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Physiological Bases of Electric Stimulation as a New Approach to Glaucoma IOP Control

Luis Nino-de-Rivera, Diego Cervera and Paola Castillo-Juarez

Abstract

This Chapter focuses in the electrophysiological bases to support Trans Palpebral Electrical Stimulation TPES as a new alternative to control Intraocular Pressure IOP. Primary open Angle Glaucoma POAG is described in our approach as a dysfunction of the membrane potential of TM cells due to the dysfunction of the Maxi potassium depended Calcium Channels $BKCa_{2+}$ of the Trabecular Mesh TM. We review through the paper the main contributions about Trabecular mesh dysfunction related with Voltage dependent ionic channels. We also present in this paper new results in controlling intra ocular pressure IOP during one year of trans palpebral Electric stimulation in patients with Primary open-angle glaucoma (POAG).

Keywords: Glaucoma, Trans Palpebral Electrical Stimulation TPES, IOP

1. Introduction

Glaucoma is the first cause of blindness all over the world [1]. The main risk of this disease is an increase in intraocular pressure (IOP); this is due to the dysfunction of the trabecular mesh that does not let ocular drainage flux properly [2]. Most POAG treatments go to lower IOP decreasing the production of the aqueous humor (AH), however they do not go to the origin of the problem: the dysfunction of the trabecular mesh to control aqueous (AH) flux system [3–6]. We show in **Figure 1** an approach of the IOP regulation mechanism, regulated by the flux that goes among TM cells. Cells have the capacity to grow or decrease their volumes adaptively, regulating the AH to go out. Consider the dysfunction of the conventional drainage of the TM cells if they lose the capacity to regulate their volume avoiding the right passage of intraocular flux among them. The Trabecular mash cells work like inside a tube, they let the aqueous humor pass amid the cells, then the AH goes from top to bottom passing trough the free spaces the cells liberate. The control of the AH flux is like balls in a tube varying their volume. The function of the TM cells is to regulate the passage of the humor through the free spaces depending on its volume. The highest cell volume, the lower flux to circulate among the balls, then higher pressure over inside the ocular globe surface. Ionic channels are device like swivels that allow to liberate pressure. Once the ionic channels fails closing abnormally, TM Cells do not control the AH passage among the “cell-ball”. Inside the ball there is a continuous production of water and K^+ ions, if no liberation way of them, the cell grows in volume, increasing the pressure over the eye globe wall.

Figure 1.
The scheme shows how aqueous humor AH, shown in the scheme like arrows, pass thought out TM cells. TM cells regulates the AH flux varying their volume in order to control the amount of AH flux.

The unfixed regulation on the opened-closed processes of depended voltage ionic channels ($BKCa_{2+}$) affects the volume regulation of the cell. This inflammatory process regulation is related with Voltage-dependent $BKCa_{2+}$ channels VDCH which deregulation plays a central role in POAG illness [7–10]. $BKCa_{2+}$ ionic channels works like a hinge closing (holly or partially) to regulate the positive charge inside cell due to an increase of Ca^{+} inside the TM cells. $BKCa_{2+}$ works as a control system to regulate the positive charge ions inside the cell and then regulating the elasticity, contractility and then the volume of the cell. $BKCa_{2+}$ regulates the positive charge inside the cell regulating the cell membrane potential.

2. Glaucoma and TM ion channel dysfunction

Stumpff and Soto [8, 9] reported that some tyrosine kinase in the trabecular mesh can capture the regulation function of the $BKCa_{2+}$ channels, avoiding its volume regulation. Some Kinases avoids VDCH to act as a hinge regulating the volume of the cell capturing the Voltage sensor of the $BKCa_{2+}$ sensor. The deregulation of the volume of the cell is, due to a dysfunction of some ionic channels is a typical channelopathy, it goes to an uncontrolled typical inflammatory process. TM cell dysfunction goes cell to its highest volume, losing the ability on going back them to a lower volume. This lost of flexibility shows: a) The incapacity of the $BKCa_{2+}$ channel to open and consequently to liberate H_2O plus K^{+} , as required.

