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Title: Therapeutic Impacts of Hyperbaric Oxygen Therapy and Risperidone on Children With Autism: A Clinical Trial

Running Title: Hyperbaric Oxygen Therapy and Risperidone Effect on Autism

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Abstract

Background & Objectives: In this research, we investigated any possible effect of receiving Hyperbaric oxygen therapy (HBOT) or Risperidone on the autism core symptoms in children diagnosed as autism spectrum disorder (ASD).

Methods: A randomized, controlled clinical trial, in Minia and Assiut University hospitals in Egypt with three parallel groups. One hundred and eighty children with autism, ages 5–8 years, divided into equal three groups, Group1 (G1): (N=60) received 40 sessions of (HBOT) within two months. Group2 (G2): (N=60) received Risperidone (0.25 mg daily for children under 20 kg; 0.5 mg daily for children equal to or over 20 kg) for six months. Group3 (G3): (N=60) control group received a placebo for six months. Assessment of their Childhood Autism Rating Scale (CARS) and Autism Treatment Evaluation Checklist (ATEC) scores was done at the beginning of the study (baseline) and after one year.

Results: The mean total CARS, total ATEC, and ATEC subscales scores were significantly decreased (improved) by varying degrees in the three groups after a year of follow-up compared to the baseline scores, but the best results were in order (G1) then (G2) and finally (G3).

Interpretation & conclusions: There is a clear effect of using (HBOT) or Risperidone in treating the core symptoms of autism in children diagnosed as autism spectrum disorder. But using (HBOT) gives better results than using Risperidone therapy.

Trial registration number: Clinical trials.gov ID: NCT03887754

Keywords: Autism, ATEC, CARS, HBOT, Risperidone

Highlights

- Non-pharmacologic therapy can be used as a therapy for autism core symptoms.
- Both HBOT and Risperidone reduces the autism core symptoms.
- Hyperbaric oxygen therapy gives better effects than Risperidone in reducing the core symptoms of autism.

Plain Language Summary

Since the prolonged use of drug therapy in children with autism leads to the appearance of side effects in addition to the difficulty in patient compliance for using drugs for long periods, attempts have begun to use non-traditional alternative therapy such as Hyperbaric oxygen therapy. The current study assessed the therapeutic effect of HBOT and Risperidone on the autism core symptoms. The collected results revealed that both HBOT and Risperidone reduced the autism core symptoms, but Hyperbaric oxygen therapy gives better therapeutic results than Risperidone.

Introduction:

A developmental disorder (ASD), is characterized by a wide range of symptoms. It has an impact on communication as well as behavior. Since signs usually occur in the first two years of life, it is said to be a "developmental disorder" (Health, March 2018).

The American Psychiatric Association developed Diagnostic and Statistical Manual of Mental Disorders (DSM-5), a guide for diagnosing mental disorders, and it states that people with ASD have: problems in the communication and limited contact with other people, limited interests, and repetitive habits that hinder people's ability to function normally in the community (Association, 2013).

As the continuously increasing number of children with autism spectrum disorder (ASD) by an unknown cause. Researchers have begun to use pharmacological and non-pharmacological therapy to improve treatment outcomes. The greatest challenge in this disease is to resolve the mystery of the causes leading to it and to know the appropriate treatment methods for it.

Hyperbaric oxygen therapy is a treatment that involves patients entering a chamber with concentrated oxygen pressured above sea level (1 atmosphere absolute) and breathing oxygen (Lam, Fontaine, Ross, & Chiu, 2017).

Increasing cerebral perfusion during the treatment of children with autism may be one of the HBOT benefits. More pressurized oxygen inhalation may increase the partial oxygen pressure in the blood and hence raise the amount of oxygen delivered to the brain (Calvert, Cahill, & Zhang, 2007).

Risperidone is a second-generation antipsychotic, used for the treatment of autism-related irritability. It is approved by the Food and Drug Administration (FDA) in 2006 for children equal to or over five years only (LeClerc & Easley, 2015).

The results of conventional treatment for (ASD) are not satisfactory so far. Therefore, the aim of this study was to evaluate whether using (HBOT) or Risperidone can decrease the core symptoms of autism by the comparison between three groups of children with (ASD) about their probable effect. This study hypothesized that using either (HBOT) or Risperidone in children with (ASD) would reduce the core symptoms of autism. We also tested which of them can give better results. The null hypothesis is that there would be no effect of (HBOT) or Risperidone on the core symptoms of

autism. We used (CARS) and (ATEC) scores to measure their effect on features of autism.

