

Application of biotechnologies in the treatment of haemorrhoidal disease and optimisation of patient management

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Abstract

Introduction: Haemorrhoidal disease is one of the most common nowadays. It is often associated with a sedentary lifestyle. The leading cause of its development is also a functional disorder of the intestine and chronic constipation. To date, there is a steady growth rate of this disease, leading to its “rejuvenation”. The current stage of development indicates the need for further improvement of surgical treatment and optimisation of patient management methods and the creation of uniform standards of care for this contingent of patients.

Aim: To evaluate the clinical effectiveness of the use of platelet-rich plasma therapy and the biologically active substance “ozoyl” in the treatment of haemorrhoidal disease.

Material and methods: The main group included 100 patients with chronic haemorrhoids who were operated on in the period from March 2021 to March 2022. For this group, autoplasm was used during surgery, and an ozoyl-based drug in the postoperative period. The remaining 100 participants of this study, assigned to the control group, underwent a conventional haemorrhoidectomy operation and standard patient management using a hydrophilic ointment based on chloramphenicol.

Results: After the conducted clinical studies, it was established that in the main group, the pain syndrome decreased by about 30%, considering the period from the first day of the postoperative period compared to the control group. The postoperative wound healed in the main group in the third week after the operation, unlike the control group, in which this event was noted in the fourth week. The patients did not complain during the examination 3 months later.

Conclusions: This study is of practical significance because haemorrhoidal disease today has a high prevalence, and an integrated approach is required for the treatment of such patients. Ozoyl is a powerful cell and tissue repairer.

Introduction

Haemorrhoids are one of the most common human diseases, and among the diseases of the colon and rectum it ranks first in frequency. According to statistics, 15% of the adult population fall ill with it. The specific weight of haemorrhoids in the structure of diseases of the colon and rectum is 41% [1, 2]. To the greatest extent, the development of the disease is promoted by constipation, muscular contractions, prolonged diarrhoea, pregnancy and childbirth, sedentary lifestyle, prolonged sitting, systematic weightlifting, spicy food,

and alcohol abuse. There are 2 theories of the occurrence of this disease, which explain the process of its development. These include mechanical and haemodynamic theories [3]. According to the first of them, haemorrhoids are formed due to distal movement of anal rollers. Anal rollers have the correct anatomical structure and perform the function of retaining the faecal contents of the rectum. Connective tissue formations fix venous plexuses in the submucosa. The movement of the rollers downwards occurs as a result of an increase in intra-abdominal pressure. The fixing device

wears out over time with prolonged constipation and muscular contractions. As a result, haemorrhoidal tumours swell and fall out.

The haemodynamic theory says that haemorrhoids is caused by stagnation of venous blood, which in turn develops due to mechanical obstacles in the form of solid faeces, which is constantly present in the ampoule of the rectum. In addition, the stagnation of venous blood is facilitated by incomplete relaxation of the internal sphincter during the act of defecation. Then the reverse flow of venous blood contributes to the opening of arteriovenous shunts and spasm of precapillary arterioles, thereby causing aggravation. In the pathogenesis of haemorrhoids, the described mechanisms are important. Most often, venous congestion develops due to node thrombosis. The increased influx of arterial blood and the opening of shunts provoke the expansion of veins with inflammatory phenomena in the mucous layer of the rectum and bleeding [4]. Haemorrhoidal disease is characterised not only by a chronic course but also by attacks of the disease, i.e. it also has an acute course. Thrombosis of haemorrhoids is acute haemorrhoids. Bleeding develops because of inflammatory changes developing in the node itself and surrounding tissues [5].

The main symptoms of inflammation of varicose veins of the rectal ampoule are bleeding in 51% of cases and loss of nodes from the anal canal in 37% of cases [4]. There are also other important symptoms, such as itching of the anal canal in 9% of cases, foreign body sensation in the anal canal in 5% of cases, and mucus discharge in 2% of cases. It is important to differentiate haemorrhoids from other similar diseases in the form of polyps or cancer in time. An important distinguishing feature of haemorrhoids from colorectal cancer is the appearance of blood drops after the act of defecation. Therefore, with any manifestations of intestinal discomfort and especially with bleeding from the rectum, a thorough history collection, finger examination, recto-, colon-, or irrigoscopy is necessary.

