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Original Article

Meta-analysis on autologous stem cell transplantation in the treatment of limb ischemic

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Abstract: Aim: Meta-analysis on the effectiveness of the autologous stem cell transplantation in curing limb ischemic. Method: Consulting papers relate to the autologous stem cell transplantation in curing limb ischemic in PubMed, CNKI, Wan-fang Data and VIP. Based on include and exclude standards, we arrange at least 2 evaluators sifting these papers separately, doing Quality evaluation and information extraction and then cross checking. Negotiate through a third party if any disagreement comes out. Review Manager 4.2 is used in Meta-analysis. Result: Involved 7 papers, all in English version. Patients involved all diagnosed as critical limb ischemia (CLI). Results show that no adverse reaction occurred during this study. Amputation rate in patients with stem cell group treatment is lower than control group ($P < 0.05$). And no notable difference in improving ABI ($P > 0.05$). Conclusions: Applying autologous stem cell transplantation in curing limb ischemic does not have obviously effectiveness in the improvement of ABI of the limb ischemic patients. But it can dramatically reduce the rate of amputation. So autologous stem cell transplantation is a good and safe choice for patients have no choice but amputation.

Keywords: Stem cell, limb ischemic, meta-analysis

Introduction

Limb Ischemic is common form of peripheral arterial disease which arise from various types of vasculitis such as diabetes mellitus (DM) gangrene, arteriosclerosis obliterans (ASO) and thromboangiitis (TAO) [1]. It was reported that there were approximately 5~10 new cases per 10 000 in both the U.S. and Europe annually [2]. Limb Ischemic is characterised of the involvement of both the iliac artery and infrainguinal outflow vessels [3]. Once patients with critical limb ischemia (CLI) haven't received interventional or surgical limb salvage in time, 40% will lose their leg within 6 months and 20% will die [4]. It is therefore of importance to apply effective therapies so that can relieve exertional symptoms, improve walking capacity, relieve ischemic pain at rest, heal ischemic ulceration, prevent limb loss and improve quality of life of patients with limb Ischemic [5].

Numerous new therapy strategies have also been found in limb Ischemic such as endovascular treatment or surgical revascularization [6]. Autologous stem cell transplantation (ASCT) is an important new treatment which has been widely used in various of diseases. Kamber et al. reported that the mortality decrease 66% patients with herpes zoster after ACST compared with patients without treatment of ASCT which suggested ASCT is more beneficial than most tumor-directed therapies [7]. According to examine the impact of ASCT and discuss the clinical utility of ASCT proved that ASCT was an effective therapy for myeloma patients [8]. Besides, ASCT have also been confirmed to play vital role in the treatment of Hodgkin's lymphoma, type 2 diabetes mellitus, lymphoma, extramedullary plasmacytoma and so on [9-12]. Moreover, ASCT also served as an effective mehod in treating critical limb ischemia in a number of studies in previous. Thus, discover-

Table 1. General characteristics of included studies

References	Write time	Design Method	Treatment group (cases)	Control group (cases)	Treatment group interventions	Control group interventions	Follow-up time (month)	Evaluation	Adverse reactions
Mark D Iafrati [2]	2011	A randomized controlled	34	14	Intramuscular injection of bone marrow stem cells	Intramuscular placebo	3	Amputation rate, TcPO2, Pain score	No
Ahmet Ozturk [3]	2012	A randomized controlled	20	20	Intramuscular injection of peripheral blood stem cells	Intramuscular placebo	3	Amputation rate, ABI, TcPO2, Magnetic resonance angiography, Pain score	No
Pingping Huang [4]	2005	A randomized controlled	14	14	Intramuscular injection of peripheral blood stem cells	Intravenous injection of prostaglandin E1	3	Amputation rate, ABI, Pain score	No
Debin Lu [5]	2011	A randomized controlled	18	37	Intramuscular injection of bone marrow stem cells	Intramuscular saline	6	Amputation rate, ABI, TcPO2, Magnetic resonance angiography, Ulcer healing rates, Pain score	No
Richard J Powell [6]	2011	A randomized controlled	32	14	Intramuscular injection of bone marrow stem cells	Intramuscular placebo	6	Amputation rate, ABI, Ulcer healing rates	No
Douglas W Losordo [7]	2012	A randomized controlled	16	12	Intramuscular injection of stem cells	Intramuscular placebo	12	Amputation rate, ABI, TBI, Rest pain, Ulcer healing rates, Quality of Life	No
C.Luedemann [8]	2011	A randomized controlled	26	21	injection bone marrow stem cells	Intramuscular placebo	3	Rutherford score, Larger amputation rate, TcPO2, KAI, Ulcer area	No

ing the application of ASCT on limb ischemia could better introduce this efficient therapy.

