

# The acute effect of high-dose intravenous vitamin C and other nutrients on blood pressure: a cohort study

Karin Ried, Nikolaj Travica and Avni Sali

**Background** Regular intake of vitamin C/ascorbate reduces blood pressure (BP) in hypertensives. High-dose intravenous vitamin C (IVC) achieves higher plasma levels; however, there is a paucity of research on acute BP effects. Our study is the first to investigate the effect of high-dose IVC, with or without concomitant i.v. nutrients, on BP during i.v. treatment.

**Methods** A cohort of adult patients scheduled to receive IVC treatment for infection, cancer or fatigue, as prescribed by their treating doctor, participated at a Melbourne clinic, Australia. Ambulatory BP was assessed every 10 min over 90 min during i.v. treatment. Patients received 15–100 g of IVC alone or in addition to i.v. vitamin B, glutathione, magnesium or zinc. BP change over time adjusted for baseline BP, IVC dosage, i.v. treatment and BMI was analysed.

**Results** A total of 77 mostly normotensive patients participated, with a third receiving IVC alone ( $42 \pm 20$  g), and two-thirds also received other i.v. nutrients. IVC alone ( $>30$  g) reduced the mean BP up to 8–9 mmHg in prehypertensive patients. In contrast, concomitant intravenous vitamin B12 (IVB12) significantly increased the mean BP by 11–13 mmHg. Comparison of BP change

during IVC versus IVC + IVB12 indicated a highly significant difference [systolic blood pressure: mean difference (SD) = 16.6 (17.8) mmHg,  $P < 0.001$ ; diastolic blood pressure: mean difference (SD) = 12.5 (16.7) mmHg,  $P = 0.003$ ].

**Conclusion** Our study suggests an acute BP-reducing effect of high-dose IVC, particularly with dosages above 30 g, and in patients with prehypertension and normal BMI. Furthermore, our study indicated a marked and clinically relevant hypertensive effect of IVB12, suggesting routine BP monitoring during i.v. therapy in clinical practice. *Blood Press Monit* 21:160–167 Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

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**Keywords:** ascorbate, blood pressure, cobalamin, intravenous, parenteral, vitamin B12, vitamin C

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## Introduction

Epidemiological research has linked higher vitamin C status with lower blood pressure (BP), reducing BP by 2–4 mmHg with every 50  $\mu\text{mol/l}$  increase in vitamin C plasma levels [1]. In addition, a meta-analysis of 29 randomized-controlled clinical trials including more than 1400 participants showed that oral supplementation of 500 mg of vitamin C (ascorbic acid) per day for 8 weeks resulted in an average reduction of  $3.8 \pm 1.5$  mmHg systolic ( $P < 0.01$ ) and  $1.5 \pm 1.4$  mmHg diastolic ( $P = 0.04$ ), and 4.9 mmHg systolic in hypertensive patients ( $P < 0.01$ ) compared with placebo [2].

In contrast, no significant acute BP effect was observed after 2 h of a 2 g dose of oral vitamin C supplementation [3]. However, a protective BP-lowering effect was observed after 3 g daily of an oral sustained-release vitamin C supplementation for 2 weeks in a group of 60 healthy normotensive healthy adults exposed to a stressor

(Trier Social Stress Test) [4]. While the placebo group experienced a 35 mmHg systolic blood pressure (SBP) spike within 1 min of the stress test, the vitamin C group experienced a lower BP spike of 27 mmHg (mean difference  $\pm$  SD =  $8.3 \pm 2.2$  mmHg;  $P < 0.001$ ) [4]. In addition, BP returned to prestress test levels within 40 min in the vitamin C group, whereas the placebo group's BP remained slightly elevated (5 mmHg,  $P < 0.001$ ), indicating a slower recovery time, which has been associated with greater cardiovascular risk [4,5].

There is a paucity of research on the effect of intravenously administered vitamin C on BP. One study explored the acute effect within 30 min of a bolus of 1 or 2 g (6 or 12 mmol) of intravenous vitamin C (IVC) and observed an immediate but short-term BP reduction of 10–15 mmHg systolic at 10–20 min with return to baseline after IVC administration in patients with mild hypertension [6].

Intestinal absorption of orally administered vitamin C is tightly regulated by a dose-dependent active transport process to a threshold plasma level (50–100  $\mu\text{mol/l}$ ),

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whereby absorption of doses of greater than 1 g/day is less than 50%, with excretion of the remainder in the urine [7,8]. In contrast, intravenous administration of high doses of ascorbate (1–200 g) can lead to plasma concentrations of up to 20 mmol/l, up to 100-fold greater than by oral administration within 1–2 h of administration [9,10].

IVC therapy is used to boost immune function and as part of integrative cancer treatment [11,12]; however, much higher dosages between 10 and 100 g per day (150–710 mg/kg/day) are used than generally tolerable with oral vitamin C intake. High-dose IVC therapy boosts the immune system by promoting antiviral, antibacterial and anticancer activities, helps recovery from injury and surgery, alleviates disease-related fatigue and improves quality of life [11–15].

