Indication of Treatment For Children And Adolescents With Postural Tachycardia Syndrome By Intravenous Saline Infusion

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Research Article

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Abstract

Background: Intravenous saline infusion is considered effective for the treatment of postural tachycardia syndrome (POTS) in adults. However, few studies have assessed the efficacy of intravenous saline infusion for POTS in children and adolescents.

Aim: This study aimed to evaluate the efficacy of intravenous saline infusion in children and adolescents with POTS.

Methods: A total of 107 children with POTS (median age: 13 years, range: 10–15 years) were enrolled. Eighty-eight children were in the intravenous saline infusion group and 19 children were in the comparison group. Blood pressure (BP) and pulse rate (PR) were recorded before and after standing. A standing test was performed early in the morning for 2 consecutive days. A volume of 1.5 L of saline was administered intravenously to each participant in the intervention group for a mean duration of 17 hours between the two standing tests.

Results: The mean change in PR was significantly lower in the intervention group than in the comparison group during the second test (36.9 vs. 52.8 beats/minute, $p<0.001$). Additionally, the mean change in PR was significantly lower in the second test than in the first test (44.7 beats/minute) in the intervention group ($p<0.001$). However, the mean change in systolic BP was not different before and after intravenous saline infusion between the two groups or between the two tests in each group.

Conclusion: Intravenous saline infusion reduces the increased PR on standing in children with POTS. Intravenous saline infusion improves tachycardia in children with POTS when standing.

1. Introduction

Psychosomatic symptoms and school refusal (SR) among children and adolescent are increasing in Japan. Postural tachycardia syndrome (POTS), which is defined as a subtype of orthostatic dysregulation, is one of a cause of SR and an important psychosomatic disease in children and adolescent [1]. Physical treatment is essential as well as psychosomatic treatment to improve pathological conditions, symptoms and self-esteem.

POTS is a common cardiovascular and autonomic nervous disorder in children and adolescents [1–3]. An expert consensus statement defines POTS as an increase in pulse rate (PR) of ≥30 beats per minute (bpm) within 10 minutes of standing or head-up-tilt, and ≥40 bpm in children and adolescents (<19 years old), in the absence of orthostatic hypotension [4]. The pathophysiology of POTS is heterogeneous, including alpha-receptor dysfunction, β-receptor super sensitivity, venous pooling, brainstem center dysfunction, autonomic dysfunction, and cardiovascular deconditioning [5, 6]. Autonomic dysfunction causes circulatory disturbance, which leads to a decrease in cerebral blood flow. Concurrent, tachycardia, a characteristic finding in the diagnostic criteria for POTS [1], occurs in the periphery as a compensatory reaction.

Benrud-Larson et al. previously showed that symptoms of POTS are associated with quality of life (QOL) in patients with POTS [7]. In Japan, symptoms of POTS make getting up early in the morning and attending school difficult for children and adolescents. Severe OD causes withdrawal from school and society, and its occurrence is increasing among children and adolescents, despite a decline in birth rate [8]. This problem due to OD requires investigation.

Conventional treatment of POTS consists of both nonpharmacological and pharmacological approaches. Patient education, physical countermeasures (e.g., leg crossing), sodium and water intake, support garments (e.g., compression stockings), and exercise training are widely used as nonpharmacological therapeutic options. Pharmacological treatment of POTS includes the α1-adrenergic agonist midodrine, the mineralocorticoid fludrocortisone, β-blockers including propranolol, and the cholinesterase inhibitor pyridostigmine [9]. Because of their effects on hypovolemia, water and salt intake are effective for improving POTS [10–12]; in our clinical experience, many patients with POTS have difficulty maintaining water and salt intake because of their POTS symptoms. Expert centers have reported that 1 L of normal saline infused over 1 hour decreases orthostatic tachycardia and improves symptoms for several hours to 2 days [5, 13]. Jacob et al. found that 1 L of normal saline infused intravenously over 1 hour normalized orthostatic tachycardia (before: 33±5 bpm; after: 15±3 bpm) [13]. Additionally, astronauts receive intravenous saline infusion for the recovery of orthostatic tolerance when they return from space [14, 15]. Robertson et al. reported a decrease in cardiovascular plasma volume after space flight, which was caused by cardiovascular deconditioning due to long-term bed rest or weightlessness [16]. Notably, there have been several reports regarding the relationship between a decrease in plasma volume and the onset of cardiovascular deconditioning [16–20].