In this study, we present a meta-analysis of research about the treatment of limb Ischemic with ASCT. The "stem cells" and "limb ischemia" were taken as the theme to search the English articles and extracted the data from the database including PubMed, CNKI, Wanfang Data and VIP. This may reveal the effectiveness of the ASCT in curing limb ischemic.

Materials and methods

Include and exclude criteria

Include criteria: (1) Research type: Randomized controlled trial (RCT), non-randomized controlled trial/controlled clinical trial (CCT) and cohort study. (2) Study object: Patients diagnosed as CLI, without good conventional medical treatment effectiveness, haven't received amputation or lower limb blood flow reconstruction interventional surgery. No special requirements in age, sex and race. (3) Intervention measure and observational index: ① Intervention measure: The test group accepts autologous stem cell transplantation treatment, and control group accepts only placebo or other medical treatment. ② observational indexes are amputation rate, ABI, TcP02, ulcer heal rate, pain score and magnetic resonance arteriography. (4) Uniform and comparable in age, sex, biochemical and other parts between two groups. (5) Published papers at home and abroad.

Exclusion criteria: (1) Non-CLI patients. (2) Survival CLI greater than 1 year. (3) Repeat the same test on published literature or subgroup analyzes. (4) Data provided by the literature cannot be converted or used in the analysis.

Search strategy

Search strategy: We searched PubMed, CNKI, Wan-fang Date, VIP and other database storage, from the database start time to December 2013, traced all the documents incorporated by reference. We used "stem cells" and "limb ischemia" as the English search terms, also used their Chinese names.

Determine the efficacy index

We compare the difference of amputation rate, ABI, TcP02, magnetic resonance angiography, ulcer healing rates, pain scores is difference between stem cell transplantation group and non-transplant group, and take this as the criterion of judgment.

Quality assessment and data extraction

According to the inclusion and exclusion criteria, at least 2 evaluators separately sift these papers, do Quality evaluation and information extraction and then cross checking. Negotiate through a third party if any disagreement comes out. Quality assessment of randomized controlled trials refers to the Jadad scale [13]. Extraction of information including basic research, sample size, intervention characteristics (interventions, follow-up time, etc.), the efficacy evaluation (amputation rate, ABI, TcP02, magnetic resonance angiography, ulcer healing rates, pain scores) and results.

Statistical analysis

We do analysis with the help of one software (review manager 4.2) provided by the Cochrane Collaboration. Count data are presented by odds ratio (odds ratio, OR) and 95 % confidence intervals (95% confidence interval, 95% CI); continuous data will presents by the weighted average number of (weighted mean difference, WMD) and 95% confidence intervals. If the study was not statistically homogeneous, using fixed effects model analysis; if between studies heterogeneity, using a random effects model analysis. Significance level set as 0.05. It indicates significant difference in the efficacy of different treatments if $P < 0.05$. Funnel plot was used for showing difference.

Results

General characteristics of included studies

Included seven English literature (both RCTs) [14-20]. A total of 292 cases of limb ischemia patients, including 160 cases in treatment group and 132 cases in control group. The basic characteristics of each study are shown in **Table 1**.

The quality evaluation of the included papers

Retrieval of English literature includes 500 papers, among them 344 Chinese literature. After removing duplicate and irrelevant ones, totally get 11 English literatures and 4 Chinese literatures. After assessment with study entry

