HGF Treatment Promotes Cardiac Function and Cardiac Repair: Meta-analysis of Pig Models With Myocardial Infarction

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Abstract

Background: Previous studies reported that hepatocyte growth factor (HGF) could promote angiogenesis and cardiac function after myocardial infarction (MI) in pigs. However, the results of these studies were controversial. To clarify the therapeutic efficacy of local HGF administration after MI, we performed a systematic review and meta-analysis of data from the pig models, which could provide evidence for the feasibility of clinical HGF application.

Methods: PubMed, EMBASE, and China National Knowledge Infrastructure were searched for randomized studies that correspond to our subject. The search terms included (hepatocyte growth factor OR HGF) AND (heart failure OR HF OR myocardial infarction OR MI OR AMI OR coronary heart disease OR CHD). The primary endpoint indicators were identified as the left ventricular ejection fraction (LVEF) and capillaries density. Other parameters reflecting cardiac function and ventricular remodeling were analyzed as secondary indicators, including ventricular volume, infarct size, apoptotic index and others.

Results: In total, 9 studies were finally included in the meta-analysis. On comparing the cardiac function indexes, the HGF group was found to be better than the control group in regard to LVEF, stroke volume, left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV). However, no statistically significant differences were found in heart rate. Furthermore, HGF treatment promotes angiogenesis in ischemic areas, which is manifested by increased capillary density. In addition, the HGF group was found to be better than the control group when it comes to infarct size, arteriole densities, and other indicators of cardiac remodeling.

Conclusions: HGF treatment can effectively promote cardiac function and cardiac repair including angiogenesis, and this strategy is a promising cardio-protective approach that merits further clinical studies.

Background

Myocardial infarction (MI) remains a leading cause of death among people worldwide and has become a serious public health problem [1]. The ischemic cardiomyocytes undergo irreversible apoptosis and necrosis post MI, and the infarcted area will be subsequently replaced by fibrous scar tissue, resulting in ventricular remodeling and heart failure (HF) [2, 3]. Although early revascularization can improve the blood supply in the ischemic area to a certain extent, necrotic cardiomyocytes cannot regenerate and cardiac remodeling followed by postischemic HF remains a very frequent (approximately 50%) consequence [4]. The only way to reverse the process is heart transplantation, which is, however, limited by donor organ shortage, high cost and the need of immunosuppressive medications [5]. Therefore, it is of great significance to explore effective strategies to attenuate cardiac remodeling and promote cardiac repair after MI. Among the many potential therapies, gene therapy based on cytokines is one of the most promising.

A variety of vascular growth factors have been studied for gene therapy aiming at ameliorating cardiac function post myocardial injury, among which hepatocyte growth factor (HGF) and insulin-like growth factor (IGF-1) have attracted wide attention [6]. HGF, an important active factor for cell development and differentiation, could regulate the expression of cardiomyocyte specific transcription factors and structural genes through its unique tyrosine kinase receptor c-Met [7], and then play functions such as promoting angiogenesis, regulating inflammation, inhibiting fibrosis, and activating tissue regeneration [8]. HGF and its c-Met receptor have been reported to alleviate chronic myocardial injury in acute MI, myocarditis, cardiomyopathy and other disease models [9]. In animal experiments, local HGF application were mainly conducted through intracoronary gene transfer based on catheter and intramyocardial agents injection based on catheter or thoracotomy [10, 11]. Furthermore, it was demonstrated by preliminary clinical studies that adenovirus-based HGF gene therapy could bring no subjective or objective adverse reactions [12]. So far, there are few clinical studies on the local application of HGF in the treatment of MI. In contrast, HGF has been extensively studied in large animal models, and the results of these studies remained controversial. Therefore, we pooled the experimental data of pigs, which are close to humans in species, to clarify the effect of HGF on cardiac function and cardiac repair after MI, and to provide evidence for clinical transformation of HGF treatment.

