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What has changed over 10 years in neonatal therapeutic hypothermia? Part 1: Hypothermia in paediatric brain injury – a literature review

Co się zmieniło przez 10 lat w hipotermii terapeutycznej noworodka? Część 1: Hipotermia w pediatrycznym incydencie mózgowym – przegląd piśmiennictwa

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Abstract

It is estimated that brain injury, broadly understood, is the most common cause of death and severe neurological complications in the paediatric population under 18 years of age. A number of preclinical studies have demonstrated the effectiveness of moderate cooling in terms of neuroprotection. In paediatrics, mild therapeutic hypothermia is a well-established procedure in the treatment of term or near-term newborns with deep asphyxia. Since 2015, in accordance with the guidelines of the American Academy of Pediatrics, mild therapeutic hypothermia is no longer an experimental method and it is widely recognised as a factor that improves survival and long-term neurological prognosis compared to traditional treatments. Thus, it is not surprising that, based on strong preclinical data from animal studies and the acceptance of mild therapeutic hypothermia in neonatology, opportunities to extend the range of patients benefiting from it beyond neonates in the first 6 hours of life as well as its new applications beyond the neonatal period are still being sought. In adults who underwent successful resuscitation due to sudden cardiac arrest in shockable rhythms, therapeutic cooling was recommended as a treatment method in post-resuscitation management almost a decade earlier than in newborns; however, a simple extrapolation of data from the adult population to the neonate population or from adults to neonates did not prove effective. The variation in terms of mechanisms leading to cardiac arrest (i.e. respiratory cause in children vs. cardiac cause in adults) entails differences in neurohormonal modulation between these two groups, which affects the results. This paper presents aspects of the use of mild therapeutic hypothermia over the last decade and discusses the mechanisms of encephalopathy development in the paediatric population, the conditions for its effective application as well as its place in the treatment of brain injury unrelated to perinatal asphyxia.

Keywords: child, therapeutic hypothermia, brain injury

Streszczenie

Szacuje się, że szeroko rozumiany incydent mózgowy jest najczęstszą przyczyną zgonów i ciężkich powikłań neurologicznych w populacji pediatrycznej poniżej 18. roku życia. W wielu badaniach przedklinicznych wykazano skuteczność stosowania umiarkowanego chłodzenia w zakresie neuroprotekcji. W pediatrii umiarkowana hipotermia terapeutyczna znalazła swoje stałe miejsce w leczeniu noworodków donoszonych lub prawie donoszonych urodzonych w głębokiej zamartwicy. Od 2015 roku umiarkowana hipotermia terapeutyczna, zgodnie z wytycznymi Amerykańskiej Akademii Pediatrycznej, nie jest już metodą eksperymentalną i w grupie tej jest powszechnie uznawana za czynnik poprawiający przeżywalność oraz odległe rokowanie neurologiczne w porównaniu z zastosowaniem metod tradycyjnych. Nie dziwi więc fakt, że opierając się na mocnych przedklinicznych danych z badań na zwierzętach i akceptacji umiarkowanej hipotermii terapeutycznej w neonatologii, wciąż poszukuje się możliwości poszerzenia grona pacjentów odnoszących z niej korzyści poza noworodkami w pierwszych 6 godzinach życia i jej nowych zastosowań poza okresem noworodkowym. W grupie dorosłych po skutecznej resuscytacji w przebiegu nagłego zatrzymania krążenia w rytmach defibrylacyjnych chłodzenie terapeutyczne jako metoda leczenia było rekomendowane w postępowaniu poresuscytacyjnym prawie dekadę wcześniej niż u noworodków, jednak prosta ekstrapolacja danych z populacji dorosłych na populację noworodków lub z dorosłych na noworodki się nie sprawdziła.

Mechanizmy prowadzące do zatrzymania krążenia są zróżnicowane (przyczyna oddechowa u dzieci *vs* sercowa u dorosłych), dlatego modulacja neurohormonalna w tych grupach jest odmienna, co wpływa na wyniki. W niniejszym opracowaniu przedstawiono aspekty wykorzystania umiarkowanej hipotermii leczniczej w ciągu ostatniej dekady i omówiono mechanizmy rozwoju encefalopatii w populacji pediatrycznej, warunki skutecznego zastosowania tej metody oraz jej miejsce w leczeniu incydentu mózgowego niezwiązanego z zamartwicą okołoporodową noworodka.

