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Original article

Adverse events in a chiropractic spinal manipulative therapy single-blinded, placebo, randomized controlled trial for migraineurs

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ABSTRACT

Background: Unlike pharmacological randomized controlled trials (RCTs), manual-therapy RCTs do not always report adverse events (AEs). The few manual-therapy RCTs that provide information on AEs are frequently without details, such as the type and-, severity of the AE and reason for withdrawal.

Objective: To prospectively report all AEs in a chiropractic spinal manipulative therapy (CSMT) RCT.

Design: A prospective 3-armed, single-blinded, placebo, RCT.

Methods: Seventy migraineurs were randomized to the CSMT or a placebo, with 12 intervention sessions over three months. The recommendations by CONSORT and the International Headache Society's Task Force on AEs in migraine RCTs were followed. A standardized reporting scheme designed for pharmacological RCTs was used, and the AEs were described as frequencies and percentages within each group. The 95% confidence intervals (CIs) for the percentages (absolute risk) of AEs in each group were calculated when possible. Attributable risk (%) and relative risk were calculated with the corresponding 95% CIs.

Results: AEs were assessed in 703 sessions, with 355 in the CSMT group and 348 in the placebo group. Local tenderness was the most common AE, reported by 11.3% and 6.9% of the CSMT group and the placebo group, respectively, and tiredness on the intervention day was reported by 8.5% and 1.4% of CSMT group and the placebo group, respectively. The highest attributable risk was for tiredness on the treatment day, 7.0% (CI 3.9–10.2%) which presented a relative risk of 5.9 (CI 2.3–15.0).

Conclusions: AEs were mild and transient, and severe or serious AEs were not observed.

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1. Introduction

Migraines represent a common worldwide challenge that present substantial health and socioeconomic costs (Vos et al., 2012), and pharmacological management is often the first treatment choice. However, certain patients exhibit low tolerance to migraine medication because of co-morbidities of other diseases, adverse events (AEs), or choose to avoid medication altogether (Olesen et al., 2006; Diener et al., 2015; Schulte and May 2015).

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Manual-therapy is a non-pharmacological prophylactic treatment option that appears to have a similar effect as the drug topiramate on migraine frequency, migraine duration, migraine intensity and medicine consumption (Brandes et al., 2004; Chaibi et al., 2011; Chaibi and Russell, 2014).

Although the frequency of reported AEs has increased since the introduction of the 2010 CONSORT guidelines (Correll et al., 2016), manual-therapy randomized controlled trials (RCTs) do not always report AEs, which is a requirement of pharmacological RCTs (Gross et al., 2015). The few manual-therapy RCTs that have provided information on AEs have often failed to include information on the type and severity of AEs, or whether withdrawal from the RCT was caused by the AE (Moher et al., 2010). Thus, reporting all AEs in prospective manual-therapy RCTs is important for increasing the scientific quality of these RCTs to the level of pharmacological RCTs.

The primary objective of this study was to report on all AEs in a prospective chiropractic spinal manipulative therapy (CSMT) single-blinded, placebo, RCT for migraineurs.

2. Materials and methods

2.1. Design

The present study reports on AEs from a prospective single-blinded, placebo, RCT with three parallel groups: (i) active group, receiving CSMT, (ii) placebo group, receiving sham manipulation and (iii) control group, continuing usual pharmacological management (Chaibi et al., 2017). The frequency of the most important AEs findings was reported in this RCT, while details are presented here (Chaibi et al., 2017). The control group was added to assess the treatment efficacy for migraineurs. The RCT included 12 intervention sessions over 12 weeks with follow-up at 3, 6 and 12 months post-treatment, and it was conducted in accordance with the recommendations by CONSORT and the International Headache Society's Task Force on AEs in migraine RCTs (Moher et al., 2010; Tfelt-Hansen et al., 2000; Silberstein et al., 2008). The full trial protocol has been published previously with explicit details (Chaibi et al., 2015a).

2.2. Participants

The participants were recruited in 2013 from Akershus University Hospital as well as from general practitioners and media advertisements in Akershus and Oslo Counties, Norway.

Eligible participants were migraineurs (aged 18–70 years old) who were diagnosed according to the ICHD-II (ICHHD, 2004) and reported at least one migraine attack per month.

