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Continuous Transversus Abdominis Plane Nerve Blocks: Does Varying Local Anesthetic Delivery Method—Automatic Repeated Bolus vs. Continuous Basal Infusion—Influence the Extent of Sensation to Cold?:

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Submitted as a Research Report:

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This study was conducted with written informed consent from the study subjects.

This report describes a prospective randomized clinical trial. The author states that the report includes every item in the CONSORT checklist for a prospective randomized clinical trial.

The study was registered prior to patient enrollment.

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This was not an observational clinical study.

A Randomized, Triple-Masked, Crossover Study in Volunteers

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Abstract

Background—It remains unknown whether continuous or scheduled intermittent bolus local anesthetic administration is preferable for transversus abdominis plane (TAP) catheters. We therefore tested the hypothesis that when using TAP catheters, providing local anesthetic in repeated bolus doses increases the cephalad-caudad cutaneous effects compared with a basal-only infusion.

Methods—Bilateral TAP catheters (posterior approach) were inserted in 24 healthy volunteers followed by ropivacaine 2 mg/mL administration for a total of 6 hours. The right side was randomly assigned to either a basal infusion (8 mL/h) or bolus doses (24 mL administered every 3 hours for a total of 2 bolus doses) in a double-masked manner. The left side received the alternate treatment. The primary endpoint was the extent of sensory deficit as measured by cool roller along the axillary line at Hour 6 (6 hours after the local anesthetic administration was initiated). Secondary endpoints included the extent of sensory deficit as measured by cool roller and Von Frey filaments along the axillary line and along a transverse line at the level of the anterior superior iliac spine at Hours 0–6.

Results—While there were statistically significant differences between treatments within the earlier part of the administration period, by Hour 6 the difference in extent of sensory deficit to cold failed to reach statistical significance along the axillary line (mean=0.9 cm; SD=6.8; 95% CI -2.0, 3.8; p=0.515) and transverse line (mean=2.5 cm; SD=10.1; 95% CI -1.8, 6.8; p=0.244). While the difference between treatments was statistically significant at various early time points

for the horizontal, vertical and estimated area measurements of both cold and mechanical pressure sensory deficits, no comparison remained statistically significant by Hour 6.

Conclusion—No evidence was found in this study involving healthy volunteers to support the hypothesis that changing the local anesthetic administration technique (continuous basal versus hourly bolus) when using ropivacaine 0.2% and TAP catheter at 8 mL/h and 24 mL every 3 hours significantly influences the cutaneous effects after 6 hours of administration. Additional research is required to determine whether changing variables (e.g., local anesthetic concentration, basal infusion rate, bolus dose volume and/or interval) would provide different results.

INTRODUCTION

Single-injection transversus abdominis plane (TAP) blocks provide effective postoperative analgesia for a variety of surgeries involving the abdominal wall.¹ To extend the duration of analgesia beyond the 8–12 hours provided with a bolus of ropivacaine or bupivacaine,² investigators have reported perineural catheter insertion to allow for subsequent local anesthetic administration.^{3–10} Indeed, retrospective studies suggest there may be benefits to using this technique.^{11,12} Unfortunately, the only randomized, placebo-controlled study involving surgical subjects revealed no differences in pain scores between a basal infusion of ropivacaine 0.2% (10 mL/h, no bolus) and normal saline, although it was under-powered.¹³

In contrast, the only other published randomized trial involving TAP catheters and surgical subjects suggested effective analgesia delivery given that no differences were detected between the TAP treatment group and controls with a potent epidural infusion.¹⁴ One major difference between this study and the negative randomized, placebo-controlled trial was that it involved repeated, large-volume bolus doses administered every 8 hours instead of a continuous basal infusion. While it remains unknown if the varying administration techniques were at least partially responsible for the apparent differing results of these two studies, there are at least theoretical reasons to believe that repeated bolus doses may be a superior strategy for TAP catheters. TAP blocks target multiple nerves that are somewhat distant from each other, yet lie within the same fascial plane.¹⁵ Therefore, a large bolus of local anesthetic spreads further from the injection point relative to a smaller volume, consequently affecting a higher number of nerves and increasing the area of analgesia/anesthesia.¹⁶

