid infusion, or initiation of the demand dose by individuals other than the patient (PCA by proxy or surrogate PCA). In this study none of these delivery complications occurred. On the other hand, opioids have side effects regardless of the method of administration including sedation and miosis (which may mask signs of an intracranial event), ventilatory depression (which may lead to hypercapnia and increased intracerebral blood volume), pruritus, nausea, vomiting, constipation, and hypotension. In fact, the 2 most feared adverse consequences of intravenous PCA management of postcraniotomy pain (respiratory depression and excessive sedation) did not occur in this study. Thus, one of the most important findings of this study was our ability to improve analgesia by providing more opioids via the PCA pump safely. This is especially notable since the patients in the PCA arm used nearly twice as much fentanyl as their counterparts in the PRN arm.

This study also found no difference in other adverse outcomes including nausea and vomiting, uncontrolled nausea and vomiting, pruritus, and uncontrolled pain. Indeed, only 2 patients in this study had uncontrolled pain and both were in the PRN group. The tendency toward greater intensity and duration of nausea and vomiting, when it did occur in the PCA group, warrants attention, especially given that nausea and vomiting are commonly associated with intracranial surgery. The increased nausea and vomiting in the PCA group is likely to be due to the higher total doses of fentanyl received by this group and underscores the need for aggressive and effective regimens to control this opioid-induced side effect. If similar doses had been available in the PRN arm, a similar intensity of nausea and vomiting may have been seen.

We recognize several other limitations in this study. As noted previously, the study was not blinded as to the drug administration groups. There was no obvious way to implement blinding since the bedside nurse is an active participant in the PRN administration arm and the patient is an active participant in both arms. Given that the outcomes have rather clear and agreed on definitions,
Use of PCA following major intracranial surgery

we believe that the bias introduced by lack of blinding was minimal. The possible exception to this would be the pain scores that are self-reported and hence carry additional measurement bias. Given the safety demonstrated in this study, future testing of postcraniotomy analgesic regimens in addition to or in conjunction with PCA may be implemented using blinding.

Although we did not observe any respiratory events requiring naloxone administration or neurological events attributable to opiate administration, these data should be interpreted cautiously as the study was not powered with respect to safety. The observation of no events in the intervention group that contained 29 patients has a 95% CI of 0–11.9%. If all 64 patients in the study are considered, the 95% CI becomes 0–5.6%. If major adverse events are, in fact, rare, demonstrating this in an appropriately powered study could be challenging. If a major adverse event rate of 1% is assumed, 100 patients would be required to achieve a 95% CI of 0–3%, 200 patients for it to be 0–2.5%, and 400 patients for it to be 0–2%. Therefore, a study much larger than the current one would be required to substantiate our findings supporting the safety of intravenous PCA.

Another possible criticism of this study is that we only studied patients undergoing supratentorial craniotomy. We did this because patients undergoing infratentorial surgery experience substantially more pain than those undergoing supratentorial craniotomy and because of the concern that posterior fossa procedures may be more prone to adverse neurological events. Thus, our results may not extend to that population. We are currently conducting a prospective randomized controlled trial to answer this question. Finally, we acknowledge that this was a small study (< 70 patients) powered to detect differences in pain control. Larger studies designed to assess safety are warranted. Additionally, this was a single-institution study, and our hospital has a dedicated NCCU that is highly specialized in the care of neurosurgical and critical neurological patients and is staffed 24 hours a day by a group of neurointensivists as well as its specially educated critical care nurses. Therefore, our results may not be easily duplicated in other environments that are less specialized or in other neurosurgical populations.

Conclusions

Intravenous PCA with fentanyl provides superior pain relief compared to a conventional PRN dosing strategy for the management of supratentorial craniotomy pain and does not appear to increase the incidence of major adverse events. We encourage others to improve the quality of pain relief in this patient population by instituting intravenous PCA.

Disclosure

This study was supported in part by grants from the Jacob and Hilda Blaustein Foundation (Yaster), National Institutes of Health Grant No. NS041865 (Dr. Gottschalk), and Richard J. Trastman endowed chair (Dr. Yaster). The authors report no other conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Acknowledgments

The authors wish to acknowledge the support of Dr. James Campbell, Dr. Henry Brem, Dr. Donlon Long, and Dr. John Ulatowski of the Departments of Neurosurgery and Anesthesiology and Critical Care Medicine of the Johns Hopkins School of Medicine. Additionally, the authors wish to acknowledge the support of the nursing staff of the NCCU of the Johns Hopkins Hospital and the clinical research coordinators of the Department of Anesthesiology and Critical Care Medicine. Finally, this study would not have been possible without the generous financial support of the Jacob and Hilda Blaustein Foundation.

References


J Neurosurg / Volume 111 / August 2009

349
26. Stoneham MD, Cooper R, Quiney NF, Walters FJ: Pain following craniotomy: a preliminary study comparing PCA mor-


Manuscript submitted June 25, 2008. Accepted November 18, 2008. Portions of this work were displayed at an oral presentation for the Society of Critical Care Medicine meeting in Honolulu, Hawaii, on February 3, 2008. Please include this information when citing this paper: published online February 27, 2009; DOI: 10.3171/2008.11.JNS08797.

Address correspondence to: Athir Morad, M.D., Department of Anesthesiology and Critical Care Medicine, Meyer 8-134, Johns Hopkins Hospital, 600 North Wolfe Street, Baltimore, Maryland 21287-4965. email: morada@jhmi.edu.