Scientific Research Publishing

Open Journal of Anesthesiology, 2023, 13, 119-133
https://www.scirp.org/journal/ojanes
ISSN Online: 2164-5558
ISSN Print: 2164-5531

Acute and Persistent Post-Craniotomy Pain: A Prospective 6-Month Follow-Up Questionnaire Study

Pasi Lahtinen[1*], Ville Koskela[1], Pawel Florkiewicz[1], Juha E. Jääskeläinen[2], Timo Koponen[3], Jari Halonen[4], Tadeusz Musialowicz[1]

[1]Department of Anesthesia and Intensive Care Medicine, Kuopio University Hospital, Kuopio, Finland
[2]Department of Neurosurgery of Neuro Centre Unit, Kuopio University Hospital, Kuopio, Finland
[3]Department of Anesthesia and Intensive Care Medicine, North Karelia Central Hospital, Joensuu, Finland
[4]Heart Center Department, Kuopio University Hospital, Kuopio, Finland
Email: *pasi.lahtinen@pshyvinvointialue.fi

How to cite this paper: Lahtinen, P., Koskela, V., Florkiewicz, P., Jääskeläinen, J.E., Koponen, T., Halonen, J. and Musialowicz, T. (2023) Acute and Persistent Post-Craniotomy Pain: A Prospective 6-Month Follow-Up Questionnaire Study. *Open Journal of Anesthesiology*, **13**, 119-133.
https://doi.org/10.4236/ojanes.2023.136012

Received: May 11, 2023
Accepted: June 25, 2023
Published: June 28, 2023

Abstract

Introduction: The incidence of acute pain after craniotomy differs remarkably in previous studies, and the prevalence of persistent pain is not precisely known. We conducted 6-month follow-up surveys on the incidence and intensity of acute and persistent pain after elective craniotomy. **Methods:** We carried out a prospective cohort study via a series of structured questionnaires to record acute pain intensity preoperatively and postoperatively, and the incidence of persistent pain 3 and 6 months after a craniotomy in a tertiary care center. Patients scheduled for elective craniotomy were interviewed the day before surgery, postoperatively before discharge from the hospital, and 3 and 6 months after surgery. Pain was assessed on a numeric rating scale (0 - 10) at rest and movement, as well as expectations of pain before surgery, efficacy of pain therapy, and satisfaction with pain treatment. The incidence of adverse events, sleep time and interruptions caused by pain, different pain types, and drugs used for pain treatment were also recorded. **Results:** A total of 152 patients were enrolled in the study and completed the preoperative questionnaire; 123 (81%) completed postoperative questionnaire and 108 (72%) completed the 3- and 6-month follow-ups. The average pain score at the time of the postoperative questionnaire was moderate, 4 at rest and 5 upon movement. The percentage of patients experiencing mild pain at rest and upon movement was 52% and 49%, and moderate pain was 15% and 16%, respectively. Severe postoperative pain was detected in 5% and 8% of patients at rest and upon movement, respectively. Three months after surgery, 6% of patients reported mild pain at rest, 3% moderate pain at rest, and 1% severe pain at rest. Persistent mild and moderate pain at rest after 6 months was re-

ported by 3% and 1% of patients, respectively. The most common adverse events were postoperative nausea and vomiting (11%) and abdominal discomfort (8%). During postoperative pain treatment in the intensive care unit or post-anesthesia care unit, 92% of patients received acetaminophen, 88% fentanyl, and 24% oxycodone. During neurosurgical ward care, ibuprofen was used in 61% of patients. Satisfaction with analgesia was high throughout the study period with a median satisfaction score of 9 postoperatively and 10 at 3 and 6 months on the 0 - 10 scale. **Conclusion:** The findings indicate that most patients experience moderate or mild pain after craniotomy, but patient satisfaction with pain treatment is high. Persistent pain after 3 and 6 months is rare and mild in nature.

Keywords

Craniotomy, Acute Pain, Persistent Pain, Pain Treatment, Adverse Events, Neurosurgery

1. Introduction

For many years, it was believed that patients need fewer analgesics after craniotomy procedures compared to other surgical treatments because of a retrospective study [1] in which pain after craniotomy was estimated as mild with low analgesic requirements. This study was challenged by prospective studies, which revealed that approximately 60% of patients undergoing elective intracranial surgery had moderate to severe pain that was often treated inadequately [2] [3]. These studies led to better pain treatment with a multimodal and individually tailored approach [4]. Insufficient treatment of postoperative pain after craniotomy can predispose the patient to persistent pain, which is a major problem for the patient and an economic challenge for public healthcare. Persistent pain after craniotomy may lead to low quality recovery and increased healthcare cost. The International Association for the Study of Pain defines chronic pain as pain that persists after the normal tissue healing time, usually after 3 months [5]. The other criteria for chronic pain are pain developing after the surgical procedure, the pain that is a continuation of acute post-surgery pain, or pain that develops after the asymptomatic period. Pain should be within the surgical side and other causes of pain, such as infection or malignancy, should be excluded. The International Headache Society published a classification of post-craniotomy headache and the cut-off for persistent headache attributed to a craniotomy is also 3 months [6] [7]. Only a few studies have examined persistent pain after craniotomy [8] [9] [10], and there is a great discrepancy between studies in the incidence of persistent pain.

We carried out a prospective, longitudinal series of questionnaires preoperatively, in the immediate postoperative days, and 3 and 6 months after intracranial surgery. The aim of the present study was to evaluate the prevalence of acute and persistent postsurgical pain after craniotomy within the surgical site. Patient

expectations of pain before surgery and satisfaction with the pain treatment, the efficacy of current pain therapy, and relevant adverse events were also recorded.

