Pain relief by electrical stimulation of the periaqueductal and periventricular gray matter

Evidence for a non-opioid mechanism

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Pain relief following stimulation of the periaqueductal gray matter (PAG) or periventricular gray matter (PVG) in man has been ascribed to stimulation-induced release of endogenous opioid substances. Forty-five patients were studied and followed for at least 1 year after placement of chronic stimulating electrodes in the PAG or PVG to determine if pain relief due to stimulation could be ascribed to an endogenous opioid mechanism. Three criteria were assessed: 1) the development of tolerance to stimulation; 2) the possibility of cross-tolerance to morphine; and 3) reversibility of stimulation-induced pain relief by the opiate antagonist naloxone. Sixteen patients (35.6%) developed tolerance to stimulation, that is, they obtained progressively less effective pain relief. Twelve (44.4%) of 27 patients undergoing stimulation of the thalamic sensory relay nuclei for treatment of chronic pain (a presumably non-opioid mechanism) also developed tolerance. Morphine sulfate was administered in a blind, placebo-controlled protocol to 10 patients who had become tolerant to PAG-PVG stimulation and none showed evidence of cross-tolerance. Fifteen of 19 patients, already tolerant to morphine at the time of PAG-PVG electrode implantation, experienced excellent pain relief by stimulation, also indicating a lack of cross-tolerance. Twenty-two patients who experienced excellent pain relief from chronic PAG-PVG stimulation received intravenous naloxone in a double-blind, placebo-controlled protocol. Pain intensity as assessed by the visual analog scale was increased to the same degree by both placebo and naloxone. Eight patients showed no increase in pain intensity with either placebo or naloxone.

Although tolerance to PAG-PVG stimulation developed in these patients, the frequency of tolerance was similar to that seen in patients undergoing thalamic sensory nuclear stimulation. Since the latter technique presumably relieves pain by a non-opioid mechanism, the development of tolerance to PAG-PVG stimulation does not, in itself, confirm an opioid mechanism. Cross-tolerance between PAG-PVG stimulation and morphine was not seen and cross-tolerance to PAG-PVG stimulation in patients already tolerant to morphine was rare. The pain-relieving effect of PAG-PVG stimulation was reversed to an approximately equal degree by naloxone and placebo. The authors do not believe that, in most patients, pain relief elicited by PAG-PVG stimulation depends on an endogenous opioid mechanism. It appears that other, non-opioid mechanisms are primarily responsible for such pain relief.

KEY WORDS • periaqueductal stimulation • periventricular stimulation • depth electrodes • chronic pain

A number of reports have described effective relief of intractable pain by electrical stimulation in the periaqueductal gray matter (PAG) and periventricular gray matter (PVG) of the upper midbrain and medial thalamus. 1,2,7,12,26,27,29,35,36,39-42 Efforts to treat intractable pain by this method evolved from the demonstration in animals of analgesia caused by PAG stimulation. 1,4,9,23,34,38 Several clinical reports, notably those of Adams, et al. 1,2 Hosobuchi, et al. 26-29 and Richardson and colleagues, 5,39-42 have ascribed pain relief elicited by PAG-PVG stimulation to the release of endogenous opioid substances ("endorphins"). This hypothesis rests on its analogy to the experimental animal model, to the demonstration of elevated ventricular cerebrospinal fluid (CSF) concentrations of endogenous opiates following stimulation, 5,29 and to the attenuation of stimulation-induced pain relief by the narcotic antagonist naloxone. 1,5,27 Several recent reports
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...have questioned the relationship between CSF endorphin levels and pain relief.5,13,14,35,36,49

A group of 45 patients who underwent electrical stimulation in the PAG-PVG region via implanted electrodes for treatment of chronic pain were studied in order to ascertain if criteria to support an endogenous opioid mechanism for their pain relief were met. Three criteria were evaluated: 1) the development of tolerance to stimulation; 2) the presence of cross-tolerance to morphine; and 3) the reversibility of stimulation-induced pain relief by naloxone. Although our clinical success in providing pain relief is similar to that reported by others, our reports do not support an endogenous opioid mechanism in most patients. We believe that other, non-opioid mechanisms are primarily responsible for pain relief induced by PAG-PVG electrical stimulation.

