Double-Blind, Placebo-Controlled, Randomized Pilot Study of Cerebral Blood Flow Patterns Employing SPECT Imaging in Dental Postsurgical Pain Patients With and Without Pain Relief

Andrew B. Newberg, MD1; Elliot V. Hersh, DMD, MS, PhD2; Lawrence M. Levin, DMD, MD2; Helen Giannakopoulos, DDS, MD2; Stacey A. Secreto, RMA, EMT2; Nancy A. Wintering, MSW1; and John T. Farrar, MD, PhD3

1Division of Nuclear Medicine, Department of Radiology, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania; 2Department of Oral Surgery and Pharmacology, University of Pennsylvania School of Dental Medicine, Philadelphia, Pennsylvania; and 3Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania

ABSTRACT

Background: Single-photon emission computed tomography (SPECT) has been employed in the study of altered regional cerebral blood flow (CBF) in experimental and chronic pain. CBF patterns have not been evaluated in patients with acute postoperative pain.

Objective: The purpose of this pilot study was to employ SPECT to measure CBF distribution associated with postoperative dental pain and to compare these CBF patterns to subsequent images in the same patients who were experiencing pain relief versus continued or worsening pain who had received active or placebo analgesic interventions. The primary outcome measure was the percentage change in blood flow in various regions of interest.

Methods: Twenty-two healthy individuals (10 males and 12 females, age range 20–29 years) who underwent the removal of ≥1 partial or full bony impacted mandibular third molars were evaluated for pain intensity as the local anesthesia dissipated, employing a 0 to 10 numeric rating scale (0 = no pain; 10 = worst imaginable). When the subjects’ pain level reached ≥4/10, they were injected intravenously with 260 MBq of technetium Tc 99m bicisate (ethyl cysteinate dimer). Under double-blind conditions and 10 minutes before being placed in the SPECT scanner, the first 10 subjects were randomized to receive intravenous ketorolac 15 mg or saline while the remaining 12 subjects were randomized to receive by mouth either ibuprofen 400 mg, ibuprofen 200 mg, acetaminophen 1000 mg, or placebo. One hour after drug administration, subjects were reevaluated for pain, injected with 925 MBq of technetium Tc 99m bicisate, given rescue medication if required, and then rescanned. CBF ratios were obtained for regions of interest and by normalizing to average whole brain activity.

Results: Subjects generally had a moderate degree (mean [SD], 7.3% [4.0%]) of thalamic asymmetry on initial scans with pain; after treatment, subjects reporting worsening pain regardless of the intervention had higher thalamic asymmetry (8.1% vs 2.8%) than those reporting relief of pain. Subjects who reported reduced pain after the intervention had significantly different (P < 0.05) mean CBF changes compared with those reporting worsening pain in the left prefrontal cortex, left sensorimotor area, right anterior cingulate, and right caudate.

Conclusions: Acute postoperative dental pain was associated with moderate thalamic asymmetry that improved following successful pain management. Sustained or worsening pain was associated with increased CBF in brain regions associated with pain pathways, whereas pain relief was associated with decreased activity in the same areas. (Clin Ther. 2011;33:1894–1903) © 2011 Elsevier HS Journals, Inc. All rights reserved.

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INTRODUCTION

Pain perception is a final common pathway response to a broad range of neurophysiologic stimulations that are often difficult to classify. A widely accepted definition for pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.” Pain is usually classified as either nociceptive or neuropathic and can occur in either visceral or somatic tissues. Acute somatic nociceptive pain, which is the usual pain that serves to warn individuals about actual or potential tissue damage, is the most consistently responsive to analgesic therapy. It most commonly occurs as a result of accidental trauma, surgery, or experimental procedures. Postsurgical pain in the acute setting can be treated adequately with various interventions, including nonsteroidal antiinflammatory drugs (NSAIDs), acetaminophen, and opioids.