2. Patients and Methods

2.1. Study Design and Participants

All patients were informed of the study preoperatively and provided written consent. Patients were considered eligible for the study when scheduled for elective craniotomy between 18 and 70 years of age. Patients who were unable to fill out the form or verbally answer the questions or died during follow-up were excluded. When the research physician and coordinating research nurse were available, all eligible patients during the 2-year period were asked to participate.

2.2. Data Collection

Patients scheduled for elective craniotomy were interviewed using the structured questionnaire [11] four times: the day before surgery, postoperatively before discharge from the hospital, and 3 and 6 months after surgery. Postoperative questionnaires were answered within the first week after surgery depending on the recovery of the patient with guidance from the study nurse if requested. Persistent postsurgical pain was evaluated 3 and 6 months after surgery using a standardized telephone interview by a research physician (T.M. or P.F.). Each standardized questionnaire sheet included seven questions and six pictures of the head for pain localization.

Pain was assessed on an 11-point numeric rating scale (NRS) at rest and upon movement [12]. Zero indicated "no pain" and 10 "worst pain". Pain was classified as mild with a score of 1 - 3, moderate with a score of 4 - 6, and severe with a score of 7 - 10. Preoperatively, patients were asked how much pain they anticipated after surgery and the pain intensity they were prepared to tolerate without pain medication. Patients were asked to evaluate their satisfaction with pain treatment on an NRS of 0 (very dissatisfied) to 10 (very satisfied). Patients were asked to evaluate how well pain medication alleviated their pain on a NRS of 0 (no pain relief) to 10 (1 - 3 poor pain relief; 4 - 6 moderate pain relief; 7 - 10 good pain relief). Patients were asked to mark the pain location, and the type of pain they anticipated preoperatively and experienced postoperatively on pictures representing a human head from four angles. Four different types of pain were given to choose from: sharp pain, burning sensation, hypersensitivity, and numbness. The possible adverse effects of pain medications, such as gastric complaints, fatigue, and nausea and vomiting, were also recorded. Patients were also asked preoperatively to approximate their normal sleeping time and number of awakenings during the night. Postoperative sleeping times and sleep disturbances were reported in all postoperative questionnaires.

2.3. Anesthesia and Postoperative Pain Treatment

Anesthesia was administered according to a standardized departmental protocol

for neurosurgical patients. Oral premedication included 0.15 - 0.25 mg·kg^{-1} diazepam, up to 10 mg and 15 mg·kg^{-1} acetaminophen, up to 2 g. Anesthesia was induced using 0.1 mg·kg^{-1} midazolam, 2 μg·kg^{-1} fentanyl, and 2 mg·kg^{-1} propofol. Neuromuscular blockade was achieved with 0.65 mg·kg^{-1} rocuronium or 0.15 mg·kg^{-1} cis-atracurium and was monitored throughout the surgery with stimulation mode train-of-four (TOF; S/5™ monitor, GE, Healthcare, Helsinki, Finland). Total intravenous anesthesia (TIVA) was used; anesthesia was maintained with continuous infusion of propofol (2 - 4 mg·kg^{-1}·min^{-1}) and remifentanil (0.1 - 0.3 μg·kg^{-1}·min^{-1}). Routine monitoring included five-channel electrocardiogram (ECG), radial artery pressure, capnography, pulse oximetry, central temperature, and continuous monitoring of end-tidal carbon dioxide. Anesthesia depth was monitored continuously by Entropy monitoring (M-Entropy™, GE, Finland) with a target range of 40 - 60.

A cranial stabilization (Mayfield cramp) and head fixation system was used routinely in all patients. Scalp infiltration at the incision site of 1% lidocaine with adrenalin in the beginning and at the end of the procedure was performed in all patients [13]. The standard craniotomy technique was used with the scalp muscle turned as a single layer flap, preserving the superficial arteries. The skin incision was closed with surgical staples.

Anesthetics were discontinued in the operating room at the end of the surgery and neuromuscular blockade reversed using neostigmine. Remifentanil was discontinued before extubation and 1 - 2 μg·kg^{-1} intravenous fentanyl administered before transporting the patient to the intensive care unit (ICU) or post-anesthesia care unit (PACU). The routine pain management after surgery was not influenced by the investigators. Acetaminophen (3 g per day) was continued postoperatively, with intravenous fentanyl (1 - 2 μg·kg^{-1}) and intravenous oxycodone at the patient's request. Pain medication at the neurosurgical ward included 1 g acetaminophen three times daily, oral ibuprofen and intramuscular oxycodone as requested [14]. Pain medication consumption was recorded during the ICU or PACU period and in the neurosurgical ward in the electronic medical records system (Centricity™ Critical Care Clinisoft version 8.1, GE Healthcare and Uranus™, CGI, Finland). The average ICU and neurosurgical ward length of stay (LOS) was recorded. Before hospital discharge, all patients received a prescription for acetaminophen and non-steroidal anti-inflammatory analgesic (NSAID; ibuprofen).

2.4. Statistical Analysis

No formal sample size calculations were performed. We determined that approximately 100 patients completing all questionnaires would give a representative picture of typical craniotomy patients. Results are given as median (range) or number of patients (percentage of patients) as appropriate. Chi-squared was used for dichotomous variables. Acute and persistent pain scores were analyzed by two-way analysis of variance (ANOVA) for repeated measurements with

mixed design with Bonferroni correction. $P < 0.05$ was considered significant. All statistical analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA).