Clinical Material and Methods

Fifty-two patients underwent placement of stimulating electrodes either in the PAG or PVG utilizing methods described previously.50,51 For the PAG placement the intended target was 1 to 2 mm lateral to the rostral aqueduct at approximately the midaqueductal level. For the PVG site the target was that described by Richardson and Akil;41 that is, 10 mm posterior to the midpoint of the line joining the anterior commissure (AC) and the posterior commissure (PC), 2 to 3 mm lateral to the midline, and at the level of the AC-PC plane. All intraoperative and postoperative x-ray films, ventriculograms, and computerized tomography scans were carefully reviewed in order to assess exact electrode locations. Seven patients did not receive effective pain relief during a trial stimulation period and the electrodes were removed. The remaining 45 patients have been followed for periods ranging from 12 to 86 months.

Pain intensity was assessed with the visual analog scale;10 based on this scale of measurement, the patient was instructed to estimate the magnitude of his or her pain by placing a mark along a 10-cm horizontal straight line. The left end of the line represented absence of pain and the right end represented maximal pain intensity. The distance from the left end of the line to the patient's mark was measured with a millimeter ruler and the analog value was converted to a digital value in which zero represented the absence of pain and 10 maximal pain. Changes in pain intensity on the visual analog scale were evaluated for statistical significance using the Student t-test. Narcotics intake and functional status as reflected by a visual analog scale were evaluated for statistical significance using the Student t-test. Narcotics intake and functional status as reflected by a visual analog scale were evaluated for statistical significance using the Student t-test.

In 12 patients who developed irreversible tolerance (their pain was no longer relieved by stimulation) the possibility of cross-tolerance to morphine was evaluated. Patients were given either a saline placebo or morphine sulfate (30 mg, in three equally divided doses over 40 minutes) and naloxone (0.4 to 0.8 mg, intravenously) in a blind protocol. Pain intensity was assessed before, during, and after drug administration on the visual analog scale. Results after the development of tolerance were compared to those obtained prior to stimulator implantation.

Cross-tolerance between morphine and PAG-PVG stimulation was assessed in another way as well. Nineteen of the original group of 52 patients who underwent placement of PAG-PVG electrodes were already tolerant to opiates at the time of electrode placement. Nearly all of these patients had pain due to progressive malignancies since our policy had been to insist that all patients with intractable noncancer pain be fully detoxified from opiates prior to being considered for treatment by PAG-PVG stimulation. Thus, we could assess whether the patients in this group already tolerant to exogenous opiates were also cross-tolerant to PAG-PVG stimulation.
Evaluation of naloxone reversibility of pain relief was attempted in 22 patients, all of whom experienced excellent pain relief from PAG-PVG stimulation. These patients received naloxone (0.4, 0.8, or 10 mg) or saline placebo intravenously in a double-blind protocol. Pain intensity was evaluated on the visual analog scale before, during, and after administration of drugs.

Results

All of the 45 patients who underwent permanent electrode placement in the PAG-PVG region experienced virtually complete pain relief in the immediate postimplantation period. Sixteen patients (35.5%) subsequently developed partial or complete tolerance to PAG-PVG stimulation, that is, the magnitude of pain relief steadily decreased and pain intensity increased. Mean preoperative pain intensity in the group of 45 patients with permanently implanted electrodes was 8.47 ± 1.2 (± standard error of the mean) on the visual analog scale. In the immediate postimplantation period mean pain intensity with regular stimulation had decreased to 1.35 ± 0.78. By 1 year after electrode implantation the mean pain intensity in the 16 patients who developed tolerance had increased to 7.77 ± 2.1, whereas in the 29 patients who had not developed tolerance the mean pain intensity was 2.13 ± 0.94 (Table 1).

Alterations in stimulus parameters, increases in duration of stimulation, temporary cessation of stimulation, and the administration of L-tryptophan orally (4 to 6 gm/day) were ineffective in overcoming tolerance. Twelve patients eventually became completely refractory to the pain-relieving effect of stimulation, whereas another four continued to receive partial pain relief at a level considerably less than that experienced in the immediate postimplantation period.

