Eur Arch Otorhinolaryngol (2014) 271:163–169
DOI 10.1007/s00405-013-2523-z

HEAD AND NECK

Dynamic contrast-enhanced ultrasound for differential diagnosis of submandibular gland disease

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Received: 11 November 2012 / Accepted: 19 April 2013 / Published online: 27 April 2013

Abstract Intensity-time gradients (ITGs) of contrast-enhanced ultrasound (CEUS) can be used for non-invasive monitoring of gland-preserving treatment effects in sialolithiasis-related chronic sialadenitis as well as for imaging vascularization in tumors. The aim of this clinical trial was to evaluate feasibility to distinguish different entities of submandibular gland disease including inflammatory alterations of the submandibular gland as well as benign and malignant tumors. In this prospective clinical study, ITGs in 30 patients with sialolithiasis-related chronic sialadenitis or an unilateral submandibular mass and 18 disease-free submandibular gland controls were quantitatively analyzed by CEUS using the contrast agent *SonoVue*. In addition, clinical complaints according to visual analog scales (VAS) were documented. VAS data documented significantly less complaints only in benign tumors compared with the other pathologies of the submandibular gland. In parallel, CEUS-derived ITGs revealed significantly reduced ITGs only in benign tumors ($n = 5$) compared to the controls ($n = 18$). Despite of comparably reduced wash-in velocities in malignant lesions ($n = 3$) statistical significance was not reached. Chronic sialadenitis ($n = 18$) and its sclerosing variant (Küttner tumor, $n = 4$) revealed comparable ITGs as controls. Tumors of the submandibular gland present with reduced functional microcirculatory networks comparing with healthy gland controls and chronically inflamed submandibular glands. Thus, dynamic CEUS-derived ITGs in combination with conventional clinical measures—for example VAS—appear as a safe and promising strategy for non-invasive diagnostic workup of submandibular lesions and warrant further validation in a larger set of patients.

Keywords Intensity-time gradient · Wash-in velocity · *SonoVue* · Microcirculation · Sialadenitis · Küttner tumor

Introduction

Chronic sialolithiasis-related sialadenitis and end stage-chronic sclerosing sialadenitis—the latter also called 'Küttner tumors'—are quite common diseases in the submandibular gland. With regard to neoplasms differential diagnosis remains challenging and is sometimes not possible prior to the surgical removal of the gland. In cases of chronic non-sclerosing sialadenitis due to sialoliths, resection of the gland is not obligatory as novel gland-preserving techniques as sialendoscopy have been established [1]. In contrast, any tumor or a Küttner tumor mimicking a neoplasm should be surgically removed because ~50 % of tumors within the submandibular gland turn out to be malignant and even benign pleomorphic adenomas can show transformation [2].

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There are predominant diagnostic techniques that are routinely used for the evaluation of salivary gland lesions like ultrasound and magnetic resonance imaging (MRI) [3]. Besides computed tomography, sialography and sialendoscopy are applied in individual cases [3, 4]. But so far, there is no non-invasive diagnostic method that reliably differentiates salivary gland lesions especially distinguishing benign from malignant tumors in a percentage as high as fine needle aspiration (FNA) [5]. Some authors consider FNA as an unnecessary invasive procedure as the gland is removed anyway regardless of the diagnostic test result, while others argue that a more detailed preoperative diagnostic workup by FNA or imaging is important for planning surgery and patient counseling [6, 7]. With regard to non-invasive diagnostic evaluation it is advisable to combine several methods in the diagnostic workup in individual cases [8]. However, if any doubt about the underlying entity remains the gland will be resected with regard to the very aggressive behavior of malignant submandibular gland tumors and despite of the risk of facial or lingual nerve palsy.

Using Doppler flow ultrasound, Martinoli et al. [9] and Ahuja et al. [10] demonstrated that inflammation of the salivary gland is often associated with increased perfusion. It was therefore reasonable to consider dynamic contrast-enhanced ultrasound (CEUS) revealing functional microvascularization for monitoring the inflammatory state within the glands [11, 12]. The contrast agent *SonoVue* is a dispersion of small microbubbles containing sulfur hexafluoride surrounded by a phospholipid monolayer and improves signal-to-noise ratio in ultrasound imaging [13]. Resulting gas during in vivo applications can easily be eliminated by the lungs within a few minutes. Recently, dynamic CEUS was shown to be a novel tool to monitor submandibular gland-preserving treatment effects using extracorporal shock wave lithotripsy (ESWL) [11] or sialolithomy [12]. Comparably, perfusion analyses of chronic sialadenitis types as well as of benign and malignant tumors might contribute valuable information to optimize preoperative evaluation of submandibular masses.

