Markers of inflammation: data from the MOSAIC randomised trial of CPAP for minimally symptomatic OSA

ABSTRACT The Multi-centre Obstructive Sleep Apnoea Interventional Cardiovascular (MOSAIC) trial compared 6 months of CPAP therapy, versus no CPAP, in 391 patients with minimally symptomatic obstructive sleep apnoea (OSA). We now report some exploratory outcomes, markers of systemic inflammation (interleukin 6 (IL-6), IL-10, C reactive protein, tumour necrosis factor). We found no consistent changes (all p values >0.13).

Trial registration number: ISRCTN 34164388.

INTRODUCTION

Intermittent hypoxia may generate free oxygen radicals and oxidative stress, activate expression of adhesion molecules and proinflammatory cytokines, and in turn damage the vascular endothelium with chronic low grade inflammation, ultimately leading to atheroma formation and vascular events.[1] There are very few randomised controlled treatment trials in patients with OSA, and a recent meta-analysis relied exclusively on uncontrolled and non-randomised trials for its conclusion that there were small reductions in some markers of inflammation following CPAP.[1] The MOSAIC randomised controlled trial looked at the effects of 6 months CPAP in 391 patients with minimally symptomatic OSA. We have now analysed stored plasma for markers of systemic inflammation, from MOSAIC patients with sufficient samples remaining, recruited at the Oxford, Reading and Taunton centres (303 patients).

METHODS

Details of the MOSAIC study have been published previously.[2 3] The online repository for this current research letter contains details of the main entry criteria, statistical analysis and analyses performed on the blood samples: interleukin 6 (IL-6), IL-10 (anti-inflammatory), highly sensitive C reactive protein (CRP) and tumour necrosis factor. Patients with CRP values over 8 mg/L, at baseline or 6 months, were discarded from each analysis as they were assumed to represent significant intercurrent infection. As in the primary outcomes paper, the analysis was on an intention-to-treat basis, but with secondary analyses to explore the effect of CPAP compliance, as this was low overall (median 2:39, IQR 0:36 to 4:59, hour:min/night).

RESULTS

Patient characteristics, pre and post levels of oxygen desaturation index (ODI), and compliance data are in the original paper.[2] Table 1 shows the results of the blood assays. There were no consistent changes in any of the outcomes, with all p values >0.13, and no differences were seen when comparing high and low CPAP compliers (online data supplement). Sensitivity analyses using all subjects, regardless of whether the CRP was >8 mg/l or not, were no different (data not shown).

DISCUSSION

We have shown no changes in a limited set of inflammatory markers following 6 months of CPAP therapy versus untreated controls, in patients with mild-to-moderate OSA from the MOSAIC trial. This is despite there being a clear improvement in sleepiness,[2] and an improvement in endothelial function (albeit in a subset of patients).[3] Low CPAP compliance is unlikely to be the explanation for these negative findings, given that there was no suggestion of an effect even in the higher CPAP compliers (≥4 h/night). Our results are in agreement with our earlier 1 month randomised controlled trial in a more severe group of patients with OSA.[4] It is also in agreement with a recently published randomised controlled trial which showed no effect of 24 weeks CPAP on highly sensitive CRP in obese patients with moderate-to-severe OSA, despite a small fall in systolic blood pressure.[5] The small effect on CRP, IL-6 and tumour necrosis factor seen in some uncontrolled trials is likely to be the result of regression to the mean.[1] Reductions in catecholamine levels seem a more likely explanation for the improved endothelial function.

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Competing interests None.

Patient consent Obtained.

Ethics approval COREC No: 05/Q1604/159.

Provenance and peer review Not commissioned; externally peer reviewed.

Table 1 Baseline, 6 month, mean change and treatment effect data for all outcomes (excluding patients with CRP values >8 at baseline or follow-up)

	Standard care				CPAP					
	N	Baseline	6 months	Mean change (SD)	N	Baseline	6 months	Mean change (SD)	Treatment effect (95% CI)	p Value
Highly sensitive CRP (mg/L)	113	1.56 (0.84–3.48)	1.66 (0.87–3.44)	+0.03 (1.78)	125	1.86 (0.84–3.32)	1.49 (0.82–2.75)	−0.19 (1.56)	−0.20 (−0.59 to +0.18)	0.30
Interleukin 6 (pg/mL)	111	0.48 (0.19–0.92)	0.58 (0.26–1.09)	+0.14 (0.61)	125	0.44 (0.24–0.79)	0.52 (0.22–0.96)	+0.11 (0.45)	−0.04 (−0.17 to +0.10)	0.62
Interleukin 10 (pg/mL)	111	0.59 (0.33–1.02)	0.70 (0.39–1.21)	+0.11 (1.22)	125	0.61 (0.29–1.01)	0.60 (0.33–1.04)	+0.48 (2.50)	+0.35 (−0.12 to +0.83)	0.14
Tumour necrosis factor (pg/mL)	113	1.56 (0.84–3.48)	1.66 (0.87–3.44)	+0.03 (1.78)	125	1.86 (0.84–3.32)	1.49 (0.82–2.75)	−0.19 (1.56)	+0.05 (−0.05 to +0.15)	0.37

Baseline and 6 month values are summarised by median (25th–75th centiles).
CRP, C reactive protein.