Material & Methods:

This study is a randomized controlled clinical trial. It used a blind, parallel-group design. Patients were assigned to one of three parallel groups at random, in a 1:1:1 ratio, to get the one of three regimens (HBOT), Risperidone, or placebo. Eligible participants were all children male or female aged 5 to 8 years, previously or newly diagnosed as an autism spectrum disorder (Schulz, Altman, & Moher, 2010). Exclusion criteria were 1-The presence of major medical problems as well as any other neuropsychiatric disorder that necessitates drug therapy (e.g., Bipolar disorder, psychosis). 2-Because of dosing considerations for Risperidone, weight less than 15 kg was excluded. 3-Other systemic diseases may affect the psychological and nervous state of the child.

The study was conducted in pediatric and neuropsychiatry outpatient clinics - Minia and Assiut University hospitals where all evaluated medical assessments were done, then follow up was done by both physicians and clinical pharmacists in these departments in the above-mentioned hospitals.

Diagnosis and confirmation of autism spectrum disorder (ASD) was done by using (DSM-5) (Association, 2013). Then assessment by the child's baseline score on scales, including CARS (Rellini, Tortolani, Trillo, Carbone, & Montecchi, 2004) and ATEC (Al Backer, 2016).

Patients (N=180) were divided into three groups called (G1), (G2), and (G3), and randomly assigned to receive (HBOT) (N=60), Risperidone (N=60), or placebo (N=60) in sequence.

All children were subjected to the following:

1-Written informed consent was obtained legal caregivers after a description of the study's goals and advantages for their children. The study protocol was approved by the Minia University Ethical Committee.

2-Data were collected by a structured questionnaire filled by the investigator himself.

3-History taking: Course of the disease, age, gender of the children, both mental and motor developmental history, consanguinity between parents, mother's age, smoking in

the family, past history and family history about similar condition or any other mental disorders. Also history of most important childhood diseases, and medications were taken.

4-Neuropsychiatric and systemic clinical examination

G1: received 40 one-hour sessions of (HBOT). In these sessions, the oxygen concentration is 100% and the pressure is 1.5 atmosphere absolute (in a mono or multiplace chamber). Minimum five sessions per week were required. Forty sessions were required for all children in this group within two months. G2: received Risperidone (0.25 mg daily for children under 20 kg; 0.5 mg daily for children equal to or over 20 kg) for six months. In the first two months, the dose was determined by the child's bodyweight and clinical outcome. Modifying the total daily dose in accordance to the patient's reaction and/or side effects, at the end of these six months the discontinuation phase was done by lowering the dose by 25% a week every week. G3: the control group received a matching placebo in the same manner as G2.

Outcomes: The primary endpoint concerning the efficacy of treatment in autism measured by comparison between the baseline scores of CARS and ATEC scores and after one year to identify any effect of HBOT or Risperidone and compare this effect with the control group.

Randomization and Blinding

In equal proportions the eligible participants were simply randomized. We used a computer-generated randomization list for this. This list was prepared by persons who were not involved in the study.

All study employees and participants were blinded to group assignment for this study. In this study, the first group was double-blinded to treatment allocation as all study clinicians and employees did not know the type of treatment but patients knew the type of treatment (HBOT). The second and third groups were triple blinded to treatment allocation as all study employees, clinicians and participants did not know the type of treatment (Risperidone or placebo).

Statistical Analysis

Distributions, frequencies, and percentages for each of the variables were analyzed and explored. We used Statistical Package for the Social Sciences (version 26 statistical software). The Independent t-test was used to compare two independent groups with quantitative data and parametric distribution. Paired t-test was used to compare two dependent groups with quantitative data and parametric distribution. Chi-square test was used for the comparison between two groups with qualitative data. For quantitative data, a one-way ANOVA test was used comparing the three groups, followed by a Post Hoc Tukey analysis for each pair. A p-value less than 0.05 was set as a statistical significance.

