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The Utility of Comparative Local Anesthetic Blocks Versus Placebo-Controlled Blocks for the Diagnosis of Cervical Zygapophysial Joint Pain

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Abstract:

Background: The development of target-specific local anesthetic blocks has enabled pain physicians to explore the anatomical source of chronic spinal pain. However, such blocks rely on subjective responses and may be subject to the placebo effect. Comparative local anesthetic blocks have been advocated as a means of identifying true-positive cases and excluding placebo responders. This paradigm employs two local anesthetics with different durations of action; only patients who obtain reproducible relief and correctly identify the longer-acting agent are considered positive.

Objective: Our objective was to evaluate the reliability of comparative blocks of the medial branches of the cervical dorsal rami in the diagnosis of cervical zygapophysial joint pain.

Design: We compared comparative blocks and the criterion-standard of randomized, double-blind, placebo-controlled blocks.

Setting: The study was conducted at a tertiary referral center.

Patients: We studied the first 50 consecutive patients referred for assessment of chronic neck pain (>3 months' duration) after a motor vehicle accident, who completed a series of placebo-controlled blocks after an initial positive response. Patients were 41 ± 11 years (mean ± SD) old with a male/female ratio of 1:2.

Methods: Patients underwent three blocks using three different agents—lignocaine, bupivacaine, and normal saline—administered on separate occasions, in random order and under double-blind conditions. The diagnostic decision based on comparative blocks alone was compared with that based on placebo-controlled blocks.

Results: Comparative blocks were found to have a specificity of 88%, but only marginal sensitivity (54%). Although comparative blocks result in few false-positive diagnoses, their liability is that they result in a high proportion of false-negative diagnoses. Expanding the comparative blocks diagnostic criteria to include all patients with reproducible relief, irrespective of duration, increases sensitivity to 100% but lowers specificity to 65%.

Conclusions: Whether physicians use comparative or placebo-controlled blocks depends upon the implications of their results. If innocuous therapy will be prescribed, comparative blocks might suffice. However, when diagnostic certainty is critical, such as in a medicolegal context or when surgical intervention is contemplated, placebo-controlled blocks are recommended.

Key Words: Cervical zygapophysial joint pain—Diagnostic blocks—Local anesthetic—Neck pain—Placebo effect—Whiplash.

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In other fields of medicine, diagnostic tests are typically based on objective physical data, such as blood tests, biopsies, or radiographs. The diagnosis of pain, however, differs in that it relies on the subjective response of the patient; but subjective responses, particularly to diagnostic blocks, are liable to placebo responses.

"Placebo response," however, is potentially a pejorative term. When, in the course of a diagnostic block, a patient responds to placebo, it may be tempting to infer either that they are malingering or that they do not have genuine, nociceptive pain. The psychological literature is somewhat more generous and explains that the placebo response can be due to such factors as expectancy, conditioning, or a rush of endorphins and does not exclude genuine nociceptive pain (1,2).

It is, nonetheless, important that diagnoses made on the basis of local anesthetic blocks are true-positive and are not confounded by placebo responses. To this end, eminent authorities in pain treatment have recommended that diagnostic decisions be reserved until two blocks have been performed: one block with lignocaine and a second block with bupivacaine (3–5). Only those patients who respond to both blocks and who obtain longer-lasting relief when the longer-acting agent is used should be considered true-positive responders. The implication is that any other pattern of response is some form of placebo response and should be considered negative.

While it is attractive in principle, this comparative block paradigm had not been tested until recently. Under randomized, double-blind conditions, Barnsley et al. (6) performed comparative local anesthetic blocks on patients suspected of having cervical zygapophysial joint pain. They encountered a variety of responses (Table 1). There were patients who obtained no relief after either block, and there were patients who exhibited discrepant responses, in that they obtained relief on the occasion of the first block but not after the second block. These responses were classified as clearly negative. A substantial number of patients obtained complete relief after both blocks and obtained longer relief with bupivacaine. Their responses were concordant with the expected effect of the agents used and accordingly were classified as "concordant." Because these patients behaved in accordance with the comparative block paradigm, they were interpreted as having true-positive responses.

A smaller number of patients responded on both occasions and had a longer-lasting response to bupivacaine, but the duration of relief after lignocaine, bupivacaine, or both was in excess of the known maximum duration of response of these agents (7–10). These responses were classified as "prolonged concordant," but nonetheless were interpreted as true-positive. Particularly vexatious were patients who exhibited "discordant" responses. They obtained complete relief on both occasions, but the response to lignocaine outlasted the response to bupivacaine. "Prolonged discordant" responses were the inordinately prolonged ones to lignocaine.