IVC has a high safety profile. In a survey of 199 practitioners using IVC (mean dose 28 g, median 50 g, range 1–200 g per treatment) mainly for infection or cancer, it was found that 1% (101 out of 9328 patients) reported side effects, including minor fatigue ( $n=59$ ), change in mental status ( $n=21$ ) and vein irritation/phlebitis ( $n=6$ ) [16]. Two deaths related to IVC therapy were because of known risk factors, renal impairment and glucose-6-phosphate-dehydrogenase deficiency. Patients with these risk factors should be excluded from IVC therapy.

Our study is the first to systematically assess the acute effect on BP of high-dose IVC alone and in conjunction with other standard i.v. nutrients including vitamin B12 and other B vitamins, glutathione, zinc and magnesium in a cohort of patients treated for a variety of conditions in an integrative medical practice.

## Methods

### Participants and study design

A cohort of adult patients, scheduled to receive IVC treatment for infection, cancer or fatigue, as prescribed by their treating doctor at the National Institute of Integrative Medicine (NIIM) clinic, Melbourne, Australia, were recruited between March 2014 and May 2015. Patients with renal impairment, defined by abnormal levels of estimated glomerular filtration, albumin, creatinine or blood urea nitrogen levels, or patients with glucose-6-phosphate-dehydrogenase deficiency were not eligible because of contraindications to IVC therapy. Patients with arrhythmia, or those not able to provide informed consent, were also excluded.

Participation was not restricted by the reason for IVC therapy or underlying illness, or the number of previous IVC treatments received. Ninety percent of patients scheduled to receive IVC treatment consented to participate in the BP study.

Consenting participants' sociodemographic data, reason for IVC treatment, concomitant therapies (hyperthermia, chemotherapy, any medications), treatment schedule,

**Table 1** Baseline characteristics

	<i>N</i> = 77 [ <i>n</i> (%)]	Mean	SD
<b>Demographics</b>			
Age (years)		54.0	17.4
BMI (kg/m <sup>2</sup> )		24.9	4.6
Female/male	39/38 (51/49)		
<b>Treatment</b>			
IVC dosage (g)	77 (100)	42	20
IVC treatments $\geq$ 4/month	49 (62)	6.6	2.5
IVC alone	26 (34)		
Cancer patient/immunity	15/11 (19/14)		
IVC + additional all	51 (66)		
Cancer patient/immunity	28/23 (36/30)		
+ Glutathione	30 (39)		
+ Zinc	19 (25)		
+ Magnesium	17 (22)		
+ IVB (no B12)	13 (17)		
+ VitB12	8 (10)		
+ BDF	7 (9)		
+ ALA	7 (9)		
+ Bicarbonate	5 (6)		
+ Other	2 (3)		

ALA,  $\alpha$ -linoleic acid; BDF, vitamin B forte contains vitamin B1, B2, B3, B5, B6 and B12 as cyanocobalamin; IVB, intravenous vitamin B contains vitamin B1, B2, B3, B5 and B6, but not B12; IVC, intravenous vitamin C; *N*, number of participants; vitB12, methylcobalamin.

including dose of vitamin C, number of IVC treatments and time period, and concomitant intravenous agents (type, dosage) were obtained.

### Blood pressure monitoring

Baseline BP was recorded before start of the intravenous drip using an oscillometric ambulatory BP monitor (Mobil-O-Graph; IEM GmbH, Stolberg, Germany) [17] with appropriate-sized brachial cuffs on the opposite arm with the intravenous drip with the patient seated and the arm at the heart level. The Mobil-O-graph device was programmed to record BP at 10 min intervals throughout the duration of the intravenous treatment (up to 1.5 h). Participants were advised to keep the arm still through the cuff inflation.

### Intravenous treatments

Patients received ambulant treatment in the i.v. clinic at NIIM. Pharmaceutical-grade sodium ascorbate solution (Biological Therapies, Melbourne, Victoria, Australia) was diluted in H<sub>2</sub>O as necessary to provide the target dose at an infusion rate of 500 ml/h (8.5 ml/min) or 20 drops/ml (170 drops/min). IVC dosage was less than or equal to 1.3 g/kg bodyweight up to a maximum of 60 g per at least 60 kg patient. Up to 30 g of sodium ascorbate is usually diluted in 500 ml H<sub>2</sub>O and administered within 1 h, whereas 60 g of sodium ascorbate is diluted in 750 ml H<sub>2</sub>O and administered within 1.5–2 h. Patients' IVC tolerance levels are gradually built up, usually starting with 15 g (75 mmol) of IVC in the first session, up to 30 g (150 mmol) of IVC in the second session and up to 60 g (300 mmol) of IVC in the third and consecutive sessions. A number of participants received additional i.v. treatments alongside the ascorbate solution. A variety of