Ethical Consideration:

Minia University Ethical Committee approved all methods and procedures used in this study. This research was conducted in compliance with the World Medical Association's (WMA) code of ethics for human experimentation (Declaration of Helsinki). There was no risk to study subjects during the application of the research. All clinical research ethical principles were followed in the study. Before data collection written consent was obtained from legal caregivers of enrolled children. The right of refusing to participate and withdraw at any time from the study without any reason was assured to every participant.

Results:

Figure (1) flow diagram of the study sample.

There was withdrawn in many cases in this study as we began with 180 children with (ASD), but after the first year, we followed up 154 children because of many reasons like partial or non-compliance to treatment, cost, adverse effects, loss of efficacy of treatment, loss of contact with the child and withdraw consent.

Children were enrolled from January 2019 to July 2020.

Table (1): Baseline descriptive data of the patients							
			Group			Total	P-value
			G1 HBOT	G2 Risp.	G3 Plac.		
Age	Mean		6.53	6.47	6.68	6.56	0.52
	S.D.		1.05	1.14	0.98	1.06	
Mother age	Mean		32.05	29.43	28.02	29.83	<0.001
	S.D.		4.62	5.39	5.57	5.45	
Father age	Mean		33.47	33.75	31.68	32.97	0.12
	S.D.		4.65	6.81	6.12	5.97	
Sex	Male	Count	47	43	51	141	0.21
		%	78.3%	71.7%	85%	78.3%	
	Female	Count	13	17	9	39	
		%	21.7%	28.3%	15%	21.7%	
Labor	Normal	Count	22	25	22	69	0.81
		%	36.7%	41.7%	36.7%	38.3%	
	Cesarean	Count	38	35	38	111	
		%	63.3%	58.3%	63.3%	61.7%	
Family history	Positive	Count	10	12	10	32	0.86
		%	16.7%	20%	16.7%	17.8%	
	Negative	Count	50	48	50	148	
		%	83.3%	80%	83.3%	82.2%	
Residence	Rural	Count	8	14	12	34	0.36
		%	13.3%	23.3%	20%	18.9%	
	Urban	Count	52	46	48	146	
		%	86.7%	76.7%	80%	81.1%	
Consanguinity	Positive	Count	9	5	4	18	0.27
		%	15%	8.3%	6.7%	10%	
	Negative	Count	51	55	56	162	
		%	85%	91.7%	93.3%	90%	
Vaccination	Vaccinated	Count	60	60	60	180	<i>a</i>
		%	100%	100%	100%	100%	
Exposure to smoking	Positive	Count	21	17	19	57	0.74
		%	35%	28.3%	31.7%	31.7%	
	Negative	Count	39	43	41	123	
		%	65%	71.7%	68.3%	68.3%	

a. No statistics are computed because vaccination is a constant.
 (HBOT) = Hyperbaric oxygen therapy, Risp. = Risperidone and Plac. = placebo.

Table (1) shows baseline descriptive data of the patients. This study included 180 Egyptian children with (ASD), there were 141 males (78.33%), and 39 females (21.67%) with male to female ratio $\approx$ of 4:1, their ages ranged from 5 to 8 years. Normal labor in 69 children (38.33%). Positive family history of psychiatric illness in 32 children (17.77%) of cases. 146 children live in urban areas. Positive consanguinity between parents in 18 children (10%) of cases.

Table (2): Assessment scores of the children in the three groups before and after intervention in addition to the percent change.							
Scale		G1 (HBOT)		G2 Risperidone		G3 Placebo	
		Mean ±S.D.	P	Mean ±S.D.	P	Mean ±S.D.	P
CARS	Before	36.2±1.47	<0.001	34.85±1.9	<0.001	33.45±2.33	0.33
	After	31.63±1.73		31.75±2.02		32.94±2.71	
	%	-12.62%		-8.9%		-1.52%	
ATEC	Before	67.82±4.21	<0.001	73.31±3.72	<0.001	71.6±3.02	0.004
	After	58.24±3.83		69.52±5.27		69.77±3.11	
	%	-14.11%		-5.17%		-2.56%	
Speech	Before	14.33±1.69	<0.001	15.63±1.22	<0.001	17.49±2	0.02
	After	12.14±1.71		13.81±2.22		16.51±1.97	
	%	-15.28%		-11.64%		-5.61%	
Social	Before	15.78±1.59	0.07	16.92±1.73	0.76	14.47±1.42	0.057
	After	15.24±1.77		17.06±2.56		13.96±1.34	
	%	-3.42%		0.83%		-3.52%	
Cognition	Before	16.82±2.36	<0.001	18.71±1.09	<0.001	18.89±1.45	0.71
	After	14.96±2.07		16.71±2.19		19 ±1.53	
	%	-11.06%		-10.69%		0.58%	
Behavior	Before	20.9±2.62	<0.001	22.04±2.51	0.838	20.75±1.56	0.07
	After	15.9±2.55		21.94±1.94		20.3±1.15	
	%	-23.92%		-0.45%		-2.17%	

