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Commentary

On the validity and clinical utility of comparative local anesthetic blocks for the diagnosis of spine pain

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1. Introduction

An article [1] and an editorial [2] recently raised questions about the validity and utility of comparative local anesthetic blocks. In some situations, these blocks can provide a practical alternative to placebo controls in the diagnosis of spine pain. However, understanding how their validity should be evaluated can be difficult because of the technical nuances of the biostatistics involved. Therefore, since this issue has become topical it is appropriate to revisit the rationale of comparative local anesthetic blocks and the currently available data on their validity.

2. Origin

Before the advent of Evidence-Based Medicine at the turn of the 20th century, medical practice was steered by Eminence-Based Medicine [3]. Eminent, respected authorities in a discipline would proclaim what should be done in practice, even when evidence for those proclamations was lacking. This was the intellectual milieu in which comparative local anesthetic blocks emerged.

In the early days of pain medicine, it made sense that local anesthetic blocks could be used to determine either the source of pain or the nerves that mediated the pain. However, advocates of local anesthetic blocks also recognised that, for various reasons, patients with pain might express a placebo response, or an otherwise false response, to a single diagnostic block. Some form of control was necessary. Eminent authorities at the time suggested that comparative blocks provided such a control [4–6].

The concept was that if a diagnostic block was repeated, using a local anesthetic agent with a different duration of action, a genuine response would be long-lasting relief when a long-acting agent was used, and short-lasting relief when a short-acting agent was used. Because this rationale sounded sensible, the concept was accepted, and became the standard of care amongst those who practised controlled blocks, even though no-one had produced empirical evidence to validate comparative blocks.

3. Principles

The validity of a diagnostic test is a measure of how well the test detects the presence and absence of a condition, and distinguishes between the two [7–9]. Classically, validity is determined by comparing the results of the test with the results of a criterion standard test. The criterion standard is a test whose validity is not doubted, or is substantially less in doubt than that of the test in question. Examples include using imaging findings as the criterion standard for physical examination, or using biopsy results as the criterion standard for imaging tests.

Sometimes such conventional criterion standards are not available, but surrogates that are not diagnostic tests might be used as a substitute criterion standard. One example is to use the results of treatment, but for that to be a suitable criterion standard the treatment needs to have perfect or near perfect outcomes.

In the case of diagnostic blocks for spinal pain, no imaging tests or classical tests are available to serve as a criterion standard, but a suitable alternative are placebo-controlled blocks. The rationale is that if a patient

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has genuine, physiological responses to diagnostic blocks they will report relief when local anesthetic agents are used but no relief when a placebo is administered. Conversely, if a patient cannot distinguish placebo from an active agent, and reports relief when a placebo is used, their responses to blocks cannot be regarded as physiologically and pharmacologically valid. Accordingly, the validity of responses to diagnostic blocks (relief or no relief) can be compared with the responses to placebo (relief or no relief) where the correct response for presence of the condition being diagnosed is relief from diagnostic blocks but no relief from placebo.

When a diagnostic test is compared with a criterion standard, two, basic statistics can be derived. The sensitivity of the test measures how often it correctly detects the presence of the condition being diagnosed; and can also be called the true-positive rate of the test [7–9]. How often the test correctly detects the absence of the condition is referred to as it specificity, or true-negative rate. The complement of the specificity (1 – specificity) is the false-positive rate [7–9].

These two statistics can be combined into a single, summary statistic known as the positive likelihood ratio [7–9]. This is the ratio between the sensitivity of the test and the complement of its specificity (1 – specificity), which is the same as the ratio between the true-positive rate of the test and its false-positive rate. Metaphorically, the positive likelihood ratio is the true-positive rate discounted by the false-positive rate. This quantifies the extent to which the chances of a positive result being true exceed the chances of it being false [9].

The complement of the positive likelihood ratio is the negative likelihood ratio, which measures how well the test excludes, or rules out, the presence of the condition being diagnosed. The negative likelihood ratio is calculated as [1 – sensitivity]/[specificity] [7,8].

