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Research Article

The impact of vagal nerve stimulation from the lateral neck region on venous cannulation pain: A randomized controlled trial

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ABSTRACT

Background: As the cranial nerve with the longest and widest distribution area of the body, the vagus nerve (N.Vagus) has both antinociceptive and neuromodulatory effects and plays a role in the regulation of the heart rate. The objective of this study is to investigate the impact of cold stimulation on vascular access discomfort and heart rate variability, specifically by separately stimulating the N. Vagus nerve on both the right and left sides of the neck thereby assessing any lateralization effect.

Methods: 140 patients, ranging in age from 18 to 75, were randomly assigned to one of two groups: Group Left (Group L) or Group Right (Group R). Following cold application to the left lateral neck region of Group L and the right lateral neck region of Group R, venous cannulation was performed. Prior to, following, and subsequent to vascular access, the heart rate, noninvasive blood pressure, oxygen saturation, and numeric pain scale (NRS) values for venous cannulation pain of the patients were documented.

Results: Average heart rates and average heart rates after cannulation were considerably lower in both groups after vagal stimulation ($p<0.05$). No significant difference was observed when comparing the average heart rate values for each time period in Group L and Group R, including the mean heart rate values before vagal stimulation, after vagal stimulation, and after vascular access ($p>0.05$). The mean heart rate change percentages before and after vagal stimulation were 7±5.8% and 7.1±7.0% in group L and group R respectively, suggesting that heart rate variability was greater in Group R, although this difference was not statistically significant ($p>0.05$). NRS values were found to be 2.64±1.28 in Group L and 2.85±1.62 in Group R, with no significant difference ($p>0.05$).

Conclusion: While heart rate variability exhibited more prominence on the right side, the difference was not statistically significant. Analyzing the analgesic impact revealed no discernible difference between the analgesic effects of stimulation from the right and left sides.

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1. Introduction

The vagus nerve (N. Vagus) extending from the brainstem to the final third of the large intestine, possesses the most extensive distribution area of and is the longest cranial nerve [1,2]. Numerous systems are regulated by N. Vagus, such as the respiratory, endocrine, immune, and autonomic systems. It originates on the lateral aspect of the medulla, traverses the jugular foramen to exit the cranium, and proceeds towards the thorax, abdomen, and neck [2,3]. The vagus nerve comprises of motor, sensory, and parasympathetic fibers, with 80% of these fibers being afferent and 20% efferent. A, B, and C fibers possess distinct physiological functions. Animal studies

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have demonstrated that vagal afferent C fibers are antinociceptive [2–4]. Originating in the brainstem, the vagal system extends throughout the thoracic and abdominal organs through descending branches from both sides of the anterior cervical area. The anatomical extent of the right and left branches of the N. Vagus the primary neuronal element of the parasympathetic system, varies along its trajectory. There is significant data indicating that vagal stimulation has an impact on both pain perception and gastrointestinal motility [3]. Vagal activation is recognized to contribute to pain regulation by reducing inflammation and modulating neuronal activity in pain pathways [2]. The cymba conchae region of the ear contains an afferent branch of the Vagus nerve, while the neck region is densely populated with its cervical branch [5]. These areas are used to stimulate the N. Vagus different sides and for different purposes [6].

Aside from its application as a neuromodulatory treatment for vagal stimulation resistant epilepsy and depression, it's efficacy has been demonstrated in the treatment of headache, tinnitus, atrial fibrillation, schizophrenia, and different forms of pain [2,7,8]. For millennia, Eastern medicine has harnessed the pain-relieving properties of ear acupuncture [9]. Various methods of stimulating the vagus nerve have been developed, including invasive techniques as well as non-invasive approaches such as transcutaneous, transcervical, and transauricular stimulation devices [2,6,10].