In terms of the comparative block paradigm, discordant responses should be interpreted as negative because the response is not consistent with the known pharmacology of the agents used. Barnsley et al. (6), however, were concerned about the legitimacy of this interpretation. Discordant responses might be placebo responses or they might be genuine responses and their paradoxical nature might stem from the fact that local anesthetics have a different effect on chronic pain than on cutaneous sensation (6).

Barnsley et al. (6) defended the comparative block paradigm, in so far as concordant responses allowed true-positive responders to be identified. However, they defended their arguments using a statistical test that showed that patients with concordant responses were unlikely to have guessed the responses correctly. While this method may nominally be legitimate, these researchers (6) did not test comparative blocks against placebo. To do so is critical in order to determine the clinical utility of comparative blocks as a diagnostic test.

The present study was undertaken to do just this.

TABLE 1. *Response groups and their definitions*[a]

Response group	Definition
Concordant	Longer pain relief with bupivacaine, with lignocaine lasting <7 h and bupivacaine lasting <24 h
Concordant prolonged	Longer pain relief with bupivacaine, with lignocaine lasting >7 h and/or bupivacaine lasting >24 h
Discordant prolonged	Longer pain relief with lignocaine, with lignocaine lasting >7 h and/or bupivacaine lasting >24 h
Discordant	Longer pain relief with lignocaine, with lignocaine lasting <7 h and bupivacaine lasting <24 h
Discrepant	Relief after only one of the two local anesthetics
Negative	No relief from blocks at any cervical level

[a] From Barnsley et al. (6).

It tested the diagnostic decision based on comparative blocks versus placebo. The study used patients undergoing diagnostic blocks of their cervical zygapophysial joints. However, the study was not intended to determine the prevalence of cervical zygapophysial joint pain or its treatment; these tissues have been addressed elsewhere (11,12). The present study specifically examined whether diagnostic decisions based on comparative blocks were robust or confounded by placebo responses.

METHODS

Subjects

The study sample was drawn from patients referred to the Cervical Spine Research Unit for assessment of chronic neck pain after whiplash injury. The criterion for referral was that patients must have neck pain of more than 3 months' duration after, and attributed to, a motor vehicle accident. The study protocol was approved by the hospital and university ethics committees, and informed consent was obtained from all subjects. A baseline medical assessment was performed; it included a comprehensive medical history and physical examination. Based on the distribution of each patient's pain, a putatively symptomatic cervical zygapophysial joint was selected for investigation, using the method described by Dwyer and colleagues (13,14).

A protocol of placebo-controlled, double-blind, comparative local anesthetic blocks was employed to test the hypothesis that the selected joint was the source of the patient's neck pain. In addition to the use of two local anesthetics with different durations of action—lignocaine and bupivacaine—this protocol incorporated a third, placebo injection of normal saline. The first 50 patients to complete this protocol constituted the study sample.

Diagnostic blocks

All blocks were performed under image-intensifier guidance, using a lateral approach to the medial branches of the cervical dorsal rami, which innervate the target cervical zygapophysial joint. The medial branches below the third occipital nerve do not consistently have cutaneous representation (15–17) and, therefore, are suitable for study using double-blind placebo-controlled blocks. The target points and target specificity of cervical medial branch blocks have been established in antecedent studies (17,18). Each procedure was performed in the presence of a medically qualified, independent observer who corroborated the radiographic position of the operator's needle before any injection.

Each patient was randomly allocated to receive either a short-acting local anesthetic (2% lignocaine) or a long-acting anesthetic (0.5% bupivacaine) for the first block. If a patient obtained no pain relief from the first block, the series was restarted at another, usually adjacent level. This iteration was repeated until pain relief was obtained or until all putatively relevant joints were excluded as the source of neck pain. If a patient obtained relief from the first block at any level below the third occipital nerve, they returned on two more occasions, usually separated by intervals of $\geq$2 weeks. On the second occasion, they were randomly allocated to receive either normal saline or the local anesthetic that they did not receive on the occasion of the first block. On the third occasion, they received the remaining agent. All procedures involved the injection of 0.5 ml of solution onto the target nerve, irrespective of which agent was used.