combinations of additional i.v. treatments administered included an average of 1 g (3 mmol) of glutathione solution, 2.47 mg (20 mmol) of magnesium sulphate in 5 ml and 5.1 mg of zinc chloride in 2 ml or 400 mg (1.4 mmol) of  $\alpha$ -linoleic acid, as well as B vitamins (Table 1). B vitamins were administered as an intravenous vitamin B (IVB) dose (B1 – 10 mg, B2 – 5 mg, B3 – 100 mg, B5 – 20 mg and B6 – 50 mg), as vitamin B forte = B1 – 250 mg, B2 – 5 mg, B3 – 50 mg, B5 – 50 mg, B6 – 100 mg, B12 – 1 mg (0.7 mmol cyanocobalamin) or as methylcobalamin injection vitamin B12 (10 mg, 7 mmol, in 2 ml).

Intravenous therapy administration was performed by experienced registered NIIM clinical nurses according to a doctor's prescription. Administration of sodium ascorbate injection followed the protocol provided by Biological Therapies at the Injectable Nutrients Workshop supported by the Australasian College of Medical Nutrition. Care of patients consenting to take part in the study followed standard clinical practice.

### Statistical analyses

Baseline characteristics were descriptively analysed. Primary outcome measures were SBP and diastolic blood pressure (DBP) at all time points compared with baseline by analysis of covariance, adjusting for baseline BP, IVC dosage, i.v. treatment or BMI. Extreme outlier BP values, because of movement during cuff inflation, were removed. We also carried out subgroup analyses by IVC dosage, baseline BP, BMI and concomitant intravenous agents, and explored BP changes by health condition (cancer vs. infection/fatigue). All analyses were carried out using IBM SPSS, version 22 (SPSS Inc., Chicago, Illinois, USA).

A sample size calculation indicated that 50 participants ( $n = 25$  per group) were sufficient to detect a significant and clinically relevant difference of 8 mmHg ( $SD = 10$ ) in BP between groups with 80% power and 95% confidence.

The study received ethics approval from the NHMRC registered HREC committee at NIIM (Trial number 252).

## Results

### Participants

A total of 77 adult patients participated in the study. Baseline characteristics are shown in Table 1. Participants' mean age was  $54 \pm 17$  years, with a mean average BP of 124/78 mmHg at baseline, with three participants on BP medication and only one participant reporting major cardiovascular issues in the past. No participants were smokers and the sample had an average mean BMI of  $25 \text{ kg/m}^2$ . A third ( $n = 26$ , 34%) received IVC alone, whereas two-thirds ( $n = 51$ , 66%) received additional treatments plus IVC. The average IVC dosage was  $42 \pm 20$  g (range 15–100 g), with treatment lasting an

average of 80 min. About half (56%) of the participants received treatment for cancer, whereas 44% underwent IVC treatment for general immunity (colds/flu), Lyme disease and chronic fatigue. About two-thirds of the participants ( $n = 49$ , 62%) had received IVC treatment more than once per week, with an average of  $6.6 \pm 2.5$  times per month (Table 1).

### Blood pressure

The mean changes in SBP and DBP compared with baseline were analysed every 10 min throughout the i.v. treatment, with the main changes observed at three time points (20–30/50–60/70–75 min; Tables 2 and 3).

In the majority of patients, SBP decreased during the first 20–30 min of i.v. treatment and increased at 50–60 min. However, BP response at 70–75 min was significantly dependent on whether concomitant treatments were administered in addition to IVC. While the mean BP decreased in the group receiving IVC alone at the end of i.v. treatment, BP increased when additional treatments were administered (mean difference  $SBP \pm SD_{\text{time3}} = 7.0 \pm 16.6$  mmHg;  $P = 0.003$ ; mean difference  $DBP \pm SD_{\text{time3}} = 6.8 \pm 15.7$  mmHg;  $P = 0.02$ ) (Figs 1a and 2a and Tables 2 and 3).

Therefore, main analyses were separated into two groups with patients receiving IVC alone ( $n = 26$ ) or IVC plus additional treatments ( $n = 51$ ). Data were further analysed by IVC dosage, baseline BP, and BMI.

### IVC treatment alone

The mean BP in all patients receiving IVC alone ( $n = 26$ ) changed only slightly over the course of the treatment. However, analysis by IVC dosage showed a marked difference BP pattern/change over time.

While BP tended to decrease more over time in patients receiving higher concentrations of IVC ( $>30$  g), the mean BP did not alter appreciably in patients receiving less than 30 g of IVC (mean difference  $SBP \pm SD_{\text{time3}} = 4.5 \pm 13.8$  mmHg;  $P = 0.07$ ; mean difference  $DBP \pm SD_{\text{time3}} = 5.5 \pm 13.1$  mmHg;  $P = 0.09$ ) (Figs 1b and 2b and Tables 2 and 3).