However, to the best of our knowledge, there have been few reports regarding the efficacy of intravenous saline infusion for POTS in children and adolescents. Consequently, assessment of the efficacy of a single intravenous saline infusion is required. Therefore, we investigated the efficacy of intravenous saline infusion on the change in cardiovascular function when standing in children with OD.

2. Methods

Participants

A total of 107 children with POTS aged 10–15 years (median age: 13 years, range: 10–15 years; 49 boys and 58 girls) were enrolled. All participants were admitted to the pediatric ward of Kansai Medical University Medical Center between 2014 and 2020 for assessing POTS. Eighty-eight of these children (intervention [IV] group), who were admitted between 2014 and 2016, received 1.5 L of intravenous saline infusion. The remaining 19 children (comparison group), who were admitted between 2019 and 2020, they did not receive saline. The number of participants differed between the two groups because we collected each group data in different periods. The diagnosis of POTS was based on the criteria of the clinical guidelines for juvenile POTS edited by The Japanese Society of Psychosomatic Pediatrics, which define POTS as follows: an increase in PR ≥35 bpm or heart rate ≥115 bpm when standing for 10

minutes, and the absence of orthostatic hypotension (>20 mmHg drop in systolic blood pressure [SBP]) [1]. All participants had no comorbidities and were free from medication for the 3-day test period, which is set by authors. Moreover, there were no differences in characteristics between the two groups regarding age, sex, and meals during hospitalization. According to activity differences during hospitalization, children in the comparison group attended school within the pediatric ward, beginning on day 2.

Standing test and data collection

The standing test was performed twice during admission: at 7:00 am (before breakfast) on days 2 and 3 after admission (Figure 1). The procedure of the standing test was as follows. First, participants lay down on a bed in the supine position for 10 minutes. Second, they were asked to stand from the supine position to upright on the bedside by themselves without support. PR and blood pressure (BP) were recorded before standing, and at 1, 3, 5, and 10 minutes after standing.

Intravenous saline infusion

A volume of 1.5 L of saline was administered intravenously to each participant in the IV group for a mean duration of 17 hours. The infusion started after lunch on day 2 and finished at 6:00 am on day 3 (Fig. 1). Participants in the comparison group did not receive this intravenous saline infusion.

Statistical analysis

Changes in PR and BP during standing were assessed. Data were compared between the two groups using the Mann–Whitney U test. Comparison of data between the first and second tests in each group was performed by the Wilcoxon rank-sum test. SPSS Statistics version 22.0 (IBM®, Armonk, NY, USA) was used for analysis. A p value <0.05 was considered statistically significant.

Ethics

All procedures were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The purpose and procedure of the study were explained in advance to all participants and their guardians, and written informed consent was obtained from them. This study was approved by the ethical committee of Kansai Medical University (approval number: 26-6).

3. Results

Change in PR

The change in PR in each participant was defined as maximum PR in the standing position − PR in the supine position. Figure 2 compares the change in PR during each standing test between the two groups. The mean change in PR in the IV group (i.e., determined on the basis of the change in PR for all participants in that group) was significantly lower than the mean change in PR in the comparison group

during the second test (after intravenous saline infusion) (36.9 vs. 52.8 bpm, p< 0.001). However, no significant difference in the mean change in PR was found between the groups in the first test (before intravenous saline infusion).

Figure 3 compares the change in PR within each group between the two tests. The mean change in PR in the IV group was significantly lower in the second test than in the first test (36.9 vs. 44.7 bpm, p<0.001). However, no significant difference in the mean change in PR was found between the two tests in the comparison group.

Change in SBP

The change in SBP in each participant was defined as the maximum SBP in the standing position − SBP in the supine position. Figure 4 compares the change in SBP during each standing test between the two groups. No significant difference in the mean change in SBP (i.e., determined on the basis of the change in SBP for all participants in that group) was observed between the two groups during either test. Figure 5 compares the mean change in SBP within each group between the two tests. No significant difference in the mean change in SBP was found between the two tests in either group.

Safety

We found no remarkable side effects due to intravenous saline infusion, such as edema or pollakiuria, among the participants of our study.

4. Discussion

Efficacy of intravenous saline infusion

The main findings of our study were as follows. Our study showed that an increase in PR among participants with POTS who had a standing test early in the morning was significantly decreased after 1.5 L of intravenous saline infusion. Although increasing plasma volume is considered important for children with POTS [21], few reports have shown its objective efficacy. However, our finding that intravenous saline infusion was effective for improving tachycardia in children and adolescents with POTS supports this notion. We presume that this efficacy in the pathophysiology of POTS results from increases in the venous return volume, cardiac output, and total blood volume.