Exclusion criteria were contraindication to spinal manipulative therapy (SMT), spinal radiculopathy, pregnancy, depression and CSMT within the previous 12 months. Any participants' who received any manual interventions by chiropractors, physiotherapists, osteopaths or other health professionals including massage therapists, or who changed their prophylactic migraine medicine or became pregnant during the trial period, were excluded at the time of violation and regarded as drop-outs. The participants were allowed to continue and change their acute migraine medication throughout the trial.

The participants who fulfilled the inclusion criteria were invited to an interview and physical assessment by a chiropractor, including meticulous investigation of the spinal column. Participants randomized to the CSMT or the placebo group received a full spine radiographic examination (Chaibi et al., 2015a).

2.3. Randomization

Numbered sealed lots prepared for the three interventions (CSMT, placebo and control) were subdivided into four subgroups by age and gender, i.e., age groups of 18–39 and 40–70 years for both men and women. The participants were equally allocated to one of the three groups by allowing the participant to draw one lot only (Chaibi et al., 2015a). Block randomization was exclusively administered by a single external party.

2.4. Intervention

Active treatment consisted of CSMT using the Gonstead method, i.e., a specific contact, high-velocity, low-amplitude, short-lever spinal with no post-adjustment recoil that was directed to spinal biomechanical dysfunction (full spinal column approach) as

diagnosed by standard chiropractic tests performed during each individual treatment session (Cooperstein, 2003).

The placebo intervention consisted of sham manipulation, i.e., a broad non-specific contact approach via a low-velocity, low-amplitude sham push manoeuvre in a non-intentional and non-therapeutic directional line. All of the non-therapeutic contacts were performed outside the spinal column and included adequate joint ligament slack without soft tissue pre-tension so that joint cavitations did not occur (Chaibi et al., 2015b). The sham manipulation alternatives were equally interchanged among the placebo participants according to the protocol (Chaibi et al., 2015a). The intervention included 12 15-min consultations over a period of 3 months. All of the interventions were conducted at Akershus University Hospital by a single experienced chiropractor, i.e., the clinical investigator (AC). A detailed description of the interventions are included in the trial protocol (Chaibi et al., 2015a).

The control group continued their usual pharmacological management without receiving manual intervention by the clinical investigator.

2.5. Blinding

After each intervention session, the participants in the CSMT and the placebo group completed a questionnaire on whether they believed the CSMT treatment was received, and how certain they were that active treatment was received on a 0–10 numeric rating scale, where 10 represented absolute certainty (Chaibi et al., 2015b).

2.6. Adverse event data collection

All AEs were registered in accordance with the recommendations of CONSORT and IHS Task Force on AEs in migraine RCTs (Moher et al., 2010; Tfelt-Hansen et al., 2008). The AEs records were collected by the clinical investigator prior to each intervention session. AE data were not collected for the control group. The participants were instructed to report back to the clinical investigator after the 12th intervention if serious AEs occurred. Thus, AEs were only collected during the first 11 intervention sessions.

A standardized recording scheme designed for pharmacological RCTs was used to collect the AE data (NIH, 2013). The AE recording scheme was completed after each intervention session whether AEs were experienced or not. The first question was whether the participant had experienced an AE, and it was recorded by a dichotomous “yes” or “no” answer. If the answer was yes, then the clinical investigator asked “what type of AE did you experience?” followed by the question “when did the AE start and stop?” Finally, the participant was asked whether they considered the AE(s) to be mild, moderate or severe. The clinical investigator filled in the remaining questions regarding the relationship of the AE to the intervention (definitely related, possibly related or not related), and described any actions taken as well as the outcome and seriousness of the AE(s) (NIH, 2013). Serious AEs, i.e., permanent or severe disability, hospitalization or death, were indicated in a separate serious AE scheme by the clinical investigator (NIH, 2013). The clinical investigator was available throughout the study period via cell phone.

2.7. Statistical analysis

The baseline demographic and clinical characteristics in the CSMT and the placebo groups were presented as the means and standard deviations (SDs) or as percentages and frequencies, as appropriate, and they were compared using a Z-test for proportions or independent samples *t*-test. All of the AEs registered during the

intervention period were described as frequencies and percentages within each group. The 95% confidence intervals (CIs) for the percentages (absolute risk) of AEs in each group were calculated when possible. The attributable risk (%) and relative risk were calculated with the corresponding 95% CI. The analyses were also stratified according to whether the patients had previously received CSMT. All data were analysed (using SPSS v22) by a statistician (JSB), blinded to the group allocation.