B) The deregulation of the membrane potential V_m , is due to an excess of positive charge (+ch) inside the cytosol, not properly liberated by the BKC_a+ channels, this is equivalent to keep closed the VDCH channel by keeping the membrane potential in the depolarization region avoiding the liberation of (+ch) and water. The right regulation of charges in the cell and its signaling (+ch) depends on the right V_m swing performance. A key point on this is how the V_m properly swings. We illustrate in **Figure 2a** the membrane potential V_m . The depolarization region shows the +charge (+ch) growing inside the cell, this region goes from the equilibrium or rest voltage V_r to its highest positive value. The repolarization region occurs when the channel opens liberating K^+ . It goes from the highest V_m positive voltage (the highest positive charge allowed inside the cell), to the rest voltage V_r . This new approach to understand glaucoma let us to think in new solutions to force the cell membrane to get the right potential by an external voltage.

Moreover, Stumpff et al. showed [8] that tyrosine kinase inhibitors, like the Genestein with different dozes, reactivate the maxi-channels $BKCa2+$ sequestered by the tyrosine kinases. This relevant founding let understanding that repolarization

Figure 2.
We illustrate in **Figure 2a** the typical TM cell membrane potential V_m , and its depolarization, repolarization and hyperpolarization regions. We notice that the regulation of ions flux through the cells (K , Na , etc.) depends strongly on the right V_m levels. The dysfunction of the V_m potential keeping TM cells in the depolarization region, spouses high levels of water inside the cell due to lower BKC_a currents, this increases TM cell volume avoiding the output of the AH flux through TM cells. Then this V_m potential dysfunction increases intraocular pressure. **Figure 2b** shows V-I relationship between glaucoma GTM and healthy TM cells. **Figure 2c** shows the set of $BKCa2+$ ionic currents measured by Grant after the application of tyrosine kinase inhibitors

and hyperpolarization region in TM cells play a central role in TM inflammatory dysfunction. We have concluded from this finding that relaxation of the trabecular meshwork is related with a dysfunction of the membrane voltage. Consequently, we can assure that POAG is a membrane potential V_m illness due to the dysfunction of BKCa²⁺ channels that affects the membrane potential V_m , keeping the cell membrane at the repolarization region for long time avoiding relaxing the TM cells.

A relevant result showed by Stuff [8] was that the re-activation of BKCa²⁺ channels resulted with the application of an agonist of tyrosine kinase, showing that ionic current of BKCa²⁺ are rectifier channels type [8–10]. Stumpff results let us understand that inhibitors of tyrosine kinase recovers the ionic current flow through the channel, and that as a consequence of that V_m goes to a normal status. We infer that the inverse is feasible too, recovering the BKCa⁺ open and close functionality by the right membrane potential. This can be done from the application of an exogenous membrane V_m voltage, if it is properly selected. This principle is widely used in Electrophysiology where patch clamp techniques apply a set DC voltage from positive to negative values to stimulate the cell membrane to measure the answer of the ionic currents in the cell varying the membrane voltage. Based on the above considerations we formulate the hypothesis that to recover the functionality of the BKCa⁺ maxi-channel can be achieved by a right exogenous membrane potential V_m . We proposed as our main working hypothesis that this can be achieved through an specific exogenous voltage applied to the tissue. A properly chosen exogenous voltage to the tissue will provide the right repolarization, depolarization and hyperpolarization voltages over the membrane of the TM cells in order to recover its flexibility.

Another important result reported by Grant, et al., [10] shows that the V-I relationship between glaucoma GTM and healthy TM cells is clearly different in Electrophysiology analysis, as shown in **Figure 2b**. They study the performance of BKCa⁺ maxi-channel Ionic channels expressed in GTM and healthy TM cells, founding important differences among its current measured from a set of DC values. Reported results show important differences in the V-I relationship between GTM and TM for each specific ionic currents studied, consequently the performance regulation of normal TM is different from glaucoma GTM cells. Those differences founded in the electrophysiological properties of both groups let us to understand that POAG glaucoma illness is a dysfunction of the membrane potential of the GTM cells [9–12]. **Figure 2c** shows that for healthy TM cells BKCa⁺ is a rectifier current in the depolarization zone, however GTM shows a depressed BKCa⁺ current for positive DC voltages.