Studies of brain function have begun to define some of the brain areas that are involved in the processing of painful input, but less is known about the neurophysiologic response to effectively treated pain. Both cortical and subcortical brain structures play an important role in pain processing and perception. The spinothalamic tract is the primary transmission pathway for the processing of many sensory stimuli. Animal studies have reported that the thalamus, sensory cortex, hypothalamus, and brain stem nuclei are involved directly in the processing of sensory information, with the posterolateral thalamic nucleus reported to be a relay for pain processing. In humans, a study of frontal lobe activity as a “higher order” processing center suggested that the frontal lobes help to suppress the subjective intensity of noxious stimuli.

Several recent studies have utilized a model of injecting saline into facial muscles or subcutaneously and then evaluating changes in the brain in response to the noxious stimuli. For example, 1 study showed that both muscle and cutaneous noxious stimuli evoked bilateral increases in blood flow in the ventral posterior thalamus as well as in the face region of the somatosensory cortex from injections of hypertonic saline into the right masseter or overlying skin. These results suggest that noxious information ascends bilaterally from the face to the somatosensory cortex through the ventroposterior thalamus in humans. Another recent study of orofacial pain demonstrated alterations in activity in the primary motor cortex with an initial increase of blood flow with acute pain followed by a progressive decrease in cerebral blood flow (CBF).

Functional brain imaging studies employing single-photon emission computed tomography (SPECT), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI) have been performed in humans receiving various acute experimental pain stimuli (noxious heat, cold, pressure, electrical stimulation, and injection of algesic compounds). The principle of employing a functional imaging technique such as SPECT or fMRI is that regional increases of blood flow in the brain parallel neural activity, with a reported delay of only 1 to 5 seconds after the onset of such activity.

Although providing insight into the neurophysiologic mechanisms of pain processing, experimental pain paradigms differ from the acute and chronic pain syndromes typically observed in clinical practice. In particular, areas of the brain activated during experimental pain stimuli may differ from those activated in patients experiencing acute postsurgical or traumatic pain, or both, during which a multitude of inflammatory mediators are released and central sensitization is likely to occur.

Recently a number of studies have evaluated CBF patterns in patients with various chronic pain syndromes. In addition, several of these studies have also evaluated the effects of therapeutic interventions, such as acupuncture, ketamine, and deep nerve stimulation on these blood flow patterns. However, with regard to acute postsurgical pain, a PubMed search employing the terms postsurgical pain or postoperative pain and functional brain imaging revealed a lack of information in the literature evaluating brain activity in patients before and after therapeutic interventions. The purpose of this pilot study was to employ SPECT imaging to characterize CBF patterns in patients experiencing acute postsurgical dental pain and to compare these with subsequently acquired images after therapeutic or placebo interventions.

PATIENTS AND METHODS

The protocols and informed consent documents were reviewed and approved by the Institutional Review Board and Radiation Safety Committee of the University of Pennsylvania and were conducted in accordance
with the Declaration of Helsinki and the Guidelines for Good Clinical Practice.\textsuperscript{28} Patients were enrolled in this study between June 6, 2005, and September 10, 2007.

**Patients**

Patients were recruited from the University of Pennsylvania’s Department of Oral and Maxillofacial Surgery. Eligible patients were aged 18 to 65 years, were scheduled to undergo the surgical removal of \( \geq 1 \) mandibular partial or full bony impacted third molar teeth, and had given written, informed consent before the initiation of any study-related procedures. All patients were medically cleared for study participation by both the examining oral surgeon and the nuclear medicine physician. Immediately before the oral surgery procedure, females of childbearing potential underwent a urine pregnancy test, the results of which had to be negative for continued study participation. Key exclusion criteria included the ingestion of any over-the-counter or prescription analgesic agent within 48 hours of dental surgery; the ingestion of any over-the-counter or prescription central nervous system–altering drugs such as antihistamines, antidepressants, benzodiazepines, and other antianxiety or antipanic agents (other than the surgical sedation agents) within 48 hours of dental surgery; previous untoward reactions to ketorolac, ibuprofen, related NSAIDs, acetaminophen, or opioids. All surgery was performed in the Department of Oral and Maxillofacial Surgery employing 2% lidocaine with 1:100,000 epinephrine and 3% mepivacaine and Maxillofacial Surgery employing 2% lidocaine.