Słowa kluczowe: dziecko, hipotermia lecznicza, incydent mózgowy

INTRODUCTION

Brain injury can be caused by a variety of factors, such as: traumatic brain injury (TBI), sudden cardiac arrest (SCA), perinatal asphyxia (PA), carbon monoxide poisoning, status epilepticus, local (brain) infection, systemic infection, and metabolic, genetic or immunological factors. The consequence of each brain injury (BI), regardless of the causative agent, is encephalopathy, which in some cases leads to death or deteriorates – chronically or, less often, permanently – individual and/or social functioning[1,2]. Many experimental and clinical data indicate a positive neuroprotective effect of low temperature in BI. Based on clinical work, mild therapeutic hypothermia (MHT) was recommended in PA-related BI by the European Resuscitation Council already in 2010. Five years later, MHT became widely accepted as the primary treatment for hypoxic-ischaemic encephalopathy (HIE) in neonates with PA[1].

MECHANISMS OF HYPOXIC-ISCHAEMIC ENCEPHALOPATHY IN NEWBORNS

The mechanisms underlying the development of hypoxic-ischaemic lesions in the paediatric population, particularly in neonates of ≥35+0 gestational age (GA), have been well known and described. It should be emphasised that oxidative stress, which is one of the phase II mechanisms, is of particular importance in neonatology and leads to the development of a now somewhat forgotten disease – namely, free radical disease (FRD), as defined by Saugstad[3]. In terms of the central nervous system, FRD manifests itself in premature infants as periventricular leukomalacia, and in newborns (hereinafter, unless stated otherwise, a newborn/neonate will be defined as a child born ≥35+0 GA) – as changes in the basal ganglia and intraventricular haemorrhage[4,5]. The aetiology of FRD involves physiologically high oxygen consumption during postnatal adaptation and high content of unsaturated fatty acids in the newborn's brain with not fully developed antioxidant systems. The excess of oxygen free radicals (OFR) formed in phase II with overlapping hyperoxia, as a result of e.g. improperly conducted resuscitation, favours the intensification of both early and late irreversible changes, particularly in premature infants[3,5]. The optimum time of therapeutic intervention is phase I. The latent phase, which the patient enters after blood circulation is restored, is the stage of recovery – in some cases, unfortunately, only apparent. The duration of this period varies, sometimes up to 9–12 hours after the hypoxic event; the stronger the causative stimulus, the shorter the latent phase lasts. If the apparent recovery group is not identified and treatment is not started before the critical point of phase I, severe HIE symptoms will appear or the patient will die (phase II)[4,6] (Fig. 1).

It is also quite significant that in the paediatric population, the primary stimulus is almost always hypoxia, and blood flow disorders are only secondary to it[4,7]. This physiological difference modulates the child's neurohormonal response, making it difficult to simply extrapolate the results of studies conducted in adults[8].

MILD THERAPEUTIC HYPOTHERMIA IN NEWBORNS <36+0 GA

In experimental animal studies, cooling has been shown to significantly reduce the loss of neurons in the parasagittal cortex, the basal ganglia (striatum), the CA1 region of the hippocampus and the thalamus, as well as the loss of immature oligodendrocytes in the periventricular white matter[7,9,10]. In the brain of an individual subjected to cooling, the production of ORF and glutathione as well as oxygen demand are reduced[6]. Brain metabolism slows down, cerebral blood volume (CBV) decreases, intracranial pressure (ICP) also decreases, and cerebral perfusion pressure (CPP) increases[11,12]. Hypothermia shows an inhibitory effect on phase II mechanisms: it delays and minimises the risk of massive apoptosis of nerve cells and cellular inflammatory processes caused by primary hypoxia and secondary ischaemia[4,6,8]. Similar studies were also conducted on immature sheep foetuses, confirming the neuroprotective effect of cooling[10].

In the early research reports (TOBY, CoolCap, NICHD) evaluating the long-term effectiveness and safety of MHT, newborns of ≥36+0 GA were qualified for treatment with this method[13]. Younger (but ≥35+0 GA) children were only qualified in one randomised study – ICE, conducted between 2001 and 2007. In this group, MHT has been proven to be effective and carry a comparable risk as in children a week older[14].