Twelve (44.4%) of 27 patients who underwent nucleus ventralis posterior medialis (VPM) or nucleus ventralis posterior lateralis (VPL) thalamic stimulation also developed tolerance to stimulation. Tolerance appeared to develop more quickly (mean 3.4 months) in patients undergoing thalamic stimulation compared to tolerance in patients with PAG-PVG electrodes (mean 8.7 months). Partial tolerance was uncommon in patients with VPL or VPM electrodes, and developed in only two patients.

Nineteen patients with intractable pain, who were tolerant to the analgesic effects of opiates or who were receiving such large doses of opiates that they were severely lethargic, underwent PAG-PVG stimulation. Maximum intravenous narcotic dosage in these patients was 80 mg/hr. In addition, four patients had been receiving intraspinal morphine in doses of 250 to 300 mg/day. Fifteen of the 19 patients experienced excellent pain relief from PAG-PVG stimulation. Their mean pain intensity dropped from 8.75 ± 0.70 to 2.31 ± 0.73 on the visual analog scale. Two patients had partial relief and two others experienced no pain relief from PAG-PVG stimulation. Interestingly, only about half of these patients developed withdrawal symptoms as exogenous opiate dosage was decreased following electrode placement and effective stimulation. A few patients did develop severe withdrawal symptoms, demonstrating convincingly the lack of cross-tolerance between morphine and PAG-PVG stimulation.

Twelve patients who developed tolerance to PAG-PVG stimulation were evaluated for cross-tolerance to morphine. All patients tested showed a marked reduction in intensity of their pain after receiving intravenous morphine sulfate, which was antagonized by naloxone (Fig. 1 left and Table 2). All of these patients had undergone preoperative evaluation of the effect of morphine sulfate on their pain intensity, and the results after the development of tolerance were similar or identical to those seen preoperatively (Fig. 1 left and Table 2). Based on this form of assessment, no patient convincingly demonstrated cross-tolerance to morphine.

Twenty-two patients received intravenous naloxone and saline placebo in a double-blind protocol at the time when they experienced excellent pain relief from

TABLE 1

<table>
<thead>
<tr>
<th>Time &amp; Group</th>
<th>Mean VAS Score</th>
<th>No. of Cases</th>
</tr>
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<tbody>
<tr>
<td>preimplantation</td>
<td>8.47 ± 1.2</td>
<td>45</td>
</tr>
<tr>
<td>immediately postimplantation</td>
<td>1.35 ± 0.78</td>
<td>45</td>
</tr>
<tr>
<td>1 year postimplantation tolerance</td>
<td>7.77 ± 2.1</td>
<td>16</td>
</tr>
<tr>
<td>no tolerance</td>
<td>2.13 ± 0.94</td>
<td>29</td>
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* Pain intensity is expressed as mean (± standard error of the mean) visual analog scale (VAS) scores.

Fig. 1. Left: Effect of various pharmacological agents on mean pain intensity measured by the visual analog scale (VAS), preoperatively and following electrode implantation in the periventricular gray matter (PGV), in 12 patients who developed tolerance to stimulation. A = saline placebo; B, C, D = morphine sulfate, 10 mg intravenously; E = naloxone, 0.4 mg intravenously; F = conclusion of study. Right: Effect of naloxone and placebo on mean pain intensity measured by the VAS in 22 patients following PGV stimulation. A = onset of stimulation; B = stimulation discontinued and either naloxone or saline placebo administered intravenously. Curve C = effect of naloxone, and Curve D = effect of placebo.
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PAG-PVG stimulation (Table 3). Mean pain intensity on the visual analog scale in these patients was 8.29 ± 1.0 prior to stimulation. After 20 minutes of stimulation mean pain intensity dropped to 0.97 ± 0.2 (p < 0.001). Mean pain intensity increased to 4.43 ± 1.3 after naloxone, and was 4.05 ± 0.9 after placebo. Figure 1 right shows the time course of changes in mean pain intensity measured on the visual analog scale before and after stimulation and following administration of naloxone and placebo. Although the values for mean pain intensity after both naloxone and placebo are significantly different from the mean intensity following stimulation (p < 0.01), they are not significantly different from each other (p > 0.05). Thus, naloxone and placebo both appeared to produce a partial reversal of the pain relief generated by PAG-PVG stimulation. Surprisingly, no statistically significant differences were noted in the effects of naloxone doses of 0.4, 0.8, and 10 mg in reversing stimulation-induced pain relief, and the values presented for the effect of naloxone represent the mean of all three dosage levels. A statistical examination of the effect of naloxone and placebo in an individual patient was impossible since sufficient data were not available in any one patient for statistical analysis. An arbitrary change of at least 3.0 on the visual analog scale was selected as the criterion for a significant change in a single patient. Based on this evaluation scheme, six patients showed a greater reversal of stimulation-induced pain relief with naloxone than with placebo; four showed a greater reversal with placebo than with naloxone; eight showed no reversal with either placebo or naloxone; and six showed reversal with both placebo and naloxone.

