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Original Research Article

Sympathetic Blocks as a Predictor for Response to Ketamine Infusion in Patients with Complex Regional Pain Syndrome: A Multicenter Study

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Abstract

Background. Ketamine infusions are frequently employed for refractory complex regional pain syndrome (CRPS), but there are limited data on factors associated with treatment response. Sympathetic blocks are also commonly employed in CRPS for diagnostic and therapeutic purposes and generally precede ketamine infusions. **Objectives.** We sought to determine whether demographic and clinical factors, and technical and psychophysical characteristics of sympathetic blocks are associated with response to ketamine infusion. **Methods.** In this multi-center retrospective study, 71 patients who underwent sympathetic blocks followed by ketamine infusions at 4 hospitals were evaluated. Sympathetically maintained pain (SMP) was defined as $\geq$ 50% immediate pain relief after sympathetic block and a positive response to ketamine was defined as $\geq$ 30% pain relief lasting over 3 weeks. **Results.** Factors associated with a positive response to ketamine in univariable analysis were the presence of SMP (61.0% success rate vs 26.7% in those with sympathetically independent pain; $P = .009$) and post-block temperature increase (5.66 $\pm$ 4.20 in ketamine responders vs 3.68 $\pm$ 3.85 in non-responders; $P = .043$). No psychiatric factor was associated with ketamine response. In multivariable analysis, SMP (OR 6.54 [95% CI 1.83, 23.44]) and obesity (OR 8.75 [95% 1.45, 52.73]) were associated with a positive ketamine infusion outcome. **Conclusions.** The response to sympathetic blocks may predict response to ketamine infusion in CRPS patients, with alleviation of the affective component of pain and predilection to a positive placebo effect being possible explanations.

Key Words: Complex Regional Pain Syndrome; Ketamine; Predictive Test; Reflex Sympathetic Dystrophy; Stellate Ganglion Block; Sympathetic Block

Introduction

Complex regional pain syndrome (CRPS) is a debilitating clinical condition that is challenging to diagnose and treat [1–3]. Similar to other syndromes that are phenotypically variable, lack distinct pathophysiological mechanisms, and are devoid of biomarkers, the most common

form of CRPS- type 1, which comprises nearly 90% of cases- is often classified as a nociplastic condition, of which central sensitization is a hallmark [1, 4]. Clinically, CRPS type 1 and type 2, which bridges the gray zone between neuropathic and nociplastic pain, are clinically indistinguishable [4, 5].

Two of the most common treatments for CRPS are sympathetic blocks and ketamine infusion, neither of which has been studied in high-quality randomized studies. A systematic review evaluating sympathetic blocks for CRPS found scant evidence for meaningful therapeutic benefit based on predominantly low-quality studies [6]. Nevertheless, most algorithms still advocate sympathetic blocks to distinguish between sympathetically maintained pain (SMP) and sympathetically independent pain (SIP), which may have treatment implications [7]. For ketamine, there is weak evidence, also based on low-quality studies, for benefit lasting at least 4 weeks [8, 9].

Although ketamine infusions may provide pain relief in select individuals with refractory CRPS, infusions are labor intensive, are associated with frequent and occasionally significant side effects, and are currently devoid of current procedural terminology (CPT) codes, which translates to high out-of-pocket expenses for desperate patients who might benefit [9]. Moreover, studies have failed to identify a subpopulation likely to respond to treatment, though it has been hypothesized that long-term benefit may derive more from attenuation of the affective-motivational component of pain than the sensory-discriminative component; this may be especially relevant in CRPS, which is associated with a high burden of psychopathology [1, 4, 10]. For procedures that carry significant risks and costs, and where a subset of responders has not been clearly identified, pre-procedure screening tests may have clinical utility. Previously, sympathetic blocks have been used to screen CRPS patients for botulinum toxin injections and surgical sympathectomy and have had mixed results in predicting response to spinal cord stimulation [11–14]. However, their prognostic value has not been studied for ketamine infusions despite growing utilization. Our objectives are to determine whether temperature change and response to sympathetic blocks are correlated with response to ketamine, and to identify a subset of responders.

Methods

Selection Criteria

Permission to conduct this study was granted by the Institutional Review Boards of the Johns Hopkins School of Medicine, Seoul National University and Cleveland Clinic, and the public affairs office at the Uniformed Services University. Patients diagnosed with CRPS based on clinical Budapest Criteria [7] between January 2011 and December 2021 were identified by International Classification Diseases (ICD)-9 (e.g., 337, 354, 355) and ICD-10 (G90) codes and cross-referenced with those who received sympathetic blocks (e.g., 64510, 64520) and ketamine infusions (96365) based on Current Procedural Technology (CPT) codes.