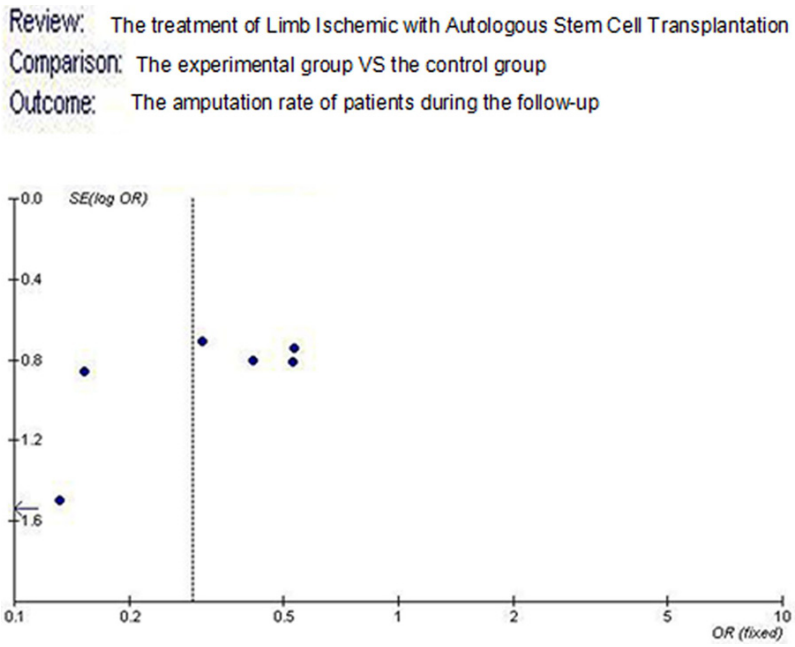

Figure 1. Put these 7 literatures into funnel plot, and shows that the true value of the included studies is the symmetric distribution center, suggesting that difference is less.

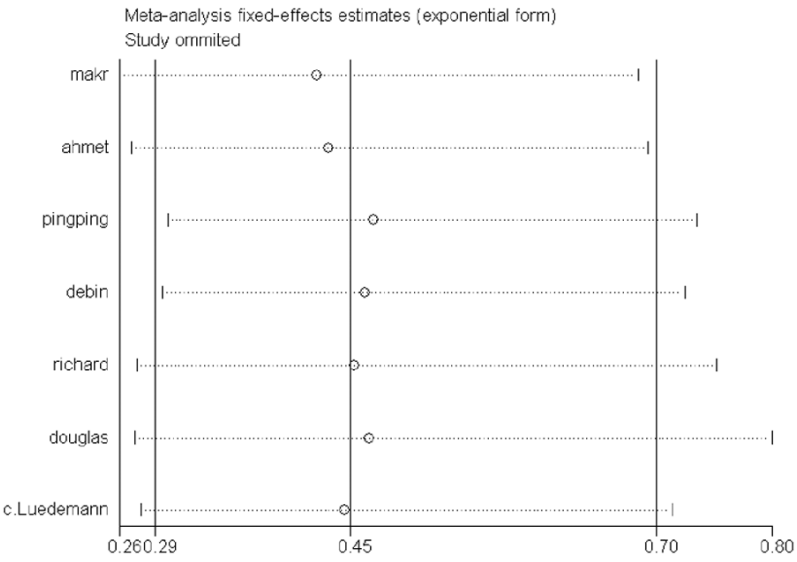

Figure 2. Sensitivity analysis shows the various research studies included did not deviate from the true value was found, the weight is too large or too small.

criteria, final 7 English literatures (both RCTs) were selected into the meta-analysis. Each paper describes include and exclude criteria of the object, sources of cases, basic characteristics, treatment and control groups with comparable baseline. 7 literatures all refer to "random", only the literature [14, 15] have brief description of stochastic methods, included into randomized controlled study but failed to determine whether hide randomly or not; literature [14, 17, 19, 20] propose double-blind method; literature [17, 18] report a case of lost and exit, describe the reasons for lost and exit in detail; All results data are complete; no selected reporting results. During quality assessment of these 7 literatures, the literature [14, 17, 19, 21] are high quality, literature [15, 16, 18] are low quality. Put these literatures into funnel plot (**Figure 1**), the date indicates that the true value of the included studies is the symmetric distribution center, suggesting that difference is less. To further examine the reliability of the Meta-analysis, sensitivity analysis was used on the results (**Figure 2**), each of the included studies found no deviation from the true value, no larger or smaller weight. Begg's test (**Figure 3**) shows that Pr > |z| = 0.548, publication bias was not found.