Over the last decade, newborns who would not have met the criteria for hypothermia treatment before 2010 have been qualified increasingly more often. Therefore, speculations about the possibility of further lowering the limit of

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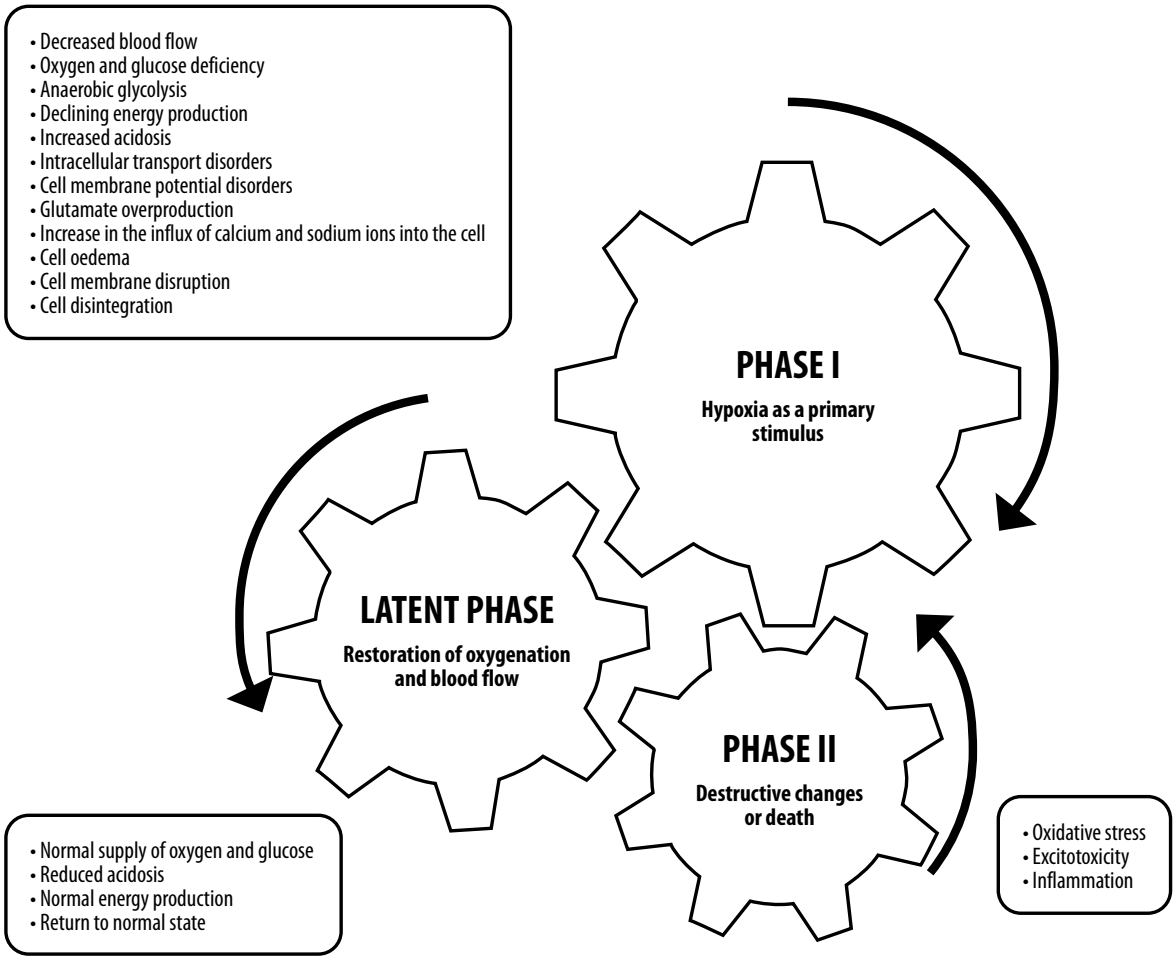

PHASE I – changes take place up to 6 hours after the occurrence of the stimulus, they may be reversible; **PHASE II** – lasts from 6 to 48 hours after the occurrence of the stimulus, leads to irreversible changes in the form of cell death in an immediate mechanism (death due to disintegration and necrosis) and/or a delayed mechanism, related to the degeneration of the structure – i.e. programmed cell death (apoptosis); **LATENT PHASE** – begins when normal blood flow is restored, the stronger the decompensating factor, the shorter this phase lasts[6,9,10].