3. Results

A total of 545 elective craniotomies were performed in our institution during the 2-year study period; 152 patients were included in the study and completed the preoperative questionnaire. Of these patients, 123 (81%) completed the postoperative questionnaire and 108 (72%) completed the 3 and 6-month follow-ups. The study flowchart is presented in Figure 1. Most patients underwent craniotomy due to intracranial tumors or vascular aneurysms. Demographic data are presented in Table 1. Eighty-five patients were treated postoperatively in the ICU and 23 in the PACU. The average ICU LOS was 22 h. After treatment in the ICU and PACU, patients were transferred to the neurosurgical ward until they were discharged home or to a lower-level hospital or rehabilitation center. The average neurosurgical ward LOS was 5 days (range 2 - 9 days).

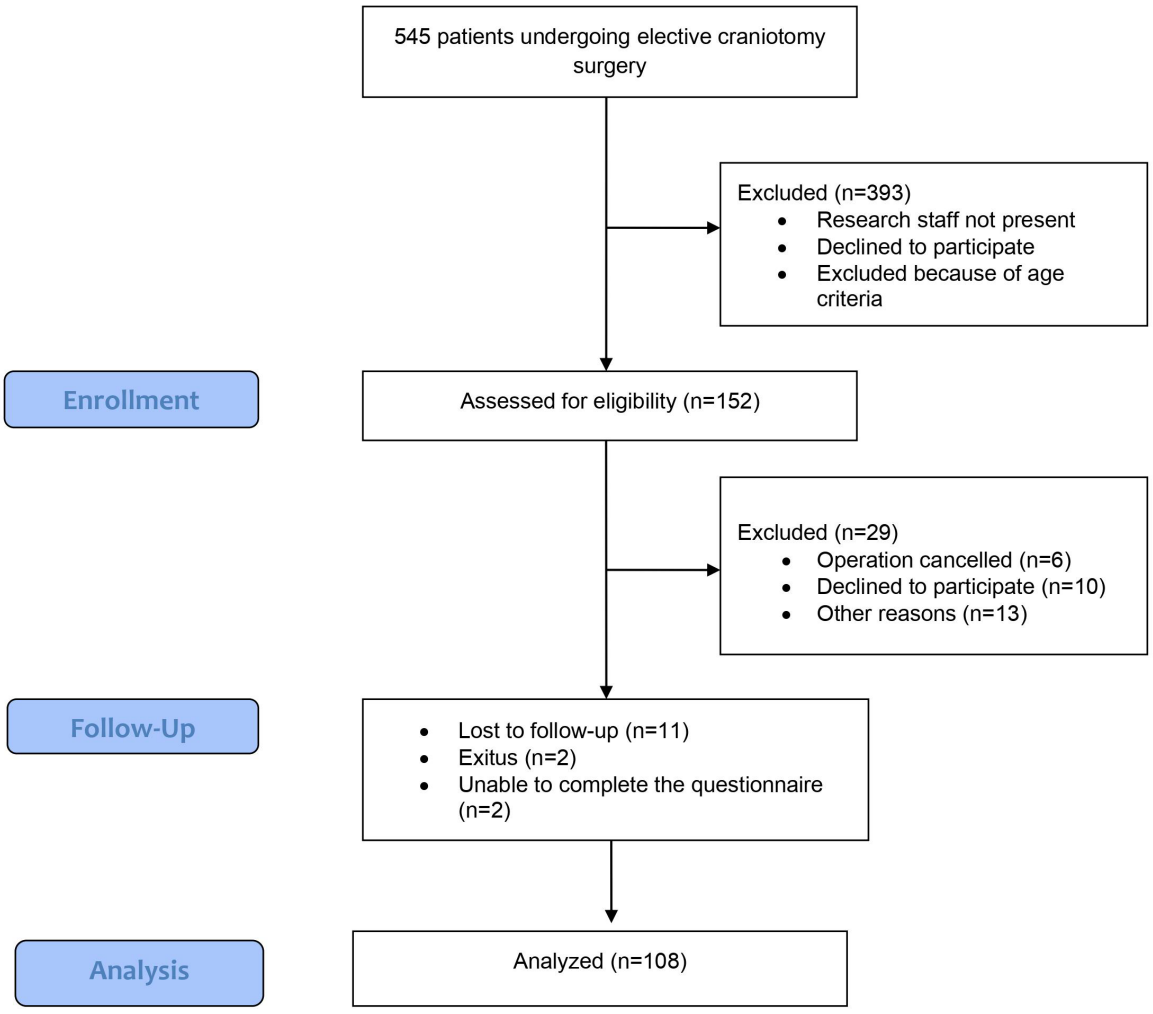

Figure 1. Study flowchart.

Table 1. Clinical characteristics and perioperative data of study population.

Gender (n) Male/Female	45/63
Age (years)	49 ± 13
Height (cm)	170 ± 9
Weight (kg)	79 ± 16
BMI (kg/m^2)	27 ± 5
Diagnosis (n)	
Tumor	60
Aneurysm	34
Epilepsy	10
Other	4
Surgical approach (%)	
Temporal	41
Frontal	32
Occipital	13
Parietal	8
Others	6
ICU or PACU length of stay (hour)	22 ± 8
Neurosurgical ward length of stay (days)	5 ± 4

Values are mean ± SD or number of patients, BMI—body mass index. ICU—Intensive Care Unit; PACU—Post-operative Care Unit.

3.1. Patient Expectations

On the preoperative questionnaire, the median pain that patients were willing to tolerate without pain medication was moderate at rest and upon movement. The maximum anticipated postoperative pain was worse at rest (NRS score 7) than pain patients were willing to tolerate without pain medication (NRS score 6, $P < 0.01$ (Table 2). Half of the patients anticipated adverse effects of pain medication. The most common anticipated adverse effects were gastric complaints (22%), fatigue (18%), and nausea and vomiting (17%). The normal median sleeping time was 7 hours. Preoperatively, patients claimed to normally wake up once per night.