Stimulating the vagal nerve activates the baroreceptor reflex arc. Consequent release of 'substance P' resembling molecules are thought to be responsible for antinociceptive properties [11–13]. Applying cold to the neck area triggers the baroreceptor reflex arc by stimulating the vagus nerve, which activates the parasympathetic system leading to pain-relieving effects [12,14].

Prior to any anesthetic surgery, it is imperative to establish vascular access, which is frequently performed by anesthesiologists both inside and outside the operating room. Venous cannulation is a procedure that causes mild pain and discomfort for patients, leading to an increase in patient stress [15]. Numerous approaches have been explored to alleviate the discomfort associated with venous cannulation. Various techniques, including injecting local anesthetic into the affected area, using topical anesthetic, applying cold, and using a vibrating buzzy device, have been employed to alleviate the patient's pain and to divert their attention. The use of local anesthetic only decreases the physical aspect of pain, but the Valsalva technique, which stimulates the vagus nerve, has been shown to reduce both the physical and psychological aspects of pain [13]. Activation of the cardiopulmonary baroreceptor reflex arc or the sino-aortic baroreceptor reflex arc, along with the Valsalva maneuver, leads to antinociception while increased intrathoracic pressure caused by this maneuver results in a decrease in venous return, making the veins more visible and facilitating venous cannulation [16]. It is believed that the pain relieving effect of the vagus nerve in humans may be due to inhibition of pain signals in the central nervous system rather than through peripheral pain-relieving processes [14].

We previously discovered that the N. Vagus was activated, resulting in a decrease in heart rate and alleviation of vascular pain when ice was applied to the neck area. We believe that the application of cold to the neck area stimulates the baroreceptor reflex arc through vagal stimulation, thereby activating the parasympathetic system. The aim of the study is assess the impact of lateralization on vascular access discomfort and heart rate variability by separately stimulating the right and left vagus nerves with cold application in the neck area.

2. Materials and Methods

The study was carried out between 20 February and 30 March 2024 at Samsun University Samsun Training and Research Hospital, following ethics committee approval (GOKAEK 2024/3/9) and Clinical Trials (NCT06253299) registration. Patients arriving in the operating room following anesthesia and surgical prep were informed about the study and their written consent was obtained.

- Study Inclusion Criteria: The study comprised patients between the ages of 18 and 75 who underwent elective surgery and were classified as American Society of Anesthesiologists (ASA) class I-III.
- Study Exclusion Criteria: The study excluded individuals with neurocognitive disorders, patients undergoing oncological treatment, those who had undergone surgery on the back of the hand, individuals with skin disorders, peripheral vascular disease, chronic use of analgesics and steroids, users of gabapentinoids, individuals with substance and alcohol addiction, those with peripheral neuropathy, and pregnant women.
- Randomisation and Intervention: Patients were transferred to and observed in the preoperative waiting room. Sample size for each cohort was calculated to be 70 individuals, accounting for loss to follow-up. Using a lottery system, patients were randomly divided into two groups: Group L (left) and Group R (right). Following standardization of its temperature, a specialized marble stone measuring 4×5 cm was utilized to apply cold to the neck region. Temperature standardization was achieved by placing the stone in the vegetable shelf of a refrigerator set between 4 and 8 °C (degrees Celsius) for 10 minutes (min), leading to a stone temperature of 11 °C that increases to 18 °C after five min of exposure to room temperature. The stone was administered to each patient immediately following its removal from the refrigerator, without any waiting period.
- Group R: Just before the vascular cannulisation, a 4×5 cm cold marble stone was held on the carotid in the right lateral neck region (2–3 cm above the clavicle, on the sternocleidomastoid muscle (SCM)) for 30 seconds, and then cannulisation was performed.
- Group L: Just before the vascular cannulisation, a 4×5 cm cold marble stone was held on the carotid in the left lateral neck region (2–3 cm above the clavicle, on the SCM) for 30 seconds, and then cannulisation was performed.