Baseline BP also influenced response to IVC treatment. In prehypertensive patients ( $SBP/DBP > 130/85$  mmHg), SBP decreased by an average of 8–9 mmHg and DBP by 6–7 mmHg over the course of the IVC treatment, whereas BP remained steady in normotensive patients ( $SBP/DBP \leq 130/85$  mmHg) (mean difference  $SBP \pm SD_{\text{time3}} = 6.7 \pm 12.8$  mmHg;  $P = 0.07$ ; mean difference  $DBP \pm SD_{\text{time3}} = 5.5 \pm 13.1$  mmHg;  $P = \text{NS}$ ) (Figs 1c and 2c and Tables 2 and 3).

BMI significantly influenced DBP response to IVC treatment, whereby DBP decreased by almost 8 mmHg in the healthy-weight group ( $BMI \leq 25 \text{ kg/m}^2$ ), but did not alter appreciably in the overweight/obese group

**Table 2** Systolic blood pressure mean changes within groups and mean differences between groups at three time points compared with baseline

	Time 0			Time 1 (20–30 min)			Time 2 (50–60 min)			Time 3 (70–75 min)								
	Baseline SBP (mmHg)			Mean SBP change within group (mmHg)		Mean difference between groups (mmHg)		Mean SBP change within group (mmHg)		Mean difference between groups (mmHg)		Mean SBP change within group (mmHg)		Mean difference between groups (mmHg)				
	N	M	SD	M	SD	M	SD	P	M	SD	M	SD	P	M	SD	M	SD	P
<b>Subgroups</b>																		
IVC alone	26	120.9	18.4	−3.2	10.3				−0.2	10.2				−3.8	9.9			
IVC + additional	51	126.8	18.5	−0.6	12.4	3.8	16.2	NS	1.8	14.3	2.0	17.6	NS	3.2	13.3	7.0	16.6	0.003
<b>IVC alone – subgroup</b>																		
<b>IVC dosage</b>																		
> 30 g vitamin C	12	115.8	15.2	−5.6	7.7				2.2	10.6				−6.2	8.9			
≤ 30 g vitamin C	14	125.48	20.2	−1.2	12.1	4.4	14.4	NS	−2.2	9.8	4.4	14.4	NS	−1.7	10.6	4.5	13.8	0.07
<b>Baseline SBP (mmHg)</b>																		
> 130	8	142.8	12.7	−7.5	9.8				−5.5	13.6				−8.4	7.7			
≤ 130	18	111.2	10.21	−1.3	10.2	6.2	14.2	NS	2.2	7.6	7.7	15.6	0.09	−1.7	10.3	6.7	12.8	0.07
<b>BMI</b>																		
Overweight/obese	11	129	21.4	−1.8	9.2				−2.3	11.9				−6.7	9.1			
< 25 kg/m <sup>2</sup>	15	114.9	13.7	−4.3	11.3	2.5	14.6	NS	1.3	8.9	3.6	14.9	NS	−1.6	10.1	5.1	13.6	NS
<b>IVC + additional – subgroup</b>																		
<b>IVC dosage</b>																		
> 30 g vitamin C	29	128	15.8	−1.7	12.1				4.8	12.9				1.2	12.3			
≤ 30 g vitamin C	22	125.2	21.8	1	13	2.7	17.7	NS	−2.2	15.4	7	20.1	0.06	5.7	14.5	4.5	19	NS
<b>Baseline SBP (mmHg)</b>																		
> 130	30	144.4	12.7	−2.8	15.2				0.1	17.6				0.8	12.5			
≤ 130	21	114.5	9.9	1	10.1	3.8	18.2	NS	2.9	11.7	2.8	21.1	NS	4.9	13.9	4.1	18.6	NS
<b>BMI</b>																		
Overweight/obese	30	129.4	15.9	−1	12.5				−1.1	15				−0.3	11.1			
< 25 kg/m <sup>2</sup>	21	123.1	21.6	0.1	12.7	1.1	17.8	NS	5.8	12.6	6.8	19.5	NS	8.2	14.8	8.5	18.6	0.05
<b>IVC alone – subgroup compared with IVC + specific additional</b>																		
All B vitamins	27	131.1	19.8	−0.1	14.1	3.2	17.4	NS	0.2	15.9	0.4	18.9	NS	4.8	15.6	8.6	18.5	0.008
IVB	13	127.3	18.0	−2.4	11.9	0.8	15.7	NS	−4.4	9.7	4.2	14.1	NS	−3.8	11.7	0	15.3	NS
BDF/vitB12	14	134.5	21.4	2.1	15.9	5.3	19.0	NS	4.4	19.5	4.6	22.0	NS	12.8	14.8	16.6	17.8	<0.001
Glutathione <sup>a</sup>	24	127.7	16.2	−0.5	11.0	3.7	15.1	NS	0.1	12.8	0.2	16.4	NS	−1.8	11.0	1.9	14.8	NS
Zinc <sup>a</sup>	15	119.9	16.4	1	11.2	4.2	15.2	NS	1.7	13.8	1.9	17.2	NS	−0.6	9.0	3.2	13.4	NS
Magnesium <sup>a</sup>	10	126.9	10.7	−2.4	11.4	0.8	15.4	NS	−1.4	8.7	1.21	13.4	NS	−6.4	8.9	2.6	13.3	NS