Discussion

Reynolds first described the phenomenon of stimulation-produced analgesia by PAG stimulation in the rat. Subsequent investigations in animals revealed that this analgesia could be at least partially reversed by naloxone, and gave rise to the concept that the phenomenon was dependent on release of endogenous opiates. In addition, repeated applications of PAG stimulation led to decreasing effectiveness in eliciting analgesia: the phenomenon of tolerance. Cross-tolerance with morphine was also demonstrated. Several recent animal studies have further elucidated the basis for stimulation-produced analgesia. Cannon, et al., for instance, have shown that analgesia evoked from ventral but not dorsal PAG stimulation appears to be opiate-mediated.

The hypothesis that relief of chronic pain in man by PAG-PVG stimulation depends on endogenous opiate release rests on two sources of data in addition to analogy from the animal experiments mentioned above. Akil, et al., demonstrated apparent elevations in concentrations of methionine-enkephalin-like material in the ventricular CSF after PAG stimulation in man. Hosobuchi, et al., reported apparent elevations in CSF beta-endorphin levels following PAG stimulation. Subsequently, Fessler, et al., indicated that radioiodinated contrast material could interfere with the radioimmunoassay methods used to measure endorphins. We then showed that metrizamide and sodium iothalamate quenched the radioactivity of the labeled antibody in the same manner as the natural ligands, producing an apparent elevation in endorphin concentrations. At concentrations of metrizamide calculated to be in the ventricular CSF after ventriculography, apparent elevations in endorphin levels up to two to five times baseline levels could be measured. We studied beta-endorphin concentrations in the ventricular CSF after PAG and PVG stimulation when contrast medium was not utilized. These measurements were made up to 3 months after electrode implantation, when excellent pain relief was achieved from PAG-PVG stimulation. We have never seen CSF endorphin concentrations elevated by stimulation under such circumstances. Amano, et al., and Tsubokawa, et al., reported a lack of correlation between CSF endorphin levels and pain relief induced by brain stimulation; however, these two reports do not identify the relationship between sampling methods and contrast agents and thus interpretation of their results is difficult.

The second source of data concerning an endogenous opiate mechanism for pain relief elicited by PAG-PVG stimulation in man is the reversal of pain relief with naloxone. Adams reported that naloxone (0.05 to 0.25 mg) reversed pain relief induced by PAG-PVG stimulation in a single patient, but that a saline placebo had...
no reversal effect. Hosobuchi, et al.,27 reported the complete reversal of stimulation-induced pain relief in five of six patients by naloxone in doses of 0.2 to 1 mg. Akil, et al.,4 stated that analgesia induced by PVG stimulation was partially reversed by naloxone in unspecified doses in 80% of their patients. These results are quite different from those reported by Akil, et al.,4 in which naloxone produced a mean reversal of the analgesia induced in rats by PAG stimulation of only 38%. In contrast to these results, Carstens, et al.,11 were unable to reverse with naloxone the inhibition of dorsal horn neuronal responses to noxious stimuli induced by PAG stimulation.