3.2. Postoperative Questionnaire before Discharge from Hospital

Postoperatively, the percentage of patients experiencing no pain, mild pain, moderate pain, and severe pain at rest was 28%, 52%, 15%, and 5%, respectively. Upon movement, the percentage of patients experiencing no pain, mild pain, moderate pain, and severe pain was 26%, 49%, 16%, and 8%, respectively. The average pain score at the time of the postoperative questionnaire was 4 at rest and 5 upon movement (Table 3). At the time of the postoperative questionnaire, five and nine patients experienced severe pain at rest and upon movement, respectively (Figure 2(a) and Figure 2(b)).

Table 2. Preoperative expected intensity of pain after craniotomy at rest and upon movement on an 11-point numeric rating scale (0 = no pain, 10 = worst pain). Values are median (range).

	At rest	on movement
Pain willing to accept without medication	5 (0 - 10)	5 (0 - 10)
Expected-worst	4 (0 - 10)	7 (0 - 10)
Expected-average	4 (0 - 10)	5 (0 - 10)

Table 3. Intensity of pain after craniotomy at rest and upon movement on an 11-point numeric rating scale (0 = no pain, 10 = worst pain).

	At rest	*P* value	On movement	*P* value
Average postoperative	4 (0 - 10)		5 (0 - 10)	
The worst postoperative	7 (0 - 10)		6.5 (0 - 10)	
3 months	0 (0 - 7)	<0.001	0 (0 - 7)	<0.001
6 months	0 (0 - 6)	0.020	0 (0 - 6)	0.008

During the hospital stay, 71% of patients woke up because of pain at least once a night. The median number of waking times was 2. Fifty-three patients were expecting an adverse effect related to postoperative pain medication; 34% and 7% of the patients who were and were not expecting an adverse effect preoperatively had an adverse effect postoperatively. The most common adverse effects were nausea and vomiting (11%) and gastric complaints (8%).

The efficacy of pain relief with medication was better than expected; the median score was 9 compared to the expected pain relief value of 7 ($P < 0.001$). Eighty-seven patients (80%) had good pain relief (NRS score > 6), but 6 patients (5%) rated the efficacy of pain medication as poor.

3.3. Postoperative Pain Treatment

During the postoperative pain treatment in the ICU or PACU, 92% of patients received acetaminophen, 88% received fentanyl, and 24% received oxycodone (**Table 4**). During neurosurgical ward care, ibuprofen was used in 61% of patients.

3.4. Persistent Pain

The median pain scores 3 months after craniotomy were 0 at both rest and upon movement (**Table 3**). We found a significant decline in pain scores up to 3 months ($P < 0.001$). After 3 months, 6% of the patients reported mild, 3% moderate, and 1% severe pain at rest (**Figure 2(a)**). The incidence of persistent mild and moderate pain at rest was 3% and 1% after 6 months (**Figure 2(b)**). Satisfaction with analgesia was high throughout the study period, with median satisfaction scores of 9 postoperatively and 10 at both 3 and 6 months. The median efficacy score for pain medications at 3 and 6 months was 10. At 3 and 6 months,