2.8. Ethics

Good clinical practice guidelines and the Declaration of Helsinki were followed (Dixon, 1998; WMA, 2013). Oral and written information on the project was provided to each participant, and written informed consent was obtained prior to inclusion in the study and group allocation. Information on the intervention groups included the benefits and possible AEs. Insurance was provided by the Norwegian System of Compensation to Patients (NPE). A stopping rule for withdrawing study participants was defined in accordance with the recommendations in the CONSORT extension for Better Reporting of Harms (Moher et al., 2010). The Norwegian Regional Committee for Medical Research Ethics and the Norwegian Social Science Data Services approved the project. All of the methods were conducted in accordance with the approved guidelines and regulations. The funding sources were non-commercial, and the study was designed and conducted by the authors without any influence by the funding sources. The original study was registered on 2 December 2012 at ClinicalTrials.gov (ID no. NCT01741714) (Chaibi et al., 2015a).

3. Results

Our RCT included 70 participants, with six men and 29 women in each of the CSMT and placebo groups. The baseline demographics and characteristics were similar in the two groups (Table 1).

A total of 703 of the potential 770 intervention sessions included a AEs assessment, with 355 assessments in the CSMT group and 348 assessments in the placebo group. The reasons for missing AE assessment included drop outs and missed intervention session appointments. One woman in the CSMT group dropped out after the 2nd intervention session because of local tenderness, one woman in the placebo group dropped out after the 4th intervention session because of time concerns, and one man in the placebo

group was excluded prior to the 9th session, because he was experiencing a cluster headache and not a migraine during the intervention period. Intervention session appointments were missed 20 times in the CSMT group, and 23 times in the placebo group. A total of 557 spinal manipulations was delivered over the 355 interventions in the CSMT group distributed between the cervical- (60%), thoracic- (29%), lumbar- (9%) and pelvic spinal region (2%).

3.1. Efficacy outcomes

Migraine days were significantly reduced within all groups from the baseline to post-treatment period ($p < 0.001$). The effect continued in the CSMT and the placebo groups at three, six and 12 months follow-up, whereas the number of migraine days reverted to the baseline level in the control group. The results of the linear mixed model did not indicate overall significant differences in migraine days between the CSMT and the placebo group ($p = 0.04$) or between the CSMT and the control group ($p = 0.06$). The pairwise comparisons at individual time points, however, showed significant differences between the CSMT and the control group at all post-treatment time points (Chaibi et al., 2017). The blinding was concealed throughout the entire trial presented with an odds ratio of >10 at all intervention sessions in both groups (Chaibi et al., 2015b).

3.2. Adverse events related to the intervention

AEs were reported in a significantly higher number of CSMT group intervention sessions than in the placebo group intervention sessions, with AEs reported in 73/355 in the CSMT group versus 29/348 in the placebo group ($p < 0.001$). In the majority of the intervention sessions, only a single AE was reported, with 63 single reports in the CSMT group and 26 single reports in the placebo group. Two AEs were reported ten times in the CSMT group and three times in the placebo group. None of the participants reported three or more AEs during a single intervention session.

Ten participants in the CSMT group and 17 participants in the placebo group did not experience AEs in any of the interventions sessions, whereas the remaining participants experienced AEs in at least one intervention session.

Local tenderness, tiredness and neck pain were the most common AEs, whereas other AEs were rare ($<1\%$) (Table 2).

Table 1
Baseline demographics and characteristics.

