THE BRITISH PAIN SOCIETY

Original Article

Temporary sympathectomy in chronic refractory angina: a randomised, double-blind, placebo-controlled trial

British Journal of Pain
2015, Vol. 9(3) 142–148
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DOI: 10.1177/2049463714549775
bjp.sagepub.com

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Abstract

Background: Temporary sympathectomy by injection of bupivacaine at the site of the left stellate ganglion is used in the management of refractory angina at several UK centres. Although patients frequently report significant reduction in symptoms, efficacy has not been established by double-blind, randomised placebo-controlled trial (RCT).

Objective: To investigate the efficacy of the procedure for the first time by a double-blind RCT.

Methods: Consecutive patients referred to the authors' National Health Service (NHS) angina centre who were candidates for temporary sympathectomy were invited to participate in a trial. A total of 65 patients were randomised to receive either bupivacaine or saline injections. Identical syringes were prepared remotely, blinding patients and staff from randomisation. Cardiac autonomic function was measured 3 hours pre- and post-injection using new heart rate variability (HRV) analyses. Angina episodes were recorded contemporaneously by patients in study diaries in the 7-day periods pre- and post-injection.

Results: In 51 patients suitable for analysis, no significant differences between the active and placebo groups were found in patient-recorded frequency or intensity of angina episodes pre- and post-injection. However, across both groups combined, a significant difference was found in the frequency of angina episodes pre- and post-injection.

Conclusion: The reduction in frequency of angina episodes produced by this procedure may not be due to drug pharmacology. It may be a placebo response or due to the mechanical effects of the injection of fluid. There is a need for further work using a larger patient cohort considering both mechanical and psychological factors.

Keywords

Stellate, angina, heart rate variability, randomised placebo-controlled trial, palliative treatment, Gaussian process, Lomb–Scargle

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Introduction

The symptoms associated with chronic refractory angina are of major concern both for patients and for health economics of service delivery. This condition results in frequent unplanned hospitalisation, reducing the quality of life of patients and carers and exerting a significant financial impact on the National Health Service (NHS). Local anaesthetic blockade of the stellate ganglion has been advocated for a variety of clinical conditions, including refractory angina. However, the efficacy of the therapy in this disorder remains controversial, with reports generally based on anecdote or case study rather than on formally designed large-scale clinical trials.¹

The objective of this trial was to investigate the efficacy of the procedure for the first time by a double-blind, randomised placebo-controlled trial (RCT). In both angina associated with ischaemic coronary artery disease² and angina occurring in the absence of ischaemia,^{3,4} a relationship between episodes and cardiac autonomic activity has been demonstrated. This, together with the absence of angina during ischaemic cardiac events in patients with impaired autonomic function,⁵ suggests autonomic activation as a useful objective measurement of the presence of angina. Heart rate variability (HRV), specifically the analysis of the variation in electrocardiogram (ECG)-recorded RR intervals (the time interval between adjacent R waves) occurring in the non-ambulatory and relaxed patient, is established as an indirect non-invasive measure of cardiac autonomic activity.^{6–8}

Cardiac sympathetic and parasympathetic control is associated with two spectral HRV parameters: low-frequency (LF) and high-frequency (HF) spectral power and their ratio (LF/HF). Furthermore, cardiac sympathetic activity measured indirectly by LF is associated with angina symptoms in refractory angina.⁹ A full description of these parameters and their calculation is beyond the scope of this article. HF and LF (and their ratio) were considered as secondary outcome measures in this study.

There are practical difficulties applying conventional spectral HRV analysis to real-world clinical ECG data. Commercial Fourier-based methods are not suitable for analysing the discontinuous or otherwise 'non-stationary' RR series frequently encountered as a result of angina episodes. To avoid significant measurement error, the authors developed and validated a novel and robust HRV analysis method appropriate to 'real-world' RR data^{10,11} combining Gaussian process (GP) band-pass filtering (time domain) and Lomb–Scargle (LS) periodogram analysis of the RR tachogram (frequency domain). Interactive demonstrations of these robust methods are available online.¹²

Methods

Study design and setting

The RCT was conducted at the authors' NHS angina centre, having received ethical review and approval from the local Liverpool Research Ethics Committee.