Index analysis

Amputation rate: 7 selected papers regard amputation rate as an indicator of the judgment of effectiveness, including 160 cases in the test group and 132 cases in the control group. Test for heterogeneity Chi? = 3.36, df = 6, P = 0.76, show no heterogeneity between studies, the application of the combined effect of the amount of the fixed effects model OR, OR combined = 0.29, 95% CI is (0.16, 0.54), argyle forest map all located on the vertical left side, test the amount of the combined effect, Z = 3.86, P

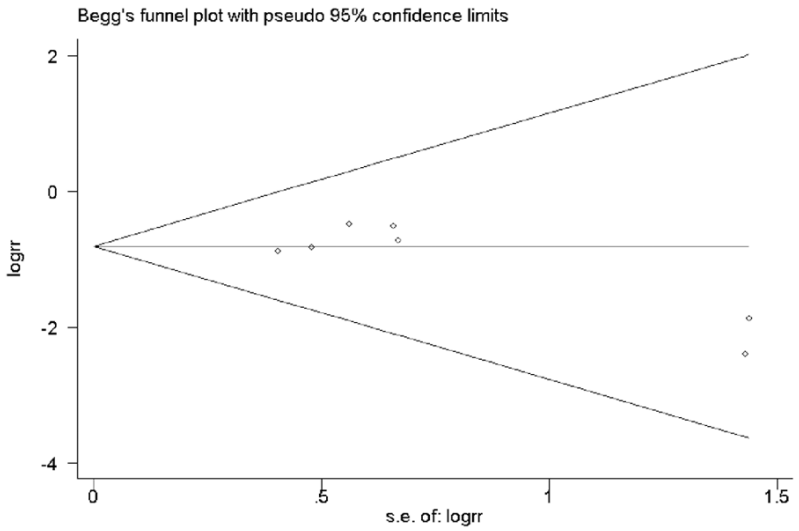

Figure 3. Various studies by Begg's test shows Pr > |z| = 0.548 no statistical significance was not found published offset.

= 0.0001, means that in reducing the amputation rate, compared with the control group, autologous stem cell transplantation can significantly reduce the amputation rate among patients with limb ischemia, difference between them has statistically significant (**Figure 4**).

ABI index: literature [15-18] regard ABI as an indicator of the judgment of effectiveness, 84 cases in the treatment group and 85 cases in the control group. Test for heterogeneity Chi? = 3.28, df = 3, *P* = 0.35, did not show any heterogeneity between studies, the application of the combined effect of the amount of the fixed effects model WMD, WMD = 0.03, 95% CI is (-0.02, 0.07), diamond forest map located above the vertical pattern, test the amount of the combined effect, Z = 1.08, *P* = 0.28, regarding prompted in improving ABI, compared with autologous stem cell transplantation, the treatment group and the control group had no significant improvement in the treatment, the difference between the two groups has no statistically significance (**Figure 5**).

TcPO2: literature [14, 15, 17, 20] regard TcP02 as an indicator of the judgment of effectiveness, the literature [20] shows that the difference between stem cell transplantation group and control group has no statistical significance. Statistical analysis was not used in literature [14], but the results showed that autologous stem cell transplantation group was better than the control group, the difference between the treatment group and control group has statistically significant.

Magnetic resonance angiography: Literature [15, 17] regards the result of magnetic resonance angiography as an indicator of the judgment of effectiveness in lower limb vascular regeneration. Literature [15] indicates that in promoting lower extremity revascularization, the difference between autologous stem cell transplantation group and the control group has no statistically significant, but much better than the control group. Literature [17] indicates that in promoting lower extremity revascularization, the difference between autologous stem cell transplantation group and the control group has statistically significant.

Ulcer healing rates: Literature [15, 17-20] regard ulcer healing as an indicator of therapeutic efficacy. The literature [15, 17] indicates that in promoting ulcer healing aspect, the difference between autologous stem cell transplantation group and the control group has significant differences. Literature [18] indicates that in promoting ulcer healing aspect, the 6 months follow-up of autologous stem transplant group has no difference with the control group. 12 months follow-up of autologous stem group has no significant difference with the control group, but much better than the control group. Literature [19] indicates that in promoting ulcer healing, the difference between autologous stem cell transplantation group and the controlled group after 12 months has no statistical significance. Literature [20] indicates ulcer area reduced by 27% in the autologous stem cell transplantation in the treatment group, but increased by 32% in the control group.