Given the high prevalence of haemorrhoidal disease among working age patients, an important point in surgical treatment is accelerated recovery of working capacity, which is restored due to rapid regeneration of wounds. The authors of the study investigated the main methods of accelerated regeneration, such as the use of autoplasm and ozone therapy. One of the ways to optimise the accelerated regeneration process is platelet-rich plasma (PRP) therapy. PRP therapy a method based on the use of autologous PRP for the treatment of various diseases, including skin wounds – acute, chronic, and postoperative – especially with delayed regeneration. PRP contains cytokines, growth

factors, chemokines, and fibrin obtained from the patient's blood, the mechanism of action of which is the molecular and cellular induction of the normal wound healing process.

According to literature data, when using autologous platelet-rich plasma, complete epithelisation of the wound occurs significantly faster than when using conventional methods of treatment. According to several authors, the use of PRP therapy is a cost-effective method of treatment and leads to a reduction in complications and treatment costs, positively affecting the quality of patients' lives. According to foreign literature, the use of PRP therapy accelerates the onset of complete epithelisation of the wound, helps to prevent complications, and reduces pain, rehabilitation time, and scarring [6–9].

The therapeutic activity of ozonated oil was explained by its antibacterial, antifungal, antiviral, antiparasitic, antihypoxic, analgesic, and immunomodulatory effects on biological systems [10–12]. Moreover, the phenomenon of improved wound healing after ozone therapy was associated with rapid changes in cell types and the release of cytokines that modulate the complex healing process [12, 13]. Ozoyl is used to treat diseases of the mucous membrane and to heal the skin. It is a biological inducer capable of modulating the main metabolic pathways by determining cellular and tissue reactions that restore damaged functions. Studies have also shown anti-inflammatory and analgesic activity [10, 14]. Ozoyl is an active ingredient and a biological inducer that, through oxidoreductions and activation of signalling functions, regulates the main metabolic pathways, stimulates the endogenous defence system, and, through the regulation of gene transcription, promotes rapid tissue regeneration and restoration of skin lesions [15]. Ozoyl is also a powerful inducer that brings oxygen to the tissues and acts as an anti-inflammatory and microbicidal agent [16].

Aim

Authors aim to evaluate the clinical effectiveness of the use of PRP therapy and the biologically active substance “ozoyl” in the treatment of haemorrhoidal disease.

Material and methods

The study is conducted in the conditions of a multidisciplinary surgical department of the regional diagnostic centre and the proctology centre of the clinic of the International Institute of Postgraduate Education. The study involved 200 patients on a voluntary basis with stage 2–3 chronic haemorrhoids, the duration of the disease from 1 year, in the age category from

20 to 70 years, who were divided into 2 groups: main and control. The main group included 100 patients with chronic haemorrhoidal disease who were operated on in the period from March 2021 to March 2022. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by National Ethics Commission of the Ministry of Health of the Republic of Kazakhstan, No. 1823-A.

For this group, autoplasm was used during surgery and an ozoyl-based drug in the postoperative period. The control group included 100 patients who underwent a conventional haemorrhoidectomy operation and standard patient management using a chloramphenicol-based hydrophilic ointment from 2019 to 2020. The exclusion criteria for the study were patients who had previously undergone surgical interventions on the anal canal, the presence of concomitant inflammatory diseases of the anal canal and perineum, and concomitant chronic diseases in the decompensation phase [17].

When conducting a comparative analysis of patients divided into groups by gender, age, duration of the disease history, stages of haemorrhoids, and risk factors for the development of the disease, there were no statistically significant differences between the main and control groups of patients, which in turn allowed an objective assessment of the results of haemorrhoidectomy with PRP therapy in comparison with Milligan-Morgan haemorrhoidectomy – an operation, the essence of which is the radical removal of haemorrhoidal nodes in a single complex. In contrast to minimally invasive techniques, this intervention involves the simultaneous excision of all haemorrhoidal nodes together with the underlying tissues [18].