Inclusion criteria included adult patients with CRPS who received a stellate ganglion or lumbar or thoracic sympathetic block followed at various time intervals (median interval 209 days, interquartile range 77–499) by a ketamine infusion; individuals with pre- and post-block temperatures and pain scores recorded; and those with pre- and 4–8-week post-infusion ketamine scores recorded. Excluded from analysis were patients with insufficient documentation of pre- or post-block or ketamine infusion outcomes (e.g., temperatures and pain scores); those who failed to meet full Budapest criteria for CRPS including individuals with a diagnosis of CRPS-NOS (not otherwise specified); and patients who received concomitant analgesic therapy (e.g., opioid therapy, a new adjuvant) between their ketamine infusion and follow-up that might confound analysis; in those who received concurrent analgesic therapy before their 4–8-week intermediate-term post-block follow-up, these follow-up data were omitted. In patients who underwent serial blocks or repeat ketamine infusions (n = 41 including nine non-responders), only data from the initial procedure was analyzed.

Procedures

Sympathetic Blocks

All procedures were performed in accordance with previously published standards using image guidance [5, 11, 14]. Patients were pre-hydrated with intravenous fluids, monitored by an anesthesiologist, and received light sedation with fentanyl and midazolam as indicated (n = 18). Stellate ganglion blocks (SGB) were performed for upper extremity CRPS, and lumbar sympathetic blocks (LSB) for lower extremity symptoms. For SGB done with ultrasound, local anesthetic (LA) was injected between the prevertebral fascia and longus colli muscle or just anterolateral to it at C6, while fluoroscopically guided procedures were done by injecting LA just anterior to the medial part of the C6 or C7 transverse process. Lumbar sympathetic blocks were performed at one or more than one (n = 5) level between L2 and L4 using digital subtraction or real-time contrast injection to confirm spread to the antero-lateral aspect of contiguous lumbar vertebral bodies, as well as to ensure the absence of intravascular, muscular or nerve root spread. When the treating physician was satisfied with contrast spread, a LA solution comprised of lidocaine 1%–2% (n = 9), bupivacaine or levobupivacaine 0.25%–0.5% (n = 52), or a 50:50 mixture of the two (n = 10), was incrementally injected at volumes ranging from 5–10 mL for SGB and 10–20 mL for LSB.

Ketamine Infusions

Most ketamine infusions were performed in an outpatient setting over a 4-hour period, with vital signs monitored by a nursing team and anesthesiologist. One patient received a multi-day inpatient procedure. The mean dose of ketamine was 174.54 mg (SD 149.45). Midazolam or clonidine was given preemptively or as needed to prevent or treat psychomimetic and sympathomimetic effects, and antiemetics were utilized as needed for nausea and vomiting.

Data Collection

Data were collected on a range of demographic, clinical, and technical factors chosen based on their effects on outcomes for CRPS treatment [7, 15, 16]. Baseline demographic and clinical information collected included age, sex, type of CRPS, etiology, location, co-existing psychosocial conditions, baseline pain score, secondary gain, smoking and obesity status, and opioid consumption. Technical block parameters recorded included type, location, volume and anesthetic mixture, and baseline and post-block temperatures. Block volumes were defined as high when volumes exceeded 16 mL for lumbar sympathetic blocks or 8 mL for SGB. Procedural data recorded for ketamine infusions included type (single or multi-day), dose, and post-discharge pain score.

Outcomes Measures

Pre- and post-block temperatures were measured by applying non-contact infrared thermometers or skin temperature sensors at two or three areas on the distal palmar and plantar surfaces of the hands or feet, with the mean temperature calculated. These techniques have been shown to be reliable and highly correlated [17]. Sympathetic blocks were considered technically successful when the increase in temperature in the affected extremity exceeded 2° C [5, 18].

A diagnosis of SMP was rendered for individuals who experienced $\geq$ 50% immediate pain reduction based on 6-hour pain diaries or prior to clinic discharge in those who did not receive or return diaries [5, 13–15]. In 44 patients, a post-block pain score was not recorded, with only a designation of SMP or SIP reported. A positive intermediate-term outcome was pre-defined as a $\geq$ 30% diminution in average pain score at 4–8-week follow-up visits for sympathetic blocks and after ketamine treatment [9, 19].