Informed consent was obtained from all subjects according to the process approved by the research ethics committee. The primary outcome measure of relative percentage change in frequency of angina episodes was measured using diaries contemporaneously completed by patients during the 7-day periods before and after injection. Patients were also asked to record angina episode intensity, but it was regarded as a less promising outcome measure for angina as differences between descriptors used by patients (e.g. 'pain', 'tightness', 'pressure') can generate ostensibly homogeneous samples of dissimilar experiences. A simple 5-point numerical rating scale was therefore selected to rate intensity of angina episodes (1 = 'mild angina', 5 = 'worst possible angina'). RR interval sequences were extracted from ECGs recorded at least 1 hour before and 1 hour after injection from which pre- and post-treatment HF and LF (and their ratio), the secondary outcome measures, were determined. The statistical model employed in the analysis, described in full in the supplementary Appendix, took into consideration the effect of gender, age, beta-blocker usage, prior glyceryl trinitrate (GTN) usage, New York Heart Association (NYHA) classification, Canadian classification and angina radiation into the left arm.

As no substantially similar study data were available, the study was powered using data routinely collected from 48 refractory angina patients treated at the angina centre over the previous 12 months. It should be noted that powering of LF used in the original study design, based on conventional Fourier spectral HRV analysis, estimated that a total of 68 patients would be required to provide statistically significant results. However, the rate of recruitment to the trial, begun in 1999, slowed significantly as the National Refractory Angina Centre (NRAC, subsequently renamed 'Liverpool Angina Management Programme') service evolved towards a greater emphasis on patient education and cognitive therapy to address patients' counter-therapeutic cardiac misconceptions.¹³ The impact of the educational and psychological interventions reduced the number of patients electing to undergo invasive pain interventions, significantly reducing recruitment to this trial and leading to a suspension of the study.¹⁴ The last patient was recruited on 17 February 2006. However, the recent development of a new and optimal method of HRV analysis in 2012^{10–12} enabled the study to be re-powered, reducing the required number of patients to conduct HRV analysis to fewer than the 51 suitable patients

Table 1. Canadian class definitions.

Canadian class	Definition
Class I	Usual physical activity, for example, walking or climbing stairs does not cause angina; angina is evoked by strenuous and/or rapid work or recreation.
Class II	Slight limitation of ordinary activities, for example, after walking two blocks, climbing one flight of steps, under normal circumstances, after meals, in the cold, wind, in the morning or when under emotional stress.
Class III	Marked limitation of ordinary activities, for example, walking one to two blocks or climbing stairs under normal circumstances.
Class IV	Inability to carry out any physical activity without discomfort – angina may be present at rest.

already measured. The chair of the Liverpool Research Ethics Committee gave permission to break the seals on the existing double-blind data on the basis of the revised power calculation for LF and the impossibility of further recruitment of refractory angina patients with the same disease/treatment path as those already recruited at NRAC.

A total of 65 consecutive patients who were prescribed stellate blockade for management of their refractory angina participated. Following randomisation by a third party, identical syringes were prepared remotely, blinding patients and clinical staff providing the treatment to the syringe contents.

Protocol

Refractory angina patients were assessed for suitability and appropriately invited to consent to participate at least 2 weeks before their scheduled stellate blockade appointment. After consideration at home, patients returning a completed and signed consent form were recruited and interviewed by a research nurse who graded their angina using both the Canadian Cardiovascular Society Functional Classification¹⁵ and the NYHA Functional Classification Questionnaire,¹⁶ detailed in Tables 1 and 2, respectively.

Additionally, patients provided information concerning their use of beta-blockers, GTN and angina radiation into their left arm. All participating patients were issued with a study diary in which they recorded each episode of angina, GTN used and peak angina intensity during each episode occurring in the 7-day periods pre- and post-injection.

Table 2. NYHA class definitions.

NYHA classes	Definition
Class I	Cardiac disease, but no symptoms and no limitation in ordinary activity, for example, shortness of breath when walking and climbing stairs.
Class II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
Class III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, for example, walking short distances (20–100 m).
Class IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

NYHA: New York Heart Association.

