Clinical Benefits of High And Low Dose Antivenom Serum 2 For The Treatment Of Snakebite A Meta-Analysis.

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Abstract

UV radiation Venomous snake bite is considered to be a kind of critical illness, which requires immediate emergency measures to ensure the life safety of the patients.
Objective: To compare and analyze the clinical effect of high and low dose of antivenom serum on patients.
Methods: Seven databases (PubMed, EMBASE, Cochrane, web of science, Wanfang, HowNet, VIP) were searched systematically to include the published papers on the effect of different doses of antivenom serum on clinical benefits of patients with randomized controlled trials. The analysis indexes included: cure rate, allergic reaction, length of hospital stay, patients' acceptance, liver and kidney function indexes (alt, BUN), myocardial enzyme indexes (AST, LDH, CK, CK-MB), coagulation indexes (PT, TT).
Results: A total of 10 references were included. Among 10 randomized controlled trials, the high-dose antivenom serum group was the experimental group, and the low-dose antivenom serum group was the control group, 1856 in the experimental group and 656 in the control group. The results of meta-analysis showed that: (1) There were significant differences in cure rate, allergic reaction, length of stay, patients' acceptance, ALT level, adverse reactions, adverse reactions, hospitalization time, bun, and Pt. (2) There was no significant difference in AST, LDH, CK, CK-MB, and TT.
Conclusion: The dosage of antivenom serum has a certain influence on the treatment of patients bitten by venomous snakes, and this study can be used as a clinical reference.

Keywords: Antivenom serum, Dose, Clinical benefit, Comparative analysis.

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Introduction

There are as many as 650 kinds of poisonous snakes in the world, including about 50 kinds in China, which are mainly distributed in Yunnan, Fujian, Guangxi, Guangdong and other related areas in China. Generally, people in southern China eat snakes as supplements, resulting in a large number of killings and eating of poisonous snakes, resulting in more patients with snake venom injuries in hospitals. Venomous snake bite is considered to be a kind of critical illness. The main clinical manifestations are weakness of limbs, weakness of breath, and weakness of the whole body and so on. Serious cases will lead to systemic organ failure and even death. Therefore, it is necessary to take some emergency measures immediately after 51 the snakebite to ensure the life safety of the patients. Snake venom is mainly neurotoxin, blood circulation toxin and mixed toxin. In addition, it also includes phospholipase A2, proteolytic enzyme, hyaluronidase and other toxic proteins. Antivenom serum is recognized as a specific drug for the treatment of snakebite. It can directly neutralize the free snake venom antigen which does not cause toxic effect on the target organs, so that the activity of snake venom disappears. If the venomous snake has combined with the tissues and organs to damage the functions of the organs, the antivenom serum will not play a great role, nor can it detoxify. Therefore, the earlier the antivenom serum is used and the more sufficient the dosage is, the better the efficacy is (Isbister, 2010; Isbister, Buckley, & Brown, 2014; Isbister, O'Leary, Schneider, Brown, & Currie, 2007). However, there are still some controversies about the effect of antivenom serum on the clinical efficacy of patients (Gadwalkar et al., 2014; Paul et al., 2004). We therefore, undertook this systemic review of randomized clinical trial to address this issue. We found that the appropriate increase of antivenom serum dose is conducive to the recovery of patients' health, at the same time, the incidence of allergic reaction is low, the length of hospital stay is short, and patients are easy to accept, as the significant different cure rate, allergic reaction, length of stay, and acceptance rate after treatment with different doses of antivenom serum. This study can be used as a clinical reference.

Materials and Methods

Study type this study was meta-analysis. Search Methodology In this study, we searched appropriated literatures in seven databases (PubMed, EMBASE,Cochrane, web of science, Wanfang, HowNet, VIP) from 2000 to 2021. The key words were"antivenom serum", "clinical benefits", "dose", and "treatment". In addition, the original literature mand references of previous meta-analysis were searched manually. Literature screening two reviewers were invited to screen the original literature. If they disagree, the third reviewer was invited to

make the final judgment. First of all, the preliminary screening, mainly through reading the Randomized controlled trial (RCT) research topics and abstracts to exclude irrelevant literature, and then full-text screening, in order to obtain the reference of the composite standard. Any disagreement in the literature screening was resolved through discussion. Cochrane's bias risk assessment tool was used to control the quality of this study. Inclusion criteria Inclusion criteria include: 1) All patients in the study were having evidence of envenomation; 2) The patient had no serious heart disease, liver and kidney failure; 3) The patients were treated with antivenom serum; 4) RCT; 5) English and Chinese literature. Exclusion criteria Exclusion criteria include: 1) Non-human research; 2) Lack of full text; 3) Review; 4) Non randomized controlled study (including coharts, case reports, before-after study, eyc.); 5) Conference papers / abstracts.

