SUBSTANCE P LEVEL IN SYNOVIAL FLUID MAY PREDICT PAIN RELIEF AFTER KNEE REPLACEMENT

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Substance P is readily detected in the synovial fluid of the knee in which it acts as a powerful inflammatory agent in response to injury and disease. It may be an objective predictor of pain after knee replacement surgery.

The level of substance P was measured in the synovial fluid in both knees of 114 patients having unilateral and in 86 patients having bilateral total knee replacement for osteoarthritis. All had severe pain in the knee to be replaced and joint destruction. Substance P was elevated in 73% of replaced knees but not in normal or asymptomatic knees. Good or excellent pain relief was achieved in 97% of patients with an elevated preoperative level of substance P and in 61% of those with a normal preoperative level (p < 0.05 compared with preoperative values).

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It has been estimated that 80% of individuals over 55 years of age have degenerative arthritis of the knee and that 10% have pain that limits activity. It is not clear why some have more pain than others. Pain is a subjective sensation, the severity of which may not directly related to the apparent cause. This variable response to pain is multifactorial. Neurogenic inflammation, measured in serum and joint fluid, has been postulated as one reason why some degenerative joints hurt and others do not.

In 1931, von Euler and Gaddum extracted a powder, which they designated as substance P, from brain tissue. This peptide is manufactured in the neurons of the dorsal root ganglion and is transported to the peripheral primary afferent end organs and is released peripherally after afferent activation. It is an undecapeptide that produces vasodilatation and increases smooth muscle activity. Substance P is found in synovial fluid after stimulation of articular type-C nerve fibres. It is a powerful inflammatory agent in the joint fluid which allows the extravasation of plasma proteins into the synovial cavity.

In the knee, most substance P receptors are found in the joint capsule, although there are some in the fat pad, patellar periosteum, menisci, and synovium. In addition to having an afferent, peptidergic innervation, the joint capsule also has considerable sympathetic innervation. Sympathectomy significantly attenuates symptoms of joint inflammation and sympathetic efferents may modulate activity in primary afferent nociceptors. Knee replacement surgery eliminates these receptors and allows the levels of substance P to return to normal. If substance P is an objective measurement of pain, clinicians will have a key tool to aid treatment. The distinction between pain (a sensory and emotional experience) and nociception (a physiological response) is crucial for any treatment protocol.

The aim of this study was to evaluate the usefulness of preoperative levels of substance P in the synovial fluid in the prediction of postoperative pain relief after knee replacement surgery.

PATIENTS AND METHODS

A total of 200 patients was included in the study and divided into two groups: 86 had bilateral knee replacement and 114 unilateral knee replacement. Their average age was 74 years (49 to 83) and 70% were women. They were seen consecutively from February 1992 to February 1995. Exclusion criteria included inflammatory conditions known to increase baseline levels of substance P in the synovial fluid such as rheumatoid arthritis, psoriatic arthritis or Reiter’s syndrome.

All patients had severe pain in the knee to be replaced. Pain was measured on a scale divided into four categories: none, mild (pain with vigorous activity), moderate (pain limits activity and requires medication or walking aids), and severe (pain at rest and limitation of activities of daily living). Marked pain reduction meant that pain was reduced by two grades after surgery.

Samples of synovial fluid were obtained immediately before operation by aspiration from each knee in all patients and also at three months postoperatively. They were analysed in blinded samples at the Interscience Insti-
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Inglewood, California and evaluated by radioimmunoassay. Normal reference samples from 7000 volunteer subjects gave values of 50 to 410 pg/ml for women and 88 to 488 pg/ml for men. Values were reported for each patient as elevated or normal: each patient’s test was compared with the reference range. In addition, serum levels of substance P were measured in 15 patients randomly chosen from the bilateral knee replacement group.

Each patient had a preoperative radiological index of arthritis determined by a radiologist who had no knowledge of the diagnosis which was based on findings of joint-space narrowing, sclerosis, osteophytes, and cysts. Ratings on the index were as follows; 0, normal; 1, suspect; 2, minor; 3, moderate; and 4, severe.

We performed statistical analysis using SPSS software (Chicago, Illinois). Paired t-tests were used to compare appropriate preoperative and postoperative mean levels of substance P. Differences were considered to be significant when p < 0.05.

