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Original Article

Mechanistic analysis of Qianggu Bushen Huoxue formula on improving bone metabolism

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Abstract: Objective: This study was designed to explore the effects and mechanism of Qianggu Bushen Huoxue Formula (QGBSHXF) in improving the bone metabolism of postmenopausal osteoporotic vertebral compression fracture (POVCF) patients after percutaneous vertebroplasty (PVP). Methods: A total of 97 POVCF patients who received PPV in our hospital from January 2018 to January 2019 were divided into the Study Group (SG, n=50) treated by QGBSHXF and the Control Group (CG, n=47) treated by routine drugs after the same surgery. L2-L4 bone mass density (BMD) before treatment, at 1 week, 1 month, 2 months and 3 months after the treatment, bone gla protein (BGP), alkaline phosphatase (ALP), urinary hydroxyproline (U-HYP) and urinary calcium (U-Ca^{2+}) levels, Oswestry dysfunction index (ODI) and visual analogue scale (VAS) scores before and after treatment; as well as the incidence of adverse reactions during treatment were compared between the two groups. Results: At 1 month, 2 months and 3 months after the treatment, the SG had higher BMD as compared with the CG ($P<0.05$); after treatment, higher levels of ALP and BGP, lower levels of U-Ca^{2+} and U-HYP, and lower scores of ODI and VAS were observed in the SG ($P<0.05$). For incidence of adverse reactions, the difference was not statistically significant ($P>0.05$). Conclusion: QGBSHXF has demonstrated satisfactory effects of safely improving the BMD and bone formation, vertebrae function and long-term pain intensity, and inhibiting bone resorption in POVCF patients after PVP.

Keywords: PVP, QGBSHXF, postmenopausal osteoporosis, vertebral compression fracture, bone metabolism

Introduction

With the continuous population aging in China in recent years, the incidence of all kinds of degenerative diseases is increasing year by year. Oteoporosis, a metabolic bone disease, is characterized by the decrease of bone tissue per unit volume and the change of bone microstructure [1, 2], and it can occur in individuals of any gender and age, but mostly in postmenopausal women and older men. The main clinical manifestations of patients with osteoporosis include pain, shortened body length, hunchback, fracture, decreased respiratory function, etc. Some patients may also have joint deformation or disability, which seriously impacts their normal life [3, 4].

As mentioned, postmenopausal women are highly susceptible to osteoporosis because of the sharp reduction in estrogen levels after pausimenia, which then leads to degraded inhibition of calcium signaling in osteoclasts. As a result, the bone resorption amount exceeds the bone formation amount, and osteopenia and degenerative bone diseases occur [5, 6]. Other studies pointed out that the fall in estrogen levels will affect the individual's utilization of vitamin D and cause reduction in calcium absorption, which further increases the relative deficiency of bone formation amount and can induce osteoporotic vertebral compression fractures [7-9]. Percutaneous vertebroplasty (PVP) is one of the common surgeries for patients with osteoporotic vertebral compression fractures. Its advantages include minimal invasion, rapid recovery, low risk and outstanding effects in mitigating clinical symptoms. However, altering osteoporosis in postmenopausal women, is in fact, the basic approach to reduce the incidence of vertebral compression fractures [10, 11]. In traditional Chinese medicine, a lot of experience has been accumulated in improving the prognosis of fracture patients. Qianggu Bushen Huoxue Formula (QGBSHXF), a traditional Chinese prescription, could impro-

ve bone metabolism and density [12]. In this paper, QGBSHXF's positive contributions to the BMD and bone formation, effective inhibition of bone resorption, improvement of vertebrae function and long-term pain intensity as well as high safety in POVCF patients after PVP were observed and introduced as follows.

Materials and methods

General materials

A total of 97 POVCF patients treated by PVP in our hospital from January 2018 to January 2019 were divided into the SG (n=50) and the CG (n=47) according to the treatment therapies. In the SG, there were 5 cases of T8 fracture, 5 cases of T9, 4 cases of T10, 5 cases of T11, 5 cases of T12, 5 cases of L1, 7 cases of L2, 8 cases of L3, 3 cases of L4, and 3 cases of L5 fracture segments. In the CG, there were 4 cases of T8 fracture, 4 cases of T9, 4 cases of T10, 4 cases of T11, 5 cases of T12, 5 cases of L1, 7 cases of L2, 8 cases of L3, 3 cases of L4, and 3 cases of L5 fracture segments.