Therefore, the aim of this feasibility study was the clinical evaluation of CEUS as a non-invasive diagnostic tool for distinguishing different entities of the submandibular gland. Chronic sialolithiasis-related non-sclerosing sialadenitis, chronic sclerosing sialadenitis (Küttner tumors) as well as benign and malignant tumors were compared with healthy glands as controls. The diagnostic significance of quantitative CEUS-derived intensity-time gradients (ITGs) was analyzed with regard to clinical complaints scored on visual analog scales (VAS) reflecting submandibular gland-specific symptoms.

Materials and methods

Patients

Thirty patients with unilateral pathology of the submandibular gland were enrolled into the study. Eighteen submandibular glands without pathology—i.e. on the contralateral side of patients with chronic sialadenitis—served as controls. This yielded five groups (1, control; 2, benign tumor; 3, malignant tumor; 4, chronic non-sclerosing sialadenitis and 5, chronic sclerosing sialadenitis/Küttner tumor).

All screened patients completed the study protocol. The study protocol was approved by the Ethics Committee of the University of Munich (LMU) and all patients gave written informed consent.

Study protocol

Prior (range 1–24 h) to treatment—sialolithotomy, ESWL or sialadenectomy, respectively—dynamic CEUS examination was performed. Symptom-specific as well as a comprehensive clinical complaint scoring VAS evaluations were assayed. In these questionnaires, the patients had to estimate their complaints with regard to the specific symptoms such as swelling during ingestion, permanent swelling, redness, pain, pressure or xerostomia as described earlier in detail [12].

The dynamic CEUS measurements were carried out by an independent radiologist (D.-A. C.) applying a Siemens ACUSON S2000 sonography device (Siemens Healthcare, Erlangen, Germany) with a linear multifrequency transducer system (9 MHz; S 2000, Siemens Healthcare, Erlangen, Germany). The contrast agent *SonoVue* was injected as a bolus (1.6–2.4 ml of 8 µl/ml suspension; Bracco Diagnostics, Milano, Italy) into a cubital vein followed by 10 ml of saline solution (0.9 %, Braun Melsungen AG, Germany). Ultrasound data were recorded during bolus injection and continued for up to 90 s after arterial contrast dye concentration peaked within the glands.

According to an animal experimental validation study tumor microcirculation can be reliably assessed by measurement of wash-in velocities of the contrast agent [14]. The measurements were normalized with regard to the arterial input derived from CEUS data of the gland supplying artery. Color-coded Doppler flow ultrasound imaging was used before CEUS measurements for identification of the afferent artery and draining vein. Intensity–time curves of every respective gland were fitted and gradients were derived offline as reported previously [11, 12].

In 18 patients with chronic sialadenitis due to sialolithiasis a gland-preserving treatment (ESWL, sialolithotomy) was performed after CEUS. In 12 patients with sonographic evidence of an unilateral tumor sialadenectomy was performed and histological analysis was performed to distinguish between benign, malignant, and Küttner tumors.

Statistical evaluation

VAS data [range: 0 (no complaints) to 10 (serious complaints)] and CEUS-derived ITGs are presented as mean ± SD. Data were analyzed using Kruskal–Wallis ANOVA on ranks (SigmaStat; Jandel Scientific, San Rafael, CA, USA). P values smaller than 5 % were considered to be significant.

Results

Patients

Out of 30 patients with pathology in the submandibular gland 18 suffered from chronic sialadenitis due to unilateral submandibular sialolithiasis (12 female and 6 male). The contralateral disease-free submandibular glands of these patients ($n = 18$) served as controls. In these two groups treated with gland-preserving techniques the age ranged from 24 to 69 years (mean age 48 years).

The remaining 12 patients (8 female and 6 male) presented with an unilateral mass in the submandibular gland. In five patients pleomorphic adenoma was revealed by histology. In three patients a malignant tumor was found (2 squamous cell carcinoma, 1 adenoid cystic carcinoma). In four patients a Küttner tumor was diagnosed.