	Chiropractic spinal manipulative therapy		Placebo
	% (n)		% (n)
Number of participants (N)	35		35
Males	17 (6)		17 (6)
Females	83 (29)		83 (29)
Age \pm SD (range)	41.3 \pm 11.3 (19–63)		39.6 \pm 9.7 (18–65)
Migraine without aura	94 (33)		89 (31)
Migraine with aura	29 (10)		34 (12)
Years with migraine \pm SD	22.6 \pm 13.6		21.1 \pm 11.2
Migraine days (30 days/month) in the run-in period \pm SD	6.5 \pm 3.3		8.3 \pm 5.6
Co-morbid tension-type headache	71 (25)		77 (27)
Tension-type headache days (30 days/month) in the run-in period \pm SD	1.0 \pm 2.0		2.1 \pm 3.5
Previously received CSMT	34 (12)		37 (13)
Previously experienced			
Cervical pain	86 (30)		83 (29)
Thoracic pain	71 (25)		74 (26)
Lumbar pain	71 (25)		77 (27)

*No statistically significant difference between the groups, all $p > 0.05$.

Tiredness presented the highest attributable risk at 7.0% (95% CI 3.9–10.2%) and a relative risk of 5.9 (95% CI 2.3–15.0), and local tenderness and neck pain presented an attributable risk of 4.4% and 1.7% (95% CI 0.1–8.6% and 0.1–3.2%), respectively, and a relative risk of 1.6 and 6.9 (95% CI 1.0–2.7 and 0.9–55.5), respectively.

The attributable risk and relative risk for local tenderness, tiredness and neck pain in the CSMT group was not influenced by previous experience of a CSMT attributable risk 3.6% (95% CI -3.4–10.9%), 2.7% (95% CI -3.7–9.1%) and 4.7% (95% CI 0.6–8.8%), respectively; and relative risk 1.4 (95% CI 0.8–2.5), 1.4 (95% CI 0.7–2.7) and 12.2 (95% CI 1.5–100.2), respectively (Table 2).

All of the AEs but one were mild and transient. The one moderate AE was reported as a migraine attack. No severe or serious AEs were reported.

3.3. Adverse events unrelated to intervention

The AEs that were not related to the interventions were rare (<1%) except for neck and lower back pain (Table 3). Two participants in the CSMT group reported lower back pain as an AE after two and three intervention sessions, although this result was regarded as non-related because both participants only received CSMT at the cervical spine and not the lumbar spine. Furthermore, both participants had lower back pain at study inclusion and experienced daily lower back pain after strenuous activities. Two participants in the CSMT group reported neck pain six and seven days after the intervention session.

4. Discussion

This paper presents the first report of a prospective 3-armed, single-blinded, placebo RCT reporting AEs for migraineurs receiving CSMT or sham manipulation (placebo) over an intervention period of three months (Chaibi et al., 2011; Chaibi and Russell, 2014). The AEs were reported as mild and transient, and no severe or serious AEs were reported.

4.1. Methodological considerations

Although surgical RCTs use inconsistent definitions and severity grading when reporting AEs (Rampersaud et al., 2016) and certain pharmacological RCTs may use heterogeneous definition for AEs and lack systematic assessments and reporting (Oosten et al., 2015), most manual-therapy RCTs do not utilize standardized AE reporting tools. Monitoring all AEs in manual-therapy RCTs is important for the early identification of AEs. Thus, we applied an applicable standardized reporting tool used in pharmacological RCTs to monitor AEs and participant safety (NIH, 2013). We adhered to the recommendations of CONSORT and the International Headache Society's Task Force on the reporting of AEs in migraine RCTs (Tfelt-Hansen et al., 2008; Ioannidis et al., 2004).

The advantage of collecting AEs in house with the participant is related to common differences in the perception of AEs between participants and clinical investigators (Carlesso et al., 2011). The participants reported the type, severity and duration of the AE, and the clinical investigator interpreted the reported AEs in relation to the onset and region affected. Thus, the AEs with non-musculoskeletal characteristics that occurred several days after an intervention were deemed unrelated to the intervention session; however, because this was performed at the discretion of the clinical investigator, it could be viewed as a limitation of the study (Tfelt-Hansen et al., 2008). Therefore, the objectivity of the clinical investigator in terms of their communication and reporting of AEs is a valid source of concern. General recommendations indicate that placebo interventions should resemble the active treatment in terms of procedure, treatment frequency and time spent with the investigator to allow for similar expectations in both groups (Turner et al., 1994). The fact that the participants were blinded throughout the trial substantiated the fact that the patient-provider interaction was not skewed and resulted in similar expectations (Chaibi et al., 2015b).