Here, we sought to analyze and conclude the applicability and therapeutic efficacy of local HGF delivery post MI, and to review different vectors of HGF delivery, including plasmid, adenovirus and injectable hydrogel. Finally, more effective treatment options and potential future research directions would be discussed.

Methods

Search strategy

Two investigators retrieved literatures through PubMed database, the Excerpta Medica Database (Embase), and the China National Knowledge Information database. Following search terms were used: (hepatocyte growth factor OR HGF) AND (heart failure OR HF OR myocardial infarction OR MI OR AMI OR coronary heart disease OR CHD). The languages and initial time periods of the searches were not limited, with a deadline of March 28, 2020. The retrieved studies were carefully examined to exclude similar articles, and the literatures related to the topic in the references would be also manually retrieved to prevent omissions. Two authors conducted all of the searches independently.

Study selection

Two investigators independently reviewed all of the retrieved studies, screened them by reading titles, abstracts and full texts, and then extracted relevant data. Only the articles that investigated the effect of local HGF application on cardiac function and structural repair in swine models with MI were included. The primary endpoint indicators were identified as the left ventricular ejection fraction (LVEF) and capillaries density. The secondary indicators included ventricular volume, infarct size, apoptotic index and others. By reading the abstract and full text of the article, the eligible articles would be selected according to the selection criteria. As for the disagreements in the study selection, more experienced individuals would be invited to make choices.

Quality assessment and data extraction

Two authors independently assessed the quality of the included studies according to five aspects of evaluation index, including randomization and control (yes/no), adequate allocation (y/n), adequate method of randomization (y/n), blinding of the operator (y/n), and blinding of the functional analysis (y/n). If there was disagreement, it would be resolved by the third individual. The following information was extracted from the full text carefully: pig breed, gender, weight and number of pigs, intervention form, follow-up time, and others. The data were extracted by two investigators independently, and any ambiguities of the studies would be solved by a more experienced third individual.

Data analysis and statistical methods

The mean difference (MD) and 95% confidence interval (CI) were used to calculate and assess evaluation data of the continuous results. Statistical analysis was performed using Review Manager (version 5.3). Furthermore, I^2 values were used to assess the heterogeneity among the included articles. If $I^2 \geq 50\%$, the random-effect model would be used; On the contrary, if $I^2 < 50\%$, the fixed-effect model would be adopted. In addition, to test the robustness of the results, sensitivity analysis was performed by excluding the included studies one by one.

Results

Search results

According to the above query method, a total of 1224 articles were retrieved. By reading the titles and abstracts, we excluded literatures that were not related to the research topic and articles that focused on rats and other non-pigs. Non-controlled studies were also dismissed in this process. We finally included 9 studies after excluding similar and identical articles by analyzing the full text. The detailed selection process for included studies is represented in Figure 1.

3.2 Risk of bias assessment and study characteristics

All the 9 studies included in the meta-analysis met our selection criteria. The methodological quality of each study was assessed, and table 1 show the detailed contents of quality assessment. In all included studies, MI pig models was established by ligating the left descending coronary artery or performing balloon occlusion, and then was randomly divided into HGF treatment group and control group, which conformed to the randomization and control method. However, All studies did not indicate whether blinded analysis of cardiac function and Angiogenesis. After finishing the quality of studies assessment, we extracted basic characteristics from the included literature, including pig breed, gender, weight and number of pigs, intervention form, follow-up time, and others (table 2). Finally, 115 pigs with MI were analyzed, of which 57 pigs received HGF treatment and the remaining 58 pigs received control treatment.