Each patient was counselled prior to entry into the trial and informed of the possibility of receiving either active or placebo treatment. The patient was instructed by appointment letter to take no food or drink 4 hours prior to injection and to take no caffeine in the 24 hours before the procedure. On the day of the procedure, the patient was fitted with a Spacelabs Lifecard three-lead ambulatory ECG recorder which remained in place until discharge that day. The patient was then accompanied to a quiet communal waiting room to remain seated until being called into the treatment room for the procedure after an interval of at least 1 hour. Once on the treatment couch in a procedure room with full resuscitation equipment, ECG, pulse oximetry (SPO₂) and non-invasive blood pressure monitoring were established and intravenous access secured with a 20-G cannula. The patient was placed in a semi-recumbent position with the chin slightly raised and the mouth open to relax the neck musculature. A gauze eye pad was secured over the left eye to conceal the presence of Horner's syndrome from clinical staff.

After preparing the skin with a solution of chlorhexidine in alcohol, the left transverse process of the sixth cervical vertebra was identified by gentle digital pressure to the anterior part of the neck, about 3 cm lateral to midline. The palpating finger maintained transdermal contact with the bony prominence while controlling the left carotid artery, thus avoiding risk of inadvertent carotid puncture. A 20-mL syringe containing 20 mL of liquid (prepared by the Pharmacy Department and randomised to contain either 0.9% saline or 0.5% bupivacaine) was connected to a 21 standard wire gauge (SWG) 1.5-in needle through a 2 m length of fine-bore connector tubing and the dead space eliminated by flushing the tube so that 15 mL remained in the syringe. The needle was passed gently

through the skin and subcutaneous tissues so that its tip touched the anterior surface of the C6 transverse process. Following aspiration of the syringe to confirm that the needle was not intravascular, the syringe contents were injected around the left stellate ganglion, checking that the needle tip had not migrated by re-aspirating at 5 mL intervals. One operator performed all skin punctures and controlled the needle, and one operator performed all injections.

After withdrawing the needle and applying a dressing, the patient was kept in the semi-recumbent position for 15 minutes, checking blood pressure, pulse rate and SPO₂ at 5-minute intervals.

When all physiological parameters were stable, the patient was moved to a sitting room and observed for 2 hours. The patient was then discharged home, following removal of the ambulatory ECG recorder, with instructions to leave the eye patch in situ until the following morning and to report frequency and intensity of angina episodes in the study diary. The patient returned a week later for collection of diaries and to report any other symptoms.

Measurement of HF and LF

HF and LF were estimated by GP/LS spectral HRV analysis.^{10–12} Frequency and intensity of angina and autonomic activity were compared pre- and post-stellate injection in the 51 of 65 consented patients for whom adequate data had been recorded (excluding participants with, for example, incomplete or lost diaries).

The spectral HRV parameters LF and HF are defined as the spectral power density of RR interval variation in the frequency ranges 0.15–0.4 and 0.04–0.15 Hz, respectively. HF is associated with cardiac parasympathetic activity, while LF and the ratio LF/HF are associated with cardiac sympathetic activity⁸ and angina pain.⁹ The RR sequences were extracted using a Spacelabs Pathfinder ECG analysis system. From each recording, two 20-minute segments of RR intervals were extracted 30 minutes after the recorder was fitted and 30 minutes before removal, respectively. GP/LS HRV analysis was applied to the RR sequences to estimate pre- and post-procedure values of HF and LF.

Results

Demographics

Complete data sets were achieved for 51 of the 65 recruited subjects. The demographics of both the active ($n = 29$) and placebo ($n = 22$), receiving bupivacaine or saline, are given in Table 3. (Note that since the completion of the study, levobupivacaine has replaced

Table 3. Demographics.

		Total	Active	Placebo
Drug		51	29	22
Gender	Male	43	26	17
	Female	8	3	5
Age (years)	Mean	61	60	63
	Median	63	62	65
	<54	13	8	5
	55–69	31	18	13
	>70	7	3	4
Beta-blockers	Yes	37	21	16
	No	14	8	6
Canadian class	III	35	18	17
	IV	16	11	5
NYHA class	I/II	13	8	5
	III	33	18	15
	IV	5	3	2
Mean GTN usage per day	0–20	38	22	16
	30–39	10	5	5
	>40	3	2	1

GTN: glyceryl trinitrate; NYHA: New York Heart Association.

bupivacaine in stellate ganglion blockade at the authors' NHS angina centre because of reported lower cardiac risk.)