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Following surgery, patients entered the SPECT imaging portion of the study if their pain intensity reached \( \geq 4 \) on a validated 0 to 10 Numeric Rating Scale for Pain Intensity (NRS-PI)\textsuperscript{29} within 5 hours of surgery. All 22 patients who enrolled in this trial met this criterion and were assigned to 1 of 2 protocols, both carried out under double-blind conditions within the Department of Nuclear Medicine. In protocol 1, 10 subjects were randomized to receive intravenous ketorolac 15 mg (\( n = 5 \)) or placebo (\( n = 5 \)). In protocol 2, 12 subjects were equally randomized to receive by mouth either ibuprofen 400 mg, ibuprofen 200 mg, acetaminophen 1000 mg, or placebo. Blinding of all study medication was performed by the Investigational Pharmacy Service at the Hospital of the University of Pennsylvania. Study medication in each protocol appeared identical.

**Pain Intervention and SPECT Scan Acquisition Sequence**

Following randomization, an IV line that was still in place from the administration of conscious sedation agents was maintained for subsequent administration of the radioactive tracer technetium Tc 99m bicisate for SPECT imaging. Each patient underwent 2 SPECT scans. The first SPECT scan, termed the *pain scan*, was conducted after surgery when the patient reached a pain level \( \geq 4/10 \). When this pain intensity level was achieved, the patient was injected immediately with a dose of approximately 250 MBq technetium Tc 99m bicisate. Ten minutes after injection of technetium Tc 99m bicisate, patients received their assigned intravenous or oral study medication. Patients were then positioned in the SPECT scanner, and images were obtained beginning 15 minutes after injection of technetium Tc 99m bicisate and were acquired over the next 40 minutes.

When the pain scan was completed, patients again reported their level of pain and received a second injection of approximately 925 MBq technetium Tc 99m bicisate. Patients with worsening or unimproved pain received a “rescue” oral analgesic (acetaminophen 750 mg plus hydrocodone 7.5 mg) but not until 10 minutes after the second injection of technetium Tc 99m bicisate. The second SPECT scan, termed the *postinterventional scan*, was conducted 15 minutes after the radioactive tracer injection (5 minutes after the ingestion of rescue medication if it occurred), and images were acquired over 30 minutes. The injection and scan scheme were designed so that the pain state could be captured at the time of injection, even though the scan could be performed later. Once the radioactive tracer is injected, after the 3- to 5-minute uptake period, any changes in pain state do not affect the scan obtained later.\textsuperscript{30}

It should be noted that radioisotope uptake by the brain tissue occurs most rapidly during the first 3 to 5 minutes after injection when the isotope blood level is high. Furthermore, the technetium Tc 99m bicisate becomes “trapped” in the brain cells within 5 to 10 minutes of injection.\textsuperscript{24,25,30} Therefore, the images acquired reflect the actual state of the brain during the immediate postisotope injection period. In the current study,
the initial set of images (the pain scan) correlate with the postoperative pain state before the administration of study analgesic or placebo; the second set of images (the postinterventional scan) reflect the CBF changes induced by the active analgesic or placebo interventions before the intake of rescue analgesic, if required.

SPECT images of the brain were acquired on a triple-headed gamma camera equipped with ultrahigh resolution, fan beam collimators (Picker 3000XP, Cleveland, Ohio). Projection images were obtained at 3-degree angle intervals on a 128 × 128 matrix over 360 degrees by rotating each head 120 degrees. Images were reconstructed in the transaxial, coronal, and sagittal planes using a low-pass filter with ramp back projection and Chang’s first-order attenuation correction.

**Region of Interest Analysis**

Selected regions of interest (ROIs) from a standardized template developed to analyze functional brain images were used for analysis. The selection of ROIs was hypothesis driven and was chosen before the enrollment of study patients. It included regions for the frontal lobe, parietal lobe, occipital lobe, visual cortex, sensorimotor cortex, thalamus, striatum, cerebellum, and midbrain. All ROIs were made slightly smaller than the anatomic structure they represented to omit the extreme axial ends, minimizing the effects of volume averaging. ROIs were placed on the pain scan manually to achieve the best fit and then copied directly onto the intervention scan. Some minor manual adjustments were made to account for the different position of the patients’ head in the scanner during the second scan.