Study	randomized controlled study	Adequate allocation	Method of randomization described	Operator blinded	Analyst blinded
WANG et al. 2006 [13]	Y	Y	N	N	N
Saeed et al. 2008 [14]	Y	Y	N	N	N
Carlsson et al. 2008 [15]	Y	Y	N	N	N
Koudstaal et al. 2014 [10]	Y	Y	N	N	N
Cho et al. 2008 [16]	Y	Y	N	N	N
Chen et al. 2013 [20]	Y	Y	N	N	N
Yang et al. 2010 [17]	Y	Y	N	N	N
Saeed et al. 2011 [18]	Y	Y	N	N	N
Zhang et al. 2008 [19]	Y	N	N	N	N

Table 1
Table 1. Methodological quality of the included studies

Y, yes; N, no

Author, year	pig breed	Sex	Weight (kg)	nt/nc	intervention	dose	administration method	Timing of HGF therapy	Control factors	follow-up
WANG et al. 2006 [13]	Suzhong swine	male	30±5	6/6	Ad5-HGF	4×10 ⁹ pfu/mL	Intracoronary gene transfer	4 weeks post MI	null-Ad5	7 weeks
Saeed et al. 2008 [14]	not mentioned	Female/male	30±4	8/8	VM202	2 mg	intramyocardial injections	30s post MI	saline	50 days±3
Carlsson et al. 2008 [15]	not mentioned	Female/male	30–40	8/8	plasmid HGF	2 mg	intramyocardial injections	1 hour post reperfusion	saline	50 days±3
Koudstaal et al. 2014 [10]	Dalland landrace pigs	female	~70	5/5	IGF-1/HGF in hydrogel	1 µg	intramyocardial injections	4 weeks post MI	hydrogel alone	8 weeks
Cho et al. 2008 [16]	Yorkshire swine	male	31.5±2.1	7/7	plasmid pCK-HGF-X7	1 mg	intramyocardial injection	4 weeks post MI	pCK-LacZ	8 weeks
Chen et al. 2013 [20]	mini-pigs	male	36±3.4	6/6	Ad-HGF	1×10 ¹⁰ genome copies	Intramyocardial Delivery	4 weeks post MI	saline	8 weeks
Yang et al. 2010 [17]	not mentioned	male	23 ± 3	6/6	Ad5-HGF	5×10 ⁹ Pfu/ml	Intracoronary gene transfer	4 weeks post MI	null-Ad5	7 weeks
Saeed et al. 2011 [18]	not mentioned	Female/male	30–32	6/6	plasmid pCK-HGF-X7	3.96×10 ¹¹ viral copies	intramyocardial injection	5 weeks post MI	pCK-LacZ	10 weeks
Zhang et al. 2008 [19]	mini-pigs	Female/male	26 ±3	5/6	Ad5-HGF	5×10 ⁹ Pfu /ml	Intracoronary gene transfer	4 weeks post MI	null-Ad5	7 weeks

Table 2
Table 2. Summary of characteristics of the included studies

Note: the study conducted by Zhang et al. [19] was published on the China National Knowledge Information database. n, number of animals (nc, control; nt, treated); HGF, Hepatocyte growth factor; Ad5-HGF, adenovirus-mediated human HGF

3.3 Outcomes of meta-analysis

3.3.1 Cardiac function recovery after the application of HGF

Eight studies[10, 13-19] provided data (n=103) on evaluation indicator of heart function after local HGF application, including LVEF, left ventricular end-systolic volume (LVESV) left ventricular end-diastolic volume (LVEDV) , stroke volume and heart rate. A fixed-effect model was used in the analysis of the data, due to no significant heterogeneity existing among the studies (LVEF: $I^2=2\%$, $P=0.40$; LVESV: $I^2=44\%$, $P=0.17$; LVEDV: $I^2=13\%$, $P=0.32$; stroke volume: $I^2=0\%$, $P=0.79$; heart rate: $I^2=0\%$, $P=0.71$). The results of analysis suggested that, compared with the control group, local application of HGF could significantly reduce LVESV and LVEDV, and therefore increase LVEF and stroke volume (LVEF: six studies, 82 pigs, MD:9.73, 95% CI:8.70, 10.76, $P=0.00001$; LVESV: three studies, 42 pigs, MD:-8.79, 95% CI:-10.87, -6.71, $P=0.00001$; LVEDV: three studies, 36 pigs, MD:-6.92, 95% CI:-11.51, -2.32, $P=0.003$; stroke volume: two studies, 26 pigs, MD:7.07, 95% CI:5.35,8.79, $P=0.00001$). However, no significant statistical differences were found in the effect of heart rate between the HGF treatment group and the control group (heart rate: two studies, 28 pigs, MD:1.59, 95% CI:-1.01, 4.19, $P=0.23$; figure 2).