RESULTS

Bilateral total knee replacement. Of the 86 patients with a bilateral total knee replacement, 61 (71%) had a mean (±sd) elevated preoperative level of substance P in both knees of 569 ± 102 pg/ml (449 to 1029) (Table I). All reported marked reduction of pain after knee replacement.

In 18 patients, the level of substance P was normal in both knees. Eleven of these (61%) had marked reduction in postoperative pain after knee replacement.

In the remaining seven patients the level of substance P was normal in one knee and increased in the other. Pain was relieved in six of the seven knees with an elevated substance P and in four of the seven with a normal level but the numbers were too few to determine statistical significance.

The radiological index of degeneration was 3.6 in each of the three subgroups. Postoperatively, the level of substance P was in the normal range in all patients. The difference was statistically significant when compared with the preoperative elevated levels. The serum levels of substance P were normal (219 to 456 pg/ml) in all 15 patients from the randomly selected group with bilateral knee replacement.

Unilateral knee replacement. Of the 114 patients with a unilateral knee replacement, 78 (68%) had a mean elevated preoperative level of substance P in the replaced knee of 581 ± 110 pg/ml (418 to 898) (Table II). The radiological index in these patients was 3.5. Seventy-five (96%) patients in this group had marked reduction of pain after knee replacement. In 48 of these 78 patients the contralateral knee was asymptomatic, had a normal level of substance P and had no significant degenerative disease (radiological index 1.6). In 16 patients, the contralateral (not replaced) knee had pain symptoms and degenerative disease (radiological index 2.7). In these knees, the mean level of substance P was 532 pg/ml (410 to 790). The remaining 14 patients had radiological evidence of degenerative arthritis (index 2.9), but were without pain. All of these patients had normal levels of substance P in their contralateral (not replaced) knee.

In 36 (32%) patients with unilateral knee replacement, the level of substance P was normal in both knees. The preoperative radiological index was 3.2. Of these 36

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<td>Number of patients</td>
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<td>61 (71%)</td>
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<th>Table II. Mean (±sd; range) levels of substance P and details of 114 patients having unilateral knee replacement</th>
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patients, 22 (61%) (Table II) had marked reduction in their preoperative pain after knee replacement and 27 had a normal radiological index (1.5) in the contralateral knee but had pain. Nine had a normal radiological index in the contralateral knee and no pain symptoms.

Postoperatively, the level of substance P was normal in every patient. This difference was statistically significant ($p < 0.05$) when compared with the preoperative levels in the 78 patients with elevated preoperative levels. Two patients with unilateral knee replacement (a 64-year-old woman and a 78-year-old man) had deep infections after surgery. The level of substance P in their synovial fluid remained normal at 119 and 137 pg/ml, respectively.

**DISCUSSION**

Pain from neoplasms, degenerative disorders, and severe injury can reduce function. Such pain responds well to opiates and to surgical treatment. In conditions in which pain is the primary complaint and is resistant to therapy its pathogenesis may differ from that caused by activation of nociceptive afferents. The former type responds much less well to surgical treatment. Because more than half of all patients have pain as a major complaint, distinguishing between pain and nociception is a first crucial step in deciding medical or surgical intervention.

Our findings indicate that preoperative levels of substance P in the synovial fluid may be a predictor of pain relief after knee replacement. While all patients in our study had severe pain in their affected knees, those with elevated preoperative levels of substance P in the synovial fluid had consistently better pain relief (97%) than those with normal preoperative levels (Tables I and II); 61% of patients with normal levels achieved good or excellent pain relief. This was true for both unilateral or bilateral knee replacement although the radiological index was equal to or less than that of patients with elevated levels (Tables I and II). Postoperative levels of substance P dropped significantly when compared with elevated preoperative levels.

The normal serum levels in knee replacement patients in our study confirm the earlier findings of Marshall et al.2 In their report the levels of substance P in the synovial fluid were increased in the knee after trauma and in osteoarthritis in the presence of normal serum values.

Our findings suggest that the preoperative level of substance P in the synovial fluid may serve as a predictor of pain relief after knee replacement surgery.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

**REFERENCES**