The main group of 100 people with chronic haemorrhoids aged 20 to 70 years was subject to surgical intervention. Autoplasm was used during the operation. The method is carried out in the following way. Before surgery, venous blood is taken from patients in test tubes containing sodium citrate in an amount of 12 ml. The blood is then centrifuged at 3000 rpm for 8 min. From the plasma obtained, its upper layer in the amount of 2.0 ml is collected into syringes and disposed of. The remaining plasma layer is transferred to a sterile tube that does not contain any impurities. A solution of calcium chloride is added to the plasma at the rate of 1.0 ml of 10% calcium chloride solution per 10 ml of autoplasm and is injected after the main stage of the haemorrhoidectomy operation into the base of the wounds in the projection of the removed haemorrhoids into the walls and bottom of the wound with a mesh in

3-mm increments of 0.1 ml. Patients in the main group of the study in the postoperative period were treated with an ozoyl-based cream for 20 days. The complex subsequent treatment included conventional methods of combating constipation and wound healing therapy: candles, thermal procedures, and hygiene measures.

For almost 40 years, ozone, a very unstable gas with strong oxidising ability, has been used for treatment. The effects of ozone have been extensively investigated; in particular, its strong oxidising ability has been tested to verify its disinfecting properties [10, 11, 18]. Ozonides are a class of chemical compounds in which ozone is stabilised by reaction with unsaturated fatty acids of oils. Ozonides are an alternative to pharmacological therapy [19] and are used as a topical preparation with antibacterial properties [20, 21]. It has been reported that ozonated olive oil is non-toxic, accelerates wound healing, and has an anti-inflammatory effect [19]. In particular, upon contact with the skin and mucous membranes, ozonated olive oil in environments characterised by proton increase, such as ischaemic, hypoxic, or damaged tissues, releases molecular oxygen, stimulating the production of radical species with the generation of moderate oxidative stress. These effects contribute to the release of growth factors, activation of local antioxidant mechanisms, and tissue repair [19, 12]. To date, some studies have shown the therapeutic use of ozonated oil in skin diseases [22].

In the postoperative period, the patients underwent analysis of the pain scale, the use of frequency and quantity of analgesics (narcotic and non-narcotic), the healing period (cytomorphology), the level of haemostasis, the development of an elastic scar, the period of normalisation of intestinal function, the period of rehabilitation, the analysis of questionnaires on quality of life, and evaluation of wound healing, visually and cytomorphologically, within a month. As a result, the healing time of the postoperative wound was 3–4 weeks in the main group, compared with 4–6 weeks in the control group. The duration of disability in the main group was 16.1 ± 4.8 days, versus 22.5 ± 4.5 in the control group. During a routine examination after 3 months, patients of both groups did not complain, and mucosal defects are not detected.

Results and Discussion

The study was conducted in the conditions of a multidisciplinary surgical department of the regional diagnostic centre and the proctology centre of the clinic of the International Institute of Postgraduate Education. Haemorrhoidal disease has a high prevalence among patients of working age. It was found that an important point in surgical treatment is an accelerated recovery of

the ability to work, which is restored by rapid wound regeneration. The use of the main methods of accelerated regeneration, such as autoplasm and ozone therapy, is an effective, safe, and cost-effective approach. By reducing the time of treatment of patients and reducing the cost of expensive treatment and rehabilitation, the use of this method of wound treatment after haemorrhoidectomy gives a considerable economic effect. In the analysis of the clinical effectiveness of operations, such evaluation criteria as the severity and duration of the pain syndrome, the manifestations and severity of complications in time and in the early postoperative period, the number of hospital bed days, and the recovery period of patients, and as a result, complete recovery, were used.

As a result of the study, it was noted that in the main group the pain syndrome decreased by about 30%, considering the period from the first day of the postoperative period in comparison with the control group. The postoperative wound healed in the main group in the third week after the operation, unlike the control group, in which this event was noted in the fourth week. The patients did not complain during an examination 3 months later. The intensity of pain severity evaluated by patients on the VAS scale was maximal on the first day after surgery and was estimated at an average of 3 ± 0.2 points in the main group and 6.1 ± 0.3 points in the control group. Therewith, a day after the intervention in all 2 groups, there was a considerable decrease in the severity of pain – by 0.9 ± 0.2 and 1 ± 0.2 points, respectively ($p < 0.001$). The duration of pain continuation after surgery averaged 3.1 ± 0.2 days in the main group and 4.4 ± 0.2 days in the control group. The development of early postoperative complications in the main group was seen in 6 (12%) patients, while in the control group, complications were diagnosed in 14 (28%) cases. The methods of operations used for chronic haemorrhoids have certain advantages, i.e. the number of complications does not increase but decreases.

