Brain Collagen in Post Operative Cognitive Dysfunction

Can brain collagen be used as a target for novel POCD treatment?

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9th of April, 2021

Summary

Post Operative Cognitive Decline (POCD) is a relative common complication in elderly patients that underwent surgery. POCD is not only characterised by cognitive impairments but also by a delay in recovery and increased morbidity. POCD is becoming more prevalent due to the increased number of surgeries performed in the elderly population. However, the exact mechanism of POCD development remains unknown.

Currently, the prevailing theory is that neuro-inflammation plays a major role in POCD development. Pro-inflammatory cytokines are released as a response to the tissue trauma from surgery. These pro-inflammatory cytokines are believed to increase the blood brain barrier permeability, which will induce further inflammation in the central nervous system. The neuro-inflammation will cause microglia activation and consequently neuronal damage. Interfering with these processes may provide a rational way for treatment. Accordingly, here are two potential approaches: decreasing neuro-inflammation or protecting the neurons.

Most research on novel POCD treatment has been focussed on decreasing neuro-inflammation. However, none of these have as yet reached clinical practice. There is evidence that lowering neuro-inflammation may not be enough to counteract POCD development. Hence, this thesis will focus on the alternative; an approach to enhance neuro-protection.

An endogenous neuroprotective system is brain collagen. Hence, we will explore whether brain collagen could provide a target for POCD treatment. Two potential ways of increasing brain collagen, oral collagen supplements and whole body vibration are discussed. Based on previous research, a pilot study by *R.G. Schoemaker et al* at the University of Groningen (2021) and a combination of pharmacokinetics and the physiology of the brain, whole body vibration seemed a promising way to increase brain collagen to be studied as candidate for a novel POCD treatment.

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Foreword

This thesis has been written as a continuation of my research project: the effect of whole body vibration on neurophysiology. Within this research project, data was used from a pilot study by *R.G. Schoemaker* that focussed on POCD, brain collagen and whole body vibration. This thesis is meant to place these findings in the context of literature. The general idea was to find a new innovative approach to treat POCD. I want to thank *R.G. Schoemaker* for providing the unpublished findings of the pilot study and for guidance in both the preceding research project and this thesis.

Introduction

A rising problem

During the past couple of years, the number of elderly patients that undergo surgery has steadily increased [1]. Due to the increase in surgical intervention in our elderly population, the number of reports of post-operative complications has also increased. One of these complications is Post Operative Cognitive Decline (POCD). POCD is characterised by cognitive impairments in addition to longer hospital recovery time and greater morbidity of the patient [2]. POCD can thus heavily impact the condition of the patient after surgery. While POCD is a growing problem, research has not yet found an effective treatment option. Treatment rational may be hampered by the lack of understanding the pathophysiology.

A possible treatment

An increasing number of studies have been performed focussing on POCD and possible target mechanisms. Currently, the prevailing theory is that neuro-inflammation is the major component of POCD development [3]. Treatment against POCD development can take two forms: decreasing neuro-inflammation or increasing neuro-protection. At the moment, a majority of the research focusses on limiting neuro-inflammation during and after surgical intervention [4]. However, certain research has found that altering neuro-inflammation levels not always directly affect POCD development [5]. Thus, the focus might need to shift onto the other possible treatment target: neuro-protection.

There are many different mechanisms and compounds in the brain that ensure neuro-protection. One of these neuro-protective mediators that we may be able to target is collagen. A recent pilot study *(Schoemaker et al* ., non-published) showed preliminary evidence that brain collagen decreases after surgical intervention in rats. Although brain collagen in the perineuronal net has described protective functionality in the brain, its potential therapeutic value has not yet been researched in much detail [6]. Brain collagen may provide a perfect target for further POCD treatment development. Still, ways of interfering with brain collagen are not well known.

Research aim

This thesis will explore brain collagen as a possible target for POCD treatment. Firstly, the current preventative strategies of POCD focussing on decreasing neuro-inflammation will be discussed. From this, we will better understand what the current preventative strategies are lacking and what an effective treatment focussing on increasing neuro-protection should thus aim for. Collagen will be used as a main target for this treatment. However, to make sure that collagen does provide appropriate neuro-protection, this thesis will include an excursion into the type-specific protective functionality of collagen. This is also largely important because brain collagen is quite a new frontier in neurobiological research and thus this subject is not yet explored to its fullest potential. Finally, we will focus on what form collagen-targeted POCD development might take. Specifically, we will look at two options: collagen supplements and whole body vibration. The current usage and the possible usage as a POCD treatment will be discussed for both these options. At the end, we can make an informed suggestion on whether collagen supplementation, whole body vibration or a combination of the two could possibly be used as an effective neuroprotective POCD treatment. In addition, we will discuss whether combination therapy composed of a neuroprotective and an anti-inflammation component may be effective or if the neuroprotective POCD treatment could suffice on its own.