ANCOVA, analysis of covariance; BDF, vitamin B forte contains vitamin B1, B2, B3, B5, B6 and B12; IVB contains vitamin B1, B2, B3, B5 and B6, but not B12; IVC, intravenous vitamin C; M, mean; N, number of participants; NS, not significant; SBP, systolic blood pressure; vitB12, vitamin B12.

<sup>a</sup>ANCOVA analyses controlled for/without patients also receiving vitB12 and BDF.

(mean difference DBP ± SD<sub>time3</sub> = 8.8 ± 12.4 mmHg; P = 0.02) (Table 3).

Subgroup analyses by health condition (cancer vs. infection or fatigue) did not show any appreciable difference in BP change between the groups (data not shown).

**IVC and additional i.v. treatments**

In the subgroup of patients receiving IVC and additional treatments, IVC dosage (mean difference SBP ± SD<sub>time2</sub> = 7.0 ± 20.1 mmHg; P = 0.06) and BMI (mean difference SBP ± SD<sub>time3</sub> = 8.5 ± 18.6 mmHg; P = 0.05) slightly influenced SBP response at selected time points (Table 2).

Further analyses indicated that administration of B vitamins, in particular vitamin B12 independent of dosage, was responsible for a significantly different BP response over time compared with IVC alone.

While patients’ BP decreased with IVC alone, their BP increased markedly with the addition of vitamin B12 (vitamin B forte or vitamin B12) (mean difference SBP ± SD<sub>time3</sub> = 16.6 ± 17.8 mmHg; P < 0.001; mean difference DBP ± SD<sub>time3</sub> = 12.5 ± 16.7 mmHg; P = 0.003) (Figs 1d and 2d and Tables 2 and 3).

In contrast, administration of glutathione (SBP), magnesium, zinc and B vitamins other than vitamin B12 did not alter the BP response pattern appreciably compared with IVC alone (Table 2).

**Discussion**

Our study is the first to report on acute BP effects of high-dose IVC over a 1.5 h period with or without concomitant nutrient treatment. We found IVC to significantly reduce BP of up to 6–7 mmHg systolic and diastolic if administered at dosages above 30 g and up to 8–9 mmHg in patients with prehypertension (SBP/DBP ≥ 130/85 mmHg) at baseline. In contrast,

**Table 3 Diastolic blood pressure mean changes within groups and mean differences between groups at three time points compared with baseline**