The doses of naloxone employed in earlier human studies are now thought to be insufficient to reliably reverse the effects of endogenous opiates although they may effectively reverse exogenous opiates. In the present study we employed 10 mg of naloxone in some patients, a dose sufficient to reverse endogenous opiates, and also used a double-blind and placebo-controlled protocol. We were surprised to find that the degree of reversal of stimulation-induced pain relief did not vary with different naloxone doses. If endogenous opioids were responsible for the pain relief induced by PAG-PVG stimulation, one might have expected a greater effect with the 10-mg dose than with the smaller doses. Other investigators,5,35,36 have also reported reversal of stimulation-induced pain relief by small doses (0.05 to 1.0 mg) of naloxone. It is clear from our data that significant reversal of pain relief by PAG-PVG stimulation may occur with placebo. If we had not compared the effect of placebo and naloxone, we might have concluded that 73% of our patients experienced reversal of stimulation-induced pain relief by naloxone when, in fact, only 27% of tested patients showed greater reversal with naloxone than with placebo. Butler, et al.,8 recently reported placebo reversal of analgesia induced by the synthetic opiate fentanyl citrate in man. These investigators also reported that the effects of the placebo on cortical evoked potentials elicited by painful dental stimulation were identical to those seen with naloxone. The authors postulated that the experimental subject’s expectation of reversal of narcotic analgesia may have resulted in release of a previously undescribed, naturally occurring opiate antagonist. In addition, some authors have reported reversal of placebo analgesia by naloxone and have suggested that release of endogenous opiates may account for placebo analgesia.8,15,16,20 Gracely, et al.,19 however, showed that significant placebo analgesia could occur after blockage of opiate mechanisms by naloxone. They suggested that naloxone and placebo may reverse analgesia by different mechanisms, opioid in the former and non-opioid in the latter. Fields and Levine,16 in attempting to reconcile these disparate findings, suggested that factors such as the site, intensity, and controllability of the test subject’s pain as well as the instructions given to subjects, consent form, remuneration, time and method of placebo administration, and time and method of pain ratings could all affect experimental results. Hill25 reviewed the use of naloxone as a tool to evaluate opioid-mediated pain control mechanisms and concluded that specific correlations were difficult. For instance, there is some evidence that naloxone may release an endogenous hyperalgesic substance rather than antagonizing opiates.21 In addition β-endorphin receptors appear to exist for which no other agonist or antagonist, including naloxone, has been identified.24 These and other recently described complexities of the effects of naloxone make it impossible to interpret simplistically the results of attempted naloxone reversal of putative opiate analgesic mechanisms. Using the reasoning of Gracely, et al.,19 one might conclude that naloxone reversed stimulation-induced pain relief in our patients by an opioid mechanism, whereas placebo reversed pain relief by a non-opioid mechanism. Using this rationale, we would have to postulate that both opioid and non-opioid mechanisms acted simultaneously in the six patients we studied who showed reversal of pain relief with both naloxone and placebo. On the other hand, eight of the 22 patients we tested showed no attenuation of their stimulation-induced pain relief with either naloxone or placebo. In these patients, under the conditions existing at the time testing was carried out, pain relief appears to have been related to non-opioid mechanisms. Meyerson, et al.,26,27 described the rare occurrence of tolerance with PVG stimulation. Although the mechanism of pain relief by thalamic stimulation is unknown,6,12,44 there is no evidence that endogenous opiates contribute to such an effect. Thus, the development of tolerance does not by itself provide compelling evidence that pain relief induced by PAG-PVG stimulation is mediated by opiates. Freeman, et al.,17 demonstrated that pain relief engendered by electrical stimulation of the spinal cord is not opiate-mediated, yet the development of tolerance to analgesia induced by spinal cord stimulation is well known.

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Our data also indicate that cross-tolerance between exogenous morphine and pain relief due to PAG-PVG stimulation is unusual. Our patients who became tolerant to pain relief from PAG-PVG stimulation did not demonstrate cross-tolerance to intravenously administered morphine. Likewise, patients who were tolerant to exogenous opiates were not necessarily tolerant to pain relief induced by PAG-PVG electrical stimulation. In fact, only two of 19 opiate-tolerant patients failed to show pain relief with PAG-PVG stimulation. The occurrence of narcotic withdrawal symptoms in at least half of these patients when exogenous opiate dosage was decreased, following effective stimulation-induced pain relief, also provides evidence against opiate and stimulation cross-tolerance. Only four of these 19 patients could be considered to demonstrate partial (two patients) or total (two patients) cross-tolerance based on failure of stimulation to relieve their pain.