Fig. 1. Evolution of changes in HIE (original work)

GA where MHT can be safely and effectively used should not be surprising[14].

In 2017, a centre which had previously participated in the ICE program published the results of studies from 2007 to 2015 based on a retrospective assessment of medical records of premature infants born at 34–35 GA, in which the control group consisted of term newborns (≥37+0 GA). Short-term (up to 10 days of age) results obtained in magnetic resonance imaging (MRI) were assessed. Compared to the control group, the premature infants included in the study had a higher risk of complications (90% vs. 81.3%; $p = 0.30$) and the need for early termination of MHT (19.4% vs. 0.0%; $p = 0.009$). All deaths during MHT were recorded in the group of premature infants (12.9% vs. 0.0%; $p = 0.04$), and the MRI showed a higher incidence of lesions in premature infants than in term infants (80.6% vs. 59.4%; $p = 0.07$) but with no difference in their severity. It also should be pointed out that the most common cause of BI in the premature infants was placental abruption, which in itself could have deteriorated the results[3].

A randomised clinical trial (ClinicalTrials.gov: NCT01793129) involving pre-term infants between 32 and 35 GA has been conducted since 2015. In order to avoid whole-body cooling while maintaining a neuroprotective effect on the brain, selective cooling of the head has been used – the so-called cool-cap. In 2015, Walsh et al. published a preliminary report on 4 premature infants. Its findings are not encouraging. Despite the use of cool-cap, systemic hypothermia was not prevented and none of the subjects had a positive therapeutic effect – the children died or showed severe neurological disability. In their conclusion, the authors warn against the use of MHT <34 GA, except in strictly controlled research reports[15].

Thus, in 2022, MHT remains the treatment of choice for infants of ≥35+0 GA born with deep PA. With caution, this method may also be considered in neonates between 34 and 35 GA, provided that the expected benefits outweigh the expected risks of death and complications. Despite the positive results of studies on animal models, it is not recommended to use or consider MHT in human newborns of

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<34+0 GA due to the high risk of exacerbating problems associated with premature birth[15–17].

MHT THERAPEUTIC WINDOW

In the adult population, where the primary stimulus tends to be ischaemia caused by a cardiogenic agent, the time to implement cooling, i.e. the therapeutic window, is short, lasting only 4 hours[18]. This period is longer for the newborn population, with 6 hours being the cut-off point[1,16].
A newborn is physiologically able to survive longer periods of hypoxia than an adult. This is due to evolutionary mechanisms, namely: centralisation of circulation, gasping triggered automatically by the spinal centres, and high glycogen content in myocardial cells. They protect vital organs – the brain and the heart – allowing to maintain blood circulation and blood pressure in conditions of significantly disturbed biochemical balance, even up to 20 minutes from exposure to the triggering stimulus, thanks to which the accumulation of anaerobic glycolysis metabolites in the initial period is slower than in adults in the same state[4,18].
If that is the case, the question arises whether hypothermia in children could also be effective when started later than 6 hours after birth. The results of a study by Li et al. (2009) on the use of MHT up to 10 hours after birth were encouraging. The authors noted that the results at 18 months of age regarding the number of deaths and cases of severe neurological damage were uniform regardless of whether MHT was started within 6 hours after birth or later (6–10 hours)[19].
In 2017, Laptook et al. published the results of an 8-year randomised multi-centre clinical trial on the effect of MHT applied between 6 and 24 hours after the hypoxic event. The study confirmed, with a 64% probability, a 2% reduction in deaths and cases of severe neurological damage at 18 months of age in newborns treated outside the therapeutic window[2]. In a 2014 study by TOBY, in which cooling was implemented ≤6 hours after the hypoxic event, significantly better results were obtained. It was estimated that the mortality rate in the group of children treated with standard methods compared to the group of newborns subjected to MHT was comparable (approximately 30%), but the number of children surviving with a good neurological outcome was larger [28% vs. 45%; relative risk (RR) 1.60; 95% confidence interval (CI): 1.15–2.22] and the risk of long-term complications such as cerebral palsy was significantly reduced (36% in children not treated with MHT vs. 21% in children treated with MHT)[16].