Although sensitivity, specificity, and positive likelihood ratio are intrinsic properties of a diagnostic test, they alone do not show how useful the test is in clinical practice. The clinical utility of the test is affected by the prevalence of the condition being diagnosed. In that regard, the positive likelihood ratio serves as a coefficient that can be applied to the prevalence of the condition being diagnosed in order to calculate the positive predictive value of the test, for that particular prevalence [9]. In the formal language of statistics, this process amounts to converting the odds that the condition is present before the test is applied (pre-test odds) to the odds that the condition has been correctly detected after the test has been applied (post-test odds) [7,8].

For reasons of mathematical simplicity these calculation are performed with the prevalence, the likelihood ratio, and the resultant positive predictive value being expressed as odds [9]. However, once the positive predictive value is known, it can be converted into a percentage. That percentage provides the diagnostic confidence that users of the test can have in its results, for it shows the chances that a positive result is correctly positive [9].

These principles provide two important conceptual messages relevant to the discussion of the validity of comparative local anesthetic blocks. Validity is not a binary property; there is no absolute value of the likelihood ratio that determines if a test is valid or not valid. The value of a likelihood ratio can be anywhere between zero and infinity. Whether or not a particular value of the likelihood ratio makes the test clinically useful depends on the prevalence of the condition being diagnosed. The clinical utility of a diagnostic test can be calculated by applying its likelihood ratio to the prevalence of the condition being diagnosed, in order to determine the positive predictive value and diagnostic confidence that the test provides in that context.

4. Evidence

4.1. Barnsley et al

The first investigation into the validity of comparative blocks was conducted by Barnsley et al. [10]. Barnsley was interested in using cervical medial branch blocks to determine the prevalence of cervical zygapophysial joint pain. However, he recognised that he needed to validate these blocks before they could be used as a dependable, investigative tool.

When he consulted the literature, Barnsley discovered that there appeared to be a firm foundation for comparative blocks. Studies in patients undergoing regional blocks for surgical procedures showed that bupivacaine had a significantly longer duration of action than did lidocaine. Indicative figures for the duration of action of lidocaine were 1–3 hours, with a two standard deviation upper limit of 7 hours. For bupivacaine the figures were 3–10 hours with an upper limit of 24 hours [11–16]. Furthermore, a study in normal volunteers, who simultaneously received symmetrical injections of bupivacaine and lidocaine had shown that nearly always did bupivacaine outlast lidocaine [14].

In his study, Barnsley tallied the responses of consecutive patients, with neck pain after whiplash, who underwent cervical medial branch blocks. His paper reported 47 patients [10], but his PhD Thesis reported an additional 8 patients [17]. In the study, each patient was randomized to undergo a first block using either 0.5% bupivacaine or 2% lidocaine, on a double-blind basis. If this block proved positive, a second block was performed using the opposite agent. The criteria for a positive response were complete relief of pain, defined by an answer of “yes” to the question: has your pain gone?, and an answer of “no” to the question: do you have any pain left?, corroborated by an entry of zero on a visual analog scale. Duration of complete relief was measured as the period to the time at which the patient first clearly perceived the return of pain.

Of 58 patients who had a positive response to an initial block, 55 were also positive to the second block. Of these latter patients, 41 reported longer-lasting relief when bupivacaine was used.

For the purposes of testing the validity of comparative blocks, Barnsley ingeniously used the binomial test. This showed that the probability that such a large proportion of consecutive patients could have reported correct responses by chance alone was vanishingly small. Therefore, by and large, the responses had to be valid.

Barnsley displayed his data in a manner appropriate to the hypothesis that he tested. If those data are displayed in a different way they reveal features that are pertinent to concerns raised later about the validity of comparative blocks.

Fig. 1 shows the frequency distributions of the durations of action of the two local anesthetic agents used. Plotting these data shows immediately that referring to mean values is inappropriate, because the distribution is heavily skewed to the left, with modal scores in the range of 1, 2, or 3 hours. Indeed, the mean duration of action is 11 hours for lidocaine and 17 hours for bupivacaine, which are bizarre values compared with the available normative data [11–16]. The median values (interquartile range) were 5 (2–17) for lidocaine, and 8 (4–24) for bupivacaine, which are closer to the normative data but nevertheless still somewhat large.