The study had other limitations. Although the RCT was sufficiently powered, the sample size was certainly too small to detect uncommon AEs. However, serious AEs are rarely observed in manual-therapy RCTs (Gouveia et al., 2009); thus, conducting large-scale RCTs to observe these AEs is naturally difficult. Because of the

Table 2

Adverse events related to the interventions stratified by ± previously received CSMT. N is total number of interventions.

Type	Chiropractic spinal manipulative therapy (CSMT) (N = 355)			Placebo (N = 348)		
	%, [95% CI] (n)					
	Previously received CSMT		Total	Previously received CSMT		Total
	Yes	No		Yes	No	
Total number of intervention sessions	117	238	355	134	214	348
Local tenderness	14 [9–21] (16)	10 [7–15] (24)	11 [8–15] (40)	4 [2–8] (5)	9 [6–14] (19)	7 [5–10] (24)
Tiredness on treatment day	10 [6–17] (12)	8 [5–12] (18)	9 [6–12] (30)	3 [1–7] (4)	<1 [0–3] (1)	1 [1–3] (5)
Neck pain	5 [2–11] (6)	<1 [0–2] (1)	2 [1–4] (7)	<1 (1)	0 (0)	<1 [0–2] (1)
Low back pain	<1 (1)	<1 (1)	<1 [0–2] (2)	0 (0)	<1 (1)	<1 [0–2] (1)
Face numbness	0 (0)	<1 (1)	<1 (1)	0 (0)	0 (0)	0 (0)
Nausea	<1 (1)	0 (0)	<1 (1)	0 (0)	0 (0)	0 (0)
Provoked migraine attack	0 (0)	<1 (1)	<1 (1)	<1 (1)	0 (0)	<1 (1)
Fatigue in arms	0 (0)	<1 (1)	<1 (1)	0 (0)	0 (0)	0 (0)
Total % of adverse events	31 (36)	20 (47)	23 (83)	8 (11)	10 (21)	9 (32)

Table 3
Adverse events unrelated to the intervention. N is total number of interventions.

Type of adverse event	Chiropractic spinal manipulative therapy	Placebo
Total numbers of intervention sessions	(N = 355)	(N = 348)
	% (n)	% (n)
Low back pain	1.4 (5)	2.3 (8)
Neck pain	0.8 (3)	1.1 (4)
Knee pain	0.8 (3)	0.0 (0)
Influenza	0.6 (2)	0.3 (1)
Arm pain	0.0 (0)	0.3 (1)
Dizziness	0.3 (1)	0.0 (0)
Ear infection	0.3 (1)	0.0 (0)
Epiretinal fibrosis operation	0.3 (1)	0.0 (0)
Hip pain	0.3 (1)	0.0 (0)
Inflammation lip	0.3 (1)	0.0 (0)
Kidney stones	0.3 (1)	0.0 (0)
Pneumonia	0.3 (1)	0.0 (0)
Sinusitis	0.3 (1)	0.3 (1)
Sore throat	0.3 (1)	0.0 (0)
Tonsil removal	0.3 (1)	0.0 (0)
Chest pain after fall on ice	0.3 (1)	0.0 (0)
Urinary tract infection	0.3 (1)	0.0 (0)
Wrist pain	0.3 (1)	0.0 (0)
Benign breast tumors operation	0.0 (0)	0.3 (1)
Unilateral breast infection	0.0 (0)	0.3 (1)
Total % of unrelated adverse events	7.3 (26)	4.9 (17)

lack of 3-armed RCTs that include a successfully concealed placebo group in manual therapy, and because of current inadequate and unacceptable level of AE reporting in manual-therapy RCTs (Gorrell et al., 2016), the results of the present study will contribute to the design of future large-scale studies and pooled meta-analyses, which have the potential to establish the frequency of uncommon AEs in relation to manual-therapy RCTs and estimate the incidence rates for AEs.

An RCT with a single clinical investigator eliminates inter-observer variability (Kendall, 2003). Therefore, the AEs reported in this study might not be representative of all CSMT studies because inter-professional skills and selected techniques might vary. Different AEs may occur with different interventions which is consistent with the finding that different AEs profiles occur with different pharmacological medication.