Results of statistical analysis

The objective of analysis was to compare the impact of injection on occurrence of angina and changes in spectral HRV indices in the active and placebo groups, taking into account for each patient age, beta-blocker usage, treatment arm (active/placebo), GTN usage, NYHA and Canadian classification, gender and radiation of angina into the left arm. Full details of parameterisation and the statistical model employed are reported in the supplementary Appendix. In this statistical analysis, no significant differences were found between the placebo and active drug groups' frequency of angina episodes or intensity of angina (mean, median or peak) recorded in diaries pre- and post-injection. Nor were there any changes in autonomic activity measured by HRV on the day of injection. However, a significant difference was found in the frequency of angina episodes pre- and post-injection across both active and placebo groups combined.

Angina intensity was not considered as a predictor since a partial correlation analysis (taking into account the treatment) showed a non-negligible correlation between the variation in peak levels of intensity with variation in the number of angina episodes, pre- and post-injection; this correlation could have induced collinearity problems in the model.

Analysis considered whether there was a significant reduction in the number of angina episodes pre- and post-injection and whether any reduction was linked to active drug treatment. The change in the frequency of angina episodes was determined from the number recorded in the diaries in the 7-day periods pre- and post-injection, the difference being quantified as percentage relative change.

Single-sided Student's paired T-tests were initially applied separately to the placebo saline and active drug injectate groups' measured parameters. The most significant reduction, post-injection, was in the frequency of angina episodes. However, unexpectedly, this statistically significant reduction was seen in *both* the active and placebo groups alike.

A more rigorous examination of this initial finding was carried out by applying a Wilcoxon signed-rank one-sided test to both the 'active' and 'placebo' groups combined, the null hypothesis being no relative reduction versus a reduction in the frequency of angina episodes across everyone receiving an injection of 15 mL of either fluid. The null hypothesis was rejected to a very high significance ($p = 0.00007$) with a median reduction in angina frequency of 31%, clearly demonstrating that injection of 15 mL of either fluid into the palpated anatomical site of the stellate ganglion produces a significant reduction in the frequency of angina.

In these circumstances, determining whether there was a significant difference in the reduction produced by the placebo and active injectate is challenging. Regional anaesthetic techniques are known to have failure rates, that is, despite an apparently correct technique being performed, not every subject receiving active drug would necessarily have a successful stellate ganglion block. Techniques are described (e.g. ultrasound-guided) in which failure rates are reduced, but there is no fool-proof method of ensuring 100% success. Furthermore, some subjects receiving the placebo injection may have undergone partial or complete stellate ganglion blockade simply by the effect of a volume of injectate exerting direct pressure on the ganglion.¹⁷

The literature indicates that without ultrasound needle guidance, there is about a 10% chance of unsuccessful blockade.^{18,19} In analytical terms, this means that the a priori classification of subjects into treatment and placebo groups is noisy and that this classification error is one-sided since it only affects the treatment.

These challenges can be addressed by careful formulation of binary logistic regression of treatment indicator against relative percentage difference in the number of angina episodes pre- and post-injection. Details of the binary logistic regression analysis methodology are fully described in the supplementary Appendix. The outcome of the analysis is a chi-squared

statistic with p-value of 0.18, suggesting that there is no evidence that the drug has any effect; furthermore, there is no evidence of heterogeneity of the treatment among the subjects ($p = 0.75$).

Discussion

These results suggest that stellate ganglion injection reduces only the frequency of angina episodes and that this change is not due to the active drug. This further suggests that either the benefit of the treatment is placebo with a psychological axis or that injection of 15 mL of liquid in the vicinity of the stellate ganglion exerts a beneficial mechanical effect.

The absence of evidence for change in spectral HRVs associated with autonomic activity is unexpected, especially in the group receiving the active drug that is expected to interrupt cardiac sympathetic nerve traffic for at least the 3-hour half-life of the drug at the ganglion. This lack of evidence may be due to weakness in the experimental method of not recording ECGs with the patient alone and supine in a fully controlled environment. Any reduction in HRV may then have been masked by adrenal stimulation resulting from the uncontrolled environment of the waiting room.