Regarding the treatment of POTS in children, Medow et al. reported that the effectiveness of oral rehydration was equal to or better than the effectiveness of intravenous saline infusion for POTS [22]. Although oral rehydration is reportedly convenient, safe, and effective, many children with POTS experience difficulty during oral intake because of nausea, indigestion, and general fatigue. In our clinical experience, these manifestations are symptoms of orthostatic intolerance due to POTS; to the best of our knowledge, there are no reports regarding treatment for patients with POTS who have difficulty with respect to water and salt intake. Our findings suggest that intravenous saline infusion is a suitable, effective treatment for patients who experience difficulty during oral intake due to symptoms of POTS.

Pathophysiology of POTS

The etiology and pathophysiology of POTS are unknown, but are presumably heterogeneous. The syndrome is associated with deconditioning, recent viral illness, chronic fatigue syndrome, and limited or restricted autonomic neuropathy [4]. Because of these various pathophysiologies, hypovolemia with reduced systemic venous return occurs, along with reduced cardiac output and reduction in total blood volume; these changes lead to orthostatic intolerance [22]. Orthostatic intolerance is accompanied by signs and symptoms that can include loss of consciousness, cognitive deficits, loss of vision or hearing, lightheadedness, headache, fatigue, nausea, abdominal pain, sweating, and tremor [23].

Cardiovascular deconditioning

Joyner et al. reported that cardiovascular deconditioning plays a major role in POTS because it causes orthostatic intolerance [6]. Cardiovascular deconditioning is defined as circulatory disturbance due to hypoactivity in a microgravity environment, such as in space or during confinement in bed. This condition causes lower limb muscle atrophy and myocardial atrophy, thereby reducing cardiac output. A previous study reported that cardiovascular deconditioning due to the bed rest test, which was created by an artificial microgravity situation, caused POTS [24]. Confinement in bed is similar to microgravity and causes orthostatic intolerance and deconditioning, which are caused by the microgravity environment in a bed rest test [14]. We previously reported that 10 days of a bed rest test led to a decrease in orthostatic intolerance in 10 of 12 participants [24] and increased tachycardia when standing. Some other studies have also reported orthostatic intolerance in the bed rest test [25, 26].

The prevalence of POTS in pediatric patients has increased in recent years and is caused by changes in their lifestyle, such as a lack of physical exercise and prolonged time in bed watching television [27]. These findings indicate that POTS is pathophysiologically heterogeneous because of autonomic dysfunction, psychosomatic stress, and cardiovascular deconditioning. Therefore, we presume that cardiovascular deconditioning has an important role, as shown by previous reports regarding bed rest tests [14, 24, 25, 26].

Efficacy of intravenous saline infusion for cardiovascular deconditioning

It is unclear whether autonomic dysfunction or cardiovascular deconditioning is improved by intravenous saline infusion. We suspect that cardiovascular deconditioning is involved. While intravenous normal saline infusion increases circulating plasma volume, cardiovascular deconditioning decreases circulating plasma volume [16]. Therefore, we presume that patients with POTS have a chronic decrease in circulating plasma volume by cardiovascular deconditioning and an increase in plasma volume by intravenous normal saline infusion, which improves tachycardia. This possibility suggests that the cause of worsening POTS in children and adolescents in Japan is deconditioning. The mechanism by which intravenous normal saline infusion affects the autonomic nervous system remains unclear. Further research is needed regarding the response of the autonomic nervous system to intravenous normal saline infusion.

Limitations

There were some limitations in this study. First, we did not measure the oral intake and plasma volumes. Water and salt intake are effective for improving POTS [10–12]. Therefore, the volume of oral intake during the previous day might have affected the degree of symptoms, postural tachycardia, and the efficacy of intravenous saline infusion. Measurement of the absolute value of plasma volume is impossible, but echocardiographic assessments and measurement of water intake should be performed in a future study. Second, this study did not investigate whether postural tachycardia is influenced by discomfort, anxiety, or previous therapy before admission to our hospital because those factors were not assessed in this study. Third, this study did not assess changes in symptoms caused by intravenous saline infusion. We cannot conclusively determine whether intravenous saline infusion is effective for children and adolescents with POTS without a clear assessment of symptom improvement following this treatment. Assessment of efficacy for specific symptoms should be also performed. We expect some improvement of the patient's QOL because intravenous saline infusion improves the physical condition. Long-term efficacy and QOL following intravenous saline infusion therapy for POTS should be further investigated.