3.3.2 Angiogenesis after the application of HGF

Five literatures[10, 14, 16, 18, 20] studied the effect of HGF administration on the angiogenesis in pigs with CMI, involving 64 animals. Angiogenesis was represented by capillaries density (capillaries/mm²), arterioles density (arterioles/mm²), and peak signal intensity (au). A fixed-effect model was used in the analysis of peak signal intensity (au) of blood flow measured by MR in the infarcted area, because that no significant heterogeneity ($I^2=0\%$,

$P=0.32$) was found between studies. As for the analysis of the densities of capillaries (capillaries/mm²) and arterioles (arterioles/mm²) in peri-infarcted regions, we applied the random-effect model because of the significant heterogeneity between the studies (capillaries density: $I^2=98\%$, $P=0.00001$; arterioles density: $I^2=97\%$, $P=0.00001$). The analysis showed that compared with the control group, the capillary and arteriole densities in the ischemic area increased significantly in the HGF group, and subsequently peak signal intensity of blood flow improved (capillaries density: five studies, 64 pigs, MD:79.98, 95% CI:24.58,135.39, $P=0.005$; arterioles density: two studies, 28 pigs, MD:13.07, 95% CI:3.57, 22.58, $P=0.007$; peak signal intensity: two studies, 28 pigs, MD:294.31, 95% CI:202.52, 386.09, $P=0.00001$; figure 3).

3.3.3 Ventricular remodeling after the application of HGF

Six literatures[10, 14, 15, 17-19] studied the effect of HGF application on ventricular remodeling including infarct size, cardiac hypertrophy and apoptosis in pigs with CMI, involving 77 animals. A fixed-effect model was used to analyze the data of infarct size (% LV) measured by MR and TTC staining, myocyte diameters in peri-infarcted regions and apoptotic index, as no significant heterogeneity existed among the studies (infarct size measured by MR: $I^2=49\%$, $P=0.16$; infarct size measured by TTC staining: $I^2=0\%$, $P=0.53$; apoptotic index: $I^2=0\%$, $P=0.85$; myocyte diameter in peri-infarcted regions: $I^2=0\%$, $P=0.92$). The result showed that, within several weeks after HGF application, the infarct size (%LV) measured by either MR or TTC staining was significantly diminished than that of the control group (infarct scar measured by MR: two studies, 28 pigs, MD:-5.77, 95% CI:-6.76, -4.78, $P=0.00001$; infarct scar measured by TTC staining: two studies, 28 pigs, MD:-5.07, 95% CI:-5.81,-4.33, $P=0.00001$). In addition, HGF treatment significantly diminished the myocyte diameter in the peri-infarcted regions, and attenuated apoptosis index (the myocyte diameter: two studies, 26 pigs, MD:-5.02, 95% CI:-5.95, -4.09, $P=0.00001$; apoptotic index: two studies, 23 pigs, MD:-2.42, 95% CI:-3.30,-1.54, $P=0.00001$; figure 4)

Sensitivity analysis performed by excluding the studies one by one demonstrated that the results were the same as before, which indicated that results of the meta-analysis were robust. Furthermore, some certain publication bias may exist in the funnel plot, since the values were not completely and evenly distributed around the overall estimate (figure 5).

Discussion

For decades, the application of early revascularization techniques post MI, including Percutaneous Coronary Intervention (PCI), has been proved to rapidly restore the blood perfusion of the ischemic region, and significantly reduce the short-term mortality [21]. However, the reperfusion injury may be aggravated after revascularization, and the infarcted myocardium cannot be resurrected from death, which may accelerate the occurrence of HF after MI [22]. For this part of patients, long-term use of Angiotensin Converting Enzyme Inhibitor (ACEI), β -Blocker and other drugs could delay the process of ventricular remodeling and improve the prognosis to some extent. However, it is difficulty for the existing therapies to bring further benefits for patients [23]. Therefore, it is urgent to take further combination therapies, even new therapeutic agents, to achieve effective management of patients with CMI.