Heart rate (HR) and noninvasive blood pressure (NIBP) were measured prior to the application of the cold marble to the neck area, 30 seconds after the application as well as before and after the establishment of vascular access. For venous cannulation a skilled practitioner

placed an 18-gauge green coloured catheter on the back of the patient's left hand. The patients were then asked to rate their pain levels on a scale of 0 to 10 using the Numeric Rating Scale (NRS), and this value was recorded. Patients where immediate vascular access was not established were excluded from the study. Another researcher, who was unaware of the lateralization, recorded all data.

2.1. Statistical analysis

Patients' data was analyzed using SPSS 21 and sample size analysis was completed using G*Power 3.1.9.7. Sample size was calculated assuming $\alpha = 0.05$, power $(1-\beta) = 0.80$, and effect size 0.5, with equal distribution amongst the groups. Calculations revealed a sample size of 128, 64 for each group. Considering recording errors and drop outs, 70 people were determined to be included in each group and the total sample size was determined as 140 people. Patients were randomized into 2 groups: Group R (right side) and Group L (left side) using the lottery method. The relationship between the NRS scores of both groups and the HR and NIBB values of the patients before and after marble application as well as after vascular access was examined. Kolmogorov Smirnov and Shapiro Wilk tests were used to assess data for normal distribution. In the analysis of data complying with normal distribution, t-test in independent groups (Independent t-test) and significance test of the difference between two pairs (Paired Samples Test) were used. Mann-Whitney U test was used to analyze data that did not comply with normal distribution. Additionally, Chi-square test was used to compare some data. Mean±Standard deviation (Mean±SD) and percentages were used in descriptive statistics. The results were evaluated with a 95% confidence interval and significance was accepted as $p<0.05$.

3. Results

The data of 133 patients (67 in Group L and 66 in Group R) were analyzed (Fig. 1). Both groups were similar in terms of age, gender, and body mass index (BMI) (Table 1).

The initial heart rates and non-invasive blood pressure (NIBP) measurements of the groups were comparable. The average heart rate values following vagal stimulation in both groups were significantly lower than the heart rate values before vagal stimulation. Additionally, the average heart rate values after vascular access were also significantly lower than the values before vagal stimulation ($p<0.001$). In Group R, the mean heart rate following vascular access was determined to be considerably greater than the mean heart rate following vagal stimulation ($p=0.815$) (Table 2).

When comparing the average heart rate values for each time period in Group L and Group R, there was no significant difference observed in the mean heart rate values before vagal stimulation ($p=0.645$), after vagal stimulation ($p=0.971$), and after vascular access ($p=0.656$) between the two groups. Upon examining the heart rate change percentages, it was observed that the heart rate change percentages before and after vagal stimulation in Group L were 5.7±5.8%, while in Group R it was 7.1±7.0%. This indicates that the heart rate variability was greater in Group R. However, it is important to note that this difference was not statistically significant ($p=0.219$). When the NRS values of both groups were examined, the Mean±SD was calculated as 2.64±1.28 in Group L and 2.85±1.62 in Group R, and no difference was observed between the average pain scores of both groups ($p=0.941$).