% Percent changes of scores.

Table (2) shows that in (G1) CARS score had significantly improved ($p < 0.001$). Also, ATEC scores had significantly improved in total, speech, cognition, and behavior subscales ($p < 0.001$) but not social subscale ($p = 0.07$). The total CARS score was significantly decreased from 36.2 ± 1.47 to 31.63 ± 1.73 . The total ATEC score was improved significantly from 67.82 ± 4.21 to 58.24 ± 3.83 . These results indicated an improvement in the (ASD) symptoms severity.

In (G2) CARS score had significantly improved ($p < 0.001$). Also, ATEC scores had significantly improved in total, speech, and cognition subscales ($p < 0.001$). The total CARS score was significantly decreased from 34.85 ± 1.9 to 31.75 ± 2.02 . The total ATEC score was significantly decreased from 73.31 ± 3.72 to 69.52 ± 5.27 . These results indicated an improvement in the (ASD) symptoms severity. Insignificant increase in social subscale ($P = 0.76$). Insignificant decreases in the behavior subscale ($P = 0.838$).

In (G3) had an insignificant decrease in CARS score from 33.45 ± 2.325 to 32.94 ± 2.713 ($P = 0.33$). Also, ATEC scores improved in total and speech subscales only with $P = 0.004$ and 0.02 sequentially. The total ATEC score was improved significantly from 71.6 ± 3.02 to 69.77 ± 3.11 ($P = 0.004$). The speech subscale significantly decreased from 17.49 ± 2 to 16.51 ± 1.97 ($P = 0.02$). Social and behavior subscales scores were insignificantly decreased with $P = 0.057$ and 0.07 sequentially. Insignificant increases in cognition subscale ($P = 0.71$).

According to the percent change in scale scores: In CARS score the best change was in G1 then G2 and finally G3. In ATEC score the best change was in G1 then G2 and finally G3. In speech subscale score the best change was in G1 then G2 and finally G3. In social subscale score the best change was in G1 then G3 and finally G2. In cognition subscale score the best change was in G1 then G2 and finally G3. In behavior subscale score the best change was in G1 then G3 and finally G2.

CARS (0) = Baseline mean of CARS score, CARS (1) = Follow-up mean of CARS score.

% Percent changes of scores.

Figure (2) shows the comparison between the groups according to CARS score.

ATEC (0) = Baseline mean of ATEC score, ATEC (1) = Follow-up mean of ATEC score.

% Percent changes of scores.

Figure (3) shows the comparison between the groups according to ATEC score.

% Percent changes of scores.

Figure (4) shows the (%) changes in Assessment scores in the three groups.

Figure (4) shows the (%) changes in Assessment scores in the three groups. In the G1 CARS and total ATEC scores, percent changes were 12.63% and -14.11% sequentially. In the G2 CARS and total ATEC scores, percent changes were -8.89% and -5.17% sequentially. In the G3 CARS and total ATEC scores, percent changes were -1.52% and -2.56% sequentially.