Daniel A. Ryskamp, et al. Published in 2016 an interesting paper about how TRPV4 regulates calcium homeostasis in mammalian eye. A. Ryskamp, et al. [12] shows that TRPV4 inhibition lowers IOP in GTM cells. They show too that an agonist of TRPV4 is a potential protector of the optic nerve. Due to TRPV4 are transient voltage dependent channels they could be manipulated, by exogenous voltages. TPES has demonstrated its beneficial effects in Retinosis Pigmentaria and IOP control properties [13–18], however new research is required to evaluate its protecting effects.

Figure 2b shows V-I relationship between glaucoma GTM and healthy TM cells. The voltage current V-I for healthy TM and GTM is clearly different. Healthy TM cells V-I curve shown in black squares is a typical rectifier function. However GTM in white squares vary its rest potential and decreases the V-I slope cells compared with healthy TM cells, this strongly modifies V_m . membrane potential in GTM cells. This V_m dysfunction keeps GTM cells in depolarization region, then avoiding the right control of the TM cells volume.

Figure 2c shows the set of BKCa²⁺ ionic currents measured by Grant after the application of tyrosine kinase inhibitors that goes back TM cells to normal V_m membrane potential. Signals in **Figure 2c** fits more alike rectifier function depending on the tyrosine kinase inhibitors dosage.

Figure 3.
 Our stimulator system can reproduce any ionic current from a mathematical model or from any real biological ionic currents with 99.9% accuracy. Typical calcium-activated chloride current ($ICl(Ca)$) and calcium-activated potassium current ($IK(Ca)$) like Usui's model [11], and as many others ionic currents must be available in dedicated TPES stimulators.

2.1 Micro stimulation procedure

The set of signals that fits more alike BKCa2+ after the application of tyrosine kinase inhibitors is shown in **Figure 2c** according with Stuff et al reports [8]. Consequently an exogenous voltage can be used as an adjuvant treatment to control IOP in patients with POAG. The waveform shown in **Figure 2c** fits more accurately with BKCa2+ ionic cells in TMC, however an enormous set of different signals conform the ionic currents environment in any cell. We show in **Figure 3** a survey of the ionic currents that could be required to stimulate specific VDCH. A deeper understanding about the effects of TES in GTM cells is required to adjust the optimum parameters in TES, among others, waveform, frequency, amplitude and DC offset. TES requires special adjustment to fix the repolarization, depolarization and hyperpolarization zone for each target.

Our TES device reproduces electric profiles analogous to those reported by Stumpff [8, 9] in the BKCa2+ after the application of tyrosine kinase inhibitors, as well as many other ionic signals like Usui's mode [11]. The flexibility to generate any desired action potential opens fresh opportunities to brand new experiments in TPES. Our stimulator system can reproduce any real biological ionic currents with 99.9% accuracy. These new approaches to stimulate TMCs open brand new opportunities to understand more precisely the neuro-regulation effects of electrical stimulation in glaucoma and other degenerative illness.

2.2 Transpalpebral electrical microstimulation

TPES is not an invasive procedure as seen in **Figure 4**. This treatment modality is advantageous to conventional medical treatment consisting of hypotensive ocular drugs, which are associated with local and possible systemic side effects. This procedure induces no changes on the ocular surface in opposition to ocular surface changes induced by the topical medication and the preservatives. No inflammatory phenomenon is generated; moreover, the immunological apparatus remains unaltered.

Figure 4.

Shows the Transpalpebral electrical stimulation procedure on a POAG patient. TPES is applied over the eyelid by an electrode array and through an electronic system with control of wave-forms and its parameters, like: Amplitude, frequency, DC offset and stimulation time.

Electrical micro stimulation focuses to the true cause of ocular hypertension, that is, the treatment of the dysfunctional trabeculum, while the rest of the therapy is focused on reducing the production of the aqueous humor or the exit of it through the unconventional route. In addition, it is important to emphasize the fact that this approach is highly cost efficient, when compared to anti-glaucoma therapy. We report here, a one year follow-up clinical study with patients with POAG.