The superiority of repeated bolus doses over a continuous basal infusion has been demonstrated in some studies for various catheter locations,^{17–20} yet not others.^{21–23} As with other aspects of continuous peripheral nerve blocks, effects often vary depending upon the anatomy of the catheter location.²⁴ The relationship between administration strategy and ensuing effects remains unexamined for TAP catheters.²⁵ There is real potential for analgesic benefits if intermittent bolus doses improved spread for TAP catheters compared with a basal infusion, as suggested by one trial involving healthy volunteers that found only a 1.5-dermatome distribution after 24 hours of a basal ropivacaine 0.2% infusion (5 mL/h).²⁶

The investigators therefore executed this randomized, triple-masked, controlled trial to determine if delivering local anesthetic as a repeated bolus dose results in improved local anesthetic spread/effects compared with a continuous basal infusion for TAP catheters. The

primary hypothesis was that for TAP catheters, providing local anesthetic in repeated bolus doses compared to a continuous basal infusion involving an identical local anesthetic dose/mass increases the extent of sensory deficit. The primary endpoint was the distance of sensory deficit to cold along the mid-axillary line at Hour 6 (6 hours after initiation of local anesthetic administration).

METHODS

Enrollment

This study followed Good Clinical Practice and was conducted within the ethical guidelines outlined in the Declaration of Helsinki. The trial was prospectively registered at clinicaltrials.gov (NCT02662023). The University of California San Diego Institutional Review Board (San Diego, California) approved all study procedures and provided oversight of the data and safety issues for the duration of the trial. Written, informed consent was obtained from all participating subjects.

Healthy adult male and female volunteers (18 years and older, weighing more than 45 kg) were recruited using an established University of California San Diego Investigational Review Board-approved volunteer database. Exclusion criteria included any known neuromuscular deficit of the abdominal wall, a body mass index greater than 40 kg/m², regular opioid use within the previous 2 months, allergy to study medications, known renal insufficiency (creatinine > 1.5 mg/dL), pregnancy, or incarceration. The study was conducted at the University of California San Diego Clinical and Translational Research Institute (San Diego, California).

Catheter Insertion

Following written, informed consent, bilateral TAP catheters using a posterior approach (FlexBlock, Teleflex Medical, Reading, PA, USA) were inserted using a standardized ultrasound-guided technique in each volunteer using a posterior approach technique previously described.¹³ Subjects were placed in a lateral decubitus position with the side to be blocked up. A rolled blanket was placed under the dependent side to extend the space between the nondependent iliac crest and costal margin. Standard American Society of Anesthesiologists monitors and oxygen by nasal cannula at 3 L/min were applied. When sedation was given, intravenous midazolam (1 mg) and/or fentanyl (50 µg) were administered for patient comfort. The skin surrounding the insertion site was prepared with chlorhexidine gluconate/isopropyl alcohol solution and a fenestrated sterile drape applied.

The TAP was visualized with a 13–6 MHz 38-mm linear array transducer (M-Turbo, SonoSite, Bothell, Washington) in a sterile sheath that was placed at the mid-axillary line in a transverse orientation. The external oblique, internal oblique and transversus abdominis muscles were identified with ultrasound. After the skin was anesthetized with 1% lidocaine, a 17-gauge Tuohy needle was introduced posterior to the transducer and advanced in-plane in an anterior direction. The final needle tip position was in the plane between the internal oblique and transversus abdominis muscles. Normal saline was injected under direct visualization to confirm proper positioning of the needle tip and the volume of normal saline

was recorded. A flexible 19-gauge, single-orifice catheter (FlexBlock, Teleflex Medical, Research Triangle Park, North Carolina) was advanced 3 cm beyond the needle tip. The needle was withdrawn over the catheter.

To check the perineural catheter placement accuracy, 5 mL of normal saline was administered *via* the catheter under ultrasound guidance to confirm an increase in fluid volume within the TAP (the plane between the transversus abdominis muscle and internal oblique muscle). The skin entry site was covered with a sterile clear occlusive dressing with care taken to not cover the skin along any areas that would be subsequently tested. The catheter was secured with an anchoring device and additional sterile occlusive dressings. If the amount of normal saline administered on one side was less than the other, additional normal saline was administered via the catheter to ensure equivalent volumes of saline on both sides.

Treatment Group Assignment

The Investigational Drug Service created a computer-generated randomization table in blocks of four, with a 1:1 ratio, stratified by sex. Each subject's right catheter was randomized to one of two possible local anesthetic (ropivacaine 0.2%) administration techniques: a basal infusion (8 mL/h) or bolus doses (24 mL administered every 3 hours for a total of 2 bolus doses). The left catheter received the other possible treatment. This split-body study design enabled subjects to act as their own controls. Although the basal rate and bolus volume differed for each treatment group, the total dose/mass of local anesthetic was the same for each (24 mg every 3 hours, Table 1).