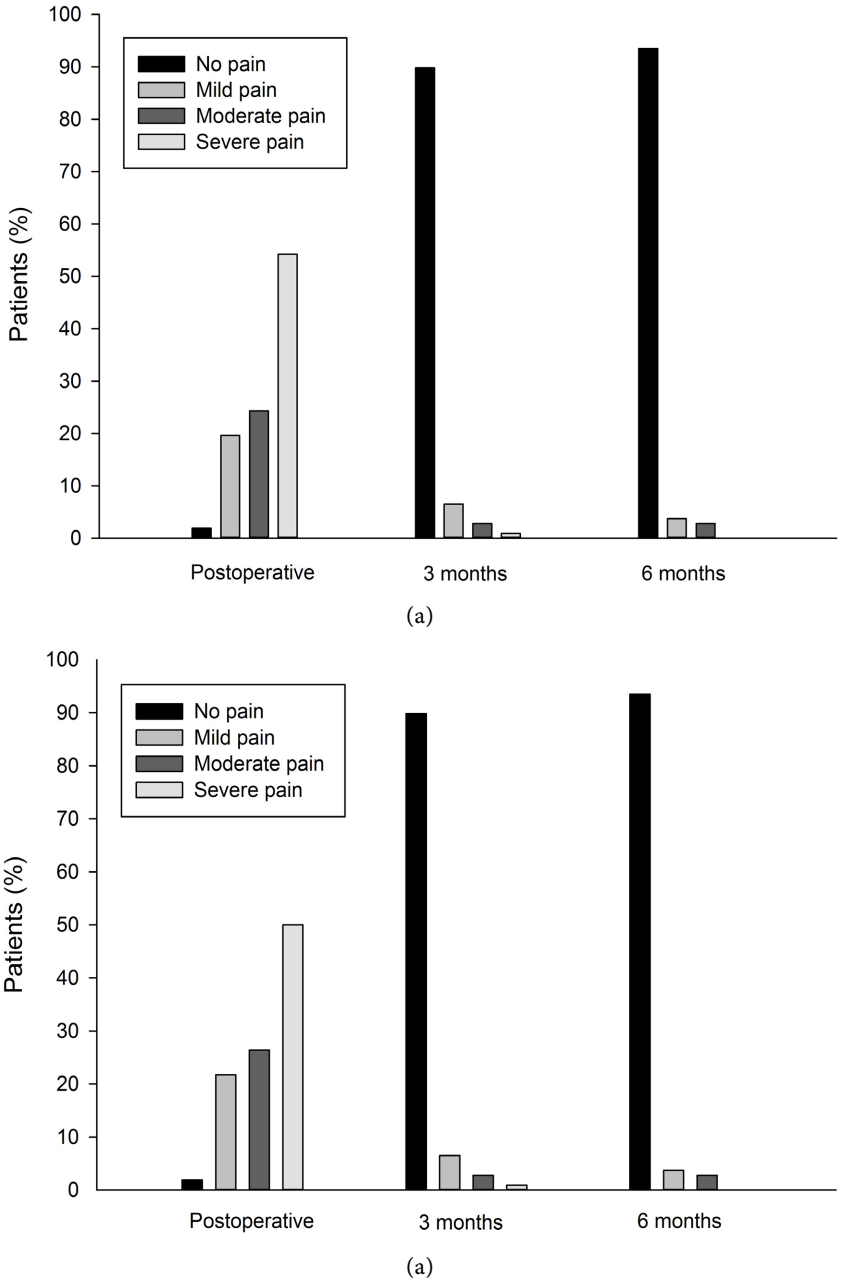

Figure 2. Incidence and intensity of acute postoperative and chronic pain (3 and 6 months) after craniotomy. (a) At rest and (b) upon movement. Incidence is presented as a percent of patients' suffering pain. Intensity of pain was determined on a numeric rating scale (NRS): no pain = 0; mild pain = 1 - 3; moderate pain = 4 - 6; severe pain = 7 - 10. (a) Pain at rest; (b) Pain at move.

only 3 and 1 patients, respectively, rated the efficacy as poor (NRS < 4). At 3 and 6 months, 26% and 8% of patients, respectively, reported still waking up because of pain at least once a night. Temporomandibular joint dysfunction was common at 3 months, as 12 (11%) patients complained of these problems. At 6 months, only two patients complained of dental problems and two patients had consulted a dentist.

Table 4. Postoperative pain medication.

Paracetamol (g)	99 (92%)	2.2 ± 1.0	2.1 ± 1.0	101 (94%)	13 ± 6.3	2.5 ± 0.9
Fentanyl (μg)	95 (88%)	274 ± 228	260 ± 208	0 (0%)	0	0
Oxycodone (mg)	26 (24%)	15 ± 5	15 ± 5	52 (48%)	13 ± 22	2.5 ± 3.9
Ibuprofen (g)	0 (0%)	0	0	66 (61%)	3.6 ± 4.3	0.73 ± 0.82
Ketoprofen (mg)	3 (2.7%)	100	100	0 (0%)	0	0

The amount of analgesics administered during postoperative care in Intensive Care Unit (ICU) or Post-operative Care Unit (PACU) and during neurosurgical ward care. Values are mean (±SD).

3.5. Different Types of Pain

In the postoperative period, most of the patients perceived pain related to the surgical wound in the temporal (41%) and frontal (32%) region, and less frequently in other regions (occipital 13%, parietal 8%, and other 6%). Sharp pain sensation in the incision site was the most common pain in the postoperative period and was present in 68% of patients, followed by tenderness (14%). Numbness was most common at the 3- and 6-month follow-ups (38% and 33%, respectively).

A supratentorial surgical approach was used in 85.2% of the patients and infratentorial in 15%.

3.6. Pain Treatment 3 and 6 Months after Surgery

At 3 months, 14 (13%) patients occasionally used NSAIDs and acetaminophen. Two patients were using paracetamol-codeine tablets or tramadol sporadically. One patient still needed oxycodone at 3 months. At 6 months, 15 (14%) patients were using NSAIDs and acetaminophen sporadically. Two patients were using acetaminophen-codeine tablets.

4. Discussion

In this prospective follow-up study, we were able to demonstrate that patients undergoing craniotomy experience mostly mild, if any, pain postoperatively, but one-fifth of the patients suffered moderate to severe pain after surgery. However, the average pain was mostly mild to moderate at most, and many patients still experienced severe pain at worst, waking up many times during the night due to pain postoperatively.

Pain after craniotomy has many disadvantages for the patient´s recovery after neurosurgery. Poorly controlled pain may lead to agitation, restlessness, vomiting, and hypertension and may predispose the patient to postoperative bleeding and persistent postoperative pain after surgery. In the current study, persistent postoperative pain 3 and 6 months after craniotomy was rare. Only 4% of patients had moderate to severe pain on these occasions, but temporo-mandibular dysfunction was more common, presumably because the surgical approach was most commonly temporal. Limited mouth opening and temporal muscle atro-

phy have been shown to occur after a craniotomy [15]. The main cause of limited mouth opening is temporal muscle shortening and scarring [16]. Our data showed that a considerable portion of patients had temporomandibular joint dysfunction after craniotomy 3 months after surgery. However, a modified surgical approach may not be an easy path forward in this regard, as reported previously [17].

Different timing of questionnaires, various types and locations of surgery, ambiguous anesthesia methods, and inadequate reporting of pain therapy make it difficult to compare the pain intensity between the current and previous studies in the literature. When comparing previous investigations after craniotomy, post-surgical pain was less intensive in our study. There may be several reasons for the difference. First, we did not inquire about postoperative pain immediately after surgery or on the first postoperative days. Post-craniotomy pain decreases significantly over time after surgery, similar to other operative procedures [2] [18] [19] and this was also the case in our study. Our assessment was performed during the first week after surgery before leaving the hospital, which may have diminished the pain evaluation compared to an inquiry immediately after surgery. In addition, the surgical approach was supratentorial in most of our patients, and infratentorial procedures have been reported to induce more severe pain and require more analgesics after surgery [2] [20] [21]. Furthermore, patients received strong opioids more liberally in the current study than in studies with more intensive pain after craniotomy [2] [22]. Ninety percent of our patients received fentanyl or oxycodone during their ICU or PACU stay, whereas 50% of patients in the neurosurgical ward still received oxycodone for analgesia. However, Gottshalk *et al.* [2] reported that only 37% and 5% of patients received intravenous opioids during the first and second postoperative day, respectively. Unfortunately, many studies do not describe the analgesic medication in detail or report the use of only weak opioids postoperatively [3] [19] [21] [23]. Finally, our patient cohort was anesthetized by TIVA, which has been reported to result in lower pain scores after craniotomy compared to sevoflurane [24].