Statistical Analysis

All statistical analyses were conducted in R version 3.6 software. Descriptive statistics are presented as counts or proportions for categorical variables and means/standard deviations (SDs) for continuous variables. χ^2 tests were used to assess statistical significance of differences in proportions for categorical variables, while Student *t*-tests were used to assess statistical significance of differences in means for continuous variables. Correlation between two continuous variables were calculated via Pearson correlation coefficient. In the multivariable logistic regression model, where response to ketamine was the outcome of interest, we adjusted for age, sex, obesity, SMP, positive intermediate-term outcome after sympathetic block, and increase in temperature based on predetermined assumptions and P values $< .2$ in univariable analysis. Multivariable regression results are presented as adjusted odd ratio (aOR) with 95% confidence intervals (CI). Statistical tests were considered significant if two-sided P values were $< .05$.

Results

Baseline Data

Three hundred and fifty-three patients were screened, with 71 meeting selection criteria. These patients had a mean duration of symptoms of 49.73 (SD 41.60) months, moderate-to-severe pain (mean NRS pain score 7.08 $\pm$ 1.79) and 59.2% were females. Most had CRPS 1 (84.5%), had lower extremity involvement (91.5%), and had at least one psychiatric co-morbidity (60.6%), with a slight majority being on opioids (54.9%). Twelve (16.9%) patients were obese and all but 4 (94.4%) reported an inciting event.

Results of Sympathetic Blocks

Most blocks were performed using low volume plain bupivacaine or levobupivcaine (67.6%), with the mean temperature rising 4.60° C (SD 4.11) from a baseline of 28.10° C (SD 3.84). Nine (12.7%) patients experienced a temperature rise $< 2^{\circ}$ C (a technically unsuccessful block), though all but one of these patients had their procedure performed in an operating room with a long-acting local anesthetic, and their post-block temperature was recorded right before transfer (< 10 minutes). In these patients, 44.4% experienced $\geq$50% decrease in pain immediately post-block (i.e., were diagnosed with SMP) and 44.4% had a positive response to ketamine. When a sensitivity analysis was performed eliminating these 9 patients from the data set, there were no significant changes in any variable (Supplementary Data Tables 1 and 2).

The average percent reduction in immediate post-block pain was 54.7% (SD 30.0%) for those with this data recorded, with 41 (57.7%) being diagnosed with SMP. The use of sedation had no effect on the diagnosis of SMP, with 61.1% (n = 11) of patients who were sedated experiencing $\geq$ 50% immediate pain reduction vs 56.6% of those who did not receive sedation ($P = .954$). Four to eight weeks post-block, the average reported pain score was 6.96 (SD 1.89), with only 6 (8.5%) experiencing a positive intermediate term outcome, defined as $\geq$ 30% pain reduction lasting > 1 month.

Table 1. Demographic and clinical characteristics stratified by response to ketamine infusion

Demographic and Clinical Characteristics	Total Cohort (N = 71)	Positive Response to Ketamine Infusion (N = 33)*	Negative Response to Ketamine Infusion (N = 38)	*P* Value
Age (mean, years ± SD)	40.33 ± 12.62	39.42 ± 12.55	41.13 ± 12.79	.573
Sex (% female)	59.15	63.64	55.26	.636
Duration of pain (average, months ± SD)	49.73 ± 41.60	45.64 ± 40.82	53.29 ± 42.49	.442
Presence of inciting event (n, %)				
None	4 (5.63)	2 (6.06)	2 (5.26)	1
Surgery	21 (29.58)	8 (24.24)	13 (34.21)	.511
Fall	10 (14.08)	6 (18.18)	4 (10.53)	.560
Other	38 (53.52)	18 (54.55)	20 (52.63)	1
CRPS type (n, %)				.799
Type 1	60 (84.51)	27 (81.82)	33 (86.84)	
Type 2	11 (15.49)	6 (18.18)	5 (13.16)	
Coexisting psychiatric disorder (n, %)†				
None	28 (39.44)	13 (39.39)	15 (39.47)	1
Depression	32 (45.07)	14 (42.42)	18 (47.37)	.858
Anxiety	18 (25.35)	9 (27.27)	9 (23.68)	.942
PTSD	22 (30.99)	11 (33.33)	11 (28.95)	.888
Substance abuse	1 (1.41)	1 (3.03)	0 (0)	.943
Other	2 (2.82)	2 (6.06)	0 (0)	.412
Multiple†	25 (35.21)	13 (39.39)	12 (31.58)	.661
Obesity (n, %)	12 (16.90)	9 (27.27)	3 (7.89)	.064
Baseline pain score (0–10, ± SD)	7.08 ± 1.79	6.86 ± 1.57	7.26 ± 1.97	.345
Opioid use (n, %)	39 (54.93)	17 (51.52)	22 (57.89)	.764