Age in these groups treated with sialadenectomy ranged from 21 to 85 years (mean age 58 years).

Clinical complaint assessment

Healthy glands of the control group provoked no symptoms.

The main symptom of all patients with a benign tumor (pleomorphic adenoma) before sialadenectomy was permanent swelling of the gland (2.7 ± 3.7), followed by feelings of pressure (0.9 ± 1.5). Hardly mentioned were xerostomia, redness, swelling during ingestion (0.04 ± 0.8). The general symptom score was 1.1 ± 0.9.

In malignant tumors the main symptom before surgery was permanent swelling of the gland (4.4 ± 4.6), followed by feelings of pressure (3.3 ± 1.0), xerostomia (2.2 ± 3.3), redness (1.7 ± 2.6) and pain (1.7 ± 2.5). Swelling during eating was a minor symptom (0.07 ± 0.1). In this group the general symptom score was 3.6 ± 2.7.

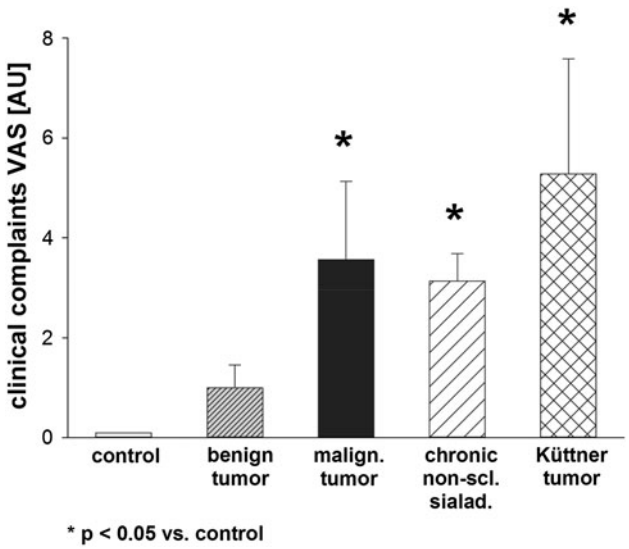


Fig. 1 VAS-derived comprehensive clinical symptom scores of the different diagnostic groups: only benign tumors provoked no significant clinical symptoms comparable to healthy gland controls in contrast to any other submandibular pathology

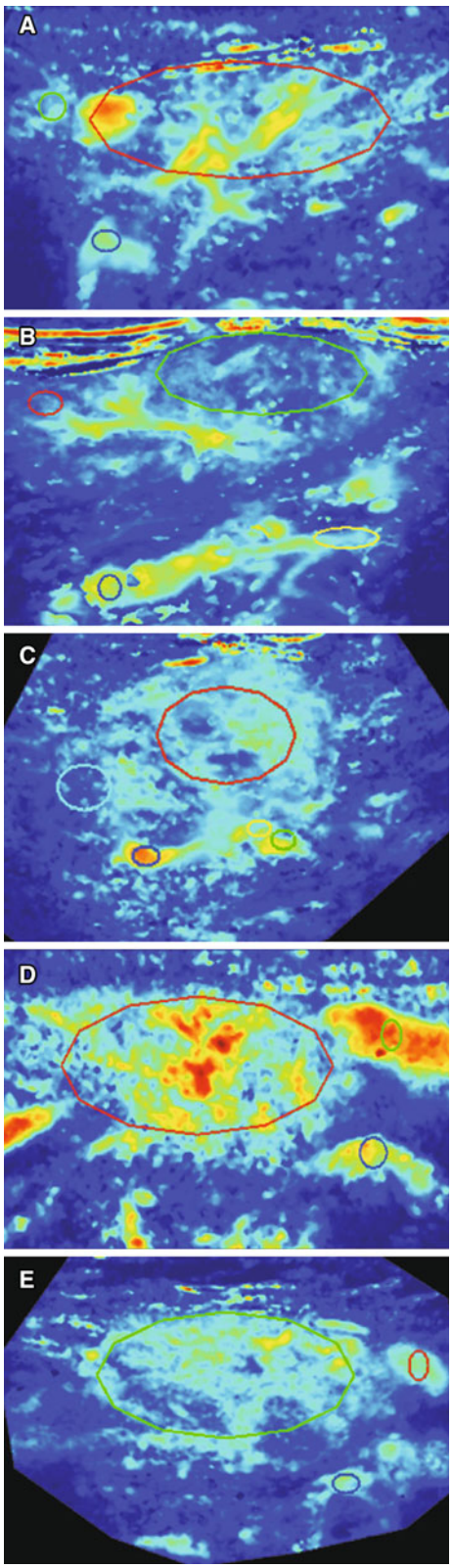
The main symptom of all patients with chronic non-sclerosing sialadenitis before gland-preserving treatment was swelling during ingestion (4.1 ± 2.2), followed by pain (1.6 ± 1.2), feelings of pressure (2.3 ± 2.1) and permanent swelling of the gland (1.7 ± 1.9). Less common were xerostomia (0.8 ± 0.8) and redness (0.26 ± 0.2). Here the general symptom score was 3.2 ± 2.0.