Pain rating: Selected literature [14-17, 19] will determine the effectiveness by pain scores, only literature [19] said the difference between autologous stem cell transplantation treatment group and control group has no statistical significance in reducing the patient's limb pain (*P* > 0.05), more than literature are tips on improv-

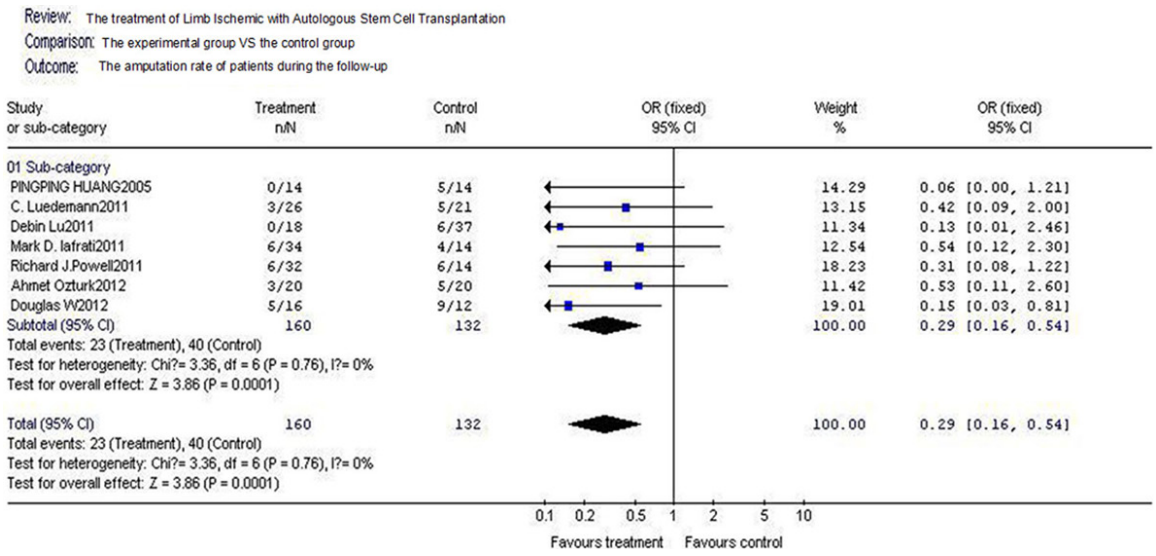

Figure 4. The reducing amputation rate compared with the control group shows that autologous stem cell transplantation can significantly reduce the amputation rate among patients with limb ischemia, difference between them has statistically significant.