Inclusion criteria: (1) Women with pausimenia for over 1 year and age ≤70; (2) Clinically diagnosed with osteoporotic vertebral compression fracture and treated by PVP; (3) Clear consciousness and able to cooperate with the investigation; (4) Complete medical records; (5) This study obtained approval from the Ethics Committee of the Ningbo No. 6 Hospital; (6) Informed consent was obtained from all patients.

Exclusion criteria: (1) Complications such as mental disorders, malignant tumors, severe diseases in the stomach, intestine and kidney or severe angiocardiopathies, rendering BMD testing impossible; (2) Allergic to the drugs studied; (3) Osteoporosis as a result of long-term administration of hormones; (4) Spinal injury due to fracture.

Removal criteria: (1) Failure to participate in the follow-up; (2) Active request for withdrawal during the study; (3) Death during the study.

Methods

After hospitalization, all patients received routine imaging examinations, testing of liver and kidney function, and PVP. Thereafter, patients in the CG were administered with routine drugs, including Caltrate D (Product name: Calcium Carbonate and Vitamin D 3 Chewable, manufacturer: Wyeth Pharmaceutical Co., Ltd., specification: 300 mg/tablet, approval document No.: GYZZ No. H10950030) at a dose of 600 mg/time, twice a day, and Alendronate Sodium Tablets (Product name: Fosamax, manufacturer: MSD Hangzhou Pharmaceutical Co., Ltd., specification: 70 mg/tablet, approval document No.: GYZZ No. J20130085) at a dose of 10 mg/time, once a day. For patients in the SG, in addition to drugs provided to the CG patients, QGBSHXF was followed. The formula included Radix Rehmanniae Praeparata (20 g), Radix Salviae Miltiorrhizae (30 g), lignum millettiae (30 g), Ligusticum chuanxiong Hort (15 g), radix achyranthis bidentatae (15 g), Rhizoma Dioscoreae (15 g), Angelica sinensis (15 g), radix dipsaci (15 g), drynaria rhizome (15 g), Antler Glue (15 g), Eucommia ulmoides (12 g), Semen Cuscutae (12 g), fructus corni (12 g), herba epimedii (12 g), rhizoma alismatis (10 g), Aulastomum gulo (10 g), radix angelicae tuhuo (10 g) and prepared radix glycyrrhizae (6 g). The herbs were boiled in water to obtain a liquid preparation of 400 ml, which was taken two times. Both groups were treated for 3 months.

Observation indexes and evaluation criteria

Changes in BMD before and after treatment: All patients were tested for L2-L4 BMD by an X-ray instrument before treatment and at 1 week, 1 month, 2 months and 3 months after treatment for intergroup and intragroup comparison.

Changes in bone metabolism indices before and after treatment: Blood samples were collected from all patients in the morning in a fasting status before treatment and at 3 months after treatment, and centrifuged. The serum was used for measurement of BGP, ALP, U-HYP and U-Ca^{2+} levels with a Hitachi 7600 automatic biochemical analyzer from Japan for intergroup and intragroup comparison.

Changes in ODI and VAS scores before and after treatment: ODI and VAS were used to measure the waist and back functions and pain intensity, respectively. ODI consists of 9 indexes, such as independence in daily activities, lifting, walking and sitting; each assigned with a grade between 0 and 5. Scores of all items were summed to reflect the functions.

Table 1. Intergroup comparison of general clinical materials ($\bar{x} \pm s$)/[n (%)]

Materials		SG (n=50)	CG (n=47)	t/X^2	*P*
Age (y)	45-55	19	18	0.231	0.445
	56-65	21	20		
	66-75	10	9		
Pausimenia duration (y)	<10	18	17	0.198	0.512
	10-20	22	21		
	21-30	10	9		
BMI (kg/m^2)		23.98±2.21	24.03±2.19	0.112	0.911
Marital status	Married	45	43	0.064	0.801
	Unmarried	5	4		
Monthly revenue (RMB)	<1000	9	6	0.343	0.211
	1000-3000	32	32		
	>3000	9	9		

Higher scores indicated worse functions. VAS is a common clinically used tool to evaluate pain intensity. Patients made a mark on a 10 cm straight line according their subjective feelings [13, 14]; on which, 0 indicates no pain and 10 the worst possible pain.