In Fig. 1, the values for lidocaine and bupivacaine might not appear to

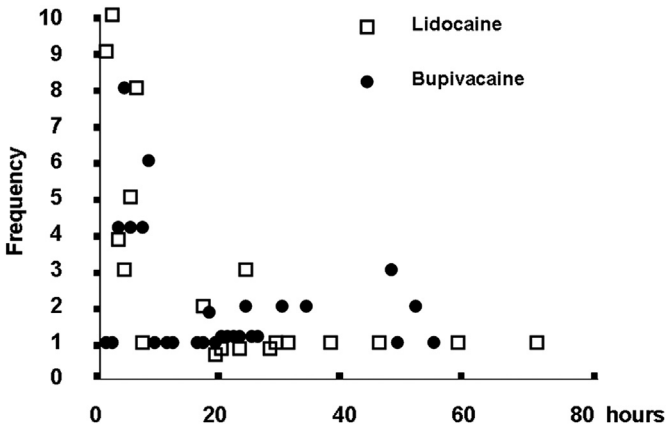

Fig. 1. The frequency distributions of different durations of action for lidocaine and bupivacaine.

be significantly different statistically, but they are. There are no differences between the two agents for the distributions in the ranges of between 7 and 24 hours and longer than 24 hours, but a large difference occurs in the range under 7 hours. This becomes more evident when the data are tabulated.

Table 1 shows that lidocaine was significantly more often represented in range of 0–7 hours. The table also shows that 73% of responses to lidocaine and 75% of responses to bupivacaine were in the expected range of duration for those respective agents. The strange distribution evident in Fig. 1 arises because of the 28% of responses to lidocaine, and the 24% of responses to bupivacaine that were prolonged, beyond expected duration of action.

Table 2 shows that these data become more revealing when they are stratified according to if patients had concordant responses (longer-lasting relief after bupivacaine) or discordant responses (longer relief after lidocaine).

Concordant responses occurred in 75% of patients. In 53% of patients those concordant responses occurred when the durations of action of each of the local anesthetic agents used were in the expected range. In 13% and 9% of patients, concordant responses occurred when patients had prolonged responses to bupivacaine or to both agents.

Discordant responses occurred in 25% of patients. In 7% of patients those discordant responses occurred when both of the agents used had expected durations of action. In 15% and 4% of patients, discordant responses occurred when the patient had a prolonged response either to lidocaine or to both agents.

In the first instance, only 60% of patients had responses for the expected duration of action of the local anesthetic agents used; 40% had prolonged responses to bupivacaine, lidocaine, or both. This implies that, in a large proportion of patients with chronic pain, local anesthetic agents may act in a different way than they do in patients who are pain-free. One possibility is that when acting on open sodium channels local anesthetics have a longer duration of action than when they act only on cell membranes.

Secondly, while it might be satisfying that 75% of patients in this cohort had concordant responses, in keeping with the rationale of comparative local anesthetic blocks, it is sobering that 25% had discordant responses, largely because of prolonged responses to lidocaine. Discordant responses render the interpretation of comparative blocks complicated, but not impossible.

Barnsley's study was helpful in that it showed that comparative blocks seemed, on average, to be valid, but it also warned that discordant responses and prolonged responses to local anesthetics threatened the validity of comparative blocks. However, Barnsley's study did not show how often comparative blocks were valid in a given patient. That question requires a different methodology.

4.2. Lord et al

Having assisted Barnsley in his study, Susan Lord recognised that the validity of concordant and discordant responses had to be established rigorously. For her study [18] she adopted placebo controls as the criterion standard.

Table 1
The number and proportions of durations of responses to lidocaine and bupivacaine that occurred in the expected range for lidocaine (0–7 hours), the expected range for bupivacaine (0–7 hours and 7–24 hours), and beyond those ranges (>24 hours).