HGF, a promising biomarker for CHD, is released into the bloodstream following the damage of endothelial cells [24]. In addition, HGF has been shown to attenuate chronic tissue damage, promote angiogenesis, inhibit fibrosis and apoptosis, regulate inflammation and improve prognosis [25, 26] in various ischemic disease models such as MI [27] and peripheral arterial occlusive disease (PAOD) [28]. The biological function of HGF is mediated by its unique tyrosine kinase receptor c-Met [29], and the activation of c-Met receptor further activates many intracellular signaling pathways including RAS-mitogen activated protein kinase (MAPK), signal transducer and activator of transcription (STAT), phosphatidylinositol-3 kinase (PI3K), protein kinase B (AKT), mammalian target of rapamycin (mTOR) and β -catenin pathway [30-32]. Our research group previously demonstrated that local administration of Ad5-HGF could improve cardiac function through the above potential mechanisms in porcine hearts with MI [17].

HGF has been widely studied in some certain large animal models with MI, but its efficacy remains controversial, which, to some extent, prevents the clinical translation of the HGF application. Our study showed that the heart function of pigs in the HGF treatment group was significantly better than that in the control group within the following 1-2 months after MI, which was manifested as the enhancement of cardiac pumping function (about 7.07ml increase in stroke volume, and 9.40% increase in LVEF), and the reduction of ventricular volume, especially the LVESV (LVESV decreased by 8.79ml on average, and LVEDV by 6.92ml). In addition, no significant heterogeneity among the included studies was found, suggesting that the pooled results obtained from our analysis were relatively reliable. However, the effect of HGF treatment on heart rate was negligible, which may owe to the short follow-up time or the other possible factors.

In terms of heart repair post-infarction, local application of HGF was proved to promote angiogenesis, diminish the infarction size, and attenuate LV remodeling. We found that the number of vessels in ischemic regions, as a primary endpoint indicator, was significantly increased in the HGF treatment group (capillaries density increased by 79.98 capillaries/mm² on average, arterioles density by 13.07 arterioles/mm², and peak signal intensity of blood flow by 294.31au). In addition, Wang et al [13] and Yang et al [17] respectively showed that there were significant differences between the two groups in regard to a-SMA⁺ blood vessels (56.1 $\pm$ 4.2 vessels/mm² VS 16.4 $\pm$ 3.5 vessels/mm², 22.75 $\pm$ 5.85 vessels/mm² VS 14.50 $\pm$ 2.08 vessels/mm²), suggesting that HGF treatment could promote angiogenesis. In terms of secondary indicators, we demonstrated that HGF treatment could contribute to a reduction (approximately 6%) in infarcted size measured by MR or TTC staining. Furthermore, the myocyte diameter at the peri-infarcted regions in the HGF group was smaller than that in the control group (about 5.02 μ m), which may be due to either inhibition of cardiac hypertrophy and LV remodeling, or promotion of the new cardiomyocytes proliferation.

Previous portions of this paper summarized the function of HGF, however, there are strong clinical concerns about the selection of appropriate vectors delivering exogenous HGF genes or proteins to the target area. Gene therapy based on plasmid or adenovirus is a relatively recognized method. Some studies have shown that local injection of HGF plasmid or Ad-HGF would be safe [33]. However, local injection of virus was found to potentially increase the risk of ventricular arrhythmia in animal experiments, which may have a negative impact on the clinical transformation of gene therapy. In recent years, injectable hydrogels, a kind of promising synthetic biomaterials with advantages of mild gelation and cardiac-compatible properties [34, 35], have been proved to improve cardiac function after local myocardial injection alone [36]. In addition, hydrogels can also encapsulate therapeutic drugs, deliver them to target areas, and subsequently achieve continuous therapeutic effects [37]. Therefore, hydrogels may become a kind of more attractive method of exogenous administration.