5. Conclusion

Our study suggests that intravenous saline infusion improves orthostatic tachycardia in children and adolescents with POTS when standing in the morning. We presume that intravenous saline infusion is rescue for children and adolescents with POTS who have difficulty with oral intake due to orthostatic intolerance symptoms. Intravenous normal saline infusion for children or adolescents with POTS might improve biopsychosocial health of them.

Abbreviations

POTS: Postural Tachycardia Syndrome

PR: Pulse Rate

BP: Blood Pressure

Bmp: beats per minute

QOL: Quality of Life

OD: Orthostatic Dysregulation

IV: Intervention

SBP: Systolic Blood Pressure

Declarations

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Consent to participate: Written informed consent was obtained from the patients and parents for participation in this study.

Consent for publication: Written informed consent was obtained from the patients and parents for publication.

Availability of data and material: Not applicable

Authors' contributions: Y.Y. conceptualized and analyzed the study, and drafted the initial manuscript. Y.N., M.M., R.T., K.I., and N.M. collected the data, and critically reviewed and revised the manuscript. Y.I. supervised the study, performed statistical analysis, and critically reviewed and revised the manuscript. K.K. supervised the entire study process and critically reviewed the manuscript. All authors read and approved the final manuscript.

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Figures

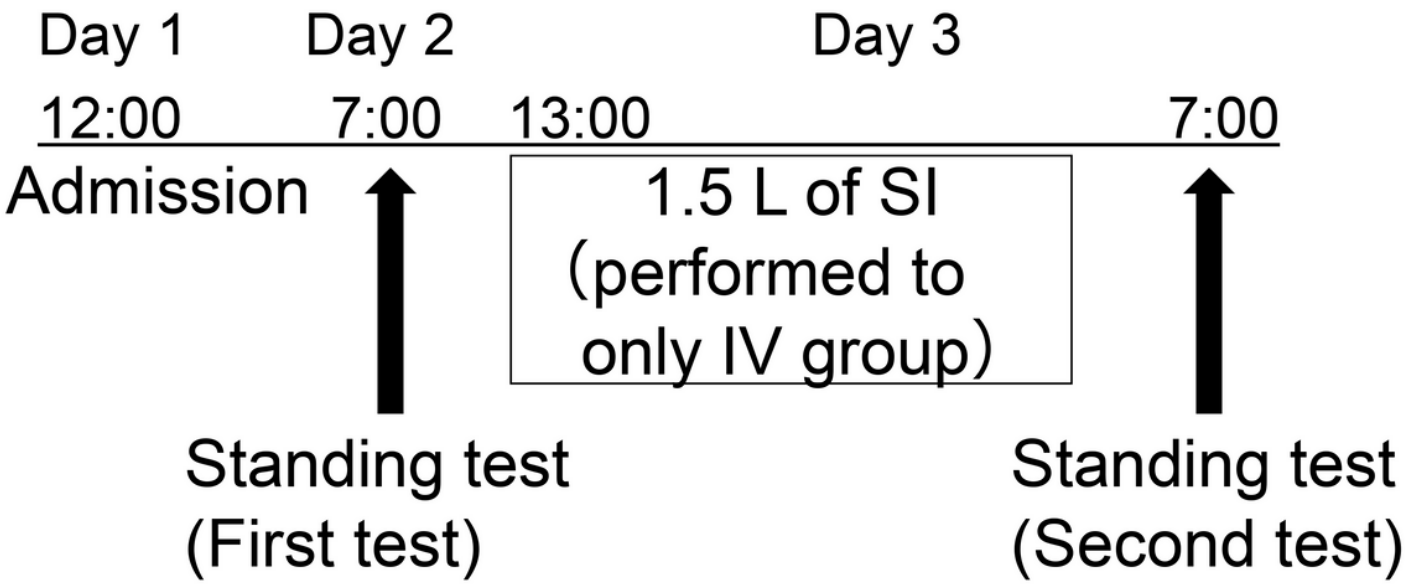

Figure 1

Schedule of the investigation.