CRPS = complex regional pain syndrome; PTSD = posttraumatic stress disorder.
[1]≥ 30% decrease in average pain score lasting ≥ 3 weeks.
†Individuals with ≥ 2 psychiatric conditions counted in "multiple" and the individual categories.

Ketamine Infusion Outcomes and Factors Associated with Success

Thirty-three (46.5%) patients had a positive ketamine infusion outcome, with the mean NRS pain decreasing from 7.24 (SD 2.00) pre-infusion to 3.64 (SD 2.28) at > 4-week follow-up. In univariable analysis, temperature increase (5.66° C ± 4.20 in those with a positive outcome vs 3.68° C +/- 3.85 in those with a negative outcome; $P = .043$) and SMP (61.0% success rate vs. 26.7% in those with sympathetically independent pain; $P = .009$) were associated with success. Seventy-five percent of the 12 obese patients experienced a positive ketamine outcome vs 25% of non-obese subjects ($P = .064$). There were no associations between depression ($P = .858$) or any psychiatric condition ($P = 1$) and response to ketamine. Neither immediate post-block pain relief nor intermediate-term outcome (83.3% success rate in the 6 individuals who experienced ≥30% pain relief 4–8 weeks post-block vs 43.1% in those with a negative intermediate-term outcome; $P = .143$) were significantly associated with ketamine outcome (Tables 1 and 2, Figure 1).

In multivariable analysis, the presence of SMP (OR 6.54 [95% CI 1.83, 23.44]) and obesity (OR 8.75 [95% CI 1.45, 52.73]) were associated with response to ketamine, while temperature rise (OR 1.03 [95% CI 0.87, 1.20]) was not secondary to collinearity with SMP (Table 3).

Discussion

Main Findings

Our main findings were that immediate pain relief after sympathetic block and obesity predicted response to ketamine infusion. We also found no significant difference in ketamine response between individuals with psychiatric co-morbidities and those without. There have been few studies evaluating prognostic factors for ketamine infusion, with most being performed in depressed patients [20]. In one cohort study evaluating inpatient ketamine infusions performed in 85 children with sickle cell crises, the authors found male sex, younger age, longer infusions and generalized pain to be associated with greater reductions in pain scores 1-day after infusion discontinuation [21].

Rationale for Predictive Tests and Comparison to Other Literature

Studies have shown that only a small percentage of people derive long-term benefit from sympathetic blocks [5, 6, 14], and while sympathetic blocks have been advocated to improve one's ability to participate in physical therapy, the evidence for this is anecdotal [22]. Studies evaluating predictive tests, which may be more beneficial and cost-effective in identifying patients for therapeutic interventions that are expensive and risky, typically involve a short-term test or treatment (e.g., an infusion)

Table 2. Parameters and results of sympathetic blocks stratified by response to ketamine infusion

Parameters and Results of Sympathetic Block	Total Cohort (N = 71)	Positive Response to Ketamine Infusion (N = 33)*	Negative Response to Ketamine Infusion (N = 38)	*P* Value
Local anesthetic choice (n, %)				0.343
Bupivacaine	8 (11.27)	4 (12.12)	4 (10.53)	
Lidocaine	9 (12.68)	6 (18.18)	3 (7.89)	
Bupivacaine- Lidocaine	10 (14.08)	6 (18.18)	4 (10.53)	
Levobupivacaine	44 (61.97)	17 (51.52)	27 (71.05)	
% Immediate pain relief from block[†]	54.73 ± 30.03	56.04 ± 29.93	52.82 ± 31.52	0.793
Sympathetically maintained pain[‡]				**0.009**
Yes	41 (57.75)	25 (75.76)	16 (42.11)	
No	30 (42.25)	8 (24.24)	22 (57.89)	
Positive intermediate-term outcome after sympathetic block[§]				0.143
Yes	6 (8.45)	5 (15.15)	1 (2.63)	
No	65 (91.55)	28 (84.85)	37 (97.37)	
Baseline temp (average, degrees C ± SD)	28.10 ± 3.84	27.61 ± 4.53	28.52 ± 3.12	0.336
Increase in temperature (mean, ± SD, degrees C)	4.60 ± 4.11	5.66 ± 4.20	3.68 ± 3.85	**0.043**
High volume blocks (>8 for SGB, >16 for LSB) (n, %)	9 (12.68)	5 (15.15)	4 (10.53)	0.821
Location (n, %)				0.200
LSB	65 (91.55)	29 (87.88)	36 (94.74)	
SGB	5 (7.04)	4 (12.12)	1 (2.63)	
TSB	1 (1.41)	0 (0)	1 (2.63)	