Data extraction

Two reviewers extracted the data from the selected references. The extracted data include: 1) Basic information (article title, author, publication time, research type); 2) Intervention measures (the number of research objects, grouping situation, medication situation); 3) Outcome measures (cure rate, allergic reaction, length of hospital stay, patients' acceptance, liver and kidney function indexes such as alt, BUN, myocardial enzyme indexes including AST, LDH, CK, CK-MB, coagulation indexes PT and TT). Any disagreement in the extracted data was resolved through discussion. Statistical analysis Revman 5.3 software was used for statistical analysis, and "mean / median" was used for data estimation ± The effect scale was weighted mean difference (WMD) or standardized mean difference (SMD); 95% confidence interval was selected for interval estimation. Heterogeneity passed Cochrane's Q test or I2 index. If Q test was used, $P > 0.10$, low heterogeneity was considered; For I2 index, the heterogeneity was considered as follows: 1) if I2 is less than 20%, we consider low heterogeneity; 2) I2: 20-50%, with obvious heterogeneity; 3) I2: 50-75%, considering substantial heterogeneity; 4) I2 > 75%, considering the large heterogeneity, it is not conducive to direct data consolidation. For I2<20% or low heterogeneity, fixed effect model can be used directly; In other cases, random effect model was used. Publication bias means that statistically significant results (positive) are more likely to be published than no significant results (negative). This may exaggerate the therapeutic effect of positive interventions. For publication bias, we used Revman 5.3 software to make funnel plot. 119

Results

Literature search results

In this study, endnote document management software was used for document management. According to the article screening criteria, PubMed, EMBASE, Cochrane, web of science, Wanfang, HowNet and VIP databases were searched. The key words included "antivenom serum", "clinical","antivenom serum" and "clinical". A total of 824 related literatures were retrieved, including 87 in English, 737 in Chinese, 642 in the rest. According to the inclusion and exclusion criteria, 10 Chinese references were obtained (Du & Liao, 2010; Du & Xie, 2016; Fu, 2014; Liao, Li, Zhang, Cai, & Cai, 1292020; Peng, Zeng, Huang, Wei, & Huang, 2013; Tan, Tan, & Li, 2020; Xu, Li, & Liu, 2018; Yu, 2007; Yuan et al., 2014; Zhong, 2002). The specific retrieval process was shown in Figure 1. In the original study, the high-dose antivenom serum group was the experimental group, and the low-dose antivenom serum group was the control group. There were 1856 people in the experimental group and 656 people in the control group.

Basic information on inclusion in the study

According to the inclusion and exclusion criteria, 10 references were included in this study, all of which were Chinese references. The basic information extracted from the data included: author, time of publication, type of study, number of subjects, grouping, medication, cure rate, allergic reaction, length of hospital stay, patient acceptance, liver and kidney function index (alt, BUN), myocardial enzyme index (AST, LDH, CK, CK-MB), coagulation index (PT, BUN) TT) and other outcome indicators in different dose groups of antivenom serum. The details of the final included studies are shown in Table 1.

Cure rate

Among the 10 research literatures, two studies involved the cure rate of the two groups (Yu, 2007; Zhong, 2002). The number of patients in the experimental group and the control group was 362 and 53 respectively. The cure rate of the two groups was compared. Meta-analysis showed that the heterogeneity of the two original studies was high, and the cure rate of the two groups was statistically significant by using the random effect model (OR=46.41, 95%CI: 5.58~386.18, P=0.0004), as shown Figure 2.

Allergic reactions

The 10 included studies, 6 involved allergic reactions of patients in the two groups (Du & Liao, 2010; Fu, 2014; Liao et al., 2020; Peng et al., 2013; Yuan et al., 2014; Zhong, 2002). The number of patients in the Experimental group and the Control group were 1406 and 508 respectively. The results of meta-analysis showed that the heterogeneity of the six original studies was high. Using the random effect model, the allergic reactions of patients in the two groups were significantly different (OR=0.13, 15895%CI: 0.03~0.53, P=0.004), as shown in Figure 3.