2.3 A non-conventional signal generator

A non-conventional TPES system to stimulate POAG patients requires the developed of friendly electronic systems with strict biomedical standards to assure no damage to the eye, keeping very low current inside the ocular globe and no temperature effects over the eyelid. It requires too a software interface that let call any one of pre programmed ionic currents. A graphical user interface allows in our system to choose among sixteen different stimulation signals. The Hardware-software based waveform generator can produce practically any signals, each one characterized by its shape, amplitude, and frequency. Waveform shape is acquired from a set of discrete $X(n)$ waveforms previously defined, the reader can find important discussion about ionic currents parameters and waveforms in [19–22]. Waveforms can be acquired also graphically by a virtual draw tool or even by a mathematical model, Usui in [11] shows an interesting model to display waveforms from the retina complex network, however we require more research to find the optimum waveform parameters to apply in clinic. The selected TES stimulator signals are transmitted using a simple USB port connected to microcontroller that generates the stimulation signal required. The stimulation system designed in our group is able to recreate any complex waveform as the ones reported in electrophysiology cell. This scheme can be used to obtain a class of multichannel stimulator that can be the core part of several biomedical applications. The desired action potential is selected by a friendly software showed in **Figure 5**.

A set of sixteen predefined waveforms, as shown in **Figure 3** let the physician select the signal and the parameters required, see **Figure 5**. The selected signal is programed into a microcontroller's memory, allowing converting the digital data into an analogue output signal. Then the output of an electronic system can be connected to the microelectrodes array to stimulate the cornea, as shown in **Figure 4**.

Figure 5.
Shows TPES interface system that let the physician to select the waveform among a set of sixteen pre defined V_m potentials to apply in TPES. The interface let define all parameters in TPES like: stimulation time, frequency, DC offset and voltage stimulation range.

3. Clinical founding

A year Follow-up of patients without surgical treatment (with and without topical treatment) is reported in this section. TPES is applied over the eyelid by an electrode array and through an electronic system with control of wave-forms and its parameters, like: amplitude, frequency, DC offset, stimulation time.

We report in this paper a one year TES study In 78 eyes from 46 patients (pilot group), 35 eyes of which 34.2% (n = 12) were specifically applied micro-stimulation and 65.8% (n = 23) applied micro-stimulation and topical treatment. The mean age was 65.67 years (44–80 years), 66.6% (n = 12) were women and 33.3% (n = 6) men. The mean glaucoma diagnosis time for our sample was 82.06 months $\pm$ 58.6 (Tables 1 and 2).

3.1 Results

During the follow-up of the patients, the IOP decrease was recorded for one year, baseline IOP = 18.45 mmHg $\pm$ 2.45, one month later IOP = 15.85 mmHg $\pm$ 3.03, 3 months later IOP = 13.88 mmHg $\pm$ 1.90, after 6 months 14.65 mmHg $\pm$ 2.20 and

Variable	Man	Women	Total
Eyes (n)	12	23	35
Gender (%)	33.3	66.6	100
Mean Age $\pm$ DS (years)	68.33 $\pm$ 6.532	64.33 $\pm$ 9.717	65.8 $\pm$ 8.798
Rank (min,max)	63,80	44,77	44,80

Table 1.
Demographic data of the patients in the pilot group, one year follow-up.

Follow-up (months)	95% confidence interval			
	Mean	Inferior	Superior	Sig. (bilateral)
1	2.60000	1.78284	3.41716	< 0.001
3	4.57143	3.68859	5.45426	< 0.001
6	3.80000	2.82555	4.77445	< 0.001
12	3.80000	2.64317	4.95683	< 0.001

Table 2.
Intraocular pressure reduction mean in the pilot group, after one-year follow-up.

Figure 6.
Behavior of intraocular pressure in the one-year follow-up of the pilot group.

Figure 7.
Box diagram of intraocular pressure behavior at one-year follow-up of the group of patients with GPAA.

finally after one year IOP = 14.65 mmHg $\pm$ 3.09. Total decrease of 20.59% of the IOP after one year.

Total sample included 74 eyes of 40 patients, of which: 82.5% (n = 33) patients diagnosed with primary open-angle glaucoma, 2.5% (n = 1) with neovascular glaucoma, 2.5% (n = 1) with ocular hypertension and 12.5% (n = 5) with congenital glaucoma. The average age was 59.03 years (12–81 years), 57.5% (n = 23) were women and 42.5% (n = 17) men. The mean glaucoma diagnosis time for our sample was 125.43 months $\pm$ 159.52 (**Figures 6–11**).