LSB = lumbar sympathetic block; SGB = stellate ganglion block; TSB = thoracic sympathetic block.
*≥ 30% decrease in average pain score lasting ≥ 3 weeks.
[†]Based on 27 patients.
[‡]≥ 50% relief immediately following sympathetic block persisting for > 3 hours.
[§]≥ 30% decrease in average pain score lasting ≥ 4 weeks.

to assess response to a longer-term treatment (e.g., oral medications, or selective nerve root blocks, discography, or electrodiagnostic testing to identify surgical candidates). For example, Cohen et al. found that a low-dose IV ketamine infusion predicts response to dextromethorphan, an oral N-Methyl-D-Aspartate antagonist not typically covered by payers, and several authors have used IV opioid infusion tests to identify candidates for chronic opioid therapy, which carries significant long-term risks [23].

Two retrospective studies evaluated the use of sympathetic blocks to predict spinal cord stimulation outcomes in CRPS patients, with the smaller finding prognostic value but the larger study finding minimal predictive ability [13, 14]. In a small prospective study by Davis et al. [24], six patients with CRPS underwent sympathetic blocks and phentolamine infusions (n = 5), with 4 being diagnosed with SMP. These four patients all experienced improvement in hyperalgesia after application of transdermal clonidine, although in three the relief of symptoms was limited to the area under the patch, suggesting a local effect. As noted, sympathetic blocks in CRPS patients have also been used to successfully identify patients for blocks performed with botulinum toxin and neurolytic agents, and for surgical sympathectomy, though these studies tended to be small, uncontrolled and yielded mixed results, and the treatments themselves can result in serious complications [12, 25, 26].

Explanation of Findings

The correlations between temperature rise following sympathetic block and response to ketamine infusion, and immediate (SMP) pain relief after sympathetic block and relief with ketamine, may seem counterintuitive as the former blocks the sympathetic nervous system, while the latter indirectly stimulates it. The significant association between SMP and response to ketamine ($P = .009$) but lack of statistically significant correlation between pain reduction after sympathetic blocks and ketamine ($P = .46$) may be explained by the difference in numbers (i.e., while all patients had the binary variable SMP or SIP recorded, not all had post-block pain scores). For the non-statistically significant intermediate-term effects, neither the sympathetic stimulatory effects of ketamine nor the sympatholytic effects of sympathetic blocks are enduring, which negates the contrasting physiological effects [9, 11] One possible area of overlap is the placebo effect, which tends to be strongest for conditions associated with subjective outcomes such as chronic pain and the psychiatric co-morbidities that often accompany it [27]. This may be particularly relevant for CRPS, which contains nociplastic qualities [4]. The placebo effect is especially powerful for ritualistic procedures associated