	Time 0			Time 1 (20–30 min)					Time 2 (50–60 min)					Time 3 (70–75 min)				
	Baseline DBP (mmHg)			Mean DBP change within group (mmHg)		Mean difference between groups (mmHg)			Mean DBP change within group (mmHg)		Mean difference between groups (mmHg)			Mean DBP change within group (mmHg)		Mean difference between groups (mmHg)		
	N	M	SD	M	SD	M	SD	P	M	SD	M	SD	P	M	SD	M	SD	P
<b>Subgroups</b>																		
IVC alone	26	77.7	9.8	–3	11.1				–4.7	10.9				–4.1	9.6			
IVC+additional	51	77.6	10.4	2.3	11.3	5.3	15.9	0.06	2.94	14.2	7.6	18.0	0.03	2.7	12.0	6.8	15.7	0.02
<b>IVC alone – subgroup</b>																		
<b>IVC dosage</b>																		
> 30 g vitamin C	12	76.7	10.3	–5.8	9.9				–5.5	11.6				–7.1	8.7			
≤ 30 g vitamin C	14	78.6	9.7	–0.6	11.9	5.1	15.5	NS	–4	10.7	1.5	15.8	NS	–1.6	9.8	5.5	13.1	0.09
<b>Baseline DBP (mmHg)</b>																		
> 85	11	87.2	3.9	–6.6	13.8				–8	11.6				–6.6	9.6			
≤ 85	15	70.7	6.1	–0.3	8.1	6.3	16.1	NS	–2.3	10.1	5.7	15.4	NS	–2.3	9.4	4.3	13.4	NS
<b>BMI</b>																		
Overweight/obese	11	78.1	10.4	–0.5	9.6				–1.2	12.3				1	9.5			
< 25 kg/m <sup>2</sup>	15	77.4	9.7	–4.9	12.0	4.4	15.4	NS	–7.3	9.3	6.1	15.5	NS	–7.9	7.9	8.8	12.4	0.02
<b>IVC+additional – subgroup</b>																		
<b>IVC dosage</b>																		
> 30 g vitamin C	29	78.0	10.1	1.4	10.6				3.8	13.8				3.0	10.1			
≤ 30 g vitamin C	22	77.1	11.0	3.4	12.4	2.2	16.3	NS	1.8	15.0	2.0	20.4	NS	2.1	14.4	0.9	17.6	NS
<b>Baseline DBP (mmHg)</b>																		
> 85	20	88.2	6.5	–2.1	9.8				–0.1	14.9				–0.7	12.3			
≤ 85	31	70.8	5.8	5.1	11.5	7.2	15.1	NS	4.9	13.6	5	20.2	NS	4.7	11.6	5.4	16.9	NS
<b>BMI</b>																		
Overweight/obese	30	77.8	9.6	2.1	11.7				3.9	13.1				2.4	12.1			
< 25 kg/m <sup>2</sup>	21	77.3	11.8	2.4	11.1	0.3	16.1	NS	1.6	15.9	2.3	20.6	NS	3.0	12.2	0.6	17.2	NS
<b>IVC alone – subgroup compared with IVC+specific additional</b>																		
All B vitamins	27	78.2	10.0	2.0	12.4	5.0	16.6	NS	5.6	14.3	10.3	18.0	0.005	4.6	13.3	8.7	16.4	0.01
IVB	13	79.2	6.2	–1.2	12.5	1.8	16.7	NS	–0.7	9.3	4.0	14.3	NS	0.5	12.1	4.6	15.4	NS
BDF/vitB12	14	77.1	12.7	5.1	11.8	8.1	16.2	0.06	11.4	15.9	16.1	19.3	0.001	8.4	13.7	12.5	16.7	0.003
Glutathione <sup>a</sup>	24	77.0	7.9	2.3	10.4	5.3	15.2	0.03	2.8	11.3	7.5	15.7	0.03	1.3	9.9	5.4	13.7	0.02
Zinc <sup>a</sup>	15	76.3	9.6	–2.1	9.6	0.9	14.6	NS	–2.3	11.0	2.4	15.4	NS	–2.2	8.0	1.9	12.5	NS
Magnesium <sup>a</sup>	10	80.3	7.4	1.1	10.8	4.1	15.5	NS	–3.2	14.5	1.5	18.2	NS	–4.1	10.5	0	14.2	NS

ANCOVA, analysis of covariance; BDF, vitamin B forte contains vitamin B1, B2, B3, B5, B6 and B12; DBP, diastolic blood pressure; IVB contains vitamin B1, B2, B3, B5 and B6, but not B12; IVC, intravenous vitamin C; N, number of participants; NS, not significant; vitB12, vitamin B12.

<sup>a</sup>ANCOVA analyses controlled for/without patients receiving vitB12 and BDF.

administration of intravenous vitamin B12 (IVB12) solutions significantly increased BP response by up to 13 mmHg systolic and 11.5 mmHg diastolic during and at the end of i.v. treatment.

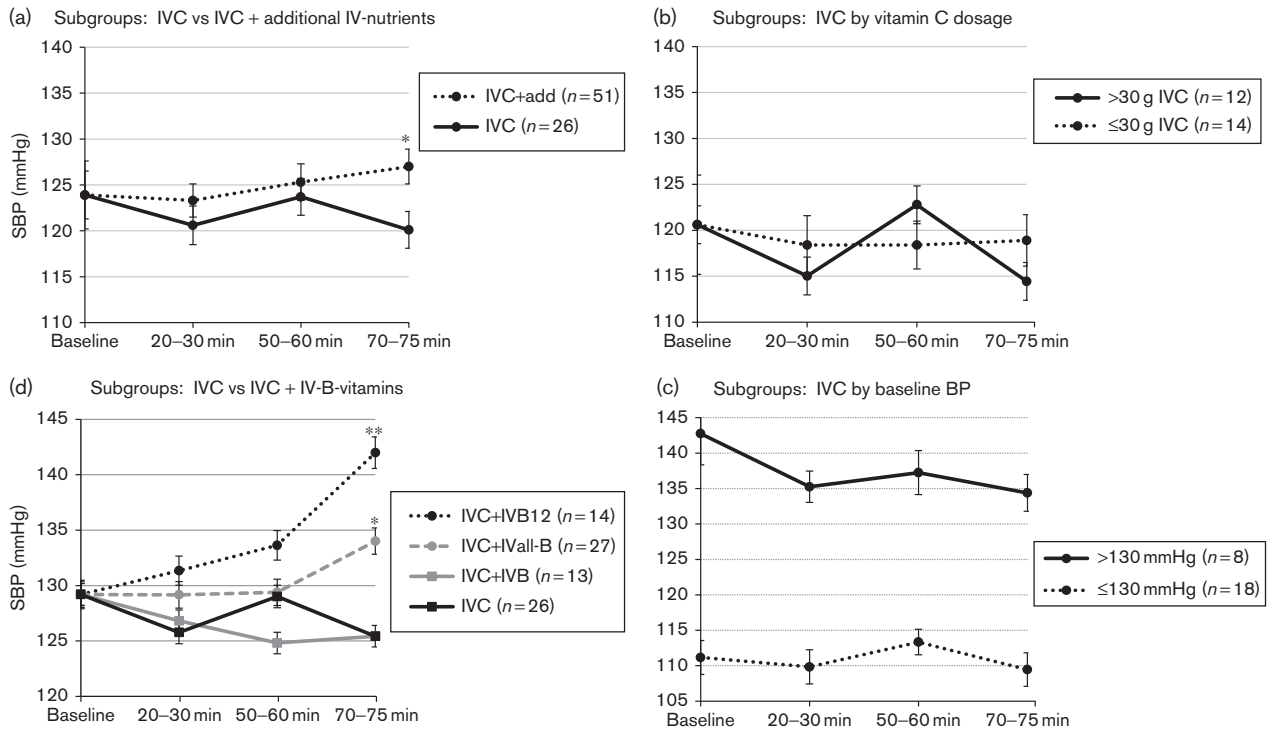
The results obtained with IVC alone were consistent with the literature, whereby a bolus of 1–2 g of IVC reduced BP by up to 10–15 mmHg in the first 10–20 min and BP returned back to baseline at 30 min [6]. In our study, for the first time, we continued the assessment of BP every 10 min until 90 min and observed a prolonged BP-reducing effect of IVC. Although the reduction in BP within the first 10–20 min may be primarily attributed to a direct vasodilatory physiological effect, described as venodilation [18], BP reduction observed after 70–90 min is likely attributable to pharmacokinetically plausible vitamin C absorption and vasodilation because of nitric oxide release [9,19,20]. Pharmacokinetic studies of IVC administration observed peak plasma levels within the first 90 min, with plasma levels reaching 13350 µmol/l for 50 g of IVC [9].