All of these factors combined may have resulted in the lower pain scores in our study compared to previous studies. It seems that strong opioids are needed after craniotomy, as well as after other surgical operations, in order to guarantee a satisfying level of analgesia. The risk of overly deep sedation and respiratory depression seems to be low, at least in the ICU and PACU, where opioids can be titrated, though our study was not designed to monitor these adverse events specifically.

Our results are in agreement with other prospective studies of acute pain after craniotomy. In a small study [25] of 37 patients 48 h after craniotomy, 60% still suffered from pain, and in 20% of the patients, the pain was moderate to severe, similar to the figures in our study. In the 53 patients with intracranial aneurysm [23] who underwent surgical treatment, the incidence of postoperative pain during hospitalization (24 h - 7 days) was almost the same as in our study (55%).

Mordhorst *et al.* [3] evaluated the intensity of postoperative pain after craniotomy in 256 patients during the first 24 hours and reported that 32% of patients had mild pain, 44% moderate pain, and 11% severe pain at rest compared to 52%, 15% and 5% with mild, moderate and severe pain in our study. The lower figures in our study most likely reflect differences in the timing of the questionnaire because pain medication was administered almost as liberally as in our study, with 70% of patients receiving piritramide and 73% receiving non-opioid analgesics. The pain intensity in this study was higher if patients received sevoflurane anesthesia compared to TIVA, and the probability of pain was increased by 147% with sevoflurane [3].

Persistent pain was rare in our study compared to earlier studies. In the current study, 6% of patients had mild pain and 4% moderate to severe pain at 3 months, and 4% of patients had mild to moderate pain 6 months after the operation. Miscellaneous surgical operations seem to result in persistent pain in 5% - 50% of patients, with pain being severe in 2% - 10% of those patients [26]. The incidence of persistent post-craniotomy headache in our study differed largely from previous investigations [27]. However, there have been very few prospective follow-up studies of persistent pain after craniotomy. The reported incidence of persistent pain after craniotomy is 18% - 29% after supratentorial craniotomy, but much higher figures have been reported after acoustic neuroma resection, with an incidence of 33% - 44% [28]. Acoustic neuroma patients were not included in the current study. In a retrospective study of a patient population similar to ours [29], one-fifth of the patients had persistent pain 3 to 6 months after surgery. Similarly, Kaur found a 17% incidence of persistent postoperative headache 2 months after anterior temporal lobectomy for epilepsy [8]. The difference in the incidences between our study and previous studies are likely due to differences in the surgical approach, different definitions of persistent pain, and the retrospective nature of many studies. In any case, the incidence of persistent post-craniotomy pain found in the current study seems reassuringly low. We are confident of the robust nature of our results because one of the authors personally contacted every patient involved by phone. Therefore, the figures in the current study seem to be reliable and the incidence of persistent post-craniotomy pain appears to be rather low, though comparable to previous studies, such as that reported for persistent pain after sternotomy [11].

Postoperative nausea and vomiting is another common problem after craniotomy, as three-fourths of patients experience it without prophylaxis and every other if ondansetron is prophylactically administered [30] [31]. In the present study, only 11% of patients reported experiencing postoperative nausea and vomiting at the time of the postoperative questionnaire, presumably because of liberal administration of antiemetics, such as ondansetron, in the ICU and neurosurgical ward [32].

The current study has several strengths. First, we studied postoperative pain prospectively in a relatively large number of patients and followed the patients rigorously up to 6 months after surgery. In addition, postoperative pain medica-

tions were recorded, as well as anesthesia methods, indications, and surgical approach.

However, this study has also some limitations. Firstly, this inquiry was a single center study and the timing of the questionnaire did not allow us to evaluate the postoperative pain in the first 24 hours after surgery, which presumably decreased the intensity of pain compared to inquiries accomplished immediately after surgery [18]. Furthermore, persistent pain was rare in our cohort and we were not able to identify the possible risk factors for persistent pain. The evaluation of persistent pain was limited to 6 months postoperatively.

Future studies should be conducted to recognize patients at risk of developing persistent postoperative pain after craniotomy. Patients were highly satisfied with the pain therapy, even though they experienced moderate to severe pain during the first postoperative days. Our results highlight the need to assess pain quantitatively after craniotomy and treat it actively, with strong opioids if necessary, and indicate that we can inform patients scheduled for craniotomies to expect moderate to severe pain only during the early recovery period and that persistent pain is rare.

5. Conclusion

Patients experienced mostly mild or no pain after craniotomy, but one-fourth of the patients still experienced moderate to severe pain and needed strong opioid medication after surgery. Persistent pain was rare after 6 months. According to our results, post-craniotomy pain may be less intense than previously reported and very seldom results in persistent pain except in special types of surgery.

Acknowledgements

The authors wish to thank research nurses Petri Toroi and Katariina Helin for their assistance in data acquisition. The study was supported by a research grant to Dr. Jari Halonen from the Government Research Foundation of Finland and a grant from Kuopio University Hospital Research Fund (16032022) for Dr. Pawel Florkiewicz.

Data Availability

The unidentified raw data supporting the conclusions of this article will be made available upon request to the corresponding author.

Ethical Approval

The Research Ethics Committee of the Northern Savo Hospital District approved the research protocol (protocol number 113/10), and the study was conducted in accordance with the latest revision of the Declaration of Helsinki.