Analysis

The patient and the operator both remained blind to the order of administration of the three agents until the series of blocks was completed. The patient's responses to these blocks were assessed by way of a structured telephone interview on the evening or day following the block. The patients were asked to report how much their pain was relieved and for how long the relief lasted. A positive response was recorded only if the patient reported complete or profound relief of their pain after the injection.

"Complete" relief was defined as the absence of pain in an anatomical region in which the patient had experienced pain immediately before the block. "Profound" relief was defined as an absence of the patient's usual preprocedural pain, but differed from complete relief in that the patient noted a minor degree of pain, in the same anatomical region, which they distinguished from their usual pain and which they voluntarily associated with the needle track sites. Minor or partial relief, consistent with the usual fluctuation of the patient's pain, was considered a negative response.

The combination of the patients' responses to each of the three agents was used to categorize them into various response groups. First, patients were categorized according to their responses to the two local anesthetics. For ease of comparison, the response group titles and definitions used in the

study of comparative local anesthetic blocks (6) (Table 1) were adopted in the present study. Subsequently, patients within each of these response groups were divided into two subgroups according to whether or not they responded to the placebo injection.

The comparative block paradigm dictates that positive responders are patients who obtain relief after each of the two local anesthetic injections provided that relief with bupivacaine outlasted that with lignocaine; other responses are to be considered negative. The criterion standard adopted in the present study was that positive responders were patients who obtained relief following each of the local anesthetic agents, irrespective of duration of relief, provided that they did not obtain relief after the placebo injection. All other responses were considered negative. The diagnostic decision based on comparative blocks was compared with the diagnostic decision based on the criterion-standard of placebo-controlled blocks. This produced a 2 × 2 contingency table through which the reliability of comparative blocks could be calculated. In essence, the study asked how reliable the diagnosis would be if only the responses to local anesthetics were considered.

RESULTS

The 50 study subjects were 41 ± 11 years (mean ± SD) old with a male/female ratio of 1:2. These patients had experienced neck pain for an average of 5 years before enrollment in the study (range, 7 months to 44 years). Most were either drivers (66%) or front-seat passengers (24%) in closed motor vehicles, but five patients were bicycle or motorcycle riders who incurred flexion-extension injuries. Of those in cars, most were involved in rear-end collisions (46%), but a substantial proportion were involved in front-on (43%) or side-on collisions (11%). Only 28% of patients were employed in the same capacity as they had been before their accidents.

TABLE 2. *Responses to comparative and placebo blocks*

Response group	Placebo negative	Placebo responder
Concordant	11	3
Concordant prolonged	2	0
Discordant prolonged	7	4
Discordant	4	2
Discrepant	6	11

TABLE 3. *Reliability of diagnostic decisions based on comparative blocks*

	Diagnosis based on placebo-controlled blocks (criterion standard)		
	Positive	Negative	
Diagnosis based on comparative blocks			
Positive	13	3	16
Negative	11	23	34
	24	26	50

χ^2 (corrected = 8.56 ($p = 0.003$); sensitivity = 54%; specificity = 88%; positive predictive value = 81%; negative predictive value = 68%; likelihood ratio of positive test = 4.7; and likelihood ratio of negative test = 0.5.

Thirty-eight percent were employed in a reduced capacity, and 34% were off work due to chronic neck pain. At the time of enrollment, all but three patients were involved in litigation with regard to their neck pain. Two had settled their cases before entering the study, and one had never initiated litigation.

The results of diagnostic blocks are summarized in Tables 2 and 3. Based on their responses to comparative diagnostic blocks, 16 patients would have been diagnosed as positive. They obtained reproducible relief from the local anesthetics and correctly discriminated the longer-acting agent. Thirteen of these 16 patients did not respond to saline and were, therefore, true-positive. However, three patients in this group also responded to the placebo injection and, hence, constitute false-positive cases.

On the other hand, based on comparative blocks alone, 34 patients would have been classified as negative, that is, they exhibited discordant or discrepant responses. Twenty-three of these patients were true-negative because either they did not obtain reproducible relief (all those in the discrepant response category; n = 17) or they obtained reproducible relief with the local anesthetics but also with the placebo injection (n = 6). However, 11 of the 34 patients diagnosed as negative by comparative blocks were, in fact, false-negatives since they obtained reproducible relief with each active agent and did not exhibit placebo responses.