Investigational Drug Service personnel prepared all ropivacaine reservoirs and infusion pumps. The electronic infusion pumps (Nimbus Ambulatory Pump, InfuTronix, Natick, Massachusetts) are capable of providing automated bolus doses as well as a continuous basal infusion. An infusion pump with ropivacaine 0.2% was attached to each of the perineural catheters. For each subject, the tubing from the pumps to the subjects was gently wound at least 5 rotations and covered with opaque tape, masking treatment allocation to investigators and subjects. Following catheter connection to the subject, both infusion pumps were activated and local anesthetic administration was initiated at Hour 0. For the infusion pump administering bolus doses, the 24 mL bolus dose was administered at Hour 0 and Hour 3. After 6 hours of administration, medical personnel removed the perineural catheters.

Outcome Measures

Outcome measurements were evaluated with the patient in the supine position with the head of bed elevated at 45 degrees on the right side first, followed by the left side at each hour for a total of 7 time points: Hour 0 (prior to local anesthetic administration), Hour 1, Hour 2, Hour 3 (immediately prior to the scheduled Hour 3 local anesthetic bolus), Hour 4, Hour 5 and Hour 6.

The sensory deficit was measured using two methods: cool roller (cold deficit)² and 5.46 Von Frey filaments (mechanical pressure deficit).²⁷ The sensory deficit was measured along two separate anatomical lines at each time point: the mid-axillary "vertical" line (measuring cephalad-caudad effects) and a transverse "horizontal" line (measuring anterior-posterior

effects) passing through the anterior superior iliac spine. A *post hoc* analysis was also performed multiplying the vertical and horizontal distances for each side of each subject to produce an estimated area of both cold and pressure sensory deficits.

The primary endpoint was determined prior to enrollment and defined as the distance of sensory deficit to cold measured in centimeters along the vertical mid-axillary line at Hour 6 (following 6 hours of continuous infusion and 3 hours following the final of 2 bolus doses). This measurement approximated the number of dermatomes (and thus the number of nerves traversing the transversus abdominis plane) that were affected by each treatment modality: a continuous basal infusion vs repeated bolus doses.

Statistical Analysis

The basal-bolus difference at each time point was assessed with paired t-tests (i.e., one-sample t-tests of basal-bolus differences for each subject). The primary hypothesis pertains to the 6 hour time point with significance level 5%. Analyses of all other time points are considered *post-hoc* and we applied no adjustment for multiplicity. Significant findings in secondary outcomes should be viewed as suggestive, requiring confirmation in a future trial before considering them as definitive.²⁸

Sample Size Calculations

Sample size calculations were based on the primary aim of detecting differences in sensory effects between the two treatment techniques at Hour 6. With $n=20$ subjects we had 95% power at the 5% significance level to detect the superiority of the administration of local anesthetic as repeated bolus doses as compared with a continuous basal infusion at Hour 6. Using an expected standard deviation of 7 cm for the primary endpoint,² and given a 2-sided Type I error protection of 5%, $n=20$ subjects provide 95% power to detect a mean difference between treatment techniques of 6 cm.¹⁶ This was a split-body crossover design in which each subject had one of each treatments on opposite sides of the body. We chose 6 cm as a detectable treatment difference because a 3 cm distance is approximately equivalent to the width of one dermatome,²⁹ and we considered a 2-dermatome difference clinically significant. To allow for larger-than-anticipated standard deviations, smaller-than-anticipated difference between treatment means, drop out subjects, or failed catheters, we chose to enroll a total of 24 subjects.

RESULTS

Twenty-four subjects were enrolled and all had bilateral TAP catheters placed per protocol (Table 1). For each subject, the right-sided TAP catheter was randomized to receive hourly boluses ($n=12$) or a continuous infusion ($n=12$) and the left-sided TAP catheter received the alternate treatment.

For the primary end point after 6 hours of treatment, mean difference in sensory deficit to cold (bolus minus basal) was 0.9 cm (SD=6.8; 95% CI -2.0, 3.8; $p=0.515$). While the difference between treatments was statistically significant at various early time points for the horizontal, vertical and estimated area measurements of both cold and mechanical pressure sensory deficits, no comparison remained statistically significant by Hour 6 (Figures 1–3).