Incidence of adverse reactions during treatment: Follow-up and return visit were combined to calculate the incidences of liver and kidney dysfunction, skin reactions and gastrointestinal reactions during treatment for intergroup comparison. The incidence of adverse reactions = [(Number of liver and kidney dysfunction incidences + number of skin reactions + number of gastrointestinal reactions)/Total number of cases] ×100%.

Statistical analysis

Statistical analysis was performed with SPSS 22.0. In case of nominal data expressed as [n (%)], comparison studies were carried out through chi-squared test for intergroup comparison. In case of numerical data expressed as Mean ± Standard Deviation, intergroup or intragroup comparison studies were carried out through one-way analysis of variance (ANOVA). For all statistical comparisons, significance was defined as P<0.05 [15].

Results

Intergroup comparison of general clinical materials

Before treatment, the two groups' age distribution, pausimenia duration (y) and BMI were not statistically different (P>0.05) but comparable (**Table 1**).

Intergroup comparison of BMD before and after treatment

No statistical difference was observed between the two groups for BMD before and 1 week after treatment (P>0.05). As the treatment continued on to 1 month, 2 months and 3 months, the BMD was significantly higher in the SG (P<0.05) (**Table 2** and **Figure 1**).

Intergroup comparison of bone metabolism indices before and after treatment

Measurement demonstrated no statistical difference between the two groups in ALP, BGP, U-Ca^{2+}, and U-HYP levels before treatment (P>0.05). After 3-months of treatment, ALP and BGP levels significantly rose, while U-Ca^{2+} and U-HYP levels significantly reduced in both groups (P<0.05). Intergroup comparison revealed that the ALP and BGP levels were higher, and the U-Ca^{2+} and U-HYP levels were lower in the SG (P<0.05) (**Table 3** and **Figure 2**).

Intergroup comparison of ODI and VAS scores before and after treatment

According to evaluation, the two groups were not significantly different in ODI and VAS scores (P>0.05) before treatment, but experienced marked reduction at 3 months after treatment (P<0.05) when both indexes were at a significantly lower level in the SG (P<0.05) (**Table 4** and **Figure 3**).

Intergroup comparison of incidence of adverse reactions during treatment

The 3-month incidence of adverse reactions was 12.00% (6/50) in the SG and 10.64% (5/47) in the CG (P>0.05) (**Table 5** and **Figure 4**).

Discussion

The concept of osteoporosis dates back to 1885 when it was put forward by the European

Table 2. Intergroup comparison of BMD before and after treatment ($\bar{x} \pm s$)

Group	n	Before treatment	week after treatment	1 month after treatment	2 months after treatment	3 months after treatment	*F*	*P*
SG	50	0.61±0.11	0.64±0.13	0.83±0.15	0.94±0.13	0.96±0.16	4.322	<0.001
CG	47	0.59±0.12	0.63±0.12	0.70±0.12	0.76±0.12	0.81±0.15	5.019	<0.001
t	-	0.856	0.393	4.695	7.073	4.756		
P	-	0.394	0.695	<0.001	<0.001	<0.001		

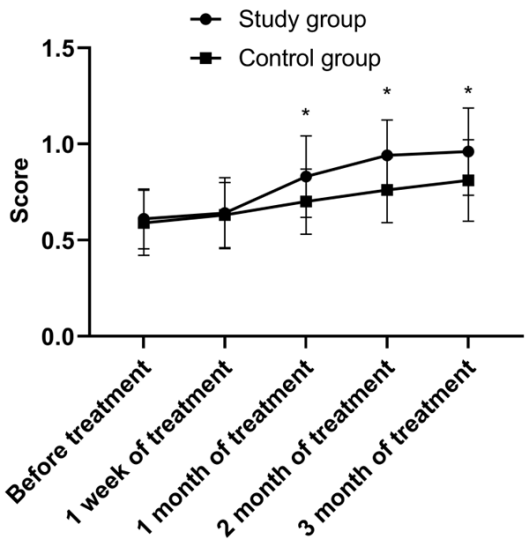

Figure 1. Intergroup Comparison of BMD before and after Treatment. Before treatment and at 1 week after treatment, a statistical difference was not found between the two groups in BMD (P>0.05). At 1 month, 2 months and 3 months after treatment, the BMD in the SG was significantly higher (P<0.05). *P<0.05 vs CG for the same index.