Data sharing statement All data in this article are freely available on request.

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2014-205958).

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Correction

Stradling JR, Craig SE, Kohler M, *et al*. Markers of inflammation: data from the MOSAIC randomised trial of CPAP for minimally symptomatic OSA. *Thorax* 2015;70:181–2.

The results for tumour necrosis factor (TNF) as shown in Table 1 are incorrect and in fact correspond to the results for CRP. The correct results for TNF are shown below:

Table 1 Baseline, 6 month, mean change and treatment effect data for all outcomes (excluding patients with CRP values >8 at baseline or follow-up)

	Standard Care				CPAP					
	N	Baseline	6 Months	Mean change (SD)	N	Baseline	6 Months	Mean change (SD)	Treatment effect (95% CI)	p-Value
Highly sensitive CRP (mg/L)	113	1.56 (0.84–3.48)	1.66 (0.87–3.44)	0.03 (1.78)	125	1.86 (0.84–3.32)	1.49 (0.82–2.75)	−0.19 (1.56)	−0.20 (−0.59, 0.18)	0.30
Interleukin 6 (pg/mL)	111	0.48 (0.19–0.92)	0.58 (0.26–1.09)	0.14 (0.61)	125	0.44 (0.24–0.79)	0.52 (0.22–0.96)	0.11 (0.45)	−0.04 (−0.17, 0.10)	0.62
Interleukin 10 (pg/mL)	111	0.59 (0.33–1.02)	0.70 (0.39–1.21)	0.11 (1.22)	125	0.61 (0.29–1.01)	0.60 (0.33–1.04)	0.48 (2.50)	0.35 (−0.12, 0.83)	0.14
Tumour necrosis factor (pg/mL)	111	0.96 (0.45–1.35)	1.07 (0.48–1.48)	0.10 (0.40)	125	1.01 (0.45–1.35)	1.17 (0.61–1.56)	0.15 (0.39)	0.05 (−0.05, 0.15)	0.37

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Online repository.

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Methods

Study design

The MOSAIC, randomised, parallel, six-month, controlled trial (Multicentre Obstructive Sleep Apnoea Interventional Cardiovascular trial) was conducted between May 2006 and February 2010. The trial was approved by all the centres' ethics committees (REC No: 05/Q1604/159) and registered (ISRCTN 34164388). Patients were randomised 1:1 to standard care plus an auto-adjusting CPAP machine (Autoset S8, ResMed, Abingdon, UK), versus just standard care alone. The joint primary outcomes at 6 months were: change in ESS, and change in a composite five-year vascular risk score. Secondary outcomes at 6 months were change in objective sleepiness, self-assessed health status, blood pressure, lipids, glucose metabolism, obesity measures, and sleep apnoea severity (ODI). These have been reported previously.[1]

Entry criteria

All patients were diagnosed with OSA using overnight respiratory polygraphy as standard in the participating centres. Eligibility included: 45 to 75 years, proven OSA with a >4% oxygen desaturation index (ODI) on the original diagnostic study of >7.5 per hour, and any sleepiness present considered by both patient and sleep physician as insufficient to warrant CPAP.

Blood markers of systemic inflammation

The exploratory endpoints for this research letter, measurements of IL-6, IL-10, TNF and hsCRP, were performed using plasma samples which were immediately frozen and stored at -80 °C. IL-6, IL-10 and TNF were measured by high-sensitivity ELISA with commercially available kits (BMS213HS, BMSF0004 and BMS223HS, Bender MedSystems GmbH, Vienna, Austria). The lower limit of detection for IL-6, IL-10

and TNF were 0.03 pg/ml, 0.05 pg/ml and 0.13 pg/ml, respectively. The intra- and inter-assay coefficients of variation were 4.9 % and 6.0 %, respectively for IL-6 and 6.8 % and 7.5 % for IL-10, and 8.5 % and 9.8 % for TNF. All cytokines were measured in duplicate and in the same batch. The Dade Behring BN method (particle-enhanced immunonephelometry), which has a range 0.18-1150 mg/L, was used to measure hsCRP as previously described and validated.[2]

Statistics

All outcomes were analyzed using multivariable regression models, with adjustment for the minimisation variables and baseline value of the corresponding variable being analyzed. This produces a treatment effect, with 95% confidence interval (CI), due to being in the CPAP arm relative to standard care.

Results

The table shows the effect of CPAP compliance on hsCRP, IL-6, IL-10 and TNF. There is no suggestion that higher compliance produced an improvement in any of these markers of inflammation.

Outcome	Treatment effect (95% CI)		p-value for difference
	<4 hrs/night vs control n=81	>4 hrs/night vs control n=44	
Highly sensitive C–reactive protein (mg/l)	-0.19 (-0.62 to +0.25)	-0.23 (-0.76 to +0.29)	0.57
Inter leukin–6 (pg/ml)	-0.06 (-0.22 to +0.09)	0.02 (-0.17 to +0.20)	0.65
Inter leukin–10 (pg/ml)	0.45 (-0.08 to +0.98)	0.18 (-0.46 to +0.83)	0.25
Tumour necrosis factor (pg/ml)	0.06 (-0.05 to +0.17)	0.02 (-0.12 to +0.16)	0.59

Reference List

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