DISCUSSION

This randomized, double-masked, crossover, split-body volunteer trial provided no evidence that administering ropivacaine 0.2% as repeated bolus doses increases the cephalad-caudad cutaneous effects compared with a basal-only infusion following 6 hours of administration *via* TAP catheters. This result is disappointing given that for local anesthetic administered through a needle, a large bolus injected into the TAP will result in spread to a greater number of cutaneous nerves compared with a smaller volume of injectate.¹⁶ Why the current study had a negative result remains unknown, although we will speculate on various possibilities.

First, it may be that medication dose/mass is the primary determinant of administration effects, as has been reported for interscalene,³⁰ femoral,³¹ posterior lumbar plexus (psoas compartment),³¹ and popliteal perineural catheters.³² This would explain why a previous study reported a larger cephalad-caudad cutaneous effect with the use of a 0.6 mL/kg bolus of levobupivacaine 0.125% compared with a bolus of half this volume—it was not the higher volume but rather the higher dose responsible for the differing results.¹⁶ While the current investigation did compare repeated large (24 mL) bolus volumes with a steady basal infusion of 8 mL/h, the mass of ropivacaine administered was equivalent at Hours 3 and 6. Supporting this theory are three negative studies comparing a basal infusion and repeated bolus doses of equivalent local anesthetic mass for interscalene,²² femoral,²¹ and adductor canal²³ catheters.

Second, the basal rate, bolus volume, interval duration, local anesthetic concentration, and catheter insertion site specified for the current study may be inadequate to detect a difference between treatment modalities (basal vs. bolus).³³ Supporting this theory is that a positive study demonstrating a benefit of intermittent boluses versus a basal infusion for ultrasound-guided perineural catheters involved the adductor canal location: ropivacaine 0.5% delivered as 15 mL boluses every 6 hours or a 2.5 mL/h basal.¹⁹ However, considering there is evidence that adductor canal infusions require a relatively high basal rate to provide adequate analgesia,^{34,35} this study might reflect an inadequate basal infusion rate rather than a clinically-relevant benefit of repeated bolus doses. An additional positive study involving ultrasound-guided femoral catheters was nominally positive (intermittent bolus over continuous basal);²⁰ yet, while the differences between treatments reached statistical significance for some variables—without any correction for multiple comparisons—they failed to reach clinical significance.^{36,37}

Third, local anesthetic within the TAP at the level of catheter insertion used in the present study may be anatomically limited.³³ The theory that has been proposed—along with supporting data—is that there is a maximum degree of cephalad spread with a traditional TAP block.³³ If accurate, the bolus volume and basal rate of the current study may have reached this maximum cephalad level. This would not invalidate the results of the study; but, rather suggest that alternative bolus and basal settings might produce different results (or, that the intermittent technique is not beneficial for TAP catheters).

Study limitations

The most significant limitation is the lack of surgical pain in the healthy volunteer subjects of this study. The main goal of postoperative perineural local anesthetic infusion is to provide post-surgical analgesia, and since the subjects of this study were healthy pain-free volunteers, we used cutaneous cold and pressure deficits as surrogate outcome measures. Whether cutaneous sensation correlates well with postoperative pain following various abdominal procedures remains unknown, making extrapolation to clinical practice more difficult.

In addition, because there is no published information on the minimally important clinical effect size for TAP infusions, we had to extrapolate from similar literature.¹⁶ We chose 6 cm as the minimum clinically meaningful treatment difference because a 3 cm distance is approximately equivalent to the width of one dermatome,²⁹ and we considered a 2-dermatome difference clinically significant. Our study does not rule out the possibility of smaller treatment differences (i.e. within our 95% confidence interval -2.0 to 3.8 cm for the primary endpoint) which some practitioners might consider to be clinically meaningful.

Lastly, the period of local anesthetic administration and cutaneous testing was limited to 6 hours. The initial 24 mL bolus doses did result in a statistically significant difference from the basal-only group for the first two hours; but, by the end of the third hour—when the two treatments had administered an equivalent dose of local anesthetic, no differences remained (Figures 1–3). This pattern recurred to a far lesser degree for the subsequent three-hour period of administration, so that by the time point of the primary outcome measure—6 hours—there were no remaining statistically significant differences between treatments. Most importantly, the overall trajectory of the two treatments suggest minimal increases past 6 hours, especially for the intermittent bolus group which appeared to have reached a steady state after just 2 hours. Therefore, we believe that additional local anesthetic administration would not have altered the results of this study.