One of the important criteria for the effectiveness of the surgical intervention is the study of the terms of recovery and medical rehabilitation. After haemorrhoidectomy with PRP therapy, by day 15, 31 (62%) patients and by day 25, 50 (100%) patients returned to work. With Milligan-Morgan haemorrhoidectomy, 32 (64%) patients of the control group began to work by day 30 and all patients by day 40. In patients who had undergone haemorrhoidectomy with PRP therapy for the haemorrhoidal disease of stages 2–3, the period of disability was considerably reduced. This is due to the accelerated onset of complete epithelisation of the wound, which contributes to the prevention of complications, helps to reduce pain and the duration of re-

habilitation, reduces of scarring, and leads to a small number of complications in the postoperative period.

A comparative analysis carried out 3 months after the intervention of reducing the frequency of patient complaints showed that when using the PRP therapy surgery technique, complaints of rectal bleeding disappeared faster than after other treatment methods. The largest proportion of patients who retained any complaints occurred after performing an open haemorrhoidectomy with the conventional method of management. Thus, the assessment of objective and subjective symptoms shows that 3 months after the intervention, the compared methods using PRP therapy give the best results. In total, the development of 2 types of long-term complications of treatment was recorded: anal fissures and strictures of the anal canal. The development of anal fissures took place only after the application of the conventional method (frequency – 3%).

The development of anal strictures was recorded in 1 patient of the main group and 2 patients of the control group. In the postoperative period, the patients were evaluated for wound healing visually and cytomorphological for a month. As a result, the healing time of the postoperative wound was 3–4 weeks in the main group, compared with 4–6 weeks in the control group. According to the results of the cytological study, the use of PRP therapy helped to optimise the healing process of postoperative wounds at all stages: inflammation, proliferation, epithelisation, and reorganisation of scar tissue, which manifested itself in the early appearance of fibroblast cells characteristic of the proliferation stage, an increase in the number of collagen fibres, the appearance of epithelial cells in patients of the main group at an earlier stage. The early appearance and increase in the number of fibroblasts indicated a positive effect of PRP therapy on the healing of postoperative wounds in the proliferation phase.

From the fourth day, in the patients of the main group, the appearance and increase in the dynamics of fibroblasts were identified; on the 12th day after surgery, collagen fibres appeared in smears in addition to erythrocytes, neutrophils, lymphocytes, macrophages, and fibroblasts. While erythrocytes were detected in patients of the comparison group, a large number of segmented neutrophils were identified, mostly destroyed. In the phase of epithelisation and reorganisation of scar tissue, the beneficial effect of PRP on the healing process was mediated by the influence of keratinocyte growth factor (KGF) and epidermal growth factor (EGF). Thus, in the smears of patients in the comparison group, fibroblasts began to predominate on the 21st–24th day, the number of loosely located collagen fibres increased, and individual epithelial cells appeared. While there

were considerably more fibroblasts and bundles of collagen fibres in the smears of patients in the main group, the number of epithelial cells also increased. On day 30, bundles of collagen fibres, fibroblasts, and individual epithelial cells located in groups were found in smears from the surface of postoperative scars in patients of the comparison group. In smears from the surface of postoperative scars in patients of the main group, compared with the comparison group, epithelial cells were detected in large numbers, often in large conglomerates.

Haemorrhoids are an urgent problem today because they cause discomfort and disrupt the functional activity of the body. It is the leading disease in coloproctology, and it affects persons of both sexes equally. According to statistics, the prevalence of haemorrhoids does not exceed 120 cases per 1000 adults, which confirms its frequent occurrence among adults. The proportion of haemorrhoids among all diseases of the colon and rectum is 41%, so we should further monitor the trend of its growth to avoid undesirable consequences by introducing preventive measures among the risk group [23]. The disease develops in people who lead a sedentary lifestyle – for example, office workers, truckers, people engaged in heavy physical labour. This leads to obstruction of blood flow to the pelvic organs, which further leads to the expansion of haemorrhoidal veins and the proliferation of cavernous tissue of the rectum. Bleeding (50%) and loss of nodes from the anal canal (36%) are the leading symptoms of haemorrhoids.