Table (3): Autism scores differences between the groups (follow up scores minus baseline scores) G1 (HBOT) versus G2 (Risperidone)							
Group		CARS	ATEC	Speech	Social	Cognition	Behavior
1	Mean	-4.57	-9.57	-2.18	-0.53	-1.86	-5
	SD	2.19	5.5	2.44	2	3.2	3.3
2	Mean	-3.1	-3.79	-1.83	0.13	-2	-0.1
	SD	2.72	6.33	2.47	3.18	2.3	3.37
P value		0.014	<0.001	0.5	0.17	0.78	<0.001
G 1 (HBOT) versus G3 (Placebo)							
Group		CARS	ATEC	Speech	Social	Cognition	Behavior
1	Mean	-4.57	-9.57	-2.18	-0.53	-1.86	-5
	SD	2.19	5.5	2.44	2	3.2	3.3
3	Mean	-.51	-1.83	-0.98	-0.51	0.11	-0.45
	SD	3.74	4.45	3	1.91	2.2	1.8
P value		<0.001	<0.001	0.02	0.97	<0.001	<0.001
G 2 (Risperidone) versus G3 (Placebo)							
Group		CARS	ATEC	Speech	Social	Cognition	Behavior
2	Mean	-3.1	-3.79	-1.83	0.13	-2	-0.1
	SD	2.72	6.33	2.47	3.18	2.3	3.37
3	Mean	-0.51	-1.83	-0.98	-0.51	0.11	-0.45
	SD	3.74	4.45	3	1.91	2.2	1.8
P value		<0.001	0.07	0.1	0.18	<0.001	0.53

Table (3) shows that G1 showed a significant difference with G2 (follow up scores minus baseline scores) in CARS, total ATEC, and behavior subscale with $P = 0.014$, <0.001 , <0.001 sequentially.

G1 showed a significant difference with G3 in (follow up scores minus baseline scores) in CARS, total ATEC, speech subscale, cognition subscale and behavior subscale with $P = <0.001, <0.001, 0.02, <0.001, <0.001$ sequentially.

G2 showed a significant difference with G3 in (follow-up scores minus baseline scores) in CARS and cognition subscale with $P = <0.001, <0.001$ sequentially.

Discussion:

Because the intervention was designed for both males and females, variable subtypes of (ASD), and at various severity levels, the results show that all of the children with autism would benefit from using any of the presented treatments noting the difference in results between using (HBOT) or Risperidone.

Expert investigations and sufficient and well-controlled clinical examinations comprise the study evidence (specialist physicians and clinical pharmacists). To determine the effectiveness of the treatment in this study, we distinguished the effect of the drug from the placebo effect, also avoidance of biased observation was done by randomization and blinding in patient enrollment, Also, there was no extensive drop-out of the trial patients and group numbers are identical at the beginning of the study and relatively close at the end of the study. The number of participants in this study was relatively sufficient for the clinical trial and withdrawal from the study was in a small percentage. The measurement of adherence to treatment was done by self-report, clinician estimates, pill counts, and clinic attendance.

With regard to gender, Table (1) demonstrated that there is an association between the prevalence of this disorder and sex. most of the children in this study were male (about 80%) with a male to female ratio $\approx$ of 4:1. This ratio displayed in the table is similar to the international reports (Kim et al., 2011; Zachor & Itzhak, 2010).

About 81.1% of the studied sample are living in urban cities with 18.9% are living in rural ones. The role of education and high culture level may contribute to early detection of this disorder and thus searching for a treatment that results in improvement of the case and achieving a better life. This notification was supported by several studies (El-Baz, Ismael, & El-Din, 2011).

Patients with autism exposed to father smoking represent 31.7%. This observation suggested that father smoking may have no clear impact on the presence of this

disorder. This observation was in agreement with that obtained by Gardener H. et al (Gardener, Spiegelman, & Buka, 2009).

In this study, the best change in CARS score was in G1 then G2, and finally G3, In ATEC score the best change was in G1 then G2, and finally G3.

In agreement with these findings, Starkstein et al. examined 30 people with autism vs 14 healthy controls. Cerebrovascular Hypoperfusion, or reduced blood flow to the thalamus, was seen in the autistic group and was found to be substantially connected with repetitive behaviors and abnormal sensory interests as determined by Single Photon Emission Computerized Tomography (SPECT) (Starkstein et al., 2000).

It can be that (HBOT) has the potential to increase cerebral perfusion in autism spectrum disorders and cerebral perfusion changes in children with autism after (HBOT). Several cases report improvement in their cerebral perfusion, and this measured before and after treatment by (SPECT) scans, by using hyperbaric oxygen therapy at 1.3 atm/24 percent oxygen, a child with autism received an hour of hyperbaric oxygen therapy daily for 10 days (Heuser, Heuser, Rodeland, Aguilera, & Uszler, 2002) and two children with autism received 40–80 treatment sessions (D. Rossignol, 2008).