MHT IN PAEDIATRIC TRAUMATIC BRAIN INJURY

Preliminary studies (2003) on the use of MHT in the range of 32–33°C for 24 hours in the management of severe TBI did not confirm the effectiveness of this method in adults or children. Nevertheless, with a prolonged period of cooling (48–72 h), the results obtained in the paediatric population seemed encouraging, which prompted further research as part of the COOL KIDS programme[20].
The 2012 TBI treatment guidelines recommended avoiding MHT (32–33°C) starting ≤8 hours post-injury and lasting only 24 hours, due to evidence of deterioration at 6-month follow-up, which suggested an increase in mortality in patients subjected to cooling compared to the control group (21% vs. 14%; $p = 0.06$)[21,22]. With level of evidence II according to evidence-based medicine (EBM), the option to consider MHT for ICP reduction was maintained, provided that it is started within 8 hours after severe TBI and continued for 48 hours[22]. One year before the publication of the above-mentioned guidelines, the multi-centre randomised adult clinical trial Hypothermia II, which did not confirm the neuroprotective effect of lowered body temperature, was discontinued[23]. Work on the COOL KIDS project, on the other hand, was continued and completed. Published in 2013, its results were consistent with those obtained in the population of >18 years of age. MHT did not improve the final treatment outcome or long-term prognosis, however it did not increase the incidence of adverse events either[24]. In 2015, the results of research on the effect of MHT on ICP management were published. In this case, too, no improvement was confirmed, and furthermore, a deterioration of the results was noted. A good (i.e. comparable to the state prior to the injury) recovery was noted in 26% of patients in the hypothermia group and 37% of patients in the control group ($p = 0.03$)[11].
According to the current guidelines (2019), the use of MHT in the treatment of severe TBI should be avoided as a standard therapy aimed at improving treatment outcomes and prognosis, but it may be considered as an add-on therapy in the late phase (EBM level of evidence III) to control ICP[25,26].

HYPOTHERMIA IN PAEDIATRIC SUDDEN CARDIAC ARREST

In a single-centre study by Fink et al. (2007), as in meta-analyses carried out by Scholefield et al. (2013) and Moler et al. (2015), no statistically significant differences in survival and neurological function were found in children post SCA unrelated to PA treated with hypothermia compared to children kept in normothermia[27–29]. Schlunt and Wang (2010) and Bistritz et al. (2015), based on a review of the available literature, came to similar conclusions[30,31]. They pointed out both the small amount of data and the heterogeneity of the paediatric population. Research by Scholefield et al. concerned a population aged from 24 hours to 18 years, and that by Moler et al. – from 48 hours to 18 years of age. A similar aspect was observed by Geva et al. (2015), who suggested the need to divide the population into smaller groups, e.g. by age, to conduct a separate assessment for each of those groups, and to narrow

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the confidence intervals in statistical analysis, which could affect the final results[28,29,32]. However, Meert et al. (2016), who evaluated infants with a history of SCA between the 2nd day and the end of the 1st month of life, found no differences in survival and neurological condition depending on the therapeutic method used[7]. In another study, Meert et al. (2016) examined the relationship between the characteristics of out-of-hospital SCA and the results of MHT treatment in children requiring mechanical ventilation after the return of spontaneous circulation. Among the many factors independent of the treatment method used and influencing the final outcome of therapy, they listed the following as prognosis-improving: short duration of cardiac arrest, primarily shockable heart rhythms, administration of fewer adrenaline doses during resuscitation, short duration of chest compressions, and low body weight[33].

Thus far, there has been no uniform scheme for qualifying and conducting MHT in post-SCA children, excluding neonates born with severe PA. In reports from various countries, the core temperature was maintained at 33°C for 12 hours, 24 hours and 48 hours[28,29,33,34]. There is no age-related relationship forcing the use of any of the schemes. The general rule seems to be to maintain a core temperature of 32–34°C for a minimum of 24 hours, with the most common procedure being MHT with a core temperature of 33°C for 48 hours[8,30,34]. Upon close examination of the meta-analysis by Moler et al. (2015), which includes data on children from 38 hospitals without differentiating the cause or type of SCA, a slightly higher survival rate can be seen in the group of children treated with hypothermia with maintaining a core temperature of 33°C for 48 hours (20% vs. 12%; $p = 0.04$), with no impact on neurological prognosis[29].