Agent	Duration of Action		
	0–7 hours	7–24 hours	>24 hours
Lidocaine	40	8	7
	73%	15%	13%
Bupivacaine	22	22	13
	40%	35%	24%

Table 2
The numbers and proportions of patients with concordant or discordant responses according to whether the durations of action were within the expected range for both lidocaine and bupivacaine, or if the duration of action was prolonged for either bupivacaine or lidocaine, or both agents.

RESPONSE	DURATION OF ACTION				TOTAL
	EXPECTED	PROLONGED			
		Bupivacaine >24 hours	Lidocaine >7 hours	Both	
Concordant	29	7		5	41
Discordant	4		8	2	14
Concordant	53%	13%		9%	75%
Discordant	7%		15%	4%	25%
	60%	40%			

In the study, patients with chronic neck pain underwent medial branch blocks. On a double-blind basis, each patient was randomised to undergo a first block using either 2% lidocaine or 0.5% bupivacaine. If their response to the first block was positive, the randomisation continued for a second block, for which the patient received either a normal saline placebo or the local anesthetic agent that had not been used for the first block. For a third block they received the agent that had not already been used. The criteria for a positive response were complete relief of pain, corroborated by a visual analog score of zero.

Table 3 shows the raw data of the results obtained. Concordant responses were strongly associated with negative responses to placebo. Two patients had concordant responses with prolonged responses to one or other of the agents used, but neither responded to placebo. The majority of the patients with discordant responses, with either expected or prolonged durations of action, did not report placebo responses.

The study also revealed that 34% of patients expressed another category of response, called discrepant. These patients had no relief from the second block with local anesthetic, and either did or did not respond to placebo. This lack of response to a second local anesthetic indicated inconsistency and, therefore, constituted a negative response.

Lord did not study the negative likelihood ratio of comparative blocks. To do so would have required subjecting to second and third, placebo-controlled blocks patients who had already had a negative response to their first block, The ethics of doing this, simply to measure a statistic, would have been questionable. However, the high rate of discrepant responses encountered by Lord indicates that performing comparative blocks serves to identify a large proportion of patients with negative responses, additional to those found negative after their first block.

Table 4 shows the data of Lord arranged to establish the sensitivity, specificity, and positive likelihood ratio of concordant responses, regardless of whether responses were prolonged or not. Although the sensitivity of concordant responses is modest, their specificity is high, and generates a positive likelihood ratio of 4.5.

Calculating the likelihood ratio for discordant responses requires a realisation that might not immediately be evident. Technically, if discordant responses are being tested, concordant responses would have to be classified as negative because, by definition, they are not discordant

Table 3
The numbers of patients who had different types of response to comparative blocks, matched with whether or not they responded placebo.

Response to Blocks	Placebo Response	
	No	Yes
Concordant	11	3
Concordant Prolonged	2	0
Discordant	4	2
Discordant Prolonged	7	4
Discrepant	6	11

Table 4
The data for deriving the sensitivity (SENS), specificity (SPEC) and positive likelihood ratio (+LR) of concordant responses to cervical medial branch blocks, with placebo constituting the criterion standard.

CONCORDANT RESPONSES					
	Condition Present		SENS	SPEC	+LR
	Yes	No			
Positive	13	3	0.54	0.88	4.5
Negative	11	23			
	24	26			

responses and, therefore, do not constitute positive discordant responses. Expressed in another way, discordant responses cannot be credited for diagnosing patients who have already been found to be positive because of concordant responses. Consequently, as shown in Table 5, the sensitivity of discordant responses amounts to 0.46, and their specificity is 0.77, with a positive likelihood ratio of 2.0. This value shows that discordant responses are valid but only weakly so.

Any confusion about this conclusion can be resolved by understanding that a physician who performs comparative blocks may encounter both concordant and discordant responses. The low sensitivity of discordant responses arises because they are used to detect only the additional cases left over after concordant responses have been taken into account. When assessing the utility of their blocks, a physician would apply the likelihood ratio of 4.5 to the concordant cases, and the likelihood ratio of 2.0 for the discordant cases.