pathologist Pommer. In 1941, Albright further explained the definition. According to the WHO, osteoporosis is a systematic bone disease characterized by low bone mass and damaged bone microstructure, which results in the elevated bone brittleness and causes the individuals to be susceptible to fractures [16]. Data shows that so far there are over 200 million patients with osteoporosis, including about 70 million that are above 50 years old in China. While the disease ranks 7th in clinical common diseases and diseases of high incidence, its annual rise in China has severely affected economic development and people's lives [17]. Clinically, the causes of osteoporosis are classified into two types: primary and secondary. Primary osteoporosis mainly includes postmenopausal osteoporosis (the focus of this study [18]), degenerative osteoporosis, and idiopathic osteoporosis.

An epidemiological investigation of the senior population pointed out that the incidence of osteoporosis was significantly higher in postmenopausal women as compared with the males of the same age; and it was up to about 50%-70% in women aged between 60 and 69 years, while in senior males, it was only around 30%. According to current clinical studies, the reason lies in the sharp reduction of estrogen levels after pausimenia, which accelerates bone turnover and loss, damages bone metabolism balance, compromises bone strength, and induces osteoporosis [5]. As a common disease in postmenopausal osteoporosis women, vertebral compression fracture is always related with reduced load bearing capacity of vertebrae and bone rigidity. After fracture, most of the patients will experience severe pain in the waist and back, limitations in activities, and obvious impacts in daily life [19]. Traditional therapies of vertebral compression fracture, such as oral administration of drugs, bed rest or orthosis, are conservative, long-term and associated with a high incidence of complications, which may worsen osteoporosis and lead to a vicious circle, and therefore are seldom applied. PVP is presently a common minimally invasive surgery developed for vertebral compression fracture. During the surgery, bone cement is injected into the vertebrae to directly reinforce the vertebral strength and stabilize the vertebrae. It plays a positive role in improving patients' clinical symptoms and accelerating the recovery of vertebrae function as well as structure reconstruction, and therefore is popularized in the clinic [20]. However, experience has figured out that regardless of the positive effects of PVP, patients are still troubled by osteoporosis symptoms and the risk of fracture again. For this reason, oral administration of drugs against osteoporosis is sug-

Table 3. Intergroup comparison of bone metabolism indexes before and after treatment ($\bar{x} \pm s$)

Observation Index	Group	n	Before treatment	3 months after treatment
ALP (U/L)	SG	50	33.77±6.72	45.98±7.54*
	CG	47	34.01±6.55	40.12±4.38*
	t	-	0.178	4.642
	P	-	0.859	<0.001
BGP (μg/L)	SG	50	7.53±2.43	9.67±2.21*
	CG	47	7.51±2.39	8.68±2.39*
	t	-	0.041	2.12
	P	-	0.967	0.037
U-Ca^{2+} (Cr)	SG	50	0.59±0.17	0.34±0.11*
	CG	47	0.61±0.15	0.41±0.12*
	t	-	0.613	2.997
	P	-	0.541	0.003
U-HYP (Cr)	SG	50	2.87±0.73	1.78±0.59*
	CG	47	2.86±0.71	2.08±0.81*
	t	-	0.068	2.094
	P	-	0.946	0.039

Note: *P<0.05 vs conditions before treatment.

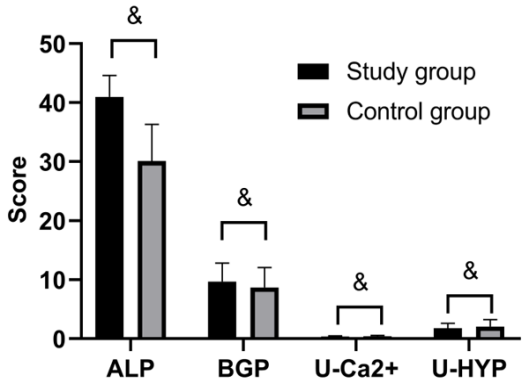

Figure 2. Intergroup comparison of bone metabolism indices after treatment. As compared with the CG, the SG had significantly higher ALP and BGP levels, and lower U-Ca^{2+} and U-HYP levels (P<0.05). & = P<0.05 vs CG for the same index.

gested to improve their bone metabolism and density [21].