The standing test was performed twice at 7:00 am before breakfast on day 2 (first test) and at 7:00 am of day 3 (second test) during admission. A volume of 1.5 L of saline was administered intravenously for an

average of 17 hours to only the IV group. This infusion started after lunch on day 2 and finished at 6:00 am on day 3. Participants in the control group did not receive saline. SI: saline injection; IV: intervention

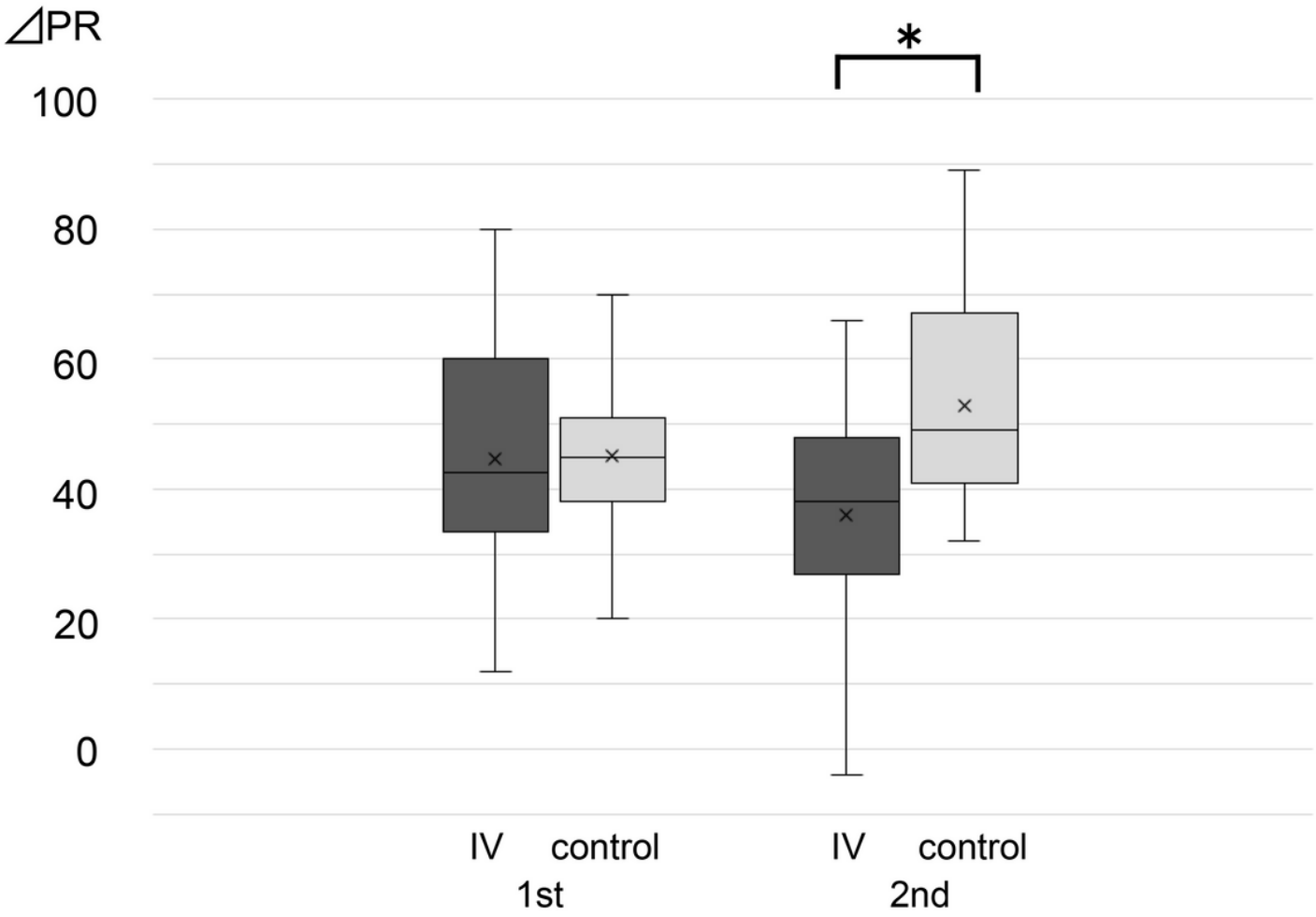

Figure 2

Comparison of the change in PR by the standing test between the two groups in each test The increase in PR in the IV group was significantly lower than that in the control group in the second test ($p < 0.001$). However, there was no difference in the change in PR between the groups in the first test ($p=0.302$).