Hospital stay

Two of the 10 studies involved the length of hospital stay of the two groups (Tan et al., 2020; Yuan et al., 2014). The number of patients in the Experimental group and the Control group were 98 and 229 respectively. The length of hospital stay of the two groups was compared. The results of meta-analysis showed that the heterogeneity between the two original studies

was low. Using the fixed effect model, there was a significant difference in the length of hospital stay between the two groups (OR=- 166 3.90, 95%CI: -4.36~-3.45, P<0.00001), as shown in Figure 4.

Patient acceptance

Among the 10 included studies, 3 involved in the "patient acceptance" of the two groups of patients (Fu, 2014; Liao et al., 2020; Peng et al., 2013). The number of patients in the Experimental group and the Control group were 362 and 53 respectively. The results of meta-analysis showed that the heterogeneity of the three original studies was high. Using the random effect model, the "patient acceptance" of the two groups was statistically significant (OR=4.34, 95%CI: 2.46~7.64, P<0.00001), as shown in Figure 5.

Liver and kidney function indexes

The 10 studies included, 2 involved the ALT level of patients in the two groups (Du & Xie, 2016; Yu, 2007). The number of patients in the Experimental group and the Control group were 90 and 90 respectively. The results of meta-analysis showed that the heterogeneity between the two original studies was high. Using the random effect model, there was a significant difference in ALT level between the two groups (OR=-44.64, 95%CI: -82.32~-6.95, P=0.02), as shown in Figure 6. In addition, 2 of the 10 studies involved in the bun level of the two groups (Du & Xie, 2016; Peng et al., 2013). The number of patients in the Experimental group and the Control group were 90 and 90 respectively. The bun level of the two groups was compared. The results of meta-analysis showed that the heterogeneity between the two original studies was high. Using the random effect model, there was a significant difference in the bun level between the two groups (OR=-3.77, 95%CI: -6.78~0.75, P=0.01), as shown in Figure 7.

Myocardial enzyme indexes

Among the 10 studies included, 2 studies related to the AST level of patients in the two groups (Du & Liao, 2010; Liao et al., 2020). The number of patients in the Experimental group and the Control group were 88 and 95 respectively. Meta-analysis results showed that the heterogeneity between the two original studies was high. Using the random effect model, the results showed that there was no significant difference in AST level between the two groups (OR=-29.00, 95%CI: -76.14~18.14, P=0.23), as shown in Figure 8.

LDH levels

Among the 10 studies included, 2 studies related to LDH levels of patients in the two groups & Liao, 2010; Tan et al., 2020). The number of patients in the Experimental group and the Control group were 88 and 95 respectively. Meta-analysis showed that there was no significant difference in LDH level between the two groups (OR=-74.49, 95%CI: -174.16~25.17, P=0.14), as shown in Figure 9.

CK levels

Among the 10 studies included, 2 studies related to the CK level of patients in the two group (Fu, 2014; Xu et al., 2018). The number of patients in the Experimental group and the Control group were 88 and 95 respectively. The results of meta-analysis showed that the heterogeneity between the two original studies was high, and the random effect model suggested that there was no significant difference in CK level between the two groups (OR=-200.57, 95%CI: -590.97~189.84, P=0.31), as shown in Figure 10.

CK-MB levels

The 10 studies included, 2 involved the levels of CK-MB in the two groups (Yu, 200Yuan et al., 2014). The number of patients in the Experimental group and the Control group were 88 and 95 respectively. The levels of CK-MB in the two groups were compared. The results of meta-analysis showed that the heterogeneity between the two original studies was high. Using the random effect model, we found that there was no significant difference in CK-MB level between the two groups (OR=-20.60, 95%CI: -58.62~17.42, P=0.29), as shown in Figure 11.

Coagulation indexes

Among the 10 studies included, 2 studies related to PT level of patients in the two groups (Yu, 2007; Zhong, 2002). The number of patients in the Experimental group and the Control group were 90 and 90 respectively. The results of meta-analysis showed that the heterogeneity between the two original studies was low. Using the fixed effect model, we found that there was a significant difference in PT level between the two groups (OR=-1.93, 95%CI: -2.53~-1.32, P<0.00001), as shown in Figure 12. Among the 10 studies included, 2 studies related to the TT level of patients in the two groups (Tan et al., 2020; Yuan et al., 2014). The number of patients in the Experimental group and the Control group were 90 and 90 respectively. Meta-analysis showed that the heterogeneity between the two original studies was high. Using the random effect model, we found that there was no significant difference in TT level between the two groups (OR=-4.19, 95%CI: -8.49~0.10, P=0.06), as shown in Figure 13.