Post Operative Cognitive Decline

Background

Post Operative Cognitive Decline (POCD) is a pathological condition that can develop in patients after surgery. While it was first believed that POCD only developed after cardiac surgery, it is now known that also patients undergoing non-cardiac surgery are at risk of developing POCD [7]. Some studies do suggest a difference between cardiac and non-cardiac surgeries and the developed POCD variant; as cardiac surgery seems to impact a wider array of brain areas while abdominal surgery mainly affects the hippocampus [8]. Because both non-cardiac and cardiac surgeries cause complications in the hippocampus, this brain area seems to be the most sensitive to POCD development. The high vulnerability of the hippocampus to many pathological conditions has also been proven by previous research [9]. POCD can include many differing cognitive impairments such as dysfunctions in language functions, problem solving skills, visual-spatial analysis and information acquisition [10]. In addition to this, POCD is associated with greater morbidity and delayed recovery [2].

While there is a lot of controversy around which risk factors do actually impact POCD development, increased age is a risk factor that has been accepted by most literature [11]. It has been found that the occurrence of POCD has been steadily increasing in the past couple of years as a consequence of increased surgery and anaesthesia usage in elderly patients [1]. In 2014, some calculations show that an average of 12% of patients over the age of 60 had developed POCD after a 3 month period after surgery [12]. Other studies, however, suggest POCD occurs at minimal in 10% and at maximum in 54% of the elderly patients after 1 week after surgical intervention [13].

Neuro-inflammation

Currently, the prevailing theory is that neuro-inflammation is the major driving force in POCD development. Multiple studies that have used rodent models have shown that inflammatory mediators and pro-inflammatory cytokines such as IL-1β are indeed increased after surgery in both peripheral tissues and in the central nervous system [14,15]. This upregulation of pro-inflammatory cytokines in the serum and cerebrospinal fluid has also already been found in human studies [16,17]. Some human studies, however, have found that both pro-inflammatory cytokines and anti-inflammatory cytokines are activated after surgery [18].

The increase in pro-cytokines is most likely mediated by up-regulation of High Molecular Group Box 1 protein (HMGB1) after surgery [19]. The increased amount of HMGB1 will bind to either Toll-Like Receptors (TLR) or the Receptor for Advanced Glycosylation End Products (RAGE) on Bone Marrow Derived Monocytes (BMDM) which in turn activate Nuclear Factor kappa B (NF-ϰB), which is a transcription factor that regulates the expression of pro-inflammatory cytokines [20]. In addition to the up-regulation of cytokines, cyclooxygenase 2 isoenzyme will also be up-regulated due to this cascade [21]. The up-regulation of these factors can then impact the Blood Brain Barrier (BBB) and thus its permeability [3]. This makes it possible for the inflammation to be reflected into the central nervous system where it activates microglia and can damage cells in the brain through oxidative stress [3,22,23]. In addition to this, brain-derived neurotrophic factor (BDNF) levels and neurogenesis have also both been found to decrease in correlation to neuroinflammation level as a consequence of surgical intervention [24].

Currently, there are a multitude of different interventions focussing on inhibiting this neuro-inflammation mechanism that are being investigated. These anti-inflammatory treatments include COX-2 inhibitors, minocycline, dexamethasone, cholinergic agents and targeted cytokine inhibitors, reviewed by *Safavynia et al.* [3]. While many of these treatments are currently in clinical trials, none have yet made it into established treatment. In addition to this, stimulation of the vagal nerve and thus stimulation of an anti-inflammatory pathway may also attenuate POCD [3,25,26]. The clinical usage of stimulating this pathway as a therapy against POCD development in patients has not been researched yet. While these treatments might seem promising for inhibiting neuroinflammation, it does not directly mean that they will also inhibit the development of POCD. This is because some recent studies have found that increases in neuroinflammation did not always cause increased POCD development [5]. While some researchers did show concern whether the conclusions by this study might be premature, the study still provides enough basis to speculate that the causative relationship between neuroinflammation and POCD is not as clear as it was first thought to be.