Based on abundant experience in osteoporosis and its related diseases, traditional Chinese medicine classifies osteoporosis to the scope of heumatism, osteanabrosis, and marrow exhaustion. Relevant records can be found in medical books such as: *Su Wen* that the kidneys are responsible for bone nurturing and essence collection. With sufficient essence, marrow is full and bones are strong, or the *Neijing* that "essence is collected in the kidneys to nourish bones and produce marrow", or the *True Legend of Medicine* that "rhe Qi flows with blood; any blockage in Qi will result in stasis". Those records have supported the close relationship between osteoporosis, kidney deficiency and stasis. Kidney deficiency is an inducer of osteoporosis while stasis accelerates its progress. Therefore, traditional Chinese medicine suggests treatment of osteoporosis based on syndrome differentiation from the two aspects [22]. By setting up the SG and the CG, this study explored the mechanism of QGBSHXF in improving the bone metabolism of POVCF patients after PVP. Results indicate that compared with the CG patients who were treated only by western medicine, the SG patients have achieved a marked rise in BMD at 1 month, 2 months and 3 months after additional treatment with QGBSHXF. According to other literature, the "kidney" accounts for most bone diseases. In TCM, kidney essence has the function of nourishing bone marrow and reinforcing sclerotin. Kidney deficiency will result in kidney essence not being sufficient enough to nourish sclerotin. As a result, BMD is reduced, and osteoporosis occurs. Furthermore, some literature also states that stasis plays an important role in the progress of osteoporosis by affecting the circulation of the main and collateral channels in the liver the kidneys, leading to muscles and bones being undernourished, and inducing osteoporosis [23]. The QGBSHXF adopted in this study contained drugs such as Radix Rehmanniae Praeparata, Radix Salviae Miltiorrhizae, lignum millettiae, Ligusticum chuanxiong Hort, etc., amongst which, Radix Rehmanniae Praeparata can nourish yin and supplement blood, promote blood circulation, invigorate Qi and produce bone marrow. Radix Salviae Miltiorrhizae can promote blood circulation, remove blood stasis, and induce menstruation to relieve menalgia. Lignum millettiae can enrich and invigorate the circulation of blood to cause the muscles and joints to relax. Ligusticum chuanxiong Hort can promote the circulation of blood and Qi, dispel the wind and stop pain. Rhizoma Dioscoreae can reinforce muscles

Table 4. Intergroup comparison of ODI and VAS scores before and after treatment ($\bar{x} \pm s$)

Group	n	ODI		VAS	
		Before treatment	3 months after treatment	Before treatment	3 months after treatment
SG	50	38.87±4.33	18.29±2.34	7.67±0.34	1.28±0.14
CG	47	38.76±4.98	23.83±2.46	7.63±0.29	1.78±0.21
t	-	0.116	11.367	0.622	13.874
P	-	0.908	<0.001	0.535	<0.001

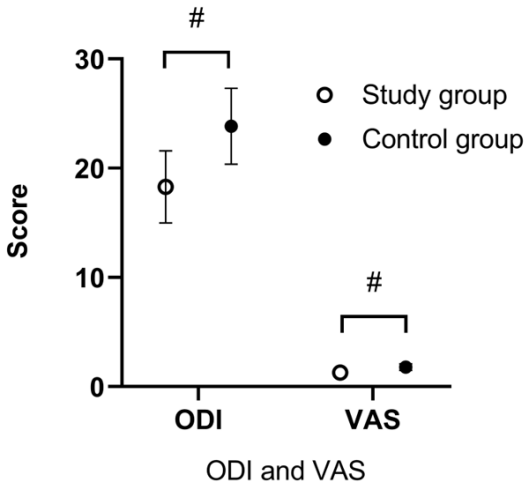

Figure 3. Intergroup comparison of ODI and VAS scores after treatment. As compared with the CG after treatment, the SG had lower ODI and VAS scores (P<0.05). # = P<0.05 vs CG for the same index.

and bones, and nourish kidney qi, and drynaria rhizome can eliminate stasis to stop pain, and reconnect muscles and ligaments. The mixture of those ingredients works on the blood and veins, supplementing the kidneys and bone marrow to effectively improve the kidney deficiency and stasis in postmenopausal osteoporosis patients, so as to rapidly raise their BMD.