A clinical trial was done on twenty children with (ASD) who received at least 20 (HBOT) sessions at pressure 1.5 ATA with one hundred percent oxygen concentration each for 1–1.5 hour. Magnetic resonance imaging perfusion of the brain was done before and after at least twenty hyperbaric oxygen therapy sessions only for six cases. The result was a significant improvement within the regional cerebral blood flow (RCBF)/substantia alba ratio post hyperbaric oxygen therapy in several brain areas in comparison to pre hyperbaric oxygen therapy. Also, there was an improvement in sociability, communication, cognitive awareness, CARS after hyperbaric oxygen therapy with significant P value (< 0.001) (El-baz, Elhossiny, Azeem, & Girgis, 2014).

The effects of hyperbaric oxygen therapy on inflammatory biomarkers in children with autism have been studied in two trials (Bent, Bertoglio, Ashwood, Nemeth, & Hendren, 2012; D. A. Rossignol, Rossignol, James, Melnyk, & Mumper, 2007). The first one consists of, twelve children who received (HBOT) at 1.3 atm/twenty-four percent oxygen, and six children received hyperbaric oxygen therapy at 1.5 atm/one hundred percent oxygen. Then inflammatory markers were measured pre and post forty sessions

of (HBOT) (D. A. Rossignol et al., 2007). There were decreases in C-reactive protein (CRP), which is a general inflammatory marker ($p = 0.021$). The biggest decline was seen in children who had the highest (CRP).

In the other study, cytokine plasma level were measured pre and post eighty sessions of (HBOT) delivered at 1.5 atm/ one hundred percent oxygen over a twenty weeks in ten children with autism (Bent et al., 2012). Improvements in the behavior were observed, However, no significant difference in cytokines were seen during the trial. Although the investigators reported at the beginning of the study that none of the children had elevated cytokine levels, it was less probable that a major change would be noticed. Furthermore, since abnormalities in cerebrospinal fluid (CSF) cytokines have been identified in certain children with autism, the authors speculated that CSF cytokines may had changed.

A systematic review identified only one small randomized clinical trial on sixty children from three to nine years. There were no improvements in autism symptoms in this study. The incidence of ear barotrauma was one of the negative outcomes. (Xiong, Chen, Luo, & Mu, 2016).

One study aimed to investigate the effects, and side effects of olanzapine, risperidone and aripiprazole on (ASD) patients that had been initiated treatment with the three drugs for a minimum of eight weeks. The three drugs significantly decreased the ABC subscales scores in 8 weeks. A decrease in irritability, hyperactivity, social withdrawal, stereotypy, and inappropriate speech. Also an increased duration of sleep, but increase in the weight was the most common side effect of all antipsychotics. Weight gain was more frequent with olanzapine than with the two other drugs (Hesapcioglu, Ceylan, Kasak, & Sen, 2020).

Another study on forty-two children and adolescents were enrolled in a twenty-four weeks' observational trial. During follow-up, concentrations of the drug in plasma, adverse effects, and efficacy were assessed. The results were increased risperidone concentrations predicted increased body mass index (BMI) during follow-up ($P < .001$), more sedation ($P < .05$), and increased efficiency as assessed by Aberrant Behavior Checklist (ABC) irritability score ($P < .01$)(Kloosterboer et al., 2020).

A case series on eighteen children with autism began treatment by risperidone or aripiprazole. The results were all children presented improvement in their core

symptoms. In forty-four percent of the cases were observed a significant improvement, and complete resolution was observed in fifty-six percent of the cases. The assessment was done by Childhood Autism Rating Scale 2-Standard Test and the Clinical Global Impression scales (Alsayouf et al., 2020).

Limitations of the study: Access to targeted children, the timing of the study, financial resources for (HBOT), and the preponderance of male patients (78.33%) are limitations of this study.

Conclusion:

There was a good improvement in patients treated with (HBOT) and Risperidone and we concluded that hyperbaric oxygen therapy has a better response than Risperidone in decreasing the core symptoms of autism. There are no serious side effects of using this type of treatment. The onset of autism treatment results requires a certain period to appear. More studies are needed to strengthen this hypothesis and may also investigate the benefit of a combination of the two therapies.

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Conflict of interest:

None.

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