Our results are not consistent with an endogenous opiate mechanism for pain relief engendered by PAG-PVG stimulation in most patients. Several possible explanations for differences between our data and those of other investigators studying either human pain relief by PAG-PVG stimulation or stimulation-produced analgesia in animals may be advanced. We have studied a phenomenon different from stimulation-produced analgesia in animals. The animal studies utilize measures of acute pain thresholds, such as the tail-flick test in rats, to assess analgesia. Hosobuchi, et al.,27 reported a decrease in sensitivity to pinprick in one of six patients during PAG stimulation; sensitivity returned to normal 5 to 10 minutes after cessation of stimulation. This analgesic effect is inconsistent with relief of pathological pain, which is reported to last for hours after PAG stimulation. Hosobuchi, et al., also reported that a second patient showed decreased sensitivity to pinprick in the lower extremities only, and this effect occurred only when the voltage used for PAG stimulation was raised to a high level, producing ocular flutter. Three patients were tested for acute pain thresholds using the Hardy-Wolf-Goodell dolorimeter, and only one patient showed a 28% increase in pain threshold in the lower extremities during high-intensity PAG stimulation as mentioned above. Richardson and Akil41 reported alterations in pinprick sensation in two of five patients during acute stimulation of the PVG and various medial thalamic sites. The same authors studied changes in pain thresholds in a series of eight patients undergoing chronic PVG stimulation.42 Of these patients, four showed marked changes and one a slight change in sensitivity to pinprick. Three of the eight patients were also tested for sensitivity to noxious radiant heat or ischemic pain. All three patients showed decreased pain sensitivity, which ranged from a low of 5% decrease in sensitivity to radiant heat in one patient to a maximum of 54% decrease in sensitivity to ischemic pain in another. Conversely, Thoden, et al.,48 found no changes in sensitivity to innocuous or noxious cutaneous electrical stimuli in five patients during medial thalamic stimulation. The relationships between changes in chronic pain appreciation in man and changes in acute pain thresholds in animals are at present unknown, but clinical data suggest that acute and chronic pain may involve different mechanisms. Hansson and Ekblo m,22 for instance, have demonstrated that afferent stimulation reduced pathological dental pain, but did not elevate the pain threshold. They stated that “... there is no correlation between pain reduction of pathological pain and pain threshold increase.”

Differences between our results and those previously reported in man may also relate to methodological differences such as previously described for measurements of CSF endorphin concentrations and assessment of naloxone reversibility of pain relief. Other factors may also be important. Lewis, et al.,31-33 and Terman, et al.,46,47 have demonstrated that stress-induced analgesia in rats elicited by inescapable electrical foot shock may be mediated by opioid or non-opioid mechanisms, depending on the stimulation parameters. Furthermore, the opioid-mediated form of stress analgesia may be related to central (brain) or peripheral (adrenal) opioids, again depending on the frequency, intensity, and pattern of stimulation. Thus, variability in stimulating techniques in studies of human pain relief due to PAG-PVG stimulation could also account for differences in mechanisms.

Electrode location is also an important factor, as was emphasized by Boivie and Meyerson.7 Recently, Liebeskind, et al.,5,9,38 showed that stimulation-produced analgesia in animals generated by ventral, but not dorsal, PAG stimulation is apparently opioid-mediated. Our PAG electrode placements were at the midaudcual level or were dorsal to that point, and thus our results are consistent with those of Liebeskind, et al. Our PVG electrode placements, however, are identical to those of Richardson and Akil41 and would not explain differences between our results and theirs.

If endogenous opioid systems are not the primary substrate for pain relief induced in man by PAG-PVG stimulation, what other systems might be responsible? Evidence from animal studies suggests that serotonin, dopamine, and norepinephrine may play important roles in analgesia produced by PAG-PVG stimulation.3,30 Hosobuchi26 studied a possible serotonergic mechanism in man but considered this system to be activated secondarily by the endogenous opioid system. There has been little other investigation of non-opioid mechanisms in man.

Mechanistic considerations are of clinical as well as theoretical importance. Our patient selection criteria for PAG-PVG stimulation in the past50,51 included demonstration that the patient’s pain could be relieved by opiates and insistence that the patient was not opiate-tolerant at the time of electrode placement. Our current data would suggest that such criteria are unnecessary and may have excluded from consideration some patients who could potentially have received pain relief by PAG-PVG stimulation.
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