Besides, this study also demonstrated QGBSHXF's role in improving bone metabolism indices, enhancing the ALP and BGP levels, and reducing the U-Ca^{2+} and U-HYP levels in postmenopausal osteoporosis patients. According to clinical practice, BGP and ALP are used to measure bone metabolism. BGP, a vitamin K-dependent calcium binding protein, plays an important role in regulating bone calcium metabolism, while ALP is an enzyme extensively distributed in our body to differentiate diseases in bones, liver and bladder systems. Both indices can reflect the bone metabolism. Their high expression indicates that Ca^{2+} deposits in the bones with little loss, which means the bone formation amount has exceeded the bone resorption amount [24]. The U-Ca^{2+} reflects the content of calcium in the 24 h urine of patients, and U-HYP output is another index of bone metabolism. When either of the indices are at a high level, our body is losing calcium rapidly [25]. According to the results of this study, ALP and BGP were at higher levels, U-Ca^{2+} and U-HYP were at lower levels in the SG after treatment, making it clear that QGBSHXF has effectively inhibited bone resorption and reinforced bone formation, which supported another finding of the study that the BMD was more satisfactory in the SG. In addition, QGBSHXF also demonstrated its effects in improving the waist and back functions and reducing the pain intensity of postmenopausal osteoporosis patients. The reason lies in the ingredients of the formula, which can promote blood circulation, remove blood stasis, induce menstruation to relieve menalgia, and effectively improve the vertebrae function. The difference between the two groups in the incidence of adverse reactions is also evidence for the formula's high safety for long-term application.

In conclusion, QGBSHXF has achieved good effects in improving the BMD and bone formation of POVCF patients after PVP, i.e., effectively inhibiting bone resorption, improving vertebrae function and long-term pain intensity, and has high safety. As a retrospective study, this study is defective in the following two aspects: limited number of samples and ambiguous or incomprehensive results; as well as failure of long-term follow-up, with insufficient analysis of effects on patients' long-term quality of life. To solve those problems, future studies shall be more detailed and representative, in order to provide a more comprehensive and scientific basis for clinical treatment.

Disclosure of conflict of interest

None.

Table 5. Intergroup comparison of incidence of adverse reactions during treatment [n (%)]

Group	n	Gastrointestinal reaction	Skin reaction	Liver and kidney dysfunction	Total incidence
SG	50	3 (6.00)	2 (4.00)	1 (2.00)	6 (12.00)
CG	47	2 (4.26)	2 (4.26)	1 (2.13)	5 (10.64)
X^2	-	-	-	-	0.045
P	-	-	-	-	0.833

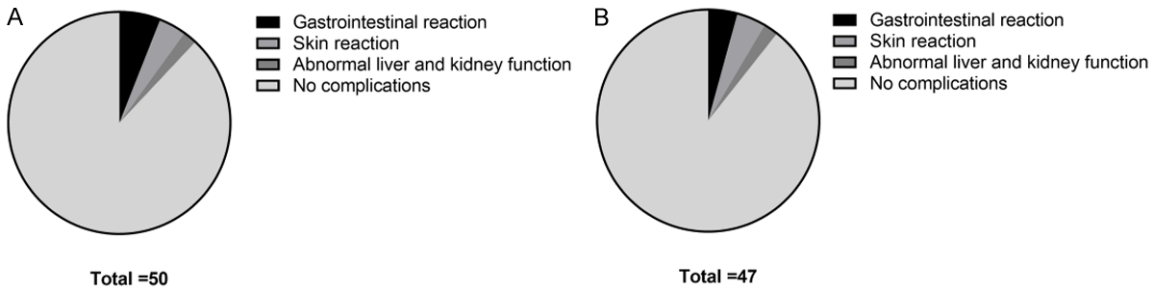

Figure 4. Intergroup comparison of incidence of adverse reactions during treatment. The number of patients with gastrointestinal reaction, skin reaction, liver and kidney dysfunction were 3, 2 and 1 in the SG (12.00%), 2, 2 and 1 in the CG (10.64%) (P>0.05).

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