Reduction of intraocular pressure in patients with GPAA, dividing the sample into 3 groups. From the previous sample, patients with GPAA were selected. 65 eyes of 34 patients were included. The mean age was 62.53 years (35–81 years), 58.82%

Figure 8.
Intraocular pressure behavior at one-year follow-up in the group of patients with GPAA, GN, GC and HTO.

Figure 9.
Intraocular pressure behavior at one-year follow-up of group 1 [microstimulation only].

Figure 10.
Intraocular pressure behavior at one-year follow-up of group 2 [microstimulation + maximum tolerated drug treatment].

Figure 11.
Intraocular pressure behavior in one-year follow-up of group 2 [microstimulation + maximum tolerated pharmacological treatment + surgical treatment].

(n = 20) were women and 41.17% (n = 14) men. The mean time of diagnosis of glaucoma for our sample was 88.94 months $\pm$ 69,289 (**Tables 3–5**).

The sample was divided into 3 groups according to the treatment received. Group 1 [microstimulation only] 17.64% (n = 6), group 2 [microstimulation + maximum tolerated drug treatment] 41.18% (n = 14), group 3 [microstimulation + pharmacological + surgical] 41.18% (n = 14). The average number of sessions per week was 1.71. In the total sample, the baseline IOP was 18.09 mmHg $\pm$ 3.97, 15.33 mmHg $\pm$ 3.37 a month, 13.86 mmHg $\pm$ 2.51 at 3 months, 14.21 mmHg $\pm$ 2.55, and 14.27 mmHg $\pm$ 2.91 at 6 months. With a decrease in IOP per year of 21.11% (**Table 6**).

Group 1 [microstimulation only] the baseline IOP was 18.83 mmHg $\pm$ 1.64, at a month of 16.16 mmHg $\pm$ 2.85, at 3 months 13.83 mmHg $\pm$ 1.46, at 6 months 15.00 mmHg $\pm$ 2.55 and at 13.41 mmHg $\pm$ 1.56. IOP decrease per year of 28.78% (**Table 7**).

Variable	Man	Women	Total
Eyes (n)	31	43	74
Gender (%)	41.9	58.1	100
Mean Age ± DS (years)	57.59 ± 17.256	60.09 ± 15.687	59.03 ± 16.203
Rank (min,max)	12,80	17,81	12,81

Table 3.
 Demographic data of patients with GPAA, GN, GC and HTO.

Follow-up (months)	95% confidence interval			Sig. (bilateral)
	Mean	Inferior	Superior	
1	2.72973	2.21911	3.24035	< 0.001
3	4.22973	3.58742	4.87204	< 0.001
6	3.91892	3.22044	4.61740	< 0.001
12	3.98649	3.20199	4.77098	< 0.001

Table 4.
 Mean intraocular pressure decrease in the one-year follow-up of the group with GPAA, GN, GC and HTO.

Variable	Man	Women	Total
Eyes (n)	27	38	65
Gender (%)	41.53	58.46	100
Mean Age ± DS (years)	60.64 ± 13.449	63.85 ± 11.018	62.53 ± 11.988
Rank (min,max)	36,80	35,81	35,81

Table 5.
 Demographic date of the group of patients with GPAA.

Follow-up (months)	95% confidence interval			Sig. (bilateral)
	Mean	Inferior	Superior	
1	2.75385	2.17932	3.32837	< 0.001
3	4.23077	3.53436	4.92718	< 0.001
6	3.87692	3.14329	4.61055	< 0.001
12	3.81538	2.98672	4.64405	< 0.001

Table 6.
 Average decrease in intraocular pressure in the one-year follow up of the group with GPAA.

Group 1 [microstimulation only] the baseline IOP was 18.83 mmHg ± 1.64, at a month of 16.16 mmHg ± 2.85, at 3 months 13.83 mmHg ± 1.46, at 6 months 15.00 mmHg ± 2.55 and at 13.41 mmHg ± 1.56. IOP decrease per year of 28.78% (**Table 8**).

Group 2 [microstimulation + maximum pharmacological treatment tolerated] the baseline IOP was 17.70 mmHg ± 2.64, a month of 14.81 mmHg ± 3.07, at 3 months 13.29 mmHg ± 1.95, at 6 months 13.74 mmHg ± 1.99 and at 14.48 mmHg ± 3.50. With a decrease in IOP per year of 18.19%. It should be noted that 4 of the 14 patients were able to suspend 1 to 3 medications during the follow-up year.