The counts per pixel in these regions were measured automatically and exported into a database, slice by slice and region by region. Because the actual values obtained for each pixel are dependent on the total amount of radioactivity injected, counts were normalized to whole brain activity, giving an uptake ratio used in analysis. Because the scans were performed on the same day, the counts in the regions from the initial pain scan were decay corrected and subtracted from the second, postinterventional scan. Percent activation was calculated between pain scan and postinterventional scan for each ROI, using Equation 1. To determine the asymmetry of homologous brain regions, a laterality index (LI) was calculated using Equation 2.

### Activation

\[
\text{Activation} = \frac{\text{Postinterventional Scan} - \text{Pain Scan}}{\text{Postinterventional Scan} + \text{Pain Scan}} \times 200 \quad (1)
\]

\[
\text{Right} - \text{Left} = \frac{\text{Right} \times 200}{\text{Right} + \text{Left}} \quad (2)
\]

### Statistical Analysis

Several different statistical methods were utilized to address specific hypotheses. To assess the relationship between pain levels and CBF, we compared activity in various ROIs during the pain scan to the reported pain level using linear regression models. Results from the pain scan were compared with those from the postinterventional scan in all groups using paired t tests to determine whether relief of pain was associated with significant decreases in the activity levels of ROIs involved in pain pathways and whether persistent pain was associated with significant increases in the activity levels of ROIs involved in pain pathways. We also compared the percentage change in the various ROIs among the different groups to assess for differences. We corrected the CBF data analysis for multiple comparisons using the False Discovery Rate method. Finally, we compared the laterality index in the thalamus between the 2 groups. It should be noted that with such small sample sizes, all results must be considered preliminary and will require confirmation in a larger trial.

### RESULTS

Twenty-two subjects (12 males, 10 females; age range 20–29 years) underwent initial SPECT imaging when their postsurgical pain reached a level of ≥4/10 and again 60 minutes after their analgesic or placebo intervention. The groups did not have any significant differences in their initial postsurgical pain scores. For subjects who had reduced pain (numeric pain score decreased by at least 1 unit, N = 7/22) after an intervention, the pre- and postintervention pain scores were mean (SD) 5.7 (1.1) and 1.3 (1.9), respectively. For subjects with no change in their pain (numeric pain score stayed the same, N = 7/22), the pre- and postintervention pain scores were 6.5 (1.4) and 6.5 (1.4), respectively. For subjects with worsening pain (numeric pain score increased by at least 1 unit, N = 8/22), the pre-and postintervention pain scores were 5.1 (1.0) and 7.4 (1.6), respectively. Subjects in each arm, including the pla-
cebo group, had a variable response, with the exception of the intravenous ketorolac group in which everyone had a reduction in pain. Because of the small sample sizes, subgroup analyses were not appropriate.

No significant differences were observed in any brain region with regard to CBF between the different treatment groups before therapeutic intervention (the pain scans). In addition, all subjects had at least a moderate degree of thalamic asymmetry (mean 7.3% [4.0%]) on their initial pain scans with no significant differences noted between the treatment groups. There was a significant correlation between the thalamic asymmetry and the initial pain score ($r = 0.43$, $P = 0.04$).

In measurements made 60 minutes after treatment, subjects who had reduced pain after the intervention had significantly different mean CBF changes compared with those with no change in their pain and those with worsening pain. Subjects with improvement in their pain had much greater changes in their thalamic asymmetry than those who had no change or worsening pain. The absolute change in asymmetry was 13.9% (9.8%) in the pain relief group versus 7.7% (5.9%) in the group with no change or worsening pain ($P = 0.05$). In general, worsening pain was associated with increased CBF in the frontal regions, sensorimotor area, and angular gyrus with relatively decreased CBF in these regions when pain improved (see Table I). The exception was the right caudate in which CBF actually increased in patients for whom pain was relieved. As illustrated in Figures 1 through 3, following a therapeutic or placebo intervention, the anterior cingulate region of the frontal cortex exhibited enhanced blood flow with increasing pain and decreased blood flow when pain was diminished. Likewise as illustrated in Figures 2 and 3, thalamic blood flow asymmetry was evident with postsurgical pain, which did not change or became worse with increasing pain but normalized with pain reduction. There were no findings that clearly distinguished the treatment groups from one another. CBF changes appeared to correlate with the perception of pain or pain relief and not to the actual treatment administered per se.