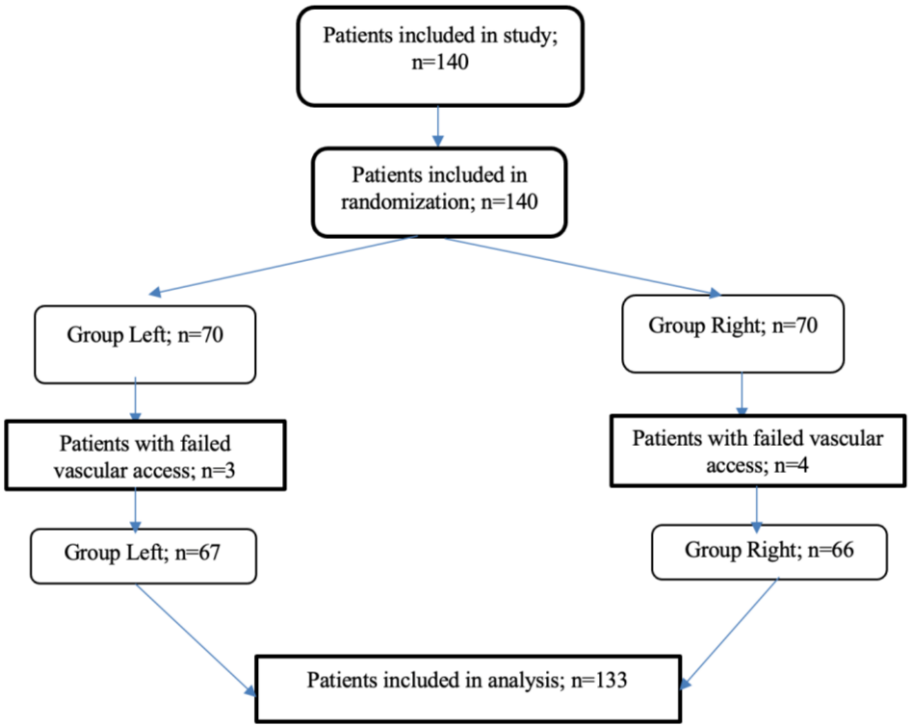

Fig. 1. Consort flow chart.

Table 1. Demographic data.

	Group Left (n=67)	Group Right (n=66)	p
Age (years) (Mean±SD)	52.3±15.4	48.0±17.5	0.318
Gender (n) M/F	33/34	30/36	0.661
ASA (n) I/II/III	9/53/5	11/49/6	
BMI (Mean±SD)	27.9±5.1	28.3±6.6	0.935

BMI: Body mass index; ASA: American Society of Anesthesiologists; (Mean±SD): Mean±standard deviation; n: Number.

Table 2. Heart rate changes.

Heart rate /minute (Mean±SD)	Group Left (n=67)	p	Group Right (n=66)	p
Before vagal stimulation	77.0±11,8	<0.001	77.9±11.7	<0.001
After vagal stimulation	72.5±11.7		72.1±10.1	
Before vagal stimulation	77.0±11,8	<0.001	77.9±11.7	<0.001
After vascular access	72.6±11.8		73.5-10.4	
After vagal stimulation	72.5±11.7	0.815	72.1±10.1	<0.001
After vascular access	72.6±11.8		73.5-10.4	

(Mean±SD): Mean±standard deviation; n: Number.

4. Discussion

In an earlier study, we assessed the efficacy of vagus stimulation in alleviating vascular access pain by applying cold bilaterally to the lateral neck region. Our findings demonstrated that vagus stimulation is useful in reducing vascular access pain. Our recent study demonstrates that vagal stimulation does not exhibit any variation in terms of lateralization when used to alleviate vascular access discomfort. In our study, we conducted vagal stimulation by applying cold to the neck region on both the right and left sides, separately. We observed that the average heart rates after vagal stimulation and after vascular access were significantly lower in both groups when compared to the heart rates before vagal stimulation ($p<0.05$). The percentage change in average heart rate after vagal stimulation compared to baseline was greater in Group R than in Group L; however, this difference was not statistically significant ($p>0.05$)