(□□0.05) The central horizontal line in the box represents the median value, and the bottom and top edges of the box represent the 25th and 75th percentiles, respectively. The central vertical lines extend from the box to the 90th and 10th percentiles. PR: pulse rate; IV: intervention.

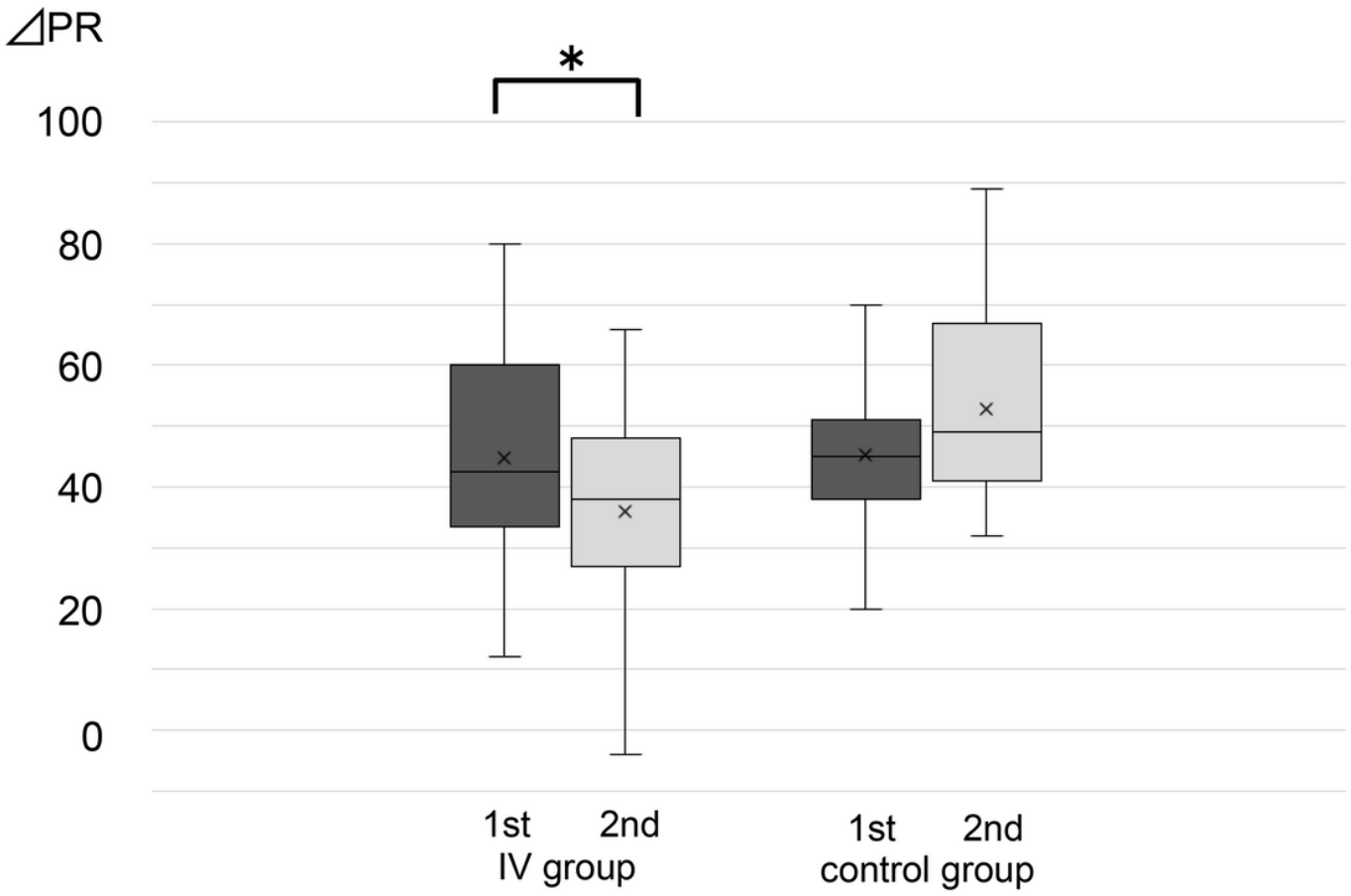

Figure 3

Comparison of the change in PR by the standing test between the two tests in each group The increase in PR after saline injection was significantly less compared with that before saline injection ($p < 0.001$). However, there was no difference in the change in PR between the two tests in the control group ($p=0.365$). (□□0.05) The central horizontal line in the box represents the median value, and the bottom and top edges of the box represent the 25th and 75th percentiles, respectively. The central vertical lines extend from the box to the 90th and 10th percentiles. PR: pulse rate; IV: intervention.