Among patients with chronic sclerosing sialadenitis the main symptom was permanent swelling of the gland (5.2 ± 3.8), followed by xerostomia (5.2 ± 4.3). Less common were pain (2.1 ± 3.5), feelings of pressure (1.7 ± 2.6), swelling during eating (0.5 ± 0.5) and redness (0.2 ± 0.1). The general symptom score among these patients with Küttner tumors was 5.0 ± 4.8.

Blotting the general symptom scores of all these five groups, patients with malignant tumors (3.57 ± 2.7), chronic sialadenitis (3.2 ± 2.0) or Küttner tumors (5.0 ± 4.8) revealed significantly increased complaints (Fig. 1). Only patients with benign tumors reported less complaints (1.1 ± 0.9) and revealed values with no significant difference comparing with healthy gland controls (0.0 ± 0.0).

Dynamic CEUS and ITG measurements

Color-coded images of dynamic CEUS examinations showed high peak intensity values of the contrast dye in healthy submandibular glands (Fig. 2). Intensity values were also high in chronic non-sclerosing sialadenitis and Küttner tumors. Interestingly, peak contrast dye signals



◀**Fig. 2** Color-coded images of dynamic CEUS findings in the different diagnostic groups: Reduced peak intensity values after contrast dye 'wash in' were found in benign (see **b**) and malignant submandibular tumors (see **c**). **a** Healthy submandibular gland control (*red circled region* of interest); supplying artery (*blue circled region* of interest); draining vein (*green circled region* of interest). **b** Pleomorphic adenoma of the submandibular gland (*green circled region* of interest); supplying artery (*blue* and *yellow circled regions* of interest), draining vein (*red circled region* of interest). **c** Squamous cell carcinoma of the submandibular gland (*red circled region* of interest); supplying artery (*yellow* and *green circled regions* of interest), and draining vein (*blue circled regions* of interest). **d** Chronic non-sclerosing sialadenitis of the submandibular gland (*red circled region* of interest); supplying artery (*green circled region* of interest), and draining vein (*blue circled region* of interest). **e** Küttner tumor of the submandibular gland (*green circled region* of interest); supplying artery (*blue circled region* of interest), draining vein (*red circled region* of interest)

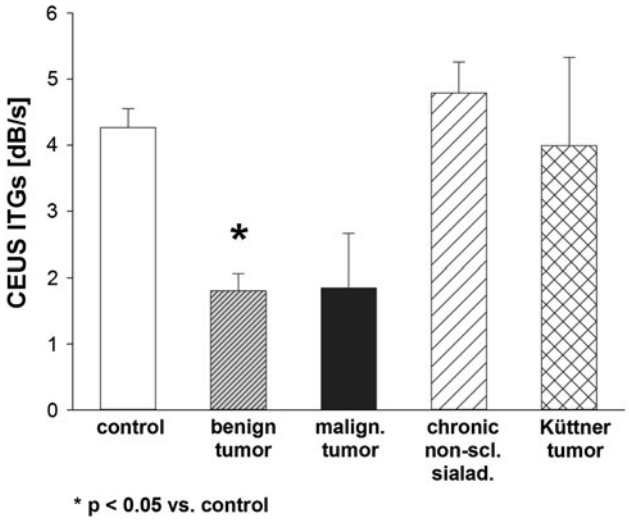


Fig. 3 Dynamic CEUS-derived intensity-time gradients (ITGs): comparable high values were found in healthy submandibular gland controls and chronic non-sclerosing sialadenitis and Küttner tumors. Low values were detected in all submandibular tumors. Statistical significance was found in benign tumors (pleomorphic adenoma)

were obviously reduced in all examined submandibular tumors (Fig. 2b, c).