As a diagnostic test for cervical zygapophysial joint pain, comparative local anesthetic blocks have a sensitivity of 54% (95% confidence interval 34–74%), a specificity of 88% (95% confidence interval 76–100%), a positive likelihood ratio of 4.7, and a

negative likelihood ratio of 0.5. That is, if a patient exhibits a concordant response to comparative blocks, the posttest odds for having cervical zygapophysial joint pain are 4.7 times the pretest odds, and, conversely, if comparative blocks are negative, the post-test odds are 0.5 times the pretest odds.

DISCUSSION

In order to calculate the sensitivity and specificity of any diagnostic test, it must be compared with a criterion standard. If the diagnostic test has high sensitivity and specificity and is superior to the criterion standard in some other respect, such as being faster, cheaper, or less invasive, then it is considered to possess good clinical utility. The present study explicitly addressed the clinical utility of comparative local anesthetic blocks for the diagnosis of cervical zygapophysial joint pain. The criterion standard used for comparison was a protocol incorporating placebo-controlled blocks. This standard was derived from a series of empirical axioms that form the foundation of pain theory. That is, if pain is of organic, nociceptive origin, then it should be relieved when the nerve supply to the painful structure is blocked by local anesthetic, the relief should be reproducible whenever these nerves are blocked by local anesthetic, and the relief should not be reproduced by injection of a placebo agent.

Comparative local anesthetic blocks are attractive because, in principle, they offer an expeditious means of ruling out placebo responders and ruling in true-positive responders. Placebo-controlled blocks are onerous because they require a third injection that consumes additional time and resources. Furthermore, the administration of placebo injections may be considered unethical in private practice, or at least subject to approval by an ethics committee. Moreover, placebo injections create a financial dilemma since they consume as much time and resources as an active block, and yet charging patients or their insurers for inactive injections might be considered unattractive in some quarters. Comparative blocks would obviate these problems.

However, for comparative blocks to replace placebo-controlled blocks they would have to be shown to be reliable. The present study shows that they are not, although fortunately only in one sense. The specificity of comparative blocks was found to be high, on the order of 88%, with a lower 95% confidence limit of 76%. Consequently, they generate few false-positive results. Therefore, few placebo responders are likely to be inappropriately accorded a positive diagnosis if diagnoses are based solely on comparative blocks.

On the other hand, the present study found comparative blocks to have only a marginal sensitivity, in the order of 54% with 95% confidence limits of 34–74%. Hence, some 46% of patients who are not placebo responders would incorrectly be labeled as placebo responders if diagnoses were based solely on comparative blocks. What the present study shows is that failure to satisfy the comparative block diagnostic criteria does not necessarily mean that the patient is a placebo responder. Indeed, of those patients who exhibited discordant responses, 11 of 17 (65%) survived formal challenge with placebo (Table 2).

The comparative block paradigm, therefore, is not as robust as it might seem in principle. The chance of a false-positive diagnosis is low (12%), but the chance of a false-negative diagnosis is high (46%). Therefore, the liability of comparative blocks is that they fail to detect a large proportion of patients who are not placebo responders but who have the condition. Some 65% of patients who obtain complete relief after both local anesthetics but fail to discriminate the longer-acting from the shorter-acting agent nonetheless survive challenge with placebo. This observation begs the question of what is happening in these patients pharmacologically and physiologically and echoes the previous concerns of Arner et al. (19) and Barnsley et al. (6): Why do some patients with chronic pain obtain inordinately prolonged relief from local anesthetics? This matter would need to be addressed by means beyond the scope of the present study.

The results of the present study, however, do have immediate implications for clinical practice. If a physician seeks to make a diagnosis using diagnostic local anesthetic blocks, certain perils obtain. A single block is unreliable because of the high false-positive rates and poor positive predictive values of single blocks (20,21). Comparative blocks go some way in improving this situation. Their positive predictive value is high, and their false-positive rate is low. But their sensitivity is poor. Their sensitivity may be increased by redefining the criterion for a positive diagnosis to include all patients with reproducible relief after the two local anesthetics, irrespective of duration of relief. Using this expanded diagnostic criterion raises the sensitivity of compar-

ative blocks to 100% but at the expense of specificity, which falls to 65%. Hence, in order to be certain that an individual patient is or is not a placebo responder, frank challenge with a placebo injection must be performed under double-blind conditions.