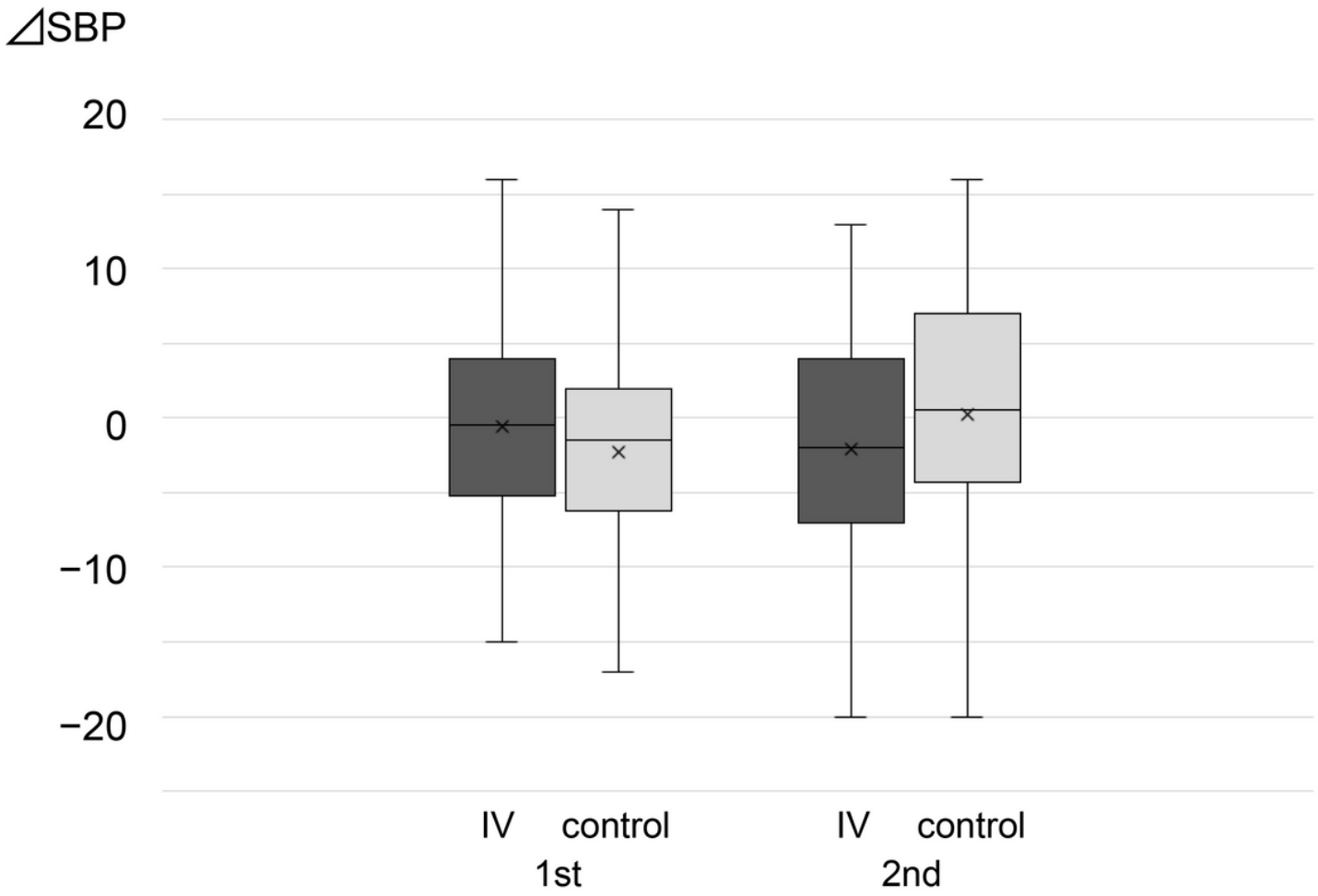

Figure 4

Comparison of the change in SBP by the standing test between the two groups in each test There was no significant difference in the decrease in SBP values between the two groups at the first or second test (p= 0.769, 0.356 respectively). The central horizontal line in the box represents the median value, and the bottom and top edges of the box represent the 25th and 75th percentiles, respectively. The central vertical lines extend from the box to the 90th and 10th percentiles. SBP: systolic blood pressure; IV: intervention.