**DISCUSSION**

The current report is the first to our knowledge to acquire brain imaging data in patients experiencing pain following the surgical removal of impacted third molar teeth and to observe the changes in brain activity following active and placebo interventions.

<table>
<thead>
<tr>
<th>Region</th>
<th>Improved</th>
<th>No Change</th>
<th>Worsened</th>
<th>$P^{‡}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right anterior cingulate</td>
<td>−3.9</td>
<td>−1.7</td>
<td>7.9</td>
<td>0.01‡</td>
</tr>
<tr>
<td>Left dorsal medial cortex</td>
<td>−10.5</td>
<td>−3.5</td>
<td>4.5</td>
<td>0.01‡</td>
</tr>
<tr>
<td>Left DLPFC</td>
<td>−2.1</td>
<td>−2.3</td>
<td>11.3</td>
<td>0.006‡</td>
</tr>
<tr>
<td>Left sensorimotor cortex</td>
<td>−4.4</td>
<td>−4.0</td>
<td>6.7</td>
<td>0.01‡</td>
</tr>
<tr>
<td>Right caudate</td>
<td>13.5</td>
<td>0.5</td>
<td>1.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Right orbital front</td>
<td>−10.1</td>
<td>−2.0</td>
<td>17.2</td>
<td>0.05</td>
</tr>
<tr>
<td>Left orbital front</td>
<td>−6.3</td>
<td>−5.0</td>
<td>10.7</td>
<td>0.04</td>
</tr>
<tr>
<td>Right angular gyrus</td>
<td>−7.2</td>
<td>3.3</td>
<td>3.6</td>
<td>0.04</td>
</tr>
<tr>
<td>Right superior frontal</td>
<td>−0.8</td>
<td>−2.2</td>
<td>7.8</td>
<td>0.04</td>
</tr>
<tr>
<td>Left fusiform gyrus</td>
<td>−7.9</td>
<td>−2.6</td>
<td>6.7</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Table I. Percentage change in cerebral blood flow between initial scan and postintervention scan in patients who had improvement of their pain, no change in pain, or worsening of pain.*

DLPFC = dorsolateral prefrontal cortex.

*The results listed are only for those regions with significant values. Structures that did not achieve significant differences included the left anterior cingulate, right dorsal medial cortex, right DLPFC, right sensorimotor cortex, left caudate, left angular gyrus, left superior frontal, right fusiform gyrus, and bilateral thalamus.

$P$ values related to the improved group versus the worsened group.

$P$ values that maintain significance when corrected for multiple comparisons based on FDR.
Care must be taken in interpreting our results because of the small sample size and the relatively few analgesic interventions that we tested; although studies with relatively small sample sizes are typically the norm in the experimental and chronic pain imaging literature. It has been reported previously that the initial SPECT images of 12 chronic back, neck, or shoulder pain patients revealed a significant degree of thalamic asymmetry and that their thalamic blood flow normalized, or in some cases reversed, when their pain levels improved following acupuncture therapy. Our current study in acute postsurgical pain patients revealed a similar thalamic asymmetric uptake of the radioactive isotope when the patients were in pain, which normalized or reversed when pain relief was obtained. With worsening pain, and apparently regardless of treatment, thalamic blood flow remained asymmetric or became even more asymmetric (Figures 2 and 3).