Consent Statement

All patients were informed of the study preoperatively and provided written

consent.

Author Contributions

P.L. conceived the study, helped design the study, recruited and anesthetized patients in the study, helped with the data analysis, reviewed, and interpreted the data, and contributed to writing the manuscript. V.K. verified and analyzed the data, reviewed statistics and interpreted the data, prepared the pictures and wrote the first draft of the manuscript. P.F. recruited patients for the study, participated in collecting the follow-up data, and was involved in the data analysis and revised the manuscript. J.J. helped design the study, recruited patients for the study, was involved in the surgical operations and helped analyze the data, and contributed to writing the manuscript. T.K. prepared the pictures, reviewed statistics, and contributed to writing the manuscript. J.H. helped with the data analysis, reviewed, and interpreted the data, contributed to write the final version of manuscript. T.M. helped in the study design, recruited patients for the study, anesthetized patients for study, collected the follow-up data and analyzed and scrutinized the original study data, and helped write the first draft of the manuscript. All the authors read and approved the final version of the manuscript.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

[1] Dunbar, P.J., Visco, E. and Lam, A.M. (1999) Craniotomy Procedures Are Associated with Less Analgesic Requirements than Other Surgical Procedures. *Anesthesia & Analgesia*, **88**, 335-340. https://doi.org/10.1213/00000539-199902000-00021

[2] Gottschalk, A., Berkow, L.C., Stevens, R.D., Mirski, M., Thompson, R.E., White, E.D., Weingart, J.D., Long, D.M. and Yaster, M. (2007) Prospective Evaluation of Pain and Analgesic Use following Major Elective Intracranial Surgery. *Journal of Neurosurgery*, **106**, 210-216. https://doi.org/10.3171/jns.2007.106.2.210

[3] Mordhorst, C., Latz, B., Kerz, T., Wisser, G., Schmidt, A., Schneider, A., Jahn-Eimermacher, A., Werner, C. and Engelhard, K. (2010) Prospective Assessment of Postoperative Pain after Craniotomy. *Journal Neurosurgical Anesthesiol*ogy, **22**, 202-206. https://doi.org/10.1097/ANA.0b013e3181df0600

[4] Sherman, M., Sethi, S., Hindle, A.K. and Chanza, T. (2020) Multimodal Pain Management in the Perioperative Setting. *Open Journal of Anesthesiology,* **10**, 47-71. https://doi.org/10.4236/ojanes.2020.102005

[5] Mills, S.E.E., Nicolson, K.P. and Smith, B.H. (2019) Chronic Pain: A Review of Its Epidemiology and Associated Factors in Population-Based Studies. *British Journal of Anaesthesia*, **123**, E273-E283. https://doi.org/10.1016/j.bja.2019.03.023

[6] Headache Classification Committee of the International Headache Society (IHS) (2018) The International Classification of Headache Disorders, 3rd Edition. *Cepha-*

lalgia, **38**, 1-211. https://doi.org/10.1177/0333102417738202

[7] Werner, M.U. and Kongsgaard, U.E. (2014) Defining Persistent Post-Surgical Pain: Is an Update Required? *British Journal of Anaesthesia,* **113**, 1-4. https://doi.org/10.1093/bja/aeu012

[8] Kaur, A., Selwa, L., Fromes, G. and Ross, D.A. (2000) Persistent Headache after Supratentorial Craniotomy. *Neurosurgery,* **47**, 633-636. https://doi.org/10.1227/00006123-200009000-00020

[9] Rocha-Filho, P., Gherpelli, J., de Siqueira, J. and Rabello, G. (2010) Post-Craniotomy Headache: A Proposed Revision of IHS Diagnostic Criteria. *Cephalalgia*, **30**, 560-566. https://doi.org/10.1111/j.1468-2982.2009.02010.x

[10] Rocha-Filho, P.A. (2015) Post-Craniotomy Headache: A Clinical View with a Focus on the Persistent Form. *Headache*, **55**, 733-738. https://doi.org/10.1111/head.12563

[11] Lahtinen, P., Kokki, H. and Hynynen, M. (2006) Pain after Cardiac Surgery: A Prospective Cohort Study of 1-Year Incidence and Intensity. *Anesthesiology*, **105**, 794-800. https://doi.org/10.1097/00000542-200610000-00026

[12] Gerbershagen, H.J., Rothaug, J., Kalkman, C.J. and Meissner, W. (2011) Determination of Moderate-to-Severe Postoperative Pain on the Numeric Rating Scale: A Cut-Off Point Analysis Applying Four Different Methods. *British Journal of Anaesthesia*, **107**, 619-626. https://doi.org/10.1093/bja/aer195

[13] Biswas, B.K., Bithal, P.K. and Parmod, K. (2003) Preincision 0.25% Bupivacaine Scalp Infiltration and Postcraniotomy Pain: A Randomized Double-Blind, Placebo-Controlled Study. *Journal of Neurosurgical Anesthesiology*, **15**, 234-239. https://doi.org/10.1097/00008506-200307000-00011

[14] Lee, R.M., Lim, B.C.L., Chong, C.T. and Lim, M.P.P. (2020) Comparison of the Efficacy of Oral Oxycodone and Oral Codeine in the Treatment of Post-Craniotomy Pain—A Randomized, Double-Blind Trial. *Open Journal of Anesthesiology,* **10**, 80-88. https://doi.org/10.4236/ojanes.2020.103007

[15] Brazoloto, T.M., de Siqueira, S.R., Rocha-Filho, P.A., Figueiredo, E.B., Teixeira, M.J. and de Sigueira, J.T.T. (2017) Post-Operative Orofacial Pain, Temporomandibular Dysfunction and Trigeminal Sensitivity after Recent Pterional Craniotomy: prEliminary Study. *Acta Neurochirurgica,* **159**, 799-805. https://doi.org/10.1007/s00701-017-3137-9