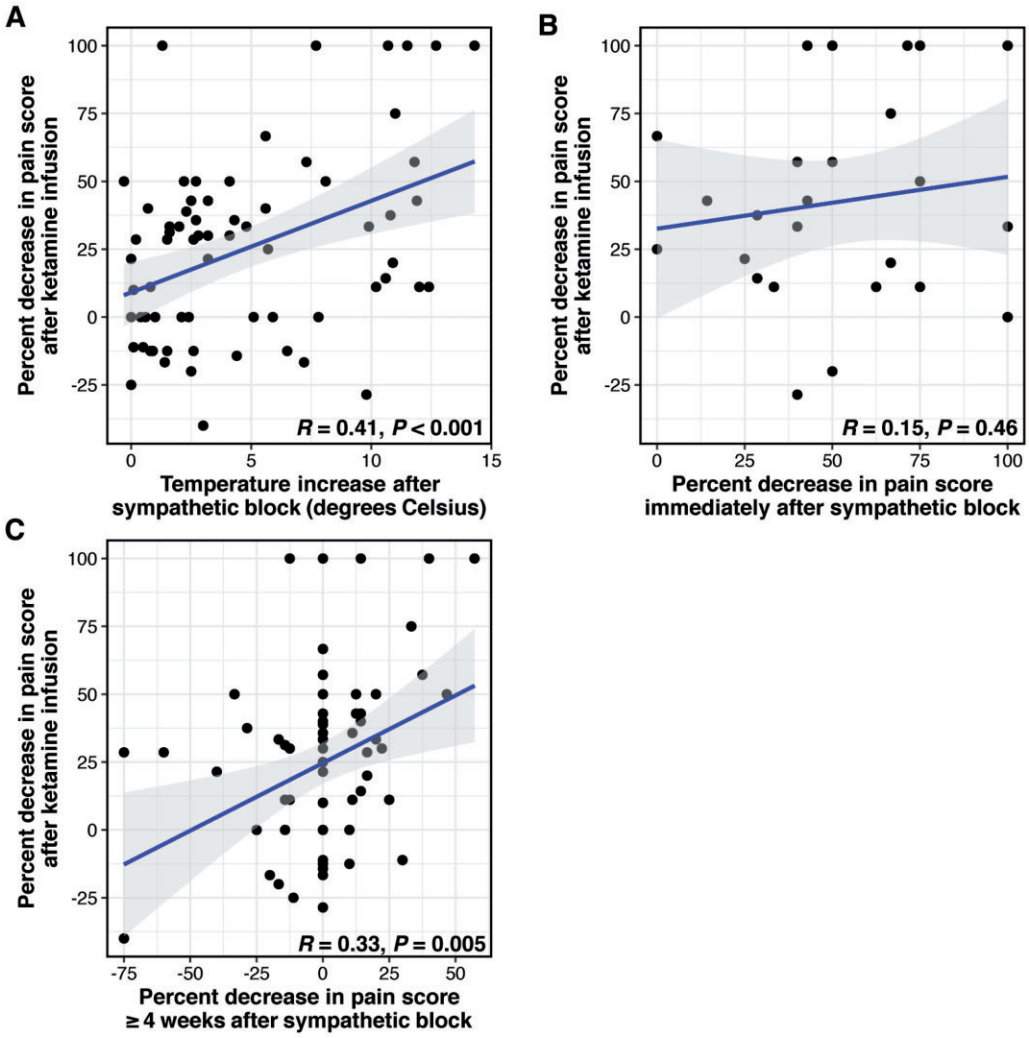

Figure 1. Graphs showing the correlation between pain relief ≥ 4 weeks post-ketamine infusion and (**A**) temperature increase after sympathetic block; (**B**) pain relief immediately after sympathetic block; and (**C**) pain relief 4–8 weeks post-sympathetic block.

Table 3. Multivariable analysis evaluating factors associated with ketamine infusion outcome.

Variable	Odds Ratio [95% CI]	*P* Value
Age at sympathetic block	0.99 [0.94, 1.03]	.549
Female sex	1.34 [0.43, 4.20]	.610
Obesity	8.75 [1.45, 52.73]	**.018**
SMP	6.54 [1.83, 23.44]	**.004**
Positive intermediate-term outcome after sympathetic block	6.13 [0.50, 75.06]	.156
Increase in post-block temperature	1.03 [0.87, 1.20]	.757

SMP = sympathetically maintained pain.

with obvious physical effects such as sympathetic blocks and ketamine infusions and is reproducible and enduring based on patient expectations [28]. Because the placebo effect depends on genetics, physician-patient relationship and expectations, individuals who experience a placebo response to one therapeutic intervention are more likely to respond to another. In one meta-analysis evaluating the placebo effect in 20 trials for CRPS, a modest placebo effect was observed for up to 1 week (18.4 points immediately post-treatment, 6.8 points at 1-week on a 0–100 pain scale), with no appreciable placebo response at intermediate or long-term follow-up [29]. However, only three trials containing 47 placebo patients received either ketamine or sympathetic blocks. In the current study, the 44.4% of patients who were diagnosed with SMP despite having a less than 2° C increase in temperature suggests there was a significant placebo response. In addition to the placebo effect, there may also be unmeasured psychological variables such as positive affect that influence treatment response [30]. Collectively, these may explain the phenomenon whereby an individual who responds to one or multiple pain treatments is more likely to respond to subsequent treatments.