This meta-analysis had certain strengths and limitations. Firstly, it was the first meta-analysis to evaluate the effect of local HGF application on animal models with MI. We explored the results of HGF treatment by integrating some small sample data, and analyzed the characteristics of plasmids, viruses and hydrogel vectors, providing a potential strategy for efficient management of MI patients. Secondly, we were strict in the selection of studies, so as to reduce the occurrence of bias. In regard to limitation, some included studies did not provide statistical data we need, and some of the endpoint indicators in the studies were not quantified, these data consequently were not included in the statistical analysis. In addition, several studies that conducted in China may have defects in terms of the experimental design, and some other studies that failed to achieve the expected results may not achieve successful publication, which may compose the possible source of publication bias in the analysis. Therefore, more carefully designed and large-scale studies should be conducted to further evaluate the efficacy and safety of HGF.

Conclusion

The safety of local HGF application has been preliminarily confirmed by previous Phase I clinical studies, however, some multicenter studies with more rigorous experimental design and longer follow-up are needed to exclude potential safety risks. By pooling the current evidence, the local application of HGF has been found to improve cardiac function and angiogenesis in the infarcted area, inhibit apoptosis and fibrosis, and attenuate LV remodeling after MI in adult pigs. Although certain species differences exist between humans and pigs, this study provides some evidence for the feasibility of clinical translation of HGF application. In addition, stronger effects on MI treatment may be found by combining HGF with other therapeutic factors including mesenchymal stem cells (MSC) and cytokines, which needs further multi-step preclinical and clinical trials to confirm.

Abbreviations

HGF: hepatocyte growth factor;

MI: myocardial infarction;

CHD: coronary heart disease;

LVEF: left ventricular ejection fraction;

LVESV: left ventricular end-systolic volume;

LVEDV: left ventricular end-diastolic volume;

HF: heart failure;

IGF-1: insulin-like growth factor;

MD: mean difference;

CI: confidence interval;

PCI: Percutaneous Coronary Intervention;

ACEI: Angiotensin Converting Enzyme Inhibitor;

PAOD: peripheral arterial occlusive disease;

MAPK: mitogen activated protein kinase;

STAT: signal transducer and activator of transcription;

PI3K: phosphatidylinositol-3 kinase;

AKT: protein kinase B;

mTOR: mammalian target of rapamycin;

Declaration

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None.

Authors' contributions

Chong Du designed and wrote the manuscript. Xiao-Wen Chen and Ze-Mu Wang collected the data and participated in the design. Hao-Yu Meng, Ya-Fei Li and Tian-Wen Wei conducted the analysis and developed the Figs. Lian-Sheng Wang (corresponding author) supervised and performed manuscript editing. All authors approved the final version of the manuscript.

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Availability of data and materials

All data and materials are available.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Flowchart of included studies on HGF therapy in pigs with MI.

Figure 2

Forest plot diagram showing the impact of HGF on cardiac function. Cardiac function is represented by the following parameters: heart rate (bpm), stroke volume (ml), LVEF (%), LVESV (ml) and LVEDV (ml). LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVEDV, left ventricular end-diastolic volume.

Figure 3

Forest plot diagram showing the impact of HGF on angiogenesis. Angiogenesis is represented by capillaries density (capillaries/mm²), arterioles density (arterioles/mm²), and peak signal intensity (au) measured by MR.

Figure 4

Forest plot diagram showing the impact of HGF on cardiac repair. Cardiac repair is represented by the following parameters: infarct size (% LV) measured by MR and TTC staining, myocyte diameters (μm) and apoptosis (%).

Figure 5

Funnel plot for LVEF improvement between HGF group and control group. Some certain publication bias exist in the funnel plot, since the values were not completely and evenly distributed around the overall estimate. SE, standard error; MD, mean difference.