5. Results discussion

All previous chiropractic RCTs which have reported AEs have used spinal manipulation as a treatment modality (Carnes et al., 2010). Two studies applied interventions to the whole spine (Cagnie et al., 2004; Walker et al., 2013), whereas five studies applied the interventions exclusively to the cervical spine (Hurwitz et al., 2004; Thiel et al., 2007; Rubinstein et al., 2007; Eriksen et al., 2011; Maiers et al., 2015). Only one previous RCT was comparable to our study, and it reported AEs after each intervention session and during the entire treatment period (Maiers et al., 2015). Two previous studies reported AEs after a single intervention session (Cagnie et al., 2004; Hurwitz et al., 2004), whereas one study reported AEs from two treatment sessions (Walker et al., 2013). The remaining studies reporting AEs include two observational cohort studies (Rubinstein et al., 2007; Eriksen et al., 2011), and one prospective survey (Thiel et al., 2007).

Our RCT reported fewer AEs in general than were reported in previous studies, although similar transient and mild characteristics were reported (Cagnie et al., 2004; Walker et al., 2013; Hurwitz et al., 2004; Thiel et al., 2007; Rubinstein et al., 2007; Eriksen et al., 2011; Maiers et al., 2015). Common AEs from previous studies included local tenderness (mean 26.4%; 95% CI 26.2–26.6) (Cagnie

et al., 2004; Walker et al., 2013; Hurwitz et al., 2004; Thiel et al., 2007; Rubinstein et al., 2007; Eriksen et al., 2011; Maiers et al., 2015), and tiredness on the treatment day (mean 10.5%; 95% CI 10.4–10.6) (Cagnie et al., 2004; Hurwitz et al., 2004; Rubinstein et al., 2007; Eriksen et al., 2011). Headache was reported as a common AE (mean 10.3%; 95% CI 10.2–10.4), which is likely because previous studies primarily investigated neck pain and not headache (Cagnie et al., 2004; Walker et al., 2013; Hurwitz et al., 2004; Thiel et al., 2007; Rubinstein et al., 2007; Eriksen et al., 2011; Maiers et al., 2015). The comparable study reported mild and transient local tenderness (38%), muscle soreness (13%) and headache (11%), although tiredness was not recorded as an AE (Maiers et al., 2015).

Few severe and transient AEs were reported in four RCTs (mean 16.4%; 95% CI 15.6–17.2) (Cagnie et al., 2004; Walker et al., 2013; Hurwitz et al., 2004; Maiers et al., 2015), and no serious AEs were reported in the previous CSMT studies (Cagnie et al., 2004; Walker et al., 2013; Hurwitz et al., 2004; Thiel et al., 2007; Rubinstein et al., 2007; Eriksen et al., 2011; Maiers et al., 2015).

The results of the current study and previous CSMT studies suggest that AEs are usually mild and transient, and severe and serious AEs are rare (Tuchin, 2012; Cassidy et al., 2008, 2016). These findings are in accordance with the World Health Organization guidelines on basic training and safety in CSMT, which has considered it to be an efficient and safe treatment modality (WHO, 2005).

AEs in migraine prophylactic pharmacological RCTs are common (Jackson et al., 2015). The risk for AEs during manual-therapy appears also, to be substantially lower than the risk accepted in any medical context for both acute and prophylactic migraine medication (Jackson et al., 2015; Ferrari et al., 2001). Non-pharmacological management also has the advantage of no pharmacological interactions/AEs because such therapies are usually mild and have a transient characteristic, whereas pharmacological AEs tend to be continuous (Carnes et al., 2010). One might argue that the AEs associated with pharmacological treatments using historical data should not have factored into the decision to allow participants to continue their acute migraine medication and the control group participants to continue their usual medication. However, we believe that AEs related to on-going pharmacological

treatment, were unlikely to influence new AEs reported immediately after a manual intervention.

6. Conclusions

CSMT applying the Gonstead technique appears to be safe for the management of migraine headache and presents few mild and transient AEs. Although the CSMT group reported significantly more AEs than the placebo group, we observed fewer AEs in our study than what is reported using prophylactic migraine medication such as topiramate, metoprolol or candesartan. Future manual-therapy RCTs should adhere to the CONSORT recommendations of reporting all AEs.

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Conflicts of interests

All authors have completed the ICMJE uniform disclosure form and no conflicts of interests were reported for this study.

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