Another approach could be to disregard both the duration of action and whether bupivacaine outlasted lidocaine. This allows the likelihood ratio to be calculated for simply two blocks, which some physicians refer to as "dual" blocks, or simply repeat blocks. Doing so combines and averages the validity of concordant and discordant responses. Table 6 shows that the sensitivity of dual blocks is 1.00, but their specificity is 0.65, with a likelihood ratio of 2.9.

These data can now be used to determine the diagnostic confidence and clinical utility that different likelihood ratios provide in different contexts. Table 7 shows some examples.

Table 7 exhibits two features. Firstly, higher likelihood ratios provide greater degrees of diagnostic confidence, for any prevalence. However, regardless of the value of the likelihood ratios, diagnostic confidence falls as the prevalence of the condition being diagnosed falls.

For a condition with a prevalence of 60%, a likelihood ratio of 4.5 provides an impressive diagnostic confidence of 87%' but even a likelihood ratio of 2.0 provides a reasonable confidence of 75%. So, concordant and discordant responses have reasonable clinical utility.

When the prevalence drops to 30%, the diagnostic confidence provided by a likelihood ratio of 4.5 falls to 66%, which might still be acceptable, but for the likelihood ratios of 2.9 and 2.0 the diagnostic confidence plummets to 55% and 46%. These latter two figures reflect diagnostic confidence barely different from that achieved by guessing. Expressed in another way, when prevalence is as low as 30%, concordant responses retain a fair degree of clinical utility, but the utility of discordant responses and the utility of "dual" blocks that disregard duration of action and concordance are both no better than guessing.

Table 5
The data for deriving the sensitivity (SENS), specificity (SPEC) and positive likelihood ratio (+LR) of discordant responses to cervical medial branch blocks, with placebo constituting the criterion standard.

DISCORDANT RESPONSES					
	Condition Present		SENS	SPEC	+LR
	Yes	No			
Positive	11	7	0.46	0.77	2.0
Negative	13	20			
	24	26			

Table 6
The data for deriving the sensitivity (SENS), specificity (SPEC) and positive likelihood ratio (+LR) of repeat cervical medial branch blocks, without regard to the duration of response.

CONCORDANT OR DISCORDANT RESPONSES					
	Condition Present		SENS	SPEC	+LR
	Yes	No			
Positive	24	9	1.00	0.65	2.9
Negative	0	17			
	24	26			

Table 7
The diagnostic confidence (DC) of a positive result after diagnostic tests with different positive likelihood ratios (LR) for different prevalences of the condition being diagnosed.

Prevalence	LR	DC	LR	DC	LR	DC
60%	4.5	87%	2.9	81%	2.0	75%
40%	4.5	75%	2.9	66%	2.0	57%
30%	4.5	66%	2.9	55%	2.0	46%
15%	4.5	39%	2.9	34%	2.0	26%

When the prevalence is as low as 15%, diagnostic confidence effectively evaporates for all three likelihood ratios, because in all cases the diagnostic confidence is well below 50%. For every patient correctly diagnosed as positive, there will be two or three diagnosed incorrectly as positive.

So, for a condition such as cervical zygapophysial joint pain, which has a prevalence of about 60% [19,20], concordant responses and discordant responses would provide similar, and possibly acceptable, levels of diagnostic confidence. For lumbar zygapophysial joint pain, which has a prevalence of only 11% [21], neither concordant nor discordant responses would provide acceptable levels of diagnostic confidence. In other words, neither concordant nor discordant responses would be valid for this condition.

5. Discussion

The studies of Barnsley [10,17] and Lord [18] are the only ones that have sought to convert comparative local anesthetic blocks from Eminence-Based Medicine to Evidence-Based Medicine. No-one else has undertaken the necessary, placebo-controlled studies. So, the evidence-base upon which to discuss challenges to the concept of comparative blocks is limited; but it is not lacking.

If critics dislike the results of Lord [18] they should repeat her study, and refute it. Conversely, those who believe her results could serve future discussions well by replicating her study to corroborate those results. If critics suspect that Lord's data do not apply to lumbar medial branch blocks or to other blocks, they should conduct the necessary placebo-controlled trials to determine the likelihood ratios for those other blocks. Science is advanced by pitting studies against studies, and comparing the evidence that they produce. It is not advanced by unfounded, alarmist assertions, regardless of how appealing those assertions might be.