In addition, the greater mean BP-reductive effect of vitamin C in hypertensives compared with normotensive patients is consistent with the literature [2]. Essential hypertension, associated with endothelial dysfunction because of an impaired nitric oxide/L-arginine pathway and impaired vasodilation can be restored by vitamin C [21].

Furthermore, a significantly greater reduction in DBP of 8–9 mmHg observed in patients within the healthy weight range (BMI ≤ 25 kg/m<sup>2</sup>) compared with the overweight/obese group is congruent with the literature, whereby obesity-related insulin resistance and higher levels of epinephrine are associated with impaired endothelial function, reduced NO production and thus increased BP [22].

Moreover, our study is the first to describe the marked increase in BP response when IVB12 is administered. The mean BP increased significantly up to 12–16 mmHg systolic and diastolic independent of the dosage of vitamin B12 (0.7–7 mmol). This marked increase in

Fig. 1



Systolic blood pressure (SBP) change over time during i.v. treatment. (a) Subgroups: IVC alone versus IVC + additional i.v. nutrients; (b) IVC alone by vitamin C dosage; (c) IVC alone by baseline BP; and (d) IVC alone versus IVC + IVB vitamins. (a, b, d) Adjusted for baseline BP. Statistically significant difference between subgroups compared with IVC: \* $P < 0.01$ , \*\* $P < 0.001$ . add, additional i.v. nutrients; BP, blood pressure; IVB, intravenous vitamin B contains vitamin B1, B2, B3, B5, B6 but not B12; IVB12, intravenous vitamin B12 as methylcobalamin (7 mmol) or in vitamin B forte (BDF) as cyanocobalamin (0.7 mmol); IVall-B, intravenous-all-inclusive vitamin B12; IVC, intravenous vitamin C.

BP – although likely attenuated by the coadministration of IVC in our patient cohort – could potentially lead to problems in already hypertensive patients.

The production of norepinephrine, which can stimulate angiotensin-II production, which in turn influences BP, has been suggested as a possible mechanism for the increase in BP with IVB12 [23]. Animal studies have found higher serum levels of norepinephrine (noradrenaline) in the adrenal medulla of rats receiving methylcobalamin (methyl-vitamin B12) [24]. In addition, excess norepinephrine levels stimulate the sympathetic nervous system, leading to increased cortisol production, which has also been linked to increases in BP [25].

The lack of a significant BP reduction with the administration of i.v. glutathione observed in our study may have been because of a lower dosage of 3 mmol compared with 6 and 12 mmol in the study by Ceriello *et al.* [6] and may have been confounded by the concomitant administration of other nutrients.

Our study had some limitations related to its observational nature and being the first study of its kind, therefore including variability in health conditions and disease status of participants, IVC dosage regime,

baseline BP, etc. Although we controlled for some of the variables in the analysis and explored heterogeneity by subgroup analysis, future studies could focus on more congruent groups.