Neuro-protection

Instead of focussing on decreasing neuro-inflammation, we could opt on focussing on neuro-protection. This would provide another rational target for treatment because it would also directly counteract the age-discrepancy in POCD. At the moment, most theories explain the age-discrepancy in POCD with the decreased brain reserve in the elderly patients [27]. This decreased brain reserve would explain why younger patients do not develop POCD, whereas elderly patients with impaired brain reserve do develop POCD, upon the same stressor [28]. Other factors that might explain the age-specific development of POCD include abnormal immune response to stressors, decreased white

matter and an increased chance of co-morbidities [28,29,30]. In addition to an exaggerated (neuro)inflammatory response, the age-associated increased risk of POCD development thus could originate from a decreased neuronal protection in the elderly patient, as well.

Hence, treatment against POCD can thus focus on increasing the neuro-protection in some way. Some anti-oxidative and pro-neuronal drugs which would increase the neuro-protection in the brain through differing mechanisms have already been proposed [3]. However, these proposed treatments have not yet made it into established treatment and generally only cover individual aspects of neuroinflammation such as inhibiting a specific enzyme or pro-inflammatory cytokine [3]. Thus, an effective POCD treatment might instead focus on covering more aspects of neuro-inflammation. Such a POCD treatment could better protect the elderly patients than a drug with only a single-mediator approach. Collagen may be a suitable candidate for this, as the variety of different types of collagen have a wide array of neuro-protective functions.

Brain collagen

Background

While collagen in the body is relatively well researched, brain collagen is a subject that only recently has been discovered and researched. The increase in research focussing on brain collagen in recent years did elucidate the importance of collagen in ensuring brain health. There are many different types of collagen that can be found in the brain [31]. For example, type IV brain collagen has been found to protect the brain against amyloid-beta proteins during Alzheimer's Disease development [32]. Other types of brain collagen have also been found to affect both inflammation and scar formation, which are two essential processes in neuropathologies [33,34].

A recent pilot study suggested that brain collagen, specifically in the CA1 region of the hippocampus, decreases as a consequence of abdominal surgery in rats. These results may thus indicate a link between surgery and POCD development, with collagen as an intermediate factor. However, in the aforementioned pilot study, Sirius red stained all collagen subtypes. Therefore, it is not known whether the decrease in collagen after abdominal surgery was type-specific and if this decrease in collagen may be a causing factor of POCD development. To further speculate on the involvement of brain collagen in POCD, we must first better understand to which scope collagen is a neuro-protective agents and whether there are large type-specific differences.

The different types of collagen

Extracellular matrix, type I and type III - The extracellular matrix (ECM) is comprised of many different components such as type I collagen, type III collagen and fibronectin [35,36]. An overview of the collagen types and their function can be found in *table 1*. Increased ECM proteins have been shown to impair the neuroplasticity, while healthy levels of ECM proteins have been shown to have beneficial effects such as neuro-protection in the form of perineuronal nets [37]. These perineuronal nets also play a direct role in signal transduction, neuroplasticity and neuro-protection [38]. Impairments in the ECM and thus also the perineuronal nets have been associated with a multitude of cognitive abnormalities, including schizophrenia, Alzheimer's disease and addictions [38,39].

Type IV - Collagen type IV is a type of collagen that is solely found in the basement membrane of for example the blood vessels in the brain [40]. It has been found that the anaesthesia administered during surgery, specifically the anaesthetic isoflurane, can cause a decrease in this type of collagen [41]. It is also known that collagen in blood vessels have a very specific organisation, which is important for sustaining healthy functioning of the circulation [42]. The decrease in collagen type IV in the blood vessels could cause disturbances in the Blood Brain Barrier (BBB), which in turn could affect cognitive functioning such as during Alzheimer's disease [43].

Type VI - Collagen type VI is another type of collagen that, in contrast to type IV collagen, can be found in many different tissues. This collagen type has also been found to protect the brain against amyloid-beta proteins, which is a characteristic of Alzheimer's Disease [32]. In addition, a lack of type VI collagen in the brain has been linked to an increased sensitivity of neuronal cells to oxidative stress and an increase in spontaneous apoptosis [44].