A recent study claimed "(to call) into question the clinical utility of considering duration of relief when performing dual medial branch blocks" and that "any emphasis on concordant duration of relief from specific anesthetics … should be reconsidered" [1]. These claims raised sufficient concern that an editorial was commissioned.

That editorial [2] was stronger in its conclusions than was the original study. It concluded that the results of the study "have contradicted years of conventional wisdom" and that "we must now question the utility of relying on concordant responses when interpreting dual diagnostic blocks".

These assertions are wrong. The results of the study do not contradict

conventional wisdom, and they do not question the validity of comparative blocks.

The conventional wisdom is that some patients with chronic neck pain may have prolonged responses to lidocaine, or to bupivacaine, or to both [10]; but nevertheless, when matched against placebo, concordant responses have a likelihood ratio of 4.5, and discordant responses have a likelihood ratio of 2.0 [18]. Either of these likelihood ratios provides acceptable clinical utility for diagnosing common conditions, such as cervical zygapophysial joint pain, but they are clinically useless for diagnosing uncommon conditions. None of this "wisdom" is challenged, let alone refuted, by the results of Schneider et al. [1].

Those results no more than describe the mean and median durations of relief in 51 patients who underwent blocks with lidocaine, and a separate group of 99 patients who underwent blocks with bupivacaine. Comparing representative durations of action of one agent in one group and another agent in a different group does not constitute a test of comparative blocks. The appropriate test is to compare the durations of action of the two agents in each individual patient, and to match concordant and discordant responses against placebo responses. Schneider et al. [1] explicitly acknowledge that they took neither of these actions. So, by definition, their study was not capable of questioning the clinical utility of comparative blocks.

To some extent the results of Schneider et al. [1] serve to corroborate the observations of Barnsley [10] that some 25% of responses, either to lidocaine or to bupivacaine, can be prolonged. However, the data reported by Schneider et al. [1] do not reveal exactly what proportion of their patients had such prolonged responses. To estimate that proportion, the mean values and standard deviations reported by Schneider et al. [1] can be disregarded because the durations of action of local anesthetics are not normally distributed (as shown in Fig. 1 above); but the median data can be used.

The data derived from numerical pain rating scores, tell us that the median duration (interquartile range) for bupivacaine was 0.5 (0.5–3.5). The upper interquartile range of these data shows that 75% of patients had durations of action less than 3.5 hours, which is substantially less than 24 hours. We can, therefore, infer that very few patients, if any, had prolonged responses beyond 24 hours. For lidocaine the median duration (interquartile range) was 9 (0.5–48), which implies that well over 50% of patients had prolonged responses beyond 7 hours.

While we might be bound to accept that a very large proportion of patients had prolonged responses to lidocaine, the median value and lower interquartile limit of the data for bupivacaine (0.5; 0.5–3.5) tell us that 50% of patients had less than half an hour of relief after bupivacaine. This portrays bupivacaine as an ultra-short-acting agent, which seems outrightly bizarre, for it is severely dissonant with common clinical experience, the data of Barnsley (Fig. 1), and other published data [11–16] on bupivacaine.

In that regard, the data reported by Schneider et al. [1], based on patients' estimate of duration of relief obtained, paint a different picture. For bupivacaine, the median duration (interquartile range) was 9 hours (2–48). For lidocaine it was 6 (0.5–13.5). These data resonate better both with clinical experience, and with the data of Barnsley (Fig. 1). Moreover, they raise no concern about the validity of comparative blocks.

Validity is measured by likelihood ratios, and clinical utility is measured by the diagnostic confidence that these likelihood ratios provide according to the prevalence of the condition being diagnosed. Retrospective studies of the average duration of action of local anesthetics in disparate samples of patients do neither.

Declaration of competing interest

The author declares no financial interests and no conflicts of interest concerning the content and topic of this manuscript.

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