Other symptoms include anal itching (5%), discomfort in the anal canal (5%), and mucus accumulation (2%) [24]. Polyps and colon cancer are also accompanied by the release of scarlet blood from the rectum. Therefore, highly qualified assistance is required. Such research methods as finger rectal examination, irrigoscopy, laboratory tests, and proctosigmoidoscopy allow the disease to be recognised in time, conducting differential diagnosis, and prescribing the correct treatment [25, 26]. The specific feature of the haemorrhoidal disease is its prevalence, which is why this problem is so relevant nowadays. It is necessary to comply with all doctor's prescriptions, seek medical help on time, conduct examinations, and remember about prevention [27]. This is what will contribute to the easy course of the disease without complications, or its prevention.

The abundance of various surgical approaches to the treatment of haemorrhoids currently indicates the fact that the problems of surgical treatment of haemorrhoids are unresolved. In recent years, modern technologies have been used in combination and with a personalised approach to the patient and even differentially to each haemorrhoid node. This leads to an increase in

the efficiency and effectiveness of surgical treatment of the disease. However, there are no clear criteria for the selection of such patients for outpatient care. The algorithms for examination, preoperative preparation, surgical treatment, and postoperative methods and technologies have not been developed. These data indicate the need for a comprehensive study [28].

PRP is an autologous plasma with a high platelet count exceeding the norm (from 1,000,000/ μ l). This drug should be used for therapeutic purposes because it contains a high concentration of growth factors necessary to activate the regeneration process of tissues with low healing potential. PRP therapy has numerous advantages because it is safe due to the use of plasma with platelets obtained from the patient's own blood. This is how complete biocompatibility is achieved. Thus, the transfers of infectious antigens, and the appearance of immunogenic and allergic reactions are excluded. Normally, 1 μ l contains 200–300 thousand platelets, which play a key role in the process of blood clotting and secrete numerous growth factors. The main target cells of growth factors are blood vessel cells, fibroblasts, and mesenchymal stem cells. This explains the restoration of blood vessels, muscles, connective tissue, and skin [29].

Growth factors are natural substances that have a wide range of biological effects. They stimulate/inhibit cell division, the development of new cells, and the differentiation of living cells. Growth factors function as signalling molecules for interaction between cells. Cell division is the basis for the development and growth of the body, providing self-renewal of tissues and restoration of their integrity after damage throughout life. Unlike hormones, growth factors act locally and do not exist in the blood in a free form. Platelets contain various growth factors and vasoactive substances (platelet growth factor, transforming growth factor, fibroblastic growth factor, epidermal growth factor, serotonin, bradykinin, etc.). They affect all phases of healing: coagulation, inflammation, matrix synthesis, angiogenesis, fibroplasia, epithelisation, scar contraction, and remodelling [30].

Two international publications of the University of Messina report on the biological and biomolecular mechanisms by which ozoyl acts as a biological inducer capable of counteracting hypoxia, stopping inflammation, and activating tissue regeneration [31]. The study, among other things, compares the effect of ozoyl with local cortisone, highlighting very interesting results. Ozoyl has an anti-inflammatory effect that is easily comparable to cortisone, which, unlike ozoyl, does not stimulate the endogenous antioxidant system, rather it inhibits it and does not have the same ability as ozoyl

to activate tissue repair. Ozoyl is a powerful anti-inflammatory agent because it regulates the transcription of cytokines involved in the inflammatory process.

The main links in the pathogenesis of the haemorrhoidal disease, a large number of developing complications of the disease, the negative effect of the prescribed therapy, and the severe consequences of the disease in the form of frequent relapses, as well as bleeding after a number of surgical interventions, indicate that this disease is relevant. To solve the issue of therapy, it is necessary to look for ways to prevent further development of haemorrhoids and improve the results of treatment of this formidable disease [1, 24, 26, 31]. According to the survey and examination of patients, it is known that most of them are young and able-bodied people. Therefore, this problem has socio-economic importance. Evidently, it is necessary to develop and introduce modern high-tech methods of treatment into clinical practice, aimed both at improving the quality of life of patients and reducing the risk of relapses and complications. It is also necessary that the treatment provided is financially affordable for the population [27].