Type VIII - Type VIII collagen is found in the ECM of many different tissues. In 1997, it was already speculated that type VIII collagen plays an important role as a substrate for many different cell types [45]. Today, we know that type VIII collagen specifically plays an important role as a substrate of astrocytes to promote scar formation [46].

Type XVII - While type XVII collagen is expressed widely in the brain, there is a large degree of variations in its distribution in the brain. For example, while collagen XVII can be found mainly on the soma and proximal axons of neurons, it is not expressed on glial cells [47]. It has been hypothesised that the presence of type XVII collagen in the neurons is important for neuronal migration and synaptic plasticity [48].

Type XIX - Collagen type XIX has been found to be expressed by a subset of hippocampal interneurons and seems to play an important role in synapse formation [49]. In this same study, it was found that deficiencies of type XIX collagen can cause dysfunction specifically in the inhibitory synapses. Another study has also found that type XIX collagen reduction can cause a reduction of telencephalic perineuronal nets through up-regulation of extracellular proteases [50]. Both these studies have found evidence to suggest that type XIX collagen deficiency can also cause some complex brain diseases such as schizophrenia.

Summary

The different types of collagen and their functionality are summarised in *table 1*. When comparing the decrease in post-operative brain collagen found in the results of the pilot study in the POCD rats, to the protective functions that the different types of collagen have in the brain, it can be speculated that collagen indeed may play a role in POCD development. If these types of collagen would decrease, they could facilitate the neuronal damage due to the neuro-inflammatory mechanism of POCD. For example, the increased permeability of the BBB discussed in the neuro-inflammation theory would be further facilitated by a possible decrease in type IV collagen [3,42,43]. Increases in oxidative stress due to neuro-inflammation can also be further facilitated by a decrease in type VI collagen [3,44]. In addition to this, decreases in the collagens in the ECM and thus the PPN may impair the protection of the neuron, which would make the neurons more vulnerable to damage from the neuro-inflammatory factors [38].

This importance of brain collagen as a neuro-protective agent together with the need of increased neuro-protection in the elderly patients to prevent POCD development makes brain collagen a suitable target for a treatment option. However, if we want to increase brain collagen as a treatment against POCD, we must find ways to accomplish that.

Table 1: A summary of the functions of the discussed collagen types

Collagen type	Collagen type involved
Type I	Major components of ECM and PPN. Important for neuroplasticity and neuro-protection.
Type III	Major components of ECM and PPN. Important for neuroplasticity and neuro-protection.
Type IV	Component of the basement membrane. Important for healthy brain circulation and BBB permeability.
Type VI	Protection against spontaneous apoptosis and against amyloid-beta proteins.
Type VIII	Promotes scar formation by astrocytes.
Type XVII	Promotes neuronal migration and synaptic plasticity.
Type XIX	Promotes healthy (inhibitory) synapse functionality and perineuronal nets.

Collagen as a treatment option

Collagen supplements

Collagen has already been marketed as one of many supplements that could be beneficial for the body. While these novel supplements are often less fact than fiction, a lot of research has been conducted to study the actual clinical effect of collagen supplements. Collagen hydrolysate, better known as gelatine, has been found to be beneficial for osteoarthritis patients or patients with other joint disorders or joint pain [51,52]. In addition to this, gelatine enriched with vitamin C has been found to promote endogenous collagen synthesis when taken before intermittent activity [53]. However, it is important to note that the collagen synthesis in this study was measured from blood samples; that is the peripheral circulation. Whether the augmentation of collagen synthesis may reach the brain is still unknown. Another major medical field that uses collagen supplements is dermatology. Collagen supplements have been found to increase both wound healing and skin ageing [54]. Collagen hydrolysate was found to specifically increase skin hydration, skin elasticity and dermal collagen [54,55]. This does suggest that exogenous collagen can indeed be incorporated into tissues.

However, this does not directly mean that collagen supplements can also be used to increase brain collagen levels. Specifically, oral collagen supplements must be able to cross to blood brain barrier and must then be able to be incorporated into the brain. Characteristics of compounds that can cross the blood brain include a small size, low molecular weight, high lipophilicity and low hydrogen-bonding potential [56]. Collagen does not meet these characteristics and it is thus unlikely that oral collagen supplements will result in an appropriate bioactivity in the brain. However, the mechanism of neuro-inflammation in POCD development is characterised by disturbances in blood brain

barrier permeability [3]. These disturbances in permeability may make it possible for collagen to reach the brain. However, this would make collagen supplementation a personalised treatment which is dependent on the degree of dysfunction of the blood brain barrier in the patients. It would be more beneficial if a novel neuroprotective POCD treatment was more standardised so it can be used in patients regardless of their blood brain barrier condition.