Estimation of publication bias

The number of original literatures is generally less than 10, and the number of meta-analysis research is less, so funnel plot is generally not recommended. Funnel plot is needed only when the original study is more than or equal to 10. Therefore, Revman 5.3 was not used as funnel plot to evaluate publication bias. 241

DISCUSSION

Venomous snake bite, as a kind of clinical common acute and severe disease, should tak emergency treatment measures, as soon as possible to determine the strength of the snake venom

and the type of snake venom, so as to carry out targeted treatment of the venomous snake bite wound. Different antivenom serum sera should be used for different snakebite to neutralize the free toxin in the body and prevent the toxin from entering the central nervous system of patients, resulting in dyspnea (Kazandjian et al., 2021; Liang et al., 2020; Lin et al., 2020). Under normal circumstances, there are two kinds of snake venom: neurotoxin and blood circulation. Neurotoxin can enter other organs with human blood circulation, which will cause liver and kidney dysfunction. Patients are prone to poor breathing, muscle weakness, and even death. The blood circulation snake venom mainly affects the blood coagulation function of patients, causing damage to human vascular endothelial cells, resulting in renal insufficiency and disseminated intravascular coagulation disorder (Koh, Armugam& Jeyaseelan, 2006; Qian et al., 2000). In order to timely diagnose and treat the life of patients bitten by poisonous snakes, the first treatment measure is to use anti venomous snake serum for patients. The effective use of anti venomous snake serum can effectively neutralize the free toxins in patients, so as to give doctors the opportunity to save patients. Antivenomous snake serum is the key and specific drug for the treatment of venomous snake bite, which can effectively neutralize the toxin that has not been combined with cell tissue in patients, and play the role of detoxification (Darsonval et al., 2010). In general, the best effect is to inject antivenom serumous serum within 4 hours after the snakebite, and the dosage of antivenom serumous serum should be sufficient. Antivenom serum is usually made from horse plasma and belongs to heterologous protein, which can easily cause allergic reaction. Therefore, before the injection of antivenom serum, allergy test should be carried out to prevent allergic reaction. The dosage of antivenom serum injection is usually selected according to the amount of snake venom in the human body, and the physical condition of patients should be considered. For example, the injection dosage of the elderly and children is different from that of healthy, so the dosage should be used as appropriate. Generally speaking, patients with mild snakebite have less influence on liver and kidney function, myocardial enzymes, coagulation function and platelet count due to their strong liver compensation ability. However, severe and critically ill patients with snake bite are more serious in the abnormal situation of various indicators, and may die due to untimely treatment. The results of meta-analysis showed that there were significant differences in cure rate (P=0.0004), allergic reaction (P=0.004), length of stay (P<0.00001) and acceptance rate (P<0.00001) between the two groups after treatment with different doses of antivenin serum. These results show that the appropriate increase of antivenin serum dose is conducive to the recovery of patients' health, at the same time, the incidence of allergic reaction is low, the length of hospital stay is short, and patients are easy to accept. In addition, there were significant differences in ALT (P=0.02), bun (P=0.01) and Pt (P<0.00001) of liver and kidney function indexes between the two groups after treatments with different doses of antivenom serum. Moreover, alt, bun and Pt indexes of patients with high dose of antivenom serum were easy to return to normal, while ast (P=0.23), bun (P<0.00001) and Pt (P<0.00001) of myocardial enzyme indexes of the two groups were easy to return to normal There was no significant difference in LDH (P=0.14), CK (P=0.31) and CK-MB (P=0.29). These data show that the level of antivenin serum dose will not have a certain impact on the myocardial enzyme indexes of patients.

Conclusions

There are several limitations to this study. Apart from Chinese and English, the other languages literature is not included in this study, which may neglect a part of the data. Additionally, although some of the results of the two groups are heterogeneous, there is no further analysis on its source. Furthermore, patients suffering from different poisonous snake species are not focused on because of the limited data. This study shows that the different dosage of antivenom serum has a different impact on the treatment of patients bitten by venomous snakes. However, the specific functional mechanism is not clear, which needs further studies to provide more data in order to guide the clinical treatment strategy.

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