To date, questions about the need to use a number of non-invasive technologies are still being discussed among proctologists and surgeons [26, 32]. The frequency of noninvasive interventions in hospitals and polyclinics over the past 10 years does not exceed 0.6%. This indicator is quite low compared to the indicators of Western Europe and the United States of America. In these countries, the rate of application of such technologies in the treatment of haemorrhoids is 83%. This is explained by the development and introduction of completely new equipment into clinical practice [33]. The effectiveness of the use of non-invasive methods of treatment of chronic haemorrhoids depends on the stage of the disease: at the second stage of the disease, the effectiveness of their use reaches about 91%, at the third stage – 70%.

A differentiated approach is necessary for the treatment of haemorrhoids. This means that it is necessary to consider not only the stage of the disease but also other factors that influence the outcome of treatment [34]. These include anatomical characteristics of the rectum, its blood supply, and the constitutional features of the patient [9, 18]. Considering the results of the study, the authors recommended the use of an integrated approach with the use of PRP therapy and an ozoyl-based cream in the treatment of chronic haemorrhoids. The ability to release oxygen and counteract hypoxia, microbicidal, anti-inflammatory, and immunomodulatory effects, and the ability to overcome oxidative stress and activate tissue regeneration and repair make ozoyl a perfect biological inducer [35].

Summing up the discussion, the authors emphasise that, with the ineffectiveness of conservative treatment in patients with chronic haemorrhoids of stages 2–3, surgical methods using PRP therapy and creams based on the biological modulator ozoyl are shown. In the postoperative period, it is mandatory to use phlebtonics from the first days according to a special scheme, taking osmotic laxatives from the third day, in combination with a diet enriched with vegetable fibre and a daily warm ascending shower.

Conclusions

Due to PRP therapy and the use of ozoyl in the main group, the pain syndrome decreased by about 30%, considering the period from the first day of the postoperative period in comparison with the control group. The postoperative wound healed in the main group in the third week after the operation, unlike the control group, in which this event was noted in the fourth week. The patients did not complain during an examination 3 months later. PRP therapy has numerous advantages because it is safe due to the use of plasma with platelets obtained from the patient's own blood. This is how complete biocompatibility is achieved. The transfer of infectious antigens, and the appearance of immunogenic and allergic reactions is excluded. Normally, 1 µl contains 200–300 thousand platelets, which play a key role in the process of blood clotting and secrete numerous growth factors.

The main target cells of growth factors are blood vessel cells, fibroblasts, and mesenchymal stem cells. This explains the restoration of blood vessels, muscles, connective tissue, and skin. This study is of practical significance because haemorrhoidal disease today has a high prevalence, and an integrated approach is required for the treatment of such patients. This work will also be useful for studying the implementation of optimised methods of treatment and management of patients with chronic haemorrhoids in medical institutions. Ozoyl is a powerful cell and tissue repairer. To restore and regenerate tissue, in addition to eliminating the infection affecting inflammation, stopping the ongoing degenerative processes, it is necessary to counteract hypoxia and saturate the tissue with oxygen, increase its vascularity, activate growth factors, and direct cells to proper healing and re-epithelisation.

Ozoyl is a biological inducer because, as reported in the studies above, it interferes with all these phases. Ozoyl releases immediately available oxygen, activates HIF-1 α , a hypoxia resistance factor, and promotes the synthesis of new blood vessels associated with VEGF activation. Based on the above, it can be concluded that the developed complex method using PRP therapy and

postoperative drug treatment, the use of ozoyl-based cream, and patient management allows for the successful treatment of chronic haemorrhoids of stage 2–3. One of the ways to optimise the accelerated regeneration process is PRP therapy. The use of PRP therapy accelerates the onset of complete epithelisation of the wound, helps to prevent complications and reduces pain, the duration of rehabilitation, and scarring. The introduction of optimised methods of treatment and management of patients with chronic haemorrhoids into the practice of medical institutions will improve the results of treatment of patients by reducing the frequency of postoperative complications and relapses of the disease, reducing the duration of treatment and temporary disability, and achieving a good economic effect.

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Ethical approval

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Conflict of interest

The authors declare no conflict of interest.

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