Whole body vibration

There may be a treatment option which does not make use of exogenous substances and which may be used as a more standardised treatment. Whole Body Vibration (WBV) is a form of passive exercise that makes use of vibrations from a vibration plate to achieve beneficial effects [57]. These beneficial effects range from improvements in mobility to improvements in brain functioning [58,59]. Intense WBV with high frequency also seems to affect the physiology of the central nervous system, for example affecting both astrocyte and microglia activity [60]. In addition to this, WBV has also been found to increase type I collagen turnover in peripheral circulation in rats [61]. This does suggest that WBV might be a potential method to increase brain collagen and thus provide neuronal protection against POCD development. How WBV might inhibit neuronal damage is depicted in *figure 1*.

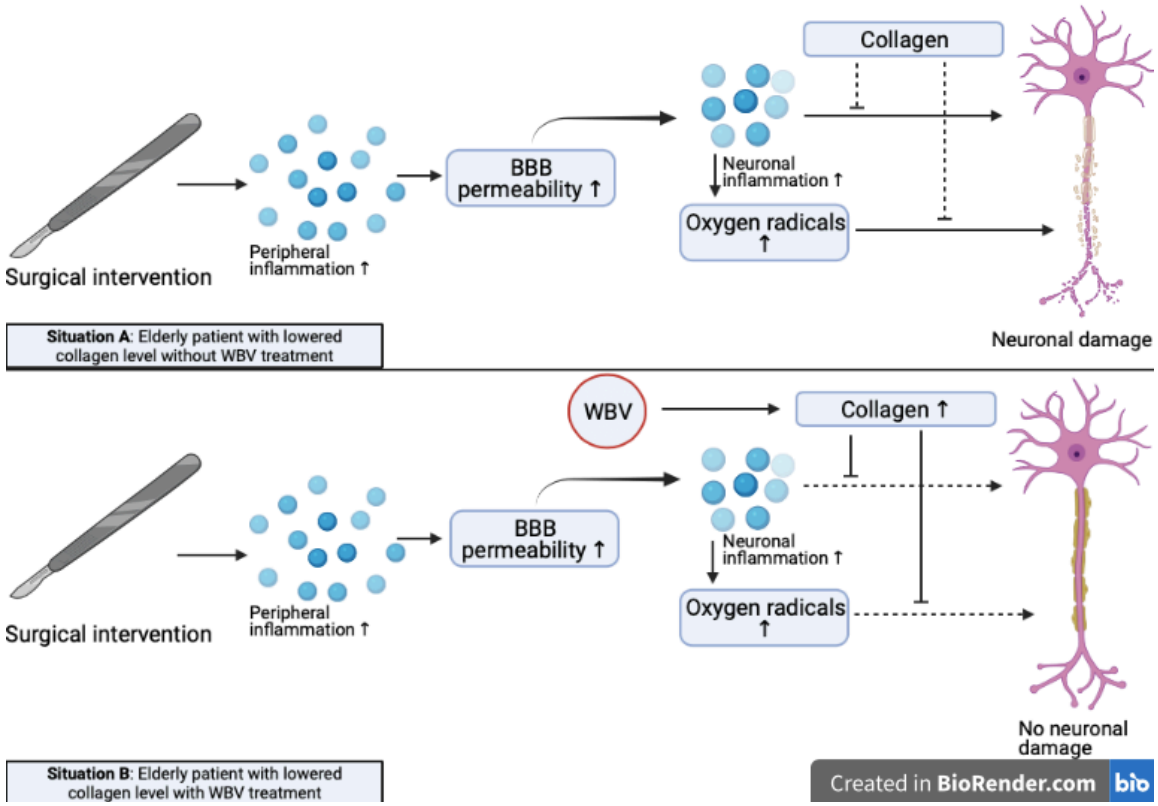

Figure 1: The proposed effect of WBV in preventing POCD via collagen stimulation.