In summary, this study involving healthy volunteers found no evidence to support the hypothesis that bolus doses of ropivacaine given within the TAP increased the distance of sensory deficit as measured by cool roller along the mid-axillary line at Hour 6 compared to a continuous infusion. Further research is warranted investigating larger volumes of local anesthetic bolus doses in a post-surgical patient population.

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Appendix

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	3
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	6–7
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	8–9
	2b	Specific objectives or hypotheses	9
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	12
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	10
	4b	Settings and locations where the data were collected	10
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	10–12
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	13
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	14
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			

Section/Topic	Item No	Checklist item	Reported on page No
Sequence generation	8a	Method used to generate the random allocation sequence	12
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	12
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	12
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	12
Blinding	11a	Whether those who generated the random allocation sequence, those who enrolled participants, care providers, those assessing outcomes) and how	12
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	13–14
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	N/A
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	15
	13b	For each group, losses and exclusions after randomisation, together with reasons	N/A
Recruitment	14a	Dates defining the periods of recruitment and follow-up	N/A
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	26
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	15
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	15
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	15
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			

Section/Topic	Item No	Checklist item	Reported on page No
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	17–18
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	16–17
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	16–18
Other information			
Registration	23	Registration number and name of trial registry	10
Protocol	24	Where the full trial protocol can be accessed, if available	N/A
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	4

* We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Figure 1.

Effects of local anesthetic administered via transversus abdominis plane catheters on *cutaneous deficits to cold* as measured with a cool roller.

a. Mean (standard error) sensory deficit measured along the **vertical mid-axillary line** from ropivacaine 0.2% delivered as either a 6-hour continuous basal infusion (8 mL/h) or 2 boluses (24 mL each) delivered automatically at Hours 0 and 3. Time points for which $P < 0.05$ denoted with an asterisk.

b. Mean (standard error) sensory deficit measured along the **horizontal transverse line** passing through the anterior superior iliac spine from ropivacaine 0.2% delivered as either a 6-hour continuous basal infusion (8 mL/h) or 2 boluses (24 mL each) delivered automatically at Hours 0 and 3. Time points for which $P < 0.05$ denoted with an asterisk.

Sensory Deficit to Von Frey Filaments

Figure 2.

Effects of local anesthetic administered via transversus abdominis plane catheters on *cutaneous deficits to mechanical pressure* as measured with Von Frey filaments.

a. Mean (standard error) sensory deficit measured along the **vertical mid-axillary line** from ropivacaine 0.2% delivered as either a 6-hour continuous basal infusion (8 mL/h) or 2 boluses (24 mL each) delivered automatically at Hours 0 and 3. Time points for which $P < 0.05$ denoted with an asterisk.

b. Mean (standard error) sensory deficit measured along the **horizontal transverse line** passing through the anterior superior iliac spine from ropivacaine 0.2% delivered as either a 6-hour continuous basal infusion (8 mL/h) or 2 boluses (24 mL each) delivered automatically at Hours 0 and 3. Time points for which $P < 0.05$ denoted with an asterisk.

Area of Deficit (Horizontal x Vertical)

Figure 3.

Effects of local anesthetic administered via transversus abdominis plane catheters on cutaneous sensory deficit estimated by multiplying the horizontal and vertical measurements for each side of each subject.

a. Mean (standard error) *cutaneous deficits to cold* as measured with a cool roller. Time points for which $P < 0.05$ denoted with an asterisk.

b. Mean (standard error) *cutaneous mechanical pressure deficits* as measured with Von Frey filaments. Time points for which $P < 0.05$ denoted with an asterisk.

Table 1

Local anesthetic administration for each treatment group: ropivacaine 0.2%

Treatment	Basal Rate (mL/h)	Basal Dose (mg/h)	Bolus Volume (mL/3h)	Bolus Dose (mg)	Total Dose (mg/3h)
Basal Infusion	8	16	0	0	48
Bolus Doses	0	0	24	48	48

Table 2

Subject characteristics

	Male (n=14)	Female (n=10)	Combined (n=24)
Age (yr)	32 (10)	39 (14)	35 (12)
Height (cm)	176 (5)	166 (9)	172 (9)
Weight (kg)	86 (22)	65 (7)	77 (20)
Body mass index (kg/m ²)	28 (9)	24 (2)	26 (7)

Values are reported as mean (SD)