Postsurgical dental pain patients also exhibited high CBF in the anterior cingulate cortex region, which is consistent with other reports describing CBF patterns in subjects experiencing experimental pain induced from pressure, subcutaneous saline injections, noxious heat, and cold. Compared with findings on preinterventional scans, CBF in the anterior cingulate cortex decreased in postsurgical dental pain patients experiencing pain relief and increased with worsening pain (Table I and Figures 1–3). Other regions of the brain displayed a similar pattern of decreased CBF with decreasing
pain and increased CBF with worsening pain, with the notable exception being the right caudate nucleus. Likewise, imaging studies of experimentally induced pain have also reported increases in CBF in similar brain regions.\textsuperscript{10,14,15,17,19}

Although the results of our study suggest that CBF changes induced by therapeutic or placebo interventions solely reflected increases or decreases in the pain state and did not relate to the mechanism of drug action, several limitations in the current study design preclude us from accepting this finding conclusively. Besides the small sample size, the limited range of doses, and the evaluation of only a single postdose time point, all 3 active drugs are thought to possess somewhat similar mechanisms of action. Ketorolac and ibuprofen are NSAIDs that inhibit both peripheral and central cyclooxygenase,\textsuperscript{33–35} whereas acetaminophen is also a potent central cyclooxygenase inhibitor.\textsuperscript{35–37} These drugs were all chosen for this study because they were single-entity analgesics that had been evaluated extensively and had displayed efficacy in postsurgical dental pain models.\textsuperscript{38–44} Single-entity opioid analgesics were not employed in this study because of their relative lack of efficacy at conventional oral doses\textsuperscript{45,46} and their undesirable side effect profile (compared with that of NSAIDs) at effective oral or parenteral doses\textsuperscript{38,47} in oral surgery outpatients. However, because of their

![Figure 2. In the top row, a patient’s initial pain single-photon emission computed tomography scan (A) shows asymmetric thalamic activity with more cerebral blood flow (CBF) on the right (thin arrow). With pain relief after IV ketorolac, the postinterventional scan (B) of the same patient exhibits a normalization or even a slight “switch” in thalamic asymmetry, with mildly greater CBF on the left (thin arrow). Also note there is slightly less blood flow in the anterior cingulate region with pain relief compared with that shown in the preinterventional state with greater pain (thick arrows in A and B). In the bottom row, another patient with an initial pain scan (C) shows mild asymmetric activity in the thalamus with more CBF on the left (thin arrow). With worsening pain after receiving IV placebo, the postinterventional scan (D) shows even greater CBF in the left thalamus or greater thalamic asymmetry (thin arrow). Note also that with worsening pain, blood flow increases in the anterior cingulate cortex compared with that shown in the initial pain scan (thick arrows in A and B).](image-url)
distinct mechanism of action and the fact that opioid combinations with acetaminophen remain the most frequently prescribed analgesics for all types of pain, including oral surgery, their postsurgical effects on brain activity should be evaluated in the future.

CONCLUSIONS
The results of this small pilot study suggest that in postsurgical dental pain, patient CBF distribution in the thalamus, anterior cingulate, and other ROIs correlates with the perception of pain and pain relief. Larger studies and studies of other treatments and pain paradigms are necessary to explain more thoroughly the neurophysiologic factors that contribute to the responses observed with pain perception and pain treatment.

CONFLICTS OF INTEREST
There are no conflicts of interest to report for any of the authors.

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Dr. Newberg contributed to the literature search, figure creation, study design, data collection, data interpretation and writing of the manuscript. He also medically cleared subjects medically for study participation, administered the SPECT imaging tracer and performed all the SPECT scans. Dr. Hersh contributed to the literature search, figure creation, study design, data collection, data interpretation and writing of the manuscript. He is also developed the informed consent document and other regulatory materials needed for IRB approval. Dr. Levin contributed to the study design, data collection and editing of the manuscript. He also medically cleared subjects for study participation and performed the oral surgery procedures. Dr. Giannakopoulos contributed to the study design, data collection and editing of the manuscript. She also medically cleared subjects for study participation and performed the oral surgery procedures. Ms. Secreto contributed to data collection and performed the informed consent procedure. Ms. Wintering contributed to data collection and performed the informed consent procedure. Dr. Farrar contributed to the literature search, figure creation, study design, data collection, data interpretation and writing of the manuscript. He is also developed the informed consent document and other regulatory materials needed for IRB approval.

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