However, not much research has yet been done focussing on the specific neurophysiological effects of WBV on brain collagen or on neuroinflammation in general. Some studies have shown that WBV did lower inflammatory biomarkers such as TNRF

and BDNF in patients suffering from fibromyalgia and that WBV may attenuate inflammation through increased circulating stem and progenitor cells [62,63]. However, this does not show clear evidence yet that WBV might actually inhibit neuroinflammation, counteract POCD development or increase brain collagen. Nevertheless, the pilot study in POCD rats did provide preliminary evidence that WBV in rats could reverse the post-operation decrease in brain collagen. In addition to this, another recent study did find that WBV is beneficial in depressed rats through multiple mechanisms such as inhibition of neuronal degeneration and alleviating the damage of neurons [64]. These results would suggest that WBV might yet be a promising candidate for effective treatment against POCD.

However, care should be taken in providing WBV treatment as too intense treatments could have side effects such as pain or increased neuro-inflammation [60,65]. This would of course be undesired as the treatment is meant to inhibit neuro-inflammation. In addition to this, it is also still unclear to which extend WBV should be used to increase brain collagen. Brain collagen homeostasis is a delicate balance, because too low brain collagen levels leave the neurons vulnerable to damage while collagen accumulation has been associated with cognitive decline and could possibly impact neuroplasticity [38,66,67]. Furthermore, vibrations have also been associated with many different vibration-induced diseases such as carpal-tunnel syndrome and ocular torsion [68,69]. Thus, WBV therapy also has possible risk factors.

Summary and conclusion

Based on the presented evidence, it can be concluded that collagen is both an important factor in neuro-protection and that it might play a role in POCD development. This may implicate that collagen can be used as a target for a novel treatment of POCD. While there is no basis yet to believe that exogenous collagen or a prodrug thereof can be used to increase brain collagen, and consequently induces neuro-protection, the pilot study by *R.G. Schoemaker et al* at the university of Groningen (2021) did provide evidence that brain collagen can be stimulated through WBV. However, to support the hypothesis that WBV could be effective against POCD development, more research should be done to quantify the neuro-protective properties of WBV. In addition to this, it should be further researched whether WBV can only reverse the post-operative decrease in collagen or to which degree WBV can increase brain collagen levels above the pre-operative level and the functional consequences thereof. Furthermore, in depth research with histochemistry should also be performed to analyse whether both WBV and POCD is associated with specific collagen types, with its specific functions.

While there is a large likelihood that WBV as treatment might be an answer to the increasing occurrence of POCD in the elderly population, the anti-inflammatory drugs currently in development might also be effective in lowering POCD occurrence. However, it is important to note that WBV might circumvent certain problems that drug development might encounter, such as drug-drug interactions and other pharmacokinetic difficulties such as transportation of the drug across the blood brain barrier. This would still make WBV an effective treatment option, especially for individuals that due to a history of drug administration might not be compatible with a novel drug against POCD. In addition to this, WBV might also be a promising addition to one of the developing pharmaceutical treatment options to elevate neuro-protection and to facilitate the recovery of surgery patients as co-treatment.

Furthermore, WBV could also be combined with an anti-inflammatory POCD treatment. This would provide both inhibition of the neuro-inflammatory pathway and would also protect the brain against the damaging effects of this neuro-inflammatory pathway. In theory, this would be a very effective way to prevent POCD development in the surgery patients. However, because there is still a lot unknown about WBV and its functional consequences on brain collagen and neuro-inflammation and because many of the anti-inflammatory drugs are still in clinical trials, we cannot discuss in detail yet the efficacy and functionality of such combination therapies. From what is currently known, WBV does seem to have an important neuroprotective effect which could be used for all patients, while many of the anti-inflammatory treatments do seem to be more specific in their target and functionality. I would suggest that WBV should be used as a more general treatment option while the anti-inflammatory treatments could be used as additional therapies for patients with increased inflammatory responses. The anti-inflammatory treatments could thus be used to further individualise the POCD treatment.

In conclusion, collagen is an important factor in neuro-inflammation and can thus be used as a target for novel POCD treatment. Based on some previous research and the preliminary findings of the pilot study of *R.G. Schoemaker et al*, it does seem that WBV might indeed be used to increase the collagen-dependent neuro-protection in surgery patients. However, more research should be done to analyse to which extent WBV has effect on brain collagen in humans and whether this collagen-dependent neuro-protection boost is enough to protect the patient against POCD development. In addition, treatment specifics should be further researched such as the effect of differing time, frequency, intervals and intensities of WBV on neuro-protection.

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