A second more intriguing possibility is that sympathetic blocks and ketamine exert long-standing analgesic effects via modulation of the affective-motivational

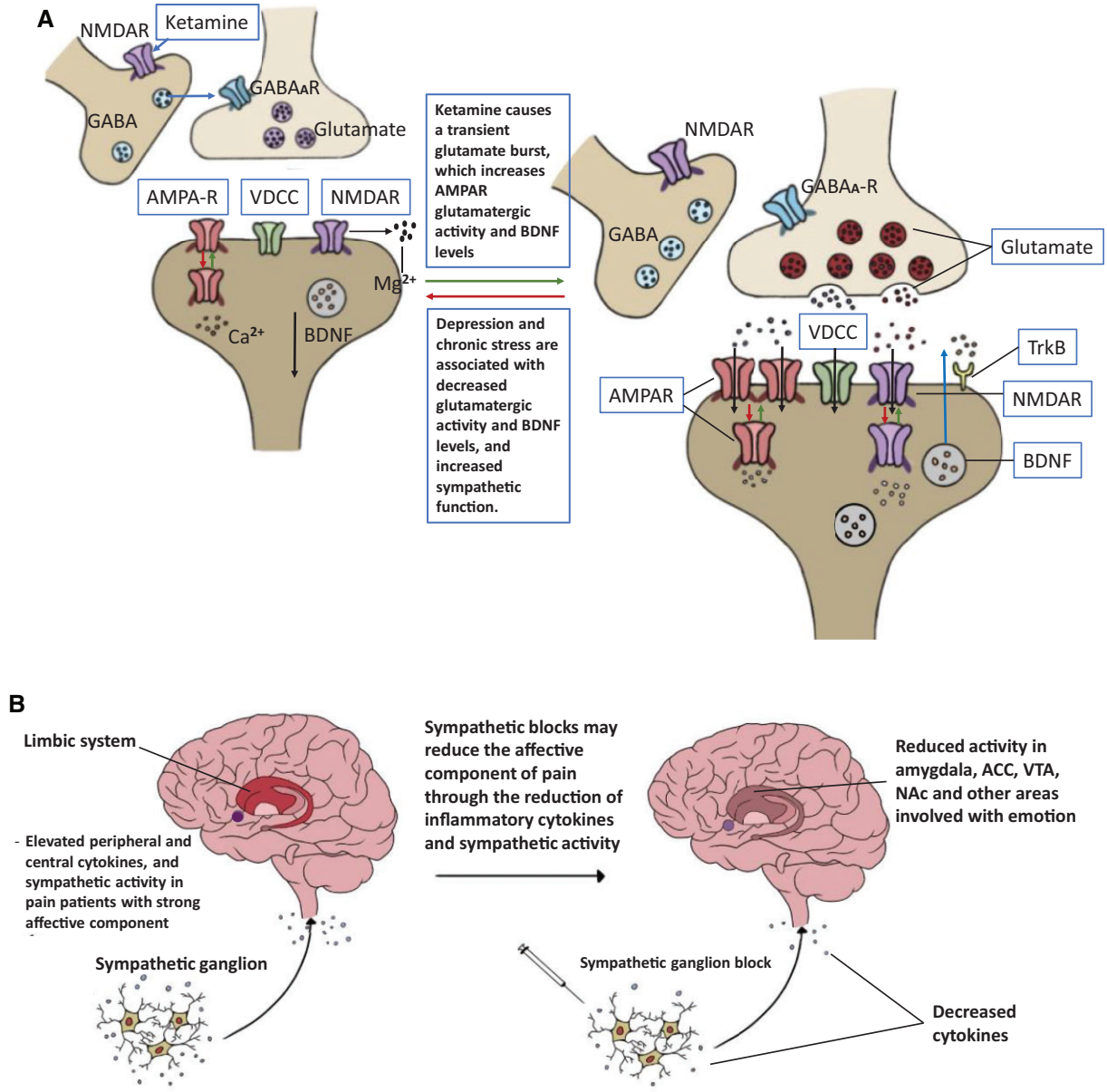

Figure 2. Mechanistic overlap between the intermediate-term analgesic effects of sympathetic blocks and ketamine: Reducing the affective-motivational component of pain (drawings by Seffrah Cohen). (**A**) Glutamate released into the synaptic cleft activates α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid (AMPA) receptors, which allows entry of sodium ions into the postsynaptic neuron. Depolarization of the postsynaptic membrane results in removal of the voltage-dependent magnesium block on the N-Methyl-D-Aspartate (NMDA) receptor, facilitating activation. This activation, which is enhanced and dysregulated in depression, is blocked by ketamine. Ketamine may also alleviate depression by increasing levels of brain-derived neurotrophic factor (BDNF) in brain regions involved in emotions such as the amygdala and nucleus accumbens and activating L-type voltage-dependent calcium channels (VDCC). (**B**) Sympathetic blocks may alleviate the affective-motivational component of pain by reducing peripheral and central cytokine levels, which are elevated in depressed people, as well as modulating sympathetic overactivity. AMPAR = α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid (AMPA) receptor; BDNF = brain-derived neurotrophic factor; $Ca2^{+}$ = Calcium ions; $GABA_A$ R = γ-Aminobutyric acid type A receptor; $Mg2^{+}$ = Magnesium ions; NMDAR = N-Methyl-D-Aspartate (NMDA) receptor; TrkB = Tropomyosin receptor kinase B; VDCC = voltage-dependent calcium channel.

component of pain; this is supported by the enduring effect on mood, at least for SGB [31] (Figure 2). If true, more complete blocks (greater temperature increases), which are associated with greater reduction in sympathetic tone and pain and possibly more powerful placebo effects, may be more predictive of ketamine response, in which placebo effects (since the unique psychomimetic effects preclude effective blinding) and improved mood play a prominent role [9, 10]. This could also explain why obese patients responded better, with studies finding little difference between obese and non-obese patients for pain sensitivity, but higher affective pain scores in

overweight individuals [32]. Although we failed to find a difference in ketamine response stratified by depression and other psychiatric co-morbidities, nearly all of these patients had stable symptoms, and we did not actually measure mood, anxiety or any other psychiatric illness. Ketamine has been shown to provide pain relief in some people for months [9], but studies have repeatedly failed to demonstrate any benefit past 48 hours on quantitative sensory testing (the sensory-discriminative component of pain) [33, 34], leading some experts to postulate that any long-term benefit derives from alleviation of anxiety and depression [10]. In one randomized controlled trial, the ability of ketamine to reduce the affective-motivational component of pain was greater than for