However, the reduction in frequency of angina in both active and placebo groups is a surprising and relevant finding, indicating the need for further study and presenting an interesting ethical question for clinical practice. The results suggest that injection of 15 mL of placebo or active drug has no impact on intensity of angina while both reduce frequency of episodes significantly. This would appear to justify continuing to offer patients the application of 15 mL of injectate to the left stellate ganglion, but if there is no difference between bupivacaine and saline, then are the additional risks associated with injection of local anaesthetic justified? Perhaps only injection of saline is justified as the means of bringing about the therapeutic (either placebo or mechanical) effect of injection.

The results of this study are of greater relevance to the design of future research than to clinical practice as some methodological shortcomings must be acknowledged. The limited '1–5' scale of angina intensity was adopted as a minimally burdensome requirement for participants, given that a difference in intensity of one angina patient's 'tightness' is not straightforwardly comparable to an apparently equivalent difference in another patient's 'pain'. However, notwithstanding this rationale, the study was powered to a 25% change being the threshold of clinical significance for both the intensity and frequency of angina episodes. A more precise scale may have detected an indicative difference in intensity, distinguishing the respective effects of bupivacaine and saline. It is also possible that the results are

marginally affected by the previously mentioned 10% chance of unsuccessful block when performing the procedure without ultrasound guidance,^{18,19} which was not so routinely used as in current practice and for which resources were not available at the time that recruitment commenced.

However, aside from these methodological caveats, it is also important to take account of current clinical practice. From a clinical perspective, these results are remarkable for their departure from patient testimony. In this one clinic, currently 51 patients regularly undergo temporary sympathectomy (41 stellate ganglion blocks and 10 paravertebral blocks) for angina relief. The great majority elect to repeat the procedure every 4–6 weeks. Of the 51 patients, 25 have continued with this treatment for between 5 and 15 years. Those who continue long-term with this treatment typically report at each appointment that the previous block had eliminated or significantly reduced the intensity and frequency of their angina. Patients schedule their next block appointment to coincide with when their own experience indicates that their angina will recur or increase in intensity or frequency. In short, patients who opt to continue with this therapy value it greatly. Interestingly, and quite apart from this research protocol, a procedure modification has been introduced into clinical practice in the past 2 years to reduce the risk profile of stellate ganglion block. Patients who undergo stellate ganglion block are now offered the choice of continuing to receive the injection from the anterior approach traditionally used, and used in this protocol, or opting for a cervical plexus block into less vascular territory. All but two patients given this choice have opted for cervical plexus block and report equivalent efficacy, with increased satisfaction associated with this less uncomfortable and lower risk approach.

Following multi-disciplinary discussion of the findings of this study (taking into account the methodological limitations identified and patient satisfaction with the treatment), it has been decided that temporary sympathectomy with 15 mL 0.5% bupivacaine should continue to be offered either by anterior or lateral cervical plexus approach or by paravertebral approach while a further study into the mechanisms of apparent efficacy is undertaken. While the necessary further study is prepared, patients undergoing regular temporary sympathectomy will receive treatment within a registered clinical audit. Patients will be informed of the conduct and results of this study and of the significance of the apparent absence of a difference in efficacy between injection of bupivacaine and saline. A further service modification is proposed, which has been endorsed by the Royal Liverpool and Broadgreen University Hospitals NHS Trust Clinical Ethics Committee. The results of

this study suggest that injection of 15 mL of either local anaesthetic or saline at the site of the stellate ganglion reduces the frequency of angina episodes – the mechanism being either placebo or mechanical. In the meantime, all patients undergoing temporary sympathectomy, from the anterior or the lateral approach, will be offered a choice of local anaesthetic or saline. Saline would enable the patient to avoid the risks specific to injection of local anaesthetic and would generate additional data within the audit to inform future research. Any patient opting for saline rather than local anaesthetic would be offered the opportunity to return to the clinic for their usual local anaesthetic block if they were to find saline less efficacious than their usual blocks.

Acknowledgements

Lifecard Holter electrocardiogram (ECG) recorders and Pathfinder ECG analysis system were kindly provided for the study free of charge by Spacelabs Healthcare (UK) Ltd.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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