Various techniques are employed for stimulating the vagus nerve, and one of these techniques involves the application of cold to the neck region [12,17]. When individuals experience stress, they instinctively employ techniques that stimulate the vagus nerve, such as splashing cold water on their face and neck, exposing themselves to a breeze, or engaging in deep breathing. Our study preferred the use of cold application as a method for stimulating the vagus nerve and revealed a notable reduction in heart rate in both groups, specifically in the patients who received cold applications to the right and left side of the neck separately. This decrease was observed in comparison to the pre-stimulation period, indicating that stimulation from either side of the neck resulted in vagal stimulation. In their investigation on autonomic modulation in individuals with heart failure, Premchand et al. [18] employed the vagal stimulation approach. One cohort of patients received stimulation from the right hemisphere, while the other cohort received stimulation from the left hemisphere. Upon evaluating the 6-minute walking distance of the patients, it was observed that the group receiving stimulation on the right side had more improvement. The study found that the heart rate, as measured by holter, fell by an average of 3.4 beats per minute in the group stimulated from the left side, and by 4.3 beats per minute in the group stimulated from the right side. Regulation is anticipated to take place through the interplay between the peripheral cardiac nervous system and the central nervous system, irrespective of the side on which the stimulus is applied. In our investigation, we found that applying cold to the right side resulted in a more pronounced decrease in heart rate. However, we did not find a significant difference in variability between left side and right side cold application. Kathrin et al. [19] assessed heart rate variability using vagus stimulation in various auricular localizations. The study's findings indicated that the heart's vagal innervation is asymmetrical.

The sinoatrial node (SAN) receives innervation from the right vagal fibers, while the atrioventricular node (AVN) receives innervation from the left vagal fibers. For instance, when the right neck region is stimulated, it leads to a negative chronotropic impact in the sinoatrial node (SAN), resulting in a decrease in heart rate. Similarly, stimulation of the left neck region creates a negative dromotropic effect in the atrioventricular node (AVN), leading to a slowdown in heart rate. The vagus nerve plays a key role in autonomic regulation of the heart, and its right and left branches exert differential

physiological effects. Right-sided vagus nerve stimulation predominantly affects the sinoatrial node, resulting in a negative chronotropic effect, whereas left-sided stimulation mainly influences the atrioventricular node, leading to a negative dromotropic response [20]. Hendrik et al. [21] investigated the effects of vagus stimulation on pigs. They specifically focused on the neck region and found that there was no significant difference in heart rate variability between stimulation from the right and left sides.

Activation of inhibitory pathways through the nucleus tractus solitarius and subsequent stimulation of other autonomic nuclei centrally leads to the analgesic effect of vagal stimulation [14,22,23]. The activation of the vagus nerve contributes to pain management by reducing inflammation and modulating neuronal activity in pain pathways [2]. In a study conducted by Marcos et al. [3] on rats, it was found that left auricular acupuncture suppressed the transmission of pain signals in the visceral-somatic nociception model. However, this effect was not detected when right auricular acupuncture was employed. The ineffectiveness of lateralization is believed to be attributed to the fact that the analgesic impact of vagal stimulation was a result of central inhibition rather than peripheral nociceptive processes [14]. In their study examining the impact of vagal stimulation on acute and chronic pain, Likar et al. [24] determined that it has the potential to be a remarkable and supplementary alternative to medication for managing chronic and acute postoperative pain.

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Conflict of Interest

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

Data Availability

The datasets created and/or analyzed during the current study are not publicly available, but are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the ethics committee of Samsun University Samsun Training and Research Hospital, following ethics committee approval (approval number: GOKAEK-2024/3/9; date: 10.01.2024). Written informed consent was obtained from the participants. All methods were performed in accordance with relevant guidelines and regulations.

Author Contributions

The author confirms sole responsibility for all aspects of the study including: conceptualization, methodology, formal analysis, investigation, data curation, visualization, writing – original draft, and writing – review & editing.

5. Conclusions

In our study, cold application to the right lateral neck region during vagal nerve stimulation produced greater changes in heart rate; however, this difference was not statistically significant. No significant difference was observed between right- and left-sided stimulation in terms of analgesic efficacy. Based on our findings, we suggest that daily cold application to the neck region may contribute to heart rate modulation and provide analgesic benefits. However, our results did not show a clinically significant lateralization effect between the right and left sides. Further studies with larger patient groups are needed to develop a standardized protocol and model for clinical application.

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