None of the above-mentioned studies clearly demonstrated a positive effect of MHT in the group of post-SCA children. This may be due to the aetiology of cardiac arrest in children being different than in the adult population[28,29,34,35]. Children rarely develop SCA from an underlying cardiac cause, in particular shockable rhythms. Most cases of cardiac arrest are secondary to a respiratory problem, and the a priori central nervous system hypoxia is exacerbated by the cessation of blood flow due to SCA, which may further modulate the neural response to MHT in the child who survived SCA[7,8].

HYPOTHERMIA IN THE TREATMENT OF ACUTE ENCEPHALOPATHY DUE TO OTHER CAUSES

Acute encephalopathy can be also caused by diffuse vasoconstriction with flow disorders in the white and/or grey matter of the brain (acute encephalopathy with reduced subcortical diffusion, AED) due to the influence of infectious, genetic, metabolic or convulsive factors. It is a disease generally found in Southeast Asia and Japan, where most of the few reports come from.

In 2011, Kawano et al. published a comparison of 43 cases of children with acute encephalopathy, including inflammatory encephalopathy, treated with hypothermia in the range of 33.5–35°C for 48 hours (27 patients) or maintained in normothermia in the range of 36–36.5°C (16 patients). The researchers assessed the patients' neurological function 12 months after discharge. Considering MHT only, they found that its prolonged duration increased the risk of death, and its inclusion after 12 hours from the onset of the episode did not improve the prognosis compared to children maintained in normothermia. However, they observed a significant improvement in prognosis with MHT implemented up to 12 hours[36].

In 2020, Sakata et al. published a study on factors influencing the prognosis in acute encephalopathy with biphasic seizures and late reduced subcortical diffusion[37]. The authors conducted a retrospective 14-year analysis of 34 patients. MHT was applied in 24 patients – in 8 after diagnosis (early hypothermia) and in 16 after the onset of phase II of the disease (late hypothermia). No seizures during MHT were observed in any of the patients. In the late hypothermia group, more patients presented phase II than in the standard treatment group. Thrombocytopenia, hypokalaemia and hypotension requiring the administration of catecholamines were more common among patients with early hypothermia than in the other groups, which adversely affected the prognoses. Early initiation and prolonged use of MHT were also unfavourable factors. MRI imaging, performed on day 6–10 of treatment, did not show normal results in any of the groups, which, according to the authors, indirectly demonstrates the ineffectiveness of the currently used MHT protocols. On the other hand, they noted the positive effect of MHT on the results of a patient with cerebral oedema (the effect of MHT on ICP).

Currently, there are no universally applicable, uniform schemes for the management of MHT in acute encephalitis or acute encephalopathy unrelated to PA. Japanese recommendations from 2016 do not include MHT as part of standard treatment whatsoever[37]. In 2014, based on the 10-year own experience of a medical centre in Dokkyo (Japan), a treatment protocol using MHT in status epilepticus in infants >6 months of age and with a body weight of at least 7,500 g was published, but it does not confirm the clinical effectiveness of MHT in AED-related BI[38]. A necessary condition would be the ability to compare a group in which MHT was used alone with a group treated with immunoglobulins, steroid therapy and anticonvulsants. The treatment scheme described in the study includes MHT in combination with the indicated pharmacological therapy.

CONCLUSION

In the light of current knowledge, MHT in the paediatric population is considered a safe and effective method and has a well-documented value in post-resuscitation management in terms of increasing survival and improving

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neurological prognosis compared to traditional methods in only one clinical situation – in neonates with deep PA in whom moderate HIE developed[1,6,18].

There are no definite recommendations regarding other groups of patients, for clinical indications, or for increasing the time interval between a hypoxic event and the commencement of MHT[15,17,25,26,39].

Conflict of interest

The authors do not declare any financial or personal links to other persons or organisations that could adversely affect the content of this publication or claim rights thereto.

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