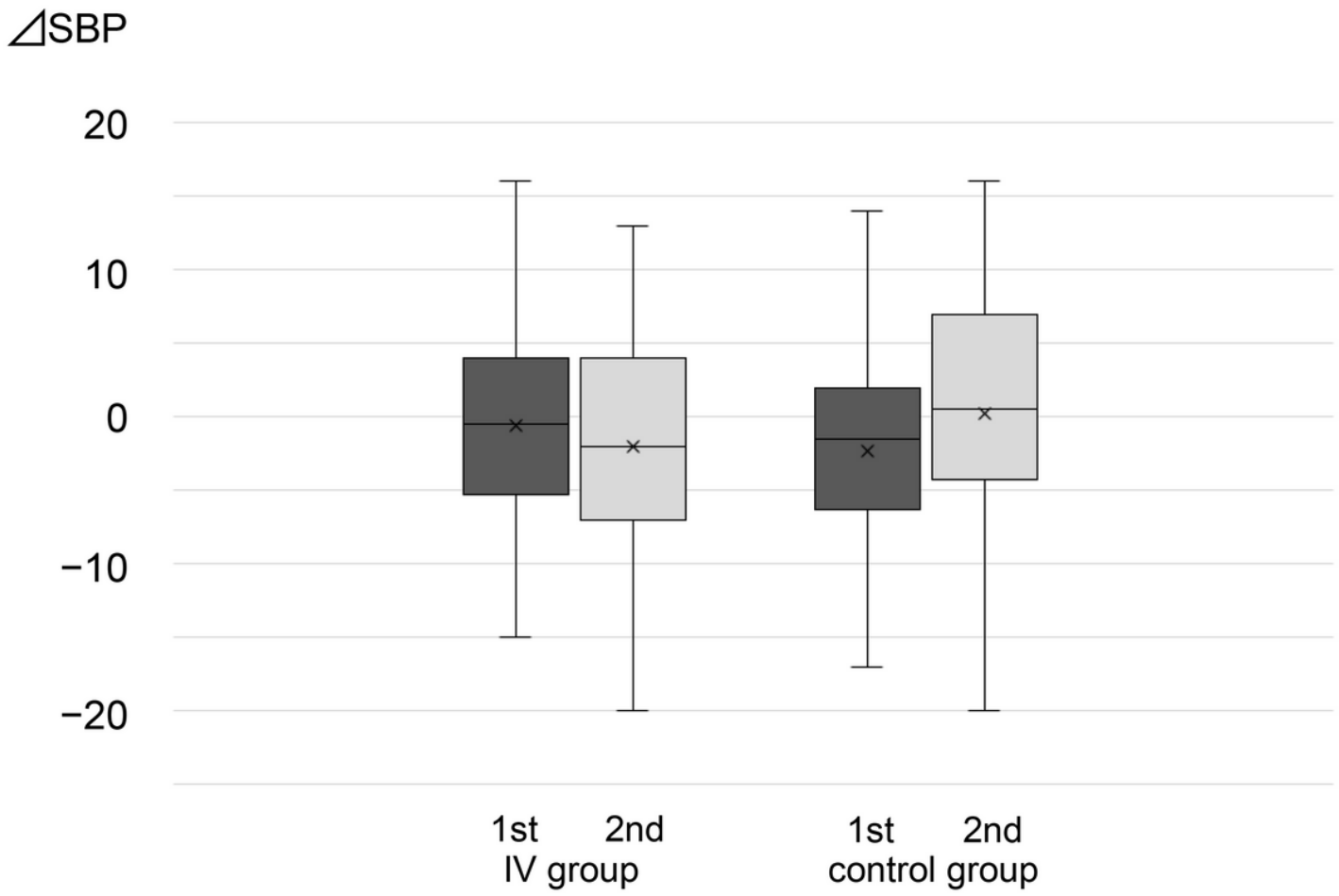

Figure 5

Comparison of the change in SBP by the standing test between the two tests in each group There was no significant difference in the decrease in SBP values between the two tests in the IV or control group (p= 0.356, 0.727 respectively). . The central horizontal line in the box represents the median value, and the bottom and top edges of the box represent the 25th and 75th percentiles, respectively. The central vertical lines extend from the box to the 90th and 10th percentiles. SBP: systolic blood pressure; IV: intervention.