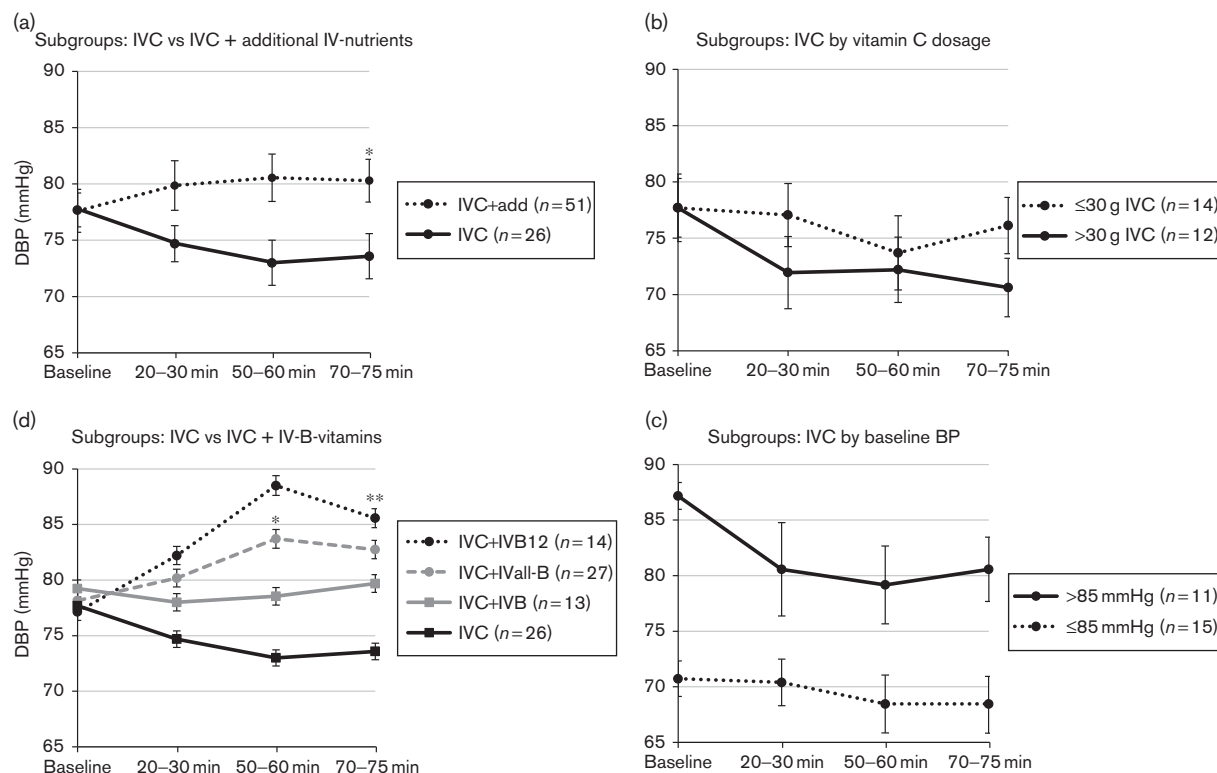
Furthermore, it would be of interest to explore the acute effects of single i.v. nutrients on BP, in particular, the influence of IVB12. The results of our study imply that BP should be monitored routinely during the administration of IVB12, in particular, in hypertensive patients, for safety reasons.

Second, measurement of selected biomarkers that influence BP levels such as cortisol, insulin and norepinephrine could shed more light on the mechanisms of BP change observed with IVB12.

Third, a controlled study comparing IVC administration compared with a saline solution as placebo could tease out any i.v. nutrient-specific effects on BP, albeit no changes in BP were observed within 10–20–30 min of saline administration in the study by Ceriello *et al.* [6].

Finally, as our study has been the first to measure the effect of IVC and other nutrients during treatment on BP for a prolonged period of 90 min, further extension of BP

Fig. 2



Diastolic blood pressure (DBP) change over time during i.v. treatment. (a–d) For details and abbreviations, see Fig. 1.

measurements and vitamin C plasma levels would broaden insights into maximal BP changes in correlation to vitamin C peak plasma levels.

### Conclusion

Our study is the first to examine the acute effects of high-dose IVC treatment on BP across 90 min of treatment and the first to incorporate additional i.v. nutrients in conjunction with IVC. Our results suggest IVC to reduce BP by 6–7 mmHg if dosages of more than 30 g are administered and up to 8–9 mmHg in patients with prehypertension (SBP/DBP  $\geq$  130/85 mmHg).

Furthermore, our study is the first to describe the marked BP-increasing effect by 12–16 mmHg of IVB12, suggesting routine BP monitoring during i.v. therapy in clinical practice.

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Author contributions: K.R. and A.S. conceptualized the study. Data were collected by N.T. N.T. and K.R. carried out data analysis and interpretation. K.R. and N.T.

prepared the manuscript. All authors approved the final version.

### Conflicts of interest

There are no conflicts of interest.

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