After identification of the supplying and draining vessels normalization of CEUS intensity values was performed with regard to the arterial input. After fitting of intensity-time curves of every respective gland the respective ITGs were blotted (Fig. 3). Indeed normalized wash-in velocity reflecting functional microcirculation appeared to be significantly lower only in benign submandibular tumors comparing with controls. ITGs in malignant tumors were also low but statistical significance was missed after multiple comparison and post hoc analysis. ITG values in chronic non-sclerosing sialadenitis and Küttner tumors did not differ significantly from healthy submandibular gland controls.

Discussion

To our knowledge, this is the first feasibility study that provides dynamic CEUS-derived data for differential

diagnosis of submandibular gland lesions. Using CEUS-derived ITGs, we could show that tumors of the submandibular glands appear less perfused than healthy gland controls and chronically inflamed submandibular glands. Significantly lower ITGs were especially found in benign pleomorphic adenomas. This was paralleled with the absence of clinical complaints only in this entity. Although additional clinical validation implying higher patient numbers with malignant tumors is necessary, in this study CEUS-derived ITG measurements in combination with conventional clinical parameters—as VAS-based symptom assessment—appear as a safe and promising new non-invasive strategy to potentially improve differentiation during the diagnostic workup of submandibular gland disease.

The non-invasive differential diagnosis of a submandibular mass is important in the preoperative planning because an elective neck dissection has not to be considered a priori if the diagnostic evaluation suggests a benign submandibular tumor. Aim of novel non-invasive imaging methods should be to predict histological diagnosis with high accuracy. This would enable a surgical plan appropriate in nature and extent to reduce morbidity. As mentioned before dynamic CEUS only takes some minutes to perform and can easily be realized in a conventional otolaryngological office setting [11, 12].

It is well known that patients' history with regard to specific clinical complaints is very important for differential diagnosis especially in submandibular gland disease. Among common submandibular gland-related symptoms are swelling during ingestion, permanent swelling, redness, pain, pressure and xerostomia. With regard to these symptoms it is also possible to assess a VAS-based comprehensive clinical complaint score [15]. However, patients' complaints alone are of course not able to distinguish tumors from chronic sialolithiasis-related sialadenitis and Küttner tumors as symptoms may be unspecific or uncommon in the individual case.

Currently, B-mode sonography is predominantly used for routine diagnostic workup to decide whether a gland has to be removed or a gland-preserving treatment attempt is justifiable. As far as the presence of any tumor or a chronic sclerosing sialadenitis—i.e. a Küttner tumor—is taken into consideration after conventional B-mode sonography sialadenectomy is usually performed. While sensitivity of conventional B-mode sonography in the evaluation of salivary gland lesions is close to 100 % in many studies, its specificity remains low [2]. Novel non-invasive imaging methods have to compete against high accuracy of FNA reaching specificity of 99.5 % in a most recent retrospective study [5]. Using conventional imaging techniques the presence of a tumor is usually recognizable in B-mode sonography and odds favor a benign tumor if there are no complaints at all. But benign and malignant tumors can only be distinguished using high-resolution sonography in 80 % of the cases [2]. CEUS-derived ITGs alone will also probably not increase the accuracy of discrimination between benign and malignant nature as both entities presented with similar values in this study. However, ITG values were lower in benign tumors with statistical significance and reduced by trend in malignancy comparing with healthy gland controls and non-sclerosing as well as sclerosing chronic sialadenitis (Küttner 'tumor'). So, even after CEUS-derived ITG measurements it will remain difficult to differentiate between a malignant tumor and a Küttner tumor. In this context additional MRI is not helpful either, as it was observed that MRI can differentiate a Küttner tumor from benign tumors, but not reliably from malignant ones [16]. However, with regard to an experienced qualitative appraisal of the gland morphology Ahuja et al. reported a diffuse cirrhotic-like echo pattern using high-resolution ultrasound and radial branching vessels detected with color-coded Doppler flow ultrasound as typical sonographic features of Küttner tumors [10]. With regard to these specific morphologic appearances of Küttner tumors ultrasound imaging—especially using contrast agents in addition—might be at least superior to MRI in differential diagnosis of malignant tumors and Küttner tumors. Regarding the differential diagnosis of benign tumors, Bozzato et al. evaluated the use of even more quantitative dynamic CEUS-derived parameters in parotid gland tumors—i.e. 'wash-in time', 'peak', 'time to peak' and 'wash-in velocity'—and found specific differences in pleomorphic adenomas and Warthin tumors [17]. Comparably, Fischer et al. [18] reported also to be able to distinguish between Warthin tumors and pleomorphic adenoma using CEUS within the parotid gland. However, no increase of accuracy in detection of malignant tumors could be reported so far by either of these groups using CEUS techniques in parotid glands.