Whether a physician chooses to use comparative blocks or triple blocks with placebo control basically depends on the implications of the result obtained. If relatively innocuous therapies are to be prescribed on the basis of a positive diagnosis, comparative blocks might suffice. If a positive response is redefined as complete relief after both anesthetics irrespective of duration, only 27% of the sample (nine of 33; Table 2) would be placebo responders.

However, if it is critical to have diagnostic certainty, for example in medicolegal proceedings or when surgical therapy is contemplated, comparative blocks may not be enough. Some 19% of apparently positive patients will be falsely positive, and some 46% of patients could be diagnosed falsely negative. Under these circumstances, only triple blocks incorporating placebo controls reduce the uncertainty.

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REFERENCES

1. Voudouris NJ, Peck CL, Coleman G. Conditioned response models of placebo phenomena: further support. *Pain* 1989; 38:109–16.
2. Peck C, Coleman G. Implications of placebo therapy for clinical research and practice in pain management. *Theor Med* 1991;12:247–70.
3. Bonica JJ, Butler SH. Local anaesthesia and regional blocks. In: Wall PD, Melzack R, eds. *Textbook of pain*, 3rd ed. Edinburgh: Churchill Livingston, 1994:997–1023.
4. Bonica JJ, Buckley FP. Regional analgesia with local anaesthetics. In: Bonica JJ, ed. *The management of pain*, 2nd ed. Philadelphia: Lea & Febinger, 1990:1883.
5. Boas RA. Nerve blocks in the diagnosis of low back pain. *Neurosurg Clin* 1991;2:807–16.
6. Barnsley L, Lord SM, Bogduk N. Comparative local anaesthetic blocks in the diagnosis of cervical zygapophysial joint pain. *Pain* 1993;55:99–106.
7. Watt MJ, Ross DM, Atkinson RS. A double blind trial of bupivacaine and lignocaine. *Anaesthesia* 1968;23:331–7.
8. Rubin AP, Lawson DIF. A controlled trial of bupivacaine: a comparison with lignocaine. *Anaesthesia* 1968;23:327–31.
9. Cousins MJ, Mather LE. Clinical pharmacology of local anaesthetics. *Anaesth Intens Care* 1980;8:257–77.
10. Moore DC, Bridenbaugh LD, Bridenbaugh PO, et al. Bupivacaine for peripheral nerve block: a comparison with mepivacaine, lidocaine, and tetracaine. *Anesthesiology* 1970;32: 460–3.
11. Barnsley L, Lord SM, Wallis BJ, Bogduk N. Lack of effect of intra-articular corticosteroids for chronic cervical zygapophysial joint pain. *N Engl J Med* 1994;330:1047–50.
12. Barnsley L, Lord SM, Wallis BJ, Bogduk N. Chronic cervical zygapophysial joint pain after whiplash: a prospective prevalence study. *Spine* 1995;20:20–6.
13. Dwyer A, Aprill C, Bogduk N. Cervical zygapophyseal joint pain patterns. I. A study in normal volunteers. *Spine* 1990; 15:453–7.
14. Aprill C, Dwyer A, Bogduk N. Cervical zygapophyseal joint pain patterns. II. a clinical evaluation. *Spine* 1990;15:458–61.
15. Johnston HM. The cutaneous branches of the posterior primary divisions of the spinal nerves and their distribution in the skin. *J Anat Physiol* 1908;43:80–94.
16. Pearson AA, Sauter RW, Buckley TF. Further observations on the cutaneous branches of the dorsal primary rami of the spinal nerves. *Am J Anat* 1966;118:891–903.
17. Bogduk N. The clinical anatomy of the cervical dorsal rami. *Spine* 1982;7:319–30.
18. Barnsley L, Bogduk N. Medial branch blocks are specific for the diagnosis of cervical zygapophysial joint pain. *Reg Anesthes* 1993;18:343–50.
19. Arner S, Lindblom U, Meyerson BA, Molander C. Prolonged relief of neuralgia after regional anesthetic blocks: a call for further experimental and systematic clinical studies. *Pain* 1990;43:287–97.
20. Barnsley L, Lord SM, Wallis BJ, Bogduk N. False-positive rates of cervical zygapophysial joint blocks. *Clin J Pain* 1993;9:124–30.
21. Schwarzer AC, Aprill CN, Derby R, Fortin J, Kine G, Bogduk N. The false-positive rate of uncontrolled diagnostic blocks of the lumbar zygapophysial joints. *Pain* 1994;58: 195–200.