the sensory-discriminative aspect [34]. There is growing evidence supporting the use of stellate ganglion blocks to treat posttraumatic stress disorder and other psychiatric conditions and while the evidence is less robust for lumbar and thoracic sympathetic blocks, small randomized studies performed for postamputation pain and CRPS, respectively, reported reductions in depression and anxiety [31, 35, 36]. The mechanism by which sympathetic blocks may modulate the affective-motivational aspect of pain is through the reduction of inflammatory cytokines and reduced sympathetic outflow, which are elevated in both CRPS and depression [1, 37–39].

Limitations

There are several limitations to this multi-center study. Follow-up periods, including for temperature measurements and immediate post-block pain relief (which were used to identify SMP), were not standardized so that temperatures recorded too early for levobupivacaine and bupivacaine blocks may have underestimated temperature rise, and variations in post-procedure follow-up could have led to variations in outcome data. Second, there was variability in the volumes used for sympathetic blocks; since we did not perform quantitative sensory testing, some of the immediate post-block pain relief may have resulted from spread to somatic nerves. Third, data on psychiatric morbidity were categorical rather than continuous, which would provide a more sensitive indicator of the interaction between psychological factors and pain relief after the interventions. We also did not evaluate post-block or post-infusion psychiatric outcomes, or a means to separate the effect of the interventions on the sensory-discriminative vs the affective-motivational components of pain [10]. Last, a substantial proportion of our patients did not have immediate post-block pain scores recorded (rather, they had coarse designations of SMP vs SIP). This lack of power likely contributed to the lack of a significant correlation between post-block pain reduction and pain reduction after ketamine.

Implications for Clinical Practice and Conclusions

The increased response to ketamine in patients who experienced greater immediate and possibly sustained pain relief after sympathetic blocks, and those who are obese, may be particularly helpful in identifying candidates for this therapy, which carries significant risks and often comes at great out-of-pocket costs. In conjunction with other variables, the strategic use of sympathetic blocks in this population may be utilized as part of a personalized medical approach to individualize care and improve outcomes for more definitive therapies. Prospective studies including more variables such as contemporaneous measurements of depression and anxiety and measuring the affective-motivational component of pain (e.g., unpleasantness) are needed to determine the precise mechanism(s) for ketamine to exert longer-term analgesic effects and the role for sympathetic blocks in identifying appropriate candidates.

Supplementary Data

Supplementary data are available at *Pain Medicine* online.

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