Nevertheless, validation of CEUS-derived parameters for clinical applications in the future is warranted: in contrast to qualitative ultrasound findings of the submandibular gland quantitative parameters might help even the less experienced examiner in differential diagnosis. Except as otherwise provided [19] reports exist on Doppler flow ultrasound findings in parotid tumors showing that a resistive index (RI) <0.8 and a pulsatile index (PI) <1.8 favor a benign over a malignant lesion [20]. In this study, Bradley et al. clearly state that there were no qualitative differences in the appearance of the respective parotid gland tumors. However, calculating RI and PI using Doppler flow ultrasound data a statistical significant difference was found. This apparently points at functional microcirculation as a promising feature for differential diagnosis and at the diagnostic potential of quantitative parameters of modern investigator-independent ultrasound examinations.

Our findings are a first step toward clinical applications using CEUS-derived ITGs for differential diagnosis in the submandibular region. Currently rating of CEUS-derived ITGs alone appears not as a valid parameter but accuracy might be increased after combination with clinical symptom assessment or other non-invasive clinical measures. There might well be some more evidence necessary before the role of CEUS in routine preoperative workup in an ordinary otolaryngologist office setting will be well defined. But as demonstrated in our study this methodology possibly implies the relinquishment of additional MRI in specific submandibular lesions.

Alternative new developments in ultrasound methodologies also provide quantitative data but focus more on tissue texture analysis than on perfusion measurements. Some of these 'sonohistology' studies introduce novel quantitative parameters—as for example 2-D pixel distribution analysis [21], fuzzy interference system analysis [22] or mean gray scale values [23]—and may further improve specificity of preoperative detection even of malignant lesions within the salivary glands.

Reflecting on the future developments of dynamic CEUS for clinical applications, multiple other quantitative parameters can be defined and evaluated accordingly in the differential diagnosis of submandibular pathologies. In this line we found CEUS-derived ITG ratios combining data from the diseased and the healthy contralateral side to be a valid quantitative parameter reflecting the effectiveness of gland-preserving sialolithotomy [12]. Another promising field is the evaluation of dynamic CEUS in Sjögren's syndrome or salivary sarcoidosis and its value for monitoring non-surgical treatment effects in these hypervascular alterations of the salivary glands [9].

Due to the limited number of patients in this study sensitivity, specificity and predictive values of this new method are not yet determined. But as Taylor et al. [8] point out it is reasonable to rely on the combination of diagnostic tools for preoperative analysis. Therefore, it appears more adequate in upcoming clinical studies not only to analyze test outcome parameters of a single new method alone, but in combination with other non-invasive diagnostic methods to approximate FNA accuracy.

The unique potential of novel ultrasonographic methods—including CEUS-derived ITG analysis—lies in the use of quantitative parameters for differential diagnosis that might increase specificity of conventional diagnostic tools in a non-invasive and examiner-independent manner.

Conclusions

Dynamic CEUS-derived ITG measurement in combination with clinical complaint assessment appears as promising diagnostic strategy in the preoperative workup of a submandibular gland disease. Further studies with higher patient numbers are needed to determine sensitivity and specificity of this diagnostic method alone and in combination with other non-invasive measures.

Acknowledgments *SonoVue* was provided by *Bracco Diagnostics*, Milano, Italy.

Conflict of interest The authors deny any conflict of interest.

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