Follow-up (months)	95% confidence interval			
	Mean	Inferior	Superior	Sig. (bilateral)
1	2.66667	.80274	4.53059	.009
3	5.00000	3.98630	6.01370	< 0.001
6	3.83333	1.77302	5.89365	.002
12	5.41667	4.04969	6.78364	< 0.001

Table 7.
Average decrease in intraocular pressure in the one-year follow-up of group 1 [microstimulation only].

Follow-up (months)	95% confidence interval			
	Mean	Inferior	Superior	Sig. (bilateral)
1	2.88889	2.07275	3.70503	< 0.001
3	4.40741	3.29792	5.51689	< 0.001
6	3.96296	2.93092	4.99500	< 0.001
12	3.22222	1.88147	4.56297	< 0.001

Table 8.
Mean decrease in intraocular pressure in the one-year follow-up of group 2 [microstimulation + maximum pharmacological treatment].

Follow-up (months)	95% confidence interval			
	Mean	Inferior	Superior	Sig. (bilateral)
1	2.65385	1.70527	3.60242	< 0.001
3	3.69231	2.39592	4.98869	< 0.001
6	3.80769	2.48514	5.13024	< 0.001
12	3.69231	2.23479	5.14983	< 0.001

Table 9.
Mean decrease in intraocular pressure in the one-year follow-up of group 3 [microstimulation + maximum pharmacological treatment + surgical treatment].

Group 3 [microstimulation + maximum tolerated pharmacological treatment + surgery] the baseline IOP was 18.15 mmHg ± 5.61, at a month of 15.50 mmHg ± 3.8, at 3 months 14.46 mmHg ± 3.24, at 6 months 14.34 mmHg ± 3.03 and per year 14.46 mmHg ± 2.73. With a decrease in IOP per year of 20.33%. It should be noted that 3 of the 14 patients were able to suspend 1 to 2 medications during the year of follow-up (Table 9).

4. Conclusions, future and challenges

Transpalpebral Electrical Stimulation focuses to the true cause of ocular hypertension, that is, the treatment of TM dysfunction, while the rest of the therapy is focused on reducing the production of the aqueous humor or the exit of it through the unconventional route [19, 20]. TPES is not only an alternative IOP therapy but also is a new way to face degenerative diseases, since the pathology is treated

from another vision; the dysfunction of the voltage dependent channels looking its functionalization from an electronic medication. Electric medication is not new, however is not understood at all. The physiopathology bases discussed in this paper opens new alternatives to deal other degenerative illness where dysfunction of VDCH can be identified as the cause of the illness, some of them as an inflammatory cell process.

TPES requires to study the effects of electrical stimulation in both: cells, tissues and complex structures like the eyeball. This new approach requires the development of new flexible biomedical tools to stimulate the eyeball. A new future is coming with Biochips inside the eye to electrically stimulate the cornea. New challenges technology development requires TES in both: clinical applications and in cell culture to study the effects of electric stimulation of the trabecular mesh and some new alternatives to couple electrodes with both electronic systems and eye ball tissue. New challenges faces the need to measure inside the eyeball IOP integrated with biochips to stimulate the trabecular mesh to close the challenge to measure simultaneously IOP and control it by electric stimulation. New biochips with flexible substrates like polyamide emerge as a new biocompatible material to be integrated inside the eye to build complex systems to help people with glaucoma [23].

We propose a new medication procedure through the application of waveforms that can be generated from electronic technology feasible at hand. These new alternatives to treat degenerative ocular illness face new challenges and opportunities. However there is a long way to understand more precisely the neuro-protection effects of electrical stimulation at the trabecular mesh and at the inner retina. Most of diseases derivative in vision lost are related to Open Angle Glaucoma, Retinal degenerations (RDs), Retinitis pigmentosa (RP) and Age-related macular degeneration (AMD). It seems to be that most of them are related with a dysfunction of several voltage dependent ionic channels.

Optimal TPES parameters to target specific VDCH is still a challenge. New experiments are required to evaluate the effects of firing specific inner retinal neural structures. In our opinion, we show in this paper excellent results in controlling IOP during one year TPES stimulation as shown above. This pushes to look for new solutions to degenerative ocular illness.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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