[16] Nitzan, D.W., Azaz, B. and Constantini, S. (1992) Severe Limitation in Mouth Opening following Transtemporal Neurosurgical Procedures: Diagnosis, Treatment, and Prevention. *Journal of Neurosurgery*, **76**, 623-625. https://doi.org/10.3171/jns.1992.76.4.0623

[17] Garzon-Muvdi, T., Jackson, C., See, A.P., Woodworth, G.F. and Tamargo, R.J. (2015) Preservation of the Greater Occipital Nerve during Suboccipital Craniectomy Results in a Paradoxical Increase in Postoperative Headaches. *Neurosurgery,* **76**, 435-440. https://doi.org/10.1227/NEU.0000000000000625

[18] De Oliveira Ribeiro, M.D.C., Pereira, C.U., Sallum, A.M., Martins-Filho, P.R., Desantana, J.M., da Silva Nunes, M. and Hora, E.C. (2013) Immediate Post-Craniotomy Headache. *Cephalalgia*, **33**, 897-905. https://doi.org/10.1177/0333102413479833

[19] Klimek, M., Ubben, J.F., Ammann, J., Borner, U., Klein, J. and Verbrugge, S.J.C. (2006) Pain in Neurosurgically Treated Patients: A Prospective Observational Study. *Journal of Neurosurgery*, **104**, 350-359. https://doi.org/10.3171/jns.2006.104.3.350

[20] Verchere, E., Grenier, B., Mesli, A., Siao, D., Sesay, M. and Maurette, P. (2002) Postoperative Pain Management after Supratentorial Craniotomy. *Journal of Neurosurgical Anesthesiology*, **14**, 96-101.

https://doi.org/10.1097/00008506-200204000-00002

[21] Thibault, M., Girard, F., Chouinard, R., Boudreault, D., Ruel, M. and Moumdjian, R. (2007) Craniotomy Site Influences Postoperative Pain following Neurosurgical Procedures: A Retrospective Study. *Canadian Journal of Anesthesia*, **54**, 544-548. https://doi.org/10.1007/BF03022318

[22] Tsaousi, G.G., Logan, S.W. and Bilotta, F. (2017) Postoperative Pain Control Following Craniotomy: A Systematic Review of Recent Clinical Literature. *Pain Practice*, **17**, 968-981. https://doi.org/10.1111/papr.12548

[23] Magalhaes, J.E., Azevedo-Filho, H.R. and Rocha-Filho, P.A. (2013) The Risk of Headache Attributed to Surgical Treatment of Intracranial Aneurysms: A Cohort Study. *Headache*, **53**, 1613-1623. https://doi.org/10.1111/head.12165

[24] Chui, J., Mariappan, R., Mehta, J., Manninen, P. and Venkatraghavan, L. (2014) Comparison of Propofol and Volatile Agents for Maintenance of Anesthesia during Elective Craniotomy Procedures: Systematic Review and Meta-Analysis. *Canadian Journal of Anesthesia*, **6**, 347-356. https://doi.org/10.1007/s12630-014-0118-9

[25] De Benedittis, G., Lorenzetti, A., Migliore, M., Spagnoli, D., Tiberio, F. and Villani, R. (1996) Postoperative Pain in Neurosurgery: A Pilot Study in Brain Surgery. *Neurosurgery*, **38**, 466-470. https://doi.org/10.1227/00006123-199603000-00008

[26] Kehlet, H., Jensen, T.S. and Woolf, C.J. (2006) Persistent Postsurgical Pain: Risk Factors and Prevention. *The Lancet*, **367**, 1618-1625. https://doi.org/10.1016/S0140-6736(06)68700-X

[27] Grodofsky, S. (2016) Chronic Pain in Neurosurgery. *Anesthesiology Clinics*, **34**, 479-495. https://doi.org/10.1016/j.anclin.2016.04.003

[28] Flexman, A.M., Ng, J.L. and Gelb, A.W. (2010) Acute and Chronic Pain following Craniotomy. *Current Opinion in Anesthesiology*, **23**, 551-557. https://doi.org/10.1097/ACO.0b013e32833e15b9

[29] Gee, J.R., Ishaq, Y. and Vijayan, N. (2003) Postcraniotomy Headache. *Headache*, **43**, 276-278. https://doi.org/10.1046/j.1526-4610.2003.03053.x

[30] Latz, B., Mordhorst, C., Kerz, T., Schmidt, A., Schneider, A., Wisser, G., Werner, C. and Engelhard, K. (2011) Postoperative Nausea and Vomiting in Patients after Craniotomy: Incidence and Risk Factors. *Journal of Neurosurg*ery, **114**, 491-496. https://doi.org/10.3171/2010.9.JNS10151

[31] Uribe, A.A., Stoicea, N., Echeverria-Villalobos, M., Todeschini, A.B., Esparza G.A., Folea, A.R. and Bergese, S.D. (2019) Postoperative Nausea and Vomiting after Craniotomy: An Evidence-Based Review of General Considerations, Risk Factors, and Management. *Journal of Neurosurgical Anesthesiol*ogy, **33**, 212-220. https://doi.org/10.1097/ANA.0000000000000667

[32] Fabling, J.M., Gan, T.J., El-Moalem, H.E., Warner, D.S. and Borel, C.O. (2002) A Randomized, Double-Blind Comparison of Ondansetron versus Placebo for Prevention of Nausea and Vomiting after Infratentorial Craniotomy. *Journal of Neurosurgical Anesthesiology*, **14**, 102-107. https://doi.org/10.1097/00008506-200204000-00003