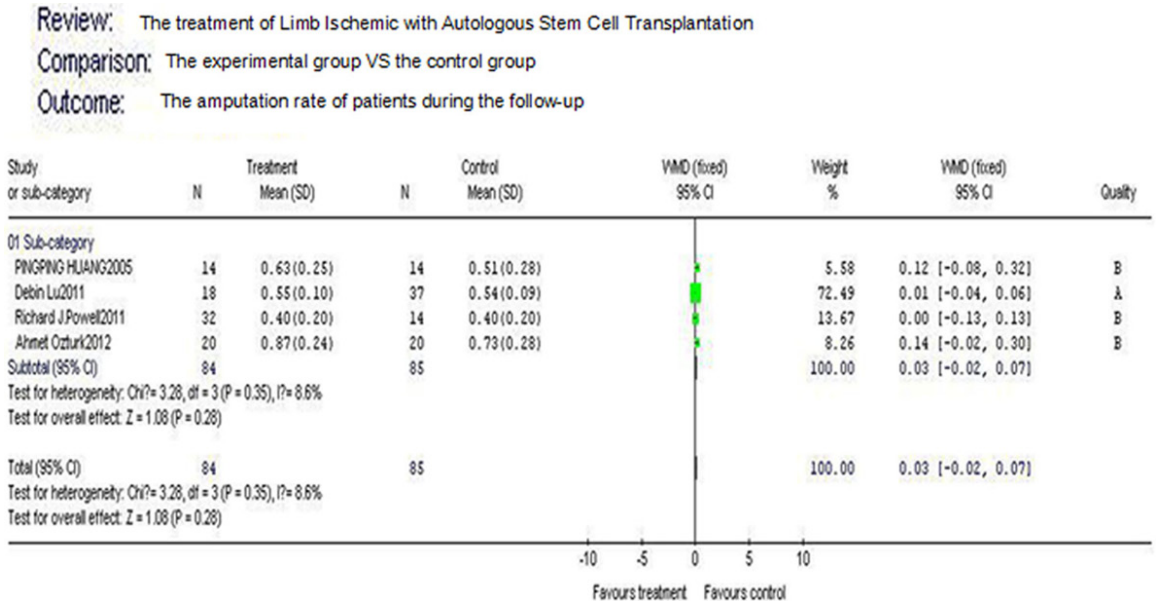

Figure 5. Prompted in improving ABI, compared with autologous stem cell transplantation shows that the treatment group and the control group had no significant improvement in the treatment, the difference between the two groups has no statistically significance.

ing a patient's limb pain, other literatures insist that the difference between the treatment group and control group has statistically significant.

Adverse reactions

All studies found no significant adverse reactions.

Discussion

Lower limb ischemic disease is a group of serious harm to human health, reduce the quality of life of patients with the disease, with the average life expectancy, the incidence was significantly increased [22-27]. Among arteriosclerosis obliterans [28, 29] and diabetic foot [30-32] is common, patients may exhibit intermit-

tent claudication, rest pain or limb necrosis. Medical treatment ineffective, surgical distal arterial occlusion also lacks a good way. In recent years, with the development of molecular biology and cell biology engineering technology and in-depth understanding of stem cell research, stem cell transplant to lower limb ischemia, promote angiogenesis and improve blood supply to the lower limbs, provides a lower limb ischemic disease kind of new treatment ideas.

Stem cells have a high degree of self-renewal and multiple differentiation potential, and its main objective is to promote the lower limb angiogenesis, differentiate into endothelial cells and further differentiate the formation of new capillaries Stem cell transplantation is by granulocyte colony-stimulating factor mobilized bone marrow or peripheral blood, and to obtain peripheral blood stem cells, mesenchymal stem cells, circulating progenitor cells, and CD34 or CDl33 such as stem cells, via a syringe multi-point injection into the gastrocnemius or shares four triceps other ischemic region, wherein the spacing between each injection point is 1-3 cm, there are stem cells were injected into the lower limb arterial ischemic lower limb ischemia or for windows (for example, tibial puncture) so that drain directly into the bone marrow stem cells surrounding muscle tissue, the stem cells are transplanted into ischemic limb muscle stem cells can secrete a series of cytokines induced differentiation, the formation of new capillaries, improve and restore blood flow in the lower limb, lower limb ischemia for therapeutic purposes.

2002 Tateishi-Yuyama et al. [21] in the international arena for the first time reported the application of autologous bone marrow stem cells to treat ischemic lower extremity vascular disease, the clinical trials a total of 45 patients, 4 to 24 weeks to receive stem cell transplants after treatment, these the patient's ankle-brachial index, transcutaneous oxygen pressure, normal walking distance, and the degree of rest pain has significantly improved. Kalka et al. [33] proved directly transplanted bone marrow mesenchymal stem cells can enhance the growth of some of ischemic vascular disease. Since then, other experiments show that bone marrow stem cells and peripheral blood stem cells in the ischemic locally laterally into vascular endothelial cells and further differentiate the formation of new blood vessels, the formation of new collateral , improve local blood supply patients to achieve therapeutic purposes [34-37].

There are many domestic and descriptive study of transplantation of autologous stem cells for the lack of reports of randomized controlled trials, meta-analysis of the collected seven RCT studies, the results showed that each study had no adverse reaction, stem cell therapy group limb ischemia the incidence of amputation in patients than the control group ($P < 0.05$), the difference between the two was statistically significant improvement in ABI stem cells in the treatment group compared with the control group showed no significant difference between them ($P > 0.05$). For the promotion of lower extremity revascularization, ulcer healing, relieve physical pain, improve TcPO2 value in patients with no statistical data, the study only set out the results of each test for reference.

In summary, this meta-analysis shows that, for conservative therapy, in addition to the amputation of limb ischemia patients with no choice, the autologous stem cell transplantation in the treatment of patients with amputations can reduce incidents and improve the quality of life for patients, their efficacy is yes, and is safe.

Disclosure of conflict of interest

None.

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